CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-015

MEDICAL REVIEW

FEB 1 5 2000

NDA 21-015

Date NDA submitted: April 28, 1999
Date NDA received: April 30, 1999
Date assigned: May 5, 1999
Draft review completed: February 11, 2000
Revisions completed: February 15, 2000

Medical Officer Review

Sponsor:	Unimed Pharmaceuticals, Inc. 2150 E. Lake Cook Road Buffalo Grove, IL 60089
Drug:	**Generic**: testosterone gel **Trade**: AndroGel™ **Chemical**: Androst-4-en-3-one, 17-hydroxy, (17β)-17β-hydroxyandrost-4-en-3one
Route:	transdermal
Dosage form:	gel
Strength:	25 mg and 50 mg
Proposed indication:	replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Related INDs:	——— Unimed, Inc.); —— (Unimed, Inc.)
Related documents:	*Major amendments* received: September 17, 1999 (Four-month safety); *Minutes of meetings* dated: January 14, 1999 (Pre-NDA/Tcon); November 3, 1998 (Pre-NDA); February 18, 1997 (End of Phase 2);

TABLE OF CONTENTS

1. Resume:

1.1 **Efficacy**: In support of the efficacy of Androgel as replacement therapy in hypogonadal men, the sponsor submitted full study reports for four controlled clinical trials. Clinical study UMD-96-017 ("017") was the only phase 3 trial. There were two, phase 2 European trials ("044" and "045") and one, phase 1 trial ("012").

The study that contained the bulk of the efficacy data was UMD-96-017. This was a randomized, active-controlled, parallel-group study conducted in 16 United States centers that compared two doses of Androgel with a testosterone patch (Androderm). The study was double-blind with respect to the random assignment to the Androgel doses, but was open-label for the patch. During the "Initial Treatment Period"(Months 1-3), three treatments were administered: 5 gm of Androgel daily (containing 50 mg testosterone), 10 gm of Androgel daily (containing 100 mg testosterone), and two Androderm patches daily (containing a total of 5 mg absorbed testosterone).

At Day 91, a fourth treatment group was added, 7.5 gm of Androgel daily (containing 75 mg testosterone). Patients who were receiving Androgel during the Initial Treatment Period and who had single-sample serum testosterone (T) concentrations within the normal range (300 and 1000 ng/dL) on Day 60 remained on their double-blind treatment for an additional 3 months (the "Extended Treatment Period"). Patients with serum T concentrations outside the normal range were titrated to receive Androgel 75 mg in an open-label fashion for an additional 3 months. Patients randomized to testosterone patch remained on the patch for an additional 3 months.

Two hundred and twenty-seven hypogonadal men were enrolled in this trial; 73 were randomized to 50 mg Androgel, 78 were randomized to 100 mg Androgel, and 76 were randomized to T-patch

In both Androgel treatment groups, mean peak, trough and average T concentrations were within normal limits on Day 30. Day 30 was defined a priori as the timepoint of primary interest. In those patients maintained on 50 mg daily or 100 mg daily, serum T concentrations were generally maintained within the normal range for the full, 180-day treatment period. Dose titration to 75 mg daily was also generally successful in bringing serum T concentrations into the normal range.

The results obtained from most secondary endpoints, including bone mineral density, libido, and various parameters of body composition (e.g. total body fat, lean body mass, etc.), supported an overall positive androgen effect.

There are two efficacy issues which are noteworthy. First, no comparative claims to the testosterone patch based on an assessment of serum T levels have been supported. Both testosterone gel and testosterone patch were efficacious in raising subnormal testosterone levels in hypogonadal men into the normal range. The reviewer is aware of no evidence that supports superior clinical benefit based on serum levels which are higher or lower within the normal range.

Second, a few patients in the low-dose Androgel group and many patients in high-dose Androgel group had serum T levels which were above the upper limit of normal at some time during the 24-hour measuring period on Day 30. The reviewer believes

that such situations have been adequately addressed by clear labeling instructions. All patients will be advised to start at the lowest dose (50 mg daily) and titrate up as necessary based on serum T levels and clinical effect. A single-sample determination of serum T should be obtained on Day 14 of treatment and appropriate management of patients on Androgel based on this surveillance technique should be self-evident.

Safety: The safety assessment of Androgel was based on results from the following studies: UMD-98-044, UMD-98-045, UMD-96-012, UMD-96-017, UMD-97-023, UMD-98-037, UMD-98-038, UMD-98-039 and preliminary results from UMD-98-035.

The extent of exposure was considered adequate to make an overall safety determination. In clinical trial UMD-96-012 alone, the extent of exposure was as follows: Androgel 50 mg, 147.1 days (N=77), Androgel 100 mg, 148.6 days (N=78), and Androgel 75 mg, 86.9 days (N=40).

The sponsor conducted additional studies that were considered adequate to allow a specific assessment of dermal irritation (Studies 017, 038 and 039). Finally, the sponsor conducted a study that was also considered adequate to allow a specific assessment of potential transfer to a partner (Study 037).

Overall, Androgel, at daily doses of 50 mg, 75 mg and 100 mg daily appeared to be safe and well-tolerated. There were no deaths and only rare serious adverse events reported. No serious adverse event was determined to be directly-related to use of Androgel and very few were determined to be possibly-related. These included depression, hypertension, and a cerebral infarct.

Use of Androgel did appear to be associated with some adverse reactions secondary to undesirable androgenic effects. These included polycythemia in a few patients, decreased serum HDL in several patients, acne and leg edema in several patients, and urogenital events in some patients. Urogenital effects included disorders of impaired urination, increased PSA levels, changes in the size of the prostate gland and gynecomastia. Clear labeling instructions should serve to minimize these risks by recommending active medical surveillance. Such monitoring as periodic hematology and chemistry laboratories, serum PSA, physical examination and medical history, as described in the proposed labeling, should effectively limit these adverse reactions.

In regard to skin tolerability, the reviewer agrees that Androgel demonstrated a relatively low incidence of application site reaction and that there were no discontinuations in the Androgel groups secondary to skin-related adverse reactions during the controlled clinical trial. However, the reviewer does not believe that the design and conduct of any trial in this application was appropriate to compare Androgel to a testosterone patch in terms of skin reactivity. The open-label nature of randomization and the open-label assessment of application site reaction posed too great a potential for bias to support comparative safety claims.

Finally, since the product is a topical gel formulation, there is some inherent risk of testosterone transfer to a female partner or a pregnant female partner. Based on the results of study "037", it is clear that covering the sites totally prevents transfer of the

gel. The current labeling should serve to minimize, but cannot totally eradicate this risk.

2. Background:

2.1 Regulatory history: On April 12, 1996, IND —— was submitted to FDA and was reviewed by the Division of Metabolic and Endocrine Drug Products (DMEDP, HFD-510). Early in the course of this IND, the Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580) was created as a splinter Division from DMEDP. The responsibility for this IND was then transferred to DRUDP.

In the first submission to the IND, the sponsor submitted the protocol for clinical trial UMD-96-012 ("012"). The sponsor anticipated performing this single phase 1 study followed by a single, 30-day, phase 2, dose-ranging study; then by a single, large, 6-month, phase 3 study.

On February 18, 1997, a face-to-face "End-of-Phase-2" meeting was held between DRUDP and sponsor. The sponsor presented results of "012". The sponsor presented a single proposed protocol ("017") which they believed would provide the bulk of clinical data to support an NDA submission. Plans for a separate, 30-day, phase 2 trial were dropped and the "dose-ranging" aspect of the previous phase 2 protocol was incorporated into the new phase 3 protocol. The sponsor also presented plans to assess dermal irritation in men and to assess potential transfer to partners in separate studies.

At the meeting, the Division voiced no major concerns regarding the sponsor's phase 3 plans. However, the Division did suggest that 100 mg/daily probably provided too much testosterone in most patients. One proposal suggested by the Division was to start all patients on 50 mg/daily and titrate up accordingly.

The single Phase 3 study ("017") was initiated subsequent to the End-of-Phase 2 meeting in February 1997. There appeared to be no formal amendment to the IND containing the final protocol.

On January 15, 1998, the sponsor submitted a proposed routine protocol revision to "017". At that time, the medical officer noted that there had been no previous formal submission of the protocol (other than at the EOP2 meeting) and therefore, the protocol was formally reviewed while the Phase 3 study was ongoing. Comments were conveyed to the sponsor by information request letter on February 20, 1998.

On March 3, 1998, the sponsor submitted a proposed protocol (UMD-98-035) designed to assess long-term safety in patients who completed "017" and wished to continue treatment with AndroGel.

On November 3, 1998, a face-to-face "Pre-NDA" meeting was held between DRUDP and sponsor. There were no major clinical disagreements at this meeting.

On January 14, 1999, a teleconference was held with the sponsor to clarify the statistical analysis plan for Study "017".

2.2 Clinical background: The principal endogenous androgens, testosterone and dihydrotestosterone, are known to promote normal growth and development of the male sex organs and to maintain and promote development of the normal secondary male sex

characteristics. These characteristics include the development of male pattern hair growth, laryngeal enlargement, vocal cord thickening, alterations in body musculature, fat distribution, and growth and maturation of the prostate, seminal vesicles, penis, and scrotum.

Androgens are also responsible for the growth spurt in adolescence and for the acceleration of linear bone growth. Androgens have been reported to increase protein anabolism and to decrease catabolism. There is also evidence that androgens stimulate the production of red blood cells by enhancing production of erythropoetin.

The term "male hypogonadism" refers to a condition in which the endogenous secretion of testosterone is "insufficient" or "inadequate" to maintain serum testosterone levels within the normal range. Some symptoms which may be associated with this condition include decreased sexual desire, changes in mood, regression of male secondary sex characteristics, and fatigue. It is also possible that prolonged hypogonadism may lead to osteoporosis.

Some conditions which may lead to a hypogonadal state in men include cryptorchidism, bilateral testicular torsion, orchitis, Klinefelter's syndrome, exposure to chemotherapy or heavy metals ("primary hypogonadism") and pituitary-hypothalamic injury secondary to radiation, trauma, tumors or other idiopathic causes ("hypogonadotropic hypogonadism").

Currently, men with clinical hypogonadism may be offered testosterone replacement therapy in the form of intramuscular injections, transdermal patches or oral tablets. Each route of administration has its own specific risks and benefits.

2.3 Scientific rationale: The sponsor has developed a novel formulation of testosterone for the purpose of replacing endogenous testosterone in men with hypogonadal conditions. The method of treatment proposed is the daily application of a testosterone-containing "gel" to the skin. Theoretically, upon application of the gel to clean, dry skin, the excipient materials in the formulation evaporate and the testosterone becomes incorporated into the epidermis. The sponsor believes that the epidermis actually serves as the "reservoir" for continuous systemic testosterone delivery during use of this gel.

2.4 Clinical Implications of Pre-Clinical Sections:

2.4.1 Chemistry: Please refer to Dr. Lin's review. No safety issues were determined by an assessment of the CMC Summary. However, it may be important for the clinician to understand that the drug product employed in the phase 3 trial ("017") was dispensed from a bottle outfitted with a unit-dose pump dispenser. The to-be-marketed formulation will be contained in individual sachets. In addition, there is a slight difference in the isopropyl myristate content between the clinical trial formulation and the to-be-marketed formulation. Finally, Dr. Lin believes that the data submitted support only an 18-month shelf-life.

Reviewer comment: Please refer to Dr Lin's and Dr Chatterjees's reviews for a discussion of the isopropyl myristate issue.

2.4.2 Pharmacology/toxicology: Please refer to Dr. Jordan's review. There are no safety issues of note for the clinician.

2.4.3 Human pharmacology (including pharmacokinetics and metabolism): Please refer to Dr. Chatterjee's review. Given the nature of this product and the assessments of its efficacy, the clinical reviewer worked in close cooperation with the clinical pharmacologist throughout this review. There appear to be no outstanding issues in Dr. Chatterjee's review compared to this Clinical review.

2.5 Dose selection: In conjunction with Besins-Iscovesco Company, the sponsor conducted clinical trial UMD-98-044 in France between 1994 and 1995. This trial employed a formulation called "TestoGel", which contained a daily dose of testosterone of 125 mg in a 2.5% formulation. The results of this trial revealed that testosterone levels attained in 6 hypogonadal men were somewhat above the normal range. It was apparent to the sponsor that the daily dose of testosterone would require reduction in future studies.

In the opening IND study ("012"), the sponsor employed a daily dose of Androgel 1%, containing 100 mg of testosterone. This study was carried out in 1996. The results of this study revealed that 100 mg of testosterone daily provided serum T concentrations which were in the high-normal range. The sponsor estimated that 9-14 mg of testosterone were actually being absorbed daily. The sponsor decided to pursue further development of a 50 mg/daily dose, which would provide about half the daily testosterone of the 100 mg dose and probably would translate into serum T levels at the mid-point of the normal range.

Therefore, the single phase 3 trial ("017") was designed to randomize patients to 50 mg/daily or 100 mg/daily in a blinded fashion. Based on a single-sample determination on Day 60, patients could be titrated from either gel group into a new 75 mg/daily group. Full pharmacokinetic panels for serum T concentration were obtained at Days 30, 90, and 180

2.6 International marketing experience:
In Section 3.3 of the NDA, the sponsor states that "Unimed is not aware of the marketing of testosterone gel outside of the U.S. Unimed does not market testosterone in any foreign country. Unimed Pharmaceuticals has not applied for marketing approval of testosterone in any foreign country."

Reviewer's comment: In their original Investigator's Brochure, in the very first submission to IND# [redacted] the sponsor acknowledges that they were aware of the existence of a product called Testogel®. Testogel® appears to be made by Besins-Iscovesco (Paris, France), the same company that formulates the drug product AndroGel. Testogel® is a 2.5% gel formulation of testosterone. Each daily dose contains 250 mg of testosterone. It is unknown to this reviewer if Testogel® is currently marketed in Europe.

Nevertheless, Testogel®(2.5%) is clearly a different product when compared with AndroGel 1%.

3. Summary of NDA Clinical Section:

In support of the proposed indication, the sponsor has submitted the results of 9 clinical trials (Volume 1, page 3-92). Of these, five studies were essentially safety studies and four contained measures of efficacy.

The efficacy studies included the single, phase 3 trial ("017") and the single phase 1 trial ("012"). In addition, there were two, phase 2 studies conducted in Europe with a different testosterone gel formulation ("044" and "045").

The safety studies included assessments of dermal toxicity, long-term safety, and the risk of transfer to a partner. Dermal irritation studies included a cumulative irritation study ("038") and a photoxicity study ("039"). There were two studies which assessed the risk of dermal transfer to a partner ("023" and "037"). Finally, there is an ongoing, long-term, safety assessment study in patients who completed the phase 3 trial ("035")

4. Clinical trial UMD-96-017

4.1 Design

This was a randomized, active-controlled, parallel-group study conducted in 16 United States centers that compared two doses of Androgel with a testosterone patch (Androderm). The objective of the study was to evaluate the effectiveness and safety of administration of a dermal application of Androgel (compared to Androderm) in hypogonadal men treated once daily for a period of 6 months. The study was double-blind with respect to the random assignment to the Androgel doses, but was open-label for the patch. During the "Initial Treatment Period"(Months 1-3) three treatments were administered: 5 gm of Androgel daily (containing 50 mg testosterone), 10 gm of Androgel daily (containing 100 mg testosterone), and two Androderm patches daily (containing a total of 5 mg absorbed testosterone).

At Day 91, a fourth treatment group was added, 7.5 gm of Androgel daily (containing 75 mg testosterone). Patients who were receiving Androgel during the Initial Treatment Period and who had single-sample serum testosterone concentrations between 300 and 1000 ng/dL on Day 60 remained on their double-blind treatment for an additional 3 months (the "Extended Treatment Period"). Patients with T concentrations <300 ng/dL who had been receiving Androgel 50 mg daily, and patients with T concentration >1000 ng/dL who had been receiving Androgel 100 mg daily were titrated to receive Androgel 75 mg in an open-label fashion for an additional 3 months. Patients randomized to testosterone patch remained on the patch for an additional 3 months.

Eligible patients were males between the ages of 16 and 68, with a morning serum testosterone concentration ≤300 ng/dL. Other than hypogonadism, the patients must have been in good health. Patients with an abnormal prostate exam, elevated serum PSA level, or reduced urine flow rate were excluded. Patients with a hematocrit greater than 50% were excluded. Patients with skin conditions known to affect the transdermal absorption of T (e.g psoriasis) were excluded. Patients with a body weight <80% or >140% of ideal were excluded.

Following extensive discussions with the Division prior to unblinding of the data, the primary endpoint selected was "the proportion of patients in each treatment group with both Cavg and Cmin values for serum testosterone within the normal range (298- 1043 ng/dL) on Day 30". Secondary endpoints included:

1. The proportion of patients in each treatment group with both Cavg and Cmin within the normal range on Days 90 and 180.
2. The proportion of patients in each treatment group with Cavg or Cmin within the normal range on Days 30, 90 and 180.

3. The proportion of patients in each treatment group with both Cavg and Cmin values within the normal range on both Days 30 and 90 ("successful maintenance").
4. Measurements of free testosterone, dihydrotestosterone, estradiol, sex hormone-binding globulin, LH and FSH
5. Psychosexual questionnaire data, measuring sexual desire, overall mood, erectile function and level of sexual enjoyment.
6. Muscle strength assessments by the one-repetition maximum technique (measuring maximal bench press and seated leg press weights).
7. Body composition using DEXA, measuring lean body fat mass, total lean body mass, percent fat and total body mass.
8. Bone mineral density measurements of the lumbar spine and left hip, using DEXA.
9. Markers of bone formation (serum bone-specific alkaline phosphatase, osteocalcin, type-1-procollagen), bone regulation (serum PTH) and bone resorption (urinary type-1-cross-linked N-telopeptide, calcium and creatinine).

Safety was assessed via physical examination, vital signs, skin irritation assessments, prostate symptom scores, clinical laboratory tests and adverse event monitoring.

> **Reviewer's comment: Skin at the application site was assessed for irritation in an unblinded manner. Since the testosterone patch was administered open-label, a comparison of irritation scores or outcomes related to application site reactions appears to be fraught with bias. The reviewer recommends that the proposed package insert should not contain any comparative claims related to skin irritation.**

The study was initiated in February 1997 and the final study report (found in Amendment 3 of the NDA) reflects all available efficacy and safety data from all patients through Day 180. The final visit was on January 21, 1999. Study visits occurred at Days 0, 1 and 30, and every 30 days thereafter until Day 180 or withdrawal from the study.

4.2 Study Population

A total of 227 patients were enrolled; 73 were randomized to 50 mg Androgel, 78 were randomized to 50 mg Androgel, and 76 were randomized to T-patch. All of the enrolled patients were male, and the majority were White (>78% in each treatment group). The mean age was approximately 51 years in each treatment group, with a range from 19 to 68 years. Approximately one half of the patients had received previous hormonal treatment, and the majority of these had taken IM injections. The most commonly specified etiologies of hypogonadism were "primary testicular failure" (of indeterminate origin, approximately 30%), Klinefelter's Syndrome (approximately 10%) and pituitary tumor (approximately 10%). There were no significant differences between treatment groups with respect to demographics or baseline characteristics of hypogonadism.

> **Reviewer's comment: The treatment groups appeared to be well-balanced at baseline with respect to the important demographic and disease characteristics.**

4.3 Withdrawals and compliance

Of the 227 randomized patients, 32 patients prematurely discontinued treatment during the first 90 days. These included 6 patients (8.2%) in the low-dose Androgel group, 5 patients (6.4%) in the high-dose Androgel group, and 21 patients (27.6%) in the Androderm group. Of the 21 who discontinued treatment in the Androderm group, 14 discontinued due to adverse reactions. Three additional patients requested a switch from Androderm to Androgel in the first 90 days due to

adverse reactions and were obliged. Discontinuations due to adverse events are discussed in detail in the Safety section of this review.

From Days 91-180, two Androgel 75 mg patients (1 due to an AE), one Androgel 100 mg patient (due to an AE) and seven Androderm patients (3 due to AEs) prematurely discontinued.

> **Reviewer's comment: No Androgel patient discontinued treatment due to application site reaction. The labeling, as proposed, does reflect this result.**

Compliance for patients was assessed by estimating the percent of study drug actually used compared to the theoretical amount that should have been used. For Androgel patients, actual amount used was the difference between the returned bottle weight and the dispensed bottle weight. For Androderm patients, the actual number of patches used was compared to the theoretical number that should have been used. During the Initial Treatment Period, the mean compliance rates for Androgel 50 mg and Androgel 100 mg were 93% and 96%, respectively, compared to 89% for Androderm.

4.4 Efficacy analyses

Total Testosterone Serum Concentrations:

At Day 30:

The primary endpoint was pre-defined as the proportion of patients with both the Cavg and Cmin for total testosterone within the normal range (298 ng/dL to 1043 ng/dL). The number of patients that had both Cavg and Cmin testosterone concentrations within the normal range on Day 30 was 38/73 (52%) for Androgel 50 mg, 48/78 (62%) for Androgel 100 mg, and 17/76 (22%) for Androderm.

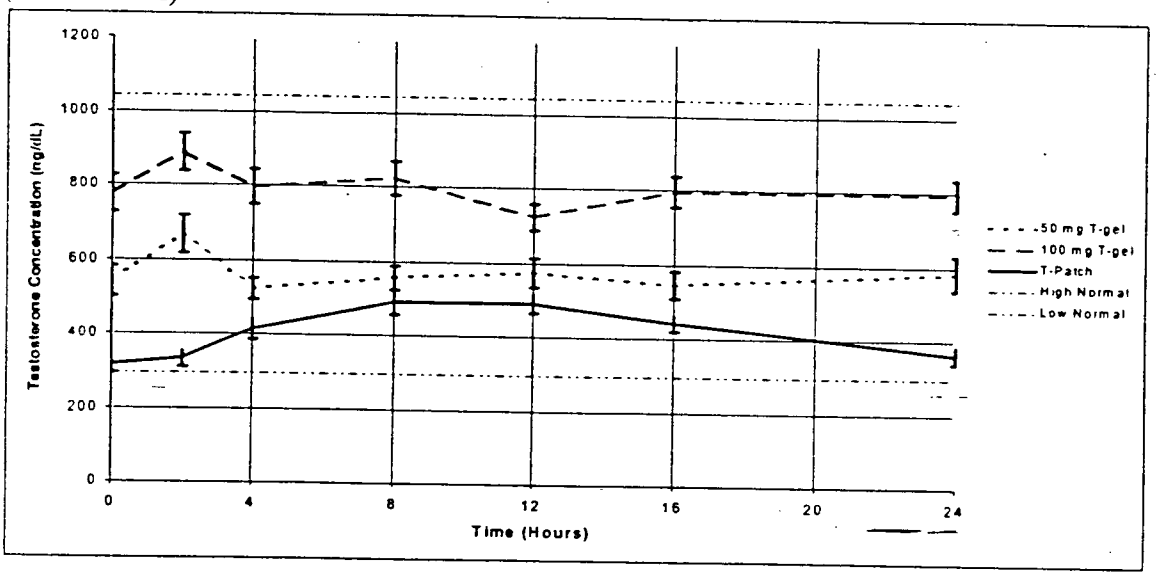
Table 1 presents the mean Cmax, Cmin, Cavg and Tmax calculated for each treatment group.

Table 1. Testosterone Pharmacokinetic Parameters, by Initial Treatment Randomization Group, on Day 30 (Mean ± SD)

	Androgel 50 mg (N=66)	Androgel 100 mg (N=74)	Androderm (N=70)
Cmax (ng/dL)	876 ± 466	1200 ± 482	576 ± 280
Cmin (ng/dL)	361 ± 149	505 ± 233	235 ± 132
Cavg (ng/dL)	566 ± 262	792 ± 294	419 ± 163
Tmax (hr)	7.9	7.8	11.3

Figure 1, taken directly from the sponsor's final report (page 460), presents these mean pharmacokinetic parameters graphically.

Figure 1. Steady-State Testosterone Concentrations on Day 30 by Initial Treatment Group (Mean ± SEM)



Reviewer's comments:

1. **In all three treatment groups, mean peak, trough and average T concentrations were within normal limits on Day 30. No evidence has been submitted (and the reviewer is unaware of any other evidence) which supports superior clinical benefit based on serum levels which are higher or lower within the normal range. Therefore, any comparative claims related to serum T levels would appear unsubstantiated and misleading. The package insert should be revised accordingly.**
2. **Figure 1 reflects the mean serum T concentrations. These means are accompanied by error bars which reflect the standard error, but should reflect the standard deviation. The package insert should be revised accordingly.**

A patient was classified as a treatment failure if either the Cavg or Cmin was outside the normal range (from 298 ng/dL to 1043 ng/dL). Table 2 presents the numbers of patients with Cavg or Cmin outside the normal range on Day 30 for each treatment group.

Table 2. Number of patients with Cavg or Cmin outside the normal range on Day 30.

	Cmin below normal range	Cmin above normal range	Cavg below normal range	Cavg above normal range
Androgel 50 mg	25	1	6	3
Androgel 100 mg	12	2	1	15
Androderm	53	0	17	0

Reviewer's comments:

1. **It is notable that average T concentrations are above the normal range in 15 (19.2%) patients in the 100 mg/daily Androgel group. This implies that in a substantial number of patients, a starting dose of 100 mg would provide unnecessarily high T concentrations. The reviewer agrees that all patients should be started on the lowest dose (50 mg) and then titrated up as needed. The Dosage and Administration section of the PI does reflect this recommendation.**

2. **It is notable that one patient (1.4%) in the 50 mg/daily Androgel group had a minimum T concentration above the normal range (>1043 ng/dL). In addition, 3 patients (4.1%) in the low-dose group had average T concentrations above the normal range (>1043 ng/dL). This implies that in some patients, even the proposed starting dose of 50 mg may produce T concentrations which are above the normal range.**

   The Dosage and Administration section of the PI recommends that serum T levels should be assessed on Day 30. The reviewer believes that the risk of prolonged high testosterone levels would be best managed by drawing blood somewhat earlier, for example, at Day 14 after starting Androgel therapy. This time will be incorporated into the label.

Table 3 presents the number of patients with Cmax outside the normal range for each treatment group.

Table 3. Number of patients with Cmax outside the normal range on Day 30.

	Cmax below normal range	Cmax above normal range
Androgel 50 mg	2	17
Androgel 100 mg	1	43
Androderm	5	3

Based on a starting dose of Androgel 50 mg, 17 patients (25.7%) had a Cmax above the normal range. In those 17 patients the average Cmax was 1490.39 ng/dL. Only 3 of these patients had a Cmax above 1600 ng/dL; these were Patient 502 (Cmax =2550.6), Patient 918 (Cmax=2336.74), and Patient 1610 (Cmax =2265.77).

Reviewer's comment: It is clear that a starting dose of 50 mg of Androgel provided appropriate testosterone replacement in most study patients. However, in some patients, the maximum and average T concentrations attained were above the upper limit of normal. The sponsor recommends that prescribers always check a serum T concentration 30 days after starting Androgel 50 mg. The reviewer believes that serum T concentration should be checked at Day 14. The reviewer believes that a 14-day exposure to maximum T concentrations slightly above the upper limit of normal should not pose a safety risk in the vast majority of patients.

At Day 90

At Day 90, the number of patients that had both Cavg and Cmin testosterone concentrations within the normal range on was 35/73 (48%) for Androgel 50 mg, 51/78 (65%) for Androgel 100 mg. and 11/76 (15%) for Androderm.

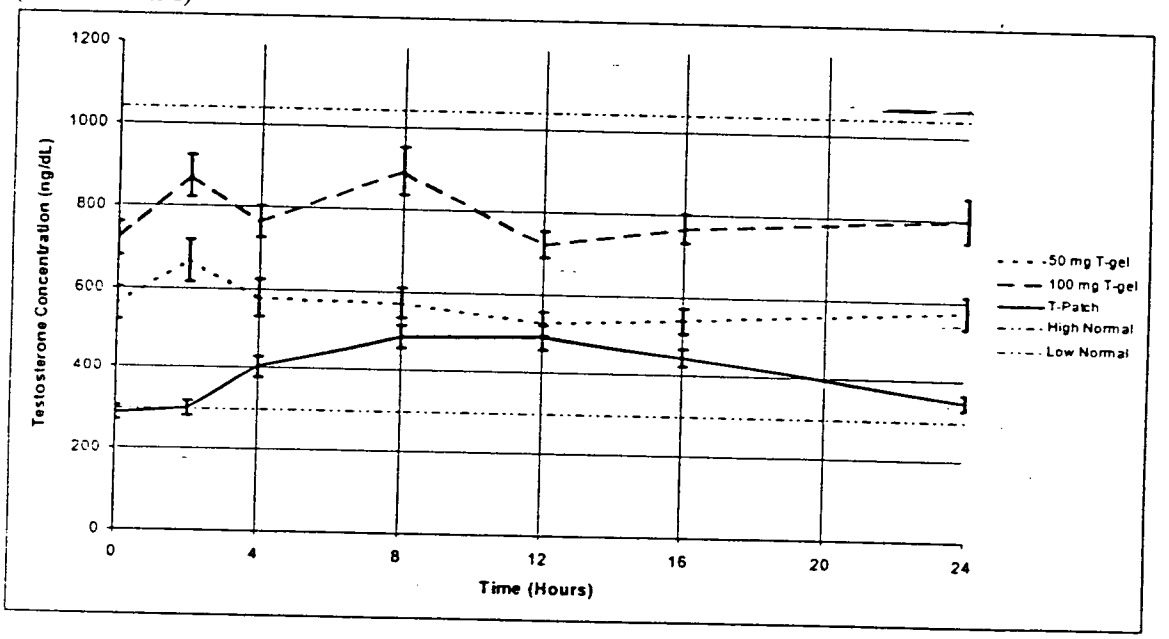
Table 4 presents the mean Cmax, Cmin, Cavg and Tmax calculated for each treatment group.

Table 4. Testosterone Pharmacokinetic Parameters, by Initial Treatment Randomization Group on Day 90 (Mean ± SD)

	Androgel 50 mg (N=65)	Androgel 100 mg (N=73)	Androderm (N=64)
Cmax (ng/dL)	846 ± 444	1204 ± 570	597 ± 242
Cmin (ng/dL)	354 ± 147	501 ± 193	213 ± 105
Cavg (ng/dL)	553 ± 247	792 ± 276	417 ± 157
Tmax (hr)	4.0	7.9	11.3

Figure 2, taken directly from the sponsor's final report (page 460), presents these mean pharmacokinetic parameters graphically.

Figure 2. Steady-State Testosterone Concentrations on Day 90 by Initial Treatment Group (Mean ± SEM)



Reviewer's comment: The concentration-time curves and pharmacokinetic parameters on Day 90 were very similar to those on Day 30 for all 3 treatment groups. The sponsor believes that this finding indicates that T pharmacokinetics were not altered by long-term therapy and the reviewer agrees.

In terms of *maintenance* of treatment effect, (patients having both Cavg and Cmin within the normal range on Day 30 and continuing on Day 90) was 26/38 (68%) for Androgel 50 mg, 33/48 (69%) for Androgel 100 mg, and 5/17 (29%) for Androderm.

Day 91 Treatment Group Switches

On Day 60, all patients had a single-sample total T concentration assessed. Based on the result of this assessment, patients could be switched to a 75 mg dose of Androgel (containing 75 mg testosterone) on Day 91. Patients on Androderm remained on Androderm.

Therefore, on Day 91, the following switches occurred:

1. Twenty patients moved from the Androgel 50 mg group to the new Androgel 75 mg group.
2. One patient moved from the Androgel 50 mg group to a "non-protocol" Androgel 25 mg group (Patient 4-06 - Day 60 single-sample total T concentration was over 1000 ng/dL).
3. Twenty patients moved from the Androgel 100 mg group to the new Androgel 75 mg group.
4. One patient moved from the Androgel 100 mg group to the Androgel 50 mg group (Patient 4-18). (a "non-protocol" switch).

A total of 195 patients entered the "Extended Treatment Phase". Of those, 51 received Androgel 50 gm, 40 received Androgel 75 mg, 52 received Androgel 100 mg, and 52 received Androderm.

At Day 180

At Day 180, testosterone pharmacokinetic parameters were described by the sponsor in terms of 5 different groups (Table 5). These groups included:

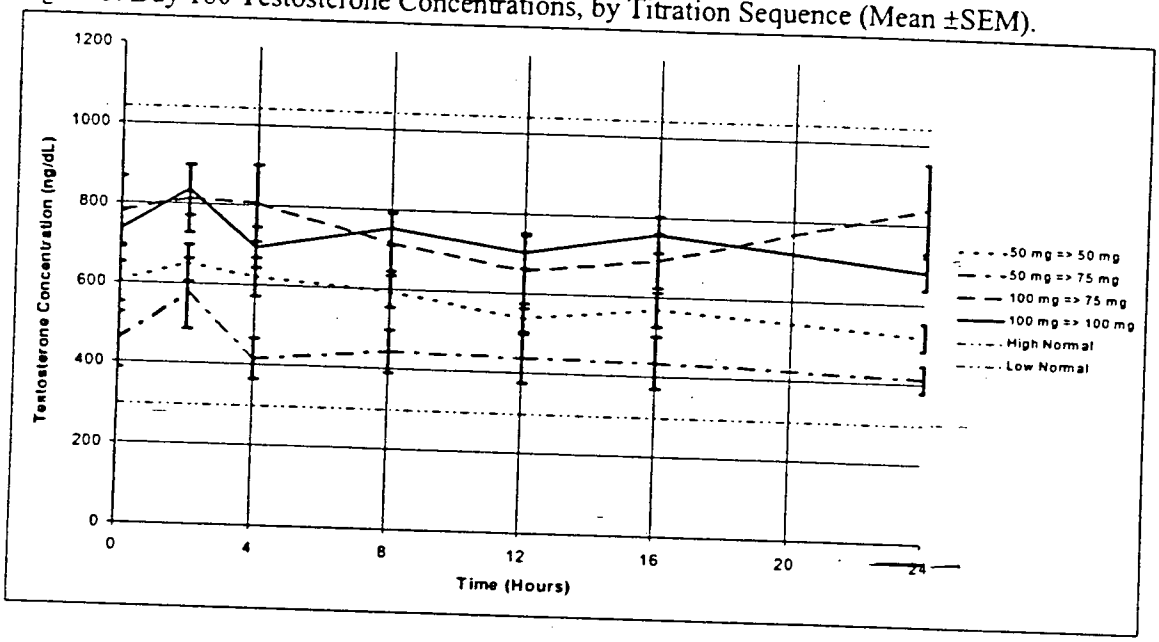
1. Patients who had been on Androgel 50 mg throughout the study (N=44).
2. Patients who had been switched from 50 mg to 75 mg Androgel on Day 91 (N=18).
3. Patients who had been switched from 100 mg to 75 mg Androgel on Day 91 (N=19).
4. Patients who had been on 100 mg Androgel throughout the study (N=48).
5. Patients who had been on Androderm throughout the study (N=41).

Table 5: Testosterone Pharmacokinetic Parameters, by Final Treatment Group, on Day 180 (Mean ± SD)

	50 mg (N=44)	50→75 mg (N=18)	100→75 mg (N=19)	100 mg	Patch
Cmax (ng/dL)	830 ± 347	680 ± 369	1110 ± 468	1083 ± 434	578 ± 245
Cmin (ng/dL)	371 ± 165	302 ± 150	505 ± 233	484 ± 156	222 ± 116
Cavg (ng/dL)	555 ± 225	450 ± 219	744 ± 320	713 ± 209	408 ± 165
Tmax (hr)	5.8	9.9	7.8	8.0	10.6

Figure 3, taken directly from the sponsor's final report (page 461), presents these mean pharmacokinetic parameters graphically.

Figure 3. Day 180 Testosterone Concentrations, by Titration Sequence (Mean ±SEM).



These results demonstrate that patients with doses reduced from 100 mg to 75 mg tended to have higher Day 180 serum T concentrations than did patients with doses increased from 50 mg to 75 mg. The sponsor believes that this difference was real and could be attributed to inherent between-group patient differences. Specifically, those patients that required up-titration had lower baseline endogenous T concentrations, and lower T concentrations at Days 1, 30 and 90, then those that required down-titration. The sponsor believes that the source of the variability is unknown, but may be related to skin permeability differences, testosterone metabolism differences, or differences in compliance.

> Reviewer's comment: **Dosage adjustment was generally successful in decreasing T levels in patients with high levels. However, increasing the dose in those with low T levels was less successful in producing a corresponding increase (noted in only about half the patients). Physicians who treat hypogonadal men are likely to draw serum testosterone levels after a change in dose and should be capable of managing such a circumstance.**

Steady-State Total Testosterone Concentrations:

Steady state was assessed by obtaining pre-dose (trough) serum samples before the application of the dose on Days 1, 2, 30, 31, 60, 90, 91, 120, 150, 180 and 181.

In the Androgel 50 mg group, steady-state concentration was reached at the end of Day 1. In the 100 mg group, steady-state was not reached at the end of Day 1. Assuming linear pK, the sponsor assumed that steady-state would be reached by the end of Day 3. Patients receiving Androderm had T levels at the end of Day 1 that were higher then their ultimate steady-state concentrations. Specifically, the mean pre-dose concentration on Day 30 was about 30% less than the pre-dose concentration on Day 2. After entertaining several alternative reasons for this finding, the sponsor believes that this decrement is probably due to decreased patient compliance in the Androderm group.

Subgroup Analyses for Total Testosterone Concentrations:
Subgroup analyses by the sponsor revealed no differences or interactions with treatment based on age, cause of hypogonadism, or Body Mass Index. There was no interaction by race when whites were compared to combined non-whites.

Other Important Sex Hormone Concentrations:
Free testosterone: Free testosterone concentrations appeared to parallel total T concentrations at all observation days and at steady-state. The free fraction was roughly 2% of the total T and this proportion was consistent across treatments.

> **Reviewer's comment: Based on the comments of DSI, the clinical pharmacology reviewer has deemed the free testosterone data as invalid for labeling purposes.**

Dihydrotestosterone: *Mean DHT concentrations* were within the normal range on all observation days for the Androgel 50 mg group and the Androderm group. In the Androgel 50 mg group, there were some patients who had mean DHT concentrations above the upper limit of normal. The number of such patients ranged from eight to nineteen, depending on the day being assessed. In the Androgel 100 mg group, *mean* DHT concentration was above the upper limit of normal by approximately 10% on any given observation day, and 26 to 40 patients had mean concentrations above the upper limit of normal, depending on the observation day assessed.

Analysis of the *mean total androgen (DHT +T) concentrations* reflected the results of mean total T and DHT data. In the Androderm group, there were many patients below the lower limit of normal on any given observation day. In the Androgel groups, there were several patients above the upper limit of normal on any given observation day. The numbers of such patients ranged from two to five in the 50 mg group, and from five to sixteen in the 100 mg group, depending on the day assessed.

Mean DHT to T concentration ratios (DHT:T) remained within the normal range for all treatment groups on all observation days. There were some patients in both the Androgel 50 mg group (thirteen to eighteen) and Androgel 100 mg group (twenty-three to thirty) in whom the mean DHT/T ratios were above the upper limit of normal on any given observation day.

> **Reviewer's comments:**
> 1. **The DHT data supports a starting dose of Androgel 50 mg in all patients prior to the use of the 100 mg dose. In addition, there appear to be some patients in whom even 50 mg Androgel will provide DHT levels, DHT+T levels, and DHT:T ratios above the upper limit of normal. Checking serum levels of testosterone on Day 14 should allow for early recognition of these cases. Even at these levels, 14 days of exposure should not be harmful.**
> 2. **It is important from a safety perspective to note that although the mean DHT concentration was above the upper limit of normal in the high-dose Androgel group, the mean DHT/T ratios remained within the normal range in that group.**

Estradiol: Mean estradiol concentrations remained within the normal range on all observation days, in all treatment groups. Higher estradiol concentrations tended to be observed in groups that achieved higher T concentrations. Examination of the individual data revealed a similar pattern to total T, DHT, DHT+T and DHT:T ratio; that is, some patients in both Androgel groups had estradiol concentrations above the upper limit of normal, with a greater number of these in the higher-dose group.

FSH: In patients with primary hypogonadism (e.g. testicular failure), mean FSH concentration was noted to decrease in all treatment groups. However, in the Initial Treatment Period (Month 1-3), mean FSH concentration decreased into the normal range in only the Androgel 100 mg group. However, in patients who were titrated from 50 mg to 75 mg Androgel, mean FSH concentration was noted to normalize by Day 150.

In patients with secondary hypogonadism (e.g. hypogonadatropic hypogonadism), mean FSH concentration decreased in all 3 groups. In the Androderm group, there were essentially no real shifts into or out of the normal range. In the Androgel 50 mg group, about half of the patients actually dropped below the lower limit of normal. In the Androgel 100 mg group, all patients ultimately wound up below the lower limit of normal

LH: In patients with primary hypogonadism, mean LH concentration was noted to decrease in all treatment groups. Mean LH concentration decreased by 50% by Day 30 in the Androgel 50 mg group, and continued to decline to Day 180. Patients who were switched from 50 mg to 75 mg showed a second decline after the switch. Of those patients maintained on Androgel 100 mg for 180 days, 65%-75% had LH concentrations below the normal range.

In patients with secondary hypogonadism (e.g. hypogonadatropic hypogonadism), mean LH concentration decreased in all 3 groups. The bulk of this change was noted by Day 30. In the Androgel groups, the mean LH concentrations was relatively consistent from Day 30 to Day 180. In the Androderm group, the mean LH concentration initially decreased by 75% at Day 30, but rose again over time to 90% of its baseline value at day 180.

Secondary endpoints:
Serum bone markers: The sponsor measured certain chemical substances in the blood which they believe suggest a measure of bone formation. An increase in such substances may be related to enhanced bone formation. These included osteocalcin, procollagen, parathyroid hormone, and skeletal alkaline phosphatase. In general, the mean concentrations of each of these substances increased compared with baseline at each measurement for each treatment group. The bulk of the improvement was noted within the first 90 days and then plateaued.

Urinary bone markers: The sponsor measured certain chemical substances in the urine which they believe suggest a measure of bone formation. A decrease in such substances in the urine may be related to enhanced bone formation. These include cross-linked N-telopeptide and calcium. In general, the mean ratio of the concentration of these substances to creatinine decreased from baseline at each measurement for each treatment group. The bulk of the change was noted within the first 3 months.

> **Reviewer comment: Currently, the Division believes that serum and urinary bone markers are exploratory indices of bone physiology. Therefore, the reviewer recommends their removal from the proposed PI.**

Bone mineral density: Bone mineral density (BMD) was measured in the hip and spine by Dual Energy X-ray Absorptiometry (DEXA) at baseline and at Day 180. When assessed by "Initial Treatment Group", no meaningful changes were noted from baseline in either the 50 mg Androgel group or the Androderm group. However, the sponsor believes that a statistically significant change was noted from baseline in the 100 mg Androgel group, in both the hip and spine measurements. When assessed by "Final Treatment Group", the sponsor believes that there were mean increases from baseline in BMD in both hip and spine in all Androgel groups, but not in the Androderm group.

Reviewer's comment: The reviewer believes that Summary Table 50 does not support the sponsor's conclusion regarding the lack of a treatment effect on BMD by Androderm. There appears to be an increase (rather than a decrease) from baseline in BMD in the Androderm group.

Muscle strength: A —— evaluation of "skeletal muscle strength" was performed using the "one-repetition maximum" technique in bench press and seated leg press. Increases from baseline in total weight pressed (leg and bench) were noted in all treatment groups at Day 90, and again at Day 180. The bulk of the improvement was seen by Day 90.

Reviewer's comment: The reviewer has some concern regarding the one-repetition maximum technique as a valid and appropriate measurement of muscle strength. In addition, there did not appear to be clinically meaningful changes from baseline in muscle strength. The reviewer recommends removing this data from the proposed PI.

Body composition: DEXA was used to assess the following endpoints: Total Body Fat Mass (TFT), Total Body Lean Mass (TLN), Percent Fat (PFT), and Total Body Mass (TBM). At Day 90, in the Initial Treatment Groups, Total Body Lean Mass and Total Body Mass increased in all groups. In addition, Total Body Fat Mass and Percent Fat decreased in the Androgel groups. In the Androderm group, the sponsor believes that Percent Fat decreased, but Total Body Fat Mass did not decrease.

When evaluated by Final Treatment Group (at Day 180), all Androgel groups showed mean decreases from baseline in fat parameters and mean increases from baseline in lean parameters and total body mass. The sponsor believes that similar changes were noted with Androderm, except for Total Body Fat.

Mood, Libido and Sexual Activity: The sponsor assessed mood, libido and sexual activity by means of a single composite questionnaire completed 7 days prior to clinic visits on Day 0, 30, 60, 90, 120, 150 and 180. There were no baseline differences in the treatment groups. In general, all parameters improved for the periods Days 0-90 and Days91-180, in all treatment groups.

Libido was assessed from linear responses to questions about sexual desire, enjoyment of sexual activity without a partner, and enjoyment of sexual activity with a partner. These responses appeared to indicate an improvement in libido at Days 90 and 180 in all groups. In addition, there was a checklist for sexual events (e.g. sexual daydreams, sexual interactions with a partner, flirting, masturbation, intercourse, etc) in which patients were asked to indicate whether they did or did not experience the event.

Reviewer's comments: Results from the libido and sexual event checklist were difficult to interpret.

Penile erection was assessed by asking patients to rate their erections mark on a scale of 10% to 100% (in increments of 10%), where 100% was a "full erection". Patients were also asked to indicate the duration of erection on a 0 (not satisfactory) to 7 (very satisfactory) scale. The results of these questions indicated modest improvements in "percentage of full erection" attained and "satisfaction with duration of erection" in all treatment groups, at Days 90 and 180.

Mood was assessed by including a "mood assessment" section in the 7-day questionnaire. Patients were asked to rate their mood on a 0 ("not at all true") to 7 ("very true") scale, to reflect how they were feeling on a given day about several mood parameters (e.g. angry, alert, irritable, full of pep, sad/blue, tired, friendly, nervous, etc.). In general, improvement was noted in various assessments of mood, in all 3 treatment groups.

> **Reviewer's comment: Although the reviewer has some concerns regarding the validation of the composite mood, libido and sexual activity questionnaire, the results appear biologically plausible in treatment of hypogonadal men with androgen replacement.**

4.5 Safety analyses:

Extent of exposure:

From Day 1 through Day 180, the extent of the exposure, as measured by mean number of days on drug, was as follows: Androgel 50 mg, 147.1 days (N=77), Androgel 100 mg, 148.6 days (N=78), Androgel 75 mg, 86.9 days (N=40), Androderm, 147.3 days (N=76).

> **Reviewer's comment: The extent of exposure in this trial was adequate to make an assessment of safety.**

Deaths

No deaths were reported during the conduct of this study.

Serious adverse events:

Serious adverse events (SAEs) were reported for three patients in the Androgel 50 mg group, two patients in the Androgel 75 mg group, no patients in the Androgel 100 mg group, and one patient in the Androderm group. These patients are discussed in detail below:

Androgel 50 mg

Patient 1-01: This 27 year old black male began Androgel 50 mg daily on 2/28/97. On 3/23/97, he experienced the onset of severe depression. On 3/24/97, he attempted suicide by Valium overdose. The sponsor believes that the patient had several recent stressful life events including the death of a friend, failure on an examination, and inability to get a desired job. Study drug was discontinued on 3/28/97. The investigator considered the event as possibly related to study drug.

The patient's past medical history was significant for Klinefelter's syndrome. The sponsor's narrative states that the patient had a history of depression, but this was not confirmed by the investigator's baseline medical history in the CRF. In addition, the patient's baseline daily diary documented that his answer to Question #3 ("Rate your mood") for the item "Sad or Blue" was 0 ("not at all true") for seven consecutive days (2/20/99-2/27/99). The linear scale used was 0 to 7, where zero was "not at all true" and 7 was "very true". The patient was included in the study despite a body weight of 130 pounds (59 kg), which was only 77.4% of ideal (<80% was an exclusion criteria). His baseline A.M. total testosterone was 197.4 ng/dL.

At the baseline visit (2/27/97), his urine toxicity screen was positive for cannabis and his blood ethanol level was elevated ("53" with units unspecified). The nursing note states, "Ethanol in blood, admitted alcohol binge night before. Positive cannabis, admitted marijuana use. Patient was interviewed and the problems of alcohol and marijuana were discussed. Patient indicated only time he used these substances since admission. He promised he will not continue excessive alcohol intake and marijuana use."

The patient did complete a daily diary (Sexual Activity/Mood Questionnaire) from 3/22/97 until 3/27/97. These dates include the day he the investigator documented severe depression (3/23/97) and an attempted suicide (3/24/97). A review of the diary follows below:

3/22/97: *Mood*: (a) Angry? 0 (b) Alert? 4 (c)Irritible? 4 (d)Full of pep/energetic? 4 (e)Sad or Blue? 0 (f)Tired? 7 (g)Friendly? 7 (h)Nervous? 0 (i) Well/good? 4.

Sexual activity: Patient's partner was unavailable. He masturbated with 100% of full erection. He attained orgasm. His level of enjoyment/pleasure was 4 (0-7, where zero is none and 7 is very high).

3/23/97: *Mood*: (a) Angry? 0 (b) Alert? 7 (c)Irritible? 0 (d)Full of pep/energetic? 4 (e) Sad or Blue? 0 (f)Tired? 4 (g)Friendly? 7 (h)Nervous? 0 (i) Well/good? 4.

Sexual activity: Patient's partner was unavailable. He masturbated with 100% of full erection. He attained orgasm. His level of enjoyment/pleasure was 7 (0-7, where zero is none and 7 is very high).

3/24/97: *Mood*: (a) Angry? 0 (b) Alert? 7 (c)Irritible? 4 (d)Full of pep/energetic? 7 (e) Sad or Blue? 0 (f) Tired? 4 (g) Friendly? 7 (h)Nervous? 0 (i) Well/good? 7.

Sexual activity: Patient's partner was unavailable. Yet, he did have intercourse. His erection was 100% of full erection. He attained orgasm. His level of enjoyment/pleasure was not rated for intercourse. In addition, he masturbated. His level of enjoyment/pleasure for masturbation was 7 (0-7, where zero is none and 7 is very high).

3/25/97: *Mood*: (a) Angry? 0 (b) Alert? 7 (c)Irritible? 0 (d)Full of pep/energetic? 4 (e) Sad or Blue? 0 (f) Tired? 4 (g) Friendly? 7 (h)Nervous? 0 (i) Well/good? 7.

Sexual activity: Patient's partner was unavailable. He masturbated with 100% of full erection. He attained orgasm. His level of enjoyment/pleasure was 7 (0-7, where zero is none and 7 is very high).

3/26/97: *Mood*: (a) Angry? 0 (b) Alert? 4 (c)Irritible? 4 (d)Full of pep/energetic? 0 (e) Sad or Blue? 7 (f) Tired? 7 (g) Friendly? 4 (h)Nervous? 0 (i) Well/good? 0.

Sexual activity: Patient's partner was unavailable. He did not masturbate masturbate. His day and night spontaneous erections were judged to be 10% of full erection and were not satisfactory in duration (0). His level of sexual desire was very low (1).

3/27/97: *Mood*: (a) Angry? 0 (b) Alert? 7 (c)Irritible? 0 (d)Full of pep/energetic? 7 (e) Sad or Blue? 0 (f) Tired? 0 (g) Friendly? 7 (h)Nervous? 0 (i) Well/good? 7.

Sexual activity: Patient's partner was unavailable. He masturbated with 100% of full erection. He attained orgasm. His level of enjoyment/pleasure was 7 (0-7, where zero is none and 7 is very high).

Reviewer comment: **The diary data and adverse experience log are in some disagreement. The investigator documented severe depression on 3/23/97 and an attempt at suicide on 3/24/97, but the diaries for those days reflect the patient's mood as "good", with a strong libido, and satisfying sexual activity, including intercourse on the day he supposedly attempted suicide. The patient's diary does, however, document an abrupt decline in the patient's mood, libido and sexual activity on 3/26/97. Perhaps the investigator simply jotted down the wrong dates of "severe depression".**

The reviewer considers the event as possibly related to study drug, but the relationship is unclear. The patient's "binge" of alcohol and use of cannabis on the night before Day 0 provides some evidence of pre-treatment substance abuse problems.

Patient 7-07: This 64 year old white male began Androgel 50 mg daily on 12/18/97. On 1/3/98, he was admitted to the hospital with a severe headache. CT and MRI revealed an old left occipital infarct and a new right occipital hemorrhagic infarct. He experienced a decrease in vision bilaterally which improved somewhat prior to discharge. On 1/9/98, he was transferred to a rehab facility. Study drug was discontinued. His past medical history included hypercholesterolemia and according to the sponsor, a cerebral infarct in 1997. The investigator considered the event as not related to study drug.

The patient's baseline total testosterone was 270 ng/dL. His baseline hematocrit was 45.0%. His baseline cholesterol was 247 mg/dL, with elevated triglycerides, LDL, and VLDL. Upon admission, his hemoglobin and hematocrit were 14.7 g/dL and 43.4%, respectively.

Reviewer's comments:
The reviewer believes that this event is unlikely to have been related to study drug.

Patient 12-10: This 51 year old white male began Androgel 50 mg on 7/11/98. On 8/11/98, he was admitted to the hospital for elective lumbar discectomy. The disc condition preceded the initiation of the trial; specifically, the patient first ruptured the disc in 1995 and had an initial discectomy in 1997. The patient underwent surgery without incident and was discharged home in 2 days. Study drug was stopped only for 2-3 days. The investigator considered the surgery not related to study medication.

Reviewer's comment: **The reviewer agrees that this event was not related to study drug.**

Androgel 75 mg

Patient 1-10: This 34 year old white male began Androgel 50 mg on 10/24/97. After completing the Initial Treatment Phase, the patient was switched to Androgel 75 mg on approximately 1/23/98. On 1/30/98, the patient experienced a seizure and was seen in the Emergency Room. He was given a single IV dose of Hydrocortisone and discharged that day. Study drug was discontinued 4 days after the seizure. The patient's past medical history included a history of previous brain tumor removal, hypopituitarism, adrenal insufficiency, abnormal thyroid function, diabetes insipidus, headaches and seizures. The investigator considered the event not related to study drug.

The patient's baseline total testosterone was 100 ng/dL, and hematocrit was 44.2%. The hematocrit was slightly lower upon study discontinuation.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Patient 12-07: This 25 year old white male began Androgel 50 mg on 3/26/98. After completing the Initial Treatment Phase, the patient was switched to Androgel 75 mg. On 8/13/98, the patient was admitted to the hospital for the diagnosis of diabetic ketoacidosis. He was discharged 5 days later in stable condition. Study drug was not discontinued. The patient had a past medical history of Type I diabetes since 1981, and hypothyroidism.

Reviewer's comment: The reviewer believes that the relationship to study drug is unlikely.

Premature discontinuations due to adverse events:
Twenty-three patients experienced adverse events associated with premature discontinuation: two patients were receiving Androgel 50 mg (Patient 1-01 and 7-07 described above), one patient was receiving Androgel 75 mg (Patient 1-10 described above), three patients were receiving Androgel 100 mg (1-24 for emotional lability and memory loss, 2-09 for hypertension, and 14-05 for increased PSA), and 17 patients were receiving Androderm. Of the 17 withdrawn from the Androderm group, 16 withdrew due to application site reactions and 1 withdrew for polycythemia). Upon their request, three additional patients were switched from the Androderm group to the Androgel 50 mg group during the Initial Treatment Phase. These patients complained of application site reactions.

Herein, the patients who withdrew from the Androgel 100 mg group are described in greater detail.

Androgel 100 mg:
Patient 1-24: This 19 year old Hispanic male began Androgel 100 mg on 6/20/98. On 7/20/98, he reported memory loss and sadness. On 7/29/98, the patient requested discontinuation from the study because he felt that the drug was interfering with his memory. The investigator considered the event to be possibly related to study drug.

Reviewer's comment: The reviewer considers the relationship to study drug as possible.

Patient 2-09: This 57 year old white male began Androgel 100 mg on 1/18/98. On 11/7/97 and 1/7/98, his blood pressure recordings were 168/82 mm Hg and 148/74 mm Hg, respectively. On 2/6/98, his blood pressure was recorded as 173/84 mm Hg and he was withdrawn from the study. The investigator considered the hypertension as possibly related to study drug.

Reviewer's comment: The reviewer considers the relationship to study drug as possible.

Patient 14-05: This 53 year old white male began Androgel 100 mg on 5/29/98. On 5/12/98, his serum prostate-specific antigen (PSA) was 0.7 ng/dL. On Day 90, the PSA had risen to 4.3 ng/dL (repeated as 3.5 ng/dL). On Day 120, the PSA was again 4.3 ng/dL. The digital rectal examination was without evidence of tumor. A prostate ultrasound and biopsy were performed on Day 123. The biopsy result was without evidence of tumor. A repeat PSA, performed on Day

150, was 5.3 ng/dL. Study drug was discontinued on Day 157. The investigator considered the rising PSA as probably related to use of Androgel.

> Reviewer comment: **The reviewer believes that the use of androgens is plausibly related to growth of latent prostate cancer. Therefore, the rise in serum PSA in this patient could signal such an event. The proposed package insert does appropriately recommend surveillance for prostate cancer in patients receiving androgens.**

Overall adverse events

Adverse events were analyzed by assessing the following data sets: data from Day 1 through Day 90, data at Day 180 in those patients who had not switched treatment assignments, and data from Days 91 through Day 180 grouped by final treatment assignment.

Day 1-90

On Day 90, 69.9% of all patients had reported at least 1 adverse event, 69.9% in the Androgel 50 mg group, 67.9% in the Androgel 100 mg group, and 77.6% in the Androderm group.

In the Androderm group, the most commonly reported AEs were "application site reaction" (59.2%), "lab test abnormal" (11.8%), pharyngitis (7.9%), headache (6.6%) and arthralgia (6.6%).

In the Androgel 50 mg group, the most commonly reported AEs were "lab test abnormal" (13.7%), "headache" (6.8%), "application site reaction" (5.5%), rash (5.5%), back pain (5.5%) and "tooth disorder" (5.5%).

In the Androgel 100 mg group, the most commonly reported AEs were "headache" (7.7%), "lab test abnormal" (6.4%), "hypertension" (5.1%), rash (5.1%), back pain (5.5%) and "rhinitis" (5.1%).

> Reviewer's comments
>
> 1. **The incidence of "urogenital disorders", including impaired urination, "testis disorder", hematuria, and gynecomastia, in both Androgel groups is conveyed in the package insert. However, Table 3 and 4 in the PI reflect those AEs thought "possibly, probably or definitely-related" to the use of Androgel.**
> 2. **The term "lab test abnormal" should be clarified in the package insert.**

Days 91-180

From Days 91-180, approximately 55-57% of each treatment group reported at least 1 AE. The overall results were similar to those at Day 90. Table 6 lists the most commonly reported adverse events:

Table 6. Incidence of Adverse Events Occurring in at least 5% of Patients in any Treatment Group from Day 91 to Day 180.

Term	Androgel 50 mg N=51	Androgel 75 mg N=40	Androgel 100 mg N=52	Androderm N=52
Number of patients with any AE	29 (56.9%)	22 (55.0%)	29 (55.8%)	29 (55.8%)
Body as a Whole	10 (19.6%)	9 (22.5%)	13 (25.0%)	9 (17.3%)
Lab test abnormal	2 (3.9%)	2 (5.0%)	1 (1.9%)	6 (11.5%)
Headache	2 (3.9%)	2 (5.0%)	3 (5.8%)	0 (0.0%)
Flu syndrome	0 (0.0%)	1 (2.5%)	4 (7.7%)	0 (0.0%)
Pain back	1 (2.0%)	3 (7.5%)	1 (1.9%)	0 (0.0%)
Injury Accidental	0 (0.0%)	2 (5.0%)	0 (0.0%)	1 (1.9%)
Skin	5 (9.8%)	3 (7.5%)	8 (15.4%)	14 (26.9%)
Application site reaction	0 (0.0%)	1 (2.5%)	1 (1.9%)	12 (23.1%)
Acne	2 (3.9%)	1 (2.5%)	0 (0.0%)	1 (1.9%)
Urogenital	6 (11.8%)	7 (7.5%)	8 (15.4%)	0 (0.0%)
Prostate Disorder	3 (5.9%)	2 (5.0%)	5 (9.6%)	0 (0.0%)
UTI	1 (2.0%)	3 (7.5%)	0 (0.0%)	0 (0.0%)
Nervous	5 (9.8%)	3 (7.5%)	4 (9.6%)	3 (5.8%)
Anxiety	3 (5.9%)	1 (2.5%)	0 (0.0%)	0 (0.0%)
Musculoskeletal	2 (3.9%)	2 (5.0%)	5 (11.5%)	3 (5.8%)
Arthralgia	1 (2.0%)	0 (0.0%)	5 (9.6%)	2 (3.8%)
Cardiovascular	2 (3.9%)	3 (7.5%)	4 (7.7%)	2 (3.8%)
Hypertension	1 (2.0%)	2 (5.0%)	3 (5.8%)	0 (0.0%)

Special Safety Issues

Skin: Sixteen patients prematurely discontinued treatment due to application site reactions. These patients were all in the Androderm group. According to the sponsor, three additional patients "would have discontinued due to skin irritation had they not been authorized to switch" to the Androgel 50 mg group.

In addition, at each visit, the skin was assessed for erythema by the investigator using a "minimal/moderate/intense" scoring system. The results through Day 90 are presented below:

Table 7: Number (percentage of randomized total) of patients with erythema as assessed by the investigator through Day 90.

	Androgel 50 mg	Androgel 50 mg	Androderm
Minimal erythema	1 (1.4%)	0 (0.0%)	18 (23.7%)
Moderate erythema	0 (0.0%)	0 (0.0%)	13 (17.1%)
Intense erythema	0 (0.0%)	0 (0.0%)	2 (2.6%)
Any erythema	1 (1.4%)	0 (0.0%)	33 (43.4%)

Reviewer's comments:

1. **The reviewer believes that the lack of adequate blinding precludes a superiority claim for Androgel in terms of application site inflammation.**
2. **The reviewer believes that these Androgel results may be described in the labeling.**

Urogenital: Seventeen adverse events related to the genitourinary system were reported by 13 patients in the Androgel 50 mg group. Twenty-six adverse reactions were reported by 18 patients

in the Androgel 100 mg group. In contrast, no genitourinary adverse reactions were reported in the Androderm group.

Table 8. Number of adverse reactions reports specifically related to the genitourinary tract.

	Androgel 50 mg	Androgel 100 mg	Androderm
UTI	3	4	0
Impaired Urination	1	3	0
Gynecomastia	1	3	0
Breast Pain	1	1	0
Enlarged Prostate by DRE	3	4	0
Hematuria	3	1	0
BPH	1	0	0
Varicocele	1	1	0
Testicular Discomfort	1	1	0
Kidney calculus	1	1	0
Penile pain	1	0	0
Prostatitis	0	1	0
Dysuria	0	1	0
Elevated PSA	0	2	0
Epididymitis	0	1	0
Hematospermia	0	1	0
Urinary Frequency	0	1	0

Of the four patients who reported gynecomastia as an adverse reaction, one patient [1-08] underwent a bilateral mastectomy two months after starting treatment with Androgel.

Reviewer's comment: Additional information has been requested for Patient 1-08.

The genitourinary system was evaluated in the trial by means of routine digital rectal exam (DRE), serum prostate specific antigen (PSA), International Prostate Symptom Score (I-PSS) and uroflowmetry.

Reviewer's comment: The reviewer believes that the proposed labeling reflects the urogenital adverse reactions for Androgel.

DRE: The last available physical examination of the prostate demonstrated enlargement from baseline in 4 patients in the Androgel 50 mg group, 5 patients in the Androgel 100 mg group, and 1 patient in the Androderm group. PSA was in the normal range for all of these patients throughout the study. Only one of these patients had a maximum urine flow rate less than 10 mL/sec during the trial. One patient reported an episode of epididymitis.

PSA: Final PSA values increased above the normal range in one patient in the Androgel 50 mg group, one patient in the Androgel 75 mg group, 3 patients in the Androgel 100 mg group, and no patient in the Androderm group. The two highest PSA values were 5.3 ng/mL (up from a baseline of 0.7 ng/mL), and 6.0 ng/mL (from a baseline of 2.5 ng/mL).

Urine flow rate: Clinically meaningful urine flow rate reductions appeared to occur in a few patients in all treatment groups.

I-PSS scores: Mean IPSS did not change significantly from baseline to endpoint in any treatment group. There were only 3 patients in whom I-PSS doubled and was ultimately greater than 15 points at endpoint (2 patients in the Androgel 50 mg group, and 1 in the 100 mg group).

Hematologic: Androgens are known to increase the production of red blood cells by direct stimulation of precursor cells and by enhancing the production of endogenous erythropoietin. The sponsor defined a clinically concerning hemoglobin as >18 g/dL at the last available visit. Four patients met this criteria, 3 were Androgel patients and 1 was an Androderm patient. Of the Androgel patients, 1 was taking 50 mg/daily (final hemoglobin = 18.1 g/dL and hematocrit = 53.9%), 1 was reduced from 100 mg to 75 mg (final hemoglobin = 18.9 g/dL and hematocrit = 49.5%), and 1 [Patient 14-05] was taking 100 mg/daily (final hemoglobin = 19.5 g/dL and hematocrit = 56.5%).

Reviewer's comment: **In this patient, an abrupt rise in serum T concentration may have contributed to polycythemia. A strengthening of the class PRECAUTION for surveillance of hemoglobin and hematocrit may be necessary.**

Lipids: It is generally believed that androgen replacement therapy is associated with decreases in high-density lipoprotein plasma concentrations. There is also some concern that androgens may increase plasma cholesterol and serum triglycerides. The sponsor defined as clinically concerning a final HDL value <30 mg/dL, where the baseline was ≥30 mg/dL. Fourteen (14) patients were found to meet these criteria. In the majority of these cases the final HDL value was 27-29 mg/dl. In one case (Patient 401), the HDL dropped from 32 to 21 mg/dL. In terms of increased cholesterol, no cases were identified which the sponsor deemed "concerning".

Hypertension: Fourteen patients demonstrated "new-onset" or "worsened" hypertension. Only one of these [Patient 2-09, a 57 year old white male] required discontinuation because of hypertension. His screening and baseline BPs were 168/82 mm Hg and 148/74 mm Hg, respectively. Three weeks after starting Androgel 100 mg/daily his blood pressure was recorded as 173/84 mm Hg and he was withdrawn from the study. The investigator considered the hypertension as possibly related to study drug.

4.6 Reviewer's assessment of safety and efficacy in Clinical Trial UMD-96-017:

Sponsor's assessment:

The sponsor believes that administration of Androgel to hypogonadal men at doses of 50 mg/daily and 100 mg/daily "increased serum testosterone levels to within eugonadal range in the majority of men and maintained those for up to 180 days". The sponsor believes that Androgel was determined to be "not inferior" to Androderm based on the analysis of the primary endpoint (Cavg and Cmin within normal limits on Day 30) and actually was superior. The sponsor believes that both Androgel groups demonstrated successful maintenance of effect from Day 30

to Day 90, which was superior to the maintenance demonstrated by Androderm. The sponsor believes that serum T levels for the 75 mg group were intermediate to those of the 100 mg and 50 mg groups.

The sponsor believes that Androgel demonstrated significant treatment effects on most of the clinical endpoints. This includes changes in serum and urine bone markers of bone formation, arm and leg skeletal muscle strength, hip and spine bone mineral density, indices of libido, erection and mood, and appropriate physiologic changes in body composition.

In terms of safety, the sponsor believes that daily application of 50 mg, 75 mg or 100 mg of Androgel was well-tolerated in hypogonadal males for up to 180 days of use. The sponsor believes that Androgel was superior to Androderm in terms of its skin irritation profile and rate of discontinuation due to skin irritation. The sponsor believes that few serious adverse events were reported and only one (depression) was considered possibly related to drug. Finally, the sponsor believes that many other adverse events including increases in hemoglobin, decreases in serum lipids, increases in incidence of prostatic hypertrophy and adverse events related to the urogenital system were "typical of those associated with chronic testosterone supplementation."

Reviewer's assessment:
The reviewer believes that Androgel 50 mg/daily and 100 mg/daily does increase the serum T levels to eugonadal range in the majority of hypogonadal males. However, the reviewer does not agree that Androgel was shown to be superior to Androderm in terms of providing serum T levels in the normal range. No evidence was submitted to demonstrate that serum T levels that are somewhat higher within the normal range provide clinically superior results. Therefore, the reviewer believes that no comparative claims related to efficacy (direct or implied) have been supported by the results of this trial.

The reviewer agrees with the sponsor's dosing recommendation; that is, all patients should begin on a daily dose of 50 mg and titrate up based on a single-sample serum T concentration. However, the reviewer believes that this blood should be drawn on Day 14 rather than Day 30 in order to minimize the potential for risk due to prolonged high serum T levels. The reviewer believes that this surveillance is clearly important for proper management of these patients.

In terms of secondary endpoints, the reviewer agrees that overall these clinical parameters appeared to support the efficacy of Androgel. However, the reviewer believes that some of these clinical parameters, including muscle strength and bone formation markers, were measured using tests or indices which may not be valid. Also, some of these parameters, including mood, energy level, libido and erection, would require a placebo control to adequately discern the actual treatment effect.

In terms of safety, the reviewer believes that overall, Androgel, at daily doses of 50 mg, 75 mg and 100 mg daily was safe and well-tolerated. In regard to skin tolerability, the reviewer agrees that Androgel demonstrated a relatively low incidence of application site reaction and that there were no discontinuations in the Androgel groups secondary to skin-related adverse reactions. However, the reviewer does not believe that the design and conduct of this trial was appropriate to compare Androgel to Androderm in terms of skin reactivity. The reviewer is concerned that the open-label nature of randomization and the open-label assessment of application site reaction poses too great a potential for bias to support comparative safety claims.

The reviewer also believes that Androgel did demonstrate adverse reactions secondary to undesirable pharmacologic effects, including polycythemia in a few patients, decreased serum

HDL in several patients and urogenital events in some patients. These urogenital effects included disorders of urination, increased PSA levels, changes in the size of the prostate gland and gynecomastia. The reviewer agrees with the need to monitor for these effects during Androgel therapy, using hematology and chemistry laboratories, serum PSA, physical examination and medical history, as described in the proposed labeling.

5. Clinical trial UMD-96-012:

5.1 Design

This was an open-label, multiple-dose, crossover study conducted at a single United States center in 10 patients. It compared two different usage regiments of Androgel. The objective of the study was to examine in hypogonadal men the pharmacokinetic characteristics and safety of 10 gm Androgel (containing 100 mg testosterone) applied as four 2.5 gm applications to the same anatomical site (Regiment A) or to four separate anatomical sites (Regiment B).

Androgel was administered once daily for 7 days during each of the 2 treatment periods. These treatment periods were separated by a 7-day washout period. Full pharmacokinetic profiles for serum testosterone (T) were assessed on the first and last day of each treatment period. Testosterone was applied at 8 a.m. daily following a shower.

Eligible patients were males between the ages of 18 and 59, with a morning serum testosterone concentration ≤250 ng/dL. Other than hypogonadism, the patients must have been in good health. Patients with an abnormal prostate exam, elevated serum PSA level, or reduced urine flow rate were excluded. Patients with a hematocrit greater than 50% were excluded. Patients with skin conditions known to affect the transdermal absorption of T (e.g psoriasis) were excluded. Patients with a body weight <80% or >130% of ideal were excluded.

In terms of efficacy endpoints, the following pharmacokinetic variables were derived for each patient: AUC, Cmax, Tmax, Cavg, and Cmin. Assays of serum samples for testosterone, DHT and estradiol were performed at [redacted] Testosterone assays were performed using a validated [redacted] using ^{125}I and a specific-antiserum against testosterone. Safety was assessed by physical examination, assessment of skin irritation (using a 0-5 erythema scale), clinical laboratories and adverse events monitoring.

5.2 Withdrawals, Protocol Deviations and Compliance

Withdrawals: A total of 10 patients were enrolled; nine completed the study. Patient number 5 received four consecutive daily doses of Androgel (to 4 application sites) but did not return for Day 5, therefore, he was withdrawn from the study. He did not participate in the second treatment period (Androgel to a single anatomical site).

Deviations: Patient number 1 had a baseline T concentration of 300 ng/dL (>250 ng/dL) but since he had a history of Klinefelter's disease he was included anyway. Patient number 9 applied Androgel earlier than instructed on one occasion. Patient number 8 incorrectly applied gel on the very first day of the single-site regiment. That application was repeated 2 weeks following Day 29 of this study and those results were used as his single-site Day 1 results.

The protocol called for the measurement of serum lipoproteins but that was not done.

Compliance: Based on expected usage and corresponding bottle weight, median compliance was estimated as 99.1% with a range of [redacted]

5.3 Study Population

All enrolled patients were male, and the majority were Caucasian (N=6). Two patients were African-American, one was Hispanic and one was Asian. The mean age was approximately 43 years, with a range from 26 to 59 years. Nine out of ten patients had received previous IM injections of testosterone enanthate. The most commonly specified etiology of hypogonadism was Klinefelter's Syndrome (40%).

5.4 Efficacy analysis:

Total Testosterone Serum Concentrations:

Baseline serum testosterone concentrations averaged 167 ± 128 ng/dL for the one-site application regimen group and 179 ± 124 ng/dL for the four-site application regimen group.

Table 10 presents the mean Cmax, Cavg and Tmax calculated for each group on Day 1 of the respective treatment period.

Table 10. Testosterone Pharmacokinetic Parameters, by Group, on Day 1 (Mean ± SD)

	Androgel 100 mg One-site	Androgel 100 mg Four-sites
Cmax (ng/dL)	1039 ± 374	1078 ± 592
Cavg (ng/dL)	597 ± 157	766 ± 458
Tmax (hr)	16.7	15.1

Reviewer's comments:

1. **It is clear that both regimens provide sufficient testosterone systemically to produce serum T concentrations at the high end of the normal range following a single application.**
2. **There is some evidence that one patient (#3) had markedly high levels on Day 1 (see figure 1.3 on page 8-2916).**

Table 11 presents the mean Cmax, Cavg and Tmax calculated for each group on Day 7 of the respective treatment period.

Table 11. Testosterone Pharmacokinetic Parameters, by Group, on Day 7 (Mean ± SD)

	Androgel 100 mg One-site	Androgel 100 mg Four-sites
Cmax (ng/dL)	1334 ± 487	1553 ± 334
Cavg (ng/dL)	846 ± 213	1041 ± 259
Tmax (hr)	7.9	6.7

Reviewer's comments:

1. **It is clear that four-site application produces serum T concentrations that are modestly greater than single-site application. These differences do not reach statistical significance; however, the sample size is too small for adequate statistical testing.**
2. **It is clear that there is a rise in serum T levels from Day 1 to Day 7.**

Pharmacokinetic steady-state was reached by the end of the first day of dosing for both regiments. Pre-dose concentrations appeared to stabilize by Day 3.

The sponsor believes that there was evidence of "diurnal variation", in that the peak concentration at steady-state was about three times the minimum concentration.

> Reviewer's comment: **It remains unclear whether the pharmacokinetic profile actually simulates a normal diurnal variation.**

The sponsor estimates that approximately 9 to 14 mg of testosterone entered the systemic circulation of these study patients daily. The sponsor believes that normal secretion of endogenous testosterone in eugonadal males is approximately 6 to 7 mg/day.

> Reviewer's comments:
> 1. **It is somewhat unclear how the sponsor derived the theoretic amount absorbed.**
> 2. **If the sponsor's estimate of absorbed testosterone from a 100 mg/daily application (9-14 mg) is true, the argument that most patients should demonstrate normal T levels and derive adequate clinical benefit from a 50 mg/daily dose would be supported.**

Following 24 hours off-drug, mean concentrations of T were about 40-50% lower on Day 8. Following an additional 2-3 days of washout time, an additional drop of approximately 50% was noted. T concentrations on Day 11 were all below 300 ng/dL. The sponsor remarked that this washout as "quite slow".

5.5 Safety analysis:

Extent of exposure: All 10 patients received Androgel for 7 days to four application sites. Nine of ten received Androgel for 7 days to one site.

Adverse events:

No deaths were reported during this study.

No serious adverse events were reported during this study.

No adverse events leading to early discontinuation were reported in this study.

Only 2 patients reported adverse events during the one-site period. These were: Patient #10 who reported depression and asthenia and Patient #9 who reported increased libido and hyperkinesia. Four patients reported 9 adverse events during the four-site period. One patient each reported asthenia, inflammation at the application site, agitation, headache, rhinitis, neck pain, dizziness, bradycardia, and an unspecified "eye disorder".

> Reviewer comment: **The product appeared to be well-tolerated during this study.**

Clinical laboratories and physical examination: There were no significant changes in clinical laboratories or physical examination in any patient, in either treatment period.

> Reviewer's comment: **Of particular interest, there were no significant increases in hemoglobin or hematocrit in any patient despite serum T concentrations in the high-normal range.**

5.6 Reviewer's assessment of safety and efficacy:

The sponsor believes that this gel formulation provided an effective once-daily dosage form capable of delivering sufficient T to hypogonadal men to raise serum T concentrations into the

normal range. However, the sponsor acknowledged that the 100 mg dose delivered approximately 2X the systemic T necessary to provide serum T concentrations near the midpoint of the target range. The sponsor believes that the surface area over which the gel was applied had only a modest impact on absorption of T into the systemic circulation.

The sponsor believes that the product was well-tolerated and that skin irritation did not occur.

The reviewer is in agreement with the sponsor's general conclusions regarding this study.

6. Clinical trial UMD-98-044:

6.1 Design

This was a phase 2, randomized, double-blinded, placebo-controlled, parallel-group study conducted at a single French center in 18 patients. It compared three different topical androgen treatments and placebo. These treatments were: 5 grams of TESTOGEL 2.5% (containing 125 mg of testosterone), 5 gram of ANDRACTIM 2.5% (containing 35 mg of dihydrotestosterone) and placebo gel. There were actually 2 different placebo groups, one was administered Testogel without active testosterone (T) and one was administered Andractim without active dihydrotestosterone (DHT).

The objective of the study was "to test the efficacy of two androgen replacement treatments on improvement of sugar metabolism in subjects having a low plasma testosterone." In addition, the study sought to "test the efficacy of the same treatments on vascular risk factors (including serum lipids and coagulation factors)" and "to check the tolerance of these treatments at the level of the prostate and liver."

The trial took place from March 1994 to September 1995.

Each treatment was initially administered as a single 5 gm application daily. After 14 days of treatment, a single-sample serum testosterone was drawn. Based on this result, the dose of each treatment was adjusted. Normal range serum T concentration was defined as 4.0 ng/mL to 10 ng/mL. If the serum testosterone was <2 ng/mL, then the dose of TESTOGEL was increased to 250 mg/daily. If the serum testosterone was between 2 ng/mL and 4 ng/mL, the dose of TESTOGEL was increased to 187.5 mg/daily. If the serum testosterone was >10 ng/mL, then the dose of TESTOGEL was decreased to 62.5 mg/daily.

Andractim was dose-adjusted in a similar fashion. In the case of placebo, dose-adjustment was authorized by a third-party monitor.

Reviewer comments:

1. **Since TESTOGEL was clearly a different formulation than the formulation of Androgel administered in phase 3 trials, the reviewer intends to focus primarily on the safety results and to only briefly describe the efficacy results.**
2. **This review will focus primarily on the pharmacokinetics, clinical outcomes and safety of the testosterone gel product, not ANDRACTIM or placebo.**

Following dose-adjustment, patients remained on their new dose for the remainder of the 3-month treatment period.

Eligible patients were males between the ages of 18 and 70, with a morning serum testosterone concentration ≤3.4 ng/mL in 1985-87 and <4.0 ng/mL in 1992-1993 OR <4.0 ng/mL in 1992-

1993 and <4.0 ng/mL in the 4 months preceding screening. Other than hypogonadism, the patients must have been in good health. Patients with prostate cancer (previous or suspected) or other prostate pathology were excluded. Patients with a hematocrit greater than 50% were excluded. Diabetic patients treated with medications were excluded.

In terms of efficacy endpoints, the primary endpoint was fasting blood glucose and fasting serum insulin concentration. Secondary endpoints included: serum T concentration, serum DHT, E2, LH and FSH concentrations, waist size, blood pressure, fasting serum insulin concentration 2 hours after an oral glucose load of 75 grams, serum lipids, serum coagulation factors, serum leptin, serum PSA, digital rectal examination of the prostate, hematology results, and adverse event reports.

6.2 Withdrawals, Protocol Deviations and Compliance

Withdrawals: A total of 18 patients were actually enrolled, six were randomized to each treatment arm. One patient in the Andractim group was withdrawn from therapy after missing 12 consecutive days of therapy.

Deviations: One patient in the Andractim arm missed 12 consecutive days of therapy (described above). Two other patients in the Andractim arm missed only 1 day of therapy. One patient in the Testogel arm missed a single day of therapy and one missed 2 consecutive days. One patient in the placebo arm missed a single day of therapy and one missed 2 consecutive days.

One subject in the Testogel group applied a non-protocol corticosteroid cream once during the fourth week of the trial.

Compliance: Compliance was assessed by measuring the amount of gel actually used compared to the theoretic amount that should have been used. In general, the amount actually used appeared somewhat greater than the amount theoretically supposed to have been used.

6.3 Study Population

All enrolled patients were male. There is no mention of ethnic group in the final study report. The mean age was 53.1 ± 3.9. The mean weight was 84.1 kg ± 3.2. The mean baseline testosterone was 2.69 ng/mL ± 0.25. The cause of hypogonadism was not specified in the final study report and neither were previous androgen treatments. There appeared to be no significant differences between groups at baseline in terms of age, weight, baseline serum T concentration, baseline fasting blood glucose, baseline serum PSA and baseline serum lipid profiles.

In terms of dose-adjustment, in the Testogel group, only 1 patient required dose-adjustment at 2 weeks. This patient was switched from 125 mg testosterone to 62.5 mg testosterone based upon a single sample serum T concentration >10 ng/mL.

6.4 Efficacy analysis:

Fasting blood glucose:

Table 12 presents the mean fasting blood glucose in the three groups at baseline and at study end. The change-from-baseline in all groups is minimal. There were no significant differences across groups.

Table 12. Mean fasting blood glucose in mmol/L (mean)

	Testogel	Andractim	Placebo
At baseline	5.6	5.4	5.5
At endpoint	5.85	5.3	5.7

Fasting serum insulin concentrations:
Table 13 presents the mean fasting serum insulin concentrations in the three groups at baseline and at study end.

The sponsor believes that a statistically significant change from baseline was noted only with Andractim and that this change-from-baseline was significant when compared with placebo.

Table 13. Mean fasting serum insulin concentrations in micromoles/L (mean)

	Testogel	Andractim	Placebo
At baseline	14	18	13
At endpoint	13.2	11.8	15.7

Mean serum T concentrations:
Table 14 presents the mean serum T concentrations concentrations in the three groups at baseline and at study end.

Table 14. Mean serum T concentrations in ng/mL (mean)

	Testogel	Andractim	Placebo
At baseline	2.38	2.94	2.74
At endpoint	12.58	3.61	3.25

Reviewer comment: It is clear that this formulation of testosterone gel provided sufficient systemic testosterone to effectively raise serum T concentrations. The mean T concentration in the six Testogel patients was actually above the upper limit of normal (10 ng/mL) at study endpoint, implying that excessive T may had been delivered systemically.

6.5 Safety analysis:
Extent of exposure: All 10 patients received Testogel for 7 days to four application sites. Nine of ten received Testogel for 7 days to one site.

Adverse events:
No deaths were reported during this study.

One serious adverse event was reported during this study. One patient in the Testogel group developed a new prostate nodule on DRE as assessed at the concluding study examination. A prostate biopsy was performed as a hospital inpatient. The pathology was benign. His PSA was normal at baseline and did not change during the course of the trial.

No adverse events leading to early discontinuation were reported in this study.

In the Testogel group, 10 adverse events were reported by 6 patients. These adverse events included the following: leg edema, acne, skin erythema on the chest, skin allergy (possibly secondary to plants), pharyngitis, prostate nodule, and headache x 4. Of these events, all episodes

of headache, pharyngitis and leg edema were considered mild in severity, skin allergy and acne were moderate in severity, and the prostate nodule and erythema of the chest wall were severe.

Reviewer's comment: Inadequate information was presented for the reviewer to determine the exact cause and nature of the chest wall erythema.

Clinical laboratories and physical examination:
In the Testogel group, there were no significant changes from baseline in serum PSA in any patient. In the Testogel group, there were no significant changes in liver function tests. In the Testogel group, there was a minimal reduction from baseline in high-density lipoproteins, but this was not statistically significant.

In terms of hemoglobin and hematocrit, there was an increase in both parameters in the Testogel group. Mean hemoglobin at baseline was 14.6 g/dL ± 0.3. This value increased by a mean of 3.7 g/dL ± 3.2. Mean hematocrit at baseline was 44.1% ± 0.8. This value increased by a mean of 6.4% ± 0.9. These results are shown for each patient in the group in Table 15.

Table 15. Mean hematocrit and hemoglobin values for each patient in the Testogel group.

	Hgb (g/dL) at baseline	Hct (%) At baseline	Hgb (g/dL) at endpoint	Hct (%) at endpoint
Patient #2	14.8	45	17.9	53.8
Patient #6	14.6	45	17.1	53.9
Patient #9	13.6	41.9	15.8	49.3
Patient #11	14.2	42.6	15.3	47.6
Patient #13	15.8	46.8	16.9	50.6
Patient #16	14.4	43.1	15.6	47.5

Reviewer's comment: There is a clear effect of Testogel (containing 125 mg testosterone) on increasing red blood cell production, in a three-month period of use. Even at lower testosterone doses, it would appear prudent to periodically check hemoglobin and hematocrit and to avoid use in patients with baseline elevated hemoglobin or hematocrit.

6.6 Reviewer's assessment of safety and efficacy:
The sponsor believes that this study revealed a favorable response of Andractim on fasting insulin concentrations. The sponsor proposes that this might signal an improvement in diabetic control with the use of androgen therapy, especially treatment with DHT gel. The sponsor believes that the both Testogel and Andractim were well-tolerated in this 3-month study.

The reviewer agrees that Testogel appeared to be well-tolerated in this study. However, there were suggestions of some undesirable androgenic effects such as polycythemia, decrease in HDL-cholesterol, a prostate nodule, acne and lower extremity edema. Although this data is derived from a clinical study in which a different dose and different formulation of Androgel was administered, the reviewer believe that these results may be used to help understand the safety of Androgel better.

In terms of efficacy, serum concentrations of T were moderately above the upper limit of the normal range in patients exposed to three months of Testogel. Since this formulation contained 125 mg of testosterone, these levels appear consistent with an oversupply of systemic testosterone.

The reviewer does not believe that any claims related to diabetic control have been supported by this study.

7. Safety study UMD-98-037:

7.1 Design:

This was an open-label, parallel-group, randomized, safety study conducted at a single United States center in 48 couples. Each male subject applied 100 mg of Androgel to the abdomen, shoulders and upper arms daily for seven consecutive days.

Couples engaged in 15 minutes of supervised, vigorous, direct physical contact on Days 1 and Day 7. In fact, the protocol specified that couples would be bound together using a hoop-like waistband. In addition, the female partner was required to wear a halter top and to perform vigorous abdomen-to-abdomen swaying and arm-to-arm touching. Couples were instructed to do the same maneuvers at home on Days 2-6.

The 48 couples were randomly assigned to 1 of 4 groups. These groups were:

1. Physical contact at 2 hours after application of the dose.
2. Physical contact at 2 hours after application of the dose with the male clothed by a long-sleeve T-shirt.
3. Physical contact at 6 hours after application of the dose.
4. Physical contact at 12 hours after application of the dose.

> Reviewer's comment: **It should be noted that the sponsor utilized a "long-sleeved" T-shirt to cover the application sites, as opposed to a standard short-sleeve or "tank-top" style T-shirt.**

All female subjects had baseline blood samples drawn for total testosterone (T) concentration, free T concentration, and 3 α-androstanediol-glucuronide level. These were drawn at 0, 1, 2, 4, 8 and 24 hours.

On Days 1 and 7, female partners had repeat blood draws for the same substances prior to physical contact and at 1, 2, 4, 8 and 24 hours after physical contact.

Eligible subjects were healthy men, aged 18 to 68 and healthy females, aged 18 to 68. Both males and females had to have heterosexual partners qualified for inclusion in the study. Females were required to be between 80% and 140% of ideal body weight by the Metropolitan Life Insurance tables. In terms of exclusion criteria, men were excluded for the following reasons: abnormal prostate by examination or elevated serum PSA, hematocrit >50%, significant psychiatric illness, generalized skin disorder that might affect absorption of test article, and the presence of diabetes mellitus. Women were excluded if they were pregnant or lactating, if they were of child-bearing potential and refused to use an acceptable method of birth control, if they were hirsute, and if they had diabetes mellitus.

There were no efficacy variables in this study. The safety variables included an assessment of adverse events and a serum hormone concentrations (in females). Clinical laboratories were obtained at screening and after 7 days of treatment. Females had a serum pregnancy test at baseline and at Day 7.

7.2 Withdrawals, Protocol Deviations and Compliance

Withdrawals: A total of 45 couples were enrolled; 38 couples completed the entire study. Three women withdrew due to "intercurrent events". These included Patient # 112, who withdrew on Day 0 due to nausea, Patient #121 who withdrew on Day 3 due to the flu, and Patient #125, who withdrew on Day #6 due to a headache. The sponsor believes that none of these events were drug-related.

One woman withdrew her consent on Day 0. One couple withdrew consent on Day 1. One man was unavailable for the Day 7 visit. One man (patient #216) had a serum PSA >4 ng/mL at baseline. When this was realized by the investigator, the subject was withdrawn on Day 3.

Deviations: Patient #216 (described above) was withdrawn on Day 3 after it was realized that he had an abnormal baseline PSA. One couple applied gel and had contact on Day 7 prior to coming to the clinical research center. In that couple, gel was reapplied at the per-protocol time in the center. The remainder of the protocol deviations were minimal.

Compliance: Compliance in men was assessed by comparing the amount of actually used to the amount of gel which should have been theoretically used. In this respect, compliance was >90% in each group.

In women, the main compliance issue was contact time. Contact time was assured in the supervised setting of the office on Days 1 and 7. At home, women maintained contact-time diaries. These diaries revealed contact time slightly in excess of the per-protocol daily amount (15 minutes).

7.3 Study Population

Of the male subjects, mean age for each group was approximately 41 years, with a range of approximately 19 to 67 years. Almost all men were Caucasian, except for three African-Americans.

Of the female subjects, mean age for each group was approximately 39 years, with a range of approximately 19 to 66 years. Again, almost all women were Caucasian except for one African-American and one Native American. Mean weight was approximately 70 kg. There was some evidence that the 2-HOUR group had a slightly greater mean weight than all other groups (73 kg).

> **Reviewer's comment: The mean weight of 70 kg (154 pounds) in women across all three groups appears relatively high. This mild obesity may actually have led to a slightly lower serum T concentration in women in all groups following contact with Androgel.**

7.4 Efficacy analysis:

There were no efficacy variables assessed.

7.5 Safety analysis:

Extent of exposure: Of the 45 couples, 38 men applied 100 mg of gel daily for seven days and 38 women had the per-protocol daily physical contact with their partner (15 minutes/daily).

Serum hormone concentrations in women:

The reference ranges for normal women in this study were as follows: for total serum T concentration, 10-55 ng/dL, for free T concentration 0.11-0.63 pg/mL, for 3 α-androstanediol-glucuronide, 35-200 ng/dL.

Reviewer's comment: It is unclear how these normal ranges for women were derived.

Table 16 presents the baseline serum total T concentrations in women at 0 hours on Day 0.

Table 16. Baseline maximum mean serum total T concentrations in women (Cmax)

Group	Total T concentration in ng/dL (Mean ± SD)	N
2-HOUR	25.67 ± 8.72	12
6-HOUR	19.36 ± 8.42	11
12-HOUR	16.47 ± 9.04	9
2-HOUR (T-shirt)	31.20 ± 11.69	10

Table 17 presents the serum total T concentrations on Day 1 and Day 7 in women in the 2-HOUR group

Table 17. Mean serum total T concentrations in women in the 2-HOUR group following physical contact.

Hours after contact	Mean total T concentration [ng/dL] on Day 1	Mean total T concentration [ng/dL] on Day 7
Pre-contact	24.90	106.91
1 hr	43.75	99.36
2 hr	59.17	125.60
4 hr	90.18	139.90
8 hr	83.80	144.45
24 hr	78.36	79.60

Table 18 presents the serum total T concentrations on Day 1 and Day 7 in women in the 6-HOUR group

Table 18. Mean serum total T concentrations in women in the 6-HOUR group following physical contact.

Hours after contact	Mean total T concentration [ng/dL] on Day 1	Mean total T concentration [ng/dL] on Day 7
Pre-contact	18.73	36.00
1 hr	29.82	39.78
2 hr	33.36	45.63
4 hr	47.36	67.25
8 hr	51.09	59.63
24 hr	43.80	60.63

Table 19 presents the serum total T concentrations on Day 1 and Day 7 in women in the 12-HOUR group

Table 19. Mean serum total T concentrations in women in the 12-HOUR group following physical contact.

Hours after contact	Mean total T concentration [ng/dL] on Day 1	Mean total T concentration [ng/dL] on Day 7
Pre-contact	23.46	70.40
1 hr	31.20	73.80
2 hr	27.90	66.60
4 hr	38.70	106.00
8 hr	42.60	80.90
24 hr	64.20	66.10

Table 20 presents the serum total T concentrations on Day 1 and Day 7 in women in the 2-HOUR (T-shirt) group

Table 20. Mean serum total T concentrations in women in the 2-HOUR (T-shirt) group following physical contact.

Hours after contact	Mean total T concentration [ng/dL] on Day 1	Mean total T concentration [ng/dL] on Day 7
Pre-contact	24.22	25.75
1 hr	26.00	31.25
2 hr	23.22	29.14
4 hr	23.67	28.13
8 hr	25.33	30.88
24 hr	30.89	32.25

Reviewer's comment: **All groups, except the T-shirt group, demonstrated clear transfer of testosterone from the male partner to the systemic circulation of the female. The package insert contains a clear PRECAUTION describing this potential for transfer, as well as means to prevent it and to manage it. The CONTRAINDICATIONS section refers to the need for pregnant women to avoid contact with Androgel. The CLINICAL STUDIES section describes this study in detail.**

Adverse events:
No deaths were reported during this study.

No serious adverse events were reported during this study.

Three adverse events leading to early discontinuation was reported in this study. Female subject No. 112 withdrew after experiencing nausea and syncope during a blood draw on Day 0 (baseline). Female subject number 121 withdrew due to influenza. Female subject # 125 withdrew on Day 6 due to vomiting and moderate headache. The site personnel considered this AE as not related to study drug.

Reviewer comment: **The reviewer believes that moderate vomiting and headache could be related to study drug.**

Four male subjects reported adverse events, and 13 female subjects reported adverse events. One man reported an ecchymosis related to plebotomy. Two men reported influenza. One man reported a mild headache. Of the 13 women, 6 reported AEs related to plebotomy. One reported influenza. Two women reported headache (one moderate and one severe in intensity).

Clinical laboratories: No clinical significant changes were noted from baseline in any laboratory parameter in any patient, except for serum triglycerides in three men. In these 3 men, change-from-baseline in serum triglycerides was marked (three to four times normal baseline values).

> Reviewer's comment: **The reviewer is impressed with the change in serum triglycerides in these 3 men. It is unclear if there was any alternative reason for these laboratory changes other than the administration of testosterone to normal men.**

7.6 **Reviewer's assessment of safety and efficacy:**
The sponsor believes that this study utilized "exaggerated" conditions to maximize potential transfer of testosterone to female partners of men administered Androgel. The sponsor believes that under conditions of normal use, potential for transfer would be "substantially reduced". In the event of transfer, the sponsor believes that the results of in vitro studies demonstrate that washing with soap and water will remove most of the applied dose from the skin surface.

The sponsor believes that adverse events in women due to androgens, such as hirsutism, are due to sustained increases in serum androgens or their metabolites, not transient increases, as may be expected with Androgel transfer. The sponsor also believes that actual virilization of an adult female would require sustained serum T concentrations of >200 ng/dL. This value is higher than those noted in any group.

The sponsor believes that wearing a T-shirt (albeit, long-sleeved) totally prevented transfer of Androgel to a partner.

The reviewer believes that a clear risk of transfer was demonstrated in this study. However, the reviewer believes that this risk can be effectively managed by appropriate use of the product. Specifically, after the product is allowed to briefly air-dry, men should put on clothing to cover the application sites. In addition, if contact with a female does occur, women should wash the area of contact on their body with soap and water.

The reviewer believes that there are clear implications of this risk for fetal development. Again, appropriate use of the product should minimize such risk. Additional wording has been added to the CONTRAINDICATIONS section of the package insert that instructs pregnant women to avoid contact with Androgel and if contact does inadvertently occur, to wash the affected area promptly. Nevertheless, the reviewer acknowledges that the risk of transfer to a pregnant female (and consequently to a fetus) cannot be totally eliminated by package instructions.

8. Safety study UMD-98-038:
8.1 **Design:**
This was a single-blinded, multiple-dose safety study conducted at a single United States center in 35 subjects. Subjects were administered 21 consecutive daily doses of 4 test articles to clean dry skin of the paraspinal region. The 4 test articles included the following:

1. Androgel 1%, 0.3 mL, dispensed onto a 4 cm^2 ——— cotton pad, allowed to air dry for 15 minutes and secured to the skin with ——— tape.
2. Androgel 1% placebo, 0.3 mL, dispensed onto a 4 cm^2 ——— cotton pad, allowed to air dry for 15 minutes and secured to the skin with ——— tape.
3. Normal saline solution, 0.2 mL, dispensed onto a 4 cm^2 ——— cotton pad and secured to the skin with ——— tape.
4. Sodium lauryl sulfate 0.1%, 0.2 mL, dispensed onto a 4 cm^2 ——— cotton pad and secured to the skin with ——— tape.

Scoring for cumulative irritation was performed every 24 hours immediately prior to re-application of the test articles. The scoring official was a single qualified person who was blinded to the test articles. Observed skin reactions were scored according to an "Inflammatory Response" scale as listed on the bottom of page 8-311 in Volume 1.18. (0=No visible erythema, 1=Mild erythema [barely perceptible], 2=Definite erythema [readily visible], 3=Erythema and papules, 4=Definite edema, 5=Erythema, edema and papules, 6=Vesicular eruption, 7=Strong reaction spreading beyond test site). Other superficial effects, such as cracking, peeling, and fissuring were also noted by an a priori scoring system. Patches were NOT replaced if a numerical score of 3 or greater was assessed at any timepoint.

Following the 21-day cumulative irritation phase, all subjects underwent a 2-week "rest period" during which no test articles were applied. Following the rest period, a "challenge phase" was conducted. This challenge phase was intended to assess the potential for contact sensitization. Specifically, all subjects were administered a single 24-hour application of all 4 test articles to naïve skin sites. Scoring of these sites was performed at 48 and 96 hours post-treatment. Following the challenge dose, the skin was assessed using a slightly different "Inflammatory Response" scale as listed on the bottom of page 8-312 in Volume 1.18. (0=No visible reaction, +=Slight, confluent or patchy erythema, 1=Mild erythema [pink], 2=Moderate erythema [definite redness], 3=Strong erythema [very intense redness]). Other superficial effects, such as cracking, peeling, and fissuring were also noted by an a priori scoring system.

Eligible subjects were men, aged 18 to 65. These subjects must have been in good health. Patients with clinically significant skin disorders were excluded. Patients with asthma, lupus, AIDS or cancer were excluded. Patients taking any anti-inflammatory, anti-histamine, or immunosuppressive drug were excluded. Insulin-dependent diabetics were excluded.

There were no efficacy variables in this study. The safety variables included an assessment of adverse events and a visible inspection and grading of the skin. Clinical laboratories were obtained at screening and after 21 days of treatment.

8.2 Withdrawals, Protocol Deviations and Compliance

Withdrawals: A total of 35 subjects were enrolled; all completed all phases of the study.

Deviations: Two subjects had contact time deviations during the cumulative irritation phase. These 2 subjects actually wore one patch for several minutes longer than 24 hours. Two subjects had contact time deviations during the contact sensitization phase. In these two, one patch was worn for less than the proscribed 24 hours.

In 2 subjects, test article (Androgel in one subject and Androgel placebo in the other) was reapplied even after maximum allowable inflammation had been reached.

8.3 Study Population
All enrolled patients were male, and all were Caucasian (N=35). Ages were evenly distributed from 18 years to 65 years.

8.4 Efficacy analysis:
There were no efficacy variables assessed.

8.5 Safety analysis:
Extent of exposure: The sponsor presented the extent of exposure in Table E on page 8-317 of Volume 1.18. This table is presented below:

Table 21. Number of subjects patched each day with test article

Day	Androgel	Androgel placebo	Sodium lauryl sulfate	Saline
1	35	35	35	35
2	35	35	35	35
3	34	34	35	~~35~~
4	31	31	33	35
5	23	27	23	35
6	18	24	14	35
7	13	23	5	35
8	11	22	3	34
9	8	19	1	34
10	7	18	1	34
11	5	17	1	34
12	5	17	1	34
13	5	17	0	34
14	5	17	0	34
15	5	16	0	34
16	5	16	0	34
17	4	15	0	34
18	3	15	0	34
19	3	15	0	34
20	3	15	0	34
21	2	15	0	34

The sponsor stated, "As the cumulative irritation phase progressed, if the observed skin reaction to a specific test article became severe, application of that specific test article was discontinued."

Reviewer's comment:

1. **In this adequately controlled study, daily application of Androgel 1%, *when occluded by an occlusive dressing*, led to discontinuation of most subjects by Day 10. These results contradict those of the larger phase 3 study (UMD-96-017), in which no patient discontinued Androgel therapy due to skin reaction in 6 months. It is likely that covering the application site with an occlusive dressing is intimately related to skin reactivity.**
2. **It appears that Androgel 1%, when covered with an occlusive dressing, is less irritating than the positive control (sodium lauryl sulfate) but more irritating then Androgel 1% placebo. It is unclear why testosterone itself might contribute to skin reactions.**

Dermal irritation results:

Cumulative irritation phase: The sponsor presented the results of mean daily skin score assessment in Table G on page 8-321 in Volume 1.18. It is important to note that the maximum score was 3.0 ("Erythema and papules"), because the patch was not replaced if the score assessed was a "3.0".

These results are demonstrated in Table 15 below.

Table 22. Mean irritation scores during the cumulative irritation phase.

Day	Androgel	Androgel placebo	Sodium lauryl sulfate	Saline
1	0.7143	0.9413	0.6000	0.1429
2	0.8857	1.1429	0.9143	0.2286
3	1.4286	1.4000	1.6286	0.0286
4	1.9143	1.4286	2.3429	0.0857
5	2.3714	1.7429	2.8857	0.0286
6	2.5143	1.9714	2.9714	0.0286
7	2.6286	1.9714	2.9714	0.0286
8	2.6667	2.1515	3.0000	0.0303
9	2.8485	2.3636	3.0000	0.0000
10	2.9394	2.5455	3.0000	0.0000
11	2.9697	2.5758	3.0000	0.0000
12	2.9697	2.6970	3.0000	0.0000
13	3.0000	2.5758	3.0000	0.0606
14	3.9697	2.7273	3.0000	0.0303
15	3.0000	2.6667	3.0000	0.0606
16	3.0000	2.8182	3.0000	0.0303
17	3.0000	2.7273	3.0000	0.0303
18	3.0000	2.8182	3.0000	0.0000
19	3.0000	2.7879	3.0000	0.0909
20	3.0000	2.6970	3.0000	0.1515
21	3.0000	2.6870	3.0000	0.1818

Reviewer's comment: The results of this trial reveal that both Androgel and Androgel placebo are irritating to skin, WHEN COVERED BY AN OCCLUSIVE DRESSING. However, the robust results of clinical trial UMD-96-017 demonstrate that skin irritation was minimal when used as labeled (uncovered by an occlusive dressing).

Challenge phase

Only four of thirty-five subjects showed moderate to marked inflammation in response to the challenge application suggesting possible contact sensitization. Three of these reacted reacted to Androgel 1%, Androgel placebo, and to the positive control (sodium laurel sulfate). However, one subject (#121) reacted only to Androgel placebo and Androgel 1% and not the active control.

Out of the four subjects, only 2 accepted re-challenge. At that time, one of these (#116) had mild erythema only. One (#122) had moderate erythema in response to sodium laurel sulfate only.

The sponsor believes that no dermal sensitization was observed at challenge.

Reviewer's comment: **It is unclear whether Patient #116 represented a case of contact sensitization. Nevertheless, overall, the results of this trial do not reflect contact sensitization.**

Adverse events:
No deaths were reported during this study.

No serious adverse events were reported during this study.

No adverse events leading to early discontinuation were reported in this study.

Twelve (12) subjects reported a total of 34 adverse events during the study. In five of these patients, the relationship to study drug was very unlikely (e.g., "cold", "body aches", "sinusitis", etc). Of the other seven patients, all reported pruritis or burning at the application site. There were 2 reports of "severe" burning, 1 at all the sites and 1 only at the Androgel site. There were several reports of moderate burning and pruritis at various application sites.

Clinical laboratories: No clinical significant changes were noted from baseline in any laboratory parameter in any patient.

8.6 Reviewer's assessment of safety and efficacy:
The sponsor believes that Androgel and Androgel placebo were both significantly irritating to skin compared to placebo when covered by an occlusive dressing. The sponsor acknowledges that the active drug was more irritating then the placebo article.

The sponsor believes that the reason for these results is the occlusive dressing that was applied to the hydroalcoholic gel application

The sponsor believes that no dermal sensitization was observed at challenge.

The reviewer agrees with the sponsor's conclusions for this study. The robust results noted in UMD-96-017 demonstrate good skin tolerability of Androgel 1% when applied as instructed and not covered by an occlusive dressing.

9. Safety study UMD-98-039:
9.1 Design:
This was a double-blinded, single-dose safety study conducted at a single United States center in 30 patients. A single, 24-hour application of 3 test articles was made to clean dry skin of the paraspinal region in all patients. The test articles included the following:

5. Androgel 1%, 0.3 mL, dispensed onto a 4 cm^2 cotton pad, allowed to air dry for 15 minutes and secured to the skin with tape.
6. Androgel 1% placebo, 0.3 mL, dispensed onto a 4 cm^2 cotton pad, allowed to air dry for 15 minutes and secured to the skin with tape.
7. Normal saline solution, 0.2 mL, dispensed onto a 4 cm^2 cotton pad and secured to the skin with tape.

Duplicate patches were applied to the contralateral paraspinal region in all patients. Thus, all patients had 6 total patches applied.

One of each duplicate patches was exposed to UVA and UVB radiation for evaluation of phototoxic potential. The contralateral patch was not irradiated. The amount of radiation that was used was 75% of the individual patient's minimum erythema dose (MED). The MED was determined 1 week prior to application of test articles. This was accomplished by exposing unprotected, naïve skin to a series of 5 UVB/UVA exposures, each 25% greater in duration than the previous exposure (16 seconds, 20 seconds, 25 seconds, 31 seconds and 38 seconds). The source of radiation was a 150 Watt —— Solar Ultraviolet simulator. Approximately 24 hours after irradiation, the sites were illuminated by a 100 Watt incandescent bulb and visually inspected for erythema. The smallest dose that produced slight visible erythema (a score of 0.5 on a scale of 0-3, [Vol. 1.18, page 8-109]) was determined to be that subject's MED.

During the clinical trial, skin evaluations were made by visual inspection on Days 2-5 (at 1 hour, 24 hours, 48 hours and 72 hours post-irradiation). Observed skin reactions were scored according to an "Inflammatory Response" scale as listed on the bottom of page 8-109 in Volume 1.18. (0=No visible erythema, 0.5=Slight erythema, 1=Mild erythema [pink], 2=Moderate erythema [definite redness], 3=Strong erythema [very intense redness]). Other superficial effects, such as cracking, peeling, and fissuring were also noted by an a priori scoring system.

Eligible subjects were men, aged 18 to 65. These subjects must have been in good health. They must have satisfied one of the following skin types based on historical responses to tanning: 1. Burns easily, never tans, 2. Burns easily, tans minimally, and 3. Burns moderately, tans gradually.

Patients with a tendency to severe reactions from exposure to sunlight were excluded. Patients taking any drugs known to interact with sunlight (e.g. tetracycline, sulfa, phenothiazines, etc) were excluded. Patients with clinically significant skin disorders were excluded. Patients with asthma, lupus, AIDS or cancer were excluded. Patients taking any anti-inflammatory, anti-histamine, or immunosuppressive drug were excluded. Insulin-dependent diabetics were excluded.

There were no efficacy variables in this study. The safety variables included an assessment of adverse events and a visible inspection and grading of the skin.

9.2 Withdrawals, Protocol Deviations and Compliance

Withdrawals: A total of 30 patients were enrolled; twenty-seven completed the study. Three subjects were dropped due to "wear-time" deviations.

Deviations: In these 3 patients, wear-time was not a full 24 hours. In one of these patients, a right-sided patch actually fell off at an unknown time. In one of these patients, one left-sided patch remained in contact with the skin for only 6 hours. In another, contact-time was maintained for only 16 hours for a single right-sided patch.

9.3 Study Population

All enrolled patients were male, and all were Caucasian (N=6). Ages were evenly distributed from 18 years to 65 years. In terms of MED, most subjects met an endpoint at 25 and 31 seconds of exposure.

9.4 Efficacy analysis:

There were no efficacy variables assessed.

9.5 **Safety analysis:**

Dermal irritation results: The sponsor presented a detailed table of dermal irritation scoring results in Table E, on page 8-114 of Volume 1.18. These scores were listed for the following times: 1 hour, 24 hours, 48 hours, and 72 hours. The sponsor believes that both placebo gel and Androgel 1% produced mild to moderate inflammation without irradiation when compared to saline. Most scores were in the range of 0 to 1.0, with a few scores of 2. The sponsor believes that irradiation did not increase inflammation relative to the non-irradiated sites.

> **Reviewer's comment: Based on the data in Table E of the final study report, the reviewer agrees with the sponsor's conclusions regarding dermal irritation.**

Adverse events:

No deaths were reported during this study.

No serious adverse events were reported during this study.

No adverse events leading to early discontinuation were reported in this study.

Eight (8) subjects reported adverse events during the study. Two of these were thought to be completely unrelated to drug therapy ("cold" and "sinusitis"). Of the other six patients, 1 had a moderate headache and five had application site reactions. Of the five patients who reported application site reactions, four patients reported "mild" reactions, and 1 patient reported 2 events ("moderate" and "severe"). The severe reaction resolved without medical therapy.

Clinical laboratories: There were no clinical laboratory examinations performed during this study.

9.6 **Reviewer's assessment of safety and efficacy:**

The sponsor believes that Androgel and Androgel placebo were generally well-tolerated, even when applied under occlusive dressings. Relative to placebo, the inflammation induced by both Androgel and Androgel placebo was considered "mild" to "moderate" in intensity. The sponsor believes that there was no phototoxic potential.

The sponsor believes that some of the irritation observed with Androgel and Androgel placebo in this study was due to "the occlusive patch application", rather than the actual test article.

The reviewer agrees that the Androgel and Androgel placebo were mildly to moderately irritating under the conditions of this study. The reviewer agrees that there was no phototoxic potential. However, the reviewer does not have adequate information to conclude that covering the test articles with a [redacted] dressing and [redacted] tape was a significant contributor to inflammation.

10. **Safety Update Report:**

The four-month safety update was submitted on September 16, 1999. It contained the following documents:

1. The final study report for UMD-96-017.
2. Revised package labeling.
3. A revised Integrated Summary of Safety, containing preliminary data from Study UMD-98-035 ("035"). Study 035 is an ongoing, 24-month extension of Study 017.

Reviewer's comments:

1. **The reviewer's summary of Study 017 (found above) reflects the final study report for 017.**
2. **The reviewer's comments on labeling, as noted in the IR letter of January 28, 2000, reflects the sponsor's final revised proposal.**

10.1 Safety study UMD-98-035

The safety update contained safety information derived from Study UMD-98-035. For this ongoing, uncontrolled study, the cutoff date for inclusion in this report was April 30, 1999. Data on 106 patients from Study 035 were included. At the time of cut-off, there were 86 patients still ongoing in this trial. There were 20 premature discontinuations. The reasons for premature discontinuation included: Lost to follow-up (N=4), Refused further treatment (N=6), Protocol violation (N=2), "Other" (N=1), Adverse event (N=7).

Reviewer's comment: **Patients discontinued due to adverse events in Study 035 are discussed later in this review.**

Extent of exposure:

In terms of dose, 72 patients had received 50 mg/daily, 20 patients had received 75 mg/daily and 32 had received 100 mg/daily. During the study, some patients received more than one dose. The duration of exposure in Study 035 varied from 6 months to 1 year (in addition to the previous 6 months exposure in Study "017").

Deaths:

In Study 035, there were no deaths reported.

Serious adverse events:

In Study 035, there were 3 serious adverse events reported. One patient developed a newly diagnosed lung carcinoma. One patient (No. 6-14), who was taking 50 mg/daily, was admitted to a hospital on November 5, 1998 for chest pain. During the hospitalization, a myocardial infarction was ruled out and the diagnosis was determined to be muscular strain.

Finally, Patient 3-15, a 59-year old male, who was taking 75 mg/daily, was admitted to the emergency room on January 2, 1999. He complained of a severe headache, and was noted to be confused. CT scan revealed the presence of a pituitary tumor. An MRI revealed an extensive cerebral infarction in the region supplied by the right posterior cerebral artery. He was discharged from the hospital on January 6, 1999 on aspirin and Dilantin. He continued in Study 035 on the same dose of testosterone gel. At his 6-month visit in Study 035, he was noted to have some residual loss of vision in the left eye. His past medical history was significant for diabetes mellitus, diabetic nephropathy, hypertension, atherosclerotic heart disease and a pituitary tumor. This patient's serum testosterone levels and hemoglobin/hematocrit results were submitted by the sponsor. The sponsor's hemoglobin and hematocrit did increase during treatment but not to clinically worrisome levels. The sponsor believes that this serious AE was not related to testosterone gel.

Reviewer's comment: **The reviewer believes that this serious AE was not likely to be related to study drug.**

Discontinuations due to adverse events:

In Study 035, there were 7 discontinuations due to adverse events. Of those, 1 included a patient who developed new lung cancer during the trial. Three patients discontinued due to application

site reactions. Of these application site reactions, 2 patients also had previous reactions to a testosterone patch and 1 patient *may* have had an allergic reaction to a soap. Three patients discontinued due to prostate disorders. In the prostate disorders group, one patient had an elevated serum PSA value that actually declined during continued treatment. One patient (No. 3-07) had a mildly elevated serum PSA (5.7 ng/mL) that provoked his discontinuation from Study 035, but he did not undergo biopsy. One patient (No. 4-17) had a mildly elevated serum PSA (PSA =6.2 ng/mL), an enlarged prostate on rectal exam, and urinary incontinence which provoked discontinuation as well as biopsy. The biopsy revealed cancer. Further details were not submitted.

Reviewer's comments: Information regarding Patient 4-17, as well as the other two cases of urogenital adverse reaction resulting in premature discontinuation, is presented in the product label. The induction of latent prostate cancer by androgens remains a real safety concern.

Overall adverse events:

In terms of overall adverse events, the safety results from 035 are described in Table 23 below:

Table 23: Incidence of Adverse Events Occurring in >5% of Patients in any Treatment Group in Study 035.

Term	Androgel 50 mg N=72	Androgel 75 mg N=20	Androgel 100 mg N=32
Number of patients with any AE	49 (68.1%)	15 (75.0%)	26 (81.3%)
Body as a Whole			
Lab test abnormal	9 (12.5%)	1 (5.0%)	4 (12.5%)
Headache	3 (4.2%)	1 (5.0%)	4 (12.5%)
Flu syndrome	4 (5.6%)	1 (5.0%)	4 (12.5%)
Pain	1 (1.4%)	0 (0.0%)	4 (12.5%)
Skin			
Application site reaction	7 (9.7%)	2 (10.0%)	1 (3.1%)
Acne	2 (2.8%)	0 (0.0%)	5 (15.6%)
Rash	4 (5.6%)	1 (5.6%)	0 (0.0%)
Urogenital			
Prostate Disorder	2 (2.8%)	2 (10.0%)	9 (28.1%)
UTI	2 (2.8%)	1 (5.6%)	0 (0.0%)
Testes disorder	0 (0.0%)	0 (0.0%)	2 (6.3%)
Nervous			
Anxiety	3 (4.2%)	0 (0.0%)	1 (3.1%)
Depression	0 (0.0%)	2 (10.0%)	0 (0.0%)
Musculoskeletal			
Arthralgia	4 (5.6%)	2 (10.0%)	5 (15.6%)
Cardiovascular			
Hypertension	3 (4.2%)	1 (5.0%)	3 (9.4%)
Metabolic			
Edema-peripheral	3 (4.2%)	0 (0.0%)	2 (6.3%)
Digestive			
Diarrhea	0 (0.0%)	1 (5.0%)	2 (6.3%)
GI disorder	0 (0.0%)	1 (5.0%)	3 (9.4%)

Reviewer's comment: **The reviewer agrees with the sponsor's conclusions that the overall AEs reported in 035 were "consistent" with those reported in 017. However, the reviewer points out that several of these AEs may have been dose-related, and that many of them were reported at higher incidence rates than in 017.**

For example, it is notable that "prostate disorders", "acne", "edema-peripheral", "hypertension", "headache", and "arthralgias" were reported at incidence rates that appeared to be dose-related. Some of these, such as prostate disorders, peripheral edema and acne, are recognized historically as side effects of androgens.

Clinical laboratory evaluations:
In terms of laboratory evaluations, there was a clear increase from baseline in mean hemoglobin and hematocrit in all treatment groups, when assessed at the last available visit. There was a greater percentage of patients in the 100 mg/daily group who had increased hemoglobin or hematocrit compared to the other dose groups. Five patients (one on 50 ~~mg/daily~~ and four on 100 mg daily) were noted to have "very high" hemoglobin values (>18 g/dL) at some time during Study 035 but not at baseline. In terms of chemistry, there were very few clinically significant changes in any parameter in the entire population. Four patients were noted to have "very high" triglycerides (>450 mg/dL) during the trial but not at baseline.

In terms of serum PSA, there was a statistically significant increase from baseline to last visit in the mean PSA in the 50 mg/daily dose, and an increase which approached statistical significance in the 100 mg/daily dose. Four patients were noted to have a "very high" serum PSA (>5.5 ng/mL) during the trial. In two of these patients, serum PSA returned to normal while continuing drug. The other two were described above.

In terms of vital signs, the only finding of clinical importance was a statistically significant increase from baseline to final visit in systolic BP in the 75 mg/daily treatment group (+7.47 mm Hg ± 3.10).

In terms of body weight, there were non-statistically significant increases from baseline in both the 75 mg/daily group (+4.3 pounds) and in the 100 mg/daily group (+3.0 pounds). This change in the 100 mg/daily group approached statistical significance.

Special safety issues:
Finally, in terms of special safety issues, several findings of interest were noted in regard to the genitourinary system, in regard to hematologic issues, and in regard to lipid profile issues.

Genitourinary issues:
Twenty-two of the 106 patients (21%) in UMD-98-035 reported adverse events related to the genitourinary tract. Fifteen of these related in some way to the prostate. Two patients reported gynecomastia. Two patients reported urinary tract infection (UTI). Two patients reported hematuria. One patient reported a kidney stone. The hematuria cases and the kidney stone case were considered by the investigator to be "not related" to Androgel. The gynecomastia cases were also considered by the investigator to be "not related" to Androgel.

Reviewer's comments:

1. **The sponsor did not submit sufficient information to allow the reviewer to comment on the attribution of any of these genitourinary adverse event cases.**

Without specific evidence to the contrary, the reviewer believes that all of them could be related to treatment with androgens, based on biologic plausibility.

2. **When available, the sponsor should submit the final study report for Study UMD-98-035.**

Table 56 of the revised ISS presents some of the urogenital AEs. Of the 6 patients with prostate disorders listed, 5 were considered at least possibly related to the use of Androgel, and one was "unknown". There were 3 cases of enlargement of the gland by digital rectal exam only. There was one case [Patient 3-07] of an elevated PSA (PSA=5.7 ng/mL). One patient reported a "weak" urinary stream. One patient [4-17] had an enlarged hard prostate, an elevated serum PSA (6.2 ng/mL) and urinary incontinence. He underwent biopsy that revealed prostate cancer. The investigator believed that this case was "almost certainly" related to treatment with androgens. Both Patients 3-07 and 4-17 were discontinued from the study for these AEs.

Reviewer's comments: **It is unclear why Table 56 presented information on only six of the 15 patients who reported a "prostate disorder".**

During Study 035, all patients underwent periodic evaluations of the genitourinary tract, including digital rectal exam of the prostate (DRE), urine flowmetry, measurement of the International-Prostate Symptom Score (IPSS) and serum PSA.

Prostate enlargement was noted on DRE in 9 patients. Five of these were reported as adverse events. In only one of these patients was urine flow noted to be significantly reduced [patient 4-17]. In only one of these was I-PSS noted to be significantly increased (baseline score of 11 to 22). In only one of these was serum PSA noted to be above normal at the final visit [Patient 4-17].

Urine flow rates were noted to be significantly decreased (defined as >12 cc/sec at baseline and <10 cc/sec at the final visit) in 13 patients. The urine flow rate results for these patients are presented in Table 57.

Reviewer comment: **The urine flow rates, as presented in table 57 of the revised ISS, reflect a possible effect of Androgel on bladder emptying in some patients. The data is inadequate to draw definitive conclusions; however, the reviewer believes that such an effect is biologically plausible.**

Final serum PSA was elevated above normal in only 3 patients. These patients have been described in detail in a previous section of this review.

Hematological issues:
Five patients in Study 035 had "very high" hemoglobin (>18.0 g/dL) or hematocrit values (>55.0%) at the final treatment visit and not at the initiation of the study. Table 61 of the revised ISS presents data on these 5 patients. All of these final hemoglobin values were between 18.0 and 19.0 g/dL. All of the hematocrit values were between 53% and 56.3%.

Serum lipid issues:
Four patients were noted to have "very high" triglycerides (>450 mg/dL) at the last trial visit but not at baseline. Data on these patients is presented in Table 64. In two of these patients, HDL-cholesterol was also noted to be low (<30 mg/dL). In one of these patients (Patient 5-11), serum triglycerides were noted to be markedly high (1190 mg/dL). The sponsor believes that this patient's results may be related to his baseline hypercholesterolemia.

10.2 Reviewer's assessment of safety update:
In the 4-month safety update, the reviewer believes that the most important data was derived from the preliminary safety results of the long-term, follow-up study UMD-98-035. The reviewer believes that these data demonstrate that in some patients, the androgenic effects of Androgel can lead to adverse outcomes over the long-term. These outcomes include negative changes in the serum lipid profile, polycythemia, adverse reactions related to the genitourinary tract, and such adverse reactions as acne, peripheral edema, gynecomastia, hypertension, anxiety and perhaps arthralgias.

The most concerning adverse effects noted are those related to the prostate. Enlargement of the prostate, diminished urinary flow rate and increased voiding symptoms may be a direct androgen effect. The occurrence of a newly-diagnosed, symptomatic prostate cancer is concerning. Finally, the development of gynecomastia and breast pain is also concerning.

Nevertheless, the reviewer believes that most patients tolerated long-term treatment with Androgel well. The reviewer believes that appropriate routine follow-up of hypogonadal males on Androgel should be successful in preventing many serious adverse reactions. Such relatively simple monitoring as serum PSA, serum lipid profile, complete blood count, digital rectal examination, physical examination and measurement of serum testosterone should be effective in limiting the risk to Androgel users.

11. Reviewer's overall assessment of safety and efficacy:

11.1 Safety: Safety data for Androgel were derived from a single, controlled, Phase 3 trial (UMD-96-017), the preliminary results of a "long-term", follow-up study (UMD-98-035), a single phase 1 clinical pharmacology trial (UMD-96-012), two European trials using a different formulation, a phototoxicity trial, a cumulative irritation trial and 2 trials related to dermal transfer.

Overall, in the majority of patients studied, Androgel was safe and well-tolerated at doses of 50 mg, 75 mg and 100 mg daily. The overall adverse event profile was consistent with Androgel's effect as an androgen. Some patients, however, reported adverse events consistent with an excessive and undesirable androgen effect. In the controlled clinical trial, there were reports of acne, emotional lability (depression and anxiety), peripheral edema, hypertension, headache, gynecomastia and genitourinary disorders. The most outstanding adverse reaction was the effect on Androgel on the prostate. Even in this 6-month trial, there were reports of prostate enlargement, increased PSA and difficulty urinating. There were several patients who reported gynecomastia, one of whom underwent mastectomy. In the controlled trial, it was clear that Androgel could also have adverse effects on several important laboratory parameters in some patients. These measures include decreased HDL-lipoproteins, increased serum PSA and increased hemoglobin or hematocrit.

In the long-term, follow-up study, comprised of 106 patients with exposure up to 18 months, the adverse event profile was similar to the controlled study. However, the incidence rates for similar adverse event terms was greater that those in the controlled trial. In this study, the effect on the genitourinary tract was more prominent. One patient, for example, required discontinuation due to the onset of symptomatic prostate cancer.

Overall, the skin tolerability of Androgel was excellent. In the controlled clinical there were no discontinuations due to application site reaction. Skin irritibility did not worsen with exposure to radiation and there did not appear to be a risk of contact sensitization.

There is a real risk of transfer of this gel from person-to-person. Trial "037" revealed clear evidence of transfer to a partner by direct skin contact. This risk predominantly involves the possible masculinizing effects on female partners, or the inadvertent masculinization of a female fetus. Fortunately, Study 037 demonstrated that this risk is mitigated by covering the application sites with clothes after application of the dose.

Overall, Androgel was safe and well-tolerated in most patients. The risks of excess systemic androgen in some patients are real; however, these may be reduced by routine follow-up using such simple measures as serum lipid profile, serum T monitoring, serum PSA, complete blood count, digital rectal exam of the prostate and physical examination. The risk of dermal transfer by physical contact is also real, but again, may be reduced by proper protection of the site.

11.2 Efficacy: The efficacy of Androgel was evaluated in a single, active-comparitor controlled, parallel-arm, 6-month, phase 3 trial (UMD-96-017) and a single phase 1 clinical pharmacology study (UMD-96-017). The primary determination of efficacy was based on the serum testosterone levels following treatment with Androgel.

In the treatment of male hypogonadism, the Division believes that the attainment of "normal" serum testosterone levels in previously "hypogonadal" men is indicative of clinical efficacy. Currently, however, it is not clear how to best define "attainment of normal range serum T levels. The sponsor and Division agreed on a single primary endpoint (proportion of patients with average serum T and minimum serum T concentrations within the normal range). This endpoint tended to increase the "success rate" for products which produce serum levels of T above the minimum range but sometimes also above the maximum range. For the best possible assessment of efficacy and safety, the reviewer evaluated several pharmacokinetic variables including Cmin, Cmax, Cavg, as well as several exploratory clinical endpoints (including muscle strength, body fat, bone mineral density, libido, erectile function and mood).

Overall, Androgel at doses of 50 mg, 75 mg and 100 mg daily was effective in producing serum total T concentrations within the normal range in the majority of hypogonadal men studied. There was evidence that several clinical parameters consistent with hypogonadism, such as bone mineral density, also improved. There was evidence that titration of dose was effective in the manipulation of the ultimate serum T level. However, there were some patients in whom serum T levels were too high, especially those patients receiving the 100 mg dose.

The risk of excessive serum T levels in the 50 mg daily group was small, but real. In order to minimize this risk, all patients will be advised to start on 50 mg daily, and all patients will be advised to have a check of the serum T on Day 14 after starting treatment. The risk of adverse events related to excess androgen should be greatly reduced by these simple instructions.

12. Recommendations for regulatory action: The reviewer recommends approval of this new drug application.

13. Labeling revisions: Clinical recommendations for labeling revisions were sent to the sponsor on January 28, 2000 in the form of an Information Request letter (see attached, as Appendix 1). Following the resolution of all outstanding labeling issues, the medical officer will submit a final labeling memorandum.

/S/

Mark S. Hirsch, M.D.
Medical Officer
Division of Reproductive and Urologic Drug Products, HFD-580
cc: Arch NDA 21-015
HFD-580/Div File
HFD-580/SAllen/MMann/DShames/KColangelo
HFD-870/AParekh/DChatterjee