CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-454

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-454	*Brand Name*	TESTIM™1%
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	Testosterone 1% gel
Medical Division	DRUDP (HFD 580)	*Drug Class*	Testosterone replacement
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	T replacement in
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	Transdermal Gel
Date of Submission	12/31/2001	*Dosing Regimen*	Once daily
Estimated Due Date of OCPB Review	10/1/2001	*Route of Administration*	Transdermal
PDUFA Due Date	10/31/2001	*Sponsor*	Auxilium Pharmaceuticals
Division Due Date	10/24/2001	*Priority Classification*	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	4		
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:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X			
multiple dose:				
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:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
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	**5**			

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?	**At this reviewer's request, sponsor submitted a worksheet compiling all relevant CPB information on the pivotal trial (Study AUX-TG-202.01**	
QBR questions (key issues to be considered)		
Other comments or information not included above	• **Sponsor confirmed by Fax dated 2/12/2002 that the clinical trial formulation was the same as the to-be-marketed formulation.** • **Pivotal clinical trial and release specifications were not submitted in the CPB section. However, this CPB review includes analysis of all of those information**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-454, HFD-850(Electronic Entry or Lee), HFD-580(CSO), HFD-870(TL, DD, DDD), CDR (B. Murphy)

Clinical Pharmacology & Biopharmaceutics Review

NDA:	21-454
Product Trade Name:	TESTIM 1%
Active Ingredient/s:	Testosterone
Indication:	Testosterone Replacement Therapy
Submission Date:	December 31, 2001
Sponsor:	Auxilium Pharmaceuticals Inc.
Type of Submission:	Original NDA, 3S
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

OCPB Briefing (on 10/18/02) attended by H. Malinowski, A. Parekh, V. Jarugula, MJ Kim, J. Christi, D. Davis and DJ Chatterjee

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Synopsis

TESTIM, the subject drug product of this submission, is a 1% hydroalcoholic gel (composition in Table 1 below) formulation of testosterone that the hypogonadal male applies once daily on the skin of his upper arms and shoulders. [redacted] the transfer of the testosterone, [redacted] 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 406 hypogonadal patients randomized in 4 groups, two doses of TESTIM (50 and 100 mg/day), placebo and a commercially available transdermal T-patch (Androderm) for non-scrotal application for the same indication. Additionally, 5 clinical pharmacology studies were conducted in support of this NDA.

Recommendation

This NDA is acceptable to OCPB.

Comments to Sponsor

Is there an effort to make available (in the future) a dose of TESTIM intermediate between 50 and 100 mg of T?

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Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

- The sponsor has provided adequate clinical pharmacological evidence in this NDA that on days 30 and 90, treatment with TESTIM adequately replaces and maintains serum T within the 'normal' physiological levels (300 – 1000 ng/dL).
- Average serum T levels following the 50 mg (T) TESTIM dose is no different than that observed with 2 X 2.5 mg T transdermal systems (ANDRODERM). At 24 hours post administration of this lower dose of TESTIM, the mean average serum T level was below 300 ng/dL. Following administration of the higher (100 mg T) dose, exposure to T was proportionally higher and well within the physiologic normal boundaries.
- Currently, there is no intermediate dose available between the 50 and 100 mg T doses. Hence, for patients who are under corrected from the lower dose yet over corrected from the higher, selection of an intermediate dose in the future would be desirable.
- Based on the data presented by the sponsor, it appears on face that efficacy for TESTIM was superior to that obtained with ANDRODERM. It is to be noted that ANDRODERM was not dose-titrated as stated in its label (to its maximum possible dose) while TESTIM was. Hence, the two arms may not be comparable in terms of their ability to replace T.
- The DHT levels following TESTIM treatment increased, but was generally found to be within clinically acceptable limits.
- A few key secondary efficacy parameters were positively affected (as expected) following TESTIM treatment. Lean body mass increased, whereas fat mass and % total fat reduced (and were significantly different from placebo and ANDRODERM). There was improvement in certain sexual function scores as well.
- In a separate study, sponsor compared ANDROGEL and TESTIM, and the two were found generally comparable in their ability to replace serum T. Exposure to T following TESTIM was found to be marginally higher (clinically insignificant).
- There was a very significant potential of T transfer into female partners. This transfer was reduced from shoulder-to-shoulder rubbing (more relevant based on the way TESTIM will be used) as compared to abdomen-to-abdomen rubbing. For shoulder-to-shoulder rubbing, there was a 50% increase over the baseline value in serum testosterone in female partners 12 hours after the males applied Testim™ even when both the partners wore shirts. The sponsor provided re-analysis of individual patient data on 10/25/2002. Based on this information, it was concluded that clothing (eg. a T-shirt to cover the area of application/contact) prevents transfer of testosterone from TESTIM to others.
- The effect of showering with a mild soap at 1, 2 and 6 hours post application of Testim™ 100 mg was evaluated in a clinical trial. The study demonstrated that washing reduced testosterone levels at each time point; however, when washing occurred two or more hours post drug application, serum testosterone levels remained within the normal range.
- Based on additional information sent by sponsor on 10/26/2002, it was concluded that thorough washing of the palms following TESTIM application completely removes any residual testosterone.
- Based on the dissolution information from the sponsor (via the CMC reviewer), the acceptance of the release specifications is deferred to the CMC team (see BIOPHARMACEUTICS section).

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 Kleinfelter's syndrome, bilateral cryptrochridism, 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 this NDA, the sponsor has defined the "normal" range of T serum level 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. Another similar transdermal gel formulation (ANDROGEL) is also available at similar dosage strengths.

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 urineas androsterone, etiocholanolone and glucuronide and sulfate conjugates of androstanediol and estrogens.

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

his upper arms and shoulders. [redacted] the transfer of the testosterone, [redacted], 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 406 hypogonadal patients randomized in 4 groups, two doses of TESTIM (50 and 100 mg/day), placebo and a commercially available transdermal T-patch (Androderm) for non-scrotal application for the same indication. This review focuses on the 5 clinical pharmacology studies conducted in support of this NDA.

Table 1. Description & Composition of TESTIM™

Testim is a clear to translucent topical gel containing 1% testosterone in a single-phase solution. The gel has an alcoholic/musk odor. Testim is filled into individual, blind end, capped, single use; aluminum tubes to a 5-g fill weight. Description of components (for 5 g) are described herein:

Component	Reference	Function	Amount (g)	% w/w
Testosterone (micronized)	USP	***Active ingredient***	0.05	1.00
Oxacyclohexadecan-2-one		[redacted]		
Carbopol	NF	[redacted]		
[redacted]				
Propylene Glycol	USP			
Glycerin	USP			
Polyethylene Glycol [redacted]	NF			
Alcohol (200 Proof), USP	NF			
Tromethamine	USP			
Purified water	USP			
Total weight			**5.00 g**	**100%**

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 406 hypogonadal men with primary end points based on clincial pharmacology, the sponsor conducted 4 additional CPB studies to address key efficacy and safety issues. Each of the 5 individual studies are reviewed below:

1. Study AUX-TG-202.01

Methodology: Subjects were to be screened within 30 days prior to randomization into the study. If all inclusion/ exclusion criteria were met, including a morning 0800 h serum testosterone of <300 ng/dL, patients were to be randomized into one of the following four treatment groups:

- AA2500 gel (50 mg testosterone (1 x 5 g tube)),
- AA2500 gel (100 mg testosterone (2 x 5 g tube)),
- Placebo gel (2 x 5 g placebo tubes)
- Androderm (2 x 2.5 mg testosterone patches).

Subjects were to receive either 50 mg of testosterone in AA2500, 100 mg of testosterone in AA2500, matching placebo gel or Androderm (2 x 2.5 mg testosterone patches) daily for study Days 1 through 60. After 60 days, subjects receiving Placebo or Androderm patches were to continue to receive the same dosage and formulations of these regimens for 30 more days. After 60 days, subjects receiving AA2500 could have their dosage titrated up from 50 mg to 100 mg, down from 100 mg to 50 mg or they could be maintained on their initial dose for 30 more days based upon individual pharmacokinetic profiles taken on Day 30.

Number of Subjects (planned and analyzed): 400 subjects planned; 407 randomized; 378 analyzed for efficacy (MITT); 301 analyzed for efficacy (PP); 406 analyzed for safety (ATS)

Diagnosis and Main Criteria for Inclusion: The male subjects were to be between 35 and 80 years old, with a morning serum testosterone level ≤ 300 ng/dL and clinical symptoms of low testosterone. The subjects were generally in good health, based upon the results of a medical history, physical examination and laboratory profile.

Test Product, Dose and Mode of Administration:

AA2500 topical gel formulation containing 1% testosterone, supplied in foil-lined tubes containing 50 mg of testosterone; doses were 50 mg of testosterone (one tube of AA2500 and one tube of placebo) and 100 mg of testosterone (two tubes of AA2500) daily. Matching placebo topical gel formulation was supplied in 1 or 2 foil-lined tubes; Androderm 2.5 mg testosterone transdermal patch (two patches daily, each containing 12.2 mg testosterone and delivering 2.5 mg) were used.

Duration of Treatment: 90 days

Criteria for Evaluation:

Primary Efficacy: Percentage of MITT responders at Day 90 (LOCF), based upon whether C_{min} and C_{avg} (minimum and average 24-hour testosterone levels) were in the range from [redacted] percentage of responders with testosterone levels at Day 90 (LOCF), based on whether C_{avg} was in the range from [redacted]

Secondary Efficay: Percentage of ATS responders based on LOCF; percentage of PP responders at Day 90, percentage of MITT and PP responders at Day 30, change from baseline for C_{min}, C_{max}, and C_{avg} at Days 30 and 90 for total testosterone, free testosterone and DHT, C_{avg} DHT/ C_{avg} testosterone at Days 30 and 90, change from baseline for body composition (total body mass, lean body mass, fat mass, and percent fat) at Day 90, change from baseline for sexual functioning (sexual performance, motivation, spontaneous erections, sexual desire, enjoyment (with or without partner), satisfaction with erection duration, percentage of full erection), and mood (positive, negative) at Days 30, 60 and 90, and change in bone mineral density of the lumbar spine, by Day 90.

Results:

The results focus primarily on the pharmacokinetic parameters of T (total and free) and DHT following administration of the different treatments, as showing in the following figures. Note: The TESTIM treatment has been denoted as "AA2500" in the figures below (and throughout the NDA):

Figure 1A. Mean Testosterone (ng/dL) Serum Concentation Profile at Baseline and Day 30 by Treatment PP Population

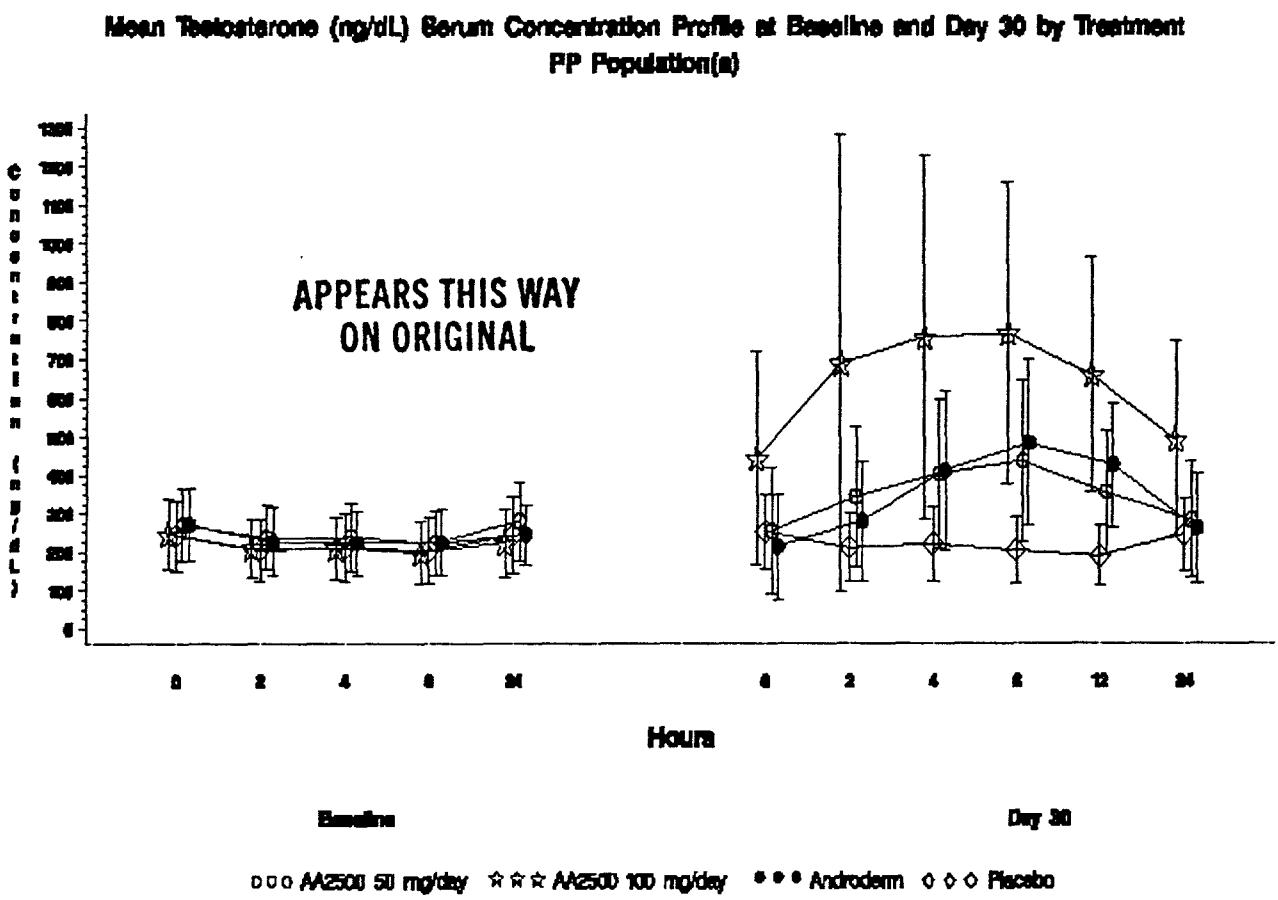


Figure 1B. Mean Testosterone (ng/dL) Serum Concentation Profile at Baseline and Day 90 by Treatment PP Population

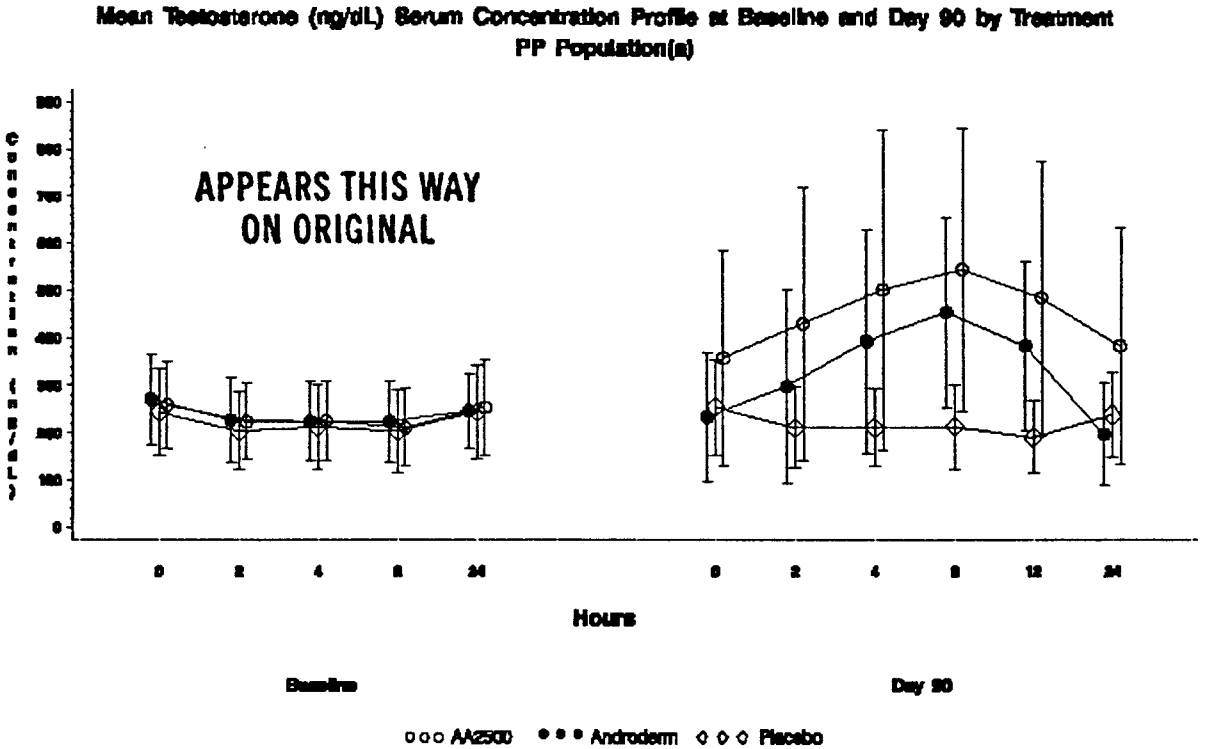


Figure 2A. Mean Free Testosterone (pg/ mL) Serum Concentation Profile at Baseline and Day 30 by Treatment PP Population

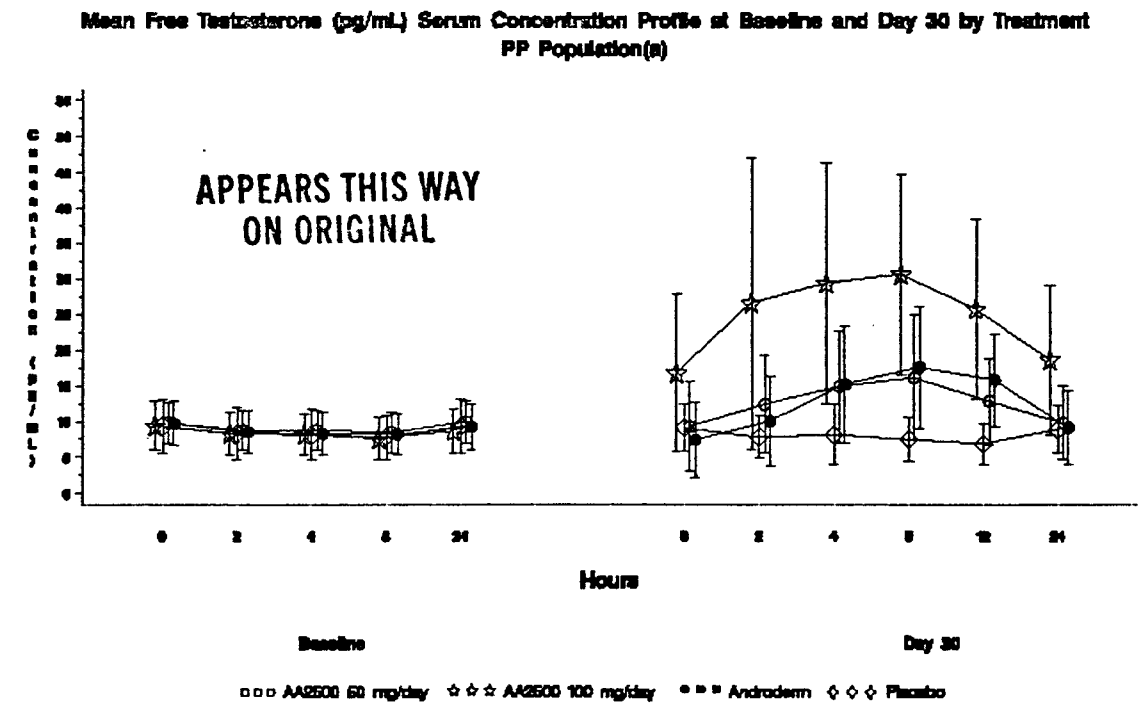


Figure 2B. Mean Free Testosterone (pg/ mL) Serum Concentation Profile at Baseline and Day 90 by Treatment PP Population

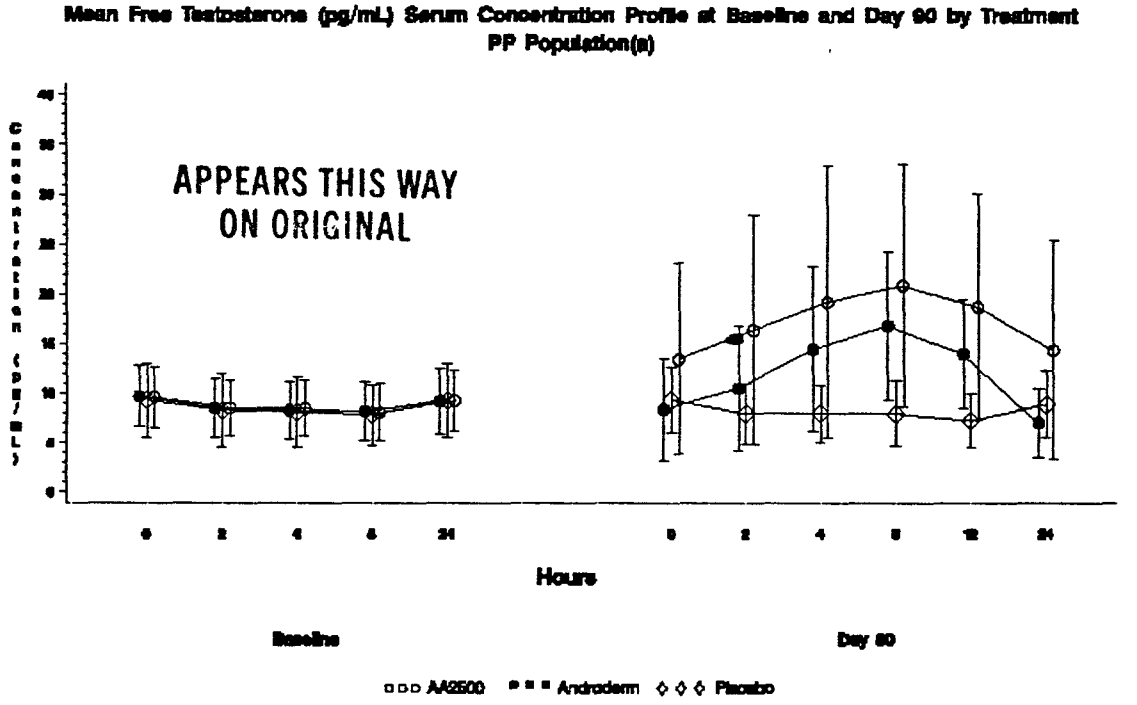


Figure 3A. Mean Dihydrotesterone (pg/ mL) Serum Concentration Profile at Baseline and Day 30 by Treatment PP Population

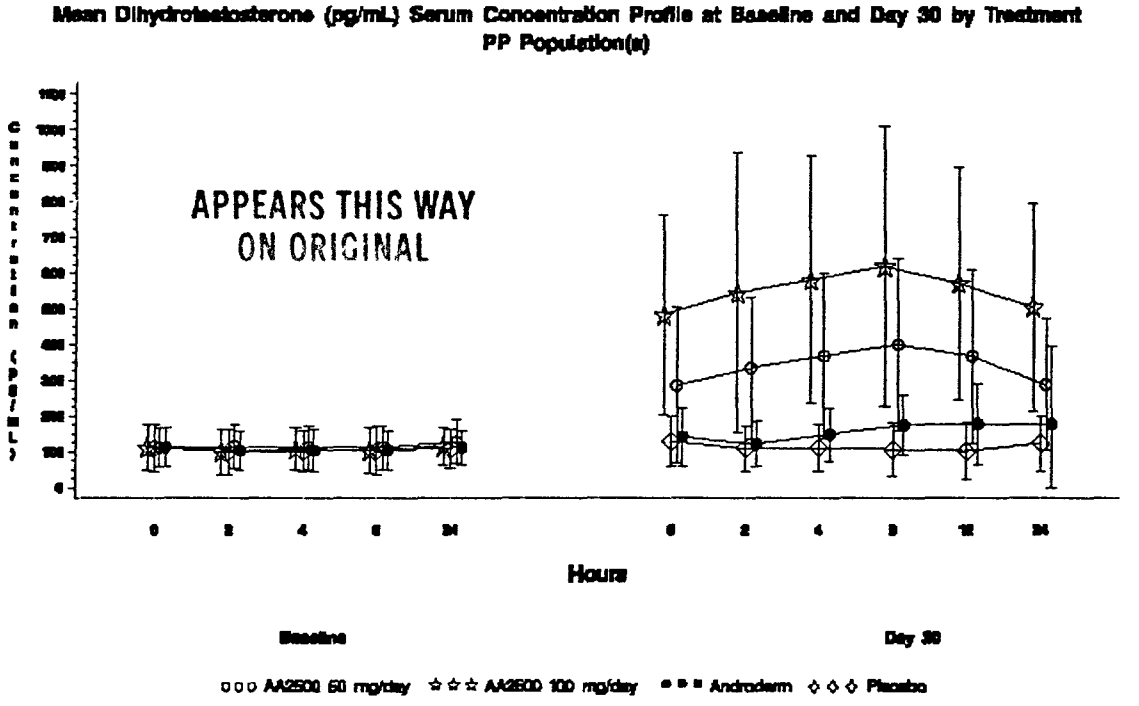


Figure 3B. Mean Dihydrotesterone (pg/ mL) Serum Concentation Profile at Baseline and Day 90 by Treatment PP Population

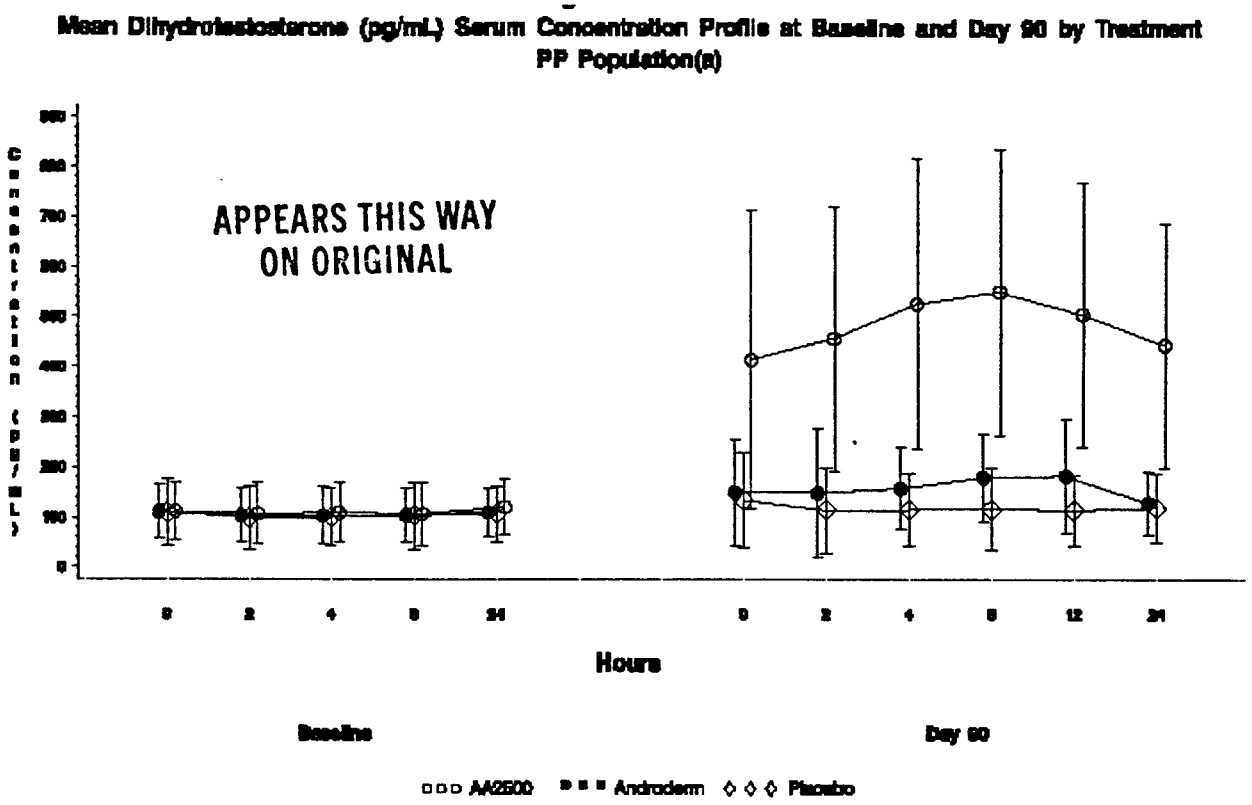
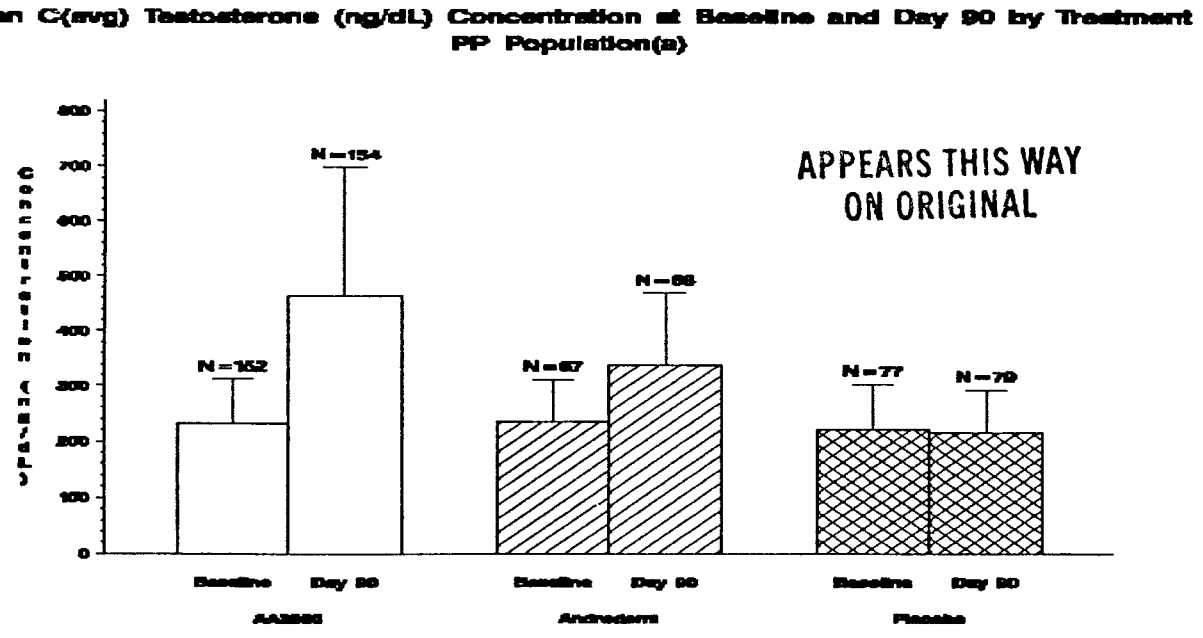
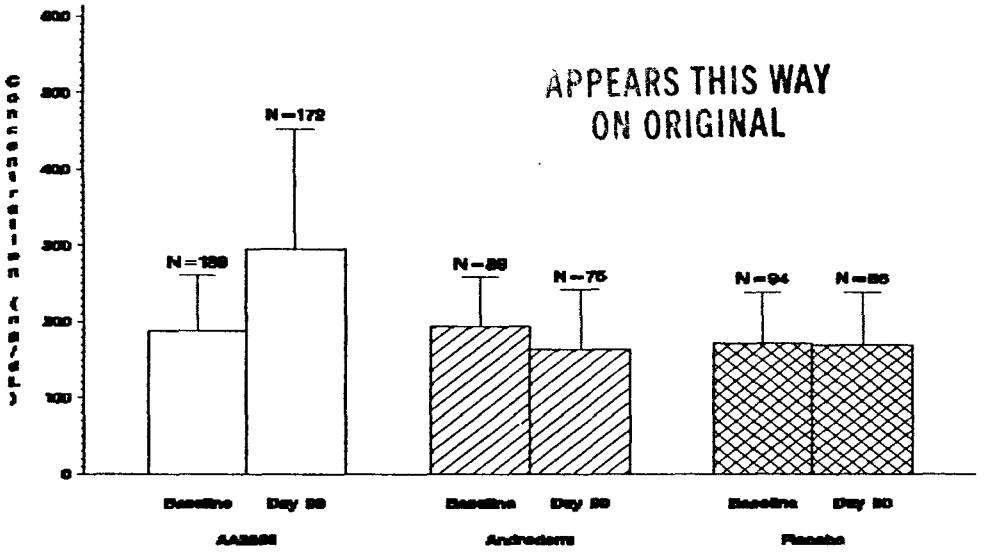


Figure 4. Mean C_{avg} and C_{min} Testosterone (ng/ dL) Concentation at Baseline and Day 90 by Treatment PP Population



Mean C(min) Testosterone (ng/dL) Concentration at Baseline and Day 90 by Treatment
MITT Population(a)



In addition to the above figures, at the request of this reviewer, the sponsor organized the clinical pharmacology data (relevant PK parameters) for all the patients into one file, and the following statistics was computed of the information for all patients (N = 192) on both the doses of TESTIM:

Table 2: Key Pharmacokinetic Parameters and Statistics

	C_{avg}* Day 30	C_{min} Day 30	C_{max} Day 30	DHT/T Day 30	C_{avg} Day 90	C_{min} Day 90	C_{max} Day 90	DHT/T Day 90
Mean	489.1	309.1	718.5	0.094	463.4	294.6	660.8	0.107
SD	271.472	182.25	509.934	0.038	236.9	158.3	385.6	0.039
Min								
Max								

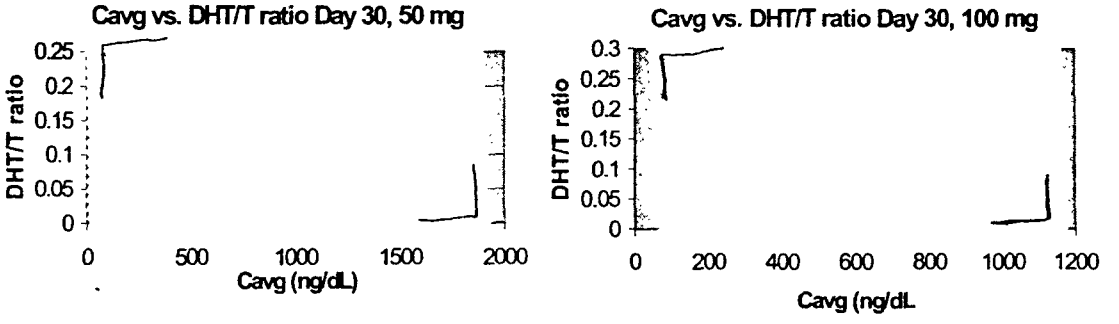
* All concentration units for T are in ng/dL

Reviewer's Comments (Primary Efficacy/safety)

- Based on C_{avg} and C_{min} values, the PK profile for T appears acceptable on Days 30 & 90 (this judgement is based also upon consideration of PK of T following ANDROGEL administration).
- It may be noted that efficacy from the 50 mg dose is no different than the Androderm arm. Only the 100 mg dose shows significantly increased C_{avg} as compared to the other 3 treatments.
- If one compares the changes from baseline in serum T following 50 and 100 mg doses on day 30, there is a perfect dose – 'response' relationship. The mean change from baseline for the 50 mg dose is 119 ng/dL, while the same for the 100 mg dose is 338 ng/dL (two-fold higher). Exactly similar trend was seen for DHT. However, there was a 3.5 fold higher change in baseline for mean free T with the 100 mg dose as compared to the 50 mg.
- The Androderm and the TESTIM treatment arms may not be comparable since the TESTIM arm employed a dose titration scheme, while the Androderm arm did not. In fact, the dose used for

Androderm is not the maximal labeled dose. The sponsor was made aware of these issues (including consideration of ANDROGEL for active comparison) prior to beginning Phase III.

- Ratios of DHT/T were elevated, but generally within an acceptable range (normally 0.05 – 0.35). The MO was notified to examine whether the elevation of DHT was clinically significant.
- On inspection of individual patient PK parameters on Day 30, about 15% of the patients had C_{max} values above 1000 ng/dL, and a few among those were above 2000 ng/dL. Upon titration of the dose based on the day 60 profile, the number of patients with C_{max} values above 1000 ng/dL reduced on Day 90. However, C_{max} levels were above 2000 ng/dL rarely (< 2 % of patients).
- It may be noted that the PK data on Day 30 following the 100 mg T dose is highly variable. To address this issue, data analysis was performed to determine whether this could be attributed to variability in T metabolism. By plotting T exposure in individual patients to DHT/T ratios as below, it may not account for total variability. Other possible contributing factors are how a patient applies contents of 2 tubes and skin permeability.



- Unlike ANDROGEL, there is no scope of intermediate titration of dosage between 50 and 100 mg of T. Hence, in the likely event of patients showing supra-physiologic exposure to T from the high dose, yet sub-physiologic exposure from the low dose, TESTIM might not provide the intended clinical benefit.

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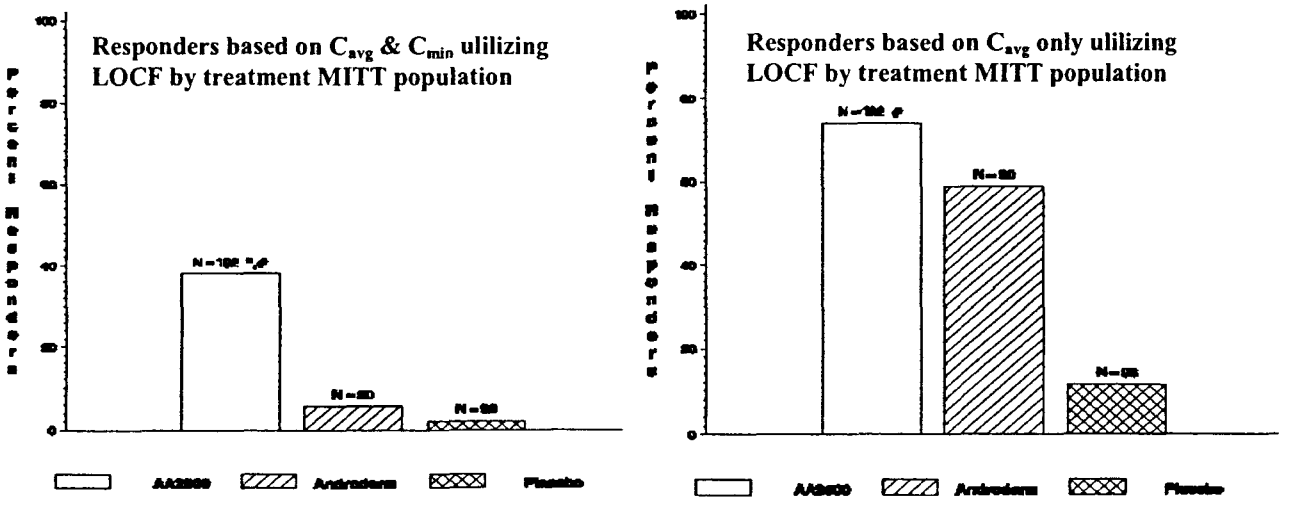
Figure 5. Responders Analysis



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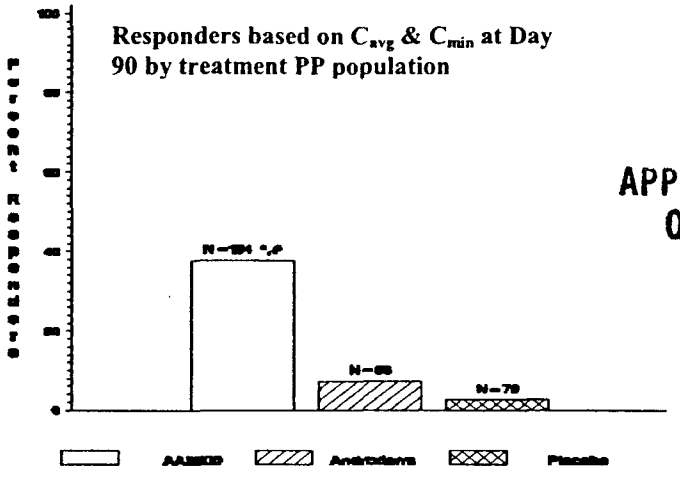

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In addition to the above, the sponsor collected certain parameters to determine secondary efficacy of TESTIM. These included body composition (lean and total body mass, fat mass and % fat), sexual functions (sexual performance, sexual motivation, spontaneous erections, sexual desire, enjoyment with/without a partner etc.), mood (positive and negative) and bone mineral density.

Reviewer's Comments (Secondary Efficacy)

- For body composition, at day 90, the changes in lean body mass (increase), fat mass (decrease) and % fat (decrease) with TESTIM were found to be statistically significantly different from either placebo or Androderm.
- Some of the sexual function scores (performance, motivation, spontaneous erections and desire) were found significantly different from either Androderm and/or placebo on days 30, 60 and 90. However, other sexual functions were not different in the groups.
- There was no significance in the differences observed for either mood or bone mineral density determinations.

2. Study AUX-TG-201.01

The sponsor had conducted the clinical study to compare the performance of TESTIM in comparison to ANDROGEL. Specifically, the objective of this study was to evaluate the pharmacokinetic profiles after a single dose of 50 mg of the new testosterone topical gel formulation (TESTIM) compared to 50 mg of the commercial testosterone topical gel preparation (ANDROGEL).

A total of 29 patients were screened and randomized to one of the treatments and crossed over to the second treatment after a 7-day washout period. Serial PK sampling was adequately planned, and the typical PK parameters were determined (for total & free T and DHT).

Results:

The following Tables compare the two treatments for total T, free T and DHT

Table 3A. C_{max}(obs) and AUC_{0-24} for Total Testosterone: Adjusted Geometric Means (CV%)

Formulation	Geometric Mean (CV_b%)	
	C_{max}(obs) (ng/dl)	AUC_{0-24} (ng.h/dl)
AA2500		5864.5 (77.9)
AndroGel®		4499.1 (77.9)

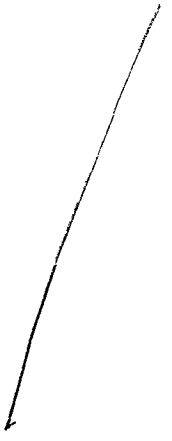
Table 3B. C_{max}(obs) and AUC_{0-24} for Free Testosterone: Adjusted Geometric Means (CV%)

Formulation	Geometric Mean (CV_b%)	
	C_{max}(obs) (pg/ml)	AUC_{0-24} (pg.h/ml)
AA2500		240.7 (75.4)
AndroGel®		164.2 (90.0)

Table 3C. C_{max}(obs) and AUC_{0-24} for Dihydrotestosterone: Adjusted Geometric Means (CV%)

Formulation	Medians (Range)	
	C_{max}(obs) (pg/ml)	AUC_{0-24} (pg.h/ml)
AA2500		4891.0 (257.5 –15259.1)
AndroGel®		4091.7 (225.0 –16034.5)

Figure 6. Serum total T Concentration – Time profile (comparison)



Reviewer's Comments

- From the results above, it is evident that the replacement of androgen from TESTIM is at a marginally higher level than ANDROGEL
- The two treatments provide comparable time profiles for total, free T and DHT (figures for latter two are not presented in this review)
- The higher levels of free & total T and DHT following treatment with TESTIM does not seem to be beyond clinically concerning limits.

A very relevant issue with transdermal gels for T-replacement in hypogonadal men is the potential of transference of T onto the skin (and thereby the systemic circulation) of the female partners. The sponsor conducted two well-designed studies to address this issue (as follows).

3A. Study AUX-TG-206

This study was a Phase I, open label, single dose, single center, 5-treatment session design in 60 (30 male and 30 female) subjects. The formulation of testosterone gel studied was the new AA2500 topical gel formulation. On Day -1, groups of 6 males and 6 females were randomized to one of 5 treatment/rubbing sessions. Females had baseline, 24-hour testosterone blood levels (7 intervals) measured on Day –1. On Day 1, a single dose of the testosterone gel (delivering 100 mg testosterone) was administered topically to the abdomen of all males. At one of 4 selected intervals after application (1 hour, 4, 8 or 12 hours), 6 males engaged in skin-to-skin rubbing for 15 minutes with 6 female partners (i.e., male abdomen to female abdomen). In an additional group of 6 males and 6 females, males wore a shirt (put on 15 minutes post study drug application) to cover their abdomens during the rubbing session at 1-hour post application. Blood sampling for testosterone levels was performed in all females at selected intervals over the 24-hour post-rubbing period. There was a 1-week follow-up safety assessment for all subjects.

Results:

Table 4A. Testosterone Systemic Exposure in Females Following Skin-to-Skin Rubbing at 1, 4, 8, and 12 Hours After Administration to Males (Study AUX-TG-206.00)

Group Time of Contact (Post male dosing)		Testosterone Systemic Exposure: Post-Skin-to-Skin Rubbing		
		$AUC_{(0-24)}$ ng.h/dL	C_{max} ng/dL	C_{avg} ng/dL
I 1 hour	N	6	6	6
	Baseline (Day -1) Mean Range	312	20	13
	Post-Rubbing Mean Range	3648	223	149
	Change from Baseline Mean (absolute) %	3336 1178%	203 1128%	136 1149%
II 4 hours	N	6	6	6
	Baseline (Day -1) Mean Range	476	30	20
	Post-Rubbing Mean Range	2656	145	109
	Change from Baseline Mean (absolute) %	2180 549%	115 441%	89 537%
III 8 hours	N	6	6	6
	Baseline (Day -1) Mean Range	391	22	16
	Post-Rubbing Mean Range	1991	118	81
	Change from Baseline Mean (absolute) %	1600 535%	96 582%	65 522%
IV 12 hours	N	6	6	6
	Baseline (Day -1) Mean Range	245	15	10
	Post-Rubbing Mean Range	1794	126	73
	Change from Baseline Mean (absolute) %	1549 919%	111 1021%	63 900%

Table 4B. Testosterone Systemic Exposure in Females Following Shirt-to-Skin Rubbing at 1 Hour After Administration to Males

Group Time of Contact (Post male dosing)		Testosterone Systemic Exposure: Post-Shirt-to-Skin Rubbing		
		$AUC_{(0-24)}$ ng.h/dL	C_{max} ng/dL	C_{avg} ng/dL
V 1 hour	N	6	6	6
	Baseline (Day -1)			
	Mean	425	29	18
	Range			
	Post-Rubbing			
	Mean	1302	77	53
	Range			
	Change from Baseline			
	Mean (absolute)	877	48	35
	%	216%	183%	210%

Reviewer's Comments

- From the results above, it is clear that there is a high potential of T transfer into the skin and systemic circulation of female partners. Plasma levels in the female partners were as high as over 10 fold than the normal base line levels in some cases.
- There was no indication of a reduction of this potential of transfer with time. The C_{avg} value was 7 fold higher than the normal even at 12 hours post administration of the gel by the male partners.
- Although there was a significant reduction of the transfer from males who wore a shirt, there was still some transfer detected. The C_{avg} value was 3 fold higher as compared to the baseline (1 hour post administration).

3A. Study AUX-TG-209

Since the previous transference study was performed with abdomen-to-abdomen rubbing, and TESTIM is indicated to be applied on the shoulders and/or upper arm, the sponsor conducted another transfer study using shoulder-to-shoulder rubbing technique.

Twenty-four eligible couples (in 4 groups of 6 couples each) were randomized into one of the following groups:

Group I: 1-hour post dose group (males with shirt, females no shirt);

Group II: 4-hour post dose group (males no shirt, females no shirt and females showered immediately after the rubbing session);

Group III: 4-hour post dose group (males with shirt, females no shirt);

Group IV: 12-hour post dose group (males with shirt, females with shirt).

The dose of study drug administered to males was the same in each group (100 mg T).

Results:

Table 5. Testosterone Systemic Exposure in Females Following Shirt-to-Skin, Skin-to-Skin, or Shirt-to-Shirt Rubbing at 1, 4, or 12 Hours After Administration to Males (Study AUX-TG-209)

Group Time of Contact (Post scheduled time for male dosing)		Testosterone Systemic Exposure: Post-Body-to-Body Rubbing		
		$AUC_{(0\text{-}24)}$ ng.h/dL	C_{max} ng/dL	C_{avg} ng/dL
I 1 hour M:Shirt	N	6	6	6
	Baseline, No Treatment (Day -1)			
	Mean	308	20	13
	Range	—	—	—
	Post Treatment (Day 1)			
	Mean	458	30	19
	Range	—	—	—
	Change from Baseline			
	Mean (absolute)	150	10	6
	%	54%	53%	51%
II 4 hours M/F: No Shirt, Female Wash	N	6	6	6
	Baseline No Treatment (Day -1)			
	Mean	270	20	11
	Range	—	—	—
	Post Treatment (Day 1)			
	Mean	1208	79	49
	Range	—	—	—
	Change from Baseline			
	Mean (absolute)	938	59	38
	%	455%	395%	444%
III 4 hours M: Shirt	N	5*	6	6
	Baseline No Treatment (Day -1)			
	Mean	537	44	21
	Range	—	—	—
	Post Treatment (Day 1)			
	Mean	743	51	31
	Range	—	—	—
	Change from Baseline			
	Mean (absolute)	206	7	10
	%	32%	20%	42%
IV 12 hours M/F: Shirt	N	6	6	6
	Baseline No Treatment (Day -1)			
	Mean	404	28	17
	Range	—	—	—
	Post Treatment (Day 1)			
	Mean	558	42	23
	Range	—	—	—
	Change from Baseline			
	Mean (absolute)	154	14	6
	%	50%	51%	47%

Reviewer's Comments

- There was a marked reduction in the transfer of T into the females in this study as compared to the previous one (abdomen-to-abdomen).
- The highest level of transfer was seen when neither the males nor females wore a shirt. The levels of exposure to T were almost 5 folds as compared to the baseline, even when the females showered immediately after the rubbing procedure.
- Although reduced, there was still detectable transfer of T to the females 12 hours after gel administration even when both the partners wore a shirt. This transfer was found to be almost at the same level as that observed 1-hour post administration to males wearing a shirt.
- For both the studies, there was nothing of significance noted in the adverse event profiles. However, both the above were single dose (and single exposure) scenarios.
- The sponsor provided re-analysis of individual patient data on 10/25/2002. Based on this information, it was concluded that clothing (eg. a T-shirt to cover the area of application/contact) prevents transfer of testosterone from TESTIM to others.
- Based on the above results (from both the studies), specific language is to be added to the label reflecting the level of T transfer, time periods as well as precautionary measures.

4. Study AUX-TG-207

Another practical issue that one has to consider with a transdermal gel formulation if how long has the patient to wait post administration before showering. To address this, the sponsor conducted another well-designed study in 12 (completed) subjects, each one with 4 treatment sequences: (I) no washing, (II) washing (5 minute shower with mild soap) at 1-hour, (III) washing at 2 hours and (IV) washing at 6 hours post administration. Serial PK samples were collected over the whole day and typical PK parameters were computed. In addition, the following specific parameters were calculated for effective comparison between each treatment arm (showering time) with the arm without showering, as follows:

C_{avg1} = weighted mean testosterone concentration over 1 to 24 hours, calculated for session I and II only: $AUC_{(1-24)}$/(actual time between 1 and 24 hour samples).

C_{avg2} = weighted mean testosterone concentration over 2 to 24 hours, calculated for session I and III only: $AUC_{(2-24)}$/(actual time between 2 and 24 hour samples).

C_{avg3} = weighted mean testosterone concentration over 6 to 24 hours and calculated for session I and IV only: $AUC_{(6-24)}$/(actual time between 6 and 24 hour samples).

$AUC_{(x-24)}$ was the area under the serum concentration versus time curve from 1 to 24 hours, from 2 to 24 hours, or from 6 to 24 hours and was estimated using the linear trapezoidal method and actual sampling times.

There was a 7-day washout period between each treatment sequence of the study.

Results:

Table 6A. Differences Between Session I (No Washing) and the Washing Sessions Using the Time Normalized AUC Values

Washing Session/ AUC Time Period	Mean Serum Testosterone Concentrations (ng/dL)				Ratio[b] 90% CI
	Session I (No Washing)		Washing Session		
	N	Mean[a]	N	Mean[a]	
Session II (1 to 24 h) C_{avg1}	16	489	16	342	0.700 (0.621, 0.789)
Session III (2 to 24 h) C_{avg2}	12	531	12	391	0.736 (0.636, 0.851)
Session IV (6 to 24 h) C_{avg3}	12	537	12	395	0.736 (0.667, 0.813)

ng/dL: nanograms/deciliter; CI: confidence intervals
a: Represents adjusted geometric mean from ANOVA.
b: Ratio is washing session/session I.

Table 6B. Mean (SD) Testosterone Concentrations

Time point	Serum Testosterone Concentrations (ng/dL)				
	Baseline and 1st Washing Session		Baseline and 2nd and 3rd Washing Sessions		
	Session I Day 1 (N=16)	Session II Day 8 (N=16)	Session I Day 1 (N=12)	Session III Day 15 (N=12)	Session IV Day 22 (N=12)
Predose Mean (SD) Min.-Max.	309 (70)	296 (62)	312 (79)	349 (95)	304 (67)
1 h Mean (SD) Min.-Max.	408 (155)	389 (77)	441 (166)	433 (264)	369 (148)
2 h Mean (SD) Min.-Max.	488 (213)	515 (155)	525 (230)	550 (353)	425 (172)
4 h Mean (SD) Min.-Max.	493 (287)	388 (120)	535 (317)	445 (138)	403 (179)
6 h Mean (SD) Min.-Max.	502 (225)	361 (93)	549 (236)	418 (120)	402 (126)
8 h Mean (SD) Min.-Max.	511 (183)	334 (81)	562 (173)	391 (111)	401 (108)
12 h Mean (SD) Min.-Max.	474 (140)	287 (86)	509 (123)	366 (104)	377 (104)
16 h Mean (SD) Min.-Max.	494 (175)	316 (104)	536 (175)	378 (124)	397 (153)
24 h Mean (SD) Min.-Max.	593 (128)	397 (122)	606 (133)	435 (117)	464 (141)

ng/dL: nanograms/deciliter; SD: standard deviation; Min.: Minimum Value; Max.: Maximum Value

Reviewer's Comments

- Based on the ratios of the C_{avg} values (Table 6A), it appears that no more than 30% reduction of exposure is achieved with showering/washing.
- There was almost no difference in T exposure among the 1, 2 or 6-hour gaps between gel administration and showering. Hence, showering may not have a significant effect on the PK profile of T from TESTIM.
- From an observation of data in Table 6B, it appears the mean T levels fall around or below 300 ng/dL (lower bound for normal T levels) after showering 1-hour post administration more clearly than the other two time gaps (i.e. showering 2 or 6 hours post administration). Following showering at the two later time points, none of the *mean* plasma T levels fall below 300 ng/dL.
- It may be advisable to instruct patients to wait at least 2 hours before taking a shower (with mild soap) for optimum performance of TESTIM.

Hand Washing

Additional information was sent by sponsor on 10/26/2002 and it was concluded that thorough washing of the palms following TESTIM application completely removes any residual testosterone.

Biopharmaceutics

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

Yes. The sponsor was specifically asked this question prior to filing this NDA and they responded via facsimile (dated Feb 12, 2002) stating that the formulation has not changed through the IND process, and is the same intended commercial formulation.

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

This is the first T-gel NDA that has formally tested the product with a drug-release method and seeking a release specification for the same.

For this NDA, none of the release experimentation information was submitted to the CPB section. At the request of the CMC review team, the sponsor sent in data from release testing performed according to the above principles.

According to the CMC reviewer, the sponsor is seeking the following specification:

The following is the supporting data for this:

At the following are the Mean and SD for

Mean (µg)	SD	CV	MIN	MAX
2444.9	203.0	8.3%		

Since this dissolution method does not have much relevance to the *in vivo* situation and is purely a Quality Control test, the decision on acceptance of the dissolution specifications is therefore deferred to the CMC review team.

Analytical Methodology

The sponsor used commercially available validated radio-immunoassay (RIA) test kits to determine the concentrations of total T, Free T and DHT. Most of the validation information for these kits have been referred to the package inserts for these commercial kits. The methods were found to be sufficiently linear and specific (with minimal but quantifiable cross-reactivity). The accuracy and precision validation including the range of the standard curves sufficiently cover the ranges of the concentration that were observed in the CPB studies conducted with TESTIM.

For total T, inter-assay precision c.v. values were <12% for concentrations . For concentrations , all precision c.v. values were < 10%. All precision c.v. values for free T were < 11%. None of the inter and intra assay precision c.v. values for DHT were above 10%.

Overall, the analytical methodology and validation results are acceptable for CPB purposes.

6 Draft Labeling Page(s) Withheld

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/s/

Dhruba Chatterjee
10/30/02 12:26:58 PM
BIOPHARMACEUTICS
OCPB Final Review

Ameeta Parekh
10/30/02 12:54:58 PM
BIOPHARMACEUTICS
I concur