

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021463Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 021463	Submission Dates: 12/09/2010 and 12/27/2010
Brand Name	Fortesta
Generic Name	Testosterone
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology (DCP) 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Endo Pharmaceuticals
Relevant INDs	IND (b) (4) 076634
Submission Type	Resubmission
Formulation and Strength	Testosterone gel in a metered dose pump (10 mg of testosterone per actuation), 10 mg – 70 mg testosterone
Indication	Testosterone replacement therapy in male hypogonadism <ul style="list-style-type: none">○ Primary hypogonadism (congenital or acquired)○ Hypogonadotropic hypogonadism (congenital or acquired)

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1 Executive Summary

The Clinical Pharmacology review of NDA 021463 (DARRTS, 12/15/2010) stated that the NDA 021463 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The agreement on the language in the package insert labeling between the sponsor and the Division was reached on 12/27/2010. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 021463 acceptable.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

HYUNJIN KIM
12/28/2010

MYONG JIN KIM
12/28/2010

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12/28/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 021463	Submission Dates: 06/21/2010, 06/30/2010, 08/30/2010, 10/11/2010, 11/22/2010, and 12/03/2010
Brand Name	Fortesta
Generic Name	Testosterone
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Endo Pharmaceuticals
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1 Executive Summary

Fortesta is a testosterone (T) gel with a proposed indication of T replacement therapy in male hypogonadism (primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)). Fortesta is supplied in 60 g metered dose canisters with a pump that is designed to dispense 0.5 g gel (10 mg T) per each actuation. Proposed dosing regimen is to start with 40 mg T applied topically to thighs once daily in the morning. Daily dose can be adjusted between 10 mg and 70 mg T based on total T concentration 2 hours post Fortesta application and at approximately 14 days after starting treatment or following dose adjustment.

The original NDA 021463 was filed on June 3, 2002 under section 505(b)(2). It received a Not Approvable (NA) action on July 3, 2003 for the concern of high supraphysiologic serum T concentrations. On April 17, 2009, the sponsor submitted a Complete Response (CR). In this CR, the sponsor submitted the results of a new phase 3 trial (FOR01C) with lower T dose to address the deficiencies listed in the NA letter dated July 3, 2003. On October 16, 2009, the Agency issued a CR action due to the unresolved deficiencies associated with the bioanalytical site for FOR01C identified by the Division of Scientific Investigation (DSI) inspection with a potential Post Marketing Requirement (PMR) trial to assess the residual T after washing.

In the current submission, the sponsor submitted a new dataset to address the deficiencies in bioanalytical assays after analyzing the back-up serum samples. In addition, the sponsor submitted a timeline to conduct a washing trial as a PMR.

On July 22, 2010, the Office of Clinical Pharmacology requested a consult to DSI to inspect the analytical site where the back-up serum samples were analyzed.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 021463 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert.

1.2 Post Marketing Requirement

A clinical trial entitled “Hand washing and application site washing trial following application of Fortesta” to assess the amount of residual T before and after washing primary user’s hands as well as thighs (application sites of Fortesta) will be conducted with a following timeline which was agreed upon between the Division and the sponsor (DARRTS, October 11, 2010):

- Final Protocol Submission: February 2011
- Trial Completion: September 2011
- Final Report Submission: April 2012

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Refer to Clinical Pharmacology review (DARRTS, October 14, 2009) by Dr. Hyunjin Kim for the important Clinical Pharmacology/Biopharmaceutics findings in the previous review cycle.

<DSI findings>

Following multiple interactions between the Division and the sponsor to address deficiencies identified in the DSI report (DARRTS, October 8, 2009), the DSI reviewer recommended that the dataset provided by the sponsor was valid, therefore, acceptable to review (DARRTS, November 25, 2009, August 9, 2010, October 6, 2010, and November 18, 2010).

<Phase 3 trial, FOR01C>

The phase 3 trial, FOR01C, was a 90-day, multi-center, open label, non-comparative trial in 149 hypogonadal males who had received prior T replacement therapy. All enrolled patients applied Fortesta once each morning (approximately same time between 7 and 11 a.m.) to the each front and inner thigh with one finger at a starting dose of 40 mg/day. The dose of Fortesta was adjusted to between a minimum of 10 mg/day and a maximum of 70 mg/day. Trial FOR01C met the primary and secondary endpoints as provided in Table 1.

Table 1. Summary of C_{avg} and C_{max} of total T on Day 90 (mITT2 Population, FOR01C)

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

2 Question-Based-Review

2.1 General Attributes

2.1.1 What is the regulatory history behind this NDA?

NDA 021463 received a CR action on October 16, 2009 with following deficiencies and the action items listed in the CR letter.

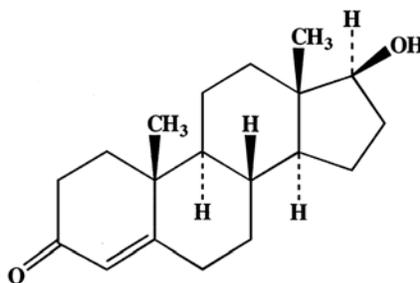
- 1) The previously submitted phase III data may be sufficient if the deficiencies identified in the DSI audit of the (b) (4) can be resolved. If these deficiencies cannot be adequately addressed, new phase III data will be required.
- 2) Sufficient information to adequately assess the known serious risk of secondary transfer of T 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.
- 3) We have determined that under section 505-1, the Risk Evaluation and Mitigation Strategy (REMS) for this product must include a Medication Guide and a timetable for submission of assessments.

In order to address the deficiencies listed above, the sponsor submitted the following in the current resubmission:

- 1) New dataset after analyzing the back-up serum samples to address the deficiencies identified in the DSI audit of (b) (4) (bioanalytical site of the pivotal phase 3 clinical study, FOR01C); submitted on June 30, 2010
- 2) Timeline (protocol submission, trial completion, and final report submission) for hand washing and application site washing trial; submitted on October 11, 2010
See section 1.2 for details.
- 3) REMS including a Medication Guide and a timeline for submission of assessment; submitted on June 30, 2010

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug?

- T, USP is a white to almost white powder described chemically as 17-beta hydroxyandrost-4-en-3-one.



Testosterone

$C_{19}H_{28}O_2$

MW 288.42

- Fortesta is a clear, colorless, odorless, hydroalcoholic gel containing T. Fortesta provides transdermal delivery of T for a 24 hour period following a single application to skin of both front and inner thighs.

- The formulation of Fortesta is provided in Table 2.

Table 2. Composition of Fortesta

Material	% w/w
T, USP	(b) (4)
Propylene Glycol, USP	
Ethyl Alcohol, (b) (4)	
Isopropyl Alcohol, USP	
Oleic Alcohol, NF	
Carbomer 1382	
Trolamine, NF	
Butylated Hydroxytoluene, NF	
Purified Water, USP	

2.1.3 What is hypogonadism?

There are two types of hypogonadism, primary and hypogonadotropic hypogonadism. Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol, heavy metals or age related degeneration. Patients with primary hypogonadism usually have low serum T concentrations and gonadotrophins (FSH and LH) above the normal range. Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, radiation, and age related degeneration or drug induced hypopituitarism. Patients with hypogonadotropic hypogonadism have low serum T concentrations but have gonadotrophins in the normal or low range.

2.1.4 What are the proposed mechanism of action and therapeutic indications?

Endogenous androgens, including T and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature and fat distribution. T and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of T and is characterized by low serum T concentrations. Signs and symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects

of the gonads, such as Klinefelter’s Syndrome or Leydig cell aplasia, whereas hypogonadotrophic hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (follicle stimulating hormone, FSH, and luteinizing hormone, LH).

The proposed therapeutic indication of Fortesta is the T replacement in male hypogonadism (both primary and hypogonadotrophic).

2.1.5 What is the proposed dosage and route of administration?

The recommended starting dose of Fortesta is 40 mg of T applied once daily to the thighs in the morning. The dose can be adjusted between a minimum of 10 mg of T and a maximum of 70 mg of T. To ensure proper dosing, the dose should be titrated based on the serum T concentration from a single blood draw 2 hours after applying Fortesta (C2h) and at approximately 14 days after starting treatment or following dose adjustment. Table 3 describes the dose adjustments required at each titration step.

Table 3. Dose Adjustment Criteria

C2h of total T	Dose Titration
≥2500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
≥1250 and <2500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
≥500 and <1250 ng/dL	No change
<500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)

2.2 General Clinical Pharmacology

2.2.1 What is the design feature of the pivotal phase 3 trial, FOR01C?

In the current submission, the sponsor analyzed the back-up serum samples to address the deficiencies identified in the analytical site, (b) (4). Therefore, there was no change of design feature of the pivotal phase 3 trial, FOR01C, which was reviewed by Dr. Hyunjin Kim in the previous review cycle (DARRTS, October 14, 2009). A brief overview of FOR01C is described below:

This was a 90-day, multi-center, open label, non-comparative trial in 149 hypogonadal males who had received prior T replacement therapy. Patients eligible for this trial were hypogonadal men (18-75 years) defined as males having a single morning serum T concentration < 250 ng/dL or < 300 ng/dL on two consecutive occasions at least one week apart. All enrolled patients applied Fortesta once each morning (approximately same time between 7 and 11 a.m.) to the each front and inner thigh using one finger at a starting dose of 40 mg/day. A shower or bath could only be taken either before daily application of Fortesta or after a minimum of 2 hours following application. The application site was covered with clothing once the gel had dried. The size of application site was approximately 100 cm² per 10 mg of Fortesta.

The dose of Fortesta, between a minimum of 10 mg/day and a maximum of 70 mg/day, was determined based on the total serum T concentrations obtained at 2 hours after the application of Fortesta at Days 14 (± 3), 35 (± 3), and 60 (± 3). Once the dose was determined, the actual dose adjustment occurred within 7 days from Days 14 (± 3), 35 (± 3), and 60 (± 3). This delay of dose adjustment is due to the processing time to get the concentration of the total T. Serum T concentrations including total T, free T, and DHT were obtained at 2 hours after Fortesta application at Days 14 (± 3), 35 (± 3), 60 (± 3), and 90 (± 3). In addition, 24-hour pharmacokinetic (PK) profiles for these parameters were obtained at Days 35 (± 3) and 90 (± 3) with following time points; pre-dose, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours after application of Fortesta. Sex hormone-binding globulin (SHBG), LH, FSH, and estradiol concentrations were obtained at 2 hours after Fortesta application on Days 35 (± 3) and 90 (± 3).

<Populations Analyzed for total T>

The efficacy analysis populations are shown in Table 4. The PK analysis of FOR01C in the previous submission was based on modified intent-to-treat (mITT) population (n=138). In the current submission, 93.5% (129/138) of the patients' back-up serum samples was available for reanalysis compared to mITT population.

Table 4. Populations Analyzed (FOR01C)

Submission	Population	Number (%) of Patients
Previous ^a submission	Safety population	149 (100)
Previous ^a submission	Intent-to-Treat (ITT) population	149 (100)
Previous ^a submission	mITT population	138 (92.6)
Current ^b submission	mITT2 population	129 (86.6)

a: submitted on April 17, 2009; b: submitted on June 21, 2010

- Safety population (n=149): patients who had at least one application of Fortesta.
- ITT population (n=149): patients in the safety population 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 on Day 90.
- mITT2 population (n=129): patients in the mITT population who had the back-up serum samples.

The complete set of serum samples for each patient on Day 90 consisted of 10 samples (at pre-dose, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours after the application of Fortesta). 77.5% (100/129) of the mITT2 population had complete set of back-up serum samples. Table 5 summarizes the number of available back-up total T serum samples of the mITT2 population on Day 90. Considering that approximately 65% (83/129) of the patients in FOR01C had T_{max} at either 2 or 4 hours post Fortesta application, missing data at the time close to or at 2 and 4 hours (i.e., 1, 2, 4, and 6 hours) are affecting the magnitude of AUC

greater than missing data at other time points (i.e., pre-dose, 0.5, 8, 10, 12, and 24 hours). There was one patient (patient ID: 014-068) with two missing data at 2 and 4 hours post dose and he was reported as a non-responder. All other patients had either one or no missing data between 1 and 6 hours and this reviewer included all patients (N=129) for PK analysis.

Table 5. Number of available back-up total T serum samples on Day 90 (FOR01C)

Number of samples per patient	Number (%) of patients
6	2 (1.6)
7	1 (0.8)
8	6 (4.6)
9	20 (15.5)
10 (complete set)	100 (77.5)
	129 (100; total)

2.2.2 What are the primary and secondary endpoints of the pivotal phase 3 trial, FOR01C?

The primary and secondary endpoints of FOR01C have not been changed since the previous submission and they are as following:

- Primary endpoint
 - C_{avg} of total T on Day 90 \pm 3 days are between 300 and 1140 ng/dL in \geq 75% of patients (lower bound of 95% CI \geq 65%)
- Secondary endpoints
 - C_{max} of total T on Day 90 \pm 3 days are:
 - \leq 1500 ng/dL in \geq 85% of patients
 - \geq 1800 and $<$ 2500 ng/dL in \leq 5% of patients
 - \geq 2500 ng/dL in no patients

2.2.3 What are the results of the pivotal phase 3 trial, FOR01C, for the efficacy?

- Summary of primary and secondary endpoints is provided in Table 6. The predefined criteria for both primary and secondary endpoints were achieved.
 - Primary endpoint: The percentage of mITT2 patients achieving C_{avg} of total T in the normal range (300 - 1140 ng/dL) on Day 90 was 77.5%, with a lower bound of the 95% confidence limit of 70.3%.
 - Secondary endpoints: The percentage of mITT2 patients achieving following C_{max} of total T on Day 90 were
 - 94.5% for $C_{max} \leq$ 1500 ng/dL
 - 1.5% for $C_{max} \geq$ 1800 and $<$ 2500 ng/dL
 - 0% for $C_{max} \geq$ 2500 ng/dL

Table 6. Summary of C_{avg} and C_{max} of total T on Day 90 (mITT2 Population, FOR01C)

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

There were 5 patients (patient ID (BMI): 003-005 (41.5 kg/m²), 003-006 (40.8 kg/m²), 004-008 (35.4 kg/m²), 032-050 (34 kg/m²), and 032-051 (35 kg/m²)) with BMI ≥ 35 kg/m² who were included in the mITT2 population, although one of the inclusion criteria was BMI ≥ 22 and < 35 kg/m². Therefore, primary and secondary endpoints were reanalyzed excluding these 5 patients (Table 7). The predefined criteria for both primary and secondary endpoints were still achieved when these 5 patients were excluded from the analysis.

Table 7. Summary of C_{avg} and C_{max} of total T on Day 90 (mITT2 Population Excluding 5 Patients Who Violated the Inclusion Criteria, FOR01C)

C_{avg} of total T on Day 90	
Mean (SD)	438.1 (163.7) ng/dL
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n ^a	76.6%, 95/124
95% CI for % Patients with Values ≥ 300 and ≤ 1140 ng/dL	69.2 – 84.1%
% Patients with Values < 300 ng/dL, n/n	23.4%, 29/124
% Patients with Values > 1140 ng/dL, n/n	0%, 0/124
C_{max} of total T on Day 90	
Mean (SD)	828.7 (360.3) ng/dL
% Patients with Values ≤ 1500 ng/dL, n/n ^b	94.3%, 117/124
% Patients with Values ≥ 1800 and < 2500 ng/dL, n/n ^b	1.6%, 2/124
% Patients with Values ≥ 2500 ng/dL, n/n ^b	0%, 0/124

a: primary endpoint; b: secondary endpoint

Table 8. Arithmetic Mean (SD) Steady-State Serum Total Testosterone Concentrations on Days 35 and 90 in Patients Who Completed 90 Days of Treatment with Fortesta (FOR01C)

	Dose of Fortesta							
	10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	70 mg	Overall
Day 35	[N=0]	[N=1]	[N=9]	[N=47]	[N=69]	[N=0]	[N=0]	[N=126]
C _{avg} (ng/dL)	393(N/A*)	672(137)	465(165)	445(168)	413(133)	365(96)	296(91)	408(154)
C _{max} (ng/dL)	781(N/A)	1685(377)	1037(381)	974(290)	793(327)	635(238)	497(185)	823(392)
Day 90	[N=1]	[N=6]	[N=16]	[N=30]	[N=26]	[N=27]	[N=23]	[N=129]
C _{avg} (ng/dL)	196(N/A)	464(205)	392(164)	444(176)	483(156)	441(163)	415(136)	439(163)
C _{max} (ng/dL)	503(N/A)	971(399)	775(278)	855(417)	964(389)	766(292)	724(313)	828(357)

*N/A

- DHT, SHBG, and LH
 - The sponsor submitted a NEW* dataset by analyzing the back-up serum samples to address deficiency in stability of the ORIGINAL** dataset.
- Free T, FSH, and estradiol
 - The sponsor submitted a NEW dataset by analyzing the back-up serum samples to address deficiencies in stability of the ORIGINAL dataset.
 - The sponsor submitted a NEW dataset by analyzing the back-up serum samples to replace the ORIGINAL dataset with deficiencies in precision and/or accuracy.

*NEW: submitted on June 30, 2010 (current review cycle);

**ORIGINAL: submitted on April 17, 2009 (previous review cycle).

Results for DHT, ratio of DHT to total T, SHBG, LH, FSH, free T, and estradiol are summarized in Table 9 and Table 10. The SHBG concentrations remained constant, with a slight reduction on Day 90. Both serum gonadotropins (LH and FSH) fell on Day 35 and 90, consistent with increased circulating T which would suppress LH and FSH secretion from the pituitary gland. Estradiol concentrations increased over time, consistent with aromatization of the exogenous T to its metabolite, estradiol.

Table 9. Mean (SD) C2h of Total T, DHT, free T, SHBG, LH, FSH, and Estradiol (FOR01C)

		Baseline	Day 14	Day 35	Day 60	Day 90
Total T (ng/dL)	NEW*	220.0 (94.7) N=122	582.5 (435.3) N=123	693.2 (397.7) N=114	745.9 (487.9) N=123	662.6 (328.1) N=120
DHT ^a (ng/dL)	ORIGINAL** w/o failed ^b runs	21.7 (7.7) N=121	65.9 (37.4) N=122	73.4 (42.2) N=122	79.3 (49.0) N=128	77.0 (43.9) N=110
Ratio of DHT/Total T	ORIGINAL w/o failed runs	0.13 (0.08) N=120	0.14 (0.07) N=117	0.12 (0.07) N=116	0.14 (0.11) N=120	0.13 (0.06) N=99

SHBG ^c (nmol/L)	ORIGINAL	37.1 (20.3) N=122	-	38.1 (21.3) N=120	-	36.4 (16.0) N=124
LH ^c (mIU/mL)	ORIGINAL	5.5 (7.3) N=124	-	2.8 (4.8) N=122	-	2.6 (4.7) N=124
FSH (mIU/mL)	ORIGINAL w/o failed runs	11.5 (17.7) N=80	-	5.4 (12.1) N=62	-	3.5 (8.1) N=48
	NEW data for failed runs	7.9 (12.5) N=45	-	4.2 (8.5) N=43	-	3.1 (9.7) N=57
Free T (pg/dL)	ORIGINAL w/o failed runs	33.7 (15.8) N=119	117.1 (110.8) N=123	172.1 (185.5) N=116	170.6 (149.4) N=124	161.0 (118.9) N=119
	NEW data for failed runs	32.5 (18.4) N=13	145.2 (140.3) N=12	159.3 (142.3) N=10	224.7 (234) N=12	159.2 (107.7) N=9
Estradiol (ng/dL)	ORIGINAL w/o failed runs	1.7 (0.8) N=87	-	2.7 (1.4) N=85	-	3.0 (1.7) N=103
	NEW data for failed runs	1.6 (0.6) N=27	-	2.7 (1.2) N=22	-	2.8 (1.0) N=14

*NEW: submitted on June 30, 2010 (current review cycle);

**ORIGINAL: submitted on April 17, 2009 (previous review cycle);

a: Sponsor did not submit a NEW dataset for failed runs;

b: Samples with deficiencies in precision and/or accuracy identified in the DSI report (DARRTS, October 8, 2009) during previous review cycle;

c: There was no ORIGINAL dataset with deficiencies in precision or accuracy associated with SHBG or LH.

Table 10. C_{avg} of Total T, DHT, and Free T (Days 35 and 90, FOR01C)

		Mean (SD)	
		Day 35	Day 90
Total T (ng/dL)	NEW*	414.6 (156.4), N=126	441.2 (163.9), N=129
DHT (ng/dL)	ORIGINAL** w/o failed ^a runs	70.1 (40.2), N=121	74.7 (40.6), N=108
Free T (ng/dL)	ORIGINAL** w/o failed runs	87.9 (41.2), N=122	97.5 (49.3), N=120

*NEW: submitted on June 30, 2010 (current review cycle);

**ORIGINAL: submitted on April 17, 2009 (previous review cycle);

a: Samples with deficiencies in precision and/or accuracy identified in the DSI report (DARRTS, October 8, 2009) during previous review cycle.

2.2.4 What is the concentration-time profile of total T on Day 90?

The Figure 1 describes the mean concentration-time profile of total T on Day 90 following three dose adjustments within 7 days from Days 14 (± 3), 35 (± 3), and 60 (± 3) after obtaining the total serum T concentrations at 2 hours after the application of Fortesta.

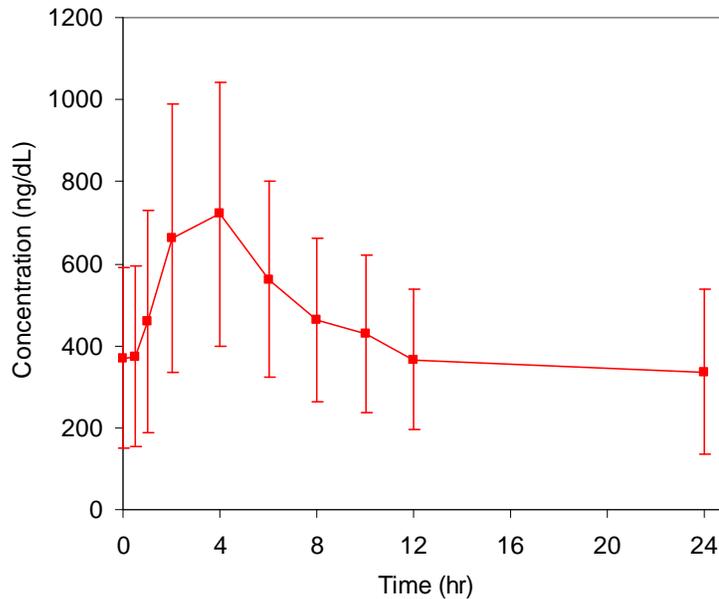


Figure 1 Mean (SD) Concentration-Time Profile of Total T on Day 90 (mITT2 population, FOR01C)

2.2.5 What is the potential of T transfer to partners?

Trial T 01-02-02 evaluating the potential of T transfer to partners was submitted on June 3, 2002. The formulation of T gel 2% used in the trial T 01-02-02 is the same as the to-be-marketed formulation of Fortesta. The trial was reviewed by Dr. Dhruva J. Chatterjee and the following are from his Clinical Pharmacology review (NDA 021463, DARRTS, July 2, 2003).

Trial T 01-02-02:

The objectives of this study were to determine

- 1) whether transfer of T gel 2% from a male to female would significantly raise the serum T and bioactive T concentrations in the female as assessed by a 24-hour serum T pharmacokinetic profile*
- 2) if transfer occurs, whether covering the application site with clothing would prevent it.*

This was an open-label, vehicle-controlled, pharmacokinetic study conducted in healthy couples. The study consisted of three phases: one non-transfer profile phase (Treatment A: Phase I - vehicle only) and two potential transfer profile phases (Treatment B for Phase II - uncovered T gel 2% exposure and Treatment C for Phase III - covered T gel 2% exposure). The order of the three phases was randomized in a three-period crossover design. Each phase was conducted on Day 25 (± 2) of three consecutive menstrual cycles of the female partner of each couple. Day 1 of the cycle was defined as the first day of menses. In Treatment A (non-transfer control Phase I), the male partner applied the vehicle to a 150 cm² area of the anteromedial thigh. In Treatment B (uncovered Phase

II), the male applied 1.5 g of T gel 2% to a 150 cm² area of the thigh, and in Treatment C (covered Phase III), the male applied 1.5 g of T gel 2% and wore boxer shorts that covered the site of application. During each phase, the female partner rubbed the application site with the volar surface of her forearm for 15 consecutive minutes, beginning 2 hours after the T gel 2% was applied. Blood samples were obtained from the female partner at Time 0 (just before rubbing), 0.5, 1, 2, 4, 6, 8, 10, 12, 15, and 24 hours. Blood samples were analyzed for determination of T, bioactive T and SHBG concentrations.

Table 11. Summary Statistics for PK Parameters: [PK Evaluable Population Including All Outlier Values (T 01- 02- 02)]

Pharmacokinetic Parameter	Statistic	A (N=6)	B ^a (N=6)	C (N=6)
AUC ₀₋₂₄ (ng-h/dL)	Mean±SD	525.0±118.90	1752.0±2073.7	508.7±101.68
	Median	531.2	933.9	487.5
	Range	383.7-665.5	520.8-5899	402.1-670.0
	Geometric Mean	513.4	1162.8	500.6
	Approximate CV (%)	62.3	91.1	61.8
C _{max} (ng/dL)	Mean±SD	26.0±4.86	275.2±547.28	26.5±6.80
	Median	26.5	46	24.5
	Range	20.0-32.0	25.0-1391	21.0-39.0
	Geometric Mean	25.6	82.1	25.9
	Approximate CV (%)	61.8	175.9	62.3
C _{12h} (ng/dL)	Mean±SD	21.6±4.90	72.3±85.49	21.0±4.23
	Median	21.9	38.5	20.1
	Range	15.8-27.4	21.7-243.3	16.6-27.6
	Geometric Mean	21.2	48	20.7
	Approximate CV (%)	62.3	90.9	61.8
C _{min} (ng/dL)	Mean±SD	17.3±5.16	26.7±9.79	15.8±3.97
	Median	17	27	17.5
	Range	11.0-24.0	14.0-37.0	10.0-19.0
	Geometric Mean	16.7	25	15.4
	Approximate CV (%)	63.6	65.7	63
T _{max} (hr)	Mean±SD	9.4±8.16	18.8±6.19	13.1±12.27
	Median	8.3	19.8	14.2
	Range	0.8-24.3	12.0-24.3	0.7-24.3

^a Analysis includes the Hour 2, 4, 12, and 15 outlier concentration values for subject 123-102, Treatment B

Treatment:

A = Phase I: Male applied 1.5g vehicle/150 cm² to one anteromedial thigh; female rubbed

B = Phase II: Male applied 1.5g CP601B/150 cm² to one anteromedial thigh; female rubbed

C = Phase III: Male applied 1.5g CP601B/150 cm² to one anteromedial thigh, application site is covered; female rubbed

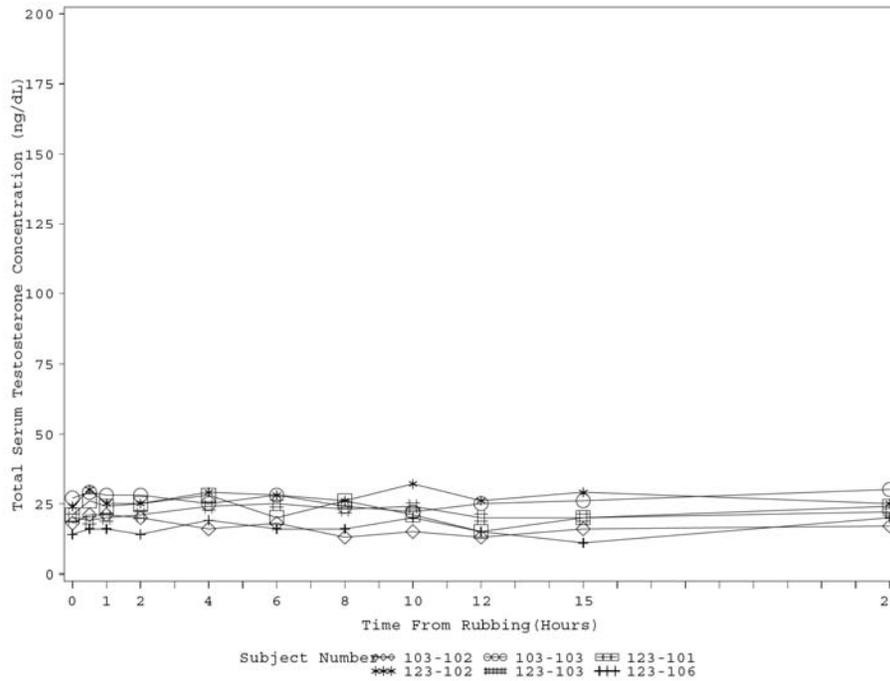
- Generally a 1.5-2 fold increase in serum T levels was observed to in female patients at each time point due to the transfer of the gel from their male partners (treatment C vs. treatment B).
- One of the females had an exceptionally high T value at 12 hours in the treatment B arm (C_{max} of ≈ 1400 ng/mL). This value may be disregarded as an outlier (probably analytical error).
- Comparison of the PK profiles and parameters between treatment A (vehicle) and C (active gel with male wearing boxer shorts to cover area of application) is essentially same, indicating that the potential for transfer may be abolished by wearing occlusive clothing to cover the application site.

In Dr. Dhruva J. Chatterjee's review (NDA 021463, DARRTS, July 2, 2003), the subject 123-102's total T value at 12 hours in treatment B was identified as an outlier. However,

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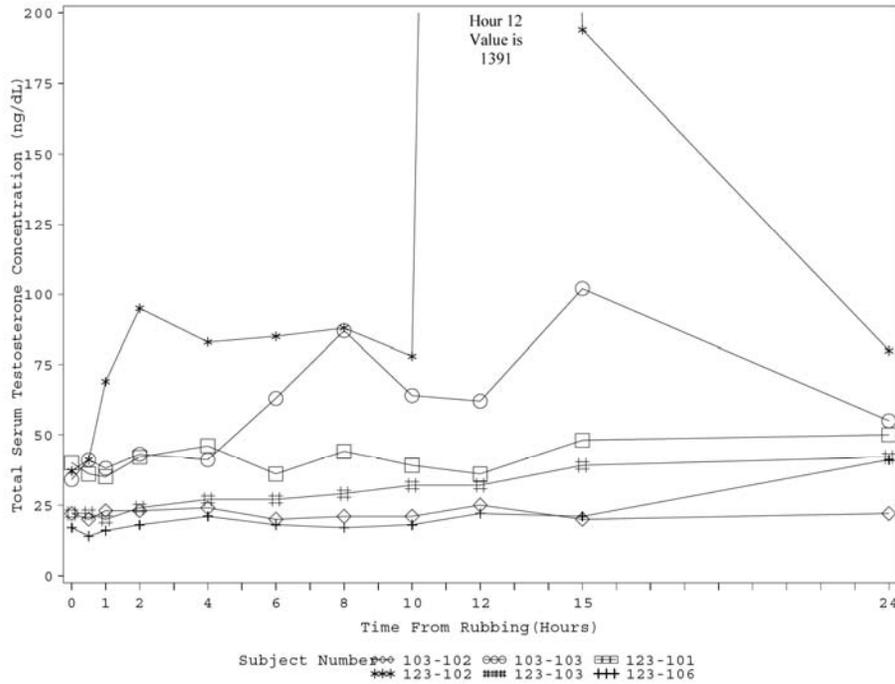
the PK parameters were calculated without excluding that value (the subject 123-102's total T value at 12 hours in treatment B, Table 11). Therefore, recalculation of PK parameters with excluding that value (the subject 123-102's total T value at 12 hours in treatment B, Table 11) is needed.

Dr. Dhruva J. Chatterjee's comment on the subject 123-102's total T value at 12 hours in treatment B, as stated above, is supported by the following figures 2-4.



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Figure 2. Concentration-Time Profile of Total T by Female Subject (Treatment A, T 01-02-02)



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Figure 3. Concentration-Time Profile of Total T by Female Subject (Treatment B, T 01-02-02)

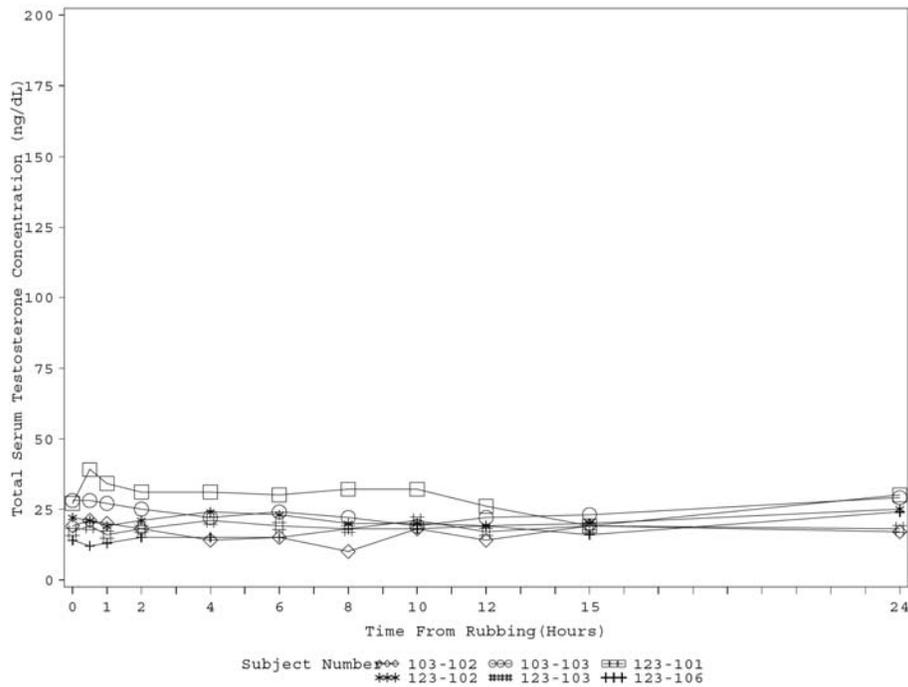


Figure 4. Concentration-Time Profile of Total T by Female Subject (Treatment C, T 01-02-02)

Overall concentration-time profile of the subject 123-102's total T values in treatments A (Figure 2) and C (Figure 4) are relatively flat without distinctive outlier by visual

observation. However, total T concentration of the subjects 123-102 at 12 hours in treatment B (1391 ng/dL, Figure 3) is exceptionally high compared to the T concentrations at adjacent measurement hours (78 ng/dL at 10 hours and 194 ng/dL at 15 hours). Although the reason for this high value (1391 ng/dL) is not clear, it may have been due to the analytical error. Therefore, PK parameters in T 01-02-02 were recalculated by excluding subject 123-102's total T concentration at 12 hours in treatment B as shown in **Error! Not a valid bookmark self-reference.**. The followings are the results and this reviewer's overall conclusions of T-01-02-02:

<Result>

- When direct skin-to-skin transfer occurred with Fortesta, mean C_{avg} increased by 134% and mean C_{max} increased by 191%, compared to direct skin-to-skin transfer with placebo (vehicle only). When transfer occurred with Fortesta while covering a thigh with boxer shorts, mean C_{avg} decreased by 3% and mean C_{max} increased by 2%, compared to direct skin-to-skin transfer with placebo (vehicle only).

<Conclusion>

- Generally a 2-3 fold increase in serum T levels was observed in female subjects due to the transfer of the gel from their male partners (treatment C vs. treatment B).
- Comparison of the PK profiles and parameters between treatment A (vehicle) and C (active gel with male wearing boxer shorts to cover area of application) is essentially same, indicating that the potential for transfer may be abolished by wearing occlusive clothing to cover the application site.

Table 12. Summary Statistics for PK Parameters: [PK Evaluable Population Excluding Subject 123-102's Total T Concentration at 12 Hours in Treatment B (T 01- 02- 02)]

PK parameter	Statistic	A (n=6)	B (n=6)	C (n=6)
AUC (ng·h/dL)	Mean (SD)	525.0 (118.9)	1224.9 (848.8)	508.7 (101.7)
	Median	531.2	933.9	487.5
	Range	383.7 - 665.5	520.8 - 2736.8	402.1 - 670.0
	Geometric mean	513.4	1023.1	500.6
	CV (%)	22.7	69.3	20.0
C_{max} (ng/dL)	Mean (SD)	26.0 (4.9)	75.7 (63.7)	26.5 (6.8)
	Median	26.5	46.0	24.5
	Range	20.0 - 32.0	25.0 – 194.0	21.0 – 39.0
	Geometric mean	25.6	59.1	25.9
	CV (%)	18.7	84.1	25.7
C_{avg} (ng/dL)	Mean (SD)	21.6 (4.9)	50.5 (35.0)	21.0 (4.2)
	Median	21.9	38.5	20.1

PK parameter	Statistic	A (n=6)	B (n=6)	C (n=6)
	Range	15.8 – 27.4	21.7 – 112.9	16.6 – 27.6
	Geometric mean	21.2	42.2	20.7
	CV (%)	22.7	69.2	20.2
C _{min} (ng/dL)	Mean (SD)	17.3 (5.2)	26.7 (9.8)	15.8 (4.0)
	Median	17.0	27.0	17.5
	Range	11.0 – 24.0	14.0 – 37.0	10.0 – 19.0
	Geometric mean	16.7	25.0	15.4
	CV (%)	29.8	36.7	25.1
T _{max} (hr)	Mean (SD)	9.4 (8.2)	19.2 (5.7)	13.1 (12.3)
	Median	8.3	19.8	14.2
	Range	0.8 – 24.3	12.0 - 24.3	0.7 - 24.3
	Geometric mean	6.2	18.5	5.7
	CV (%)	87.0	29.5	93.9

2.3 Analytical Section

The Clinical Pharmacology review (DARRTS, October 14, 2009) of the previous submissions (submission dates: April 17, 2009 and May 15, 2009) found the results from FOR01C not acceptable due to the deficiencies identified in the DSI report (DARRTS, October 8, 2009).

The following is the summary of the deficiencies based on the guidance (Guidance for Industry – Bioanalytical Method Validation, May 2001, FDA) identified in the DSI report (DARRTS, October 8, 2009).

<Analytical site>

1. All analytes (total T, free T, DHT, SHBG, LH, FSH, and estradiol)
 - Stability was not established.
 - Audit trail was not activated while running analytes. Without the activated audit trail, it is not possible for the inspector to verify the process of running the instruments for measuring analytes.
2. Total T
 - The accuracy, precision, and Incurred Sample Reproducibility (ISR) were not established.
3. Free T and FSH
 - The precision was not established.
4. DHT and Estradiol
 - The accuracy and precision were not established.

<Clinical Site>

1. There were two instances in which subject inclusion criterion (BMI ≥ 22 and < 35 kg/m²) was not met per the protocol.
 - Two patients with BMI ≥ 35 kg/m² were included in the study and their BMIs were recorded as less than 35 kg/m² in the Case Report Forms (CRFs).
2. Four cases of adverse events experienced by the trial subjects were not reported in the CRF.
3. One unanticipated problem causing hospitalization of the patient was not reported to Institutional Review Board.

In the current submission, the sponsor submitted a new dataset by analyzing the back-up serum samples to address the deficiencies associated with analytical site as following:

1. All analytes (total T, free T, DHT, SHBG, LH, FSH, and estradiol)
 - The sponsor analyzed the back-up serum samples with audit trail function activated.
2. Total T
 - The sponsor submitted a NEW* dataset by analyzing all available back-up serum samples to replace the entire ORIGINAL** dataset.
3. DHT, SHBG, and LH
 - The sponsor submitted a NEW dataset by analyzing the back-up serum samples to address deficiency in stability of the ORIGINAL dataset.
4. Free T, FSH, and estradiol
 - The sponsor submitted a NEW dataset by analyzing the back-up serum samples to address deficiencies in stability of the ORIGINAL dataset.
 - The sponsor submitted a NEW dataset by analyzing the back-up serum samples to replace the ORIGINAL dataset with deficiencies in precision and/or accuracy.

*NEW: submitted on June 30, 2010.

**ORIGINAL: submitted on April 17, 2009.

Multiple interactions between the Division and the sponsor to address deficiencies identified in the DSI report (DARRTS, October 8, 2009) are described in the four additional DSI reports (DARRTS, November 25, 2009, August 9, 2010, October 6, 2010, and November 18, 2010). The following is the summary of the conclusions of the four DSI reports (DARRTS, November 25, 2009, August 9, 2010, October 6, 2010, and November 18, 2010).

<Analytical site>

1. All analytes (total T, free T, DHT, SHBG, LH, FSH, and estradiol)
 - Stability is established.
 - The sponsor has developed and implemented standard operating procedure including the use of audit trail.
2. Total T
 - The accuracy, precision, and ISR are established.
3. Free T and FSH
 - The precision is established.
4. DHT and Estradiol

- The accuracy and precision are established.

<Clinical site>

There was no further DSI evaluation of clinical site regarding deficiencies identified in the clinical site.

Regarding the validity of the data for evaluation of NDA 021463, this reviewer concludes the following from a Clinical Pharmacology perspective:

1. The sponsor's NEW dataset for the measurement of total T, free T, FSH, and estradiol is valid.
2. The sponsor's ORIGINAL dataset for the measurement of SHBG and LH is valid.
3. The sponsor's ORIGINAL dataset for the measurement of DHT, free T, FSH, and estradiol excluding the ORIGINAL dataset with deficiencies in precision and/or accuracy is valid.

*NEW: submitted on June 30, 2010.

**ORIGINAL: submitted on April 17, 2009.

3 Detailed Labeling Recommendations

The labeling negotiation is pending. Addendum will be added once the labeling negotiation is finalized.

4 Appendices

4.1 DSI Site Inspection Report (first)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 25, 2009

TO: Scott E. Monroe, M.D.
Director
Division of Reproductive and Urologic Products (DRUP)

FROM: Carol M. Rivera-Lopez, Ph.D.
Sean Y. Kassim, Ph.D.
Martin K. Yau, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 11/25/09*
Acting Team Leader, Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Addendum to the Review of EIR Covering NDA 21-463,
FORTESTA™ (Testosterone) 2% Gel, sponsored by Endo
Pharmaceuticals*.

At the request of the Division of Reproductive and Urologic Products (DRUP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following multi-center study:

Study FOR01C

Title: "An open-label, phase III study of FORTIGEL (testosterone) 2% gel in hypogonadal males"

Following our evaluation of the Form FDA-483 items and the first written response from (b) (4) DSI forwarded an inspection summary memo for the above audit to DRUP on October 8, 2009. In a telephone conference (see Attachment 1) between the Agency (DRUP, DCP3, and DSI) and the sponsor (October 9, 2009), items that still need to be resolved were related to the sponsor and representatives from (b) (4). Thereafter, a second response (dated November 9, 2009) was received from (b) (4) (Attachment 2). This addendum is an evaluation of the second response.

* Effective 9/8/2009, previously ProStrakan, Inc.

DSI evaluation of second response to the Form FDA-483

(b) (4)
(Analytical)

- 1. Observation 1 from FDA-483 - Failure to demonstrate accuracy of the DHT RIA assay. Specifically, calibration standards were prepared in solvent (b) (4) as did for the quality control (QC) and subject serum samples. The concentrations extrapolated from the solvent based standard curve have not been shown to accurately represent the concentrations of DHT extracted from serum matrix.**

The firm conducted additional experiments to demonstrate the equivalence of standards prepared in and extracted from matrix (human serum) and standards prepared in solvent (b) (4) when using the DHT RIA method. The results indicate QCs prepared in matrix are within 20% of their nominal value when calculated using either matrix- or solvent-based calibrators. However, the firm established the nominal DHT concentrations via repeated (20 times) measurement and not by spiking a known amount of DHT into the QC samples. Therefore, the accuracy of this determination cannot be confirmed. Additionally, the firm did not explain if the nominal concentrations were determined using solvent or serum calibrators.

- 2. Observation 3 from FDA-483 - Failure to accurately demonstrate the freeze/thaw (F/T) and frozen storage stability of all analytes at -20°C. Specifically, standard curves used in the stability experiments were not freshly prepared but generated from frozen calibration standards prepared previously and stored at -20°C. The F/T test stability samples were compared to frozen reference samples stored at -70°C.**

The firm explained that fresh calibrators (in serum) were used to establish the long term frozen stability data provided in the first response (dated September 22, 2009), comparing an old lot of standards with a new lot of standards for all analytes. However, the second response did not include the information (experimental details) to allow DSI to determine how the standards were prepared or how the previous and new data provided were generated.

The second response also included new data for six cycles of Freeze/Thaw (F/T) stability experiments. However, the response does not describe how the nominal concentrations for the stability samples were determined. The results suggest the

analytes, testosterone, estradiol, FSH, sex hormone binding globulin, and DHT, are stable for at least six F/T cycles.

3. Observation 4 from FDA-483 - Audit trail of the 'Analyst' software version 1.41 was not turned on for all the validation and analytical runs. There are no audit trail records available for inspection.

The firm indicated in their first response that an audit trail for total testosterone (TT) and estradiol (E2) was available for the validation and analytical runs. In their second response they stated that audit trail records were available for only 13 of the 259 TT analytical runs. The second response did not include information regarding E2 audit trails.

4. Observation 5 from FDA-483 - Many analytical runs had > 33.3% of the total QCs and/or > 50% at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations. These analytical runs were listed in the original EIR review.

The firm has updated their standard operating procedure (SOP) to require a minimum of 6 QCs at three levels. Acceptance of a run is based on 67% of all QCs and at least one QC at each level being within 15% of the nominal value. The updated SOP is adequate, however, samples from the failed analytical runs identified during the FDA inspection (Form FDA-483 Observation 5) remain unacceptable.

5. Observation 7 from FDA-483 - The incurred sample reproducibility (ISR) of the LC/MS/MS method for TT was not evaluated. TT concentrations determined by this method were used to calculate the primary (Cavg 0-24 hr at Day 90) and secondary efficacy endpoints (Cmax at Day 90) for the study.

The firm provided an SOP for ISR assessment. It states that ISR will be conducted on 10% (for <1000 sample studies) or 5% (for >1000 sample studies) of total study samples. The firm also stated in the SOP that the sponsor can decline ISR assessments.

Conclusions:

Following evaluation of the second response to the Form FDA-483, DSI concludes the following:

- The new revised SOP for QC and Batch Acceptance is adequate. However, samples from the analytical runs with failing QCs as cited in Form FDA-483 Observation 5 remain

unacceptable. The firm should repeat all the samples from the subjects with rejected samples due to failed QCs. (see Item 4).

- The long term frozen stability data provided in the response can be accepted if (b) (4) can provide additional experimental details to explain how and when the standards were prepared and how the previous and new data provided were generated. Notably, if sample re-assay is necessary, as recommended above under Bullet 1, longer frozen stability than provided would be required.

The six cycles of F/T stability data for all analytes provided in the response can be accepted if (b) (4) can clarify how the nominal concentrations for the stability samples were determined. Also, the deviation of the stability samples versus their nominal concentrations should be calculated (see Item 2).

- The validity of the TT and E2 data from batches missing the audit trail cannot be verified (see Item 3).
- The DHT measurements remain questionable. The firm needs to further clarify (1) how repeated measurements can assure accurate nominal concentrations for the QCs and (2) whether the nominal values for QCs were determined using serum- or solvent-based calibrators (see Item 1).
- The provided SOP for ISR Assessments is adequate; however, the firm has not yet performed ISR for this study (see Item 5).

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Carol M. Rivera-Lopez
signed for by Sean Kassim 11/25/09
Carol M. Rivera-Lopez, Ph.D.


Sean Y. Kassim, Ph.D.

Martin K. Yau 11/25/09
Martin K. Yau, Ph.D.

Final Classifications:

VAI - (b) (4)

FEI: (b) (4)

cc:

DSI/GLPBB/Salewski/Yau/Kassim/Rivera-Lopez/CF
OCP/DCP3/Kim
OND/DRUP/Benson/Kaul
OND/DRUP/Roule
Draft: SYK 11/20/09, 11/23/09, 11/25/09
Revise: CRL 11/23/09, 11/24/09
Edit: MKY 11/24/09, 11/25/09
DSI: 5985
O:\BIOEQUIV\EIRCOVER\21463.pro.testo.addendum.doc
FACTS: 1073647

Email:

DSI/CDER DSI PM TRACK

4.2 DSI Site Inspection Report (second)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 9, 2010

TO: Scott E. Monroe, M.D.
Director
Division of Reproductive and Urologic Products (DRUP)

FROM: Sean Y. Kassim, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Mart K. Yau 8/9/10*
Acting Team Leader, Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Second addendum to the Review of EIR Covering NDA 21-463, FORTESTA™ (Testosterone) 2% Gel, sponsored by Endo Pharmaceuticals*.

At the request of the Division of Reproductive and Urologic Products (DRUP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following multi-center study:

Study FOR01C

Title: "An open-label, phase III study of FORTIGEL (testosterone) 2% gel in hypogonadal males"

Following our evaluation of the Form FDA-483 items and the first and second written responses from (b) (4), DSI forwarded inspection summary memos for the above audit to DRUP on October 8, 2009 and November 25, 2009. In a meeting between the Agency (DRUP, DCP3, and DSI) and the sponsor (June 10, 2010), items that still needed to be resolved were related to the sponsor. Thereafter, a third response was received from (b) (4) on June 29, 2010 (Attachment 1). This addendum is an evaluation of the third response.

DSI evaluation of third response to the Form FDA-483

(b) (4) (Analytical)

1. Observation 1 from FDA-483 - Failure to demonstrate accuracy of the DHT RIA assay. Specifically, calibration standards

* Effective 9/8/2009, previously ProStrakan, Inc.

were prepared in solvent (b) (4) as did for the quality control (QC) and subject serum samples. The concentrations extrapolated from the solvent based standard curve have not been shown to accurately represent the concentrations of DHT extracted from serum matrix.

The firm's additional DHT experiments were performed using QCs prepared at three levels by pooling commercial serum known by previous analyses to be in the high, medium, and low ranges. The medium (DHT2D) and high (DHT3F) QCs were assigned target values after repeated analysis (minimum of 20 times). The low (DHT2D) QC was placed into production after the RIA method had been replaced with the LC-MS/MS method, therefore the target value for the low QC was assigned as the inter-batch mean determined using the methanol standards during the additional studies. The additional information provided does not explain how repeated measurements establish an accurate target value. However, spiked QCs in charcoal stripped serum were used during method validation and the QC results from the additional DHT experiments were within acceptance criteria when evaluated with either solvent or serum calibrators.

2. Failure to fully validate the assays for LH and PSA in that:

- a. Study sample values were reported above 0.01 ng/mL for PSA and 0.07 mIU/mL for LH. However, precision and accuracy was only demonstrated above 0.5 ng/mL for PSA and above 0.59 mIU/mL for LH.

The firm's additional studies support the accuracy of the PSA assay to 0.01 ng/mL and LH assay to 0.24 mIU/mL. The firm has re-reported study results from the LH assay that were below 0.24 mIU/mL as "less than 0.24 mIU/mL."

3. Failure to accurately demonstrate the freeze/thaw (F/T) and frozen storage stability of all analytes at -20°C. Specifically, standard curves used in the stability experiments were not freshly prepared but generated from frozen calibration standards prepared previously and stored at -20°C. The F/T test stability samples were compared to frozen reference samples stored at -70°C.

The firm evaluated six cycles of -20°C Freeze/Thaw (F/T) for testosterone, estradiol, FSH, SHBG, and DHT by the RIA method used in the study and by an MS/MS method and the results were within acceptance criteria. As analyte free matrix was not available, the samples were evaluated at baseline and after six

F/T; both initial and final evaluations used freshly prepared calibrators using charcoal-stripped serum. The QCs were prepared from commercial sources (used as neat and fortified) and their concentrations were determined by multiple analyses - also because analyte free matrix was unavailable.

As the firm has replaced the testosterone values with analysis of samples stored at -70°C (see Item 5), they evaluated long term storage stability using these same backup samples stored at -70°C. The target values used were obtained from acceptable runs from the initial study. The final concentrations were determined with freshly prepared calibrators and QCs in charcoal stripped serum. The stability recovery was determined by comparing the final concentration with the initial baseline determination, using a ±15% acceptance criterion. The testosterone stability at -70°C for 2.6 years was within acceptance criteria for all 20 samples evaluated. The firm did not provide a rationale why their approach was equivalent to the classical approach of using prepared samples with known nominal concentrations to evaluate long term frozen stability.

The firm also provided long term -70°C frozen stability data for estradiol, free testosterone, FSH, and DHT. These evaluations also used the initial determinations from the original study analyses as the baseline target values and final evaluations using fresh calibrators and QCs where appropriate (free testosterone uses a ratio determination without calibration standards and QCs prepared by testing donor serum). Analysis of the stability determinations revealed 60% of free testosterone samples, 50% of estradiol samples, 80% of FSH samples, and 53% of DHT samples were within 20% of target. Therefore, only FSH has >66% of stability samples within acceptance criteria, and the other analytes have not been shown to be stable for 2.6 years at -70°C. The backup samples evaluated to replace the failing samples do not have sufficient frozen stability assurance.

4. Audit trail of the 'Analyst' software version 1.41 was not turned on for all the validation and analytical runs. There are no audit trail records available for inspection.

The firm indicates they have repeated the testosterone and estradiol runs with audit trail function activated.

5. Many analytical runs had > 33.3% of the total QCs and/or > 50% at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal

concentrations or mean pooled QC concentrations. These analytical runs were listed in the original EIR review.

The firm indicates they have re-analyzed all testosterone samples with available backup samples from -70° storage. For the failed DHT, E2, Free T, and FSH runs, only the failing samples had their backup samples analyzed.

6. Observation 7 from FDA-483 - The incurred sample reproducibility (ISR) of the LC/MS/MS method for TT was not evaluated. TT concentrations determined by this method were used to calculate the primary (Cavg 0-24 hr at Day 90) and secondary efficacy endpoints (Cmax at Day 90) for the study.

The firm indicates ISR assessment was conducted on the backup sample total testosterone (TT) analysis. The results were within acceptance criteria and will be included in the final bioanalytical report.

Conclusions:

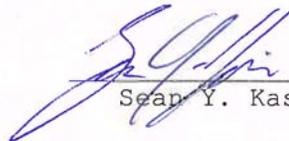
Following evaluation of the third response to the Form FDA-483, DSI recommends the following:

- The analysis of all available testosterone backup samples to replace the previous analysis is acceptable. The backup sample analysis should be inspected by DSI to assure the integrity of the analysis. The re-evaluation of the failed FSH samples appears acceptable. The free testosterone, estradiol, and DHT backup sample analyses are not acceptable due to lack of long term -70°C frozen stability assurance (see Item 5).
- Due to the endogenous nature of the analytes, the use of baseline values instead of nominal values for the six cycles of F/T stability data for all analytes provided in the response can be accepted.

The long term -70°C frozen stability data for total testosterone can be accepted, however (b) (4) should provide a rationale explaining how evaluating stability versus baseline determinations is equivalent to using nominal concentrations. Additionally, only the FSH long term frozen stability was within acceptable performance. The repeated values for free testosterone, estradiol and DHT are not acceptable as 2.6 year stability for these analytes has not been established (see Item 3).

- The backup sample experiment with active audit trail should be sufficient to reconstruct parameters changed during sample analysis (see Item 4).
- The firm's ISR experiment design appears sufficient (see Item 6).
- The DHT measurement concerns have been addressed sufficiently (see Item 1).
- Limiting LH reported values to the confirmed LLOQ of 0.24 mIU/mL is appropriate (see Item 2).

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Sean Y. Kassim, Ph.D.

Final Classifications:

VAI - [REDACTED] (b) (4)
FEI: [REDACTED] (b) (4)

cc:

DSI/GLPBB/Ball/Haidar/Yau/Kassim/Rivera-Lopez/CF
OCP/DCP3/Kim
OND/DRUP/Benson/Fang
OND/DRUP/Roule/Hirsch
Draft: SYK 07/09/10
Edit: MKY 07/19/10
DSI: 5985
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FACTS: 1073647

Email:

DSI/CDER DSI PM TRACK

4.3 DSI Site Inspection Report (third)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 6, 2010

TO: Edward D. Bashaw, Pharm. D.
Director
Division of Clinical Pharmacology III (DCP3)
Office of Clinical Pharmacology

and

Scott E. Monroe, M. D.
Director
Division of Reproductive and Urologic Products (DRUP)

FROM: Sean Y. Kassim, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 10/6/10*
Acting Team Leader, Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-463, FORTESTA™
(Testosterone) 2% Gel, sponsored by Endo
Pharmaceuticals*.

At the request of the Division of Clinical Pharmacology III (DCP3), the Division of Scientific Investigations (DSI) conducted an audit of the re-assay of the analytical portion of the following study:

Study FOR01C

Title: "An open-label, phase III study of FORTIGEL (testosterone) 2% gel in hypogonadal males"

Following our inspection of [REDACTED] ^{(b)(4)} (August 9-17, 2010) Form FDA-483 was issued (Attachment 1). The firm's response was received on September 8, 2010. Our evaluation of the FDA-483 observations and the firm's response follows.

* Effective 9/8/2009, previously ProStrakan, Inc.

(b) (4)
(Analytical)

In the bioanalytical study FOR01C regarding sample reanalyses using mass spectrometry (MS) based assays for total testosterone (TT) and estradiol (E2), and ligand binding-based assays (LBA) for follicle stimulating hormone (FSH), dihydrotestosterone (DHT), and free testosterone (Free T), we observed:

1. Failure to demonstrate adequate long-term stability at -70° for E2, DHT, and Free T in the MS assay for E2 and the LBA for DHT and Free T. Less than 66% of the samples evaluated for long-term stability for these analytes were within the acceptance criteria (15% (E2) or 20% (DHT, Free T) deviation from expected) .

The firm provided long-term stability at -70°C data in their last response to the previous inspection, including recognition that the DHT study had failed to meet their acceptance criteria. Evaluation of the results during the inspection revealed in addition to the failing DHT study, the E2 and the Free T also did not pass acceptance criteria as both had less than 66% of the samples analyzed within 15% (E2) or 20% (Free T) of the expected concentrations.

The firm's response includes additional long-term stability data for E2, Free T, and DHT. The E2 and DHT studies had greater than 66% of the samples within 15% or 20% of the expected values. Since the previous E2 results are recommended to be rejected due to poor chromatography (See FDA-483 Item 2), the new results may be evaluated alone. However, as the previous DHT and the previous Free T results remain valid, both DHT studies and both Free T studies should be evaluated together to determine long-term stability at -70°C. We noted that 27 of the 40 (67.5%) DHT samples were within 20% of their expected values (Attachment 3) and 23 of the 41 (56.1%) Free T samples were within 20% of their expected values (Attachment 4), but the average bias or decrease (-13.84%) of all 41 Free T samples was less than 15% indicating the degradation was not significant. Further evaluation of the Free T stability data showed that there was large variability in the stability data but there was no clear indication of analyte degradation.

2. Failure to reject poor chromatography. Many calibrators and quality controls (QCs) in batch E2M10042713 failed with automatic chromatogram integration.

The E2M10042713 batch to measure estradiol in long-term -70°C stability was poorly integrated and should be rejected for poor chromatography.

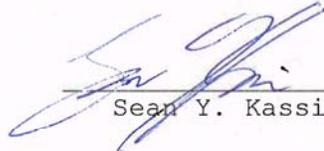
The firm's response agrees that this run should have been rejected. They have initiated SOP updates that limit manual integration and do not allow manipulation of standard and QC peaks. They also provided additional passing E2 stability data discussed above in Item 1 that used global integration parameters and no manual integration.

Conclusions:

Following evaluation of the Form FDA-483 observations and the written response from (b) (4) DSI recommends the following:

- The DHT and E2 long-term -70° stabilities have been demonstrated up to 960 and 1025 days, respectively. The re-assay for the DHT and E2 samples are therefore acceptable (~~se~~ see Item 1).
- Less than 66% of the Free T stability samples were within 20% of their target values. However, the mean decrease for Free T from the original measurement was less than 15% indicating the degradation was not significant. Further evaluation of the Free T stability data showed that there was large variability in the stability data but there was no clear indication of Free T degradation. Overall, DSI has decided to recommend accepting data of the re-assayed Free T samples (see Item 1).

After you have reviewed this transmittal memo, please append it to the original NDA submission.


Sean Y. Kassim, Ph.D.

Final Classification:

VAI - (b) (4)
FEI: (b) (4)

cc:

DSI/GLPBB/Ball/Haidar/Yau/Kassim/Rivera-Lopez/CF

OCP/DCP3/Bashaw/Kim

OND/DRUP/Monroe/Benson/Fang

OND/DRUP/Roule/Hirsch

Draft: SYK 08/24/10; 10/01/10; 10/5/10

Edit: MKY 10/01/10; 10/4/10

DSI: 5985

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FACTS: 1193886

Email:

DSI/CDER DSI PM TRACK

ORA/Hall

4.4 DSI Site Inspection Report (fourth)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 18, 2010

TO: Edward D. Bashaw, Pharm. D.
Director
Division of Clinical Pharmacology III (DCP3)
Office of Clinical Pharmacology

and

Scott E. Monroe, M. D.
Director
Division of Reproductive and Urologic Products (DRUP)

FROM: Sean Y. Kassim, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 11/18/10*
Acting Team Leader, Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Addendum to the Review of EIR Covering NDA 21-463,
FORTESTA™ (Testosterone) 2% Gel, sponsored by Endo
Pharmaceuticals*.

At the request of the Division of Clinical Pharmacology III (DCP3), the Division of Scientific Investigations (DSI) conducted an audit of the re-assay of the analytical portion of the following study:

Study FOR01C

Title: "An open-label, phase III study of FORTIGEL (testosterone) 2% gel in hypogonadal males"

(b) (4) **(Analytical)**

Following our inspection of (b) (4), (August 9-17, 2010) Form FDA-483 was issued (Attachment 1). The firm's response was received on September 8, 2010. Our evaluation of the FDA-483 observations and the firm's response was sent to the review division on October 6, 2010. This addendum is provided to

address questions raised in the 2009 inspection and examined further in the 2010 inspection at (b) (4)

In DSI's EIR addendum review for the 2009 inspection of (b) (4) sent to the review division November 25, 2009, DSI concluded the long-term frozen stability data for the sex hormone binding globulin (SHBG) lacked sufficient details to allow DSI to verify the results. During the inspection of (b) (4) from August 9-17, 2010, the process that generated these data were clarified and DSI concludes that the SHBG long term -70°C storage stability has been established to 168 days.

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

After you have reviewed this transmittal memo, please append it to the original NDA submission.


Sean Y. Kassim, Ph.D.

Final Classification:

VAI - (b) (4)

FEI: (b) (4)

cc:

DSI/GLPBB/Ball/Haidar/Yau/Kassim/Rivera-Lopez/CF

OCP/DCP3/Bashaw/Kim

OND/DRUP/Monroe/Benson/Fang

OND/DRUP/Roule/Hirsch

Draft: SYK 11/17/10

Edit: MKY 11/17/10

DSI: 5985

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FACTS: 1193886

Email:

DSI/CDER DSI PM TRACK

ORA/Hall

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

/s/

HYUNJIN KIM
12/15/2010

MYONG JIN KIM
12/15/2010

EDWARD D BASHAW
12/15/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-463	Submission Dates: 4/17/2009, 5/15/2009
Brand Name	Fortesta
Generic Name	Testosterone
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Endo Pharmaceuticals
Relevant INDs	IND (b) (4) 76,634
Submission Type	Resubmission
Formulation; Strength(s)	Testosterone 2% gel in a metered dose pump
Indication	Testosterone replacement therapy in adult male hypogonadism <ul style="list-style-type: none">o Primary hypogonadism (congenital or acquired)o Hypogonadotropic or secondary hypogonadism (congenital or acquired)

An Optional Inter-Division Level Clinical Pharmacology Briefing was held on September 22, 2009 in conference room 3300 of White Oak Bldg 51. Attendees included Drs'. Suresh Kaul, Guodong Fang, Hae-Young Ahn, Myong-Jin Kim, Sandhya Apparaju, Doanh Tran, Chongwoo Yu, Dilara Jappar, Ting Eng Ong and Hyunjin Kim

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1 Executive Summary

Fortesta is a 2% testosterone (T) gel with a proposed indication of T replacement therapy in adult male hypogonadism (primary hypogonadism (congenital or acquired) and hypogonadotropic or secondary hypogonadism (congenital or acquired)). Fortesta is supplied in 60 g metered dose canisters with a pump that is designed to deliver 0.5 g gel (10 mg T) per each complete depression. Proposed dosing regimen is to start with 40 mg T applied topically to thighs once daily in the morning. Dose can be adjusted by an increment of 10 mg T based on total T concentration 2 hours post Fortesta application.

The original NDA 21-463 was filed on June 3, 2002 under section 505(b)(2). There were several trials including a pivotal phase 3 trial (T 00-02-01), effect of showering on T concentration trial (T 00-02-03), and male to female T transfer trial (T 01-02-02). It received a Not Approvable (NA) action on July 3, 2003 with following deficiencies and the action item listed in the NA letter:

1. There is insufficient information to establish that the high supraphysiologic daily C_{max} serum testosterone levels achieved in a significant proportion of participants in the major clinical trial 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, 14% had values between 1800 and 2500, and 6% had values greater than 2500 ng/dL.
2. There is insufficient information provided to demonstrate that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological testosterone levels.

In order to address these deficiencies, the division requested the sponsor to conduct clinical trial(s) using lower doses of Fortigel (note: Fortigel is the previously proposed brand name for Fortesta) or another T gel formulation and demonstrate that physiologic levels of T can be attained while avoiding high supraphysiologic C_{max} levels of serum T.

In the current resubmission, the sponsor submitted a new phase 3 trial (FOR01C) to address the deficiencies listed in the NA letter dated July 3, 2003. This trial employed lower doses of Fortesta with the same formulation used in the previous phase 3 clinical trial, T 00-02-01.

A request for inspection of the clinical and analytical sites of this pivotal clinical trial FOR01C was made to the Division of Scientific Investigations (DSI; DARRTS on July 9, 2009). Following the DSI inspection, Form 483s were issued to both the clinical and analytical sites. Based on the major deficiencies identified by the DSI, it was determined that the data generated from the trial FOR01C were not reliable to determine efficacy and safety of Fortesta for approval (see section 4.3 DSI Report for details, DARRTS, October 8, 2009).

1.1 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 the major deficiencies identified in the DSI Report.

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

1.2 Post Marketing Commitment/Requirement

Not applicable.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Note: Sections 1.3 through 2.5 of this review were written before the DSI findings were available to this reviewer. Because the data from FOR01C were found to be unreliable based on the DSI report, the findings of this review sections 1.3 through 2.5 should not be used to support the efficacy and safety of FORTESTA. See section 2.6 Analytical Section for more details.

Efficacy of Fortesta:

Trial FOR01C met the primary and secondary endpoints.

Trial FOR01C was a 90-day, multicenter, open label, non-comparative trial in 149 hypogonadal males who had received prior T replacement therapy. Patients were screened for single serum total T concentrations < 250 ng/dL or two consecutive serum total T concentrations < 300 ng/dL, with body mass index (BMI) ≥ 22 and <35 kg/m² and 18-75 years of age. All patients enrolled in the trial applied Fortesta once each morning (approximately same time between 7 and 11 a.m.) to the each front and inner thigh at a starting dose of 40 mg/day. Taking a shower or bath was allowed either before daily application or after a minimum of 2 hours post-dose application. The application site was covered with clothing once the gel had dried. The size of application site was approximately 100 cm² per 10 mg of Fortesta.

The dose of Fortesta was adjusted to between a minimum of 10 mg/day and a maximum of 70 mg/day on the basis of total serum T concentrations obtained at 2 hours after the application of Fortesta at Days 14 (± 3), 35 (± 3), and 60 (± 3).

In trial T 00-02-01 (pivotal phase 3 trial in the previous submission) 34% of patients had T_{max} at 2 hours versus 43% of patients had T_{max} at 4 hours on Day 14. Although C_{2h} and C_{4h} would represent C_{max} of 77% of patients, the Division accepted to use a single time point of C_{2h} for titration in trial FOR01C due to the benefit of being feasible in clinical settings (IND 76,634, Clinical Pharmacology review by Dr. Doanh Tran, DARRTS, August 10, 2007).

The following endpoints were used in the pivotal phase 3 clinical trial, FOR01C.

- Primary endpoint
 - C_{avg} of total T at Day 90 \pm 3 days are between 300 and 1140 ng/dL in \geq 75% of patients (lower bound of 95% CI \geq 65%)
- Secondary endpoints
 - C_{max} of total T at Day 90 \pm 3 days are:
 - \leq 1500 ng/dL in \geq 85% of patients
 - \geq 1800 and $<$ 2500 ng/dL in \leq 5% of patients
 - \geq 2500 ng/dL in no patients

The results met both primary and secondary endpoints as provided in Table 1.

Table 1 Summary of Primary and Secondary Endpoints (mITT Population)

Primary Endpoint (C_{avg} of total T at Day 90)	
Mean (SD)	442.4 (177.7) ng/dL
% Patients with Values \geq 300 and \leq 1140 ng/dL, n/n	76.1%, 105/138
95% CI for % Patients with Values \geq 300 and \leq 1140 ng/dL	69.0 - 83.2%
% 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 \leq 1500 ng/dL, n/n	91.3%, 126/138
% Patients with Values \geq 1800 and $<$ 2500 ng/dL, n/n	4.3%, 6/138
% Patients with Values \geq 2500 ng/dL, n/n	0%, 0/138

Effects of showering and T transfer potential:

The effects of showering on the bioavailability of Fortesta and T transfer potential to non-dosed females were previously reviewed by Dr. Dhruva J. Chatterjee when the original NDA was submitted in 2002 (see Dr. Chatterjee’s review in DARRTS, July 2, 2003). Therefore, this reviewer did not conduct a separate review. Dr. Chatterjee made the following conclusions:

- Effect of showering (T-00-02-03)
 - Conclusion
 - No trend appears to indicate that showering 2 hours post gel administration leads to a detectable difference in the daily exposure profiles to total T.
 - Study design
 - The effects of showering on the pharmacokinetics of total T following topical application of FORTESTA 2% Gel in hypogonadal males was assessed in an open-label, non-vehicle-controlled, randomized, two-treatment, two-period crossover study,
- Male to female T transfer potential (T-01-02-02)
 - Conclusion:
 - Generally a 1.5-2 fold increase in serum T concentration was observed to in female patients at each time point due to the transfer of the gel from their male partners.

- The potential for transfer may be abolished by wearing occlusive clothing to cover the application site.
 - Study design
 - An open-label, vehicle-controlled, pharmacokinetic study in 6 healthy couples evaluated whether transfer of FORTESTA 2% Gel from a male to a female would significantly raise serum T concentrations in the females, and if transference occurred, whether covering the application site with clothing would prevent it. Two hours after FORTESTA 2% Gel application to males, the female partner engaged in vigorous skin-to-skin contact with the application site for 15 consecutive minutes.

T transfer potential after washing:

T transfer potential after the washing of primary user's application site to assess the known risk of secondary T exposure was not studied. Therefore such study will be requested.

2 Question-Based-Review

2.1 General Attributes

The original NDA 21-463 received NA action on July 3, 2003 with following deficiencies and the action item listed in the NA letter:

1. There is insufficient information to establish that the high supraphysiologic daily C_{max} serum testosterone levels achieved in a significant proportion of participants in the major clinical trial 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, 14% had values between 1800 and 2500, and 6% had values greater than 2500 ng/dL.
2. There is insufficient information provided to demonstrate that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological testosterone levels.

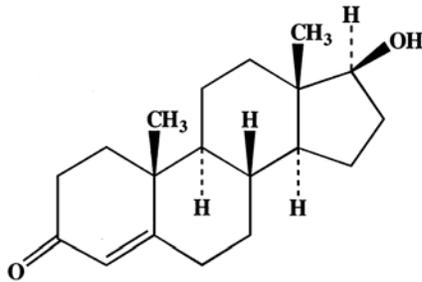
The current resubmission contains a new phase 3 trial, FOR01C with a lower starting dose and a new dose adjustment scheme. The following is the dosage comparison in two phase 3 trials:

- Dosage comparison
 - T 00-02-01 (pivotal phase 3 trial in the previous submission)
 - Start with 60 mg.
 - Dose can be modified either to 40 or 80 mg or the dose remains unchanged.
 - Dosage adjustment based on a 24 hr total T concentration time profile obtained following 14 days of continuous treatment.
 - FOR01C (pivotal phase 3 trial in the current submission)

- Start with 40 mg.
- Dose can be modified from 10 to 70 mg by a magnitude of 10 mg per each of three dose adjustments during the trial.
- Dosage adjustment based on total T concentration obtained at 2 hours (C2h) after trial drug application on Days 14, 35, and 60.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug?

- Fortesta is a clear, colorless, odorless, hydroalcoholic gel containing 2% T. Fortesta provides transdermal delivery of T for a 24 hour period following a single application to skin of both front and inner thighs.
- T, USP is a white to almost white powder described chemically as 17-beta hydroxyandrost-4-en-3-one.
- It has a following structure:



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

- The formulation of Fortesta is provided in Table 2.

Table 2 Composition of Fortesta

Material	% w/w
T, USP	2.0
Propylene Glycol, USP	(b) (4)
Ethyl Alcohol, (b) (4)	(b) (4)
Isopropyl Alcohol, USP	(b) (4)
Oleic Alcohol, NF	(b) (4)
Carbomer 1382	(b) (4)
Trolamine, NF	(b) (4)
Butylated Hydroxytoluene, NF	(b) (4)
Purified Water, USP	(b) (4)

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Endogenous androgens, including T and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature and fat distribution. T and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of T and is characterized by low serum T concentrations. Signs and symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (follicle stimulating hormone, FSH, and luteinizing hormone, LH).

The proposed therapeutic indication of Fortesta is the T replacement in adult male hypogonadism (both primary and secondary).

2.1.3 What is the proposed dosage and route of administration?

The recommended starting dose is 40 mg of T applied once daily topically to the front and inner thighs in the morning. To insure proper dosing, serum T concentrations measured 2 hours post Fortesta application (C2h) at approximately 14, 35, and 60 days and dose should be titrated based on the following Table 3.

Table 3 Dose Adjustment Criteria

C2h of total T	Dose Titration
≥2500 ng/dL	Decrease daily dose by 20 mg (1.0 g gel)
≥1250 and <2500 ng/dL	Decrease daily dose by 10 mg (0.5 g gel)
≥500 and <1250 ng/dL	No change
<500 ng/dL	Increase daily dose by 10 mg (0.5 g gel)

2.1.4 What is hypogonadism?

There are two types of hypogonadism, primary and secondary hypogonadism.

- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol, heavy metals or age related degeneration. Patients with primary hypogonadism usually

have low serum T concentrations and gonadotrophins (FSH and LH) above the normal range.

- Hypogonadotropic or secondary hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinising hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, radiation, age related degeneration or drug induced hypopituitarism. Patients with secondary hypogonadism have low serum T concentrations but have gonadotrophins in the normal or low range.

2.2 General Clinical Pharmacology

2.2.1 What is the design feature of the clinical pharmacology and clinical trial used to support dosing or claims?

Trial FOR01C:

This trial was a 90-day, multicenter, open label, non-comparative trial in 149 hypogonadal males who had received prior T replacement therapy. Patients eligible for this trial were hypogonadal men (18-75 years) defined as males having a single morning serum T concentration < 250 ng/dL or < 300 ng/dL on two consecutive occasions at least one week apart. All patients enrolled in the trial applied Fortesta once each morning (approximately same time between 7 and 11 a.m.) to the each front and inner thigh at a starting dose of 40 mg/day. A shower or bath could only be taken either before daily application of Fortesta or after a minimum of 2 hours following application. The application site was covered with clothing once the gel had dried. The size of application site was approximately 100 cm² per 10 mg of Fortesta.

The dose of Fortesta was adjusted to between a minimum of 10 mg/day and a maximum of 70 mg/day on the basis of total serum T concentrations obtained at 2 hours after the application of Fortesta at Days 14 (± 3), 35 (± 3), and 60 (± 3). Serum T concentrations including total T, free T, and DHT were obtained at 2 hours after Fortesta application at Days 14 (± 3), 35 (± 3), 60 (± 3), and 90 (± 3). In addition, 24-hour PK profiles for these parameters were obtained at Days 35 (± 3) and 90 (± 3) with following time points; 0, 0.5, 1, 2, 4, 6, 8, 12, 24 hours after application of Fortesta. Sex hormone-binding globulin (SHBG), LH, FSH, and estradiol concentrations were obtained at 2 hours after Fortesta application at Days 35 (± 3) and 90 (± 3).

- Populations Analyzed: The efficacy analysis populations are shown in Table 4. All enrolled patients were included in the safety analysis and intent-to-treat (ITT) population. Overall, 92.6% (138/149 patients) of patients contributed to the modified ITT (mITT) analysis due to the discontinuation of 7.4% (11/149) of patients from the trial. See section 4.1 Individual Clinical Study Review for details of reasons for discontinuation.

Table 4 Populations Analyzed

	Number (%) of Patients
--	------------------------

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

- Safety population (n=149): patients who had at least one application of Fortesta.
- ITT population (n=149): patients in the safety population 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.

Reviewer's comment: This reviewer used data based on mITT population as the primary data to address primary and secondary endpoints of trial FOR01C since mITT population included all patients enrolled in the trial except 11 patients who were discontinued from the trial.

- PP population (n=35): If there were significant numbers of patients, e.g., more than 10%, with protocol deviations, a secondary PP analysis was to be performed for the primary and secondary endpoints. Due to the protocol deviations (74.6% - mITT population) greater than 10%, a secondary PP analysis was performed for the primary and secondary endpoints. See section 4.1 Individual Clinical Study Review for details of protocol deviations.
- mPP population (n=84): The mPP population included PP population and patients with medication non-compliance (“% compliance” <85% or >115%) on Days 14, 35, and 60. (Efficacy evaluation was based on data from Day 90.) See section 4.1 Individual Clinical Study Review for details of “% compliance”.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical trial?

Fortesta is indicated for T replacement therapy and the following Division recommended endpoints were used in the pivotal phase 3 clinical trial, FOR01C (IND (b) (4) Information Request by Dr. Donna Griebel, DARRTS, December 16, 2004):

- Primary endpoint
 - C_{avg} of total T at Day 90 ± 3 days are between 300 and 1140 ng/dL in ≥ 75% of patients (lower bound of 95% CI ≥ 65%)
- Secondary endpoints
 - C_{max} of total T at Day 90 ± 3 days are:
 - ≤1500 ng/dL in ≥ 85% of patients
 - ≥1800 and <2500 ng/dL in ≤5% of patients
 - ≥2500 ng/dL in no patients

2.2.3 Are the active moieties in the serum appropriately identified and measured to assess PK parameters and exposure response relationship?

Yes. Serum T concentrations including total T, free T, and DHT were obtained at 2 hours after Fortesta application at Days 14 (± 3), 35 (± 3), 60 (± 3), and 90 (± 3). In addition, 24-hour PK profiles for these parameters were obtained at Days 35 (± 3) and 90 (± 3) with following time points; 0, 0.5, 1, 2, 4, 6, 8, 12, 24 hours after application of Fortesta. The details of analytical procedures are described in section 2.6, analytical section.

2.2.4 Dose-response

2.2.4.1 What are the characteristics of the dose-concentration relationship for efficacy?

- Summary of primary and secondary endpoints is provided in Table 5.
- The predefined criteria for both primary and secondary endpoints were achieved.
 - Primary objective: The percentage of mITT patients achieving C_{avg} of total T in the normal range (300 - 1140 ng/dL) at Day 90 was 76.1%, with a lower bound of the 95% confidence limit of 69.0%.
 - Secondary objectives: The percentage of mITT patients achieving following C_{max} of total T at Day 90 were
 - 91.3% for $C_{max} \leq 1500$ ng/dL
 - 4.3% for $C_{max} \geq 1800$ and < 2500 ng/dL
 - 0% for $C_{max} \geq 2500$ ng/dL
- Other populations analyzed (ITT, PP, and mPP) supported the efficacy conclusions from the primary patient population (mITT); Results based on other populations (ITT, PP, and mPP) are provided in the section 4.1 Individual Clinical Study Review.

Table 5 Summary of Primary and Secondary Endpoints (mITT Population)

Primary Endpoint (C_{avg} of total T at Day 90)	
Mean (SD)	442.4 (177.7) ng/dL
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	76.1%, 105/138
95% CI for % Patients with Values ≥ 300 and ≤ 1140 ng/dL	69.0 - 83.2%
% 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
% Patients with Values ≥ 1800 and < 2500 ng/dL, n/n	4.3%, 6/138
% Patients with Values ≥ 2500 ng/dL, n/n	0%, 0/138

There were 5 patients (patient ID (BMI): 003-005 (41.5), 003-006 (40.8), 004-008 (35.4), 032-042 (35), 032-051 (35)) with BMI > 35 kg/m² who were included in the mITT population, although they violated the inclusion criteria (BMI ≥ 22 and < 35 kg/m²). Therefore, primary and secondary endpoints were reanalyzed excluding these 5 patients (Table 6). The predefined criteria for both primary and secondary endpoints were still achieved with excluding these 5 patients.

Table 6 Summary of Primary and Secondary Endpoints (mITT Population Excluding 5 Patients Who Violated the Inclusion Criteria)

Primary Endpoint (C_{avg} of total T at Day 90)	
Mean (SD)	433.3 (166.5) ng/dL
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	75.2 %, 100/133
95% CI for % Patients with Values ≥ 300 and ≤ 1140 ng/dL	67.9 – 82.5%
% Patients with Values < 300 ng/dL, n/n	24.8%, 33/133
% Patients with Values > 1140 ng/dL, n/n	0%, 0/133
Secondary Endpoints (C_{max} of total T at Day 90)	
Mean (SD)	853.4 (402.8) ng/dL
% Patients with Values ≤ 1500 ng/dL, n/n	91.7%, 122/133
% Patients with Values ≥ 1800 and < 2500 ng/dL, n/n	3.8%, 5/133
% Patients with Values ≥ 2500 ng/dL, n/n	0%, 0/133

Results for total T, DHT, ratio of DHT to total T, free T, SHBG, LH, FSH, estradiol, are summarized in Table 7 and 8. The SHBG concentration remained constant, with a slight reduction at Day 90. Both serum gonadotropins (LH and FSH) fell at Day 35 and 90, consistent with increased circulating T which would suppress LH and FSH secretion from the pituitary gland. Estradiol concentrations increased over time, consistent with aromatization of the exogenous T to its metabolite, estradiol.

Table 7 Mean (SD) C2h of Total T, DHT, free T, SHBG, LH, FSH, and Estradiol (mITT Population)

	Mean (SD)				
	Baseline	Day 14	Day 35	Day 60	Day 90
Total T (ng/dL)	190.2 (64.4)	562.0 (421.1)	715.5 (511.6)	741.4 (522.8)	675.2 (373.1)
DHT (ng/dL)	22.0 (7.6)	68.2 (40.6)	74.2 (42.3)	79.2 (47.8)	76.5 (41.8)
Ratio of DHT/Total T	0.13 (0.07)	0.15 (0.08)	0.17 (0.07)	0.14 (0.1)	0.17 (0.06)

Free T (pg/dL)	33.1 (16.0)	118.9 (112.1)	168.4 (176.4)	178.1 (160.2)	160.8 (118.3)
SHBG (nmol/L)	37.1 (20.3)	-	38.1 (21.3)	-	36.4 (16.0)
LH (mIU/mL)	5.5 (7.3)	-	2.84 (4.8)	-	2.6 (4.7)
FSH (mIU/mL)	10.5 (15.9)	-	5.4 (11.4)	-	4.1 (11.5)
Estradiol (ng/dL)	1.7 (0.8)	-	2.8 (1.5)	-	3.0 (1.7)

Table 8 C_{avg} of Total T , DHT, and Free T (Days 35 and 90; mITT Population)

	Mean (SD)	
	Day 35	Day 90
Total T (ng/dL)	410.4 (163.9)	442.4 (177.7)
DHT (ng/dL)	69.3 (38.3)	71.5 (34.9)
Free T (pg/dL)	83.0 (40.7)	95.3 (48.9)

C_{2h}, C_{avg}, and C_{max} of total T concentration by final dose at Day 90 are presented in Table 9. Mean values within the Day 90 dose groups are all similar with exception of one patient at 10 mg. Mean C_{avg} of total T concentrations for each final dose level, with the exception of the 10 mg dose group, were within the 300 – 1140 ng/dL.

Table 9 Number of Patients and Pharmacokinetic Parameters (mean (SD)) of Total T by Dose at Days 0, 14, 35, 60, and 90

		10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	70 mg
Day 0 N=148	N	0	0	0	148 (100%)	0	0	0
	Baseline	-	-	-	213.4 (87.9)	-	-	-
Day 14 N=147	N	0	0	0	147 (100%)	0	0	0
	C _{2h} (ng/dL)	-	-	-	566.9 (430.0)	-	-	-
Day 35 N=143	N	0	1 (0.7%)	10 (7.0%)	56 (39.2%)	76 (53.1%)	0	0
	C _{2h} (ng/dL)	-	585.0 (0.0)	1081.7 (482.3)	851.8 (609.7)	602.5 (506.0)	-	-
	C _{avg} (ng/dL)	-	-	468.2 (179.9)	468.0 (260.7)	383.5 (168.3)	-	-
	C _{max}	-	-	1098	1002.6	771.2	-	-

	(ng/dL)			(463.3)	(595.0)	(512.8)		
Day 60 N=140	N	0	6 (4.3%)	12 (8.6%)	39 (27.9%)	44 (31.4%)	39 (27.9%)	0
	C2h (ng/dL)	-	755.7 (431.6)	911.7 (479.4)	958.79 (557.9)	683.6 (496.9)	504.8 (441.2)	-
Day 90 N=138	N	1 (0.7%)	7 (5.1%)	17 (12.3%)	30 (21.7%)	27 (19.6%)	31 (22.5%)	25 (18.1%)
	C2h (ng/dL)	421.0 (0.0)	684.0 (379.3)	833.4 (517.6)	718.4 (386.6)	806.2 (383.1)	474.4 (240.9)	603.7 (285.8)
	Cavg (ng/dL)	230.8 (0.0)	411.0 (220.1)	403.2 (142.0)	442.3 (182.6)	497.0 (162.8)	453.5 (215.8)	413.8 (141.4)
	Cmax (ng/dL)	587.0 (0.0)	869.7 (412.1)	905.9 (489.0)	874.6 (434.4)	998.6 (400.8)	815.4 (393.5)	746.7 (332.4)

2.2.4.3 What is the effect of showering on the concentration of T?

Trial T 00-02-03 evaluating the effect of showering on the concentration of T was submitted on June 3, 2002 during the original NDA cycle. The formulation of T gel 2% used in the trial T 01-02-02 was the same as the formulation of Fortesta. The trial was reviewed by Dr. Dhruva J. Chatterjee and the following are from his review (NDA 21-463, DARRTS, July 2, 2003):

Trial T 00-02-03:

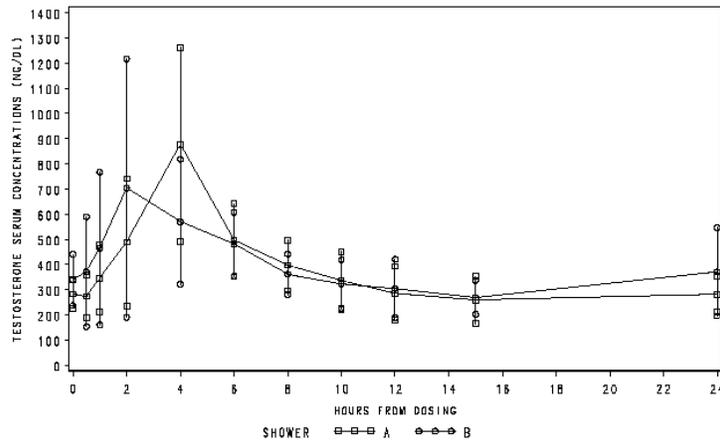
This was an open-label, non-vehicle-controlled, randomized, two-treatment, two-period crossover PK study conducted to determine the effects of showering on the pharmacokinetics of T following topical application of T gel 2% in hypogonadal males.

Seven subjects were enrolled in this study. Each subject was to participate in two 7-day treatment periods. During both treatment periods, beginning on Day 1, the subject applied 3 g of T gel 2% (60 mg T) daily, administered as 1.5 g applied to a 150 cm² area of skin on each anteromedial thigh. The dose was applied at approximately the same time each morning and the time of application was recorded in a diary. From Study Days 1 through 6 of two periods, drug administration was identical for all subjects. On the morning of Day 7 of first period, subjects, having fasted from midnight, reported to the study site for T gel administration and blood collection for a 24-hour PK profile. Venous blood samples were obtained prior to (Time 0), and at 0.5, 1, 2, 4, 6, 8, 10, 12, 15, 20 and 24 hours following application of study medication. At the time of entry to the study site, subjects were randomly assigned to a sequence of treatment (AB or BA). Subjects assigned to Treatment A were to shower as directed two hours after application of the T gel and after the two-hour post-dose blood sample was obtained. Subjects assigned to Treatment B were not to shower during the 24-hour PK profile period, but could shower at the study unit before gel application, if desired. Subjects continued to apply study medication (60 mg T daily) for at least six additional days. On Day 7 of the second period, the second 24-hour PK profile under the alternate showering condition was obtained in each subject.

Table 10 Ratios of Geometric Means and 95% Confidence Intervals of Total T for Day 7 PK parameter Estimates (A: shower 2 hours after T Gel administration; B: without shower); Trial 00-02-03

Pharmacokinetic Parameter	N	Ratio of Geometric Means (B/A)	95% Confidence Limits for Ratio
C _{max} (ng/dL)	7	0.83	(0.47-1.44)
C _{avg} (ng/dL)	7	1.03	(0.79-1.34)
C _{min} (ng/dL)	7	1.29	(0.91-1.85)

^b Exponential of difference of least square means (LSM) from the analysis of variance.
 Exponential of (difference of LSMs from the analysis of variance $\pm t(0.025, DF) \times$ standard error based on logarithms (SE) of difference), where LSM is the adjusted mean and SE is its standard error, where the error degrees of freedom (DF) = 5.



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Figure 1 Mean (SD) T Serum Concentrations Versus Time; Trial T 00-02-03

Table 11 Summary Statistics for Day 7 Pharmacokinetic Parameters; Trial T 00-02-03

Pharmacokinetic Parameter	Treatment A	Treatment B
AUC ₀₋₂₄ (ng-h/dL)		
N	7	7
Mean	8939	9199
SD	2107.4	3216.1
Median	8868	8862
Range	6632-11301	5183-15710
Geometric Mean	8723	8772
Approximate CV (%)	24.4	33.8
C _{max} (ng/dL)		
N	7	7
Mean	893.6	790.6
SD	356.87	459.36
Median	817.0	775.0
Range	422-1595	266-1734
Geometric Mean	836.5	691.3
Approximate CV (%)	41.1	61.4
C _{avg} (ng/dL)		
N	7	7
Mean	372.3	383.3
SD	87.62	134.00
Median	369.5	369.3
Range	276-471	216-655
Geometric Mean	363.3	365.5
Approximate CV (%)	24.3	33.8
C _{min} (ng/dL)		
N	7	7
Mean	201.7	246.4
SD	73.55	65.08
Median	221.0	230.0
Range	89-291	158-353
Geometric Mean	188.2	239.1
Approximate CV (%)	44.3	27.1
T _{max} (h)		
N	7	7
Mean	4.60	4.29
SD	1.50	2.43
Median	4.00	4.00
Range	4.0-8.0	2.0-8.0

Treatments:

A = Study On Day 7, shower at least two hours after application of T gel (and following the collection of the two-hour blood sample). The once daily dose was T gel 2% (60 mg T) applied as 1.5 g (30 mg T) to a 150 cm² area of skin on each anteromedial thigh.

B = On Day 7, shower (if taken) was to occur before application of T gel. The once daily dose was T gel 2% (60 mg T) applied as 1.5 g (30 mg T) to a 150 cm² area of skin on each anteromedial thigh.

• *Based on the above tables, mean and individual (results not shown here) PK plots, and consideration of the high degree of variability in PK parameters, no trend appears to indicate that showering 2 hours post gel administration leads to a detectable difference in the daily exposure profiles to total T.*

2.2.4.3 What are the characteristics of the dose-concentration relationship for safety?

The adverse events leading to premature discontinuation from the trial are presented in Table 12. There were five (3.4%) patients who were discontinued from the trial. Sponsor reported that out of 5 adverse events leading to discontinuation from the trial, 2 (contusion and dyspnea) and 3 (dermatitis contact, skin reaction, and gastric hypomotility) adverse events were “unrelated” and “probably related” to Fortesta, respectively.

Table 12 Adverse Events Leading to Premature Discontinuation from Trial (Safety population)

Adverse Events	Number (%) of Patients N=149
Patients with Any Adverse Event Leading to Discontinuation	5 (3.4)
Skin and Subcutaneous Tissue Disorders	2 (1.3)
Dermatitis contact	1 (0.7)
Skin reaction	1 (0.7)
Gastrointestinal Disorders	1 (0.7)
Gastric hypomotility	1 (0.7)
Injury, Poisoning and Procedural Complications	1 (0.7)
Contusion	1 (0.7)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.7)
Dyspnea	1 (0.7)

In order to explore the relationship between total T and adverse events experienced in five patient who were discontinued from the trial FOR01C, pharmacokinetic parameters of total T and BMI of those five patients are presented in Table 13. All five patients had BMI higher than 30 (classified as obese). Except for patient 006-004 who had C_{2h} of 2120 on Day 14, none of four patients were associated with C_{2h} higher than 1250, which is the threshold necessitating dose decrease. C_{2h} and C_{max} of those four patients were also within the predetermined target range for C_{avg} (300 – 1140). Therefore, no direct relationship between adverse events of five patients and total T can be established.

Table 13 BMI and Pharmacokinetic Parameters of Total T of 5 Patients Discontinued from the Trial Due to Adverse Events (AE)

Patient ID	AE	BMI	Day 14	Day 35			Day 60	Day 90		
			C2h (ng/dL)	C2h (ng/dL)	C _{avg} (ng/dL)	C _{max} (ng/dL)	C2h (ng/dL)	C2h (ng/dL)	C _{avg} (ng/dL)	C _{max} (ng/dL)
006-004	Dermatitis contact	32.9	2120	N/A	N/A	N/A	N/A	N/A	N/A	N/A
014-058	Dyspnea	34.8	453	N/A	N/A	N/A	N/A	N/A	N/A	N/A
027-004	Skin reaction	34.9	483	289	328	445	593	N/A	N/A	N/A
032-024	Contusion	31	152	563	553	789	N/A	N/A	N/A	N/A
032-052	Gastric hypomotility	33.9	325	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviation: N/A = not available

2.2.4.4 What is the potential of T transfer to partners?

Trial T 01-02-02 evaluating the potential of T transfer to partners was submitted on June 3, 2002 during the original NDA cycle. The formulation of T gel 2% used in the trial T 01-02-02 was the same as the formulation of Fortesta. The trial was reviewed by Dr. Dhruba J. Chatterjee and the following are from his review (NDA 21-463, DARRTS, July 2, 2003).

Trial T 01-02-02:

The objectives of this study were to determine

- 1) whether transfer of T gel 2% from a male to female would significantly raise the serum T and bioactive T concentrations in the female as assessed by a 24-hour serum T pharmacokinetic profile*
- 2) if transfer occurs, whether covering the application site with clothing would prevent it.*

This was an open-label, vehicle-controlled, pharmacokinetic study conducted in healthy couples. The study consisted of three phases: one non-transfer profile phase (Treatment A: Phase I - vehicle only) and two potential transfer profile phases (Treatment B for Phase II - uncovered T gel 2% exposure and Treatment C for Phase III - covered T gel 2% exposure). The order of the three phases was randomized in a three-period crossover design. Each phase was conducted on Day 25 (± 2) of three consecutive menstrual cycles of the female partner of each couple. Day 1 of the cycle was defined as the first day of menses. In Treatment A (non-transfer control Phase I), the male partner applied the vehicle to a 150 cm² area of the anteromedial thigh. In Treatment B (uncovered Phase II), the male applied 1.5 g of T gel 2% to a 150 cm² area of the thigh, and in Treatment C (covered Phase III), the male applied 1.5 g of T gel 2% and wore boxer shorts that

covered the site of application. During each phase, the female partner rubbed the application site with the volar surface of her forearm for 15 consecutive minutes, beginning 2 hours after the T gel 2% was applied. Blood samples were obtained from the female partner at Time 0 (just before rubbing), 0.5, 1, 2, 4, 6, 8, 10, 12, 15, and 24 hours. Blood samples were analyzed for determination of T, bioactive T and SHBG concentrations.

Table 14 Ratios of Geometric Means and 95% Confidence Intervals for Total Serum Testosterone Pharmacokinetic Parameter Estimates; Trial T 01-02-02

Pharmacokinetic Parameter	Treatment Group Ratios	Ratio of Geometric Means ^{a,b}	95% Confidence Limits for Ratio	P-value
C _{avg} (ng/dL) (N=6)	B/A	2.11	(1.20, 3.71)	0.0153
	C/A	0.85	(0.47, 1.52)	0.5324
	C/B	0.4	(0.23, 0.70)	0.0056
C _{max} (ng/dL) (N=6)	B/A	2.8	(1.01, 7.78)	0.0481
	C/A	0.77	(0.27, 2.25)	0.5937
	C/B	0.28	(0.10, 0.77)	0.0196

^a Analysis includes the Hour 2, 4, 12, and 15 outlier concentration values for subject 123-102, Treatment B

^b Ratios of geometric means, confidence limits, and p-values are computed using adjusted means from an ANOVA model that includes terms for patient, period, and treatment

Treatment:

A = Phase I: Male applied 1.5g vehicle/150 cm² to one anteromedial thigh; female rubbed

B = Phase II: Male applied 1.5g CP601B/150 cm² to one anteromedial thigh; female rubbed

C = Phase III: Male applied 1.5g CP601B/150 cm² to one anteromedial thigh, application site is covered; female rubbed

- Generally a 3 folds increase in serum T concentration was observed to in female patients at each time point due to the transfer of the gel from their male partners (treatment C vs. Treatment B).
- Comparison of the PK profiles and parameters between treatment A (vehicle) and C (active gel with male wearing boxer shorts to cover area of application) is essentially same, indicating that the potential for transfer may be abolished by wearing occlusive clothing to cover the application site.

2.2.5 Pharmacokinetics

2.2.5.1 What is the concentration-time profile of total T?

The individual concentration-time profiles of total T at Days 35 and 90 are provided in Figures 2 and 3. Mean C_{avg} of total T on Days 35 and 90 were similar (410.4 and 442.4, respectively; Table 15). In addition, mean concentration-time profiles of total T at Days 35 and 90 were similar as provided in Figure 4.

While number of patients whose C_{avg} of total T ≥ 300 and ≤ 1140 ng/dL was 101 at Day 35, it was 105 at Day 90 suggesting that one dose adjustment at Day 14 is not sufficient to find the proper dose for patients using Fortesta. Four more patients with C_{avg} of total T ≥ 300 and ≤ 1140 ng/dL at Day 90 can be explained as following:

- There were 23 patients whose C_{avg} of total T were either < 300 or > 1140 ng/dL at Day 35, but were ≥ 300 and ≤ 1140 ng/dL at Day 90.

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- There were 19 patients whose C_{avg} of total T were ≥ 300 and ≤ 1140 ng/dL at Day 35, but were either < 300 or > 1140 ng/dL at Day 90.

Table 15 C_{avg} (ng/dL) of Total T at Days 35 and 90 (mITT Population)

	C_{avg} (ng/dL)
Day 35, N=138	
Mean (SD)	410.4 (163.9)
Median	389.6
Range	151.0 - 1201.6
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	73.2%, 101/138
95% CI for % Patients with Values ≥ 300 and ≤ 1140 ng/dL	65.8 - 80.6%
% Patients with Values < 300 ng/dL, n/n	26.1%, 36/138
% Patients with Values > 1140 ng/dL, n/n	0.7%, 1/138
Day 90, N=138	
Mean (SD)	442.4 (177.7)
Median	412.1
Range	107.2 - 1132.3
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	76.1%, 105/138
95% CI for % Patients with Values ≥ 300 and ≤ 1140 ng/dL	69.0 - 83.2%
% Patients with Values < 300 ng/dL, n/n	23.9%, 33/138
% Patients with Values > 1140 ng/dL, n/n	0%, 0/138

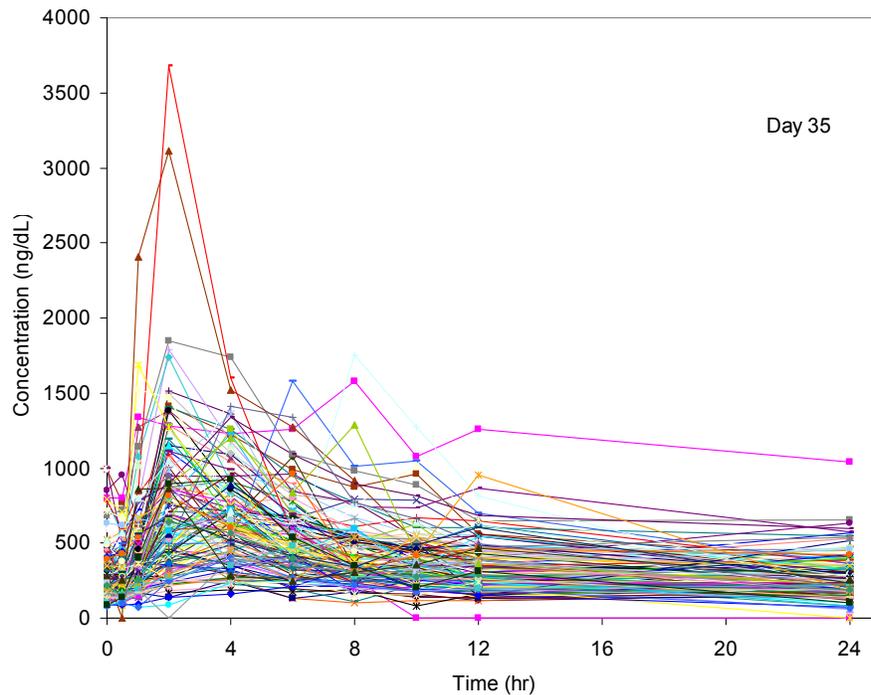


Figure 2 Individual Concentration-Time Profile of Total T at Day 35 (mITT population)

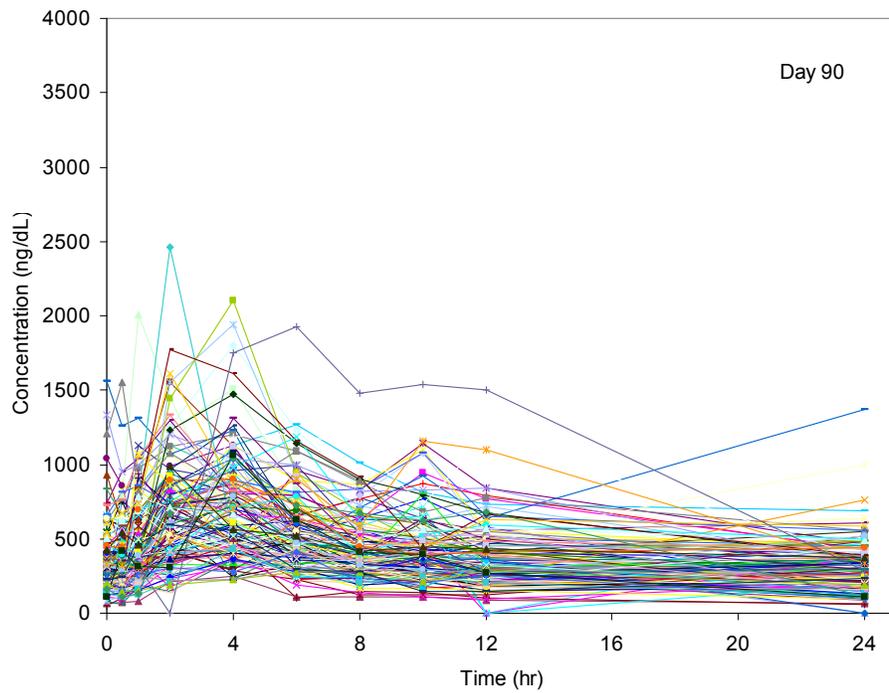


Figure 3 Individual Concentration-Time Profile of Total T at Day 90 (mITT population)

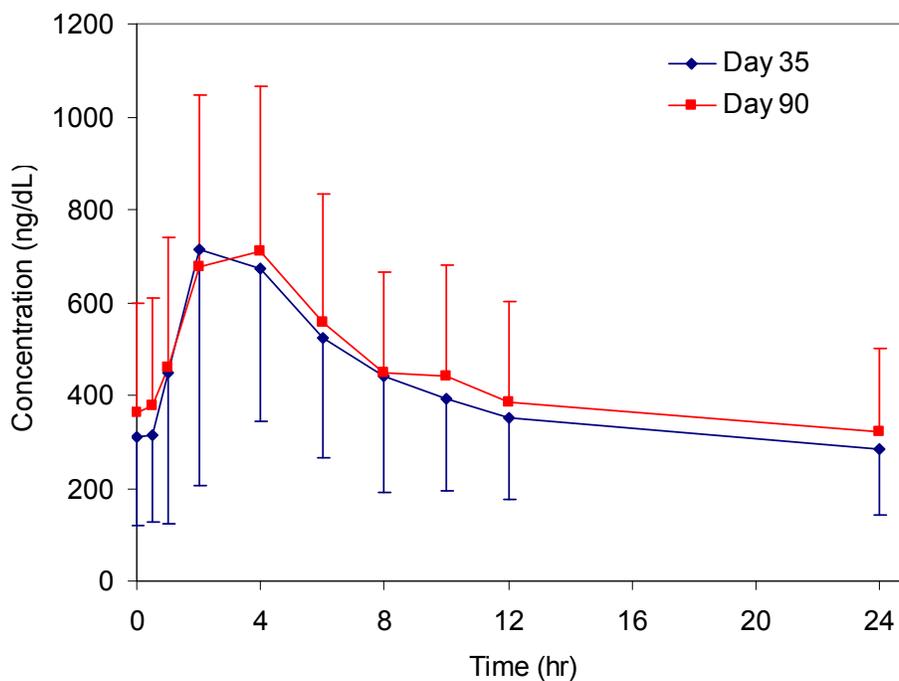


Figure 4 Mean (SD) Concentration-Time Profile of Total T at Days 35 and 90

2.2.5.2 What is the basis of using the C2h of total T for dose titration?

Due to the benefit of being feasible in clinical settings, a single time point measurement of total T was proposed by the sponsor. C2h of total T on Day 14 appeared to correlate with C_{max} ($R^2 > 0.9$; Clinical Pharmacology review of NDA 21-463 by Dr. Dhruba J. Chatterjee, DARRTS, July 02, 2003). Therefore, C2h of total T was used for the basis of each dose titration in trial FOR01C.

In trial FOR01C, 39% of patients on Day 35 and 25% of patients on Day 90 showed T_{max} at 2 hours post Fortesta application (Figure 5). Figure 6 shows mean (SD) C2h of Days 14, 35, 60, and 90. Mean values of C2h on Days 35, 60, and 90 were similar (715.5, 741.4, 675.2 ng/dL respectively).

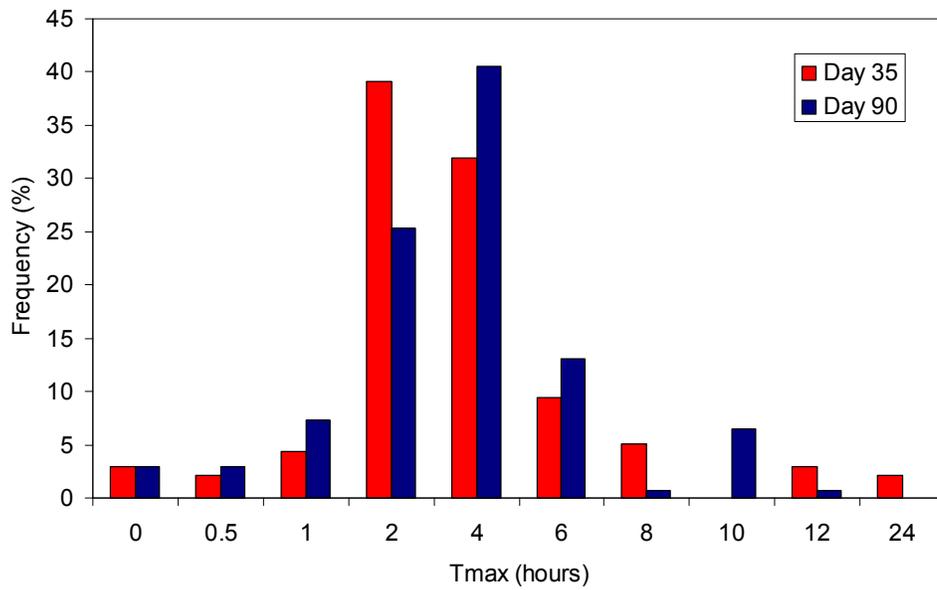


Figure 5 Frequency of T_{max} values for patients at Days 35 and 90 (mITT population)

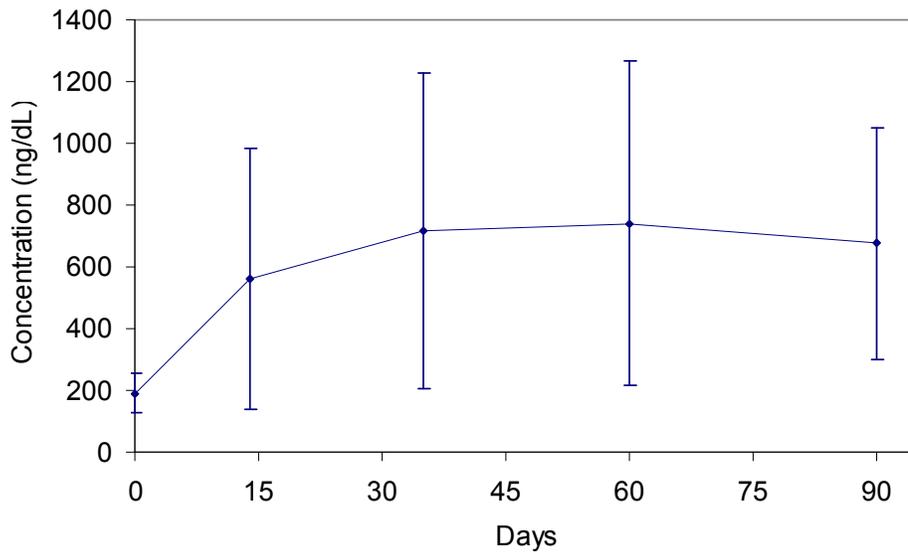


Figure 6 Mean (SD) C2h of Total T at Days 14, 35, 60, and 90 (mITT Population)

- Dose adjustment scheme of trial FOR01C based on C2h of total T is presented in Figure 7. Dose was adjusted within 7 days of date when C2h of total T was measured at Days 14 (± 3), 35 (± 3), and 60 (± 3).

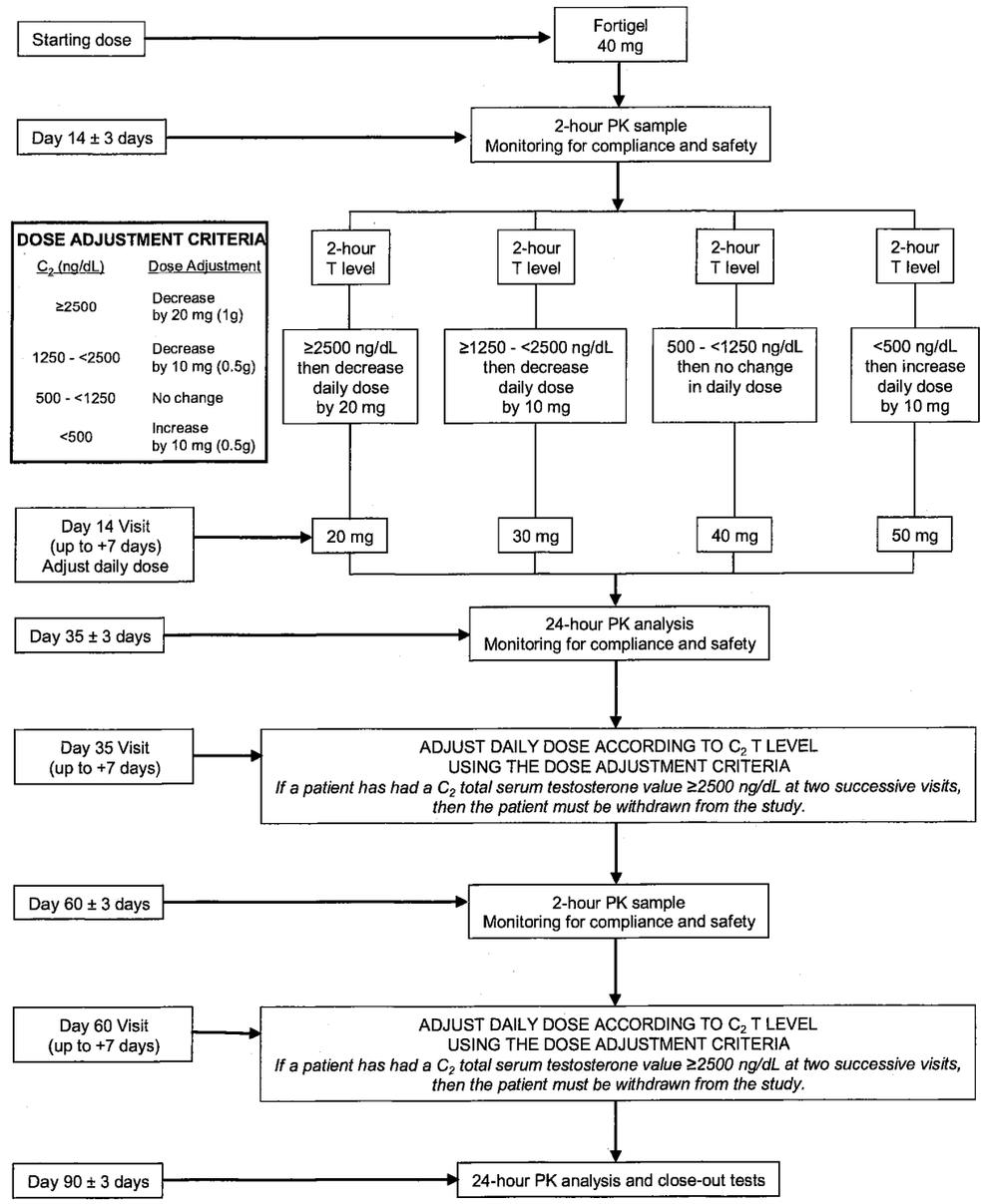


Figure 7 Dose Adjustment Scheme Based on C2h of Total T

2.2.5.3 What are the Characteristics of drug absorption?

Fortesta delivers physiologic amounts of T, producing serum T concentrations that approximate normal concentrations (>300 ng/dL) seen in healthy men.

Fortesta is a hydroalcoholic formulation. The skin serves as a reservoir for the release of T into the systemic circulation. Fortesta provides transdermal delivery of T for 24 hours following a single application to clean, dry, intact skin of the front and inner thighs.

In a controlled multicenter, open label, non-comparative clinical trial, 149 hypogonadal patients were treated with Fortesta. Serum T concentrations (including total T, free T, and DHT) were obtained 2 hours post Fortesta application on Days 14, 35, 60, and 90 (± 3

days). 24-hour pharmacokinetic profiles for these parameters were obtained on Days 35 and 90 (\pm 3 days).

Following one dose adjustment at Day 35, 73.2% of patients had C_{avg} of total T within the physiological range (300 – 1140). At Day 90, 76.1% of patients had C_{avg} of total T within the physiological range (300 – 1140).

2.2.5.4 What are the characteristics of drug distribution?

Circulating T is primarily bound in the serum to SHBG and albumin. Approximately 40% of T in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

2.2.5.5 What are the characteristics of drug metabolism?

T is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of T are estradiol and DHT.

DHT concentrations increased in parallel with T concentrations during Fortesta treatment. The mean (SD) DHT/total T ratio during 90 days of Fortesta treatment ranged from 0.14 (0.1) to 0.17 (0.07).

2.2.5.6 What are the characteristics of drug elimination?

There is considerable variation in the half-life of T as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of T given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of T and its metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of T occurs primarily in the liver.

2.3 Intrinsic factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure of efficacy or safety response? What dosage regimen adjustments, if any, are recommended for each of these groups?

2.3.1.1 Pregnant women and nursing mothers

Pregnancy Category X. Fortesta is contraindicated during pregnancy or in women who may become pregnant. It is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilisation. If the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

2.3.1.2 Nursing mothers

Although it is not known how much T transfers into human milk, Fortesta is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants.

2.3.1.3 Pediatric

The safety and efficacy of Fortesta in pediatric patients <18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

2.3.1.4 Geriatric

There is insufficient long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease. However, geriatric patients with clinical characteristics recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to the initiation of therapy. Men receiving T replacement therapy should receive surveillance for prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of benign prostatic hypertrophy (BPH).

2.3.1.5 Renal or hepatic impairment

No studies have been conducted in patients with renal or hepatic impairments.

2.3.1.6 BMI

Subgroup analysis of C_{avg} and C_{max} of total T at Day 90 by BMI was performed (Table 16 and 17). Higher C_{avg} and C_{max} were associated with patients with BMI ≥ 35 .

Table 16 C_{avg} of Total T at Day 90 by Screening BMI (mITT Population)

Statistic	BMI			
	≥ 22 and < 25	≥ 25 and < 30	≥ 30 and < 35	≥ 35
N	8	48	77	5
Mean	457.4	430.9	432.3	684.1
SD	168.8	171.1	165.4	302.0
Median	450.4	423.5	384.4	644.0
Range	265.7 - 728.9	107.2 - 958.0	170.7 - 840.9	362.5 - 1132.3
% Patients with Values ≥ 300 and ≤ 1140 ng/dL	75.0%	77.1%	74.0%	100.0%
95% CI	45.0 - 100.0%	65.2 - 89.0%	64.2 - 83.8%	100 - 100%

Table 17 C_{max} of Total T at Day 90 by BMI (mITT Population)

Statistic	BMI			
	≥ 22 and < 25	≥ 25 and < 30	≥ 30 and < 35	≥ 35
N	8	48	77	5
Mean	939.8	878.0	829.1	1143.0
SD	307.3	433.4	394.0	495.5
Median	920.5	810.5	727.0	987.0
Range	535.0 - 1510.0	250.0 - 2460.0	305.0 - 2100.0	632.0 - 1930.0
% Patients with Values ≤ 1500 ng/dL	87.5%	91.7%	92.2%	80.0%
% Patients with Values ≥ 1800 and < 2500 ng/dL	0	4.2%	3.9%	20.0%
% Patients with Values ≥ 2500 ng/dL	0	0	0	0

2.3.1.7 Ethnicity

Subgroup analysis of C_{avg} and C_{max} of total T at Day 90 by ethnicity (Hispanic or Latino vs. not Hispanic or Latino) was performed (Table 18 and 19). There was no notable difference of C_{avg} and C_{max} of total T by ethnicity.

Table 18 C_{avg} of Total T at Day 90 by Ethnicity (mITT Population)

Statistic	Hispanic or Latino	Not Hispanic or Latino
N	11	127
Mean	448.1	441.9
SD	184.8	177.9
Median	389.8	414.8
Range	265.7 - 810.3	107.2 - 1132.3
% Patients with Values ≥ 300 and ≤ 1140 ng/dL	72.7%	76.4%
95% CI	46.4 - 99.0	69.0 - 83.8%

Table 19 C_{max} of Total T at Day 90 by Ethnicity (mITT Population)

Statistic	Hispanic or Latino	Not Hispanic or Latino
N	11	127
Mean	822.3	867.5
SD	310.8	416.1
Median	787.0	782.0
Range	492.0 - 1470.0	250.0 - 2460.0

% Patients with Values ≤ 1500 ng/dL	100.0%	90.6%
% Patients with Values ≥1800 and <2500 ng/dL	0	4.7%
% Patients with Values ≥2500 ng/dL	0	0

2.3.1.8 Race

Subgroup analysis of C_{avg} and C_{max} of total T at Day 90 by race (white vs. black or African American vs. other) was performed (Table 20 and 21). Compared to white, black or African American was associated with higher mean C_{avg} and C_{max} . In order to explore the relationship between race and BMI, BMI by race is provided in Table 22. Mean (SD) values of BMI of white and black or African American were 28.1 (2.7) and 31.3 (5.2), respectively. Subgroup analysis of C_{avg} and C_{max} of total T at Day 90 by BMI did not show correlation between C_{avg} and/or C_{max} of total T and BMI in two BMI groups (≥ 25 and < 30 vs. ≥ 30 and < 35). Therefore, the higher C_{avg} and C_{max} of total T at Day 90 in black or African American than those in white were not explained by the BMI.

Table 20 C_{avg} of Total T at Day 90 by Race (mITT Population)

Statistic	White	Black or African American	Other*
N	122	13	3
Mean	429.4	560.5	459.0
SD	167.9	242.7	62.2
Median	395.7	488.2	476.9
Range	107.2 - 958.0	264.8 - 1132.3	389.8 - 510.2
% Patients with Values ≥300 and ≤1140 ng/dL	73.8%	92.3%	100.0%
95% CI	66.0 - 81.6%	77.8 - 100.0%	100.0%

*Other: one Asian Indian, one Arabic, and one mixed

Table 21 C_{max} of Total T at Day 90 by Race (mITT Population)

Statistic	White	Black or African American	Other*
N	122	13	3
Mean	832.0	1018.9	1492.3
SD	370.4	506.8	866.8
Median	765.0	1080.0	1230.0
Range	250.0 - 2100.0	356.0 - 1944.0	787.0 - 2460.0
% Patients with	92.6%	84.6%	66.7%

Values \leq 1500 ng/dL			
% Patients with Values \geq 1800 and $<$ 2500 ng/dL	2.5%	15.4%	33.3%
% Patients with Values \geq 2500 ng/dL	0	0	0

*Other: one Asian Indian, one Arabic, and one mixed

Table 22 BMI by Race (mITT Population)

Statistic	White	Black or African American	Other*
N	122	13	3
Mean	28.1	31.3	30.6
SD	2.7	5.2	3.3
Median	29.0	31.7	30.9
Range	25.0 - 30.2	23.9 - 41.5	22.1 - 40.8
% Patients with Values \geq 300 and \leq 1140 ng/dL	73.8%	92.3%	100.0%
95% CI	66.0 - 81.6%	77.8 - 100.0%	100.0%

2.4 Extrinsic factors

2.4.1 Drug interaction

Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.

Corticosteroids

The concurrent use of T with adrenocorticotrophic hormone or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.

Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

2.5 General Biopharmaceutics

2.5.1 Are the clinical trial and to-be-marketed (TBM) formulations the same?

Yes. The Fortesta formulation studied in the pivotal phase 3 trial, FOR01C is the same as the TBM formulation.

2.6 Analytical Section

Serum total T was determined using a LC/MS method.

Division of Scientific Investigation (DSI) report of the pivotal clinical trial FOR01C

The Division of Clinical Pharmacology III requested for DSI to conduct audits of the both clinical and bioanalytical sites of the pivotal clinical trial on June 9, 2009. See 4.2 DSI site inspection request and 4.3 DSI site inspection report for detail.

- Analytical Site (b) (4)
 1. Failure to demonstrate accuracy of the DHT RadioImmunoAssay (RIA). Specifically, calibration standards were (b) (4) as did for the quality control (QC) and subject serum samples. The concentrations extrapolated from the solvent based standard curve have not been shown to accurately represent the concentrations of DHT extracted from serum matrix.
 2. Failure to fully validate the assays for LH and PSA in that:
 - Study sample values were reported above 0.01 ng/ml for PSA and 0.07 mIU/ml for LH. However, precision and accuracy was only demonstrated above 0.5 ng/ml for PSA and above 0.59 mIU/ml for LH.
 - The PSA assay was not evaluated for freeze/thaw stability or matrix effects.
 - Commercial products were used for the preparation of the calibrators and QCs for the LH and PSA assays. The firm did not obtain certification of all these reagents' nominal concentrations.
 3. Failure to accurately demonstrate the freeze/thaw (F/T) and frozen storage stability of all analytes at -20°C. Specifically, standard curves used in the stability experiments were not freshly prepared but generated from frozen calibration standards prepared previously and stored at -20°C. The F/T test stability samples were compared to frozen reference samples stored at -70°C.
 4. Audit trail of the 'Analyst' software version 1.41 was not turned on for all the validation and analytical runs. There are no audit trail records available for inspection.
 5. Many analytical runs had > 33.3% of the total QCs and/or > 50% at the same concentration with deviations > 15% (for MS-based assays) or 20%

(for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations.

6. Failure to reject analytical runs when < 75% of calibration standards in a standard curve failed to meet the acceptance criteria (< 15% or < 20% (LLOQ) deviation from nominal values or mean pooled QC concentrations). In many of these runs, majority of the calibration standards either failed near the beginning or near the end of the runs suggesting possible drift in the system during the run. These runs were accepted by deleting the failed standard curve.
7. The incurred sample reproducibility (ISR) of the LC/MS/MS method for TT was not evaluated. TT concentrations determined by this method were used to calculate the primary (C_{avg} 0-24 hr at Day 90) and secondary efficacy endpoints (C_{max} at Day 90) for the study.
8. Failure to adequately monitor SHBG assay performance in that human serum lots 424 and 440 (used as quality controls) were used past their expiration dates.

Reviewer's comments for findings from analytical site

- *The **stability** of analytes were not established based on Guidance for Industry – Bioanalytical Method Validation (May 2001, FDA). - #3*
 - *Without the audit trail, it is not possible for the inspector to verify the process of running the instruments for measuring analytes. - #4*
 - *The **precision** of analytes were not established based on Guidance for Industry – Bioanalytical Method Validation (May 2001, FDA) - #5*
 - *The **accuracy** of analytes were not established based on Guidance for Industry – Bioanalytical Method Validation (May 2001, FDA) - #6*
 - *The **calibration curve** was not generated based on Guidance for Industry – Bioanalytical Method Validation (May 2001, FDA) - #6*
 - *The **reproducibility** of analytes were not established based on Guidance for Industry – Bioanalytical Method Validation (May 2001, FDA) - #7*
 - *Overall, the analytical site violated stability, precision, accuracy, calibration curve, and reproducibility of an analytical method in measuring total T. Therefore, the PK data submitted under NDA 21-463 does not have value for review.*
- Clinical Site (Panhandle Family Care Associates)
 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.
 2. Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.
 3. Failure to report to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug.

Reviewer's comments for findings from clinical site

- *There were data manipulations regarding 2 patients' BMIs to include those patients in the study. - #1*
- *Four cases of adverse events experienced by the study subjects were not reported in the CRFs. - #1*
- *One unanticipated problem causing hospitalization of the patient was not reported to Institutional Review Board. - #2 & 3*
*The **stability** of analytes were not established b*
- *Overall, the data manipulation and failure to report adverse events properly discredit the quality of the study conduct of FOR01C.*

Due to the deficiencies identified in the DSI report,, the results from Study FOR01 cannot be used to support the approval of NDA 21-463.

3 Detailed Labeling Recommendations

Labeling comments are not provided due to the violations identified in the DSI report for both analytical and clinical sites of study FOR01C.

4 Appendices

4.1 Individual Clinical Study Review

FOR01C

- Trial centers: Twenty six centers in the US
- Objectives
 - Primary Objective
 - C_{avg} of total T at Day 90 ± 3 days are between 300 and 1140 ng/dL in $\geq 75\%$ of patients (lower bound of 95% CI $\geq 65\%$)
 - Secondary Objectives
 - C_{max} of total T at Day 90 ± 3 days are:
 - ≤ 1500 ng/dL in $\geq 85\%$ of patients
 - ≥ 1800 and < 2500 ng/dL in $\leq 5\%$ of patients
 - ≥ 2500 ng/dL in no patients
 - to determine the safety of Fortesta in hypogonadal males
- Trial Design: This trial was a 90-day, multicenter, open label, non-comparative trial in 149 hypogonadal males who had received prior T replacement therapy. All patients enrolled in the trial applied Fortesta once each morning (approximately same time between 7 and 11 a.m.) to the each front and inner thigh at a starting dose of 40 mg/day. At Day 1 after completion of all baseline procedures, patients were educated with regard to correct application of trial drug, including priming (two actuations and discarding of gel dispensed) and use of trial drug canisters, a review of the appropriate application area and actual application of Fortesta. Patients were instructed to apply Fortesta to dry intact skin, at a site free of any

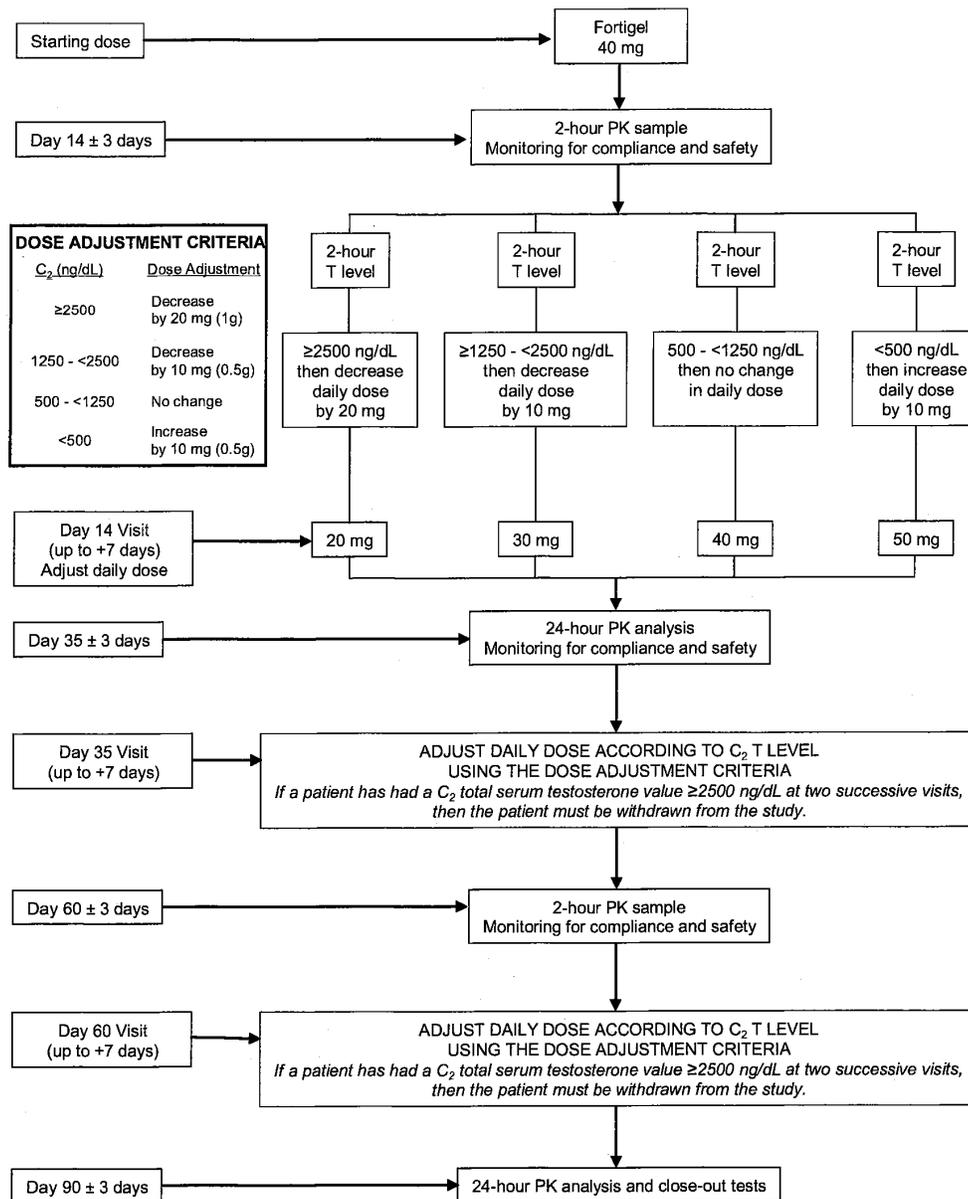
skin abnormalities (e.g., abrasions, sun burn). The entire prescribed dose was administered to the thighs. Half of the dose was rubbed gently into the skin on the anteromedial surface of one thigh using a single finger, and the second half was applied to the other thigh using the same procedure. Each 0.5 g (10 mg T) of gel was to be rubbed over approximately 100 cm². The application site was covered with clothing once the gel had dried. Patients were instructed to wash their hands thoroughly with soap and water after each application. The area of application was moved to different sites on the anteromedial surface of the thighs to reduce overlap with the site of administration on the previous day, and the patients were instructed to avoid areas of the thigh in contact with the scrotum. A shower or bath could only be taken either before daily application of Fortesta or after a minimum of 2 hours following application.

- The dose of Fortesta was adjusted to between a minimum of 10 mg/day and a maximum of 70 mg/day on the basis of total serum T concentrations obtained at 2 hours after the application of Fortesta at Days 14 (\pm 3), 35 (\pm 3), and 60 (\pm 3). Serum T concentrations including total T, free T, and dihydrotestosterone (DHT) were obtained at 2 hours after Fortesta application at Days 14 (\pm 3), 35 (\pm 3), 60 (\pm 3), and 90 (\pm 3). In addition, 24-hour PK profiles for these parameters were obtained at Days 35 (\pm 3) and 90 (\pm 3) with following time points; 0, 0.5, 1, 2, 4, 6, 8, 12, 24 hours after application of Fortesta. Sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol concentrations were obtained at 2 hours after Fortesta application at Days 35 (\pm 3) and 90 (\pm 3).
- Wash out period: Patients who received prior T replacement therapy completed a washout period of 1 to 52 weeks prior to the baseline total T measurement at Day 1. The duration of washout was dependent on the T replacement therapy as provided in Table 23.

Table 23 Prior T Replacement Therapy Washout Period

T Replacement Therapy	Washout Period
Andropatch 2.5 mg / Andropatch 5 mg	1 week
Nebido 1000 mg/4 mL solution for injection	24 weeks
Restandol 40 mg	1 week
Striant 30 mg	1 week
Sustanon 100 mg	4 weeks
Sustanon 250 mg	8 weeks
Testim 50 - 100 mg gel	1 week
Androgel / Testogel 50 - 100 mg	1 week
T Enanthate Ampoules	8 weeks
T Implant 100 - 200 mg	52 weeks
Cypionate Depo T Injections	8 weeks

- Dose adjustment scheme based on C₂h of total T



- Number of Patients
 - Enrolled: A total of 149 hypogonadal males were enrolled.
 - Analyzed: A total of 149 patients were included in the Intent-to-Treat (ITT) population, 138 were included in the modified ITT (mITT) population, 35 patients were included in the Per-Protocol (PP) population, and 84 were included in the modified PP (mPP) population.
- Populations Analyzed: The efficacy analysis populations are shown in Table 24. All enrolled patients were included in the safety analysis and ITT population. Overall, 92.6% (138/149 patients) of patients contributed to the mITT analysis.

Table 24 Populations Analyzed

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

- Safety population: patients who had at least one application of Fortesta.
 - ITT population (n=149): patients in the safety population who had an assessment of at least one total T measurement subsequent to the first application of Fortesta.
 - mITT population: patients in the ITT population who had more than one PK sample obtained during the 24-hour PK profile at Day 90.
 - Summaries and analyses of efficacy were based on the mITT population.
 - PP population: If there were significant numbers of patients, e.g., more than 10%, with protocol deviations, a secondary PP analysis was to be performed for the primary and secondary endpoints. Due to the protocol deviations (74.6% - mITT population) greater than 10%, a secondary PP analysis was performed for the primary and secondary endpoints.
 - mPP population: The mPP population included PP population and patients with medication non-compliance (“% compliance” <85% or >115%) on Days 14, 35, and 60. (Efficacy evaluation was based on data from Day 90.)
- Diagnosis and Main Criteria for Inclusion: Patients eligible for this trial were hypogonadal men (18-75 years) defined as males having a single morning serum T concentration < 250 ng/dL or < 300 ng/dL on two consecutive occasions at least one week apart. In addition, patients eligible for this trial were required to have a body mass index (BMI) ≥ 22 and <35 kg/m².
 - Test Product, Dose and Mode of Administration and Lot Number: Fortesta was administered once daily to the thighs at a starting dose of 40 mg per day. The dose was adjusted to between 10 and 70 mg/day based on serum T concentrations obtained 2 hours post dose at Days 14 (± 3), 35 (± 3), and 60 (± 3). The batch number of the Fortesta was 426810.
 - Patient Compliance: Patient compliance was determined using the following formula. If compliance with the prescribed dose of Fortesta was less than 85% or more than 115%, the importance of applying the Fortesta as directed was reiterated.

$$\% \text{ compliance} = (\text{Weight (g) of canister when dispensed} - \text{Weight (g) of canister when returned}) / (\text{Number of days from previous visit} \times \text{Prescribed dose (g) per day}) \times 100$$

- Patient Disposition: A total of 406 patients were screened for possible trial participation, 149 of whom subsequently entered the trial and received at least one application of Fortesta.
 - Patients screened: 406
 - Screen failures: 257
 - Patients entering the trial: 149 (23 patients were ≥ 65 years old)
 - Patients completing the trial: 138
 - Patients discontinuing the trial: 11
 - Primary reason for discontinuation
 - Adverse event: 5 (3.4%)
 - Patient IDs: 006-004, 014-058, 027-004, 032-024, 032-052
 - Explanations in Table 25
 - Protocol violation: 2 (1.3%)
 - Patient ID: 020-004
 - Baseline total T = 663 ng/dL – no blood draw at Days 14, 35, 60, and 90
 - Patient ID: 027-003
 - No further explanation by the sponsor – no blood draw at Days 14, 35, 60, and 90
 - Patient non-compliance: 1 (0.7%)
 - Patient ID: 008-003
 - No further explanation by the sponsor - no blood draw at Days 60 and 90
 - Patient choice: 2 (1.3%)
 - Patient ID: 006-007
 - Patient does not want blood draw - no blood draw at Days 35, 60, and 90
 - Patient ID: 007-004
 - Patient withdrew from the trial due to work schedule - no blood draw at Day 90
 - Lost to follow-up: 0
 - Other: 1 (0.7%)
 - Patient ID: 032-004
 - Lab error – no blood draw at Days 35, 60, and 90
- The adverse events leading to premature discontinuation from the trial are presented in Table 25. There were five (3.4%) adverse events leading to discontinuation from the trial.

- Sponsor reported that out of 5 adverse events leading to discontinuation from the trial, 2 (contusion and dyspnea) and 3 (dermatitis contact, skin reaction, and gastric hypomotility) were “unrelated” and “probably related” to Fortesta, respectively.

Table 25 Adverse Events Leading to Premature Discontinuation from Trial (Safety population)

Adverse Events	Number (%) of Patients N=149
Patients with Any Adverse Event Leading to Discontinuation	5 (3.4)
Skin and Subcutaneous Tissue Disorders	2 (1.3)
Dermatitis contact	1 (0.7)
Skin reaction	1 (0.7)
Gastrointestinal Disorders	1 (0.7)
Gastric hypomotility	1 (0.7)
Injury, Poisoning and Procedural Complications	1 (0.7)
Contusion	1 (0.7)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.7)
Dyspnea	1 (0.7)

Table 26 BMI and Pharmacokinetic Parameters of Total T of 5 Patients Discontinued from the Trial Due to Adverse Events (AE)

Patient ID	AE	BMI	Day 14	Day 35			Day 60	Day 90		
			C2h (ng/dL)	C2h (ng/dL)	C _{avg} (ng/dL)	C _{max} (ng/dL)	C2h (ng/dL)	C2h (ng/dL)	C _{avg} (ng/dL)	C _{max} (ng/dL)
006-004	Dermatitis contact	32.9	2120	N/A	N/A	N/A	N/A	N/A	N/A	N/A
014-058	Dyspnea	34.8	453	N/A	N/A	N/A	N/A	N/A	N/A	N/A
027-004	Skin reaction	34.9	483	289	328	445	593	N/A	N/A	N/A
032-024	Contusion	31	152	563	553	789	N/A	N/A	N/A	N/A
032-052	Gastric hypomotility	33.9	325	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviation: AE = adverse event, C2h = concentration 2hours after application of Fortesta, N/A = not available

- Protocol deviations: Protocol deviations and violations are summarized in Table 27. Overall, 69.1 % of patients had at least one protocol deviation. The most common protocol deviation was trial medication non-compliance (63.1 %).

Table 27 Protocol Deviations and Violations (mITT population)

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

- Demographic and Baseline Characteristics: A summary of demographic and baseline characteristics including age, ethnicity, race, weight, height, and BMI is presented for the safety population in Table 28. The mean age of patients in this trial was 54.5 years (range 29 to 77 years) and the most patients were white (87.9%).

Table 28 Demographic Characteristics (Safety population)

Demographic Variable	Patients, N=149
Age (years)	
Mean (SD)	54.5 (10.1)
Median	55.0
Range	29 - 77
Ethnicity (N(%))	
Hispanic or Latino	11 (7.4)
Not Hispanic or Latino	138 (92.6)
Race, (N(%))	
White	131 (87.9)
Black or African American	15 (10.1)
American Indian	0
Asian	0
Native Hawaiian or Other Pacific Islander	0
Other*	3 (2.0)

Weight (kg)	
Mean (SD)	97.65 (14.73)
Median	97.10
Range	65.3 - 147.6
Height (cm)	
Mean (SD)	178.08 (6.53)
Median	177.80
Range	162.6 - 198.1
Body Mass Index (kg/m ²)	
Mean (SD)	30.61 (3.50)
Median	30.80
Range	22.1 - 41

*Other: one Asian Indian, one Arabic, and one mixed

- Diagnosis and history of T deficiency and prior hormone replacement therapy are presented in Table 29. The mean duration since diagnosis of T deficiency was 2.2 years (range 0 to 22 years), and the majority of patients had primary hypogonadism (70.5%, 105 patients). The majority of patients (65.8%, 98 patients) had previously taken a hormone replacement therapy for their T deficiency.

Table 29 Diagnosis and History of T Deficiency and Prior Hormone Replacement Therapy (Safety population)

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

- Measurement of Treatment Compliance: A summary of trial medication compliance by trial visit in the safety population is presented in Table 30. The majority of patients at each trial visits (Days 14, 35, 60, and 90) exhibited compliance in the 85 to 115% range (72.6, 67.1, 71.9 and 68.8% of patients, respectively).

Table 30 Number of Patients by % Compliance (Safety population)

	Number (%) of Patients N=149
Day 14, N	146
< 85%	37 (25.3)
≥85 and ≤115%	106 (72.6)

> 115%	3 (2.1)
Day 35, N	143
< 85%	42 (29.4)
≥ 85 and $\leq 115\%$	96 (67.1)
> 115%	5 (3.5)
Day 60, N	139
< 85%	32 (23.0)
≥ 85 and $\leq 115\%$	100 (71.9)
> 115%	7 (5.0)
Day 90, N	138
< 85%	39 (28.3)
≥ 85 and $\leq 115\%$	95 (68.8)
> 115%	4 (2.9)

- Summary of primary and secondary endpoints is provided in Table 31.
 - The predefined criteria for both primary and secondary endpoints were achieved.
 - Primary objective: The percentage of mITT patients achieving C_{avg} of total T in the normal range (300 - 1140 ng/dL) at Day 90 was 76.1%, with a lower bound of the 95% confidence limit of 69.0%.
 - Secondary objectives: The percentage of mITT patients achieving following C_{max} of total T at Day 90 were
 - 91.3% for $C_{max} \leq 1500$ ng/dL
 - 4.3% for $C_{max} \geq 1800$ and < 2500 ng/dL
 - 0% for $C_{max} \geq 2500$ ng/dL
 - Other populations analyzed (ITT, PP, and mPP) supported the efficacy conclusions from the primary patient population (mITT).

Table 31 Summary of Primary and Secondary Endpoints (mITT Population)

Primary Endpoint (C_{avg} of total T at Day 90)	
Mean (SD)	442.4 (177.7) ng/dL
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	76.1%, 105/138
95% CI	69.0 - 83.2%
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
% Patients with Values ≥ 1800 and < 2500 ng/dL, n/n	4.3%, 6/138
% Patients with Values ≥ 2500 ng/dL, n/n	0%, 0/138

Table 32 Summary of Primary and Secondary Endpoints (ITT Population)

Primary Endpoint (C_{avg} of total T at Day 90)	
Mean (SD)	442.4 (177.7) ng/dL
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	76.1%, 105/138
95% CI	69.0 - 83.2%
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
% Patients with Values ≥ 1800 and < 2500 ng/dL, n/n	4.3%, 6/138
% Patients with Values ≥ 2500 ng/dL, n/n	0%, 0/138

Table 33 Summary of Primary and Secondary Endpoints (PP Population)

Primary Endpoint (C_{avg} of total T at Day 90)	
Mean (SD)	482.54 (159.59)
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	88.6%, 31/35
95% CI	78.0 – 99.1%
Secondary Endpoints (C_{max} of total T at Day 90)	
Mean (SD)	952.3 (352.5)
% Patients with Values ≤ 1500 ng/dL, n/n	91.4%, 32/35
% Patients with Values ≥ 1800 and < 2500 ng/dL, n/n	5.7%, 2/35
% Patients with Values ≥ 2500 ng/dL, n/n	0

Table 34 Summary of Primary and Secondary Endpoints (mPP Population)

Primary Endpoint (C_{avg} of total T at Day 90)	
Mean (SD)	442.0 (163.3)
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	81.0%, 68/84
95% CI	72.6 – 89.3%
Secondary Endpoints (C_{max} of total T at Day 90)	
Mean (SD)	879.3 (371.3)
% Patients with Values ≤ 1500 ng/dL, n/n	91.7%, 77/84
% Patients with Values ≥ 1800 and < 2500 ng/dL, n/n	3.6%, 3/84
% Patients with Values ≥ 2500 ng/dL, n/n	0%, 0/84

- Primary Endpoint (C_{avg} at Day 90): In the mITT population, the mean (SD) $C_{avgO-24hr}$ was 442.41 (177.73) ng/dL and 76.1 % of patients had T concentrations within the predetermined range (300 – 1140 ng/dL) at Day 90. The lower bound of the 95% CI, 69.0% in the mITT population was above the predefined limit of 65%.

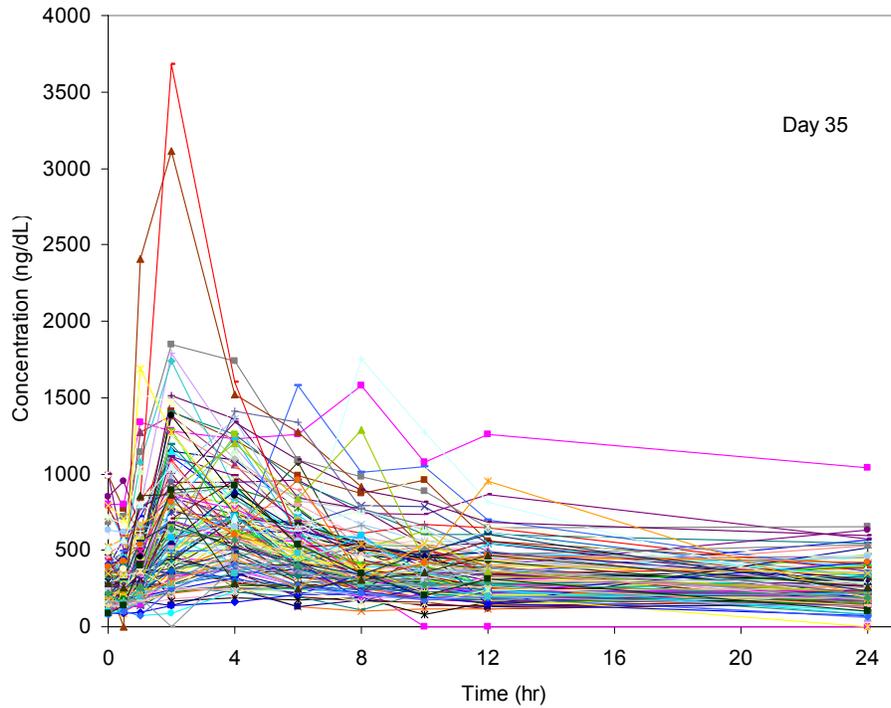


Figure 8 Individual Concentration-Time Profile of Total T at Day 35 (mITT population)

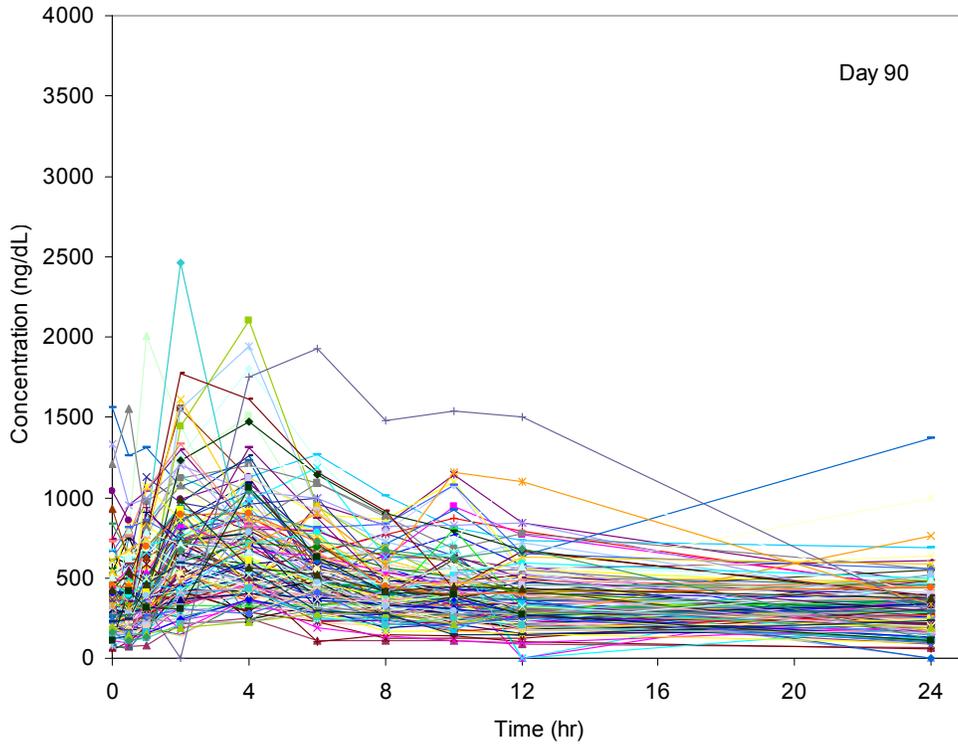


Figure 9 Individual Concentration-Time Profile of Total T at Day 90 (mITT population)

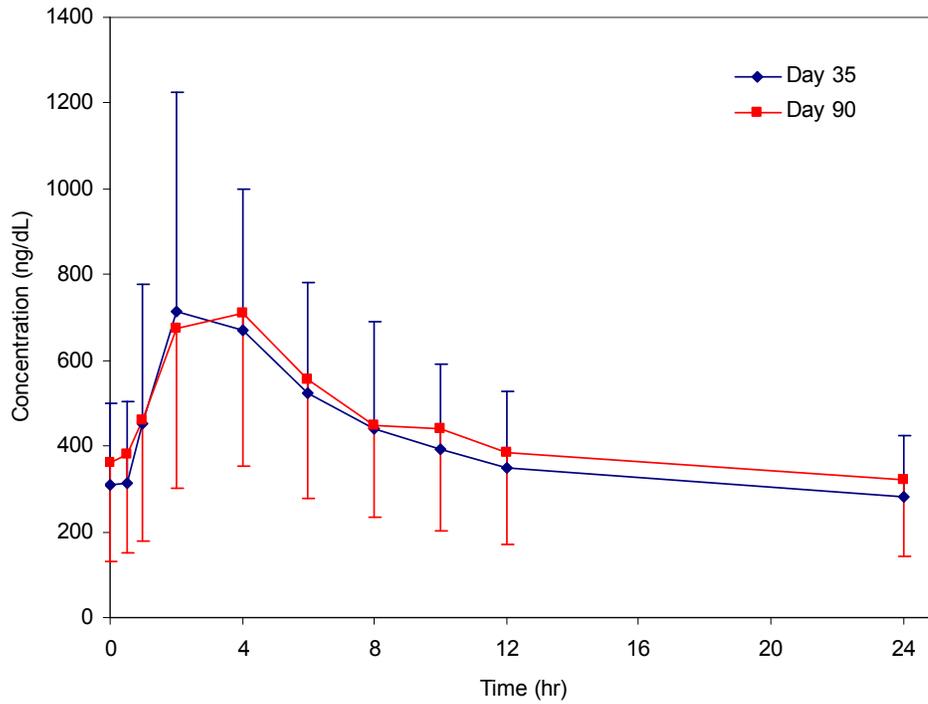


Figure 10 Mean (SD) Concentration-Time Profile of Total T at Days 35 and 90 (mITT Population)

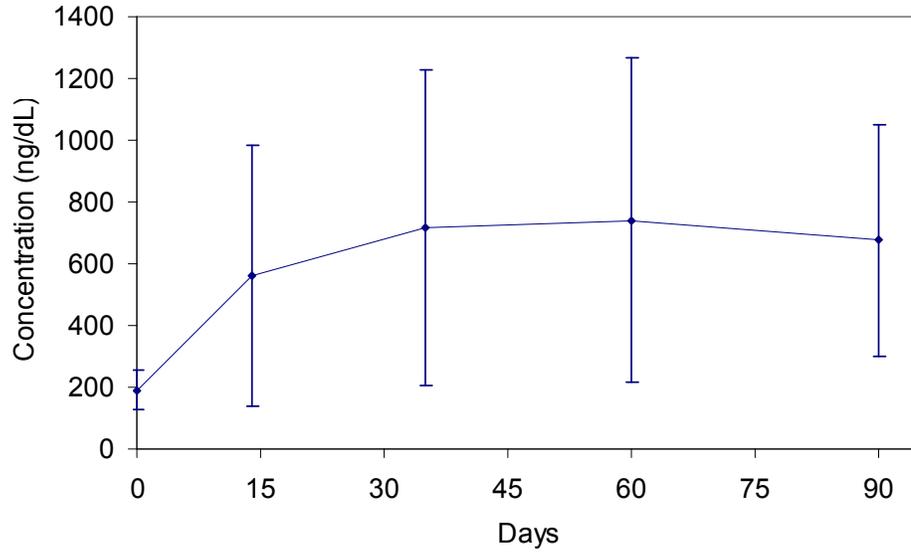


Figure 11 Mean (SD) C_{2h} of Total T at Days 14, 35, 60, and 90 (mITT Population)

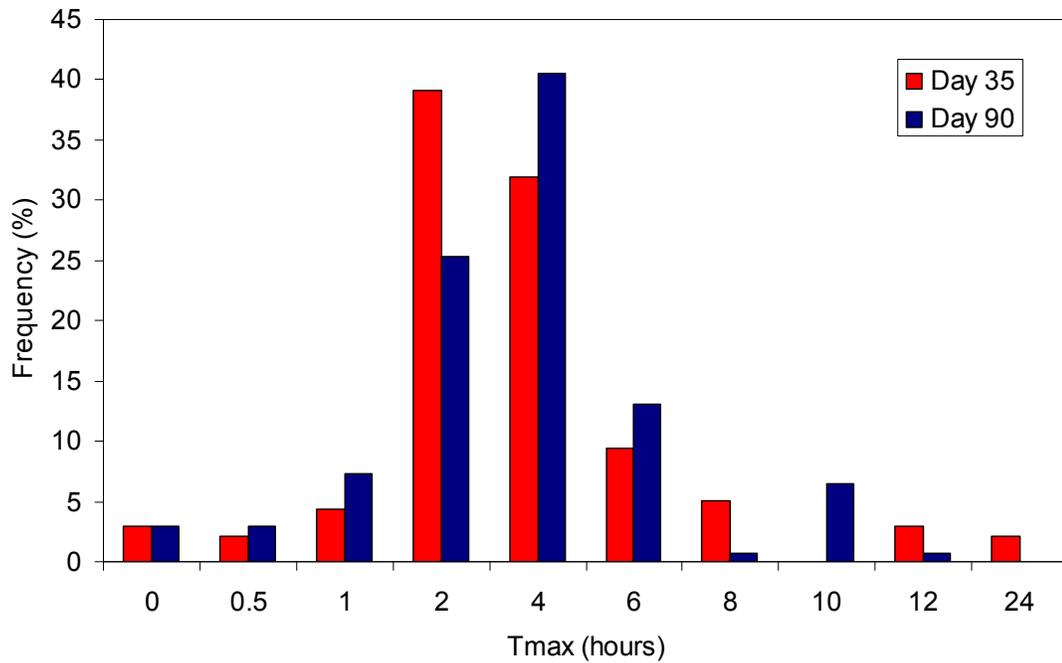


Figure 12 Frequency of T_{max} values for patients at Days 35 and 90 (mITT population)

- Time averaged serum T concentration by final dose at Day 90 is presented in Table 35. Mean values within the Day 90 dose groups are all similar with exception of the single patient at 10 mg. Mean C_{avg} of total T concentrations for each final dose level, with the exception of the 10 mg dose group, were within the 300 – 1140 ng/dL.

Table 35 Number of Patients and Pharmacokinetic Parameters (mean (SD)) of Total T by Dose at Days 0, 14, 35, 60, and 90

		10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	70 mg
Day 0 N=148	N	0	0	0	148 (100%)	0	0	0
	Baseline	-	-	-	213.4 (87.9)	-	-	-
Day 14 N=147	N	0	0	0	147 (100%)	0	0	0
	C _{2h} (ng/dL)	-	-	-	566.9 (430.0)	-	-	-
Day 35 N=143	N	0	1 (0.7%)	10 (7.0%)	56 (39.2%)	76 (53.1%)	0	0
	C _{2h} (ng/dL)	-	585.0 (0.0)	1081.7 (482.3)	851.8 (609.7)	602.5 (506.0)	-	-
	C _{avg} (ng/dL)	-	-	468.2 (179.9)	468.0 (260.7)	383.5 (168.3)	-	-
	C _{max} (ng/dL)	-	-	1098 (463.3)	1002.6 (595.0)	771.2 (512.8)	-	-
Day 60 N=140	N	0	6 (4.3%)	12 (8.6%)	39 (27.9%)	44 (31.4%)	39 (27.9%)	0
	C _{2h} (ng/dL)	-	755.7 (431.6)	911.7 (479.4)	958.79 (557.9)	683.6 (496.9)	504.8 (441.2)	-
Day 90 N=138	N	1 (0.7%)	7 (5.1%)	17 (12.3%)	30 (21.7%)	27 (19.6%)	31 (22.5%)	25 (18.1%)
	C _{2h} (ng/dL)	421.0 (0.0)	684.0 (379.3)	833.4 (517.6)	718.4 (386.6)	806.2 (383.1)	474.4 (240.9)	603.7 (285.8)
	C _{avg} (ng/dL)	230.8 (0.0)	411.0 (220.1)	403.2 (142.0)	442.3 (182.6)	497.0 (162.8)	453.5 (215.8)	413.8 (141.4)
	C _{max} (ng/dL)	587.0 (0.0)	869.7 (412.1)	905.9 (489.0)	874.6 (434.4)	998.6 (400.8)	815.4 (393.5)	746.7 (332.4)

Table 36 C_{avg} (ng/dL) of Total T at Days 35 and 90 (mITT Population)

	C_{avg} (ng/dL)
Day 35, N=138	
Mean (SD)	410.4 (163.9)
Median	389.6
Range	151.0 - 1201.6
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	73.2%, 101/138
95% CI for % Patients with Values ≥ 300 and ≤ 1140 ng/dL	65.8 - 80.6%
% Patients with Values < 300 ng/dL, n/n	26.1%, 36/138
% Patients with Values > 1140 ng/dL, n/n	0.7%, 1/138
Day 90, N=138	
Mean (SD)	442.4 (177.7)
Median	412.1
Range	107.2 - 1132.3
% Patients with Values ≥ 300 and ≤ 1140 ng/dL, n/n	76.1%, 105/138
95% CI for % Patients with Values ≥ 300 and ≤ 1140 ng/dL	69.0 - 83.2%
% Patients with Values < 300 ng/dL, n/n	23.9%, 33/138
% Patients with Values > 1140 ng/dL, n/n	0%, 0/138

Table 37 C_{avg} of Total T at Day 90 by Screening BMI (mITT Population)

Statistic	BMI			
	≥ 22 and < 25	≥ 25 and < 30	≥ 30 and < 35	≥ 35
N	8	48	77	5
Mean	457.4	430.9	432.3	684.1
SD	168.8	171.1	165.4	302.0
Median	450.4	423.5	384.4	644.0
Range	265.7 - 728.9	107.2 - 958.0	170.7 - 840.9	362.5 - 1132.3
% Patients with Values ≥ 300 and ≤ 1140 ng/dL	75.0%	77.1%	74.0%	100.0%
95% CI	45.0 - 100.0%	65.2 - 89.0%	64.2 - 83.8%	100 - 100%

Table 38 C_{avg} of Total T at Day 90 by Ethnicity (mITT Population)

Statistic	Hispanic or Latino	Not Hispanic or Latino
N	11	127
Mean	448.1	441.9
SD	184.8	177.9
Median	389.8	414.8

Range	265.7 - 810.3	107.2 - 1132.3
% Patients with Values ≥ 300 and ≤ 1140 ng/dL	72.7%	76.4%
95% CI	46.4 - 99.0	69.0 - 83.8%

Table 39 C_{avg} of Total T at Day 90 by Race (mITT Population)

Statistic	White	Black or African American	Other*
N	122	13	3
Mean	429.4	560.5	459.0
SD	167.9	242.7	62.2
Median	395.7	488.2	476.9
Range	107.2 - 958.0	264.8 - 1132.3	389.8 - 510.2
% Patients with Values ≥ 300 and ≤ 1140 ng/dL	73.8%	92.3%	100.0%
95% CI	66.0 - 81.6%	77.8 - 100.0%	100.0%

*Other: one Asian Indian, one Arabic, and one mixed

Table 40 BMI by Race (mITT Population)

Statistic	White	Black or African American	Other*
N	122	13	3
Mean	28.1	31.3	30.6
SD	2.7	5.2	3.3
Median	29.0	31.7	30.9
Range	25.0 - 30.2	23.9 - 41.5	22.1 - 40.8
% Patients with Values ≥ 300 and ≤ 1140 ng/dL	73.8%	92.3%	100.0%
95% CI	66.0 - 81.6%	77.8 - 100.0%	100.0%

Table 41 C_{avg} of Total T, DHT, and Free T (Days 35 and 90; mITT Population)

	Mean (SD)	
	Day 35	Day 90
Total T (ng/dL)	410.4 (163.9)	442.4 (177.7)
DHT (ng/dL)	69.3 (38.3)	71.5 (34.9)
Free T (pg/dL)	83.0 (40.7)	95.3 (48.9)

- Results for the secondary endpoints are summarized in Table 42 for the mITT population. Overall, 91.3% of patients had C_{max} values \leq 1500 ng/dL, 4.3% had C_{max} values within 1800 to 2500 ng/dL range, and there were no patients who had C_{max} values above 2500 ng/dL. These values met the pre-determined secondary endpoints.

Table 42 C_{max} of Total T at Days 35 and 90 (mITT Population)

c	C_{max} (ng/dL)
Day 35, N=138	
Mean (SD)	868.9 (494.8)
Median	753.5
Range	244.0 - 3680.0
% Patients with Values \leq 1500 ng/dL, n/n	92.0%, 127/138
% Patients with Values \geq 1800 and $<$ 2500 ng/dL, n/n	0.7%, 1/138
% Patients with Values \geq 2500 ng/dL, n/n	1.4, 2/138
Day 90, N=138	
Mean (SD)	863.9 (408.0)
Median	782.5
Range	250.0 - 2460.0
% Patients with Values \leq 1500 ng/dL, n/n	91.3%, 126/138
% Patients with Values \geq 1800 and $<$ 2500 ng/dL, n/n	4.3%, 6/138
% Patients with Values \geq 2500 ng/dL, n/n	0%, 0/138

Table 43 C_{max} of Total T at Day 90 by BMI (mITT Population)

Statistic	BMI			
	\geq 22 and $<$ 25	\geq 25 and $<$ 30	\geq 30 and $<$ 35	\geq 35
N	8	48	77	5
Mean	939.8	878.0	829.1	1143.0
SD	307.3	433.4	394.0	495.5
Median	920.5	810.5	727.0	987.0
Range	535.0 - 1510.0	250.0 - 2460.0	305.0 - 2100.0	632.0 - 1930.0
% Patients with Values \leq 1500 ng/dL	87.5%	91.7%	92.2%	80.0%
% Patients with Values \geq 1800 and $<$ 2500 ng/dL	0	4.2%	3.9%	20.0%
% Patients with Values \geq 2500 ng/dL	0	0	0	0

Table 44 C_{max} of Total T at Day 90 by Ethnicity (mITT Population)

Statistic	Hispanic or Latino	Not Hispanic or Latino
N	11	127
Mean	822.3	867.5
SD	310.8	416.1
Median	787.0	782.0
Range	492.0 - 1470.0	250.0 - 2460.0
% Patients with Values ≤ 1500 ng/dL	100.0%	90.6%
% Patients with Values ≥1800 and <2500 ng/dL	0	4.7%
% Patients with Values ≥2500 ng/dL	0	0

Table 45 C_{max} of Total T at Day 90 by Race (mITT Population)

Statistic	White	Black or African American	Other*
N	122	13	3
Mean	832.0	1018.9	1492.3
SD	370.4	506.8	866.8
Median	765.0	1080.0	1230.0
Range	250.0 - 2100.0	356.0 - 1944.0	787.0 - 2460.0
% Patients with Values ≤ 1500 ng/dL	92.6%	84.6%	66.7%
% Patients with Values ≥1800 and <2500 ng/dL	2.5%	15.4%	33.3%
% Patients with Values ≥2500 ng/dL	0	0	0

*Other: one Asian Indian, one Arabic, and one mixed

- Results for total T, DHT, ratio of DHT to total T, free T, SHBG, LH, FSH, ESTRADIOL, are summarized in Table 46. The SHBG concentration remained constant, with a slight reduction at Day 90. Both serum gonadotropins (LH and FSH) fell at Day 35 and 90, consistent with increased circulating T which would suppress LH and FSH secretion from the pituitary gland. Estradiol concentrations increased over time, consistent with aromatization of the exogenous T to its metabolite estradiol.

Table 46 Mean (SD) C_{2h} of Total T and other measures at Days 14, 35, 60, and 90 (mITT Population)

	Mean (SD)				
	Baseline	Day 14	Day 35	Day 60	Day 90
Total T (ng/dL)	190.2 (64.4)	562.0 (421.1)	715.5 (511.6)	741.4 (522.8)	675.2 (373.1)
DHT (ng/dL)	22.0 (7.6)	68.2 (40.6)	74.2 (42.3)	79.2 (47.8)	76.5 (41.8)
Ratio of DHT/Total T	0.13 (0.07)	0.15 (0.08)	0.17 (0.07)	0.14 (0.1)	0.17 (0.06)
Free T (pg/dL)	33.1 (16.0)	118.9 (112.1)	168.4 (176.4)	178.1 (160.2)	160.8 (118.3)
SHBG (nmol/L)	37.1 (20.3)	-	38.1 (21.3)	-	36.4 (16.0)
LH (mIU/mL)	5.5 (7.3)	-	2.84 (4.8)	-	2.6 (4.7)
FSH (mIU/mL)	10.5 (15.9)	-	5.4 (11.4)	-	4.1 (11.5)
Estradiol (ng/dL)	1.7 (0.8)	-	2.8 (1.5)	-	3.0 (1.7)

Abbreviations: T = testosterone; DHT = dihydrotestosterone; SHBG = sex hormone-binding globulin; LH = luteinizing hormone; FSH = follicle stimulating hormone; SD = standard deviation

4.2 DSI Site Inspection Request

NDA 21-463
Request for Biopharmaceutical Inspection
Page 1

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: July 9, 2009

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Hae-Young Ahn, Ph.D.
Deputy Director, Division of Clinical Pharmacology III
Office of Clinical Pharmacology

FROM: Jeannie Roule, Regulatory Health Project Manager
Division of Reproductive and Urologic Products

SUBJECT: Request for Biopharmaceutical Inspections
NDA 21-463
Testosterone 2% gel

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
FOR01C	<p>Panhandle Family Care Associates 4284 Kellson Ave., Research Department Marianna, FL 32446</p> <ul style="list-style-type: none">• Phone: 850-482-5802/2910• Principal investigator: Mark Akerson, MD <p>Quality of Life Medical & Research Center, 5350 Erickson Drive Tucson, AZ 85712</p> <ul style="list-style-type: none">• Phone: 520-733-2250• Principal investigator: John McGettigan, MD	(b) (4)

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **September 1, 2009**. We intend to issue an action letter on this application by **October 17, 2009**.

Should you require any additional information, please contact Jeannie Roule.

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

/s/

Hae-Young Ahn
7/9/2009 04:11:26 PM

4.3 DSI Site Inspection Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 8, 2009

TO: Scott E. Monroe, M.D.
Director
Division of Reproductive and Urologic Products (DRUP)

FROM: Carol M. Rivera-López, Ph.D.
Sean Y. Kassim, Ph.D.
Martin K. Yau, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. *Martin K. Yau 10/8/09*
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-463, FORTESTA™
(Testosterone) 2% Gel, sponsored by Endo
Pharmaceuticals*.

At the request of the Division of Reproductive and Urologic Products (DRUP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following multi-center study:

Study FOR01C

Title: "An open-label, phase III study of FORTIGEL (testosterone) 2% gel in hypogonadal males"

DRUP requested audit of the following clinical sites: Panhandle Family Care Associates, Research Department, Marianna, FL (site # 32) and Quality of Life Medical & Research Center, Tucson, AZ (site # 14). DRUP also requested audit of the analytical portion of the study, conducted at (b) (4)

Following the inspection at Quality of Life Medical & Research Center, Tucson, AZ (August 10-11, 2009), Form FDA 483 was not issued. At conclusion of the inspections at Panhandle Family Care Associates, Marianna, FL (September 8-16, 2009) and (b) (4) (August 31-September 3, 2009), Form FDA 483 was issued (Attachments 1 and 2, respectively). The evaluation of

* Effective 9/8/2009, previously ProStrakan, Inc.

the significant findings at all the inspected sites and their responses to the 483 observations dated September 21, 2009 (Panhandle Family Care Associates, Marianna, FL) and September 22, 2009 (b)(4) follows:

Quality of Life Medical & Research Center, Tucson, AZ (Clinical)

No significant observations were noted at this site.

Panhandle Family Care Associates, Marianna, FL (Clinical)

1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

1a. The FDA-1572, Statement of Investigator, failed to list 2 Sub-Investigators and their respective locations where the clinical study was conducted.

(b)(4)



According to Dr. Akerson's 483 response and an affidavit obtained by the FDA field investigator, Drs. (b)(4) were working at "satellite sites" technically under the supervision of Dr. Akerson, although he was apparently unaware of this arrangement. The (b)(4) representative requested Drs. Akerson and (b)(4) (the Sub-Investigator) to co-sign laboratory results (blood chemistry, serology, EKGs) from subjects that were seen at the satellite sites. However, when Dr. Akerson reviewed the source records, these co-signed laboratory results were missing and had been replaced with laboratory results apparently signed or initialed by only Dr. Akerson or (b)(4) (but were not their original signatures). See Attachment 3 for additional details.

1b. Four instances, in which adverse conditions were identified within the subjects' medical charts and not reported in the CRFs per the protocol.

Subject # 032-002

Subject # 032-007

Subject # 032-010

Subject # 032-050

1c. Two instances, in which concomitant medications were identified within the subjects' medical charts and not reported in the CRFs per the protocol.

Subject # 032-002

Subject # 032-010

1d. Four instances, in which the subjects' full medical history was not captured during screening and not reported on the CRFs per the protocol.

Subject # 032-007, Depression

Subject # 032-010, Sciatica

Subject # 032-014, Depression

Subject # 032-051, Mild Depression

1e. Three instances, in which subject inclusion/exclusion criteria was not met to enroll subjects per the protocol.

Subject # 032-014, did not comply with the 8 week washout period prior to enrollment for Depot Testosterone

Subject # 032-051, did not meet the required BMI, weight was changed on the CRF to meet inclusion

Subject # 032-050, was enrolled in 2 studies at the same site: Diabetes & Testosterone studies

Subject # 032-050, did not meet the required BMI, weight was changed in CRF to meet inclusion

All of the aforementioned observations should have been included in the case report forms (CRFs) and discussed in the clinical study report. Because subjects 032-014, 032-50 and 032-051 failed to meet inclusion/exclusion criteria, data from these subjects should be excluded from study evaluation.

2. Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

Specifically, the Principal Investigator (PI) failed to notify the IRB of a Significant Adverse Event for Subject # 032-042, which involved the subject being hospitalized.

3. Failure to report to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug.

Specifically, the Principal Investigator (PI) failed to notify the sponsor of a Significant Adverse Event for Subject # 032-042, which involved the subject being hospitalized.

It is objectionable that the firm did not report the adverse event (AE) to the IRB within an appropriate timeframe and to the sponsor. The firm needs to ensure that AEs are reported promptly and appropriately. The medical reviewer should evaluate the impact of this observation on safety of the drug.

(b) (4) **(Analytical)**

(b) (4) **Protocol: 100647)**

For the analysis of study samples, mass spectrometry (MS)-based assays were used for total testosterone (TT) and estradiol (E2). Ligand-based assays were used for dihydrotestosterone (DHT), free testosterone (Free T), sex hormone binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and prostate specific antigen (PSA).

1. Failure to demonstrate accuracy of the DHT RIA assay. Specifically, calibration standards were prepared in solvent

(b) (4) **as did for the quality control (QC) and subject serum samples. The concentrations extrapolated from the solvent based standard curve have not been shown to accurately represent the concentrations of DHT extracted from serum matrix.**

Solvent-based calibration standards were used to estimate study sample DHT concentrations without evaluating the effects of extraction and oxidation on analyte recovery. During the inspection, the firm did not provide evidence that calibrators prepared in solvent were equivalent to those prepared in serum matrix. In the firm's response (Attachment 4), samples measured with an LC/MS/MS based DHT assay are compared with measurements using the RIA assay. Although the firm suggests the methods successfully correlate, the data do not support this. Of the 100 accepted measurement comparisons, 41 differed by more than 20%. Additionally, the LC/MS/MS assay was not evaluated during the inspection so the accuracy of that method has not been verified. The firm should demonstrate the accuracy of the DHT RIA assay by comparing the results of QC samples back calculated from: (1) calibrators prepared in solvent and (2) calibrators prepared in serum (b) (4). The result of this experiment should be provided to DSI for evaluation.

The firm also committed to using the same matrix as study samples for prepared standards in future studies.

2. Failure to fully validate the assays for LH and PSA in that:

- 2a. Study sample values were reported above 0.01 ng/ml for PSA and 0.07 mIU/ml for LH. However, precision and accuracy was only demonstrated above 0.5 ng/ml for PSA and above 0.59 mIU/ml for LH.**

The PSA and LH assays were not evaluated below 0.5 ng/ml and 0.59 mIU/ml, respectively. Measurements below these levels cannot be assured. The firm's response contends the PSA and LH kit assays are FDA approved and therefore the manufacturer's detection claims can be used. It should be noted that the intended use of these kit assays is for in vitro diagnostic clinical evaluations in conjunction with other correlative clinical data. When data generated by a bioanalytical method are used to support approval of a new drug application, the precision and accuracy of the bioanalytical method should be demonstrated on site. DSI recognizes that very low measurements of PSA and LH do not significantly impact this study and the firm only reported 120 PSA measurements below 0.5 ng/ml and 72 LH measurements below 0.59 mIU/ml.

- 2b. The PSA assay was not evaluated for freeze/thaw stability or matrix effects.**

The firm did not establish the effect of freeze/thaw on site. However, the firm's response cites the manufacturer's assertion that repeated freeze/thaw cycles do not affect PSA levels.

- 2c. Commercial products were used for the preparation of the calibrators and QCs for the LH and PSA assays. The firm did not obtain certification of all these reagents' nominal concentrations.**

The firm obtained sufficient certification for the calibrators and QCs used in the kit assays following the inspection and provided in their response. Additionally, the firm committed to requesting these COAs in the future.

- 3. Failure to accurately demonstrate the freeze/thaw (F/T) and frozen storage stability of all analytes at -20°C. Specifically, standard curves used in the stability experiments were not freshly prepared but generated from frozen calibration standards prepared previously and stored at -20°C. The F/T test stability samples were compared to frozen reference samples stored at -70°C.**

In their written response, the firm acknowledged that results of the F/T and long term frozen storage stability experiments were obtained using standard curves generated from frozen calibration standards. As the frozen calibration standards might deteriorate along with the stability test samples over the stability testing period, the stability data of these experiments might not be accurate. The firm, however, explained that they had compared freshly prepared lots with older lots of working standards and claimed that the results showed the working standards were stable.

DSI is still concerned about accuracy of the F/T and long term frozen storage stability data because the data to demonstrate stability of the working standards were not included in the firm's response. Furthermore, it is not clear if the working standards were prepared in solvent or in human serum. DSI is of the opinion that the firm should repeat these stability studies using freshly prepared standard curves.

4. Audit trail of the 'Analyst' software version 1.41 was not turned on for all the validation and analytical runs. There are no audit trail records available for inspection.

During the inspection, the firm was not able to provide the audit trail records for the 'Analyst' software used in the total testosterone (TT) and estradiol (E2) assays. In their response, the firm now claims that the audit trail feature of the Analyst software was actually not disabled and therefore the silent audit trail function was active during the study. An example of the 'Analyst' audit trail for the E2 assay generated on August 10 2007 was provided in the response along with another example of audit trail generated more recently on September 21, 2009. No example of audit trails was provided for the TT assay over the period when the study analytical runs were conducted (i.e., August 2007 to April 2008). To confirm that the 'Analyst' software audit trails are available, the firm's should provide the audit trail records of 50 of the analytical runs for the TT assay to DSI for review (see Attachment 5).

5. Many analytical runs had > 33.3% of the total QCs and/or > 50% at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations. These analytical runs are listed below.

TT: Runs 07082326, 07091884, 07100939, 07102375, 07111226,
07121194, 07121813, 07122124, 08011580, 08013029, 08020134,

08020240, 08021584, 08021481, 08022208, 08022310, 08022717,
08030637, 08030638, 08031255, 08032804, 08041447

DHT: Runs 07081669, 07081875, 07090693, 07092815, 07101134,
07110773, 07111277, 07120499, 07122121, 08012164, 08020496,
08021313, 08021722, 08022128, 08030747, 08031154, 08031759,
08031860, 08032062, 08032264, 08033174

Free T: Runs 07080666, 07081175, 07081579, 07081681, 07082394,
07090515, 07091225, 07091532, 07091634, 07092141, 07093054,
07100257, 07100359, 07100462, 07101376, 07101579, 07102088,
07110210, 07111227, 07111636, 07113063, 07122811, 08011137,
08011955, 08012671, 08012977, 08020286, 08020801, 08021308,
08021309, 08021410, 08022326, 08022732, 08030952

E2: Runs 07081963, 07090487, 07090993, 07091404, 07092014,
07100238, 07100340, 07100546, 07100954, 07101261, 07101366,
07101467, 07101569, 07101875, 07101977, 07102283, 07102386,
07102901, 07103105, 07110209, 07110716, 07110920, 07111225,
07111635, 07112039, 07112141, 07120765, 07120766, 07121882,
08010809, 08011116, 08011927, 08021375, 08022695, 08022803,
08030107, 08030413, 08031428, 08032240

FSH: Runs 07080752, 07080954, 07081256, 07081458, 07081660,
07082366, 07082769, 07082870, 07083072, 07091181, 07091383,
07091484, 07092089, 07092190, 07092291, 07092896, 07100198,
07100301, 07101110, 07101412, 07103026, 07110128, 07110229,
07110330, 07110531, 07110632, 07111036, 07111641, 07111943,
07112753, 07120560, 07120762, 07121369, 07121470, 07121571,
07121772, 07122176, 07122377, 07122982, 08010384, 08011091,
08011094, 08011195, 08011396, 08011599, 08011601, 08011704,
08012107, 08012309, 08012511, 08012713, 08012914, 08013016,
08013117, 08020118, 08020219, 08020420, 08020521, 08020622,
08020926, 08021430, 08021833, 08022237, 08022742, 08030145,
08030751, 08032165, 08032366, 08032567, 08033071

The firm used the Westgard rules (see Attachment 4, Firm response to 483 Item 5) to accept or reject analytical runs. They did not use the run acceptance criteria listed in the 'FDA Guidance for Industry - Bioanalytical Method Validation'. During the inspection, the firm was requested to re-calculate the QC results in each run using criteria listed in the FDA Guidance (i.e., reject a run when > 33.3% of total # of QCs and/or > 50% of QCs at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations). Many runs (see listing above) failed the run acceptance criteria used in the FDA Guidance. It is important to note that, in all runs, the firm also included other clinical

samples not related to the study. A list of subjects that were included in the failed runs is provided in Attachments 6 and 7. Attachment 6 shows study samples that were included in the TT runs. Attachment 7 includes subject samples sorted by run for other analytes.

- 6. Failure to reject analytical runs when < 75% of calibration standards in a standard curve failed to meet the acceptance criteria (< 15% or < 20% (LLOQ) deviation from nominal values or mean pooled QC concentrations). In many of these runs listed below, majority of the calibration standards either failed near the beginning or near the end of the runs suggesting possible drift in the system during the run. These runs were accepted by deleting the failed standard curve. For example:**

TT: Runs 07091372, 07102786, 07111740, 07112146, 08030228

E2: Runs 07090286, 07090487, 07090689, 07090791, 07092013, 07092014, 08022695

In their response, the firm explained that failed standards in the above runs were deactivated by analysts due to acquisition errors, poor internal standard recoveries, and pipetting errors. Additionally, QC data which were scattered throughout the runs showed that there were no unacceptable drifts in these runs. The firm also agrees to clarify their SOPs regarding standard curve acceptance for the TT and E2 methods.

- 7. The incurred sample reproducibility (ISR) of the LC/MS/MS method for TT was not evaluated. TT concentrations determined by this method were used to calculate the primary (Cavg 0-24 hr at Day 90) and secondary efficacy endpoints (Cmax at Day 90) for the study.**

Although the FOR01C study is not a bioequivalence study, the TT data was used to calculate the Cavg (primary) and Cmax (secondary) endpoints. Therefore, the firm should have demonstrated that the TT assay is reproducible when incurred samples are re-assayed. In their response, the firm plans to establish an SOP to describe ISR testing and expect it to be implemented by the end of October, 2009.

- 8. Failure to adequately monitor SHBG assay performance in that human serum lots 424 and 440 (used as quality controls) were used past their expiration dates.**

QC samples for the SHBG assay were prepared using pooled commercial human serum. During the audit, we noticed that human

serum lots 424 and 440 were used as quality controls past their expiration dates. An examination of runs with expired QCs showed each of these runs also included adequate number of valid QCs at the low, medium and high concentration levels, and exclusion of the expired QCs did not change any runs from meeting the run acceptance criteria. Therefore, this oversight had no impact on study data integrity. However, the firm needs to improve their practices to avoid this from happening in future studies. In their response, the firm provided a copy of a system that has been implemented (September, 2008) for monthly review of all quality control lots to ensure that QC pools are not used past their expiration dates.

Conclusions:

Following evaluation of the above findings, DSI recommends the following:

- Data from the subjects listed in Attachment 6 should be omitted from data evaluation. The review division should consider if subjects with high number of failed samples be entirely removed (see (b) (4) 483 Item 5).
- The DHT measurements are not acceptable at this time. The firm should provide data to demonstrate that solvent calibrators used in the DHT RIA are equivalent to serum-based calibrators, and did not affect accuracy of data generated by this assay (see (b) (4) 483 Item 1).
- PSA measurements <0.5 ng/ml should be considered BLOQ. The remaining measurements can be accepted for review (see (b) (4) 483 Item 2a).
- LH measurements <0.59 mIU/ml cannot be assured and should be considered BLOQ (see (b) (4) 483 Item 2a).
- The accuracy of the F/T and long term frozen storage stability data is questionable, as freshly prepared standard curves were not used in these stability experiments. The response provided by the firm is not adequate. The firm should repeat the F/T and long term frozen storage stability studies of all the analytes using freshly prepared standard curves (see discussion under (b) (4) 483 Item 3).
- To confirm that the 'Analyst' software audit trails are available, the firm should provide the audit trail

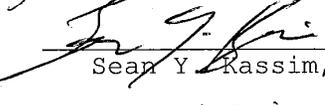
records of the analytical runs in Attachment 5 to DSI for review (see (b) (4) 483 Item 4).

- Panhandle Family Care Associates enrolled subjects that did not meet the study inclusion/exclusion criteria. DSI recommends that data from subjects 032-014, 032-051, and 032-050 be excluded from study evaluation (see Panhandle 483 Item 1c).
- Panhandle Family Care Associates failed to report all adverse conditions within four subjects' medical chart in the CRFs; failed to capture full medical history of four subjects during screening and not reported them on the CRFs; did not report the SAE (Subject # 032-042) to the sponsor and promptly to the IRB. The medical reviewer should evaluate any impact of these findings on the safety evaluation of FORTESTA™ (see Panhandle 483 Items 1b, 1d, 1e).

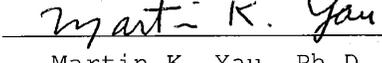
After you have reviewed this transmittal memo, please append it to the original NDA submission.



Carol M. Rivera-Lopez, Ph.D.



Sean Y. Kassim, Ph.D.



Martin K. Yau, Ph.D.

Final Classifications:

NAI - Quality of Life Medical & Research Center, Tucson, AZ

FEI: 3007816296

OAI - Panhandle Family Care Associates, Marianna, FL

FEI: 3007728352

VAI - (b) (4)

FEI: (b) (4)

cc:

DSI/GLPBB/Yau/Kassim/Rivera-Lopez/CF
OCP/DCP3/Kim
OND/DRUP/Roule
HFR-PA2540/Chavez
HFR-SE2580/Gilbert/Torres/Sinninger
Draft: CRL, SYK 10/5/09
Edit: MKY 10/6/09
DSI: 5985
O:\BIOEQUIV\EIRCOVER\21463.pro.testo.doc
FACTS: 1073647

Email:

DSI/CDER DSI PM TRACK

32 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CAROL M RIVERA-LOPEZ

10/08/2009

Dr. Yau, acting for Dr. Viswanathan, signed the paper copy on 10/8/09. Originals available on request.

4.4 Cover Sheet and OCP Filing

Memorandum for resubmission

Clinical Pharmacology

NDA: 21-463
Compound: Fortesta (pending, testosterone (T) gel) 2% (called "Fortesta" hereafter)
Sponsor: Strakan

Date: 05/14/2009
Reviewer: Hyunjin Kim, Pharm.D., M.S.

Background:

The following INDs are related to this submission:

- IND 76,634: Protocol FOR01C: An open label phase 3 study of Fortesta T gel 2% in hypogonadal males –protocol was accepted by the Division of Reproductive and Urologic Products (DRUP) on August 23, 2007
- IND (b) (4) evaluation of CP601B (T) gel in hypogonadal males – IND was withdrawn on January 17, 2006

Cellegy Pharmaceuticals, the previous sponsor of Fortesta, submitted IND (b) (4) on August 24, 1998. Subsequently, NDA 21-463 was filed on June 3, 2002 under section 505(b)(2) with a phase 3 trial, T 00-02-01. NDA 21-463 received Not Approvable (NA) action on July 3, 2003 for the following deficiencies:

1. There is insufficient information to establish that the high supraphysiologic daily C_{max} serum T 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 T C_{max} values between 1500 and 1800, 14% had values between 1800 and 2500, and 6% had values greater than 2500 ng/dl.
2. There is insufficient information provided to demonstrate that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological T levels.

In order to address these deficiencies, the division requested the sponsor to conduct clinical trial(s) using lower doses of Fortesta or another T gel formulation and demonstrate that physiologic levels of T can be attained while avoiding high supraphysiologic C_{max} levels of serum T. In addition, a safety update from all non-clinical and clinical studies of Fortesta was requested.

Subsequently, Cellegy Pharmaceuticals submitted a special protocol assessment (SPA)

for protocol CP601B 04-02-01 entitled, "A Phase 3 Study of Fortesta T Gel 2% in Hypogonadal Males." The following endpoints of the trial were agreed upon between the sponsor and the division:

- The time averaged serum total testosterone (Cavg 0-24 hr) will be between 300 and 1140 ng/dL in > 75% participants on Study day 90±3 (lower bound of the 95% CI not less than 65%).
- On study day 90±3 the maximum serum total testosterone (Cmax) will be < 1500 ng/dL in > 85% of participants, the Cmax will be between 1,800 and 2,500 ng/dL in < 5% participants, and the Cmax will be > 2500 ng/dL in none of the participants.

Reviewer's comment: The above endpoints were evaluated in FOR01C.

However, the sponsor did not initiate the study but withdrew IND (b) (4) on January 17, 2006.

In November 2006, NDA 21-463 was transferred from Cellegy Pharmaceuticals to Strakan Pharmaceuticals Limited, a division of ProStrakan Limited. On Feb 21, 2007, Strakan Pharmaceuticals submitted an SPA request for a revised phase 3 protocol "An Open Label Phase 3 Study of Fortesta T Gel 2% in Hypogonadal Males." Subsequently, Strakan completed a phase 3 study, FOR01C, under IND 76,634 to demonstrate that "Fortesta can be dose adjusted without achieving supraphysiologic T concentrations".

Resubmission (Comparison with previous pivotal phase 3 study, T 00-02-01):

To address the deficiencies listed in the NA letter dated July 3, 2003, the sponsor submitted the study result of FOR01C. This study employed the lower doses of Fortesta with the same formulation (CP601B) used in the phase 3 clinical trial, T 00-02-01.

- Dosage comparison
 - T 00-02-01 (submitted under original NDA 21-463 in 2002)
 - Start with 60 mg
 - Dose can be modified either to 40 or 80 mg or the dose remains unchanged
 - Dosage adjustment based on a 24 hr total T concentration time profile obtained following 14 days of continuous treatment:
 - FOR01C (pivotal phase 3 trial in the current resubmission)
 - Start with 40 mg
 - Dose can be modified from 10 to 70 mg by a magnitude of 10 mg per each of three dose adjustments during the trial
 - Dosage adjustment based on total T concentration obtained at two hours (C2) after study drug application on Days 14, 35, and 60.

The following table contains the protocol / report numbers of the clinical trial related to the current resubmission:

Table 1. Protocol and report numbers for the clinical studies

Study Description	Phase	Protocol Number	Report Number	Date Submitted to FDA
Phase I/II studies				
Dose ranging study	I/II	T 98-02-01	T 98-03-01	31 May 2002
Transfer of testosterone	I/II	T 01-02-02	T 01-03-02	30 Jan 2003
Skin irritation	I/II	T 00-02-09	T 00-03-09	31 May 2002
Effect of showering	II	T 00-02-03	T 00-03-03	31 May 2002
Application site area	II	T 00-02-07	T 00-03-07	31 May 2002
Application site selection	II	T 00-02-08	T 00-03-08	31 May 2002
Phase III studies				
Pivotal study	III	FOR01C	FOR01C	See Mod 5
6-month study	III	T 00-02-01	T 00-03-01	03 Oct 2002
Extension to 6-month study	III	T 00-02E-01	T 00-03E-01	17 Jan 2006
Rotation study	III	T 02-02-01	T 02-03-01	12 Jan 2004
Extension to rotation study	III	T 02-02E-01	T 02-03E-01	17 Jan 2006

The following clinical pharmacology comments were conveyed to the sponsor on June 27, 2008 prior to the pre-NDA meeting with the sponsor. Subsequently, the sponsor cancelled the meeting and resubmitted NDA 21-463 with the results from trial FOR01C.

- Confirm that the formulation and manufacturing sites of Fortesta employed in the study FOR01C are the same as that of the to-be-marketed Fortesta.
The formulation used in the trial FOR01C is the same as the to-be-marketed formulation. Sponsor submitted the in vitro release data because there was a manufacturing site change.
- Provide subgroup analyses of testosterone concentrations based on Body Mass Index (BMI, e.g. 22-25, 25-30, and 30-35) and ethnicity.
- Submit the following information in table format:
 - Serum total testosterone concentration vs. body weight
 - Testosterone concentration at 2-hour post dose at each visit for each individual

The information requested above was submitted in this current resubmission.

Division of Scientific Investigations (DSI) Site Inspection Request:

A request for inspection of the clinical and analytical sites of study FOR01C was made to the DSI on July 9, 2009 (DARRTS).

Information Request from the Office of Clinical Pharmacology:

None

Hyunjin Kim, Pharm.D., M.S.

Date

Myong-Jin Kim, Pharm.D., Team Leader

Date

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

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

/s/

HYUNJIN KIM
10/14/2009

MYONG JIN KIM
10/14/2009

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
<i>NDA Number</i>	21-463	<i>Brand Name</i>	FORTIGEL 2% Gel
<i>OCPB Division (I, II, III)</i>	DPE II (HFD 870)	<i>Generic Name</i>	Testosterone
<i>Medical Division</i>	DRUDP (HFD 580)	<i>Drug Class</i>	Hormone replacement
<i>OCPB Reviewer</i>	Dhruba J. Chatterjee, Ph.D.	<i>Indication(s)</i>	Hypogonadism
<i>OCPB Team Leader</i>	Ameeta Parekh, Ph.D.	<i>Dosage Form</i>	Gel
<i>OCPB Pharmacometrics Reviewer</i>	He Sun, Ph.D.	<i>Dosing Regimen</i>	Once Daily
<i>Date of Submission</i>	6/3/2002	<i>Route of Administration</i>	Topical
<i>Estimated Due Date of OCPB Review</i>	3/3/2003	<i>Sponsor</i>	Cellegy
<i>PDUFA Due Date</i>	4/3/2003	<i>Priority Classification</i>	3S
<i>Division Due Date</i>	3/15/2003		

<u>Clin. Pharm. and Biopharm. Information</u>	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
	"X" if included at filing			
STUDY TYPE		7		
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
body wt.				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	7			
Filability and QBR comments	"X" if yes	Comments		
	"X" if yes			
Application filable ?	X			
Comments sent to firm?				
QBR questions (key issues to be considered)	How does the PK of T relate to normal T levels? What is the frequency of outliers (high/low T values)? How does demographics affect PK? Is there an <i>in vitro</i> release test method (CMC was notified at filing)?			
Other comments or information not included above	For Sponsor: 1) Please provide electronic copies of the Clin. Pharm & Biopharmaceutics studies to the NDA. 2) Please provide a separate analysis of the C _{max} with respect to frequency and magnitude from the Phase 3 pivotal clinical trial.			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-463, HFD-850 (Electronic Entry or Lee), HFD-580(Deguia F), HFD-870(Parekh A, Malinowski M, Hunt J), CDR (Murphy B)

Clinical Pharmacology & Biopharmaceutics Review

NDA:	21- 463
Product Trade Name:	FORTIGEL 2%
Active Ingredient/s:	Testosterone
Indication:	Testosterone Replacement Therapy (in hypogonadal men)
Submission Date:	6/3/2002
Sponsor:	Cellegy Pharmaceuticals Inc.
Type of Submission:	Original NDA, 3S
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.
Pharmacometrics:	He Sun, Ph.D.

OCPB Briefing (on 6/27/03) attended by L. Lesko, H. Malinowski, J. Hunt, SM Huang, P Lee, P Hinderling, D. Bashaw, M. Mehta, H. Sun, A. Parekh, D. Griebel, G. Benson, G. Fang, V. Jarugula, S. Oriz, L. Kenna, J. Lau, S. AlHabet, DJ. Chatterjee and Summer Interns

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Synopsis

The subject (drug product) of this submission, is a 2% hydroalcoholic gel formulation of testosterone (composition in Table 1) that the hypogonadal male applies once daily on the skin of his inner thighs (b) (4). The alcohols in the gel facilitates the transfer of the highly lipophilic testosterone (T), across the stratum corneum and into deeper layers of the skin and associated fatty tissue structures. From this tissue reservoir, testosterone diffuses into the capillaries perfusing the region and enters the general systemic circulation.

In this NDA, the sponsor has submitted one pivotal clinical trial involving 200 hypogonadal men on FORTIGEL (60 mg T daily starting) with possible dose adjustment to 40 mg or 80 mg on day 28 (based on T PK profile on Day 14). This study had no placebo or active control arms. Additionally, 5 *in vivo* and 1 *in vitro* studies relevant to clinical pharmacology and biopharmaceutics were conducted in support of this NDA.

For the Phase III pivotal clinical trial, the primary efficacy was based upon C_{avg} and C_{min} within normal T serum levels (300 – 1140 ng/dL) at day 182 (6-month). The safety assessments were based upon the C_{max} for individual patients. Although the study was not specifically designed to determine clinical safety parameters, investigation into the changes in patient hematocrits (Hct), high-density lipoprotein (HDL), low-density lipoprotein (LDL), prostrate specific antigen (PSA) and hemoglobin (Hb) were made. Exposure-response analysis correlating exposure parameters to the above clinical markers were also performed.

Recommendation

This NDA is not acceptable to OCPB based on the fact that the high maximal (C_{max}) serum T levels (observed in a significant number of patients) make this product supra-physiologic in terms of T replacement, and may not mimic the normal endogenous profile of serum T. Safety of such chronic elevated serum T levels have not been established yet. Moreover, within the scope of the limited Phase III clinical trial, elevated serum T levels could be correlated to a decrease in HDL and increasing hematocrits.

The sponsor is recommended to re-evaluate the current formulation in terms of the proportions of the penetration enhancers. The penetration enhancers may have been the cause of high exposures seen with this product.

Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

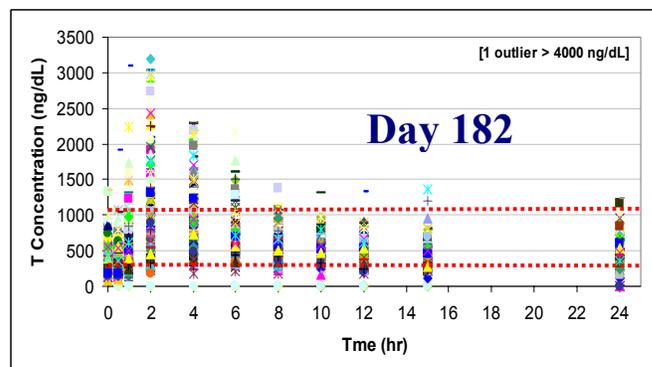
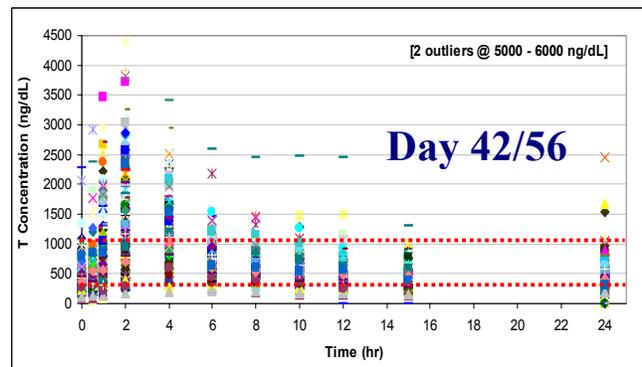
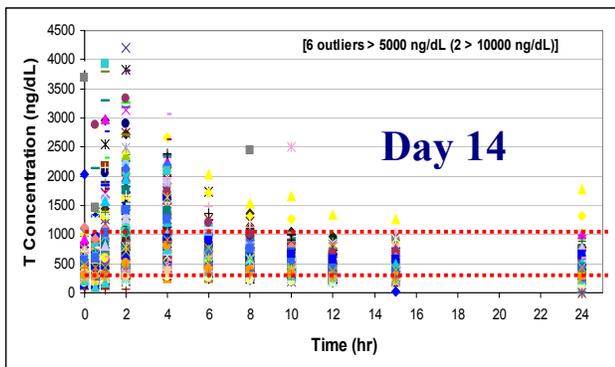
- Based on results from *in vitro* formulation screening studies, sponsor may not have optimized the formulation prior to conducting clinical studies, since the final formulation used showed considerably high serum T levels even at steady state (eg. high C_{max}).
- The Phase II dose finding study was complicated in design with a very small number of patients on each dose/regimen. It appears that the sponsor did not optimize the dose based on all essential PK information resulting in selection of a sub-optimal dose/regimen or formulation, or both.

High Exposure

Based on results of the Phase III study, this product was found to result in supraphysiologic serum T levels (as below): [Note: Normal serum total T levels are 300 – 1140 ng/dL; see Table I on next page.]

- On Day 42/56 (1 month at final dosing regimen), 5 patients out of 165 (or 3%) had C_{avg} values above 1140 ng/dL, and 1 among them had C_{avg} values > 1700 ng/dL.
- On Day 42/56, 23 patients out of 165 (or 14%) had C_{max} values between 1500 - 1800 ng/dL; 28 (or 17%) had the C_{max} values between 1800 – 2500 ng/dL and 26 of them (16%) had the C_{max} values between 2500 – 5311 ng/dL (3 values were > 4000).
- On Day 182 (6 months on final dose), no patient had C_{avg} values > 1140 ng/dL.
- On Day 182, 13 patients out of 147 (or 9%) had C_{max} values between 1500 - 1800 ng/dL; 20 (14%) had C_{max} values between 1800 – 2500 ng/dL; 9 (6%) had C_{max} values > 2500 ng/mL (with 1 value > 4000 ng/mL).
- Sponsor was alerted regarding the concerns of high exposures achieved with this product at different stages of drug development.

Note: All high T serum levels may potentially remain elevated at least 2-4 hours (daily). Please see graphs below:

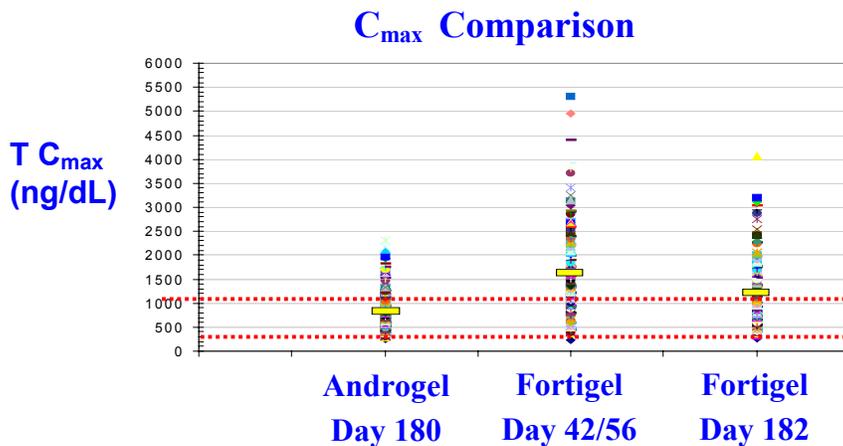


T-replacement levels as compared to other Commercial T-Gels

Table I: Comparison of PK Outliers in T- Gels at Steady State*

Product	C _{max} between 1200 – 1500 ng/dL	C _{max} between 1500 – 1800 ng/dL	C _{max} between 1800 – 2500 ng/dL	C _{max} > 2500 ng/dL	C _{avg} > 1100 ng/dL	N
Fortigel	20 (14%)	13 (9%)	20 (14%)	9 (6%)	0 (0%)	147
AndroGel	14 (9%)	11 (7%)	7 (5%)	0 (0%)	5 (3%)	151
Testim	4 (2%)	4 (2%)	4 (2%)	0 (0%)	2 (1%)	162

* 6 months post treatment for Fortigel & AndroGel, 3 months for Testim.



Compared to other commercially available products for the same indication, C_{max} of T from FORTIGEL is significantly higher.

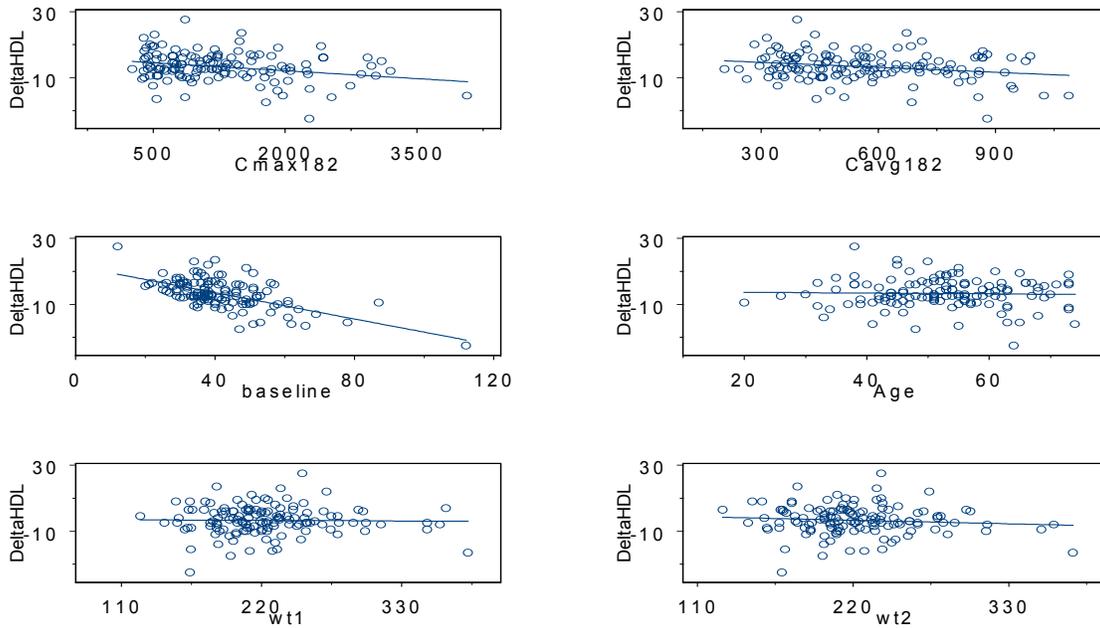
Exposure – Response

LDL, PSA, Hb vs. T serum concentrations

- No definitive and/or significant relationships between the change of patient LDL, PSA and Hb vs. T serum concentrations were observed on day 42/65 and day 182.

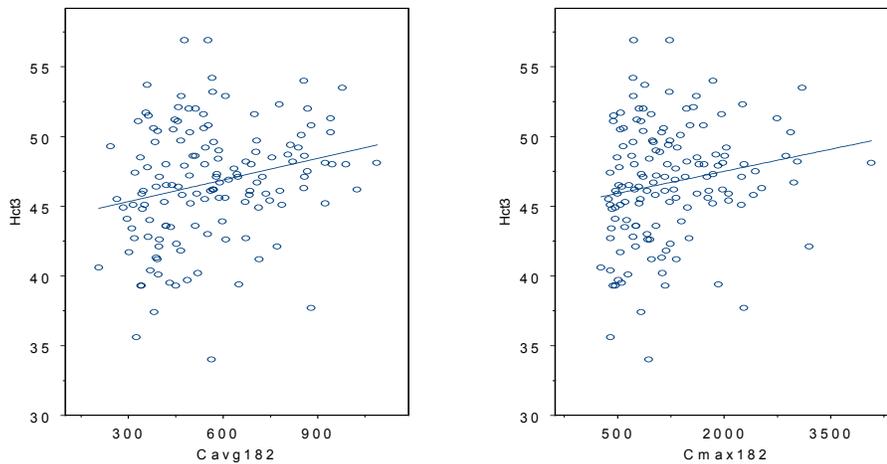
HDL

- A negative correlation between Δ HDL (defined as HDL on measurement day – baseline HDL) and T concentrations (average or maximum) was apparent, which indicated a general decrease in HDL values corresponding to an increase in T concentrations.
- Further regression analyses show that Δ HDL is significant in patients with higher HDL baseline values ($p < 0.0001$). Statistically, body weight (at 6 months) was also affected drop in HDL.



Hct

- There was a statistically significant trend of increasing Hct values with either and increase in serum T C_{avg} ($p = 0.0042$) or C_{max} ($p = 0.0303$). This trend, however, was not observed for the change (Δ) in Hct.



Intrinsic Factors

- Higher body weight resulted in marginal reduction in T-exposure on day 14. However, on adjustment of the dose, that relationship weakened.
- T exposure did not seem to correlate with age (> 55 years or < 55 years).

- All races were not studied adequately in the Phase III study, hence no race effect was determinable.
- T replacement in patients with very low endogenous serum T levels were fairly similar to that in the general group.

Miscellaneous

- Surface area of gel application (200 – 800 cm²) did not have a significant effect on T exposure. This possible deviation from principles of transdermal delivery may be due to another factor (eg. penetration enhancement) predominating over surface area in affecting drug transport.
- Application of gel in the inner thighs or abdomen resulted in comparable T exposure. Exposure following application on the upper arm was very high. Hence application of gel to the upper arm should be avoided.
- The potential for T transfer to female partners may be avoided by use of occlusive clothing (eg. shorts) on the area where gel is applied.
- Showering 2 hours post application of the gel did not affect the exposure of T from this product.

Labeling

The proposed Labeling for this product has currently not been corrected/modified and is pending final decision of action on this NDA by the Clinical Review Team.

Background

Questions addressed in this section:

- **What is male hypogonadism and what are its causes?**
- **What is the main goal for treatment?**
- **What are the “normal levels” of Testosterone for replacement therapy?**
- **What are the available treatments?**
- **Are the studies done in support of this NDA acceptable?**

Male hypogonadism is a result of inadequate production of testosterone (T) by the Leydig cells of the testes. The etiology of hypogonadism may be primary or secondary. Primary hypogonadism is associated with testicular dysfunction (affecting about 5% of the male population). Less common causes are Klinefelter's syndrome, bilateral cryptorchidism, myotonic dystrophy, polyglandular failure, gonadal dysgenesis and vanishing testis syndrome. Autoimmune testicular failure, testicular irradiation, surgical or blunt trauma, testicular torsion and infections may also cause T deficiency. Secondary hypogonadism is due to inadequate stimulation of a potentially normal testis. The causes may be of glandular (hypothalamic or pituitary) origin including GnRH deficiency, isolated FSH or LH deficiencies, acquired gonadotropin deficiencies, prolactin secreting tumors, severe systemic illness, uremia and hemochromatosis.

Treatment of hypogonadal men with an exogenous supplementary source of testosterone has a long clinical history. Appropriate doses of exogenous testosterone have long been known to return circulating testosterone to the levels observed in healthy eugonadal men. Restoration of testosterone levels to within the normal range for eugonadal men using exogenous testosterone is associated with increased libido, restoration of nitrogen balance, increased lean body mass, normalization of bone mineral density, decreased HDL cholesterol levels, body hair growth, virilization and mood enhancement.

A product designed for “testosterone replacement” should be able to (i) achieve serum testosterone levels that lie within normal values AND (ii) maintain/sustain such serum values for the entire treatment period. In general, the “normal” range of T serum level is assumed to be between 300 ng/dL – 1000 ng/dL. Currently marketed drug products indicated for the replacement of testosterone in males with a deficiency or absence of testosterone include oral, intramuscular and transdermal (for scrotal and non-scrotal application) of testosterone or testosterone esters. Similar transdermal gel formulations (ANDROGEL and TESTIM) are also available.

Testosterone is primarily cleared by metabolic processes in the liver, skin, genital and other tissues. The metabolism includes conversion to dihydrotestosterone (DHT, an active metabolite and considered by some a more potent androgen) by 5α -reductases in the skin and liver and to estradiol by aromatase complexes found in the liver, fat and testes. Administered testosterone is recovered in the urine as androsterone, etiocholanolone and glucuronide and sulfate conjugates of androstanediol and estrogens.

The subject (drug product) of this submission, is a 2% hydroalcoholic gel formulation of testosterone (composition in Table 1) that the hypogonadal male applies once daily on the skin of his thighs and

(b) (4). Alcohol in the gel facilitates the transfer of the highly lipophilic testosterone (T), across the stratum corneum and into deeper layers of the skin and associated fatty tissue structures. From this tissue reservoir, testosterone diffuses into the capillaries perfusing the region and enters the general systemic circulation.

In this NDA, the sponsor has submitted one pivotal clinical trial involving 200 hypogonadal men on FORTIGEL (60 mg T daily starting) with possible dose adjustment to 40 mg or 80 mg on day 28 (based on T PK profile on Day 14). As a result, patients on the 60 mg dose completed 1-month on this final dose on day 42, while patients adjusted to the 40 or 80 mg doses completed their 1-month on the final doses on day 56. This study had no placebo or active control arms. Additionally, 5 *in vivo* and 1 *in vitro* studies relevant to clinical pharmacology and biopharmaceutics were also conducted in support of this NDA.

Table 1. Description & Composition of FORTIGEL™

FORTIGEL is a clear, colorless hydroalcoholic gel containing 2% testosterone in a hydroalcoholic/propylene glycol gel base for topical application (intended for transdermal delivery). The final product is supplied in a 60-gm metered dose pump comprising of (b) (4) canister and a fixed volume pumping mechanism. Composition of the formulation is as follows:

Component	% w/w
Testosterone, USP	2.00
Propylene Glycol, USP	(b) (4)
Ethyl Alcohol, (b) (4)	(b) (4)
Isopropyl Alcohol, USP	(b) (4)
Oleic Acid, NF	(b) (4)
Carbomer 1382	(b) (4)
Trolamine, NF	(b) (4)
Butylated Hydroxytoluene, NF	(b) (4)
Purified Water, USP	(b) (4)

Each full depression of the canister piston of the container transfers 0.5 g of gel or 10 mg of T.

Clinical Pharmacology

Q. What clinical pharmacology studies have been conducted in support of this application and how do they relate to safety/efficacy?

For this indication of replacement of testosterone, the primary clinical end point was based on clinical pharmacology. Hence, in addition to the pivotal clinical trial in 200 hypogonadal men with primary end points based on clinical pharmacology, the sponsor presented results of 1 *in vitro* and 6 *in vivo* studies relevant to clinical pharmacology and biopharmaceutics in support of this NDA.

Each of the studies are reviewed individually below:

1. Study 0205-T-001 (*in vitro*)

In vitro skin permeation study across human cadaver skin is an established procedure performed routinely during formulation development of transdermal systems. Similarly, the sponsor conducted such studies to finalize a formulation for the T-gel that would be further tested in clinical trials.

Among many of the formulations (about 60) that were screened *in vitro*, this report focuses on the 3 final formulations. (i) CP 601B – final formulation (used in all clinical studies except Phase II Study T-98-03-01), (ii) CP 601 – same as 601B but a slight difference [REDACTED]^{(b) (4)} and (iii) 1086-87-1 – formulation similar to the final with the exception of the [REDACTED]^{(b) (4)}.

Methodology: The equipment consisted of a flow-through cell apparatus, each cell having a donor and a receptor compartment. Skin samples (mostly from Caucasian and Hispanic females) were clamped between the donor and the receptor compartments, and the buffer in the receptor compartment was serially sampled. The amount of T in each sampled was analyzed. The flux ($\mu\text{g}/\text{cm}^2/\text{hr}$) and the cumulative amount of T permeated in 24 hours were computed.

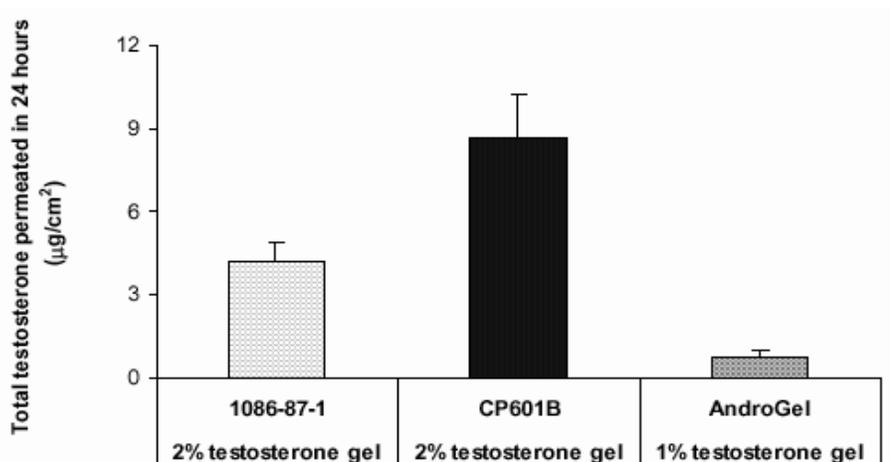
Objectives: The *in vitro* studies were designed to broadly determine the following: a) identify a final formulation, b) study the effect of minor formulation changes to T-flux, c) effect of washing, d) potential of T transfer and e) effect of application surface area on delivery.

Note: The *in vitro* studies were conducted thoroughly and the results and data analysis is insightful. However, points c, d and e above will not be discussed in details as those issues were addressed later with individual clinical studies (please see the individual study reviews following this report).

Results:

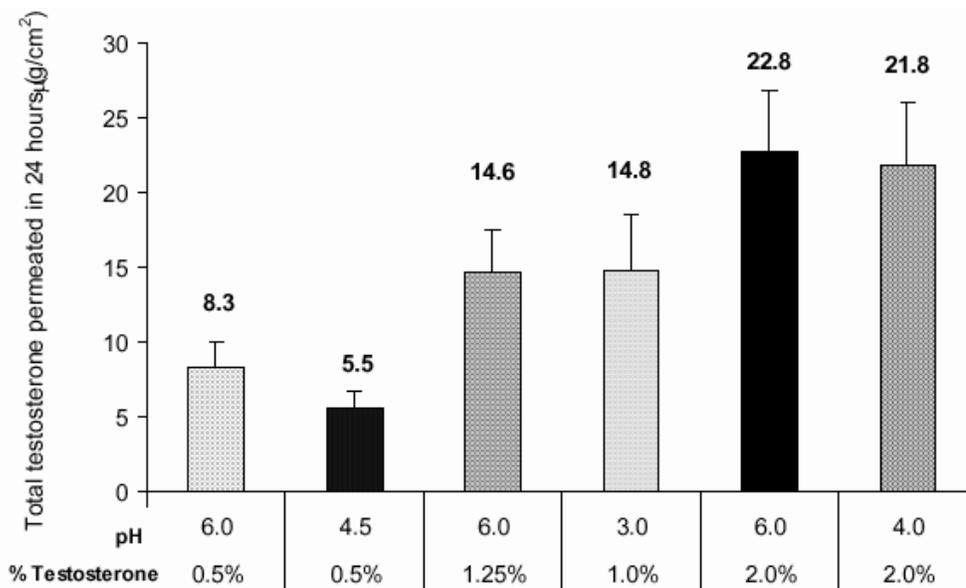
a) Identifying a final, workable formulation: Sponsor compared two developed formulations with AndroGel[®] 1%, a hydroalcoholic transdermal gel that does not contain oleic acid (commercially available for the same indication). The following figure shows a comparative capability of each of these formulations to deliver T.

Figure 1. Total amount of testosterone delivered through human skin in 24 hours following application of various testosterone gels (Donor #86, Study ST0115, mean \pm s.d., n=4-6).



Sponsor's choice was CP601B above. Additionally, sponsor studied the effect of pH of the system to maximize the flux, as below.

Figure 2. CP601 development: Total amount of testosterone permeated through human skin following a single application (about 8 mg/cm²) of prototype gel formulations of various testosterone concentrations and pHs (mean \pm s.d., n= 5-6, Donor #24, Study ST98023).



According to the sponsor, based on several other studies (results not shown in the report) and the results of rabbit irritation and guinea pig hypersensitivity studies, the formulation CP 601B (with 2.5 % oleic acid) adjusted to pH = 6.0 was then selected for further testing in clinical trials.

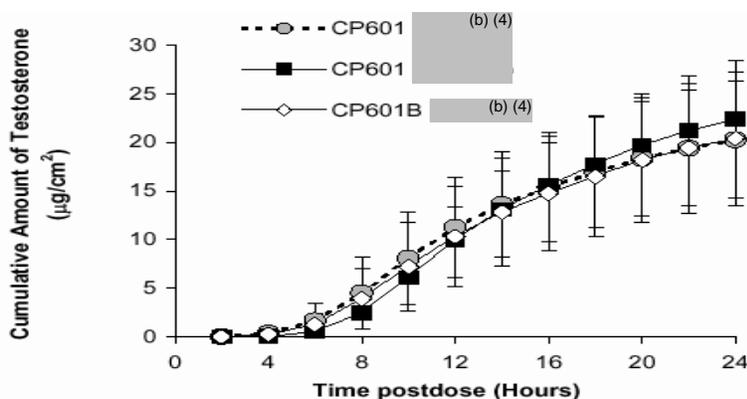
Reviewer's Comments

- It is not apparently clear on what criteria sponsor made a final choice of CP601B @ pH 6.0.
- It is clear from the above *in vitro* results that the mean flux of CP601B is ≈ 9 fold higher than the marketed AndroGel[®] 1% using the skin of the same donor. With adjustment of the pH to 6.0, this flux multiple probably have been even higher than 9.
- According to to this reviewer, a better choice may have been formulation 1086-87-1. Although the flux from this formulation was still 4 fold higher compared to AndroGel[®] 1%, at least the absence of oleic acid may have been desirable from an adverse event point of view (b) (4) and this was observed in the clinical trials with FORTIGEL)
- Prior to availability of clinical data, the choice of the above formulation would certainly point towards supra-physiological levels of T in the serum following use of CP601B @ pH=6.0 at comparable doses (if AndroGel[®] 1% is considered to provide physiological levels).
- It is to be noted that higher than desired levels of T was observed in several of the clinical trials in terms of both C_{max} and C_{avg} (please see individual study reports later).

b) Effect of minor changes in formulation: Sponsor made some minor changes in formulation during the course of the development. *In vitro* permeation studies were conducted to determine the effect of minor formulation changes on the delivery of testosterone from CP601 and CP601B gels. Specifically, the effect of changing (b) (4) in the CP601 2% testosterone formulation was studied. CP601 was originally formulated with (b) (4). CP601B was formulated with (b) (4). *In vitro* permeation studies were conducted to determine if the change had an impact on the delivery of testosterone *in vitro*.

Figure 3 below compares the cumulative amount of testosterone permeated through human skin as a function of time following application of a single dose of CP601 gel ((b) (4) lot# 1601981), CP601 gel ((b) (4) lot# 8H044A – used in clinical study T 98-02-01) and CP601B gel ((b) (4), Lot # 0C046A, used in clinical study T 00-02-01). All three formulations provided statistically identical profiles of testosterone permeation through human skin. Since the viscosity of CP601 is (b) (4) and that of CP601B is (b) (4), sponsor suggests that a change of viscosity within this range is not likely to impact testosterone delivery (*in vitro*).

Figure 3. Cumulative amount of testosterone permeated through human skin following a single application of CP601 or CP601B 2% testosterone gels (means \pm s.d., n= 7-8, (Donor #60, Study ST0015).



Reviewer's Comments

- Minor formulations changes (as described above) did not have appreciable changes in T permeation profile.
- Sponsor calculated *in vitro* bioavailability (based on amount applied vs. cumulative amount permeated in 24 hours) from all the donors and obtained a mean \pm s.d. of $14 \pm 5\%$. Historically, transdermal T Gels are known to have an *in vivo* BA of $\approx 10\%$.

2. Study T98-02-01 (Phase II - Dose Finding)

This was to be an open-label, randomized, six-treatment regimen, three-period (phase), three-way crossover matrix type study conducted at two sites. It ended with a 7th dosing regimen. Formulation used in this study was CP 601 (minor difference with the final formulation as mentioned previously).

Eighteen subjects enrolled in the study (six subjects were to participate in three treatment regimens). Each subject was randomly assigned to three Treatment Phases (I, II, and III) of testosterone gel administration. During each treatment phase, the subject was to follow one of six treatment regimens (Regimens A through F). In all treatment regimens (as below), testosterone gel was applied as 1 gram per 100 cm² surface area of skin. Sixteen patients completed the study.

- Regimen A, 1 g of 2% T gel (20 mg testosterone) was applied q.d. to the same site on the upper arm.
- Regimen B, 1 g of 1% T gel (10 mg testosterone) was applied q.d. to the same site on the upper arm.
- Regimen C, 1 g of 2% T gel (20 mg testosterone) was applied q.d. to the same site on the upper arm on Study Days 1, 3, 5, and 7 and to the same site on the outer thigh on Study Days 2, 4, and 6.
- Regimen D, 1 g of 1% T gel (10 mg testosterone) was applied q.d. to the same site on the upper arm on Study Days 1, 3, 5, and 7 and to the same site on the outer thigh on Study Days 2, 4, and 6.
- Regimen E, 1 g of 2% T gel (20 mg testosterone) was applied b.i.d. to the same site on the outer thigh in the morning and the same site on the upper arm in the evening (total daily dose 40 mg T).
- Regimen F, 1 g of 1% T gel (10 mg testosterone) was applied b.i.d. to the same site on the outer thigh in the morning and the same site on the upper arm in the evening (total daily dose 20 mg T).
- During Treatment Phase IV, in Regimen G, 1.5 g of 2% testosterone gel (30 mg T) was applied q.d. to a 150 cm² area of skin at the same site on each outer thigh (total daily dose 60 mg testosterone).

The order of treatment regimens was to be randomized, with a minimum three-day drug washout period between treatment phases. On Study Days 1 and 7 of Treatment Phase I, II, and III (Regimen A through F) and on Study Day 7 of Treatment Phase IV (Regimen G), venous blood samples were obtained before and at specified times following the morning testosterone gel administration to assay serum concentrations of testosterone. On Days 3 and 5, venous blood samples were obtained before (and additionally 1.5 hours after, in Treatment Regimen G) testosterone gel administration for assay of serum testosterone concentrations.

Results:

[Note: Of particular interest are PK parameters C_{avg} , C_{min} and C_{max} . While the former two are generally used for efficacy analysis in Phase III trials (C_{avg} and C_{min} within physiologic range, i.e. for this 300 – 1140 ng/dL for total T in this NDA), the latter is a critical factor for safety evaluations. Since C_{min} may fall just below 300 ng/dL at one time point (or may be an analytical aberration), maintaining C_{avg} (a reflection of the whole profile) within the normal range is critical for evidence of efficacy.]

Table 2A: Summary Statistics for C_{avg} on Study Days 1 and 7 (Study T 98-02-01)

		Treatment Regimen						
		A	B	C	D	E	F	G
Day 1	N	8	7	8	8	9	8	nd
	Mean (ng/dL)	360	219	385	300	352	246	nd
	SD	165	114	153	159	104	101	nd
	Median (ng/dL)	329	272	374	285	342	220	nd
	Range (ng/dL)	208-746	36-311	195-644	135-583	196-545	120-405	nd
Day 7	N	8	7	8	8	9	8	6
	Mean (ng/dL)	413	294	338	360	448	401	652
	SD	208	148	127	317	135	182	198
	Median (ng/dL)	377	264	325	264	436	351	596
	Range (ng/dL)	192-766	43-506	206-601	91-1098	272-680	210-787	434-918
	P-value ^a	0.085	0.798	0.605	0.823	0.063	0.087	<0.001

KEY: N = number of subjects; nd = not determined; SD = standard deviation

^a One-sided p-value testing that the mean is >300 ng/dL, based on ANOVA for Treatments Regimens A through F, and on normal approximation for Treatment Regimen G.

Table 2B: Summary Statistics for C_{min} on Study Days 1 and 7 (Study T 98-02-01)

		Treatment Regimens						
		A	B	C	D	E	F	G
Day 1	N	8	7	8	8	9	8	nd
	Mean (ng/dL)	185	156	155	166	173	145	nd
	SD	74	92	70	81	73	75	nd
	Median (ng/dL)	190	193	150	176	192	141	nd
	Range (ng/dL)	25-275	25-235	25-239	25-273	63-302	25-273	nd
Day 7	N	8	7	8	8	9	8	6
	Mean (ng/dL)	217	182	172	187	246	247	383
	SD	72	124	46	111	96	100	163
	Median (ng/dL)	227	172	171	168	275	203	343
	Range (ng/dL)	124-312	25-326	72-220	25-353	115-385	141-443	199-645

KEY: N = number of subjects; nd = not determined; SD = standard deviation

Table 2C: Summary Statistics for C_{max} on Study Days 1 and 7 (Study T 98-02-01)

		Treatment Regimen						
		A	B	C	D	E	F	G
Day 1	N	8	7	8	8	9	8	nd
	Mean (ng/dL)	951	366	1276	906	592	392	nd
	SD	638	128	1402	1169	259	179	nd
	Median (ng/dL)	805	427	625	448	552	337	nd
	Range (ng/dL)	252-1850	113-480	302-3743	177-3696	346-1206	209-745	nd
Day 7	N	8	7	8	8	9	8	6
	Mean (ng/dL)	1537	783	1209	632	817	683	1654
	SD	1554	581	1311	598	411	302	1138
	Median (ng/dL)	813	611	526	477	684	628	1237
	Range (ng/dL)	332-4897	76-1736	266-3558	149-2047	481-1830	333-1294	895-3910

KEY: N = number of subjects; nd = not determined; SD = standard deviation

Reviewer’s Comments:

- This was a complicated study design. The sponsor wished to accumulate a lot of information on 3 different doses, 2 different regimens (QD mornings or BID morning/evening) and on two different application sites, yet with only 18 patients (16 of whom had their data analyzed). Hence, interpretation of the data is complicated.
- The 7th treatment arm G with a larger single dose of T was added later in this study when the sponsor believed that the other 6 treatments might not be replacing T adequately.
- Within the large variability observed (across groups), a linear increase in exposure (C_{avg}) with dose was observed in this study (plot not shown here).
- While discussing C_{avg} and C_{min} , let us **focus on Day 7**, since by day 7 most of the regimens achieved steady state (as it appears from pre-dose levels on days 1, 3, 5 and 7).

C_{avg} and C_{max} : As is observed in Table 2A above, mean C_{avg} was within the normal range (albeit low) for 5 of the 6 treatment arms A – F. In all those 5 arms, the C_{max} values were above the high normal (in some cases, well above).

On examining individual PK parameters (table not presented in this review), note following:

For C_{avg} : Treatment A had 5 of 8 patients, Treatment E – 8 of 9 and Treatment F – 6 of 8 patients within normal range on Day 7.

For C_{max} , Treatment A – 2 values > 2500 ng/dL, Treatment C – 3 values > 3000 ng/dL, Treatment D – 1 value > 2000 ng/dL, Treatment E – 1 value > 1800 ng/dL (also see table below).

Table 3: C_{avg} on Study Day 7 by Treatment Regimen: Comparison with 300 ng/dL (Study T 98-02-01)

	Treatment Regimen						
	A	B	C	D	E	F	G
N	8	7	8	8	9	8	6
C_{avg} Mean (ng/dL)	413	294	338	360	448	401	652
C_{avg} SD	208	148	127	317	135	182	198
P-value ^a	0.115	0.838	0.662	0.857	0.098	0.123	<0.001
N (%) with C_{avg} >300 ng/dL	5 (62.5)	3 (42.9)	4 (50.0)	3 (37.5)	8 (88.9)	6 (75.0)	6 (100.0)
Subjects with C_{avg} >300 ng/dL ^b	70.6	48.5	61.7	57.5	86.5	71.0	96.3

KEY: N = number of subjects; SD = standard deviation

^a One-sided p-value testing that the mean is >300 ng/dL, based on ANOVA for Treatment Regimens A through F, and on normal approximation for Treatment Regimen G.

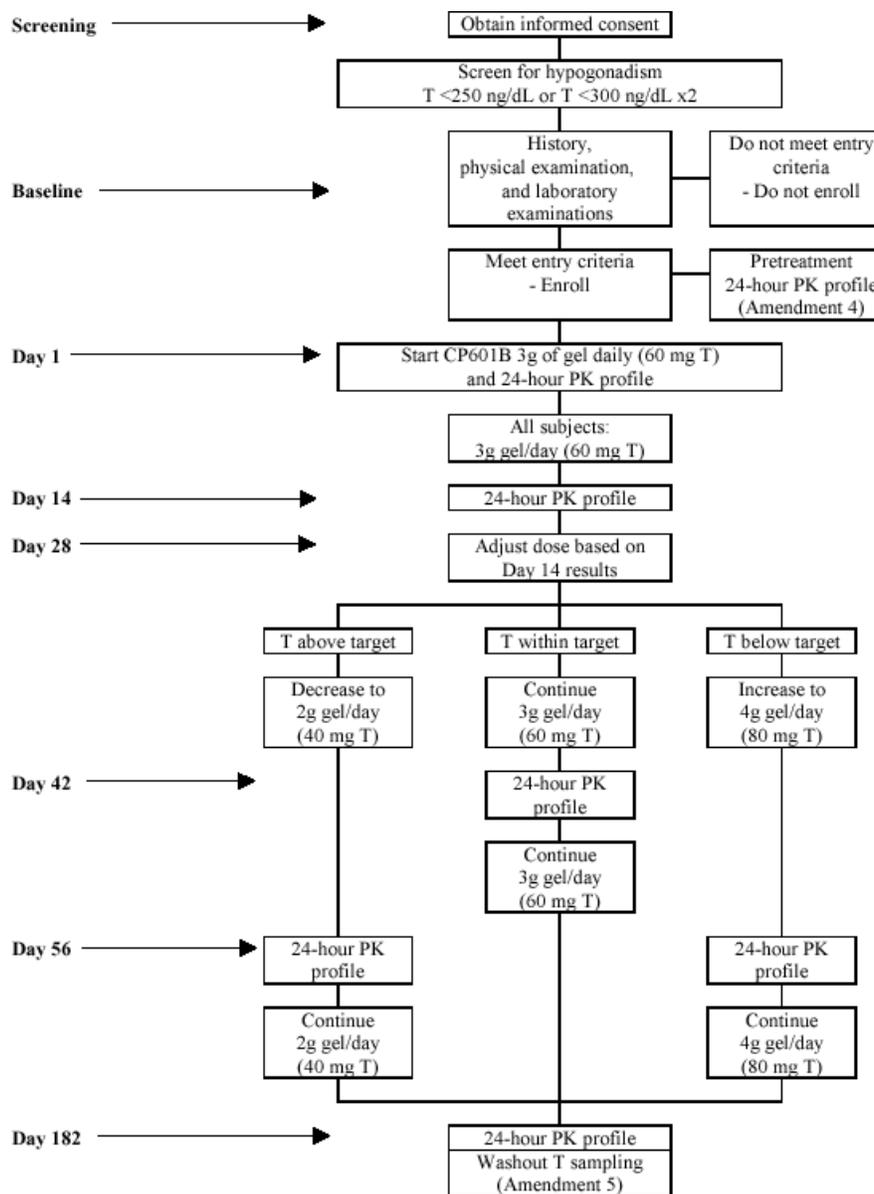
^b Percentile of normally distributed population above 300 ng/dL as predicted from observed Mean and SD.

Considering the low number of patients per arm, it is not clear why sponsor added a higher dose arm (G) without further investigating some of the above regimens (A – F). It appears that sponsor considered the achievement of C_{avg} and C_{min} within normal range the sole criteria for dose selection, with almost no regard for relatively high C_{max} values. [Note: C_{min} values fell below the low normal level, and the sponsor weighed C_{min} and C_{avg} equally.]

- For Treatment G, **all** (6 of 6) the C_{avg} values were within the normal range (with 2 of them above 800 ng/dL). However, 2 of the 4 higher-than-range C_{max} values were 1668 and 3910 ng/dL.
- Individual PK profiles were *not* presented in this study report. Hence, analysis on the nature of the PK profile and time below C_{min} or above C_{max} could not be determined.
- Based on this and the previous *in vitro* study conclusions, this reviewer believes that the sponsor did not suitably optimize formulations and/or determine lowest effective dose/regimen prior to Phase III.

3. Study T 00-02-01 (Pivotal Phase III Safety/Efficacy Trail – one Phase III study)

Methodology/Study Design (Flow Chart):



All subjects were to begin the study at a dose of 3g of CP601B (60 mg testosterone applied to skin) daily. The gel was applied once daily, in the morning only, after the one shower or bath allowed each day. The skin at the application site was to be completely dry before application of the gel. Half of the dose (1.5g gel, containing 30 mg testosterone) was to be rubbed gently into the skin over an area of approximately 150 cm² on one anteromedial thigh using a single finger. The second half of the dose was then to be applied to a 150 cm² area of skin on the contralateral thigh. For those subjects enrolled after Amendment 1, the application area could be moved to different sites on the anteromedial thighs (except the lateral thighs, and avoiding areas in contact with the scrotum) in an attempt to diminish the potential of irritation from using the same site daily. The subject was to wash his hands with soap and hot water after applying the gel. A 24-hour pharmacokinetic profile was to be obtained after application

of the first dose and at Day 14. The subject was to return to the study site at Day 28, when the results of the Day 14 pharmacokinetic studies were available. The testosterone dose could be modified at that time as follows:

- If the minimum serum concentration (C_{\min}) of testosterone measured in the Day 14 samples was <300 ng/dL and the maximum serum concentration (C_{\max}) was <1000 ng/dL, the subject's dose was to be increased to 4g gel (80 mg testosterone applied to the skin) daily. The dose was to be administered as two applications of 2g gel (40 mg T) on 200 cm² areas of skin on each anteromedial thigh (note: each pump of the canister equals 10 mg of T).
- If C_{\min} was >400 ng/dL and C_{\max} was >1000 ng/dL, the dose was to be decreased to 2g gel (40 mg testosterone applied to the skin) daily, administered as two applications of 1g gel (20 mg T) on 100 cm² areas of skin on each anteromedial thigh.
- If C_{\min} was >300 ng/dL and C_{\max} was <1140 ng/dL, the dose was to be maintained at 3g gel (60 mg testosterone applied to the skin) daily.
- If the testosterone concentrations did not meet any of the above criteria, a sponsor-appointed Medical Monitor was to make a decision about the dose adjustment.
- The subject was to continue once-daily application of the dose assigned at the Day 28 visit for the remainder of the study.

The **primary efficacy** endpoint was defined as the proportion of subjects with both total T C_{avg} and C_{\min} within physiological range (PR) of 300 –1140 ng/dL on Day 42/56. Additionally, there were three secondary endpoints:

- The proportion of subjects with C_{avg} within the PR on Day 42/56,
- The proportion of subjects with both C_{avg} and C_{\min} within the PR on Day 182, and
- The proportion of subjects with C_{avg} within the PR on Day 182.

Since the final dose (40, 60 or 80 mg) was decided based on a day 14 PK profile and the dose was adjusted on day 28, this review will focus on PK parameters only on Day 42/56 (after 28 days of dosing with final regimen) and Day 182 (after 6 months of dosing with final regimen).

A number of other analyses were also defined in the statistical plan, whose results are also reported:

- Analysis of the proportion of subjects with C_{avg} within the PR and other concentrations >300 ng/dL for more than 80% of the dosing interval,
- Analysis of the proportion of subjects with testosterone concentrations within the PR for more than 80% of the dosing interval,
- Analysis of other hormone (DHT, E2, FSH, LH) and SHBG concentrations and ratios of DHT/T and E2/T, and
- Analysis of changes in Bone Mineral Density

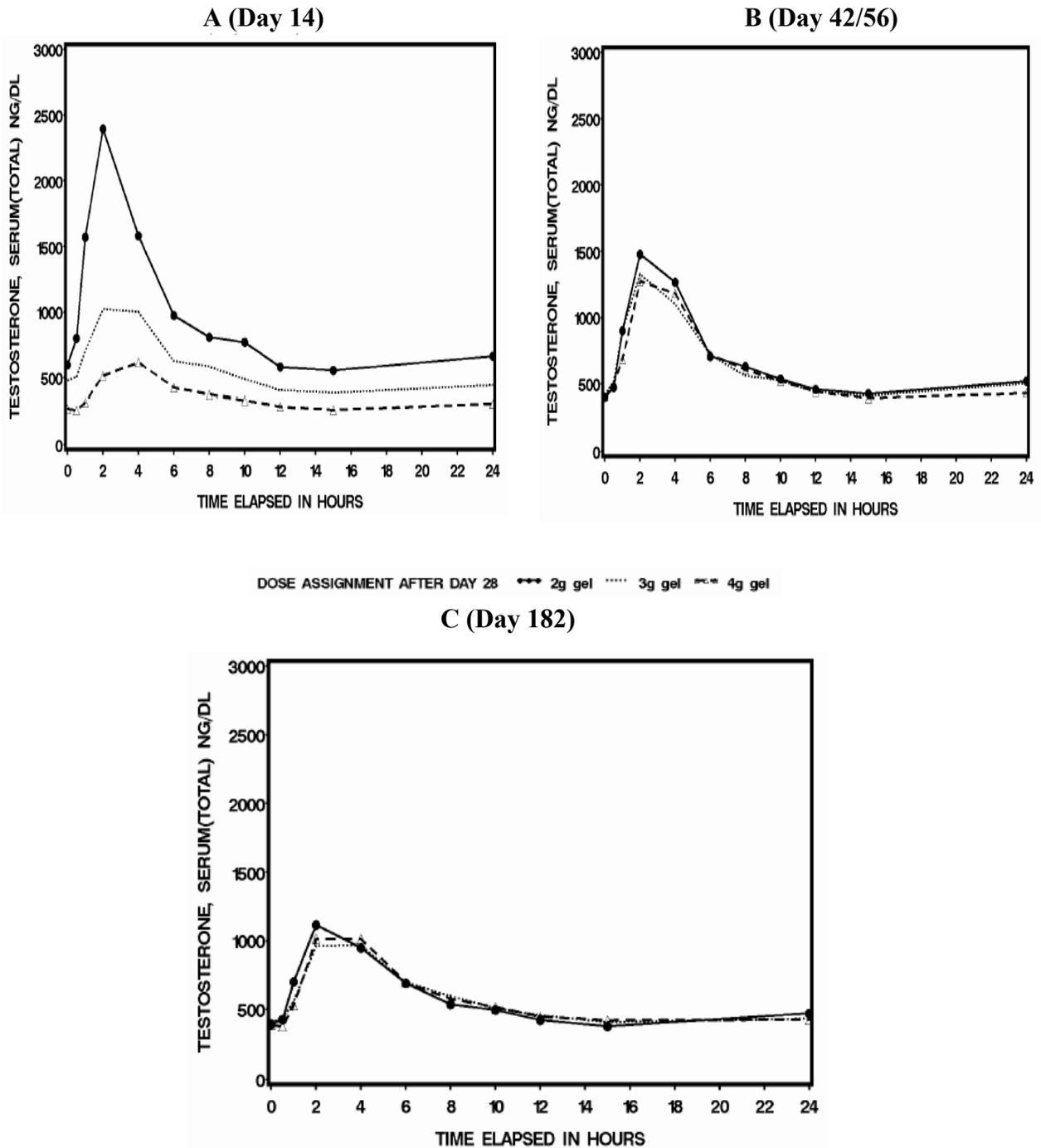
The key PK parameters for **safety** (based on clinical pharmacology results) for similar products are generally identified as C_{\max} and ratio of DHT/T.

- For OCPB analysis, C_{\max} was treated as the primary safety marker. Exposure-response relationship between C_{\max} & C_{avg} vs. Hct, HDL, LDL, PSA and HB were also critical.

Results:

Figure 4. Mean Total Serum Testosterone Concentrations on Days 14 (A), 42/56 (B) and 182 (C) by Final Dose Groups: Day 42/56 MITT subjects who completed the study through Day 182 (N=146) (Study T 00-02-01).

Note: On Day 14 (Figure A), all patients' PK were reported following 60 mg T dose (3g gel), while on days 42/56 or 182, the profiles are following adjusted doses of either 40 or 80 mg T (2 or 4g gel), or unchanged at 60 mg T.



[Subjects are divided into the three final dose groups based on the dose they were assigned to on Day 28: 2g (N=26), 3g (N=61), 4g (N=59).]

Table 4: Summary Statistics of Key Testosterone Pharmacokinetic Parameters (C_{min} , C_{max} , C_{avg}) by PK Day: Day 42/56 Efficacy Evaluable Population (Study T 00-02-01)

PK Day	Parameter	Statistic	Final Dose Group ^a			All
			40 mg ^b Testosterone in 2g 2% Gel	60 mg ^b Testosterone in 3g 2% Gel	80 mg ^b Testosterone in 4g 2% Gel	
Day 42/56	C_{min}	N	15	36	38	89
		Mean±SD	299.5±126.22	331.1±120.83	299.2±93.36	312.2±111.69
		Median	242.0	298.0	288.0	290.0
		Range	189.0-601.0	96.0-662.0	124.0-511.0	96.0-662.0
	C_{max}	N	15	36	38	89
		Mean±SD	1592.4±666.52	1608.2±835.10	1847.6±1191.43	1707.7±979.62
		Median	1630.0	1547.0	1528.5	1579.0
		Range	482.0-2820.0	384.0-3917.0	223.0-5311.0	223.0-5311.0
	C_{avg}	N	15	36	38	89
		Mean±SD	614±205.15	625.9±216.91	640.4±231.32	630.2±219.09
		Median	588.8	616.8	616.9	616.6
		Range	317.6-1002.0	265.2-1250.7	178.7-1416.9	178.7-1416.9
Day 182 ^c	C_{min}	N	15	32	36	83
		Mean±SD	295.9±111.44	306.1±116.40	299.0±102.06	301.2±108.19
		Median	332.0	305.5	297.0	305.0
		Range	117.0-457.0	25.0-562.0	133.0-498.0	25.0-562.0
	C_{max}	N	15	32	36	83
		Mean±SD	1224.7±528.13	1352.5±698.59	1387.5±887.42	1344.6±756.11
		Median	1165.0	1271.0	1107.5	1165.0
		Range	423.0-2276.0	381.0-3098.0	310.0-4071.0	310.0-4071.0
	C_{avg}	N	15	32	36	83
		Mean±SD	548.2±156.93	592.5±194.13	596.0±211.40	586.0±194.54
		Median	563.3	564.7	585.8	581.0
		Range	344.0-879.4	243.2-977.9	224.5-1087.8	224.5-1087.8

^a Subjects in the 2g and 4g groups received 3g daily only for the first 28 days; subjects in the 3g group received 3g daily for all 182 days.

^b Amount of testosterone applied to the skin.

^c Subject 007-118 (4g group) was not included in Day 182 statistics because only one testosterone sample was available for that subject on that day.

Reviewer's Comments

- As expected, following adjustment/correction of dose based on initial variability in response (Day 14), mean PK profiles were similar in all three dose groups at steady state (Day 42/56 and 182)
- Mean C_{max} value was noticeably high compared to the higher limit of PR (1140 ng/dL for total T), especially on days 14 and 42/56.
- C_{max} was beyond range for a stretch of at least 2 hours on all occasions on Day 14.

Efficacy Analysis

Sponsor computed the following:

- On day 42/56, based on enrolled and MITT analysis, 43 and 42% of patients (respectively) had T C_{avg} and C_{min} within PR (300 – 1140 ng/dL). Based on this and 95% confidence interval and non-inferiority margin (pre-specified), sponsor met the primary efficacy end point in both populations.

Due to the fact that the exposure to daily T levels appeared to be on the higher side (based on mean C_{avg} and C_{max} values), data that was electronically submitted in a Nov 2002 submission was re-analyzed and the following descriptive statistics were obtained:

Table 5A. Mean ± SD & range of PK parameters by treatment days*

	C_{avg} (ng/dL)	C_{max} (ng/dL)	DHT/T ratio (C_{avg} ratio)
Day 14	<u>Mean ± SD</u> 588 (± 277)	<u>Mean ± SD</u> 1594 (± 1425)	<u>Mean ± SD</u> 0.16 (± 0.06)
	<u>Range</u> 240 - 2064	<u>Range</u> 454 - 10800	<u>Range</u> 0.08 - 0.50
Day 42/56	<u>Mean ± SD</u> 631 (± 241)	<u>Mean ± SD</u> 1651 (± 939)	<u>Mean ± SD</u> 0.16 (± 0.05)
	<u>Range</u> 179 - 1714	<u>Range</u> 223 - 5311	<u>Range</u> 0.08 - 0.35
Day 182	<u>Mean ± SD</u> 561 (± 198)	<u>Mean ± SD</u> 1243 (± 748)	<u>Mean ± SD</u> 0.17 (± 0.07)
	<u>Range</u> 207 - 1088	<u>Range</u> 265 - 4071	<u>Range</u> 0.08 - 0.36

* Please See Attachment 3 for detailed PK data analysis in individual patients

Additionally, the following observations were also made:

- On Day 42/56 (1 month at final dosing regimen), 5 patients out of 165 (or 3%) had C_{avg} values above 1140 ng/dL, and 1 among them had C_{avg} values > 1700 ng/dL.
- On Day 42/56, 23 patients out of 165 (or 14%) had C_{max} values between 1500 - 1800 ng/dL; 28 (or 17%) had the C_{max} values between 1800 – 2500 ng/dL and 26 of them (16%) had the C_{max} values between 2500 – 5311 ng/dL (3 values were > 4000).
- On Day 182 (6 months on final dose), no patient had C_{avg} values > 1140 ng/dL.
- On Day 182, 13 patients out of 147 (or 9%) had C_{max} values between 1500 - 1800 ng/dL; 20 (14%) had C_{max} values between 1800 – 2500 ng/dL; 9 (6%) had C_{max} values > 2500 ng/mL (with 1 value > 4000 ng/mL).

Reviewer’s Comments:

- The exposure from this T-gel is higher than what normal T-replacement constitutes. This is particularly evident from the high C_{max} values.
- A substantial number of patients (please see Table 5B on the next page) from this product may be exposed to supra-physiologic levels of T at least 2 hours *daily* (T_{max} was around 2 hours, and many patients had 2 points above the high normal T levels).
- Results of the Phase III study only corroborates observations from previous studies (*in vitro* and dose-finding) that the formulation and/or dosing regimen might not have been optimized prior to this Phase III study, thus leading to extremely high (supra-physiologic) levels of T following use of this product.

T exposure from this T-Gel as compared to other Commercial T-Gels

Two similar T-GEL products, TESTIM (approved in 2002) and ANDROGEL (approved in 2000), are currently available for the same indication in hypogonadal men. The serum levels of T from FORTIGEL (subject of this NDA) were compared to a) TESTIM and b) ANDROGEL

a) FORTIGEL vs. TESTIM:

Based on review of PK parameters in individual patients enrolled in the TESTIM Phase III Clinical Trial, 3% of the patients on Day 30 and 4% on Day 90 had C_{avg} values above the normal range. Only 1 C_{avg} in the whole data base was > 2000 ng/dL, and most of the high C_{avg} values were < 1500 ng/dL.

On day 30 for TESTIM, 9% of patients had a C_{max} value between 1000 – 1500 ng/dL, 2% (3 patients) had it between 1500 – 2000, and 3% (5 patients) had a C_{max} > 2000 ng/dL. On day 90, even lower number of patients had C_{max} values in the above numerical categories. There were only 6 C_{max} values in the whole data base (out of 363 possible PK profiles) > 2000 ng/dL, and only 1 value > 4000 ng/dL.

Reviewer’s Comments:

- Serum T levels from FORTIGEL is significantly high when compared with TESTIM either for C_{avg} or C_{max} at steady state (i.e., after patients had been adjusted to the final dose)
- The above exposure information implies that either the formulation of FORTIGEL or/and its dose has not been optimized, thus leading to a much higher (supra-physiologic) degree of T-replacement

b) FORTIGEL vs. ANDROGEL:

[Note: During the Phase III study for ANDROGEL, the dose was corrected on Day 91 of the trial. Hence, only Day 180 data is obtained following administration of final corrected dose for 3 months (steady state). In contrast, for FORTIGEL, day 42/56 & day 182 represents administration of 1 month & 5 months of final (corrected) dosing regimens.]

Based on review of PK parameters in individual patients enrolled in the ANDROGEL Phase III Clinical Trial, 10% of the patients on Day 30 and 7% on Day 180 had C_{avg} values above the normal range. No C_{avg} in the whole data base was > 2000 ng/dL, and most of the high C_{avg} values were < 1500 ng/dL, with 4 values > 1500 ng/dL (N ≈ 140). The 3 highest values in the whole database were between 1100 - 1500 ng/dL.

On day 30 for ANDROGEL, 6% (9 patients) had C_{max} values between 1500 – 1800, and 9% (12 patients) had a C_{max} > 1800 ng/dL (with 7 values between 2000 - 3000 ng/dL). On Day 180, the exposure was reduced. 14% patients had C_{max} values between 1500 – 1800, and 5% (7 patients) had a C_{max} > 1800 ng/dL. There were no C_{max} values in the whole database higher than 2310 ng/dL.

Reviewer’s Comments

- Compared to ANDROGEL following corrected dose administration and achievement of steady state, FORTIGEL provided marked higher serum levels of total T (based both on C_{avg} on day 42/56, and C_{max} on all PK assessment days).

Table 5B: Comparison of PK Outliers in T- Gels at Steady State*

Product	C_{max} between 1200 – 1500 ng/dL	C_{max} between 1500 – 1800 ng/dL	C_{max} between 1800 – 2500 ng/dL	C_{max} > 2500 ng/dL	C_{avg} > 1100 ng/dL	N
Fortigel	20 (14%)	13 (9%)	20 (14%)	9 (6%)	0 (0%)	147
Androgel	14 (9%)	11 (7%)	7 (5%)	0 (0%)	5 (3%)	151
Testim	4 (2%)	4 (2%)	4 (2%)	0 (0%)	2 (1%)	162

* 6 months post treatment for Fortigel & Androgel, 3 months for Testim.

Intrinsic Factors

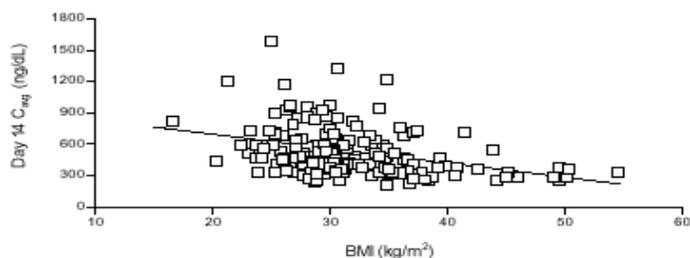
It is important to determine the effect of body weight, age and race on the clinical pharmacology of T following administration of FORTIGEL. Sponsor identified 33 subjects with BMI ≥ 36 kg/m² and presented the key PK parameters for these patients on day 42/56, i.e., after one month of receiving final dosing regimen (as Table 6A below).

Table 6A. Mean \pm SD & range of PK parameters by treatment days

Subject ID	Final Dose (a)	Day 42/56 EE	Day 42/56 MITT	EMI	Day 42/56 C _{min} (c)	Day 42/56 C _{avg} (c)	Primary Endpoint Met (d)	Secondary Endpoint Met (e)
001-114	80	Y	Y	49.5	267	527.6	0	1
003-101	80	N	Y	45.9	304	582.2	1	1
003-105	80	N	Y	37.0	435	801.8	1	1
003-108	80	N	Y	37.8	175	297.6	0	0
005-104	60	N	Y	36.3	68	285.4	0	0
007-118	80	Y	Y	44.1	286	642.3	0	1
010-101	60	Y	Y	39.3	292	707.1	0	1
010-102	60	N	Y	40.8	325	549.2	1	1
010-103	60	N	Y	36.3	423	1063.9	1	1
010-113	80	Y	Y	36.5	206	356.7	0	1
011-106	80	N	Y	36.8	218	648.5	0	1
011-113	80	N	Y	49.5	204	267.6	0	0
012-101	60	N	Y	36.2	179	450.3	0	1
012-104	80	N	Y	45.2	198	254.1	0	0
012-105	80	N	Y	38.3	218	464.8	0	1
012-110	60	Y	Y	43.9	452	731.0	1	1
012-112	40	Y	Y	41.4	475	649.0	1	1
012-130	80	Y	Y	38.6	209	498.3	0	1
014-106	60	Y	Y	37.0	374	663.9	1	1
014-128	60	N	Y	39.8	255	492.3	0	1
014-136	80	N	Y	36.0	250	517.8	0	1
014-137	80	N	Y	49.0	198	386.6	0	1
014-150	80	Y	Y	38.0	230	450.7	0	1
015-100	80	N	Y	50.2	339	395.2	1	1
015-109	80	Y	Y	54.5	131	320.6	0	1
017-104	60	N	Y	39.2	416	523.0	1	1
019-106	80	N	Y	45.0	305	489.8	1	1
020-102	80	Y	Y	50.3	232	565.5	0	1
020-104	60	N	Y	36.6	340	537.0	1	1
020-114	60	Y	Y	37.4	228	320.9	0	1
022-103	80	Y	Y	40.6	368	718.9	1	1
022-105	80	Y	Y	37.1	215	361.8	0	1
023-110	80	Y	Y	42.5	269	448.4	0	1

There was a correlation between key PK parameters and body weight and BMI on Day 14 (prior to dose adjustment). Sponsor reports that this correlation was much weaker on Day 42/56 (which can be explained by the fact that the doses were adjusted based on initial response to neutralize any intrinsic factors that might affect exposure).

Figure 5. Correlation between Day 14 C_{avg} and BMI: Day 42/56 MITT Population (Study T 00-02-01)



Reviewer's Comments

- Based on Table 6A, most of the key PK parameters appear similar to that in the normal BMI population. For the patients in this group, as well as in the “very high” BMI group (BMI ≥ 45

kg/m²), the primary efficacy value is > 33%, which is in the range of the efficacy observed in the MITT and ITT population (Table 7 later).

- Sponsor did not find significant correlation between age (< or > 55 y) and key PK parameters (C_{avg}, C_{max} and C_{min}). Table 6B below categorizes the efficacy of FORTIGEL on Day 42/56 by age.

Table 6B.

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STATISTICAL ANALYSIS OF C_{AVG} AND C_{MIN} FOR SERUM TESTOSTERONE (NG/DL) ON PHARMACOKINETIC PROFILE DAY 42/56 BY AGE GROUP (<55, ≥55): DAY 42/56 MITT POPULATION (STUDY T 00-02-01)

CRITERION	<55 (N=92)		≥55 (N=71)	
	N (%)	95% CONF. INT. ¹	N (%)	95% CONF. INT. ¹
SUBJECTS WITH C _{AVG} IN [300NG/DL,1140NG/DL] AND C _{MIN} ≥300	36 (39.1)	(29.2,49.1)	32 (45.1)	(33.5,56.6)
SUBJECTS WITH C _{AVG} IN [300NG/DL,1140NG/DL]	83 (90.2)	(84.1,96.3)	67 (94.4)	(89.0,99.7)
SUBJECTS WITH C _{AVG} IN [300NG/DL,1140NG/DL] AND CONCENTRATION ≥= 300NG/DL FOR ≥= 80% OF DOSING INTERVAL	65 (70.7)	(61.3,80.0)	51 (71.8)	(61.4,82.3)
SUBJECTS WITH CONCENTRATION IN [300NG/DL,1140NG/DL] FOR ≥= 80% OF DOSING INTERVAL	62 (67.4)	(57.8,77.0)	42 (59.2)	(47.7,70.6)

¹ TWO-SIDED 95% CONFIDENCE INTERVAL (P ± 2.05 * SE(P)) COMPUTED ON THE PERCENTAGE OF SUBJECTS MEETING THE SPECIFIC CRITERION, USING THE NORMAL APPROXIMATION TO THE BINOMIAL.
CROSS-REFERENCE: Appendix 3.7.2; Attachment 2.1

- Based on the above table, there is no appreciable difference in primary efficacy between the two age groups, although clearly, the secondary efficacy appears to be lower in the ≥ 55 year group. However, considering the excessive exposure to T that FORTIGEL might provide, no dosing adjustment is recommended in any specific age group.
- Out of a total of 201 patients enrolled, 169 (84%) were Caucasians, 27 (13%) Blacks, 1 Asian and 4 Hispanics. Due to the biased demographic composition of the study, no analysis of PK parameters was conducted (or was attempted by sponsor) based on race.
- In patients with no detectable endogenous T levels, rates of success in primary efficacy end points were found to be in the same range as those in the general population.

Miscellaneous Reviewer’s Comments on other Phase III Study Results

- Besides safety concerns due to extreme systemic exposures of T from this Gel (as discussed above), investigations were also made on the relative exposure of DHT and the DHT/T ratios. On Day 42/56, mean ± s.d. DHT/T ratios (ratio of DHT C_{avg} / T C_{avg}) were 0.15 ± 0.05 with a range of 0.08 – 0.35. The same for Day 182 was 0.17 ± 0.7 with a range of 0.08 – 0.36. Normal range for DHT/T ratio is believed to be ≈ 0.05 – 0.35. On investigation of DHT/T ratios for each patient at every time point, there were some values beyond 0.5 (as high as 0.7), but the occurrence of such values were relatively low.
- Based on the efficacy analysis, 31 – 49% of the patients (depending on the ITT, MITT or Evaluable Efficacy populations) had C_{avg} and C_{min} values within normal physiologic range of total T. Based on the lower bound of the 95% confidence intervals, prospective statistical plan, and comparison to data from the two prior T-Gel NDAs, FORTIGEL provided evidence of adequate efficacy (see Table 7 below).

Table 7: Statistical Analysis of C_{avg} and C_{min} for Serum Testosterone on Pharmacokinetic Profile Day 42/56: Day 42/56 EE, MITT, and ITT Populations (Study T 00-02-01) 114

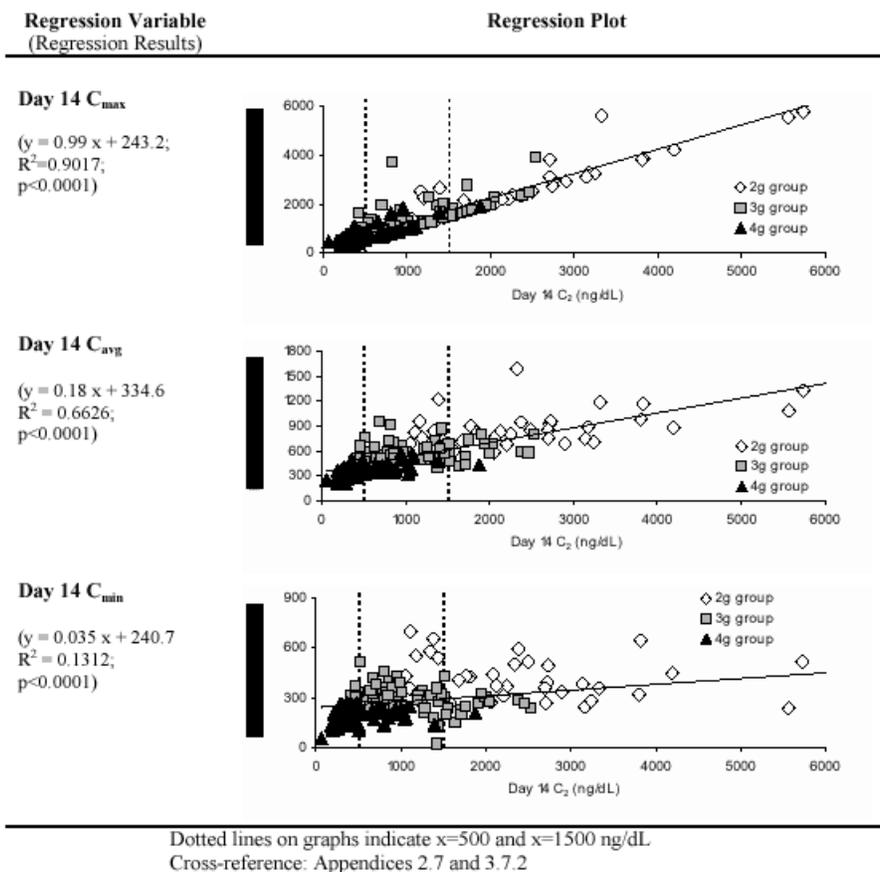
CRITERION	DAY 42/56 EFFICACY EVALUABLE POPULATION (N=89)		DAY 42/56 MITT POPULATION (N=163)		ITT POPULATION ^a (N=201)	
	N (%)	95% CONF. INT ^b	N (%)	95% CONF. INT ^b	N (%)	95% CONF. INT ^b
SUBJECTS WITH CAVG IN [300NG/DL,1140NG/DL] AND CMIN >=300	38 (42.7)	(32.4,53.0)	68 (41.7)	(34.1,49.3)	68 (33.8)	(27.3,40.4)
SUBJECTS WITH CAVG IN [300NG/DL,1140NG/DL]	82 (92.1)	(86.5,97.7)	150 (92.0)	(87.9,96.2)	150 (74.6)	(68.6,80.6)
SUBJECTS WITH CAVG IN [300NG/DL,1140NG/DL] AND CONCENTRATION >= 300NG/DL FOR >= 80% OF DOSING INTERVAL	63 (70.8)	(61.3,80.2)	116 (71.2)	(64.2,78.1)	116 (57.7)	(50.9,64.5)
SUBJECTS WITH CONCENTRATION IN [300NG/DL,1140NG/DL] FOR >= 80% OF DOSING INTERVAL	53 (59.6)	(49.4,69.7)	94 (57.7)	(50.1,65.3)	94 (46.8)	(39.9,53.7)

^a Subjects who did not have a PK profile on day 42/56 were included as failure (i.e., included in the denominator) in the analysis of the ITT population.
^b Two-sided 95% confidence interval ($p \pm z_{0.05} * se(p)$) computed on the percentage of subjects meeting the specific criteria, using the normal approximation to the binomial.

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- Sponsor claims that determination of serum T level 2 hours post administration on Day 14 may be used in the broader patient population (post marketing) to determine dose titration, and wishes to include this in the label (since it is impractical in the marketplace to enforce a full 24 hour PK profile on Day 14 in order to adjust dose, as accomplished in the Phase III study). In support of this, sponsor presents the following correlative data:

Figure 6. Linear Regression of Key Day 14 PK Parameters (C_{max} , C_{avg} , and C_{min}) With Day 14 C_2 : ITT population (Study T 00-02-01)



- It appears that C_{avg} (critical for efficacy) and C_{max} (critical for safety) do correlate with the Day 14, 2- hour serum T level, ($R^2 > 0.9$ for C_{max}).
- The above is a novel approach with merit, and proposes a scientific basis for assignment or adjustment of a final dosing regimen for a T-Gel. This labeling information can be invaluable to the physician while deciding a dosing regimen for FORTIGEL.
- However, the basis for the choice of the range 500 – 1500 ng/dL (on which the above data is focused) it is not clear. Also, it is possible that a sizeable portion of the patient population might be assigned to the wrong dose.
- Sponsor has indicated that the dose adjustment may be based upon Day 14, 2- hour serum T level *and* BMI considerations. However, since C_{max} does not really correlate with the BMI, it might not be advisable to consider BMI as a factor for dose adjustment and further complicate the procedure.

Exposure - Response

As mentioned in an earlier section, the exposure to T following application of FORTIGEL is markedly higher than what constitutes physiologic levels of T replacement, higher than the currently available marketed products for the same indication. Hence, an effort was undertaken to explore the effect of high T exposure to critical safety factors identified by the Clinical Team (the exposure - efficacy relationship of this product is a less critical issue).

Working in conjunction with the primary medical officer and the pharmacometrician, raw data on patient hematocrits (HCT), high-density lipoprotein (HDL), low-density lipoprotein (LDL), prostrate specific antigen (PSA) and Hemoglobin (Hb) values were processed and statistical analyses were performed to determine the effect of exposure to these safety parameters. Results follow: **[Please refer to Attachment 2 for statistical analysis and detailed graphs]**

- No definitive and/or significant relationships between the change of patient LDL, PSA and Hb vs. T concentrations were observed on day 42/65 and day 182.

HDL

- A negative slope was found in the relationship between HDL and T concentrations indicating a decrease in HDL (Δ HDL) corresponding to an increase in T concentrations.
- Δ HDL appears to be significant in patients with higher HDL baseline value (most significant) body weight (w2 or the weight at end of 6 months). Drop in HDL is insignificant in patients with high body weight and low HDL baseline values.
- In order to analyze all the factors together, a mixed effect modeling analyses was conducted to determine the effect of HDL baseline, body weight and T concentration at day 42/56 on the change in HDL on day 182. The objective function values suggest that baseline and body weight at the end of treatment period are statistical significant covariates for Δ HDL at a given T concentration on day 182 (please refer to the following statistical results and matrix plots following the data analysis, and Attachment 2 for detailed results).

HDL Data: (Statistical Results) - Please See Attachment 2 for more details and more graphical results.

Change in HDL:

*** Linear Model ***

Call: lm(formula = DeltaHDL ~ Cmax182, data = pkpdhdl182, na.action = na.exclude)

Residuals:

Min	1Q	Median	3Q	Max
-28.29	-4.482	0.06359	4.751	27.19

Coefficients:

	Value	Std. Error	t value	Pr(> t)
(Intercept)	0.5794	1.4343	0.4040	0.6869
Cmax182	-0.0032	0.0010	-3.2245	<u>0.0016</u>

Residual standard error: 8.396 on 132 degrees of freedom

Multiple R-Squared: 0.07302

F-statistic: 10.4 on 1 and 132 degrees of freedom, the p-value is 0.001591

*** Linear Model ***

Call: lm(formula = DeltaHDL ~ Cavg182, data = pkpdhdl182, na.action = na.exclude)

Residuals:

Min	1Q	Median	3Q	Max
-28.42	-4.763	-0.1643	5.421	26.71

Coefficients:

	Value	Std. Error	t value	Pr(> t)
(Intercept)	2.2220	2.2309	0.9960	0.3211
Cavg182	-0.0100	0.0037	-2.6734	<u>0.0085</u>

Residual standard error: 8.494 on 132 degrees of freedom

Multiple R-Squared: 0.05136

F-statistic: 7.147 on 1 and 132 degrees of freedom, the p-value is 0.008456

If we compare the slopes, Cavg has a steeper slope than Cmax.

*** Linear Model ***

Call: lm(formula = DeltaHDL ~ Cmax182 + Cavg182 + baseline + Age + wt1 + wt2, data = pkpdhdl182, na.action =

na.exclude)

Residuals:

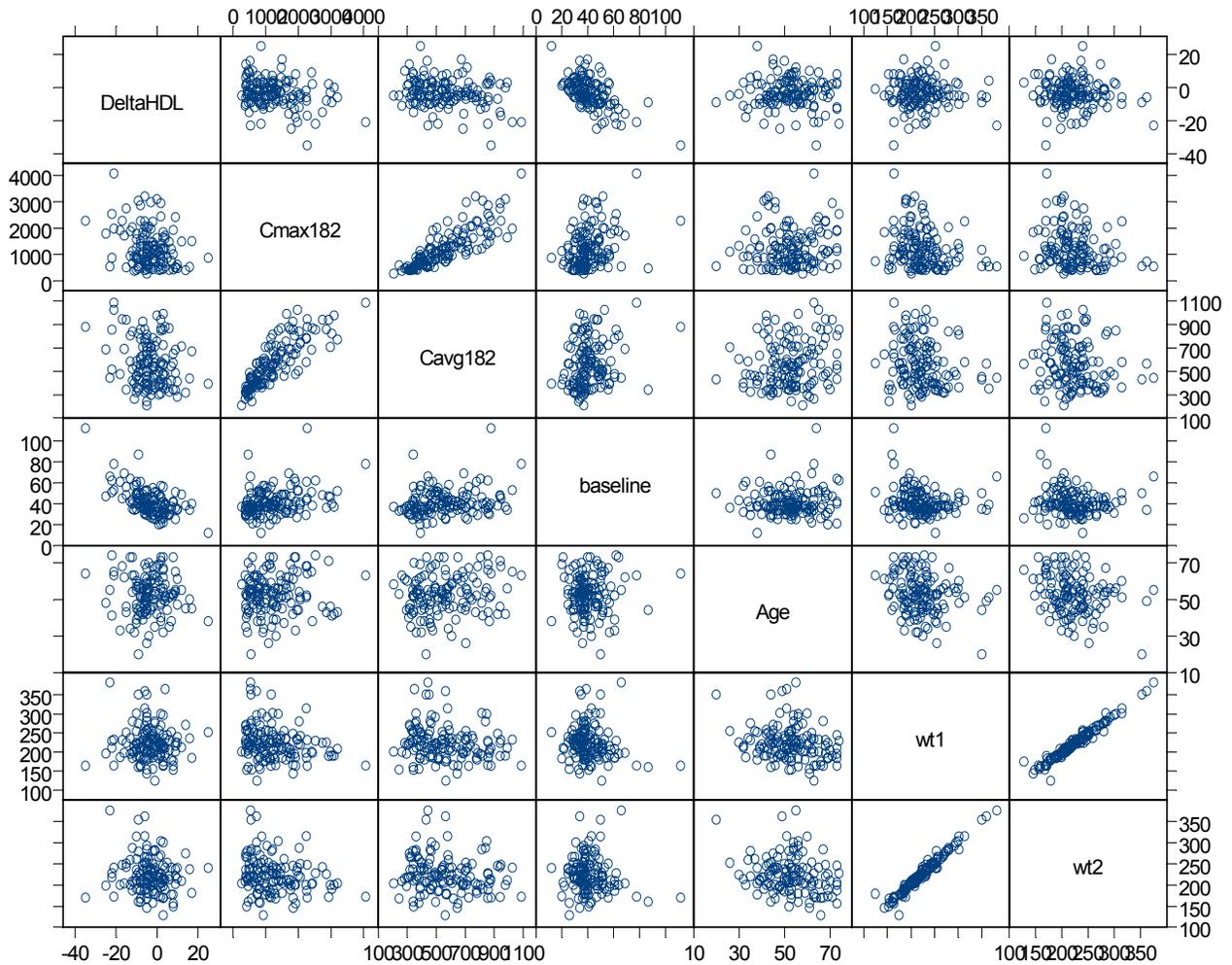
Min	1Q	Median	3Q	Max
-19.63	-4.527	-0.9232	4.562	17.96

Coefficients:

	Value	Std. Error	t value	Pr(> t)
(Intercept)	23.5274	5.7355	4.1021	0.0001

Cmax182	-0.0013	0.0016	-0.8567	0.3933	
Cavg182	-0.0011	0.0057	-0.1840	0.8543	
baseline	-0.3617	0.0516	-7.0034	0.0000	
Age	-0.0333	0.0602	-0.5530	0.5813	
wt1	0.1197	0.0690	1.7358	0.0851	[wt1 is b. wt. at the beginning of study]
wt2	-0.1543	0.0685	-2.2520	0.0261	[wt1 is b. wt. at the end of 6 months]

HDL Data: (Matrix Plots)



Change in Hematocrits (Hct):

*** Linear Model ***

Call: `lm(formula = Hct3 ~ Cmax182, data = SDF8, na.action = na.exclude)`

Residuals:

Min	1Q	Median	3Q	Max
-12.38	-2.148	0.1444	2.792	10.74

Coefficients:

	Value	Std. Error	t value	Pr(> t)
(Intercept)	45.3925	0.6910	65.6880	0.0000
Cmax182	0.0011	0.0005	2.1882	<u>0.0303</u>

Residual standard error: 4.126 on 138 degrees of freedom

Multiple R-Squared: 0.03353

F-statistic: 4.788 on 1 and 138 degrees of freedom, the p-value is 0.03034

*** Linear Model ***

Call: lm(formula = Hct3 ~ Cavg182, data = SDF8, na.action = na.exclude)

Residuals:

Min	1Q	Median	3Q	Max
-12.7	-2.396	-0.05206	2.318	10.65

Coefficients:

	Value	Std. Error	t value	Pr(> t)
(Intercept)	43.7970	1.0532	41.5847	0.0000
Cavg182	0.0051	0.0018	2.9144	<u>0.0042</u>

Residual standard error: 4.074 on 138 degrees of freedom

Multiple R-Squared: 0.05798

F-statistic: 8.494 on 1 and 138 degrees of freedom, the p-value is 0.004159

*** Linear Model ***

Call: lm(formula = Hct3 ~ Cmax182 + Cavg182, data = SDF8, na.action = na.exclude)

Residuals:

Min	1Q	Median	3Q	Max
-12.79	-2.423	-0.07287	2.367	10.57

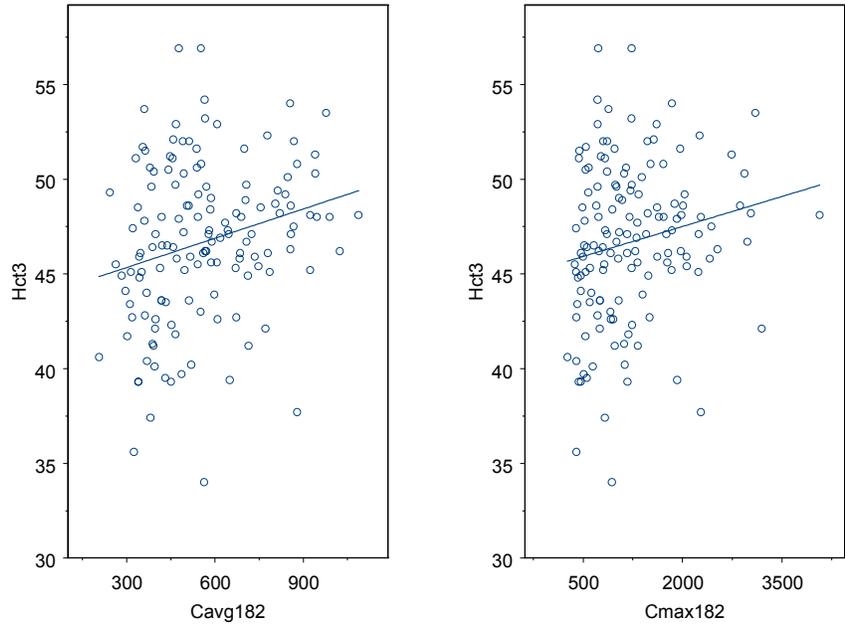
Coefficients:

	Value	Std. Error	t value	Pr(> t)
(Intercept)	43.6414	1.1397	38.2909	0.0000
Cmax182	-0.0003	0.0009	-0.3641	0.7163
Cavg182	0.0061	0.0032	1.9214	0.0568

Residual standard error: 4.087 on 137 degrees of freedom

Multiple R-Squared: 0.05889

F-statistic: 4.287 on 2 and 137 degrees of freedom, the p-value is 0.01564



This analysis (and plots) implies that there is a statistically significant trend of increasing Hct values with either an increase in serum T C_{avg} or C_{max} .

4. Study T 00-02-03 (Phase I – Effect of Showering)

This was an open-label, non-vehicle-controlled, randomized, two-treatment, two-period crossover PK study conducted to determine the effects of showering on the pharmacokinetics of testosterone following topical application of CP601B 2% testosterone gel in hypogonadal males.

Methodology: Seven subjects were enrolled in this study. Each subject was to participate in two treatment periods. During both treatment periods, beginning on Day 1, the subject applied 3 g of CP601B 2% testosterone gel (60 mg testosterone) daily, administered as 1.5 g applied to a 150 cm² area of skin on each anteromedial thigh. The dose was applied at approximately the same time each morning and the time of application was recorded in a diary. From Study Days 1 through 6, drug administration was identical for all subjects. On the morning of Day 7, subjects, having fasted from midnight, reported to the study site for testosterone gel administration and blood collection for a 24-hour PK profile. Venous blood samples were obtained prior to (Time 0), and at 0.5, 1, 2, 4, 6, 8, 10, 12, 15, 20 and 24 hours following application of study medication. At the time of entry to the study site, subjects were randomly assigned to a sequence of treatment (AB or BA). Subjects assigned to Treatment A were to shower as directed two hours after application of the testosterone gel and after the two-hour post-dose blood sample was obtained. Subjects assigned to Treatment B were not to shower during the 24-hour PK profile period, but could shower at the study unit before gel application, if desired. Subjects continued to apply study medication (60 mg testosterone daily) for at least six additional days. On Day 7, the second 24-hour PK profile was obtained in each subject.

Results:

Table 8: Ratios of Geometric Means and 95% Confidence Intervals for Day 7 PK parameter Estimates (Study T 00-02-03), where A is with shower 2 hours after Gel administration, and B is without shower.

Pharmacokinetic Parameter	N	Ratio of Geometric Means (B/A)	95% Confidence Limits for Ratio
C _{max} (ng/dL)	7	0.83	(0.47-1.44)
C _{avg} (ng/dL)	7	1.03	(0.79-1.34)
C _{min} (ng/dL)	7	1.29	(0.91-1.85)

^b Exponential of difference of least square means (LSM) from the analysis of variance.
 Exponential of (difference of LSMs from the analysis of variance \pm (0.025, DF) x standard error based on logarithms (SE) of difference), where LSM is the adjusted mean and SE is its standard error, where the error degrees of freedom (DF) = 5.

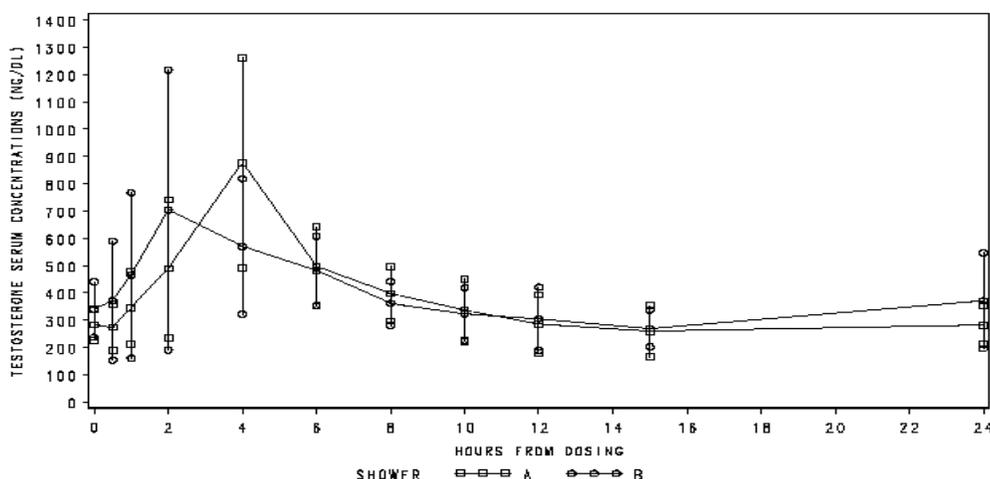


Figure 7: Mean (SD) Testosterone Serum Concentrations Versus Time: All Subjects (Study T 00-02-03)

Table 8: Summary Statistics for Day 7 Pharmacokinetic Parameter Estimates (Study T 00-02-03)

Pharmacokinetic Parameter	Treatment A	Treatment B
AUC₀₋₂₄ (ng-h/dL)		
N	7	7
Mean	8939	9199
SD	2107.4	3216.1
Median	8868	8862
Range	6632-11301	5183-15710
Geometric Mean	8723	8772
Approximate CV (%)	24.4	33.8
C_{max} (ng/dL)		
N	7	7
Mean	893.6	790.6
SD	356.87	459.36
Median	817.0	775.0
Range	422-1595	266-1734
Geometric Mean	836.5	691.3
Approximate CV (%)	41.1	61.4
C_{avg} (ng/dL)		
N	7	7
Mean	372.3	383.3
SD	87.62	134.00
Median	369.5	369.3
Range	276-471	216-655
Geometric Mean	363.3	365.5
Approximate CV (%)	24.3	33.8
C_{min} (ng/dL)		
N	7	7
Mean	201.7	246.4
SD	73.55	65.08
Median	221.0	230.0
Range	89-291	158-353
Geometric Mean	188.2	239.1
Approximate CV (%)	44.3	27.1
T_{max} (h)		
N	7	7
Mean	4.60	4.29
SD	1.50	2.43
Median	4.00	4.00
Range	4.0-8.0	2.0-8.0

Treatments:

A = Study On Day 7, shower (at least two hours) after application of testosterone gel (and following the collection of the two-hour blood sample). The once daily dose was CP601B 2% testosterone gel (60 mg testosterone) applied as 1.5 g (30 mg testosterone) to a 150 cm² area of skin on each anteromedial thigh.

B = On Day 7, shower (if taken) was to occur before application of testosterone gel. The once daily dose was CP601B 2% testosterone gel (60 mg testosterone) applied as 1.5 g (30 mg testosterone) to a 150 cm² area of skin on each anteromedial thigh.

Reviewer's Comments

- Based on the above tables, mean and individual (results not shown here) PK plots, and consideration of the high degree of variability in PK parameters, no trend appears to indicate that showering 2 hours post Gel administration leads to a detectable difference in the daily exposure profiles to total T.

5. Study T 00-02-07 (Phase I – Effect of surface area)

The objectives of this study were to determine the effect of increasing the surface area of application of a fixed dose of 601B 2% testosterone gel on the pharmacokinetics of testosterone.

Methodology: This was a multi-center, open-label, randomized, three-treatment, three-period crossover study. Twelve hypogonadal men were enrolled in the study. During each of three treatment

periods, subjects applied 1 g of CP601B 2% testosterone gel over a 100 cm² (Treatment A), 200 cm² (Treatment B), or 400 cm² (Treatment C) area of skin on each anteromedial thigh each morning for eight consecutive days (Days 1 to 8). The total daily dose of testosterone was thus to be 40 mg as 2 g of gel over a 200 cm², 400 cm² or 800 cm² area of skin. There was a washout interval of at least three days between treatment periods. During each treatment period, venous blood samples were obtained for pharmacokinetic evaluation of testosterone prior to application on Days 7 and 8 (Time 0), and at specified times (0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 hours) after application on Day 8.

Results:

Figure 8: Mean (SD) Testosterone Serum Concentrations (ng/dL) Versus Time: All Subjects (Study T 00-02-07)

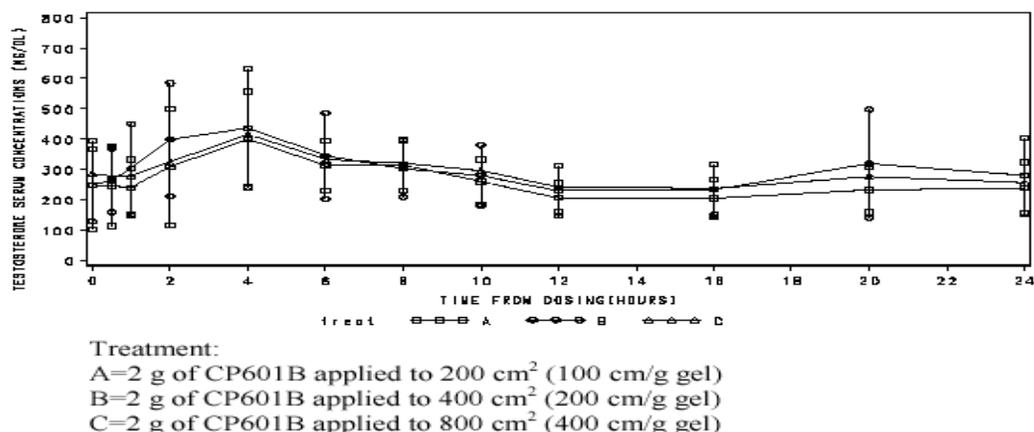


Table 9: Summary Statistics for PK Parameter Estimates on Day 8-Subjects With PK Data (Study T00-02-07)

Pharmacokinetic Parameter	Statistic	200 cm ² (A)	400 cm ² (B) ^a	800 cm ² (C)
AUC ₀₋₂₄ (ng·h/dL)	N	12	12	12
	Mean	6250	7192	6924
	SD	1573.6	2284.4	1528.4
	Median	5754	6318	6618
	Range	4003-9419	4593-11112	5253-9956
	Geometric mean	6076	6875	6781
	Approximate CV (%)	25.1	31.9	21.3
C _{max} (ng/dL)	N	12	12	12
	Mean	420.4	544.1	421.8
	SD	175.59	173.87	118.65
	Median	366.0	495.0	417.5
	Range	196-853	321-831	258-695
	Geometric mean	392.2	518.7	407.5
	Approximate CV (%)	39.6	33.4	27.7
C _{avg} (ng/dL)	N	12	12	12
	Mean	259.6	298.9	287.5
	SD	65.70	95.00	63.43
	Median	239.2	262.5	274.8
	Range	166-392	191-461	217-413
	Geometric mean	252.3	285.7	281.5
	Approximate CV (%)	25.2	32.0	21.4
C _{min} (ng/dL)	N	12	12	12
	Mean	166.1	196.6	196.8
	SD	63.58	94.95	58.60
	Median	156.5	179.0	176.5
	Range	84-300	51-324	110-310
	Geometric mean	155.9	171.2	189.0
	Approximate CV (%)	38.3	65.3	30.3
t _{max} (h)	N	12	12	12
	Mean	6.9	7.5	7.1
	SD	6.74	7.67	7.05
	Median	4.1	4.1	4.1
	Range	0-24	1-20	4-24

^a Analysis excludes one concentration value for Subject 101-106.

Reviewer's Comments

- Based on the mean profiles, the above parameters and individual patient data (results not presented here), it may be concluded that there is no real trend effecting exposure of T from this T-gel applied over 200 – 800 cm² of surface area.
- The proposed label (as well as the Phase III study was conducted) advises patients to apply the gel over a total area of 300 cm² on the inner thighs or abdomen. This is acceptable (see Study T 00-02-08).

6. Study T 00-02-08 (Phase I – Effect of site of application)

The objectives of this study were to compare the pharmacokinetics of testosterone following an eight-day course of daily application of 3 g of CP601B 2% testosterone gel (60 mg testosterone) to the thighs, abdomen or upper arms and to determine the exposure of testosterone administered transdermally to different body sites for eight days.

Methodology: This was a multi-center, open-label, randomized, three-treatment, three-period crossover study conducted at two sites in the US. Fifteen subjects were enrolled in this study. During each of three treatment periods, the subject applied 3 g of CP601B 2% testosterone gel to the thighs (Treatment A), upper arms (Treatment B), or abdomen (Treatment C) each morning for eight consecutive days. The total daily dose of testosterone was 60 mg. In Treatment A, 3 g of gel was applied to the skin of the thighs (1.5 g spread over a 150 cm² area on each thigh). In Treatment B, 3 g of gel was applied to the skin of the upper arms (1.5 g spread over a 150 cm² area on each upper arm). In Treatment C, 3 g was applied to a 300 cm² area of skin on the abdomen. The dose was applied at approximately the same time each morning. Venous serum samples were obtained just before application of study drug (Time 0) on Day 7 and Day 8 of each treatment period. On Study Day 8, venous serum samples also were obtained 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 hours following application of the testosterone gel.

Results:

Figure 9: Mean Testosterone Serum Concentration Versus Time Profiles for All Subjects (Study T-00-02-08)

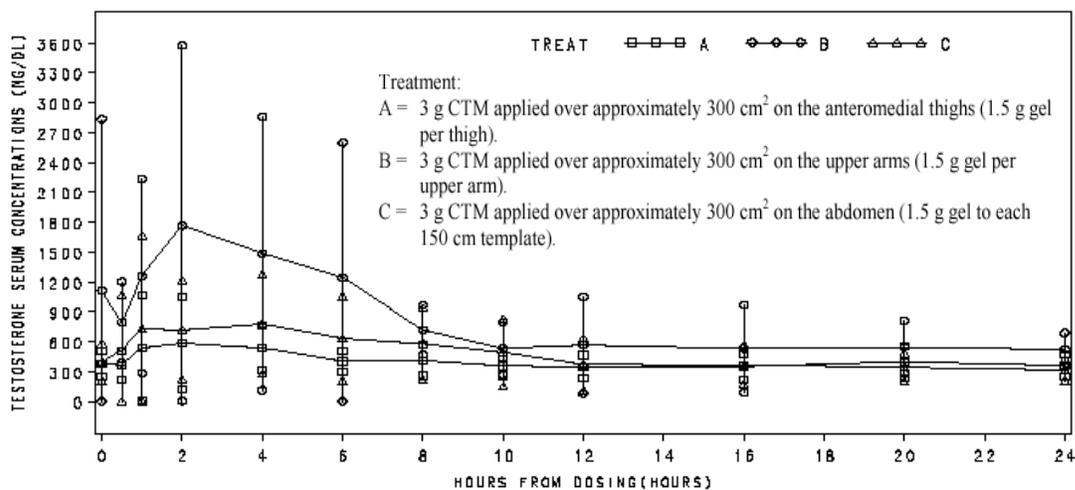


Table 10: PK Parameter Estimates/Statistics on Day 8: All Subjects With PK Data (Study T 00-02-08)

Pharmacokinetic Parameter	Statistic	Thigh (A)	Upper Arm (B)	Abdomen (C)
AUC ₀₋₂₄ (ng-h/dL)	N	12	12	13
	Mean	9699	19307	11487
	SD	2344.6	10884.5	5230.2
	Median	9957	15176	10089
	Range	6266-13334	9932-49448	5387-25822
	Geometric Mean	9434	17334	10599
	Approximate CV (%)	25.2	48.1	42.4
C _{max} (ng/dL)	N	12	12	13
	Mean	755.3	2576.5	1174.2
	SD	502.69	2134.82	905.77
	Median	584.5	2033.0	961.0
	Range	351-2134	678-7089	421-3708
	Geometric Mean	658.5	1947.0	968.0
	Approximate CV (%)	53.4	89.8	66.3
C _{avg} (ng/dL)	N	12	12	13
	Mean	402.4	800.9	476.5
	SD	97.21	452.10	217.02
	Median	413.4	628.2	418.6
	Range	260-554	412-2053	224-1072
	Geometric Mean	391.5	719.0	439.7
	Approximate CV(%)	25.2	48.1	42.3
C _{min} (ng/dL)	N	12	12	13
	Mean	250.2	359.6	251.7
	SD	62.39	117.92	71.28
	Median	237.5	312.0	252.0
	Range	172-377	249-580	132-353
	Geometric Mean	243.6	343.9	240.9
	Approximate CV (%)	24.0	31.1	33.1
t _{max} (h)	N	12	12	13
	Mean	9.0	2.6	4.1
	SD	8.27	2.63	2.75
	Median	6.1	2.1	4.1
	Range	0-24	0-8	1-10

Reviewer’s Comments

- Based on the mean profiles and the above parameters, it is clear that exposure following application of the gel in the upper arm is appreciably higher than that from the inner thighs or the abdomen. Hence, it is advisable not to administer this product on the upper arm.
- The exposure of T from this gel is somewhat higher following application to the abdomen as compared to the inner thighs. However, based on a comparison of the C_{avg} and statistics, this difference in exposure may be assumed to be marginal (C_{max} value in one patient was > 3700 ng/dL following abdominal application)
- (b) (4) use of this product either in the inner thighs or the abdomen, and this is acceptable.

7. Study T 01-02-02 (Phase I – Potential of T Transfer into partners)

The objectives of this study were to determine 1) whether transference of CP601B testosterone gel 2% from a male to female would significantly raise the serum testosterone and bioactive testosterone levels in the female as assessed by a 24-hour serum testosterone pharmacokinetic profile, and 2) if transference occurs, whether covering the application site with clothing would prevent it.

Methodology: This was an open-label, vehicle-controlled, pharmacokinetic study conducted in healthy couples at two sites in the United States. The study consisted of three phases: one non-transfer profile phase (Treatment A: Phase I - vehicle only) and two potential transfer profile phases (Treatment B for Phase II - uncovered CP601B testosterone gel 2% exposure and Treatment C for Phase III - covered CP601B testosterone gel 2% exposure). The order of the three phases was randomized in a three-period crossover design. Each phase was conducted on Day 25±2 of three consecutive menstrual cycles of the female partner of each couple. Day 1 of the cycle was defined as the first day of menses. In Treatment A (non-transfer control Phase I), the male partner applied the vehicle to a 150 cm² area of the anteromedial thigh. In Treatment B (uncovered Phase II), the male applied 1.5 g of CP601B testosterone gel 2% to a 150 cm² area of the thigh, and in Treatment C (covered Phase III), the male applied 1.5 g of CP601B testosterone gel 2% and wore boxer shorts that covered the site of application. During each phase, the female partner rubbed the application site with the volar surface of her forearm for 15 consecutive minutes, beginning 2 hours after the clinical trial material (CTM) was applied. Blood samples were obtained from the female partner at Time 0 (just before rubbing), 0.5, 1, 2, 4, 6, 8, 10, 12, 15, and 24 hours. Blood samples were analyzed for determination of testosterone, bioactive testosterone and sex hormone binding globulin (SHBG) concentrations.

Results:

Figure 10: Mean (±SE) Total Serum Testosterone Concentration Profile in Female Subjects after Transference Including All Values (Study T 01- 02- 02)

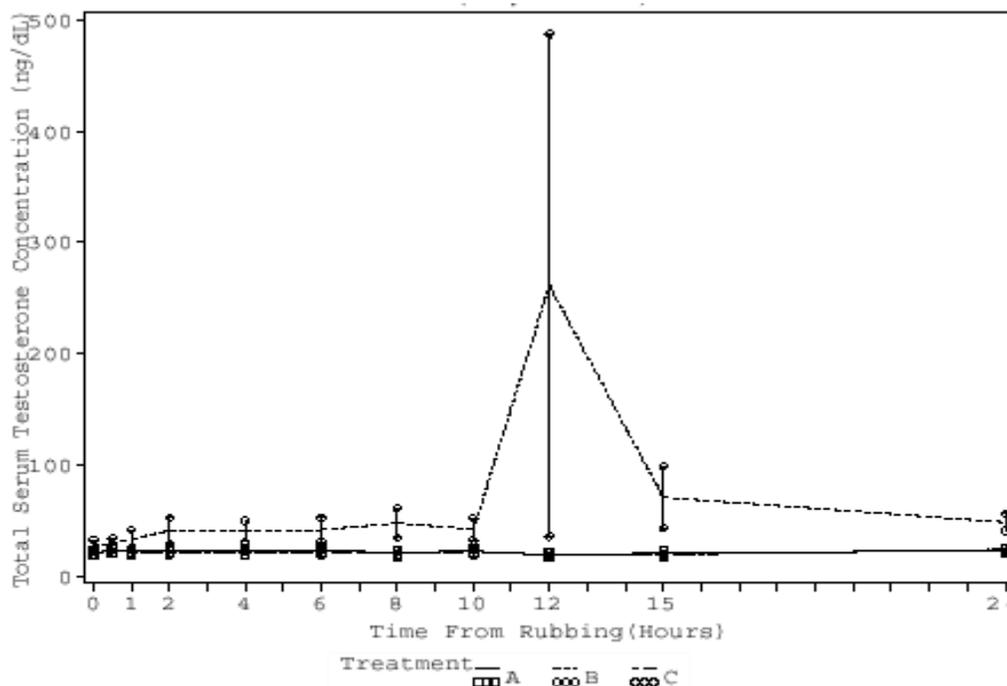


Figure includes the Hour 2,4,12, and 15 outlier concentration values for subject 123- 102, Treatment B Treatment:

A = Phase I: Male applied 1.5g vehicle/ 150 cm² to one anteromedial thigh; female rubbed

B = Phase II: Male applied 1.5g CP601B/ 150 cm² to one anteromedial thigh; female rubbed

C = Phase III: Male applied 1.5g CP601B/ 150 cm² to one anteromedial thigh, application site is covered; female rubbed

Table 11A: Summary Statistics for PK Parameter Estimates: [PK Evaluable Population Including All Outlier Values (Study T 01- 02- 02)]

Pharmacokinetic Parameter	Statistic	A (N=6)	B ^a (N=6)	C (N=6)
AUC ₀₋₂₄ (ng-h/dL)	Mean±SD	525.0±118.90	1752.0±2073.7	508.7±101.68
	Median	531.2	933.9	487.5
	Range	383.7-665.5	520.8-5899	402.1-670.0
	Geometric Mean	513.4	1162.8	500.6
	Approximate CV (%)	62.3	91.1	61.8
C _{max} (ng/dL)	Mean±SD	26.0±4.86	275.2±547.28	26.5±6.80
	Median	26.5	46	24.5
	Range	20.0-32.0	25.0-1391	21.0-39.0
	Geometric Mean	25.6	82.1	25.9
	Approximate CV (%)	61.8	175.9	62.3
C _{avg} (ng/dL)	Mean±SD	21.6±4.90	72.3±85.49	21.0±4.23
	Median	21.9	38.5	20.1
	Range	15.8-27.4	21.7-243.3	16.6-27.6
	Geometric Mean	21.2	48	20.7
	Approximate CV (%)	62.3	90.9	61.8
C _{min} (ng/dL)	Mean±SD	17.3±5.16	26.7±9.79	15.8±3.97
	Median	17	27	17.5
	Range	11.0-24.0	14.0-37.0	10.0-19.0
	Geometric Mean	16.7	25	15.4
	Approximate CV (%)	63.6	65.7	63
T _{max} (hr)	Mean±SD	9.4±8.16	18.8±6.19	13.1±12.27
	Median	8.3	19.8	14.2
	Range	0.8-24.3	12.0-24.3	0.7-24.3

^a Analysis includes the Hour 2, 4, 12, and 15 outlier concentration values for subject 123-102, Treatment B

Treatment:

A = Phase I: Male applied 1.5g vehicle/150 cm² to one anteromedial thigh; female rubbed

B = Phase II: Male applied 1.5g CP601B/150 cm² to one anteromedial thigh; female rubbed

C = Phase III: Male applied 1.5g CP601B/150 cm² to one anteromedial thigh, application site is covered; female rubbed

Table 11B: Ratios of Geometric Means and 95% Confidence Intervals for Total Serum Testosterone Pharmacokinetic Parameter Estimates: PK Evaluable Population Including All Outlier Values (Study T 01- 02- 02)

Pharmacokinetic Parameter	Treatment Group Ratios	Ratio of Geometric Means ^{a,b}	95% Confidence Limits for Ratio	P-value
C _{avg} (ng/dL) (N=6)	B/A	2.11	(1.20, 3.71)	0.0153
	C/A	0.85	(0.47, 1.52)	0.5324
	C/B	0.4	(0.23, 0.70)	0.0056
C _{max} (ng/dL) (N=6)	B/A	2.8	(1.01, 7.78)	0.0481
	C/A	0.77	(0.27, 2.25)	0.5937
	C/B	0.28	(0.10, 0.77)	0.0196

^a Analysis includes the Hour 2, 4, 12, and 15 outlier concentration values for subject 123-102, Treatment B

^b Ratios of geometric means, confidence limits, and p-values are computed using adjusted means from an ANOVA model that includes terms for patient, period, and treatment

Treatment:

A = Phase I: Male applied 1.5g vehicle/150 cm² to one anteromedial thigh; female rubbed

B = Phase II: Male applied 1.5g CP601B/150 cm² to one anteromedial thigh; female rubbed

C = Phase III: Male applied 1.5g CP601B/150 cm² to one anteromedial thigh, application site is covered; female rubbed

Reviewer's Comments

- Generally a 1.5-2 fold increase in serum T levels were observed to in female patients at each time point due to the transfer of the gel from their male partners (treatment C vs. Treatment B).
- One of the females had an exceptionally high T value at 12 hours in the treatment B arm (C_{max} of ≈ 1400 ng/mL). This value may be disregarded as an outlier (probably analytical error).
- Comparison of the PK profiles and parameters between treatment A (vehicle) and C (active gel with male wearing boxer shorts to cover area of application) is essentially same, indicating that the potential for transfer may be abolished by wearing occlusive clothing to cover the application site.

Biopharmaceutics

Q. Will the to-be-marketed formulation be the same as the clinical trial formulation?

Yes.

Q. Is there a drug release (dissolution) method and specification for this product?

The sponsor had not submitted any dissolution/release specification along with the NDA, and no dissolution information was submitted in the CPB portion of the NDA. However, with persistence from the CMC team, the sponsor did send in a proposed dissolution method.

This method was according to the general principles outlined in the FDA Guidance Document on SUPAC-SS (CMC 7) using modified Franz Diffusion Cells (as in the Table below).

(b) (4)



The results submitted by the sponsor are preliminary findings during an attempt to develop the dissolution method. Based on the theory (propounded by William T. Higuchi in 1961 & 1962), the following is the nature of plots expected:

Analytical Methodology

As with previous NDAs for T replacement, the sponsor used validated radioimmunoassay (RIA) analytical method determine the concentrations of total T, free T, bioavailable T and DHT. The assays were performed at the (b) (4) Sponsor has submitted analytical validation reports with every clinical pharmacology study. In general, the methods are standard, and the precision, accuracy, sensitivity and specificity values are within acceptable range (please see Validation Summary Table in Attachment 1.

Overall, the analytical methodology and validation results are acceptable for CPB purposes.

Labeling Comments

Labeling comments are currently deferred until the Review Team takes a decision of final action on this NDA.

Attachment 1

NDA 21-463 Tostrex™
Testosterone Gel 2%
Cellegy Pharmaceuticals, Inc.

Table 2. Validation Summary

Specification	Acceptance Criteria	Testosterone	BAT	DHT
Validation Report Reference		VP0247 V. 1.0 and V.1.1 [Vol 8, Mod 5, App 2.4.1, pg. 486 & 523] ^a	VP0290 V.1.2 [Vol 10, Mod 5, App 2.4.8, pg. 1315]	VP0227 V.1.0 [Vol 10, Mod 5, App 2.4.6, pg. 1238]
Analyte Range		50-1500 ng/dL (50µL sample)	n/a*	50-1500 ng/dL (50µL sample)
Specificity	No cross-reacting species >30% at 50% binding of the antibody.	•DHT cross reacts (22%) but influence is negligible in subject samples as extraction minimizes DHT presence	•As BAT is a measure of the in vivo fraction unbound and weakly bound T, no known interference exists.	•T cross reacts (40%) but influence is negligible in subject samples as extraction & oxidation minimizes T presence
Sensitivity	Lowest std=LOQ if across-batch CV at LOQ ≤20%	•50 ng/dL (50 uL sample)	3% (As values < 3% are rarely seen clinically, this limit was deemed as low limit).	•2.0 ng/dL (500 uL sample)
Precision	Between-batch CVs ≤15% for the L, M, H QCs and ≤20% for the LOQ QC, using a minimum of three batches	•intra-batch: LLOQ = 16.6% CV; all other QCs <10%CV	•intra-batch: all QCs <6%CV	•intra-batch : LLOQ = 18.1% CV; all other QCs <10%CV
Accuracy	Between-batch mean = ± 15% of nominal value at low, med, & high QCs and not > ± 20% at LOQ	•inter-batch: all QCs <10% CV	•inter-batch: all QCs <5%CV	•inter-batch: LLOQ = 14% CV; all other QCs <10%CV
Recovery	Bias of < ±20%	•LOQ = +19% CV with all others ≤±10% CV	n/a*	•LOQ = +13.6% CV with all others ≤±10% CV
Sample Dilution	Bias of < ±15% $r^2 > 0.95$	•Tracer label recovery= 99.9±1.6% •mean spike recovery=95±8% \	•1 hour incubation is adequate for binding to be at equilibrium •non-specific binding was 1.2%	•Tracer label recovery= 96±2% •spike recovery= 101±17% over range
Stability	Long-term, short-term, freeze-thaw, stock solution and within batch stability data meet individual test specification	•Correction for sample volume ≤10% CV •Linearity of uncorrected sample volume = r>0.99 •serum samples 6 days at RT retain 103% of control •99.4% of control value after 3 freeze-thaw cycles •Hemolyzed samples corrected for dilution retain 107% of control •serum samples at -20°C for 25 mo retain on average 104% of original target value	n/a* •serum samples ≥6 days at RT retain 103% of control •105.0% of control value after 3 freeze-thaw cycles •Hemolyzed samples (up to 5%) corrected for dilution retain 101.2% of control •serum samples at -20°C for 26 mo retain on average 105% of original target value	•Correction for sample volume 4.3-21.7% CV •Linearity of uncorrected sample volume = r≥0.989 •serum samples 6 & 7 days at room temp & 4°C retain 105% of control •104% of control value after 3 freeze-thaw cycles •Hemolyzed samples corrected for dilution retain 106% of control •serum samples at -20°C for 24-32 months retain on average 97% of original target value

*Since BAT, an expression of the bioavailable fraction of testosterone, includes the free and weakly bound forms of testosterone, it is calculated by multiplying the bioavailable fraction times the total testosterone. An analyte range and an accuracy assessment are not relevant as BAT is simply the ratio of two radioactivity levels.

^a These validation reports for testosterone are located in Appendix 2.4.1 of each clinical study report. The cited reference is for that associated with the T 00-03-01 report.

Keys: CV= Coefficient of Variation; HCG=human chorionic gonadotropin; QC= Quality control; LOQ=Limit of Quantitation; LLOQ=Lower limit of quantitation; RT=Room Temperature; TSH=Thyroid Stimulating Hormone.

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Attachment 3

**FORTIGEL Final PK Parameters by Day
(sorted by Cmax)**

(July 17, 2003)

Day 14					Day 42 or 56					Day 182				
Pat. ID	Dose	Cmax	Cmin	Cavg	Pat. ID	Dose	Cmax	Cmin	Cavg	Pat. ID	Dose	Cmax	Cmin	Cavg
21107	80	279	156	212	21107	80	223	124	179	20116	60	265	162	207
11106	80	321	106	216	2103	40	364	223	322	15109	80	310	133	225
12105	80	322	146	259	3113	80	371	270	324	10110	80	375	206	263
20127	60	328	210	258	14108	60	384	184	265	14127	60	381	165	283
15108	80	357	208	257	11113	80	390	204	268	20114	60	395	211	321
18118	80	363	196	258	12104	80	396	198	254	21107	80	395	226	315
2106	80	370	259	306	20127	60	431	295	353	3113	80	400	224	319
3101	80	370	214	281	15109	80	436	131	321	5103	60	401	275	325
15100	80	380	173	280	3121	40	482	192	318	14133	60	401	276	370
2102	80	389	245	304	14137	80	483	198	387	20127	60	414	181	311
6124	80	392	228	307	3108	80	490	175	298	5106	40	423	266	344
11108	80	393	255	317	20114	60	499	228	321	14128	60	436	241	339
1110	80	396	237	309	20116	60	506	280	345	22105	80	439	229	332
22103	80	398	189	298	2110	60	520	277	362	3121	40	446	296	363
22105	80	402	218	270	15100	80	529	339	395	20105	40	467	202	296
12130	80	403	225	286	21106	60	553	263	419	20118	60	467	236	283
3113	80	406	263	328	10113	80	593	206	357	2103	40	468	229	341
12117	80	407	232	326	22105	80	598	215	362	2100	80	469	247	347
11113	80	410	206	259	14127	60	612	155	277	20122	80	493	254	338
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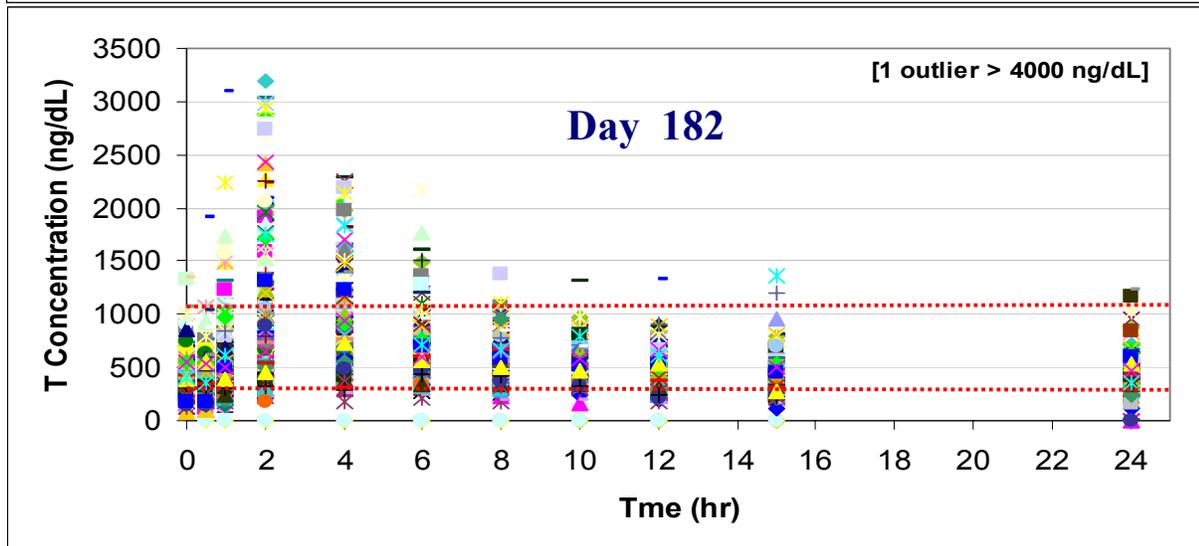
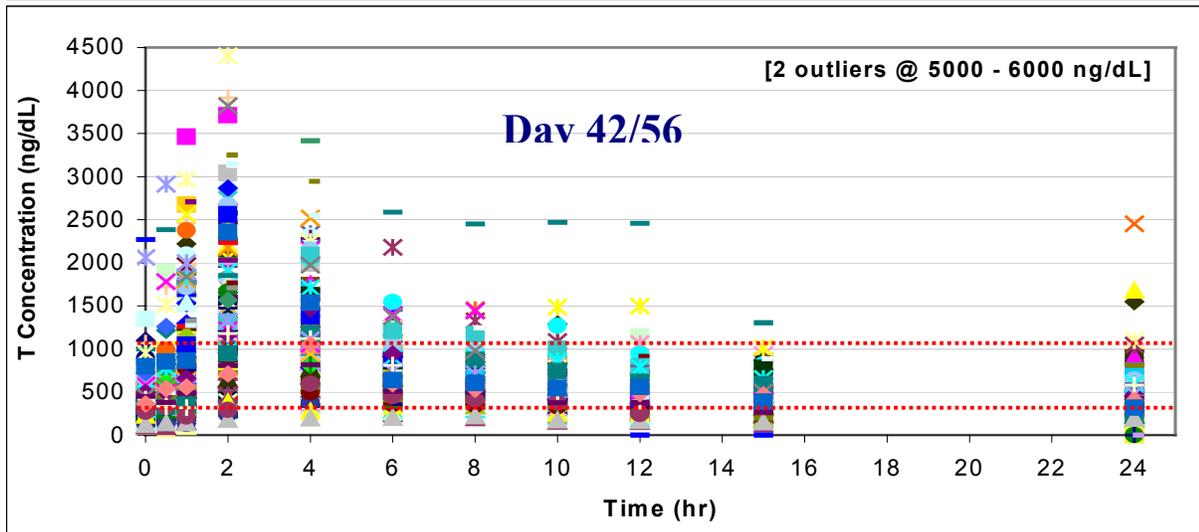
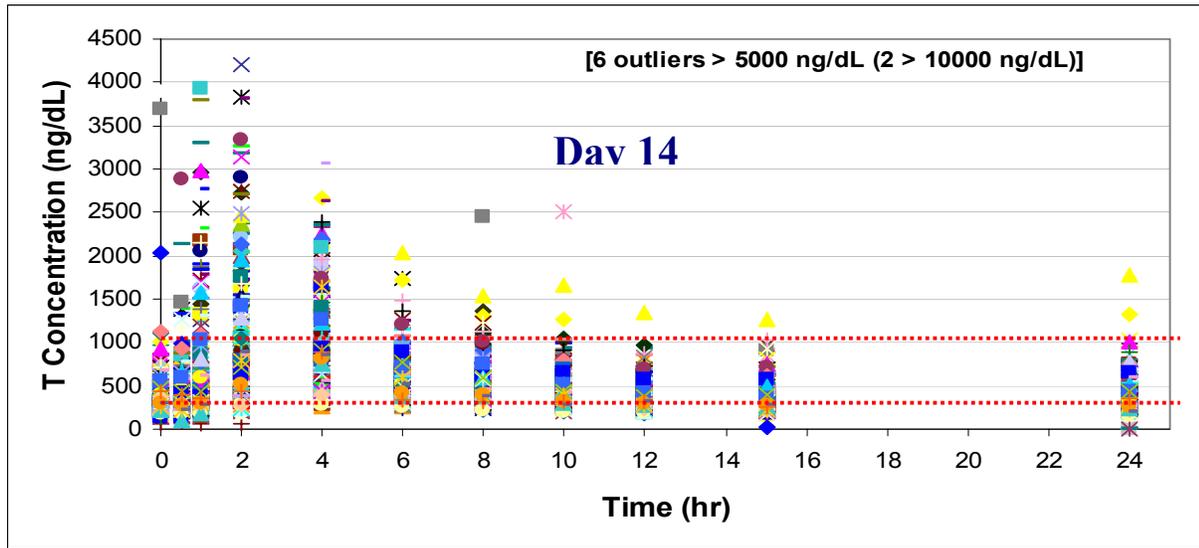
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6111	40	2900	332	686					
11101	40	2964	399	928					
14147	40	3063	356	857					
18117	40	3143	385	755					
11112	40	3252	282	708					
6115	40	3301	243	888					
6117	60	3684	360	920					
19107	40	3781	265	749					
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5101	40	3829	646	1172					
5102	60	3884	238	795					
4115	40	4195	449	890					
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Max		10800	705	2064					
Avg		1595	294	588					
SD		1426	120	277					

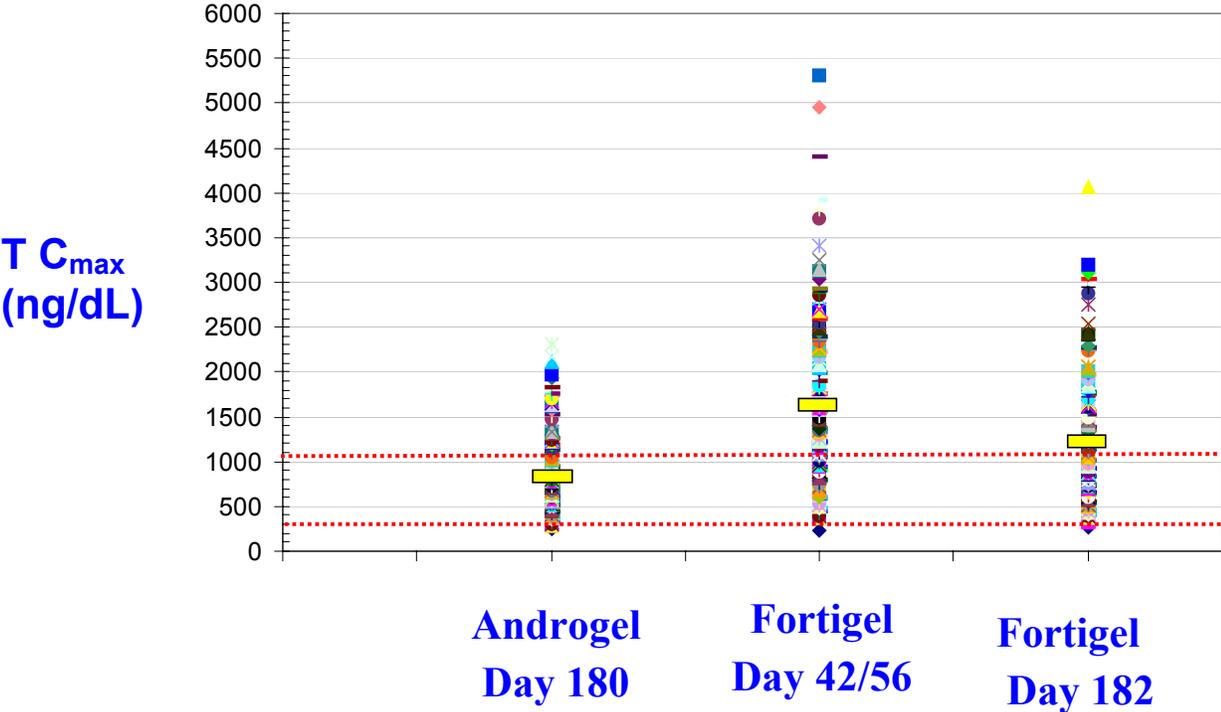
Attachment 4

Fotrtigel PK Profiles (All Patients):



Extreme Exposure Comparison between FORTIGEL and ANDROGEL (All Patients):

C_{max} Comparison



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this page is the manifestation of the electronic signature.**

/s/

Dhruba Chatterjee

7/2/03 03:39:17 PM

BIOPHARMACEUTICS

All suggested changes from (b) (4)

Ameeta Parekh

7/2/03 04:22:58 PM

BIOPHARMACEUTICS

I concur

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
<i>NDA Number</i>	21-463	<i>Brand Name</i>	Tostrex
<i>OCPB Division (I, II, III)</i>	DPE II (HFD 870)	<i>Generic Name</i>	Testosterone
<i>Medical Division</i>	DRUDP (HFD 580)	<i>Drug Class</i>	Hormone replacement
<i>OCPB Reviewer</i>	Dhruba J. Chatterjee, Ph.D.	<i>Indication(s)</i>	Hypogonadism
<i>OCPB Team Leader</i>	Ameeta Parekh, Ph.D.	<i>Dosage Form</i>	Gel
<i>Date of Submission</i>	6/3/2002	<i>Dosing Regimen</i>	Once Daily
<i>Estimated Due Date of OCPB Review</i>	3/3/2003	<i>Route of Administration</i>	Topical
<i>PDUFA Due Date</i>	4/3/2003	<i>Sponsor</i>	Cellegy
<i>Division Due Date</i>	3/15/2003	<i>Priority Classification</i>	3S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	7		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
body wt.				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	7			
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)	<p>How does the PK of T relate to normal T levels? What is the frequency of outliers (high/low T values)? How does demographics affect PK? Is there an <i>in vitro</i> release test method (CMC was notified at filing)?</p>			
Other comments or information not included above	<p>For Sponsor: 1) Please provide electronic copies of the Clin. Pharm & Biopharmaceutics studies to the NDA. 2) Please provide a separate analysis of the C_{max} with respect to frequency and magnitude from the Phase 3 pivotal clinical trial.</p>			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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this page is the manifestation of the electronic signature.**

/s/

Dhruba Chatterjee
7/31/02 12:33:32 PM
BIOPHARMACEUTICS
Fileable

Ameeta Parekh
8/21/02 02:53:48 PM
BIOPHARMACEUTICS
I concur