

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-015**

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

20000910

## MEMORANDUM

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Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation II

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Date: May 18, 1999

To: Mei-Ling Chen, Ph.D.  
John Hunt

From: Dhruva Chatterjee, Ph.D. (Pharmacokinetics Reviewer)

Re: 45-day Filing Meeting for NDA 20-015, Androgel™ (50 and 100 mg Testosterone gel) –  
Sponsor – UNIMED Pharmaceuticals Inc.

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### Introduction/Background

Testosterone (T)-gel (Androgel™) is a 1% hydroalcoholic gel formulation intended to deliver testosterone, the natural androgenic male steroid. It is intended for use as androgen replacement therapy in men to prevent symptoms due to low endogenous T levels and to prevent long-term deleterious effects of this deficiency. Specifically, the aim of this treatment is to restore normal male libido and sexual activity, maintain secondary sexual characteristics and to mimic the somatic actions of testosterone (eg. effects on muscle mass and nitrogen balance). Androgel™ is proposed to be used as a transdermal gel to be applied on the upper arm, shoulders or abdominal areas of undamaged skin. The proposed dosing would be 5 or 10 g gel (delivering 50 or 100 mg testosterone) once a day.

T is available to patients as (a) IV (testosterone enanthate injection), (b) IM (testosterone cypionate IM injection) and (c) testosterone transdermal systems (for scrotal and non-scrotal application). In the pivotal study, the sponsors in this NDA have compared the pharmacokinetic performance of Androgel™ with the non-scrotal transdermal delivery system (Androderm™).

### Overview

#### *PK/BIO Studies*

The following is a brief summary of the PK/BIO studies submitted in support of the application.

Study UMD-96-017: This is the only pivotal PK/BIO study reported in the application. This was a randomized positive-control, parallel-group, double blind (to initial T-gel dose) study

conducted in 227 patients (hypogonadal men) evaluating and comparing the PK/BIO following daily doses of a 5-gm active gel, a 10-gm active gel, and 2 simultaneous non-scrotal transdermal patches (each containing 12.2 mg T). The study has been conducted initially for 90 days (this NDA presents data till 90 days) and will be extended till 180 days. It has been agreed upon that the remaining data (for days 91-180) will be submitted within 18 weeks of the original submission. All major/relevant PK parameters were evaluated and data has been presented in a clear fashion. Serum T, free T, DHT (active primary T-metabolite), DHT/T ratios, levels of estradiol, FSH and LH were monitored.

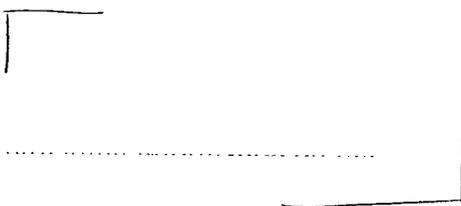
**Study UMD-96-012:** This was an open-label, fixed-dose, 2-period crossover study in 9 patients (hypogonadal men) to determine the pharmacokinetics of T following application of 100 mg of T (10-gm T-gel) daily. The study was conducted for 7 days, with a 7-day washout between and following treatments. All major/relevant PK parameters have been reported including an idea of 'transdermal bioavailability' based on the amount delivered from the skin depot, with or without the assumption that endogenous T production continued at the pre-treatment rate. DHT levels were also monitored. Results are presented clearly.

**Study UMD-98-037:** This was an open-label, randomized, parallel-group study (N=24 for 1<sup>st</sup> phase and N=TBD for 2<sup>nd</sup> phase) in male-female partners to determine the changes in serum androgen levels in the females exposed to the male partners treated with the Androgel<sup>TM</sup> containing 100 mg T for 7 days. The study determined the effects of indirect, direct/vigorous, or effect of using a T-shirt to preclude areas of direct contact on the serum T-levels in partners.

**Study UMD-97-023:** This study was designed to evaluate the effects of serum androgens in female partners of males receiving T-gel. Enrollment in this study was discontinued after 5 patients were enrolled and UMD-98-037 was continued.

**Studies UMD-98-943, UMD-99-948 and UMD-98-946:** These were *in vitro* studies performed to determine the effects of dry-wiping of the gel, the effects of soap and water washing, and to determine the influence of IPM (isopropyl myristate) concentration in gel on the skin absorption of T.

### **Analytical Methods**



## Drug Formulation

The sponsors have used the T-gel for the pivotal clinical and supportive studies similar to the 'to-be-marketed' product. The 'to-be-marketed' product will be made available in packs made of Al-foil. However, for the clinical studies, the gel was supplied in bottles fitted with pumps. The concentration of IPM in the final formulation is  $\frac{1}{10}$ . Since Al-foil absorbs IPM to a certain extent, the sponsors propose that they will make the marketed product containing  $\frac{1}{10}$  IPM, and have shown that in 30 days, the concentration of IPM drops to about  $\frac{1}{10}$  in the Al-foil packs. The sponsor has also shown *in vitro* that the concentration of IPM does not significantly affect skin absorption of T.

## Review Issues

- *In vitro* release profile of T from Androgel™ (the 'to-be-marketed' product).
- An increased level of IPM  $\frac{1}{10}$  in the 'to-be-marketed' formulation as compared to that used for the pivotal clinical study may lead to more incidences of skin irritation. Are there any topical/transdermal product in the market that uses  $\geq \frac{1}{10}$  IPM?
- Was body weight used as a covariate for the clinical PK data analysis?
- Does labeling reflect appropriate administration of the product?

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## Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, is of the opinion that the NDA 20-015 can be filed.

/S/

Date

5/21/99

Dhruba J. Chatterjee, Ph.D.  
Pharmacokinetics Reviewer  
Center for Drug Evaluation and Research, FDA  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation II

CC Original NDA 21-015  
HFD-580/Div. File  
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## Clinical Pharmacology & Biopharmaceutics Review

<b>NDA:</b>	21-015
<b>Product Trade Name:</b>	ANDROGEL™
<b>Active Ingredient/s:</b>	Testosterone
<b>Indication:</b>	Testosterone Replacement Therapy (in hypogonadal men)
<b>Submission Date:</b>	April 29, 1999
<b>Sponsor:</b>	Unimed Pharmaceuticals Inc.
<b>Type of Submission:</b>	Original NDA, 3S
<b>Reviewer:</b>	Dhruba J. Chatterjee, Ph.D.
<b>Consultant Reviewer:</b>	Venkat Jarugula, Ph.D.
<b>Team Leader:</b>	Ameeta Parekh, Ph.D.

### Background

Testosterone (T) is an endogenous compound that is responsible for maintenance of primary sexual characteristics in men. T replacement is indicated in hypogonadal men for androgen-dependent functions to be induced or maintained. Currently marketed drug products for this indication include oral, intramuscular and transdermal formulations of testosterone or testosterone esters.

### Synopsis

ANDROGEL™ is a transdermal formulation containing testosterone in a hydroalcoholic gel. The commercial formulation will be available in — foil sachets containing either 2.5 gm of gel (25 mg of testosterone) or 5.0 gm gel (50 mg of testosterone). ANDROGEL™ is indicated for the treatment of hypogonadism leading to underproduction and hence, lower levels of endogenous testosterone.

This product has been shown (details inside) to be effective in achieving and maintaining mean serum T levels within the normal range in hypogonadal male (300 – 1000 ng/dL) from both doses evaluated. However, caution has to be exercised for proper use of the product. Dose titration, product handling/ application and patient usage instructions are key factors for optimal benefit to patients from this product.

This review is question based. The questions and answers are included within each study section to provide more focus. There are no major OCPB issues/question with this application.

### Recommendation

Based on the review, NDA 21-015 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. Review of the PK data in this submission resulted in certain changes in the appropriate sections of the product label. The suggested changes have been appropriately incorporated in the label.

*The following Phase IV commitment should be communicated to the sponsor:*

Sponsor is requested to submit relevant evidence (post-approval) that there is no difference in clinical delivery of T (based on serum T levels) from the marketed ANDROGEL™ batches as compared to the clinical trial formulation.

*/S/*

Dated 2/25/00

Dhruba J. Chatterjee, Ph.D.,  
Office of Clinical Pharmacology and Biopharmaceutics (OCPB)  
Division of Pharmaceutical Evaluation II

FT signed by Ameeta Parekh, Ph.D.

*/S/*

Dated- 2/25/00

CC: NDA 21-015, HFD 870 (S. Huang, A. Parekh, DJ. Chatterjee), HFD-580 (M. Hirsch, K. Colangelo), CDR (B. Murphy).

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## List of Abbreviations & Common Usages

BMD	Bone mineral density
BMI	Body mass index
$C_0$	Observed trough concentration obtained pre-dose
$C_t$	Concentration at time = t
$C_{avg}$	Time averaged concentration over the dosing interval
$C_{base}$	Estimated concentration at the time drug was applied
$C_{max}$	Maximum observed concentration during the dosing interval
$C_{min}$	Minimum concentration during the dosing interval
DHT	Dihydrotestosterone
E2 or E <sub>2</sub>	Estradiol
Free-T	Free (unbound) testosterone
FSH	Follicle-stimulating hormone
HDL	High-density lipoprotein
IPM	Isopropyl myristate
LH	Luteinizing hormone
LDL	Low-density lipoprotein
LLQ	Lower limit of quantitation
N or n	The number of patients
PFT	Percent fat
SD	Standard Deviation
SEM	Standard Error of Mean
SHBG	Sex hormone-binding globulin
$T_{max}$	Time at which $C_{max}$ occurred
T	Testosterone
TBM	Total body mass
TFT	Total body fat mass
T-gel	Testosterone Gel (ANDROGEL™)
TLN	Total body lean mass
T-patch	Testosterone Patch (Androderm)

There were 2 doses initially evaluated in the study. In this review, '5 g T-gel' or '50 mg T-gel' will imply the lower dose (50 mg testosterone in 5g of gel), and '10 g T-gel' or 100 mg T-gel' will imply the higher dose (100 mg testosterone in 10g of gel).

## 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.

It is to be understood that 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 298 ng/dL – 1043 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) formulations of testosterone or testosterone esters.

Testosterone is primarily cleared by metabolic processes in the liver, skin, genital and other tissues. The metabolism includes conversion to the active metabolite DHT by 5 $\alpha$ -reductases in the skin and liver and to estradiol by aromatase complexes found in the liver, fat and testes<sup>1</sup>. Administered testosterone is recovered in the urine as androsterone, etiocholanolone and glucuronide and sulfate conjugates of androstenediol and estrogens<sup>2</sup>.

<sup>1</sup> Cofrancesco J, Dobs AS. Transdermal Testosterone Delivery Systems. *Endocrinologist* 1996; 6: 207-213.

<sup>2</sup> Wilson JD. Androgens. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG (Ed). *The Pharmacological Basis of Therapeutics*. McGraw-Hill, 1966:1441-1456.

Testosterone gel (T-gel), the subject drug product of this submission, is a 1% hydroalcoholic gel formulation of testosterone that the hypogonadal male applies once daily on the skin of his upper arms and shoulders, and/or the skin of the abdominal area. The alcohol in the gel (T-gel is approximately 70% ethanol) facilitates the transfer of the testosterone, which is highly lipophilic, 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 a clinical trial involving 225 hypogonadal patients. They have used two doses of T-gel (50 and 100 mg T) and have compared the PK performance of their product against a commercially available transdermal T-patch for non-scrotal application (2 x 2.5 mg). The submitted studies (details following) are acceptable in the support of this NDA.

## Highlights of Human PK/Biopharmaceutics Studies

### *Question addressed in this section:*

#### **What are the major CPB findings/conclusions from the submitted NDA?**

- The sponsor has conducted a clinical trial with two doses (50 and 100 mg) of T from the gel and compared their PK performance with a non-scrotal T-patch (Androderm, 2 patches, delivering 5.0 mg total daily dose). The sponsor claims that their T-gel achieves higher steady state serum levels of T and maintains efficacy in a much higher % of patients as compared to the T-patch. In this context, it is to be noted that the sponsor has used a considerably higher dose with the T-gel than the patch, and the gel was applied to a much higher surface area compared to the patch. Hence, the difference in performance is an expected event.
- On day 30, from the 50-mg T-gel (lower) dose, 3 (of 70 or 4%) patients showed  $C_{avg}$  T values over the upper limit of the normal T range (1043 ng/dL). Following the 100 mg T-dose, 15 (of 77 or 19%) patients showed  $C_{avg}$  T values over the upper limit. In this context, in one patient the dose was reduced to 25 mg of T-gel (protocol deviation) since the serum T-levels were higher than expected from the 50 mg dose. However, in the patient on 25 mg, day 180 serum T values were low (mostly < 300 ng/dL). Although  $C_{avg}$  was found to be linear between 50, 75 and 100 mg dose, the line did not pass through the origin (due to baseline T levels and possible PK non-linearity between 25 – 50 mg dose, Fig 1.0). Due to insufficient data for the 25 mg dose, no information can be provided for use of this dose in the label. Exposure to T over the dose range is not dose-proportional.
- Mean *pre-dose* total serum T values averaged over 1400 ng/dL for the 100 mg T-gel treatment group at the 60-day time point. In fact, from the values of SEM, it seems that a majority of the patients may have been above the higher boundary of the normal range (and this was pre-dose).
- Results show that there are no statistically significant differences in PK parameters of T following one-site (left upper arm/shoulder – smaller area) or four-site (left upper arm/shoulder, the right upper arm/shoulder, the left abdomen and the right abdomen – larger area).

- Significant transfer of T into the female partners of men who use this product is possible upon physical contact. However, this may be avoided if the patient occluded the area of application (eg. with a T-shirt or other appropriate clothing).
- The sponsor has not submitted study that conclusively determines how soon a patient may shower/swim following T-gel application. In the absence of such information, 12 hours may be suggested as optimal gap (based on the PK of T from this product, it appears that the drug is resident in the deep skin tissues as a depot by 12 hours) between application of T-gel and showering/swimming, although, very infrequently, the patient might engage in such activities sooner than 12 hours. This was discussed with the medical officer. Data to support this recommendation is provided in two PK studies (listed as 1 and 2 below).
- The to-be-marketed formulation contains \_\_\_\_\_ IPM while the clinical trial formulation contained \_\_\_\_\_ IPM due to an anticipated adsorption of IPM into the packaging material. In a discussion with the chemistry reviewer it was determined that the range of %IPM in the finished product after this adsorption is anticipated to be between \_\_\_\_\_. The sponsor has provided *in vitro* skin flux information showing that the difference in IPM between \_\_\_\_\_ does not effect skin flux. Based on the above information and the fact that patients on this product will have T serum monitored two weeks following beginning of treatment (for a dosage adjustment, if necessary), the above change in formulation is acceptable. However, sponsor is requested to submit relevant evidence (post-approval) on suitable ANDROGEL™ batches containing lowest and highest % IPM (marketed and clinical trial formulations) showing no difference in clinical T delivery (serum T profiles).

## Review of Human PK/Biopharmaceutics Studies

### List of Studies Submitted

1. A pivotal Phase III pharmacokinetics study in hypogonadal males comparing three transdermal testosterone treatments (2 x 2.5 mg Androderm® patch, 50 mg T-gel and 100 mg T-gel to be applied once daily) for up to six months (UMD-96-017). Note: This study serves as the single pivotal clinical trial in support of approval of this NDA.
2. A supportive Phase I/II steady-state pharmacokinetics study in hypogonadal men to investigate the impact of application surface area (UMD-96-012).
3. Supporting studies investigating whether transfer of a portion of the applied testosterone to the partner of the treated male occurs with physical contact (UMD-96-023 and UMD-98-037).
4. Three *in vitro* studies investigating the permeation process of testosterone through the skin, and identifying some factors that influence the extent of transdermal transfer (UMD-98-943, UMD-98-946 and UMD-96-948).

### Study 1. UMD-96-017: A Phase III Evaluation of Safety and Efficacy of the Testosterone Gel for Hormonal Replacement in Hypogonadal Men

#### Study Design

This was a randomized, multi-center, positive-control, parallel-group study that compared two doses of T-gel with a marketed testosterone patch (Androderm™). The study was double-blind with respect to the random assignment to the T-gel doses and open-label for the testosterone patch. Three treatments were administered during the Initial Treatment Phase (Months 1-3): 5 g

T-gel QD (50 mg testosterone once daily); 10 g T-gel QD (100 mg testosterone once daily); and 2 testosterone non-scrotal patches QD (5 mg absorbed testosterone dose). During the Extended Treatment Phase (months 4-6), four treatments were administered. Patients receiving T-gel and who had single-sample serum testosterone concentrations between 300 and 1000 ng/dL at Day 60 remained on their double-blind treatment for an additional three months. Patients with testosterone concentrations < 300 ng/dL who had received 50 mg T-gel and patients with testosterone concentrations > 1000 ng/dL who had received 100 mg T-gel were titrated to receive 75 mg QD testosterone (7.5 g T-gel) in an open-label fashion for the remaining three months (i.e., months 4-6). Patients randomized to Androderm™ were to have continued the same treatment during months 4-6.

Males between the ages of 18-68 years diagnosed with testosterone deficiency (morning serum testosterone concentration must have been  $\leq 300$  ng/dL) requiring testosterone replacement were included in the study. The number of patients initially enrolled in the study was 227, and about 195 patients completed the study (till the end of the extended phase for 180 days).

The drug formulation was a 1% testosterone hydroalcoholic gel containing — isopropyl myristate. The dose was administered as a daily (morning) transdermal application to the left and right upper arm and shoulders and/or the left and right site of the abdomen (depending on whether the dosage was 5 g gel or 100 g gel). Study visits were scheduled for Days 0, 1, 30, 60, 90, 120, 150, and 180. On Days 0, 1, 30, 90, and 180 patients remained in-house for at least 12 hours (up to 24 hours at some sites) for blood sampling and for clinical assessments. On Days 60, 120, and 150, patients returned to the study site prior to application of study medication for the collection of a single blood sample for hormone assay and for safety assessments.

The primary efficacy variable was the assessment of both  $C_{avg}$  and  $C_{min}$  values for serum testosterone within the normal range (300-1000 ng/dL) on Day 30. That is, a clinical "success" was defined as a patient who had both a serum T  $C_{avg}$  and  $C_{min}$  within the normal range.  $C_{max}$  values were reported for all patients groups, and that value was also judged critically (for safety) during the review of PK data. Other efficacy variables were testosterone concentrations at Day 90: DHT,  $E_2$ , LH, FSH, and SHBG trough concentrations; sexual questionnaires; muscle strength testing; and body composition. Safety assessments consisted of skin irritation assessments, international prostate symptom scores, physical examinations, vital signs, clinical laboratory tests, and adverse event monitoring. Baseline assessments were the last available evaluation prior to application of study medication.

Since the primary efficacy of the product was based on the pharmacokinetic parameters of testosterone, the sponsor performed an extensive PK analysis on total and free T concentrations. The following pharmacokinetic parameters were derived for each patient:  $AUC_{0-24}$ ,  $C_{max}$ ,  $T_{max}$ ,  $C_{min}$ ,  $T_{min}$ ,  $C_{avg}$ ,  $C_{base}$  (or  $C_0$ ), accumulation ratio (AR, on day 30, day 90, or day 180 over the AUC on day 1) and fluctuation index [the extent of variation in the serum concentration over the course of a single day, calculated as  $(C_{max}-C_{min})/C_{avg}$ ].

## Results and Conclusions

Please refer to the following Tables 1 – 5 and Figures 1.1 – 1.7 (obtained from submission) for tabular and graphic representations of the efficacy (primary and secondary) data (study results)

**Table 3. N (%) of Patients Classified as Success/Failure (Primary Efficacy Measure) at Day 30 by Treatment Group [Study UMD-96-017]**

Treatment Group	N	Success <sup>(a)</sup>	Failure <sup>(b)</sup>	p-value <sup>(c)</sup>
50 mg T-Gel	73	38 (52%)	35 (48%)	0.001
100 mg T-Gel	78	48 (62%)	30 (38%)	0.001
T-Patch	76	17 (22%)	59 (78%)	

<sup>(a)</sup> Success is defined as any patient with both  $C_{avg}$  AND  $C_{min}$  within reference range for T at Day 30.  
<sup>(b)</sup> Failure is defined as any patient with 1) either  $C_{avg}$  or  $C_{min}$  not within reference range for T at Day 30 or 2) missing data at Day 30.  
<sup>(c)</sup> p-value from chi-square test for 50 mg T-gel vs. T-patch and 100 mg T-gel vs. T-patch.

**Table 4. N (%) of Patients Classified as Success/Failure (Primary Efficacy Measure) at Day 90 by Treatment Group [Study UMD-96-017]**

Treatment Group	N	Success <sup>(a)</sup>	Failure <sup>(b)</sup>	p-value <sup>(c)</sup>
50 mg T-Gel	73	35 (48%)	38 (52%)	0.001
100 mg T-Gel	78	51 (65%)	27 (35%)	0.001
T-Patch	76	11 (15%)	65 (85%)	

<sup>(a)</sup> Success is defined as any patient with both  $C_{avg}$  and  $C_{min}$  within reference range for T at Day 90.  
<sup>(b)</sup> Failure is defined as any patient with 1) either  $C_{avg}$  or  $C_{min}$  not within reference range for T at Day 90 or 2) missing data at Day 90.  
<sup>(c)</sup> p-value from chi-square test for 50 mg T-gel vs. T-patch and 100 mg T-gel vs. T-patch.

**Table 5. N (%) of Patients Classified as Success/Failure (Primary Efficacy Measure) at Day 180, by Final Treatment Group [Study UMD-96-017]**

Treatment Group	N	Success <sup>(a)</sup>	Failure <sup>(b)</sup>
50 mg T-Gel	52	27 (52%)	25 (48%)
75 mg T-Gel	40	20 (50%)	20 (50%)
50 => 75 mg T-gel	20	8 (40%)	12 (60%)
100 => 75 mg T-gel	20	12 (60%)	8 (40%)
100 mg T-Gel	57	39 (68%)	18 (32%)
T-Patch	73	6 (8%)	67 (92%)

<sup>(a)</sup> Success is defined as any patient with both  $C_{avg}$  and  $C_{min}$  within reference range for T at Day 180.  
<sup>(b)</sup> Failure is defined as any patient with 1) either  $C_{avg}$  or  $C_{min}$  not within reference range for T at Day 180 or 2) missing data at Day 180.

Figure 1.0: Linearity of Testosterone PK (Mean ± one-sided SD) - plot showing uncertainty of linearity in PK between 0 – 50 mg T-gel dose [Study UMD-96-017]

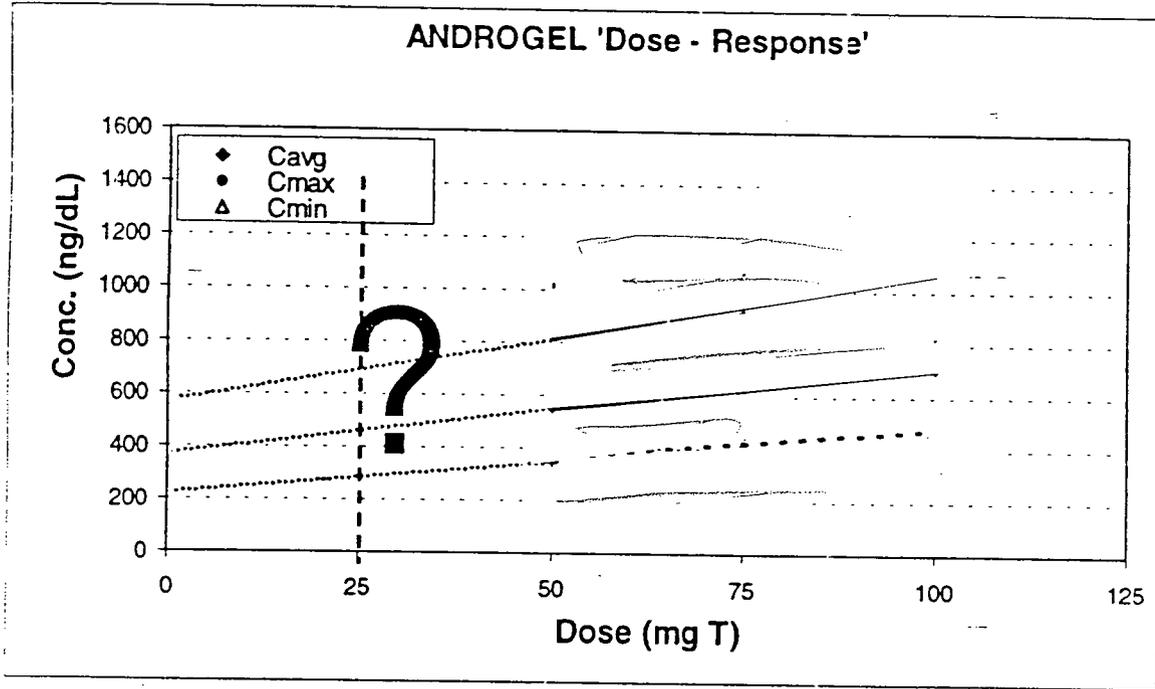


Figure 1.1: Testosterone Concentrations Pretreatment (Day 0) by Initial Treatment Group (Mean ± SEM) [Study UMD-96-017]

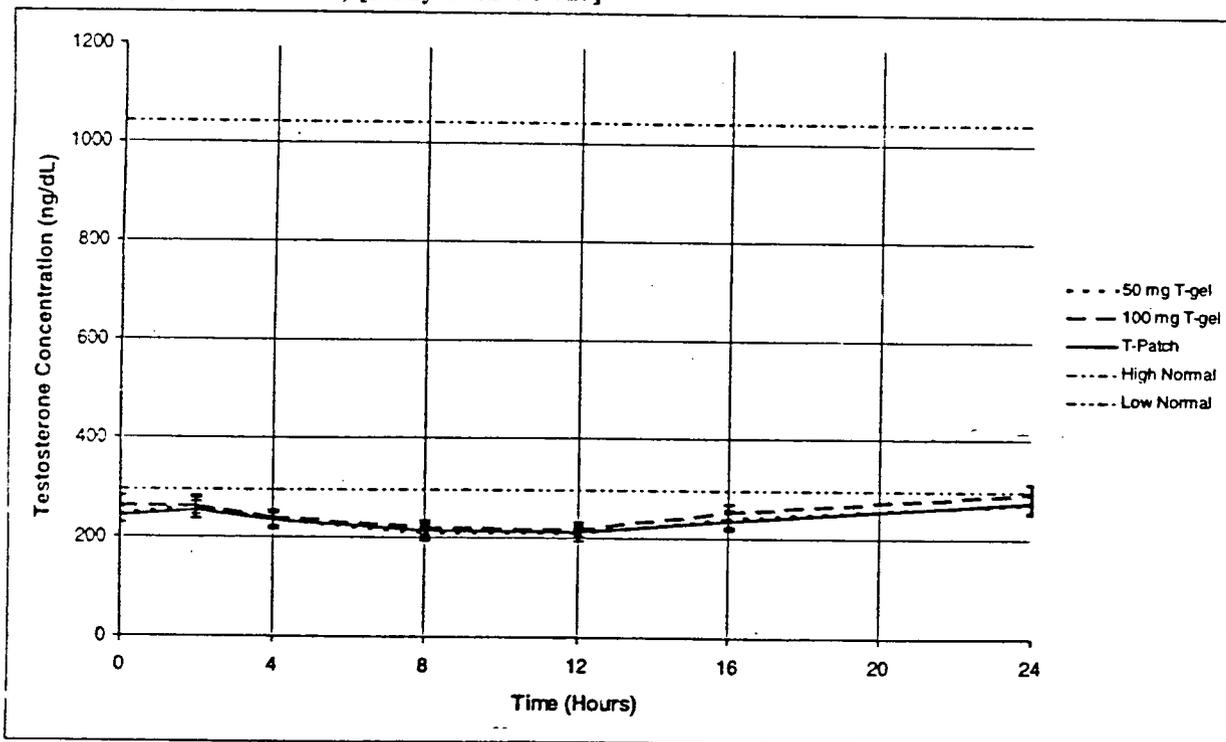


Figure 1.2: Testosterone Concentrations on First Day of Therapy (Day 1) by Initial Treatment Group (Mean ± SEM) [Study UMD-96-017]

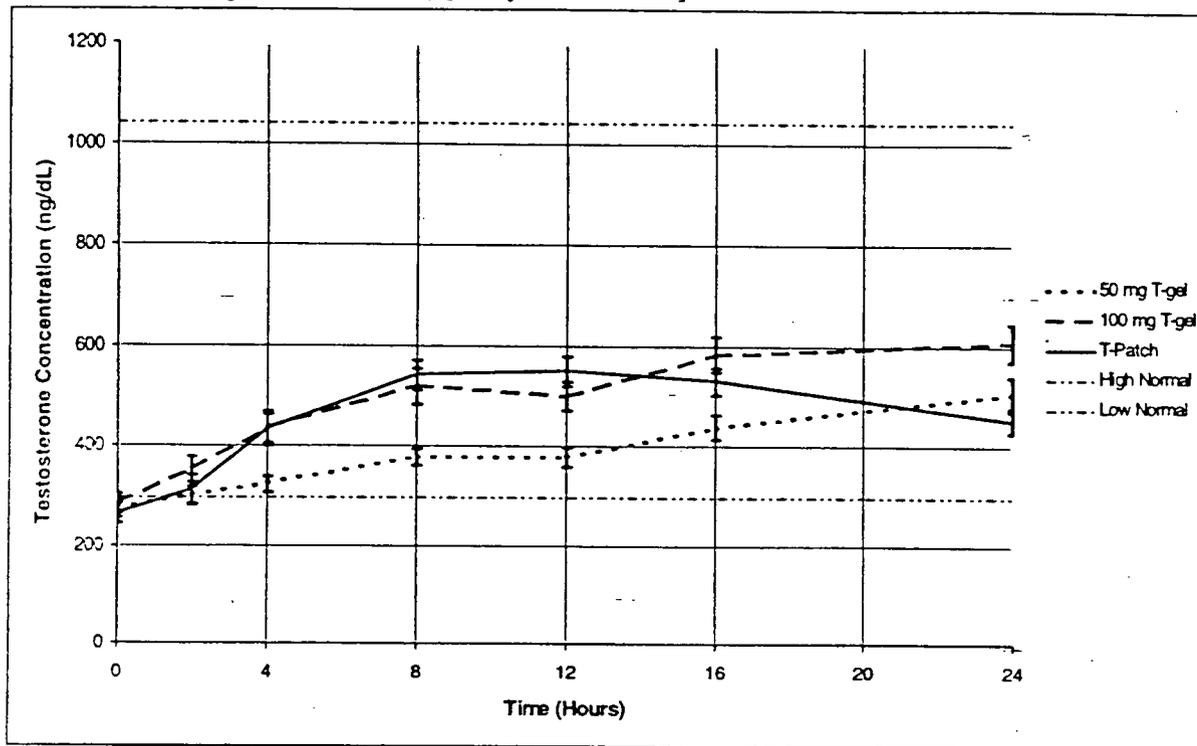


Figure 1.3: Steady-State Testosterone Concentrations on Day 30 by Initial Treatment Group (Mean ± SEM) [Study UMD-96-017]

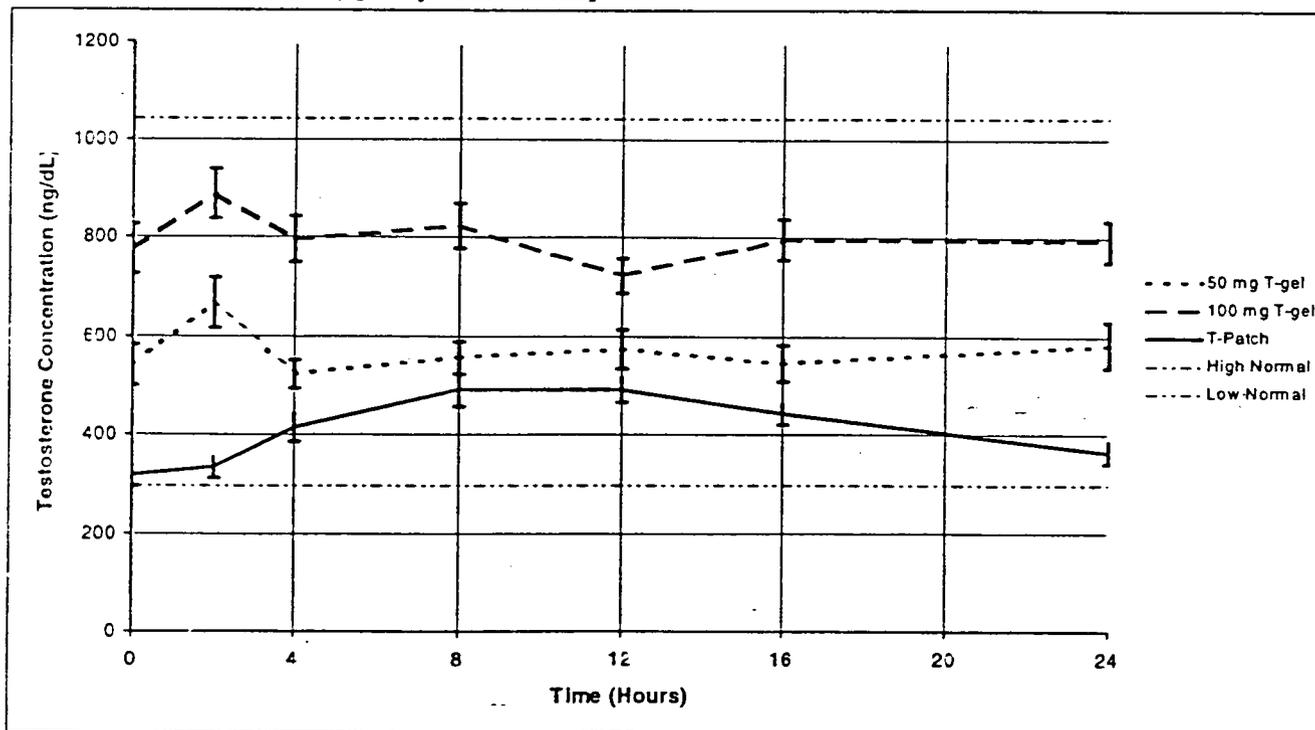


Figure 1.4: Steady-State Maintenance Testosterone Concentrations on Day 90 by Initial Treatment Group (Mean ± SEM) [Study UMD-96-017]

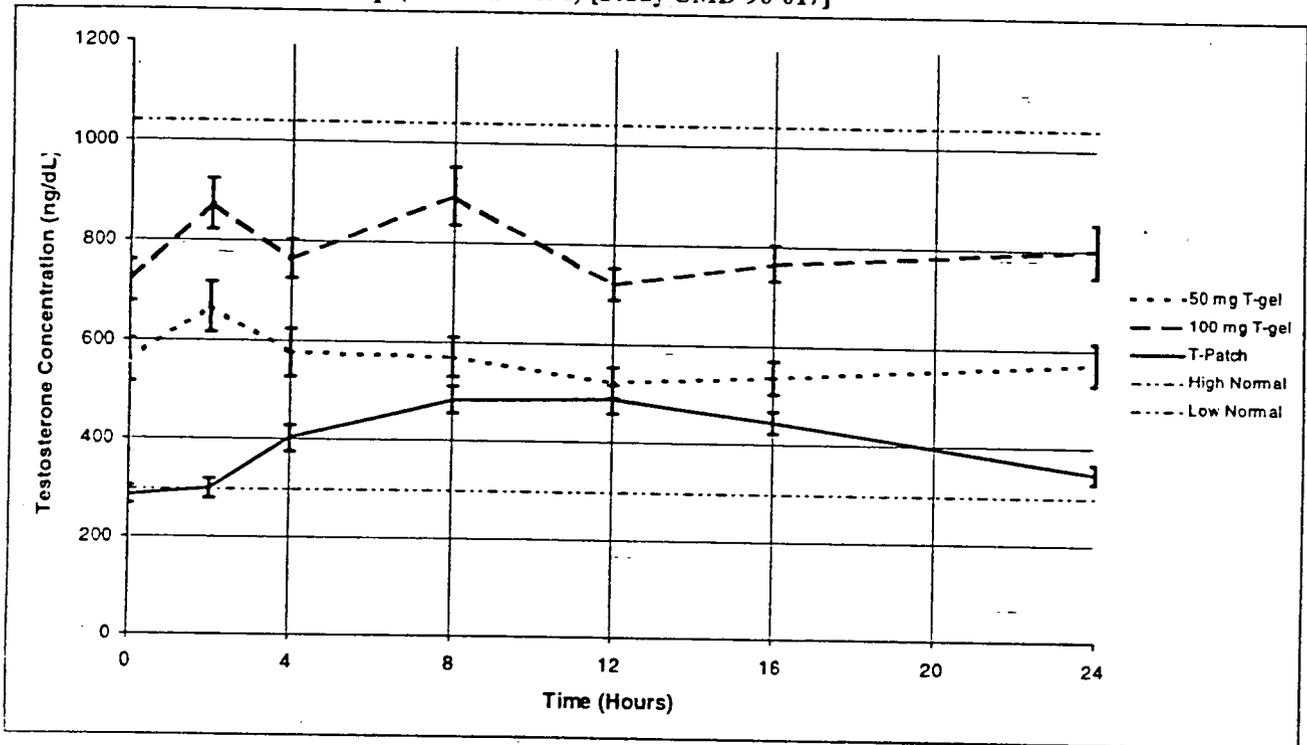


Figure 1.5: Steady-State Maintenance Testosterone Concentrations on Day 180, by Final Regimen (Mean ± SEM) [Study UMD-96-017]

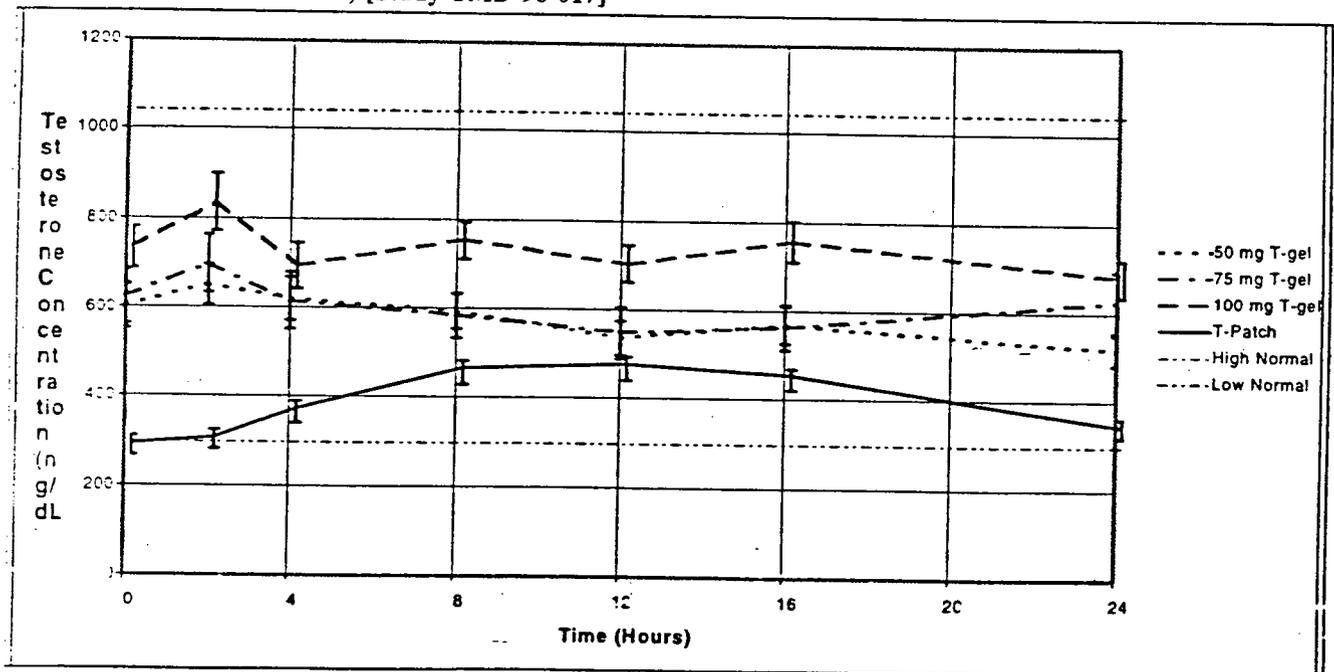


Figure 1.6: Trough (Predose) Testosterone Concentrations Over 180 Days of Treatment (Mean ± SEM) [Study UMD-96-017]

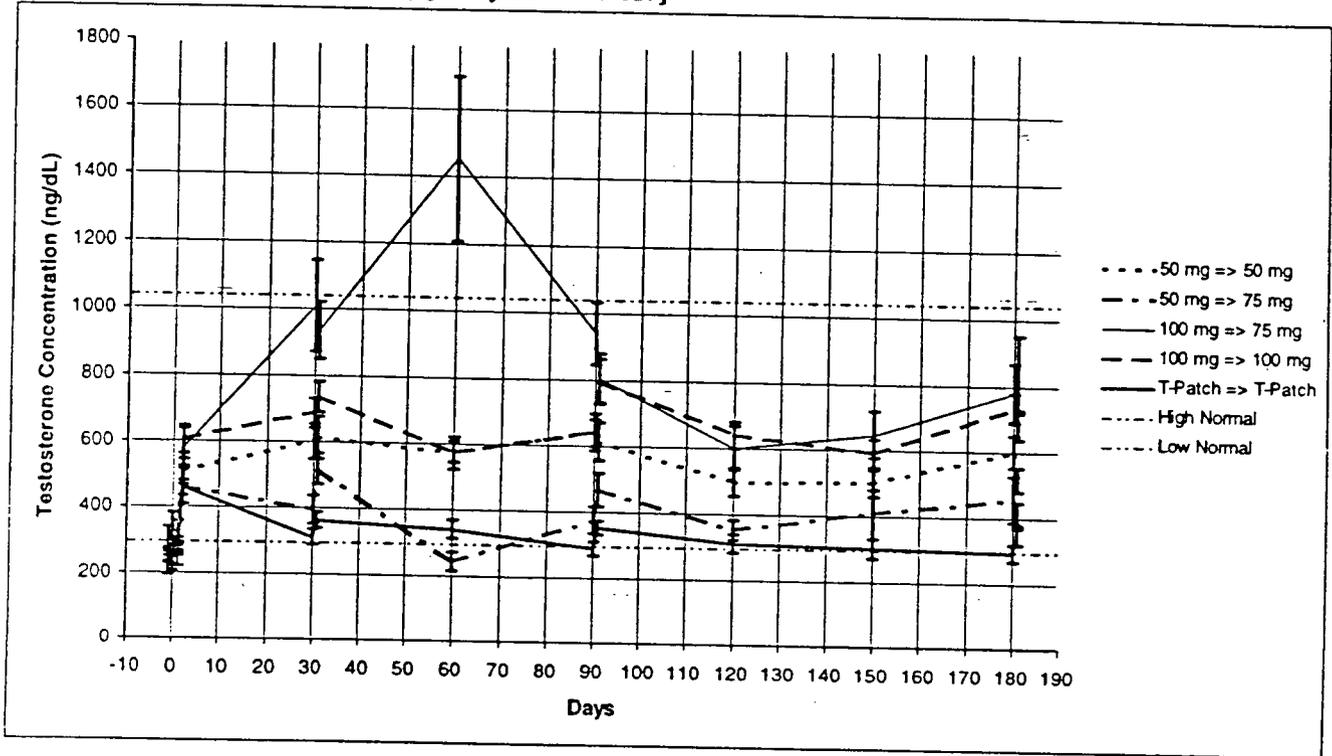
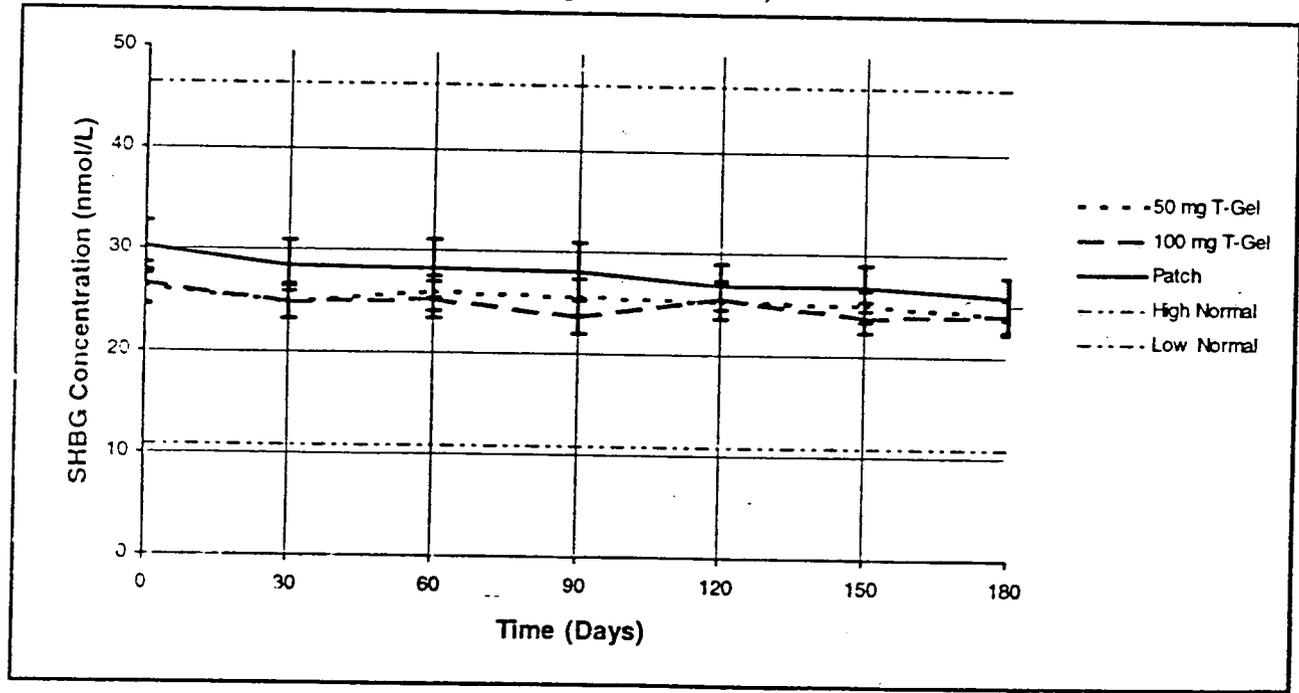


Figure 1.7: Sex Hormone-Binding Globulin Predose (Trough) Concentrations by Initial Treatment Group (Mean ± SEM)



### Conclusions:

- Testosterone replacement therapy with T-gel at doses of 50 mg/day and 100 mg/day increased mean serum testosterone levels to within the eugonadal range in the majority of hypogonadal men and maintained these for up to 180 days.
- As assessed by the primary efficacy intent-to-treat analysis (namely, the proportions of patients in each treatment group with  $C_{avg}$  and  $C_{min}$  within the normal range on Day 30), 52% and 62% of patients were successfully treated with 50 and 100 mg/day T-gel, respectively.
- Mean *pre-dose* total serum T values averaged over 1400 ng/dL for the 100 mg T-gel treatment group at the 60-day time point (Fig 1.6). In fact, from the values of SEM, it seems that a great majority of the patients may have been above the higher boundary of the normal range (and this was pre-dose). Day 60 data was neither reported in a detailed manner in this application, nor was it included in the PK analysis.
- On days 30, 90 and 180,  $C_{max}$  values for T following the 100-mg T-gel dose were too high, and might pose safety concerns.
- On day 30, even from the 50-mg T-gel (lower) dose, 3 (of 70 or 4%) patients showed  $C_{avg}$  T values over the upper limit of the normal T range (1043 ng/dL). Following the 100 mg T-dose, 15 (of 77 or 19%) patients showed  $C_{avg}$  T values over the upper limit.
- It needs to be emphasized that the plots above represent data as MEAN  $\pm$  SEM (std. error of mean). SEM being  $SD/\sqrt{N}$ , the SD error bars (eg. figure 1.3) may be enormous (definitely beyond the normal range). For a more accurate representation of the data, the sponsor is encouraged to submit all plots and data using SD and not SEM.
- SHBG (responsible for binding to about 40% of circulating T) concentrations showed a decline from pretreatment values over the 180 days of therapy. However, the decrease was small and similar for all three Initial and Final Treatments.
- Mean pretreatment DHT concentrations were 36-42 ng/dL for the three treatment groups. During treatment, mean predose DHT concentrations tripled with the 50 mg T-gel treatment, and increased five-fold with the 100 mg T-gel application. The DHT/T ratio increased in all T-gel treatment groups, with the greatest mean increase from baseline in DHT/T being found in the 100 mg group.
- Estradiol concentrations showed a statistically significant increase in the mean values during treatment, about a 55% increase for the 100 mg T-gel group. The mean changes in  $E_2$  were generally rank-ordered in keeping with serum T concentrations achieved. The mean concentrations in all Initial Treatment groups and all Final Treatments remained within the normal range (17 – 46 pg/mL, as determined by the medical center involved with this NDA) throughout the 180 days of treatment.
- Mean FSH concentrations decreased in all initial treatments by Day 30. The patients that received 100 mg dose for the entire 180 days had their mean FSH levels reduced to within the normal range by Day 60 and it remained in the normal range for the remainder of the study. Mean LH concentration decreased in all treatments by Day 30 in the patients with primary hypogonadism. Both the 50 mg and 100 mg T-gel applications reduced the mean serum LH concentrations to within the normal range by Day 30 in patients with primary hypogonadism, but for the 100 mg T-gel, the LH level was maintained longer in the normal range.

### Questions and Answers

**Question.** Does the pharmacokinetic results support efficacy and safety of the dosage form?

**Answer.** Results, as summarized in Tables and Figures, indicate that although the data is highly variable, both for *achievement and maintenance* of normal T levels in hypogonadal patients, the product is effective from the proposed doses (50 and 100 mg T-gel). However, both from 50 (infrequently) AND 100-mg (more frequently) T-gel doses, average T-levels may be above the upper level of the normal range, which might lead to safety concerns. Individual PK profiles for patients in which T levels were above normal, are not available. This warrants very careful dose selection and titration (individualization) for optimal treatment benefit.

### Study 2. UMD-98-012: Pharmacokinetic Evaluation of Testosterone-Gel in Hypogonadal Men

#### Study Design

This was a single-center, open-label, multiple-dose, crossover study. Two treatment regimens were administered as follows: Regimen A (approximately 10 g T-gel [100 mg testosterone] applied at four separate application sites - left upper arm/shoulder, the right upper arm/shoulder, the left abdomen and the right abdomen); and Regimen B (approximately 10 g T-gel [100 mg testosterone] applied at one application site - left upper arm/shoulder). Both treatment regimens were administered once a day for seven days. A total of 10 patients were enrolled in the study initially. Patients were assigned to either Regimen A or B for seven days on an alternate basis as they were enrolled into the study. Following a seven-day washout period, patients received the alternate treatment regimen. Patients were admitted to the research unit for approximately 24 hours on Days 1, 7, 15 and 21 for pharmacokinetic sampling. Patients returned to the unit on treatment Days 3, 5, 17 and 19 and on washout Days 9, 11, 13, 23 and 27 for approximately two hours. The post-treatment study visit was conducted on Day 29.

#### Results

Please refer to Figure 2 and Table 6 for a summary of results from this PK study.

Figure 2. Mean ( $\pm$  SEM) 24 Hour Testosterone Pharmacokinetics after Gel Application [Study UMD-96-012]

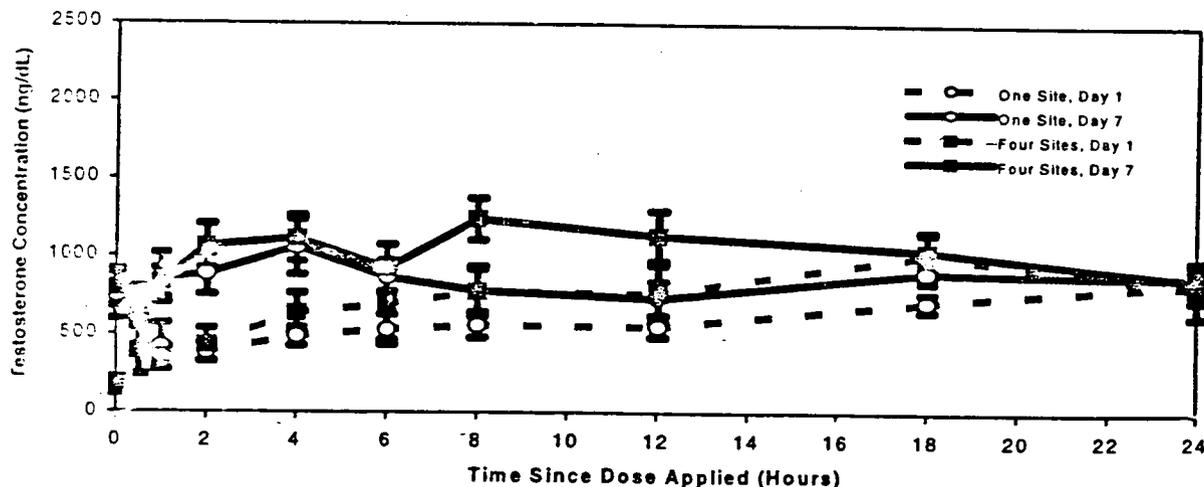


Table 6. Mean Testosterone Pharmacokinetic Parameters (Mean ± SD) [Study UMD-96-012]

	100 mg T one-site application	100 mg T four-site application	P-value 1 site vs 4 sites	P-value Within Treatment
Baseline				
C <sub>baseline</sub> (ng/dL)	167 ± 128	179 ± 124	n.s.	
AUC <sub>0-24</sub> (ng*hr/dL)	4,016 ± 3181	4,286 ± 2986	n.s.	
Day 1				
C <sub>max</sub> (ng/dL)	1,039 ± 374	1,078 ± 592	n.s.	C <sub>0</sub> , 1 site, p<0.001 C <sub>0</sub> , 4 sites, p<0.005
T <sub>max</sub> (hr)	16.7 ± 8.8	15.1 ± 6.2		
Median T <sub>max</sub> (hr)	18 (0.5-24)*	18 (6-24)*	n.s.	
AUC <sub>0-24</sub> (ng*hr/dL)	14,332 ± 3,771	18,377 ± 10,988	n.s.	Baseline, 1 site, p<0.001 Baseline, 4 sites, p<0.005
C <sub>mean</sub> (ng/dL)	597 ± 157	766 ± 458	n.s.	Baseline, 1 site, p<0.001 Baseline, 4 sites, p<0.005
C <sub>24</sub> (ng/dL)	839 ± 348	798 ± 541	n.s.	C <sub>0</sub> , 1 site, p<0.001 C <sub>0</sub> , 4 sites, p<0.01
Day 7				
C <sub>max</sub> (ng/dL)	1,334 ± 487	1,553 ± 334	p=0.10 (n.s.)	Day 1, 1 site, n.s. Day 1, 4 sites, p=0.044
T <sub>max</sub> (hr)	7.9 ± 7.9	6.7 ± 5.6		
Median T <sub>max</sub> (hr)	4 (0-18)*	6 (0.5-18)*	n.s.	Day 1, 1 site, n.s. Day 1, 4 sites, p=0.06
AUC <sub>0-24</sub> (ng*hr/dL)	20,304 ± 5,118	24,994 ± 6,214	p=0.06 (n.s.)	Day 1, 1 site, p<0.01 Day 1, 4 sites, p=0.06 (n.s.) Baseline; 1 site; p<0.001 Baseline; 4 sites; p<0.001
C <sub>mean</sub> (ng/dL)	846 ± 213	1,041 ± 259	p=0.06 (n.s.)	Day 1, 1 site, p<0.01 Day 1, 4 sites, p=0.06 (n.s.)
C <sub>0</sub> (ng/dL)	745 ± 449	794 ± 354	n.s.	Day 1, C <sub>0</sub> , 1 site, p=0.01 Day 1, C <sub>0</sub> , 4 sites, p<0.001 Day 1, C <sub>24</sub> , 1 site, n.s. Day 1, C <sub>24</sub> , 4 sites, n.s.
C <sub>24</sub> (ng/dL)	871 ± 272	857 ± 195	n.s.	Day 7, C <sub>0</sub> , 1 site, n.s. Day 7, C <sub>0</sub> , 4 sites, n.s. Day 1, C <sub>24</sub> , 1 site, n.s. Day 1, C <sub>24</sub> , 4 sites, n.s.
Accumulation Ratio	1.48 ± 0.42	1.69 ± 0.84	n.s.	
Fluctuation Index	0.97 ± 0.33	1.01 ± 0.29	n.s.	
Washout AUC <sub>Days 8-11</sub> (ng*hr/dL)	25,041 ± 8,569	29,949 ± 7,343	n.s.	

\* Median (Range)

n.s. = not significant at the 0.05 level

### **Conclusions:**

- Testosterone concentrations in hypogonadal men rose into the normal range within 1-2 hours of applying the first dose of the gel. Once-daily application of 100 mg was sufficient to bring testosterone concentrations within or above the normal range on Day 1 and maintain them there at all times. However, it is clear that the serum T-levels following the 100-mg T-gel dose (one site or four) may rise and remain significantly above the higher level for normal serum T range resulting in compromised safety. Hence, dose titration (as discussed in the label and in the 'reviewer's comments' section following Study 1) would be ESSENTIAL for the safe use of this product.
- Testosterone concentrations reached steady-state concentrations by the end of the first day of treatment.
- Testosterone washout following discontinuation of therapy was quite slow compared to the one-hour elimination half-life reported for testosterone. Testosterone washout continued for 72-96 hours after the last application. Based on this observation, showering recommendations have been made in the label (see section "Labeling Comments").
- The surface area over which the gel was applied had only a modest impact on the uptake of testosterone into the systemic circulation. Surface areas differing by 4-fold showed only 20%-30% difference in serum concentrations. T-gel application on the smaller surface area was sufficient to achieve and maintain adequate testosterone serum concentrations.
- Estradiol serum concentrations increased slightly and were within the normal range during gel application. Estradiol concentrations returned to their pretreatment concentrations within three days following discontinuation of treatment.
- Based on the AUC values of T between days 8-10 (post treatment) and PK profile, it is evident that at least from the 100 mg T-gel dose, the depot of T in skin is substantial to maintain a  $C_{p,ss}$  around the upper normal level over 24 hrs post-dose. Although T-gel is designed for transdermal delivery following topical application, it is not a patch. Hence, it does not allow the patient or the physician to remove the application if T-serum levels remain too high. Therefore, for safety, dose selection and titration is critical.

### **Questions and Answers**

*Question.* Do PK parameters differ between application of T-gel at one site or four sites?

*Answer.* No. Results show that there are no statistically significant differences in PK parameters of T following one-site (left upper arm/shoulder) or four-site (left upper arm/shoulder, the right upper arm/shoulder, the left abdomen and the right abdomen).

*Question.* Does the pharmacokinetic results from this study match with that from the pivotal trial?

*Answer.* This PK study used only one (higher) dose of 100 mg T-gel. Taking into account the variation in the data, the PK parameters match the range with that obtained from the pivotal trial. However, this study confirms that 100 mg T-gel may really be a high starting dose for T-replacement and maintenance.

**Study 3. UMD-96-023 and UMD-98-037: A Study to Determine Changes in Serum Androgen Levels in Female Partners of Men Using Transdermal Testosterone Gel.**

Study UMD-96-023 was the first study that was initiated to determine the extent of exposure of T to female partners of hypogonadal men using the T-gel. However, out of an initial plan of recruitment of 30-45 patients, the study was stopped after 5 patients were recruited. Of them, one dropped out. The study was not designed well. For example, the extent and frequency of contact, especially in relationship to the collection times of serum samples for androgen measurements, was not available. Further, the information gained from a single measurement on a specific day is limited in scope. Therefore, the conclusions drawn from the study are really not reliable. Due to the above limitations, this study will not be discussed in detail here. Study UMD-98-037 (discussed in detail below) was a more well designed study for the same purpose.

The primary objective of Study UMD-98-037 was to determine whether any changes occur in serum androgen levels in female partners of men using T-gel. This study was a single-center, open-label, parallel-group, randomized study. Approximately 48 couples (12 per group) were to be enrolled (45 completed). Each male subject applied approximately 100 mg T-gel to the abdomen, shoulders and upper arms each day for seven consecutive days. There were four parallel active groups and these included: two groups in which rigorous physical contact between partners occurred two hours following T-gel application by the male (in one of these groups, the male was required to wear a long-sleeved cotton T-shirt throughout the entire study); one group in which rigorous physical contact occurred six hours following application; and one group in which rigorous physical contact occurred 12 hours following application. Physical contact occurred at the investigative site on Day 1 and Day 7 (approximately 15 minutes of supervised physical contact). Additionally, the couples were to observe the same time interval between T-gel application and their physical contact period at home on Days 2 through 6. If it was not possible to observe the same time interval, the couples were to wait at least two hours after application before the start of the contact period.

Female subjects had baseline measurements for total testosterone, free testosterone and 3 $\alpha$ -androstenediol-glucuronide levels on Day 0 at time 0, 1, 2, 4, 8 and 24 hours. These sampling times on Day 0 corresponded to the sampling times on Day 1 and Day 7 and were based on the projected time of contact. The female partners had blood samples obtained again on Day 1 and Day 7 at time 0 (prior to physical contact with the partner) and at 1, 2, 4, 8 and 24 hours following initiation of physical contact with the male partner. Additionally, females in the 12-hour group and the two-hour group (with T-shirt) had blood samples obtained 36 and 48 hours following initiation of physical contact with the male partner on Day 7.

### Results

Please refer to Tables 7-9 below and Figure 3.1 – 3.2 for a summary of the results obtained.

**Table 7. Mean  $T_{max}$  and Mean Changes from Day 0 to Day 1 and Day 7 in  $AUC_{(0-24)}$  and  $C_{max}$  for Total Testosterone, and Mean Ratio for AUC\* [Study UMD-98-037]**

Treatment Group	$AUC_{(0-24)}$ Day 1-Day 0 & (Day 1/Day 0)	$AUC_{(0-24)}$ Day 7-Day 0 & (Day 7/Day 0)	$C_{max}$ Day 1-Day 0	$C_{max}$ Day 7-Day 0	$T_{max}$ Day 0	$T_{max}$ Day 1	$T_{max}$ Day 7
2-Hour	1075.00 (3.235)	2424.5 (5.614)	93.43	140.29	8.00	13.42	3.91
6-Hour	740.43 (3.121)	1106.60 (3.684)	44.79	62.63	8.82	8.82	9.11
12-Hour	754.06 (3.145)	1485.03 (5.773)	47.17	98.37	14.60	14.20	10.00
2-Hour (T-shirt)	41.89 (1.071)	102.71 (1.148)	1.00	7.38	7.11	17.00	14.13

\* $AUC_{(0-24)}$  and  $C_{max}$  Day 1-Day 0 and Day 7-Day 0 are the mean of the differences for individual subjects.  
 $C_{max}$  measured in ng/dL, AUC in ng\*hr/dL and  $T_{max}$  in hrs.

**Table 8. Mean  $T_{max}$  and Mean Changes from Day 0 to Day 1 and Day 7 in  $AUC_{(0-24)}$  and  $C_{max}$  for Free Testosterone\* [Study UMD-98-037]**

Treatment Group	$AUC_{(0-24)}$ Day 1-Day 0	$AUC_{(0-24)}$ Day 7-Day 0	$C_{max}$ Day 1-Day 0	$C_{max}$ Day 7-Day 0	$T_{max}$ Day 0	$T_{max}$ Day 1	$T_{max}$ Day 7
2-Hour	ND*	ND	0.85	1.62	6.92	9.25	6.18
6-Hour	ND	ND	0.38	0.70	6.36	8.64	6.89
12-Hour	7.07	13.97	0.41	0.90	12.40	12.00	11.60
2-Hour (T-shirt)	0.47	0.57	-0.01	0.06	7.89	11.78	11.00

\*ND=Not done. Data points available for four or fewer subjects.

\* $AUC_{(0-24)}$  and  $C_{max}$  Day 1-Day 0 and Day 7-Day 0 are the mean of the differences for individual subjects.  
 $C_{max}$  measured in pg/mL, AUC in pg\*hr/mL and  $T_{max}$  in hrs.

**Table 9. Mean  $T_{max}$  and Mean Changes from Day 0 to Day 1 and Day 7 in  $AUC_{(0-24)}$  and  $C_{max}$  for 3 $\alpha$ -Androstanediol-Glucuronide\* [Study UMD-98-037]**

Treatment Group	$AUC_{(0-24)}$ Day 1-Day 0	$AUC_{(0-24)}$ Day 7-Day 0	$C_{max}$ Day 1-Day 0	$C_{max}$ Day 7-Day 0	$T_{max}$ Day 0	$T_{max}$ Day 1	$T_{max}$ Day 7
2-Hour	880.86	1134.05	40.75	58.82	12.33	13.58	8.73
6-Hour	167.80	778.40	15.36	21.44	7.55	11.73	16.89
12-Hour	177.44	559.62	8.7	31.90	5.80	6.60	7.90
2-Hour (T-shirt)	33.94	-584.71	-15.67	-41.00	11.22	16.11	12.00

\* $AUC_{(0-24)}$  and  $C_{max}$  Day 1-Day 0 and Day 7-Day 0 are the mean of the differences for individual subjects.  
 $C_{max}$  measured in ng/dL, AUC in ng\*hr/dL and  $T_{max}$  in hrs.

Figure 3.1. Mean Total Testosterone AUC<sub>(0-24)</sub> on Days 0, 1 & 7 [Study UMD-98-037]

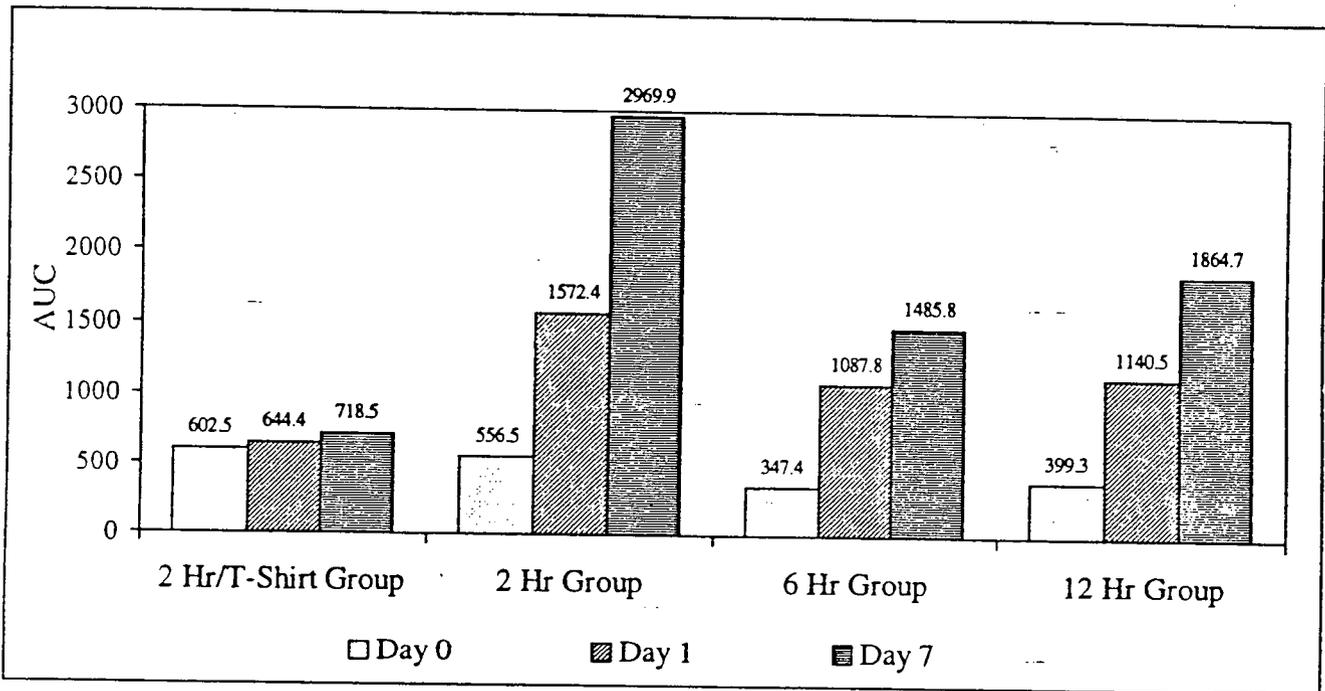
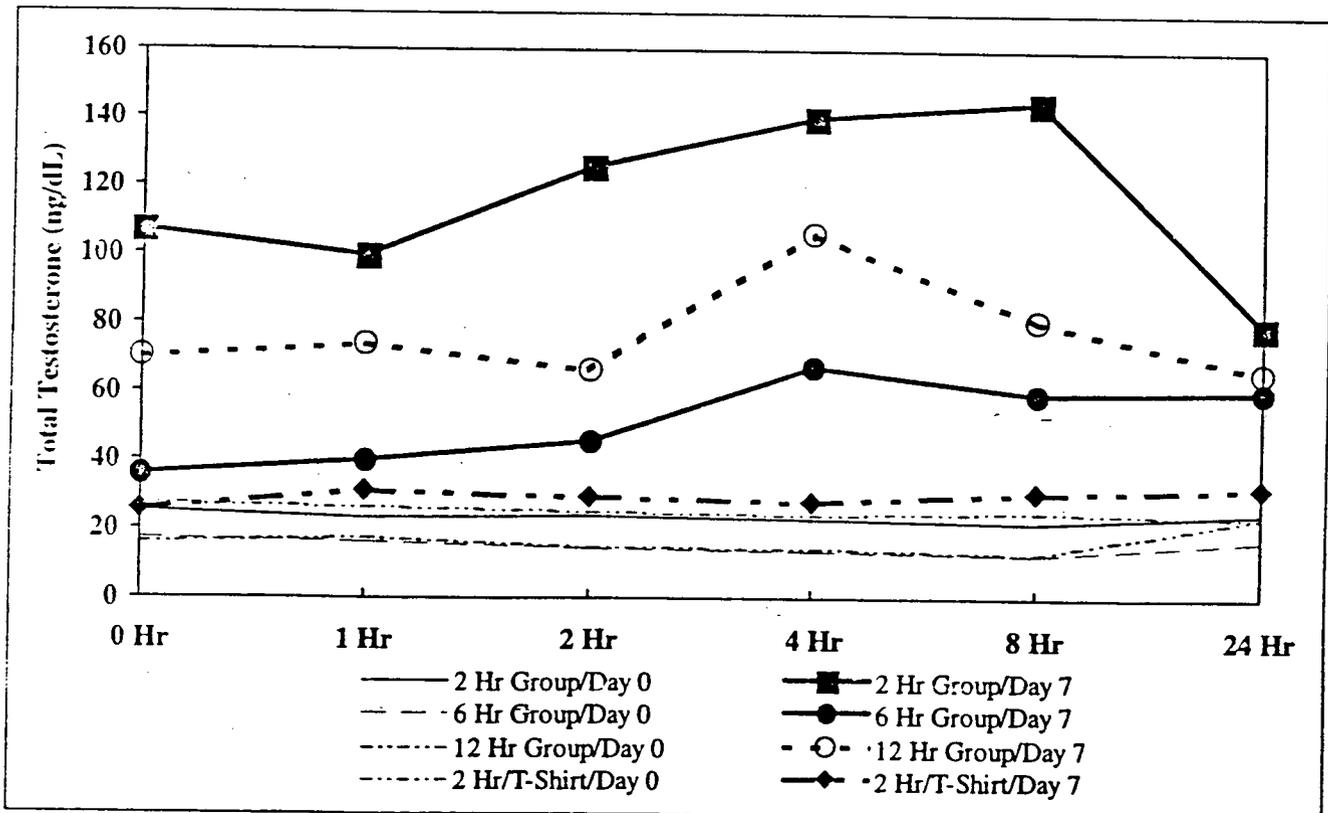


Figure 3.2. Day 7 Mean Total Testosterone Concentrations [Study UMD-98-037]



## Conclusions

- Significant transfer (see plots/tables above) of T into the female partners of men who use this product is possible upon physical contact. However, since occluding the area of application (eg. with a T-shirt or other appropriate clothing) is a solution, proper patient usage/labeling instructions should solve the problem.
- The skin-transfer study was well designed and really evaluated an exaggerated (worst case) scenario. Nevertheless, from such a scenario (especially with intimate direct contact with the application sites 2 hours post application), the mean rise in T-levels in women may be 2-4 fold higher than the high normal level of T in women, ie., 55 ng/dL.
- There were 2-patients in the 2-hr post-treatment group (without T-shirt) in whom the rise in serum T levels between day 0 – day 7 was above 250 and 350 ng/dL (transiently).

## Questions and Answers

*Question.* Does the results from this study show that there might be significant transfer of T into the partners of Androgel users? Is there a concern?

*Answer.* Yes. The transfer is more significant when exposure was 2 hours post-application than 6 or 12 hours. The main concern is high T-levels in women may lead to signs of virilization and hirsutism. The study also indicates that use of proper clothing might be able to completely prevent this transfer. Hence, proper labeling and patient instructions (for proper precautions) might abolish the concern of T-transfer into women and possible complications.

## Study 4. Three *In Vitro* Studies (UMD-98-943, UMD-98-946 and UMD-96-948) – To Determine the Effects of Wiping/Washing and Varying IPM % on T-Flux.

These were *in vitro* studies utilizing non-clinical drug formulation batches (although the formulations were similar), human cadaver skin, and radiolabeled T for assay. Although the studies are done in settings much different than the clinical trial, the results do provide some preliminary evidence on the effects of wiping/washing and formulation factors on the *in vitro* skin flux of T across cadaver skin.

## Results

### UMD-98-943

- Wiping the skin surface as soon as 1 minute after application does not significantly decrease delivery of testosterone into the skin tissue, but does result in significantly decreased absorption through the skin into the reservoir.
- Most of the testosterone applied remains on the skin surface after 24 hours (64-71%), even with wiping the skin at 0-30 minutes.
- Approximately 50% of the applied testosterone can be effectively removed at 24 hours by washing with mild detergent. Furthermore, wiping with gauze following this wash removes an additional 10-13% of testosterone. However, removal of that amount of T from the skin might not affect *in vivo* skin flux at steady state.



Table 10. (Not available electronically)

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PENETRATION IN VITRO, USING FRANZ CELLS, OF TESTOSTERONE INCORPORATED AT 1% IN A HYDROALCOHOLIC GEL (ETHANOL, CARBOPOL, NaOH 0.1M, WATER) AT DIFFERENT CONCENTRATIONS OF ISOPROPYL MYRISTATE ON A HUMAN WHITE ABDOMINAL SKIN DERMACTEMED AT  $\pm 0.01$  cm

TABLE OF NON CUMULATED VALUES

MEAN  $\pm$  Sd AS A FONCTION OF TIME

SAMPLES	VALUES	MEAN OF % AND RECOVERED QUANTITIES (ng)				
		SURVIVAL LIQUID IN THE RECEPTOR COMPARTMENT OF THE CELL				
		0-2 H	2-4H	4-6H	6-8H	8-24H
N° 1 n=8 IPM	% of applied dose $\pm$ Sd	0.12% 0.08%	0.29% 0.13%	0.32% 0.14%	0.32% 0.13%	1.81% 0.73%
	Qty RECOVERED (ng) $\pm$ Sd	46 31	108 48	120 51	120 47	681 275
	FLUX (ng/cm2/h) $\pm$ Sd	13 9	31 14	34 14	34 13	24 10

N° 2 n=8 IPM	% of applied dose $\pm$ Sd	0.08% 0.05%	0.20% 0.14%	0.25% 1.30%	0.29% 0.13%	1.84% 0.58%
	Qty RECOVERED (ng) $\pm$ Sd	31 18	77 52	96 51	109 49	699 221
	FLUX (ng/cm2/h) $\pm$ Sd	9 5	22 15	27 14	31 14	25 8

N° 3 n=8 IPM	% of applied dose $\pm$ Sd	0.08% 0.04%	0.26% 0.11%	0.33% 0.12%	0.33% 0.10%	2.04% 0.48%
	Qty RECOVERED (ng) $\pm$ Sd	29 14	98 41	126 46	125 37	768 180
	FLUX (ng/cm2/h) $\pm$ Sd	8 4	28 12	36 13	35 11	27 6

N° 4 n=8 IPM	% of applied dose $\pm$ Sd	0.06% 0.05%	0.25% 0.12%	0.32% 0.11%	0.34% 0.11%	2.41% 0.75%
	Qty RECOVERED (ng) $\pm$ Sd	24 19	94 44	122 42	128 41	910 283
	FLUX (ng/cm2/h) $\pm$ Sd	7 5	27 13	35 12	36 11	32 10

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## Changes in Drug Formulation

All clinical studies were conducted using product in pump bottles. The bottle formulation contains \_\_\_\_\_ isopropyl myristate. The market presentation will be unit dose foil laminate packets. Because the PE film of the unit dose packet has been found to absorb some of the isopropyl myristate, the amount of isopropyl myristate in the unit dose formulation was increased to \_\_\_\_\_ which after 30 days decreases to approximately \_\_\_\_\_ the same amount as is in the bottle formulation. In-vitro studies were conducted to assess the influence of isopropyl myristate concentration \_\_\_\_\_ in gel formulation on testosterone absorption. The results indicate that release rates are not affected by this change in concentration.

### Reviewer's Comments

- IPM has sometimes been used as an effective solubilizer of drug substances and a skin penetration enhancer (due to its reversible effects on the lipoprotein nature of the skin) in dermatological/transdermal products. *In vitro* results (Study UMD-98-946, see previous section) do not show any significant difference in T-flux across cadaver skin from formulations containing \_\_\_\_\_ IPM.
- The results showing that PE film of the unit dose packet absorbs the IPM at a rate which leads to a drop in IPM concentration from \_\_\_\_\_ has not been presented, at least, in this section of the NDA. In a discussion with the chemistry reviewer it was determined that the range of %IPM in the finished product (supportive stability batches) is anticipated to be between \_\_\_\_\_. Moreover, the sponsor has provided *in vitro* skin flux information showing that the difference in IPM between \_\_\_\_\_ does not effect skin flux. Based on the above information and the fact that patients on this product will have T serum monitored two weeks following beginning of treatment, the above change in formulation is acceptable.
- Based on the above facts and findings, a formal bioequivalence study linking the clinical and the to-be-marketed product was considered unnecessary.
- However, sponsor is requested to submit relevant evidence (post-approval) on suitable ANDROGEL™ batches containing highest and lowest % IPM (marketed and clinical trial formulations) showing no difference in clinical T delivery (serum T profiles).

### Questions and Answers

*Question.* Was the formulation used in the clinical trial exactly same as the to-be marketed?  
*Answer.* No. There was a minor difference in the concentration of isopropyl myristate. As described in the comments above, this change might be acceptable without a linking bioequivalence study.

### Assay Validation Summary

\_\_\_\_\_ and \_\_\_\_\_ were the techniques used for all the assays. Please refer to Appendix I for an overview of the typical assay methods utilized, the values for sensitivity, specificity and range. Overall, the methods were acceptable. However, due the complicated sample preparation and assay methods, some inter and intra assay precision values were as high as \_\_\_\_\_

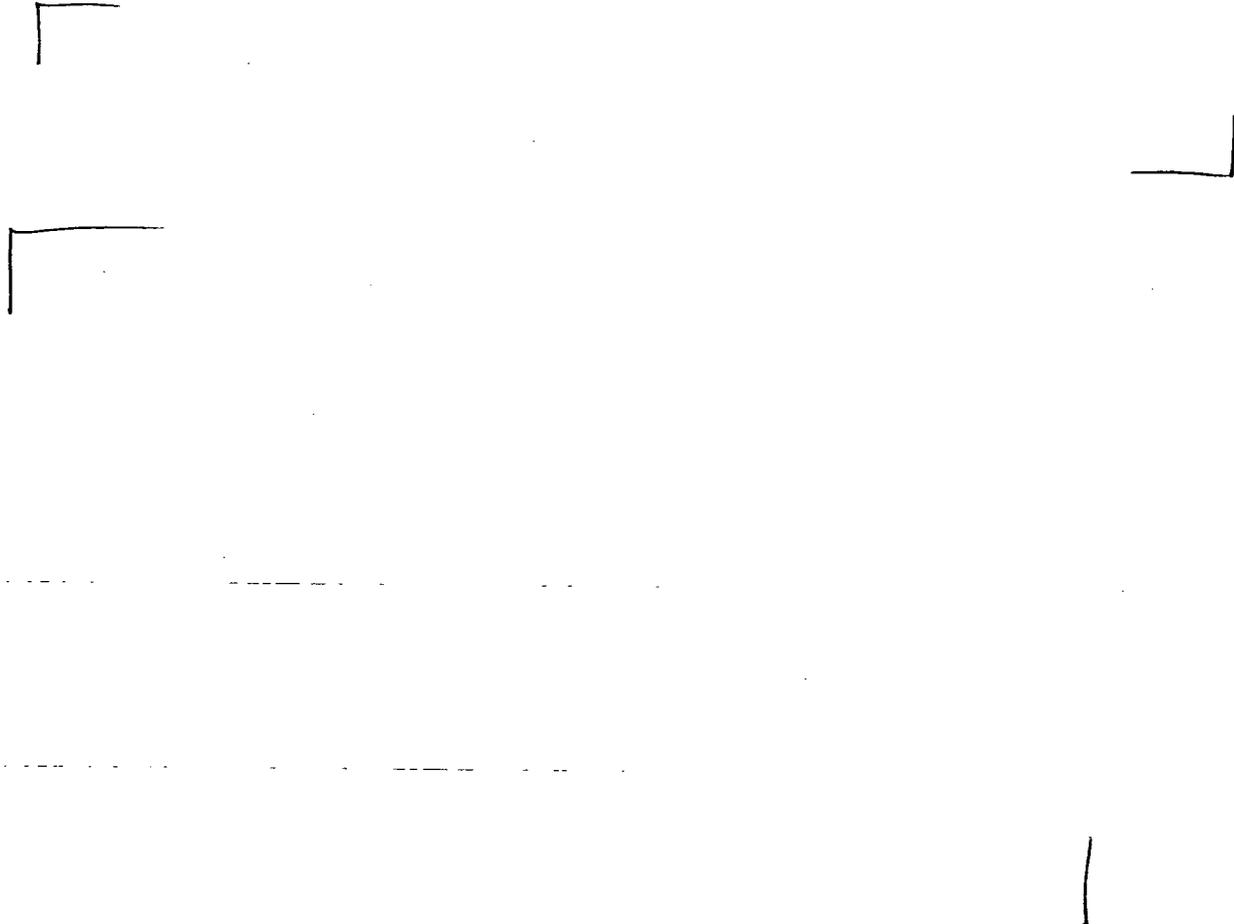
The Division of Scientific Investigation conducted an investigation of analytical methods, reports and documentation at the pivotal trial site. The investigation report suggests that the methods employed were acceptable in general, but there were a few minor shortcomings.

## Labeling Comments

Please refer to the proposed Androgel labeling text dated September 16, 1999 [~~Strikeout~~ suggests deletion of text, and underline suggests insertion]. Additional comments are bulleted.

34.	<b>CLINICAL PHARMACOLOGY</b>
35.	
36.	Androgel (testosterone gel) delivers physiologic amounts of testosterone,
37.	producing circulating testosterone concentrations that approximate normal
38.	levels (298 – 1043 ng/dL) _____ seen in healthy men.
39.	
80.	Pharmacokinetics
81.	<u>Absorption</u>
82.	Androgel is a hydroalcoholic formulation that dries quickly when applied to
83.	the skin surface. _____ The skin, _____
84.	serves as a reservoir for the sustained release of testosterone into the systemic
85.	circulation. _____
86.	serum testosterone _____ within 30 minutes; _____
87.	_____
88.	_____ Absorption of testosterone into the blood continues for the
89.	entire 24-hour dosing interval. Serum concentrations approximate the steady
90.	state level by the end of the first 24 hours and are at steady state by the second
91.	or third day of dosing. _____
92.	_____
93.	_____
94.	_____
95.	_____
96.	With single daily applications of Androgel, follow-up measurements 30, 90
97.	and 180 days after starting treatment have confirmed that serum testosterone
98.	concentrations are generally maintained within the eugonadal range. Figure 1
99.	summarizes the 24-hour pharmacokinetic profiles of testosterone for patients
100.	maintained on <input type="checkbox"/>
101.	
102.	
103.	
104.	

- The plot included within lines 105-114 should be modified as follows:



134. Testosterone is metabolized to various 17-keto steroids through two different  
135. pathways. The major active metabolites of testosterone are estradiol and  
136. DHT. \_\_\_\_\_  
137. \_\_\_\_\_ DHT binds with greater affinity  
138. to SHBG than does testosterone. In many tissues, the activity of testosterone  
139. depends on its reduction to DHT, which binds to cytosol receptor proteins.  
140. The steroid-receptor complex is transported to the nucleus where it initiates  
141. transcription and cellular changes related to androgen action. In reproductive  
142. tissues, DHT is further metabolized to 3- $\alpha$  and 3- $\beta$  androstenediol.  
143.  
144. DHT concentrations increased in parallel with testosterone concentrations  
145. during Androgel treatment. After 180 days of treatment, mean DHT  
146. concentrations were within the normal range with \_\_\_\_\_ and were  
147. about 7% above the normal range after a 100-mg dose. The mean steady state  
148. DHT/T ratio during 180 days of \_\_\_\_\_ treatment \_\_\_\_\_  
149. \_\_\_\_\_  
150. \_\_\_\_\_  
151. \_\_\_\_\_  
152. \_\_\_\_\_

- Highlighted sections (lines 136-137 and 150-151) need to be reconfirmed. The sponsor obtained these values from the \_\_\_\_\_ with studies involving eugonadal men. However, if these results are not verifiable, these lines should be omitted.

160.	<b>Special Populations</b>
161.	In patients treated with Androgel, there are no observed differences in the
162.	average daily serum testosterone concentration at steady-state based on age,
163.	race, cause of hypogonadism or body mass index. _____
164.	_____
165.	_____ <u>No formal studies</u>
	<u>were conducted involving patients with renal or hepatic insufficiencies.</u>

- All data should be presented as Mean ± SD, not \_\_\_\_\_

### Comments on "Patient Package Insert"

Page 2:

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**APPENDIX I**

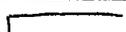
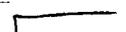
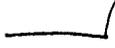
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(Not available electronically)

**APPEARS THIS WAY  
ON ORIGINAL**

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study

Testosterone (T)

Study Number (s)	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/ Range	Specificity (parent/ metabolites)
UMD-96-012	Protocol : 4/12/96 (SN 000)  Report: 3/17/99 (SN 028) and 3/30/99 (SN 030)	Serum			
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)				

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Testosterone (T)

Study Number (s)	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/ Range	Specificity (parent/ metabolites)
UMD-97-023	Protocol/ amendment: -1/15/98 (SN 008) -1/26/98 (SN 009) -3/24/98 (SN 011) -7/23/98 (SN 014)  Report: 3/23/99 (SN 029)	Serum		• • • • •	
UMD-98-037	Protocol/ amendment: -10/23/98 (SN 020) -2/10/99 (SN 027)  Report: 4/16/99 (SN 031)				

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Free Testosterone (FT)

Study Number	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)	Dialysate			

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Free Testosterone (FT)

Study Number (s)	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/ Range	Specificity (parent/ metabolites)
UMD-97-023	Protocol/ amendment: -1/15/98 (SN 008) -1/26/98 (SN 009) -3/24/98 (SN 011) -7/23/98 (SN 014)  Report: 3/23/99 (SN 029)	Serum			Not applicable.
UMD-98-037	Protocol/ amendment: -10/23/98 (SN 020) -2/10/99 (SN 027)  Report: 4/16/99 (SN 031)				

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Dihydrotestosterone (DHT)

Study Number (s)	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-96-012	Protocol : 4/12/96 (SN 000)  Report: 3/17/99 (SN 028) and 3/30/99 (SN 030)	Serum			
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)				

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Estradiol (E<sub>2</sub>)

Study Number (s)	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-96-012	Protocol : 4/12/96 (SN 000)  Report: 3/17/99 (SN 028) and 3/30/99 (SN 030)	Serum			
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)				

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Sex Hormone Binding Globulin (SHBG)

Study Number	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/ Range	Specificity (parent/ metabolites)
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)	Serum			

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Sex-Hormone Binding Globulin (SHBG)

Study Number	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-97-023	Protocol/ amendment: -1/15/98 (SN 008) -1/26/98 (SN 009) -3/24/98 (SN 011) -7/23/98 (SN 014)  Report: 3/23/99 (SN 029)	Serum			

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Androstanediol Glucuronide

Study Number (s)	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-97-023	Protocol/ amendment: -1/15/98 (SN 008) -1/26/98 (SN 009) -3/24/98 (SN 011) -7/23/98 (SN 014)  Report: 3/23/99 (SN 029)	Serum			
UMD-98-037	Protocol/ amendment: -10/23/98 (SN 020) -2/10/99 (SN 027)  Report: 4/16/99 (SN 031)				

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Follicle Stimulating Hormone (FSH)

Study Number	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)	Serum			

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Luteinizing Hormone (LH)

Study Number (s)	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/ Range	Specificity (parent/ metabolites)
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)	Serum			

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Osteocalcin

Study Number	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)	Serum			

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Carboxyterminal Propeptide of Type 1 Procollagen (PICP)

Study Number	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)	Serum			

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Parathyroid Hormone (PTH)

Study Number	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)	Serum			

6.4 Summary of Analytical Methods Employed in Each *in Vivo* Biopharmaceutics Study (Continued)

Bone Specific Alkaline Phosphatase (SALP)

Study Number	IND Submission Date	Type of Biological Fluid	Method	Sensitivity of Method/Range	Specificity (parent/metabolites)
UMD-96-017	Protocol/ amendment: -1/23/97 (SN 002) -4/14/97 (SN 004) -1/15/97 (SN 007) -7/23/98 (SN 014)  Report: 4/16/99 (SN 031)	Serum			

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