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RESEARCH**

APPLICATION NUMBER:

22309Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	April 28, 2009
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	22-309
Applicant	Abbott Pharmaceuticals Inc.
Date of Submission	October 25, 2010
PDUFA Goal Date	April 29, 2010
Proprietary Name / Established (USAN) names	AndroGel® 1.62% testosterone gel
Dosage forms / Strength	1.25 gm – 5 gm once daily
Proposed Indication(s)	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommended:	<i>Approval</i>

1. Introduction

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone. Signs and symptoms that have been reported to be associated with male hypogonadism include erectile dysfunction, decreased sexual desire, fatigue, mood depression, regression of secondary sexual characteristics and osteoporosis.

The active moiety in the proposed product is testosterone. Testosterone is available in the United States in several formulations, including topical gels and solutions (AndroGel 1%, Testim 1%, Axiron and Fotesta), a transdermal patch (Androderm), a buccal patch (Striant), intramuscular injections (testosterone enanthate and testosterone cypionate) and implanted pellets (Testopel). Currently, AndroGel 1% is the most widely used testosterone replacement therapy, and is marketed by Abbott Pharmaceuticals, the same Sponsor as for this application. The Sponsor estimates that approximately (b) (4) million patients have used AndroGel 1% since its approval in February, 2000.

The Sponsor has developed AndroGel 1.62%, a new higher strength of their approved testosterone gel product, AndroGel 1%. The Sponsor purports that the new product has (b) (4) characteristics and a higher viscosity compared to AndroGel 1%, the intent of which is to allow for a lower total volume of gel per application. The dose proposed is 1.25 gm to 5 gm once daily. The product will be applied to skin of the upper arms and shoulders. This dose translates to 1.45 mL to 5.8 mL per application, per day, respectively.

The original application was supported by a single, pivotal Phase 3 study (S176.3.104) conducted in 274 hypogonadal men (234 on active treatment and 40 on placebo), as well as

supportive evidence from five, single and multiple-dose, Phase 1 studies in a total of 172 hypogonadal men:

- S176.1.001 - a single dose PK study
- S176.1.002 - a multiple dose, dose-ranging study
- S176.1.005 - a multiple dose PK study, with and without post-dose skin washing
- S176.1.006 - a multiple dose PK study, with and without skin moisturizer or sunscreen
- S176.1.007 - a multiple dose PK study, comparing application sites

The original NDA also contained 3 “safety” studies in normal, healthy, volunteers:

- S176.1.003 – a multiple dose, transfer assessment study (n= 48 couples)
- S176.1.004 – a multiple dose, skin irritation/sensitization study (n=235 subjects)
- S176.1.008 – a multiple dose, transfer assessment study (n= 48 couples)

Headline results from a third transfer assessment study in healthy, adult, volunteer couples (S176.1.009) were submitted via NDA amendment on November 5, 2009, with a final study report for this third transfer study submitted on January 15, 2010.

On March 12, 2010, this NDA received a Complete Response (CR) regulatory action. This action was taken because while the Sponsor had demonstrated that the new “4-site” application method for 5 gm of gel would not promote transfer of testosterone through a simple t-shirt, they had not provided sufficient evidence to link the “4-site” application method to the Phase 3 “rotating method” (3 days abdomen 4 days arms/shoulders).

The current CR was submitted on October 25, 2010, and contained data from two new studies (S176.1.010 and S176.1.011) as well as a revised clinical study report for the Phase 3 pivotal efficacy study (S176.3.104) (b) (4). The two new studies are as follows:

- Protocol S176.1.010 (Study 010): “*A Multiple Dose Pharmacokinetic and Comparative Bioavailability Study of Testosterone Absorption after Administration of 5 g Testosterone Gel 1.62% to the Upper Arms/Shoulders using an Application Site Rotation or a Combination of Application Sites in Hypogonadal Males*”. This was a crossover study comparing relative bioavailability of two different application techniques (3 days to the abdomen followed 4 days to the shoulders vs. 7 days to 4-sites). This was intended to support the “4-site” application method.
- Protocol S176.1.011 (Study 011): “*An Open-Label Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62% Applied to the Upper Arms and Shoulders and Use of a T-shirt Barrier*”. This was a transfer assessment study, using just the arms/shoulders. This was intended to support the “arms/shoulders”-only application method.

2. Background

2.1 DESCRIPTION OF PRODUCT

AndroGel 1.62% (testosterone gel) is a transparent to slightly opalescent colorless gel containing 1.62% testosterone, an androgen (pharmacologic class). When applied topically, the Sponsor states that testosterone gel provides continuous transdermal delivery of

testosterone. The gel is packaged in a multi-dose pump (capable of dispensing 75 gm of gel), which consists of a (b) (4) inside a plastic canister with a pump dispenser. Each pump delivers 20.25 mg of testosterone in 1.25gm of gel (1.45 mL). Four pump actuations are therefore required for the highest daily dose of 81 mg of testosterone (5gm of gel).

Testosterone is a white crystalline powder. The gel which carries the testosterone contains: alcohol (b) (4), isopropyl myristate (b) (4), (b) (4) Carbopol 980 1.0% (b) (4), sodium hydroxide (b) (4) and purified water (b) (4).

The product's proposed indicated use is the standard testosterone replacement therapy indication: in males for conditions associated with a deficiency or absence of endogenous testosterone, (b) (4)

The proposed initial dose of the drug product is 41 mg of testosterone (2.5 gm) daily topically applied to the upper arms and shoulders. The dose may be reduced to 20.25 mg of testosterone (1.25 gm), or increased to 60.75 mg of testosterone (3.75 gm) or 81 mg of testosterone (5 gm) as needed, based upon single draw, serum total testosterone concentrations. The gel is applied to the arms/shoulders only. This method was chosen based on the results from two studies: 1) the most recent transfer Study 011, which showed that a simple t-shirt effectively blocked transfer to a non-user, and 2) the results from Study 007 which showed nearly identical systemic testosterone exposure for arms/shoulders-only compared to the recommended Phase 3 "rotating" method.

2.2 REGULATORY HISTORY

All studies for AndroGel 1.62% were conducted under IND #50,377, which is the original AndroGel 1% IND.

On August 25, 2005, the first study protocol for AndroGel 1.62% was submitted. It was a Phase 1 protocol, Protocol S176.1.011, entitled "*The Multiple Dose Pharmacokinetics and Comparative Bioavailability of Testosterone After Administration of 2.2, 3.75, 5, and 6.25 g Dose Levels of Investigational Testosterone Hydro-Alcoholic Gel Formulations in Hypogonadal Male Volunteers*" (Study 001). The results of this study showed no differences in exposure between dose strengths of 1.22%, 1.42%, and 1.62%, leading the Sponsor to continue studies with the 1.62% formulation (the highest concentration, therefore the lowest gel volumes).

The next study protocol submitted was a Phase 1, dose-ranging trial, Protocol S176.1.002, entitled, "*The Single and Multiple Dose Pharmacokinetics of Testosterone After Administration of 1.62% Hydro-Alcoholic Gel at Dose Levels of 1.25, 2.50, 3.75, 5.00 and 6.25g in Hypogonadal Males*" (Study 002). This study showed generally linear, dose-related increases in exposure from the 1.25 gm to 6.25 gm doses of the 1.62% formulation at Day 14.

Based on these results, the Sponsor decided to move forward with the 1.62% formulation at doses of 1.25 gm to 5 gm.

On October 18, 2006, an End of Phase 2 (EOP2) meeting was held. The protocol for the single, Phase 3, pivotal study (S176.3.104) was discussed. The Sponsor and Division agreed that at least 6 months data from the Phase 3 study would be submitted in the original NDA, and that the Division would accept the full 1 year of data with the 120-Day Safety Update.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

On January 21, 2008, a Pre-NDA meeting was held for the AndroGel 1.62% formulation. The Sponsor agreed not to submit the initial NDA until the second “transfer assessment” study (S176.1.008) was completed, and that this study report would be included in the original NDA submission.

On August 13, 2008, a Guidance meeting was between the Sponsor and DRUP to discuss the [REDACTED] (b) (4) issue. At this meeting, Solvay stated that 98% of all samples for all AndroGel 1.62% studies were available and were within the validated stability period for re-analysis. Because a significant portion of the study samples were available for re-assay, the Division agreed to accept results from a complete re-assay of all available samples from all the AndroGel 1.62% studies for the three critical analytes (T, DHT, and E) as an appropriate means of resolving the identified Form 483 deficiencies. It was also agreed that the NDA submission should provide data supporting the acceptability of the re-assayed samples. The Sponsor conducted the re-analysis of all samples at [REDACTED] (b) (4)

On February 11, 2009, the original NDA for AndroGel 1.62% was submitted.

The following notable events transpired during the first cycle review of the original NDA:

On August 28, 2009, the Division conveyed a regulatory letter to Sponsor voicing continued concerns and posing questions related to transfer of the product to others (when applied to the abdomen) despite a t-shirt barrier at doses > 2.5 gm.

On September 17, 2009, the Sponsor provided responses to the Division's August 28, information request letter.

On October 1, 2009, a teleconference was held between Sponsor and DRUP to discuss the Division's continued concerns related to transfer at doses > 2.5 gm (from the abdomen site), despite the Sponsor's September 17, responses.

On November 5, 2009, the Sponsor submitted additional information relevant to the issue of transfer, including headline results from a third transfer study (S176.1.1009), wherein a dose of 5 gm was spread out onto 4 application sites and a t-shirt barrier was purported to completely block transfer. This submission also included a rationale in support of the Sponsor's requested switch to a 3- or 4-site application regimen for doses of 3.75 gm and 5 gm, respectively.

On November 18, 2009, the Division conveyed 6 questions related to the November 5, submission, mostly concerning the Sponsor's rationale for exposure comparability between the 4-site application method and the rotating Phase 3 application method.

On November 24, 2009, the Sponsor provided detailed responses to the November 18, questions from DRUP. These responses included data from the Phase 3, Study 104 in support of exposure comparability between a 3- or 4-site application regimen, and the rotating regimen (abdomen, arms/shoulders) that was used in Phase 3.

On December 10, 2009, the PDUFA clock was extended 3 months based upon the Division's finding that a major clinical amendment had been submitted within 3 months of the original goal date.

On March 12, 2010, the NDA received a Complete Response (CR) regulatory action. This action was taken because while the Sponsor had demonstrated that the new "4-site" application method for 5 gm of gel would not promote transfer of testosterone through a simple t-shirt, they had not provided sufficient evidence to link the "4-site" application method to the Phase 3 "rotating method".

On October 25, 2010, a CR was submitted by Sponsor. It contained data from two new studies (S176.1.010 and S176.1.011) as well as a revised clinical study report for the Phase 3 pivotal efficacy study (S176.3.104) (b) (4) The two new studies are as follows:

- Protocol S176.1.010: This was a crossover study comparing relative bioavailability of the 4-site and rotating application methods. It was intended to support the new "4-site" application method

- Protocol S176.1.011: This was a transfer assessment study, using just the arms/shoulders. It was intended to support the “arms/shoulders-only” application method – which is ultimately, the final labeled method.

2.3 PRIMARY MEDICAL REVIEWER’S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, A. Roger Wiederhorn, stated in his final review of the CR, dated April 20, 2011:

“Recommendation on Regulatory Action: It is recommended that NDA 22-309 be APPROVED at this time. The Sponsor has provided a COMPLETE RESPONSE to resolve the safety concern relating to providing a simpler, more feasible means, in addition to shower skin washing of the application site prior to physical contact, to prevent testosterone transfer to others. The current information provided by the Sponsor in this COMPLETE RESPONSE demonstrates that the now recommended 2 site application method for AndroGel 1.62% 60.75 mg of testosterone (3.75 gm) (both upper arms/shoulders) and 81 mg of testosterone (5.0 gm) (both upper arms/shoulders) when applied to the male in association with a t-shirt barrier adequately mitigates testosterone transfer to the female partner. In addition, the Sponsor has demonstrated that this new method of application of AndroGel 1.62% has comparable exposure when applied as directed in hypogonadal males as compared to the application regimen used in the pivotal Phase 3 study.

The Sponsor has also efficacy results from the Study S176.3.104 Open-Label Safety Extension (b) (4)

Regarding efficacy, Dr. Wiederhorn further concluded:

- *“This NDA submission has provided substantial evidence from an adequate and well-controlled pivotal study showing that testosterone gel 1.62% will have the effect claimed in labeling.* (b) (4)

AndroGel 1.62% was efficacious in achieving its primary endpoint and 2 of three of three critical secondary efficacy endpoints. With respect to the third secondary efficacy endpoint (Cmax >2500 ng/dL in none of the subjects), the ten subjects who had testosterone concentrations outside the desired range were individually analyzed. In 5 of these cases, sample contamination or artifact was concluded. In 1 case, the subject was “over compliant” with study medication. In the other 4 cases, 2 may have been associated with overdosage and 1 with sample contamination. Overall, I did not feel the sporadic testosterone elevations in these 4 subjects present a safety risk. Four daily doses of AndroGel 1.62% were evaluated: 20.25 mg of testosterone (1.25 gm gel); 40.5 mg of testosterone (2.5 gm gel [the starting dose]); 60.75 mg of testosterone (3.75 gm gel); and 81 mg of testosterone (5 gm gel). Titration of dose is based upon trough serum testosterone concentrations on Days 14 and 28 after starting therapy. All 4 doses could be utilized by a patient.”

- *“The primary efficacy variable for Study S176.3.104 was the percentage of subjects with total testosterone Cavg within the normal range on Day 112. Cavg results were required to fall within the normal range of 300-1000 ng/dL, with success being defined as $\geq 75\%$ of subjects on active treatment within the normal serum testosterone concentration range (300-1000ng/dL) and the lower bound of the 95% CI was to be not less than 65% based on the Day 112 results. On Day 112, 81.6% of subjects on testosterone treatment (95% CI of 75.1% -87.0%) had Cavg values within the target range, which met the criteria for efficacy.”*

Dr. Wiederhorn also concluded that the results from Study S176.1.007 (Study 007) support the comparability of exposure between the Phase 3 recommended “rotating method” and the to-be-approved “arms/shoulders-only” method, stating:

- *The data from this study show that arm/shoulders and a “rotating schedule” (3 days abdomen than 4 days arms/shoulders) provide comparable exposure.*

(b) (4)

Dr. Wiederhorn stated:

- *On Day 364 in Study S176.3.104 in the Continuing Active testosterone treatment group (364 days of AndroGel 1.62% use) 77.9% of subjects in the Full Analysis (FA) sample had Cavg values within the target eugonadal total testosterone target range of 300-1000 ng/dL. The lower bound of the bound of the 95% CI was 70.0%.*
- *In the FA sample of the Continuing Active testosterone treatment group, 93.8 % (258/275) of Cmax observations were < 1500 ng/dL when considering the PK Days 266 and 364 combined. Analyzed for each PK day, the percentage of patients on Continuing Active testosterone treatment with Cmax values < 1500 ng/dL was 94.2% (131/139) on Day 266 and 93.4% (127/136) on Day 364.*
- *Overall 3.3% (9/275) of Cmax observations were in the range of 1800-2500 ng/dL when considering both PK Days combined. Analyzed for each PK day, the percentage of subjects on testosterone with Cmax values from 1800-2500 ng/dL was 3.6% (5/139) on Day 266 and 2.9% (4/136) on Day 364.*
- *There were no patients at any time who achieved a Cmax >2500 ng/dL of total testosterone at any timepoint in the Open-Label Period.*
- *Therefore, AndroGel 1.62% in once a day doses of 1.25 g, 2.5 g, 3.75 g, and 5 g (determined by titration) was found to be efficacious in the treatment of male hypogonadism as measured by the Primary Endpoint in the Placebo-Controlled and Open-Label Periods. All of three critical secondary endpoints were achieved in the Open-Label Period.*

(b) (4)

Regarding safety, Dr. Wiederhorn further concluded:

- *Testosterone gel 1.62% has been shown to be generally safe for its intended use as recommended in the labeling by all tests reasonably applicable to assessment of safety. The pattern of adverse events is similar to other drugs in class. The most*

common adverse events (2% greater than placebo) were: increased PSA, upper respiratory infection, back pain, headache, insomnia, hypertension, contact dermatitis, diarrhea, nasopharyngitis, and myalgia. Important safety concerns that were addressed during the review were sporadically high testosterone concentrations and transfer risk. The sporadically high testosterone concentrations are few, of short duration, and only modestly above the pre-determined limits. Further, these few, brief elevations were not associated with an increased risk of adverse event occurrence. It is also of note that in the 182 Day Safety Extension, no subject had a testosterone concentration > 2500 ng/dL. Transfer risk has been appropriately mitigated as shown in Studies S176.1.009 and S176.1.011.

Relevant to the transfer risk and the new arms/shoulders-only method of application, Dr. Wiederhorn made the following statements concerning Study S176.1.011:

- *The Sponsor concludes:*
 - *Transfer of testosterone to female subjects was prevented with a t-shirt barrier when males applied the highest clinical dose of 5 g testosterone gel 1.62% to the upper arms and shoulders.*
 - *C_{avg}, AUC₀₋₂₄, and C_{max} were similar between Day 1 and Day -1, and the 90% and 95% confidence intervals of the Day1/Day-1 ratio was within 90 to 125% for all parameters.*
 - *All testosterone concentrations at baseline and after skin contact were in the normal range for females (0-90 ng/ml).*
- *Reviewer's Comments: I agree with Sponsor's conclusions. The potential transfer of testosterone was effectively mitigated by a t-shirt in this study.*

3. CMC/Device

The Chemistry Review team, Hitesh Shroff and Moo Jong Rhee, made the following recommendation in their final review dated April 20, 2011:

“Based on 1) sufficient CMC information provide to assure the identity, strength, purity, and quality of the drug product; 2) “Acceptable” cGMP compliance of all facilities; and 3) adequate CMC labels/labeling information, CMC Review #2 made a recommendation of approval of this NDA.

In order to comply with the new labeling approach for the testosterone pump products, the CMC information on the label and labeling were revised and re-submitted via emails. These changes of the labels and labeling are deemed satisfactory, making the previous “Approval” recommendation from the CMC perspective still effective”

The CMC review contained the following items of note:

- *All labels and labeling are deemed adequate from the CMC perspective.*
- *Revised container and carton labeling received from Sponsor on April 7, 2011 are acceptable.*

- *The use of the descriptor “1.62%” next to “AndroGel” is acceptable.*
- *The Microbiology team believed that the acceptance criteria for the microbiological quality of the drug product should be listed in the drug specifications in the NDA itself, accompanied by a statement that while this is not a routine stability test, the drug product will comply with the acceptance criteria if tested at anytime during the shelf-life. This request was accepted by Sponsor on November 25, 2009 and this specific specification was included in the NDA.*

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Reviewers, Jeffrey Bray and Lynnda Reid, made the following recommendation in their final review dated February 1, 2011:

“Nonclinical data support Approval of AndroGel 1.62% solution for topical testosterone replacement in hypogonadal men.”

There were no recommendations for additional nonclinical studies. Class labeling was deemed appropriate. Several minor changes were recommended to the nonclinical labeling sections, and these were fully accepted by Sponsor. PharmTox formally concurred with final labeling on April 28, 2011.

5. Clinical Pharmacology/Biopharmaceutics

A final review from the Clinical Pharmacology (ClinPharm) review team of Hyunjin Kim, Myong-Jin Kim, and Dennis Bashaw was received on April 25, 2011. The following section of this memo provides recommendations and comments from the ClinPharm review.

Clinical Pharmacology made the following recommendation:

*“The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology find the clinical pharmacology information submitted in NDA 022309 **acceptable** provided an agreement is reached between sponsor and Division regarding the language in the package insert.”*

On April 25, 2011, the Sponsor submitted revised labeling that was deemed acceptable by the ClinPharm review team. On April 28, 2011, ClinPharm provided formal agreement to the final labeling.

Clinical Pharmacology also pointed out that a Post-Marketing Requirement study was agreed upon between Division and Sponsor. This will be a “hand-washing” study to determine the amount of testosterone left on a user’s hands before and after hand-washing. Although a protocol for this study was submitted in CR, the final protocol would be submitted by July 2011, with the study completed by October 2011 and the final study report submitted by July 2012.

In their “*Summary of Important Clinical Pharmacology and Biopharmaceutics Findings*”, ClinPharm stated:

- *“The Sponsor has provided adequate evidence to justify the safety and efficacy of the drug would remain unchanged under the proposed new application method.*
- *The proposed revision to the application instruction for Androgel (T gel 1.62%) required the application of the gel to upper arms/shoulders.*
- *The new application method:*
 - *mitigated transfer of T to the non-dosed females.*
 - *demonstrated the compatible exposure of total T by the application method used in the phase 3 study.*
 - *Demonstrated the compatible skin irritation potential by the application method used in the phase 3 study.”*

In regard to the arms/shoulders application method, the ClinPharm review team had the following summary comments:

- Regarding transferability: Study S176.1.011 (submitted with this CR) demonstrated that transferability by application of the product to the upper arms/shoulders while covering the application sites with T-shirts was not significant (increase of total T Cavg by 6-11%)
- Regarding exposure comparison: Study S176.1.007 (submitted in the original NDA) demonstrated that the new application method (upper arms/shoulders for 7 days) was bioequivalent to the application method used in the pivotal phase 3 study (abdomen for 3 days and upper arms/shoulders for 4 days).
- Regarding skin irritation potential: Skin irritation potential from the new application method (upper arms/shoulders for 7 days) was found compatible to the application method used in the pivotal phase 3 study (abdomen for 3 days and upper arms/shoulders for 4 days). The ClinPharm reviewer referred to the reader to the Medical Officer’s review for details.

(b) (4)

- The efficacy of AndroGel 1.62% was established in the original review based on the pivotal Phase 3 clinical study, S176.3.104, which had a duration of 182 days. The current submission included efficacy data from the open-label, extension period from days 183-364 in the same study.
- On Days 266 and 364, the proportion of responders for the Continuing Active Androgel 1.62% group was 78.4% and 77.9%, suggesting the long-term efficacy of AndroGel 1.62% up to 1 year.

6. Clinical Microbiology

The Microbiology review team, Robert Mello and Bryan Riley, made the following recommendation in their final review dated October 29, 2009:

“Recommend Approval”

While the review states there are no microbiology deficiencies, there was a single comment to be conveyed to Sponsor:

“It is acceptable to omit microbial limits testing for routine drug product release and stability testing. Nonetheless, the acceptance criteria for the microbiological quality of the drug product should be listed in Table 2 and Table 3, respectively, of the NDA submission Section 3.2.P.5.1, along with a statement that the drug product will comply with the acceptance criteria if tested at anytime during its shelf-life.”

On November 25, 2009, the Sponsor added the requested specification to the NDA table and provided assurance that this specification would be met if at anytime the product was tested during the shelf-life.

Of note:

- The drug product is (b) (4) and is packaged in a pump system.
- The drug product is formulated using ethyl alcohol to a final absolute alcohol concentration of (b) (4)
- (b) (4)
- Microbial limits testing is not needed for routine commercial release and stability, although a microbial limits specification has been added to the NDA and the product will be produced to meet this specification if it is tested at anytime during shelf-life.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

Clinical data submitted in the original NDA included a single phase 3 safety and efficacy trial (Study S176.3.104), and nine Phase 1 studies, including:

- single, and multiple-dose PK studies (Studies 001 and 002),
- a study to assess transfer in non-dosed females from the abdomen (Study 003),
- a study to assess skin sensitization and skin irritation of the product (Study 004),
- a study to assess the effect of skin washing on systemic exposure (Study 005),
- a study to assess the effect of concomitant moisturizer and sunscreen on systemic exposure (Study 006),
- a study to assess the effect of differing skin application sites on systemic exposure (Study 007),
- a study to assess the effect of skin washing on transfer in non-dosed females (Study 008),
- a study to assess the effect on transfer to non-dosed females of spreading 5 gm out onto both arms/shoulders and both sides of the abdomen (Study 009)

Clinical data submitted in the CR included a final, revised, complete study report for Study 104, and two Phase 1 studies:

- a study to assess the comparability of exposure between the “4-site” application method and the Phase 3, “rotating” method (Study 010)
- a study to assess transfer in non-dosed females from the arms/shoulders (Study 011)

The clinical efficacy data for this NDA comes from the single, Phase 3 Study 104. Therefore, this study is described in detail herein. The clinical information submitted with the CR is also summarized in this section, but follows the more detailed description of Study 104.

Study S165.3.104 Design, Procedures and Efficacy Results

Study S176.3.104 was a multi-center (53 investigative sites, all in the United States), randomized, double-blind, placebo-controlled study of testosterone gel 1.62% for the treatment of hypogonadism in adult males. A pump was used to dispense 1.25 of 1.62% testosterone gel per actuation.

The key eligibility criteria in the Phase 3 study were:

Inclusion Criteria

- Males, 18-80 years of age.
- Primary (hypergonadotrophic) hypogonadism (congenital or acquired) - e. g., testicular failure due to cryptorchidism, bilateral testicular torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals or:
- Secondary (hypogonadotropic) hypogonadism (congenital or acquired) - e. g., idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma or radiation.
- Average serum testosterone concentration of <300 ng/dL determined from two laboratory specimens collected at the same a.m. visit.
- Naïve to androgen replacement; or has undergone washout of 12 weeks following intramuscular androgen injections, four weeks following topical or buccal androgens, or 3 weeks following oral androgens.
- Intact skin surfaces at the gel application sites.
- No significant medical conditions that would be adversely impacted by testosterone replacement.

Exclusion Criteria

- Low serum testosterone concentrations secondary to causes other than primary or secondary hypogonadism.
- Previous history of, current, or suspected prostate or breast cancer
- International Prostate Symptom Score >15 points.
- Abnormal finding on digital rectal examination of the prostate.
- PSA > 2.5 ng/mL, or 2.6-3.74 ng/mL without a negative biopsy within the past 6 months.
- Body Mass Index (BMI) < 18 or > 40 kg/m².
- Untreated prolactinoma.
- Currently seeking fertility or seeking fertility within one year of trial participation.
- Poorly controlled diabetes.
- History of Human Immunodeficiency Virus (HIV) infection.
- History, current, or suspected, obstructive sleep apnea.

- Findings of any kind of skin lesions on the surface of the application site during the physical examination (small tattoos acceptable).
- Generalized skin disease that may affect absorption of investigational gel (e. g., psoriasis or eczema).
- Clinically significant co-morbid conditions that would interfere with the subject's participation or compromise the subject's safety.
- History of heart failure (New York Heart Association [NYHA] Class III or greater).
- Known skin intolerance to alcohol or allergy to any of the ingredients of the product.
- Sitting systolic blood pressure (SBP) >160 mmHg or <90 mmHg, or sitting diastolic blood pressure (DBP) > 100 mmHg or <60 mmHg.
- Hemoglobin (HGB) >16.0 g/dL, hematocrit (Hct) >48%
- Serum hepatic transaminases >2X ULN.
- Using any over-the-counter (OTC) steroid preparations or derivatives (e.g., dehydroepiandrosterone [DHEA]).

Eligible subjects were randomized to receive active treatment or placebo. The pivotal portion of the study utilized four active testosterone gel 1.62% doses (1.25g, 2.50g, 3.75 g and 5.00g) and placebo administered over a period of 182 days. 274 subjects (testosterone gel 1.62%: 234 subjects, placebo: 40 subjects) were randomized; 206 subjects (testosterone gel 1.62%: 179; placebo 27 subjects) had data for the primary timepoint Day 112 and were analyzed for efficacy. All eligible subjects were started at a dose of 2.50 g testosterone gel 1.62% or matching placebo on Day 1 of the study. Subjects returned to the clinic at Day 14 (Week 2), Day 28 (Week 4), and Day 42 (Week 6) for pre-dose (trough) serum total testosterone assessments. Within two days of each of these visits, the subject's dose was titrated up or down in 1.25 g increments, if necessary, based on the results of the single C_{trough} serum concentration and pre-specified criteria (see Table 1 below), by an unblinded Quintiles clinical reviewer. No dose was to be titrated below 1.25 g, or above 5.00 g, during the study. Sham titrations occurred in placebo-treated subjects to maintain blinding. Subjects were maintained at their respective Day 42 (Week 6) dose until Day 182 (Week 26).

Study medication was applied once every morning at 8 AM (+/- two hours) to the skin's surface by the subject on an outpatient basis. The subject was instructed to apply the study medication gel topically once daily to the intact, clean, dry skin of the upper arms/shoulders or abdomen for the duration of the study. Application occurred after showering or bathing and when skin was completely dry. Over any seven-day period, study gel could be rotated between the upper arms/shoulders or abdomen (e.g., four days upper arms/shoulders; three days abdomen) as long as the correct application technique (arms/shoulders only) occurred during PK visits.

During PK visit days, the following application scheme was followed for application to the shoulder/upper arm region; application(s) occurred until subject's respective dose was reached:

- The first 1.25 g was applied to one shoulder and spread across the maximum surface area.
- The second 1.25 g was applied to the opposite shoulder and spread across the maximum surface area without re-applying gel to the previously dosed area.

- The third 1.25 g was applied to one of the upper arms, from the edge of the shoulder region to just above the elbow including the back of the arm. The gel was spread over the maximum surface area without re-applying gel to the previously dosed areas.
- The fourth 1.25 g was applied to the opposite upper arm area as described above without re-applying gel to the previously dosed areas.

On Day 14, Day 56, Day 112 and Day 182, subjects were confined to the clinical site for eight hours of clinical sampling. Blood samples were obtained at pre-dose (before gel application) and at 0.5, 1, 2, 4, 8, 12, and 24 hours after study drug application. Serum testosterone concentrations for 24-hour PK assessments were measured.

After 182 days of treatment, subjects could agree to continue in the open-label, active treatment maintenance phase of the study. The Integrated Clinical Study Report submitted with the original NDA presented data that was collected up to and including Day 182. A Final Integrated Clinical Study Report including data through the end of the Study (Day 364) was included in the 120 day Safety Update. A final, revised Clinical Study Report was submitted in the CR.

Table 1: Pre-specified Testosterone Gel 1.62% Dose Titration Criteria in S176.3.104

Total Testosterone Trough Concentration	Titration Criteria
<350 ng/dL	Increase dose by 1.25 g
>750 ng/dL	Decrease dose by 1.25 g
350-750 ng/dL	Remain on previously dispensed dose

*each pump actuation delivers 1.25 g of testosterone gel 1.62 % (20.25 mg of testosterone)

Table 2 shows the total amount of gel applied based upon the dose.

Table 2: Doses Administered in S176.3.104

Gel Strength	Gel Dose (g)	T Dose (mg) Applied	Number of Pump Actuations
1.62%	1.25	20.25	1
1.62%	2.50	40.5	2
1.62%	3.75	60.75	3
1.62%	5.00	81.0	4

Source: adapted from Table 2, Clinical Study Report S176.3.104, page 25.

The Primary Efficacy Endpoint was the percentage of subjects with serum testosterone Cavg within the normal range of 300-1000 ng/dL at Day 112 (the primary timepoint). Success in the study was defined as $\geq 75\%$ of subjects on active treatment within the normal serum testosterone concentration range of 300-1000 ng/dL. The lower bound of the 95% CI was to be not less than 65% based on the Day 112 PK results for the pivotal phase of the trial.

A Critical Secondary Efficacy Endpoint was to evaluate total testosterone Cmax values during the first 182 Days of the study. The individual total testosterone Cmax values were to be in the following ranges:

- C_{max} ≤1500 ng/dL in ≥85% of the subjects
- C_{max} between 1800-2500 ng/dL in ≤5% of the subjects
- C_{max} >2500 ng/dL in none of the subjects

Secondary efficacy parameters included measurement of SHBG, LH, FSH and selected serum inflammatory and cardiovascular risk markers (TNF- α , IL-6, IL-10, hs-CRP, MMP-9, HDL2, HDL3, d-dimer, fibrinogen, and VCAM), waist to hip ratio, as well as serum markers of bone metabolism (bone –specific alkaline phosphatase and type 1 cross lined C telopeptide), and the SF-36.

7.2 DEMOGRAPHICS

The demographics for the single Phase 3 study are shown in Table 3.

The mean age for the full analysis sample was similar for the testosterone gel 1.62% groups and the placebo group (53.6 versus 55.5years). The mean height, weight (approximately 99 kg) waist-to-hip ratio, body mass index, and sitting SBP, DBP and pulse at baseline were similar between treatment groups. The mean baseline values of serum PSA were similar in the testosterone gel 1.62% group (0.9 ug/L) and the placebo group (0.85 ug/L). There are no patients with the diagnosis of Kallman's Syndrome in the protocol, and only one patient with Klinefelter's syndrome.

Table 3: Patient Demographics in S176.3.104 (Phase 3 Safety Sample)

	Statistic	T-Gel				
		Placebo N=40	1.25 g N=17	2.5g N=60	3.75g N=66	5.0g N=91
Age (years)						
<45	n (%)	8(20.0)	2(11.8)	14(23.3)	8(12.1)	16(17.6)
45-54	n (%)	8(20.0)	8(47.1)	24(40.0)	26(39.4)	32(35.2)
55-64	n (%)	16(40.0)	3(17.6)	11(18.3)	21(31.8)	34(37.4)
≥65	n (%)	8(20.0)	4(23.5)	11(18.3)	11(16.7)	9(9.9)
Ethnicity						
Hispanic/Latino	n (%)	3(7.5)	1(5.9)	6(10.0)	5(7.6)	7(7.7)
Other	n (%)	37(92.5)	16(94.1)	54(90.0)	61(92.4)	84(92.3)
Race						
American Indian or Alaska Native	n (%)	0	1(5.9)	0	2(3.0)	1(1.1)
Asian	n (%)	0	0	2(3.3)	0	5(5.5)
Black	n (%)	2(5.0)	5(29.4)	4(6.7)	9(13.6)	11(12.1)
Hawaiian/Pacific	n (%)	0	0	0	0	0
White	n (%)	38(95.0)	13(76.5)	54(90.0)	55(83.3)	74(81.3)
Other		0	1(5.9)	0	0	0

*some subjects indicated more than one racial background

Source: Clinical Study Report: S176.3.104: Table 2.0.1: page 228

7.3 DISPOSITION OF SUBJECTS

Study S176.3.104 was conducted at 53 sites throughout the United States. The trial enrolled and randomized 274 patients (234 to T-Gel 1.62% and 40 to placebo). Of these 274 patients, 196 completed the 182 day pivotal double-blind period, including 168 taking T-Gel (71.8% of randomized) and 28 taking placebo (70.0% of randomized). The most common last titrated dose was 5.00 gm testosterone gel 1.62%. Similar percentages of placebo and T-Gel patients discontinued from the study groups (see Table 4). The most common AE leading to discontinuation was increased PSA which was pre-specified as a discontinuation criteria and will be discussed separately in the Safety section of this memo.

Table 4: Reasons for Subject Discontinuation from Study S176.3.104

Subjects	Placebo N=40	Total T-Gel N=234
Completed	28 (70.0)	168 (71.8)
Premature Discontinuation	12 (30.0)	66 (28.2)
Reasons for Discontinuation		
Adverse Event	0	25 (9.1)
Lack of Efficacy	0	2 (0.7)
Lost to Follow-up	2 (5.0)	7 (2.6)
Withdrew Consent	8 (20.0)	27 (9.9)
Administrative Reason	1 (2.5)	6 (2.2)
Protocol Violation	1 (2.2)	11 (4.0)

Source: Clinical Study Report S176.3.104 adapted from Table 1.0.0: page 184

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

The primary efficacy parameter was the percentage of subjects with serum testosterone time-averaged concentration (Cavg) over the dosing interval of 24 hours within the normal range of 300-1000 ng/dL at Day 112.

Success in the study was defined as $\geq 75\%$ of subjects on active treatment within the normal serum testosterone concentration range of 300-1000 ng/dL. In addition, the lower bound of the 95% CI was not to be $< 65\%$.

Three patient populations were used in the analysis of efficacy: 1) the Full Analysis (FA) sample consisted of all subjects who were included in the Safety sample and had at least one post-baseline assessment of any efficacy measurement, 2) the Efficacy sample consisted of all subjects included in the FA Sample and had any efficacy data for Day 112 (the primary timepoint), and 3) the Per-Protocol (PP) sample, consisted of all subjects who were included in the FA sample and did not present any major protocol violation. No imputations were made for PK efficacy endpoints. LOCF was used only for the exploratory secondary endpoints.

A total of 274 subjects (testosterone gel 1.62%: 234 subjects, placebo: 40 subjects) were randomized and analyzed for safety. A total of 206 subjects (testosterone gel 1.62%: 179; placebo 27 subjects) were analyzed for efficacy.

7.4.1.1 Primary Efficacy Analysis

On Day 112 (the primary timepoint), of 179 testosterone-taking subjects with pK data for Day 112 (the Efficacy sample), 81.6% (95% CI of 75.1% to 87.0%) had C_{avg} values within the normal concentration range. Table 5 shows the percentage of subjects achieving target testosterone concentrations on Days 14, 56, 112 and 182.

Table 5: Percentage of Patients Achieving Target Testosterone Concentrations in S176.3.104

Study Day	Total T Cavg (ng/dL)	T-Gel n/N (%)	T-Gel 95% CI	Placebo n/N (%)	p-value
14	<300	66/210(31.4)		26/37(70.3)	
	300-1000	138/210(65.7)	(58.9, 72.1)	11/37(29.7)	<0.0001
	>1000	6/210(2.9)		0/37(0.0%)	
56	<300	30/183(16.4)		20/32(62.5)	
	300-1000	151/183(82.5)	(76.2, 87.7)	11/32(34.4)	<0.0001
	>1000	2/183(1.1)		1/32(3.1)	
112	<300	19/179(10.6)		17/27(63.0)	
	300-1000	146/179(81.6)	(75.1, 87.0)	10/27(37.0)	<0.0001
	>1000	14/179(7.8)		0/27(0.0)	
182	<300	24/169(14.2)		20/28(71.4)	
	300-1000	139/169(82.2)	(75.6, 87.7)	8/28(28.6)	<0.0001
	>1000	6/169(3.6)		0/28(0.0)	

Source: Adapted from Clinical Study Report S176.3.104, Table 11.1.3, page 400

Mean C_{avg} values for AndroGel 1.62% and placebo after titration to an optimal dose of treatment are shown graphically in Figure 1. With once daily applications of AndroGel 1.62%, follow-up measurements at 14, 56, 112, and 182 days after starting treatment confirmed that mean serum testosterone concentrations were maintained within the eugonadal range. AndroGel 1.62% dose titration produced average ($\pm$ SD) daily testosterone concentration of 561 ($\pm$ 259) ng/dL on Day 112 (n= 179), and 536 ($\pm$ 236) ng/dL on Day 182 (n= 169).

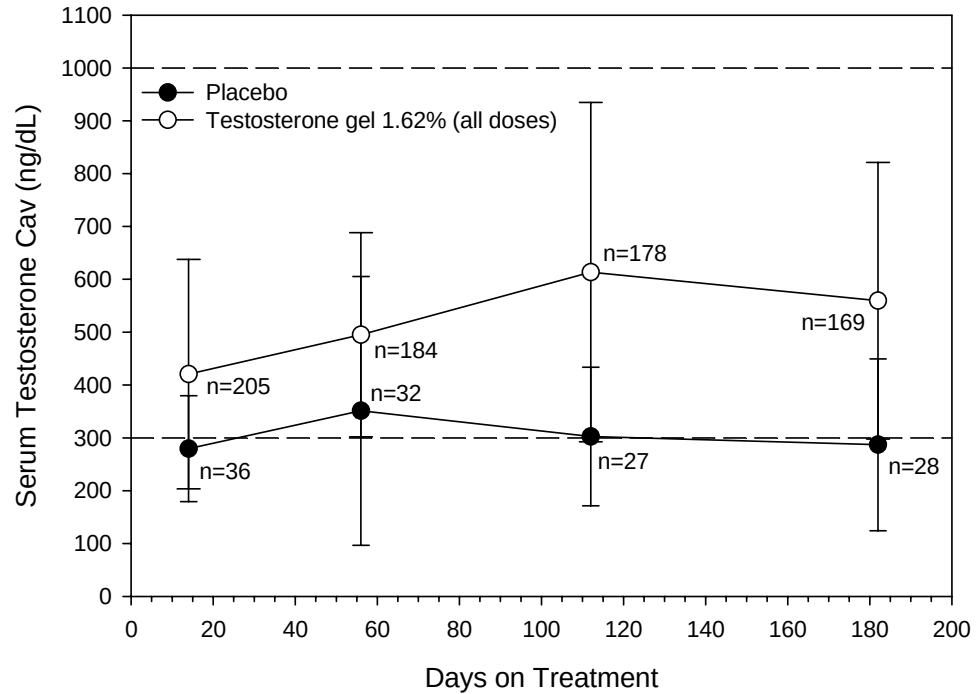


Figure 1: Mean (SD) Steady-State Testosterone C_{avg} Values in Patients on Once-Daily AndroGel 1.62% Therapy in S176.3.104

Notes for the Figure:

- SD = standard deviation.
- Patients treated with AndroGel 1.62% were all on a 2.5 g dose on Day 14, and were on 1.25, 2.5, 3.75, or 5 g doses on other days depending on individualized dose titration.
- Horizontal dashed lines represent the lower and upper limits of the testosterone concentration normal range (300-1000 ng/dL).

Statistician's Conclusion

In his final review of the original NDA, dated November 4, 2009, the Statistical Reviewer, Mahboob Sobhan, had the following conclusion:

“The results support the efficacy of T-Gel 1.62% in providing adequate testosterone replacement therapy (as shown by C_{avg} in the normal range in more than 81% of patients without exceeding C_{max} values >1500 ng/dL in more than 85% of the patients) in hypogonadal men.

From a statistical perspective, the efficacy data provided in this application do support the efficacy of T-Gel 1.62% as testosterone replacement therapy.”

The following items of note were in the Statistical review:

- There were no statistical issues in this submission.
- The statistical reviewer verified the sponsor's results using the analyses datasets provided in the submission.
- The efficacy results were descriptive in nature and presented as a percentage of subjects whose C_{avg} is within the normal range of 300-1000ng/dL and the 95% confidence interval about the point estimate.
- Treatment with AndroGel 1.62% provided adequate T replacement in 81% of the hypogonadal men with the lower bound of the 95% confidence interval for the above point estimate not below 65%.
- Approximately 89% of the subject had maximum T concentrations (C_{max}) ≤ 1500 ng/dL.
- A total of 10 subjects (5.6%) had C_{max} values in the range of 1500-2500 ng/dL and 2 subjects (1.1%) had values > 2500 ng/dL, slightly more than the pre-defined threshold. The Sponsor argued that in 9 of the 10 relevant subjects, such sporadic observations were made on one occasion on 1 PK day and resolved during the treatment period and therefore, had no impact on the overall testosterone level at endpoint. The clinical reviewer further investigated these outliers and came to a resolution that it should not affect the primary efficacy.

It should be noted that the statistician's review incorrectly reports that 10 subjects had serum testosterone C_{max} values 1500 - 2500 ng/dL, and 2 had values > 2500 ng/dL. In actuality, 10 subjects had serum testosterone C_{max} values > 2500 ng/dL. Each of these subjects is described individually in the next section of this memo.

In his final review of the CR dated April 26, 2011, Dr. Sobhan had the following conclusion:

“...the efficacy data provided in the application do support the efficacy of Testosterone gel 1.62% as testosterone replacement therapy for up to one year.”

(b) (4) He stated that the results in the primary (protocol-defined) Full Analyses (FA) sample clearly met the approval criteria. In that group, which was defined as having baseline serum T data at Day 182 and endpoint serum T data at Day 364, 106 of 139 patients (77.9%) of patients had a C_{avg} in the normal range. The 95% CI was 70.0% and 84.6%. A total of 127/136 FA patients (93.4%) had $C_{max} < 1500$ ng/dL, 4/136 (2.9%) had C_{max} of 1800 – 2500 ng/dL, and none had $C_{max} > 2500$ ng/dL. These results meet the pre-defined measures of success.

Dr. Sobhan pointed out that the Per Protocol (PP) sample was smaller than the FA group, containing a total of 71 patients. The reason for the loss of patients from FA to PP samples was the strict manner in which PP was defined, requiring that

- serum T at baseline of the OL period be < 300 ng/dL
- compliance be 80 – 120%, and
- all serum T samples be taken within the pre-specified time windows.

These were considered “protocol violators” as per the definition in the statistical analysis plan. Dr. Sobhan refers to “50% protocol violators” However, the extent of the actual patient drop out from Day 182 (n=219) to Day 364 (n=139) was approximately 35-40% and was largely due to the adverse event of “increased PSA”, a consequence of the very strict definition of increased PSA used in this protocol and requiring study discontinuation. Premature discontinuations due to loss of efficacy were few.

The efficacy results in the per-protocol population were consistent with the results in the FA population. In the PP group, 54 of 71 patients (76.1%) of patients had a C_{avg} in the normal range. The 95% CI was 64.5% and 85.4%. A total of 66/71 FA patients (93%) had $C_{max} < 1500$ ng/dL, 1/71 (1.4%) had C_{max} of 1800 – 2500 ng/dL, and none had $C_{max} > 2500$ ng/dL. Other than the lower bound of the C_{avg} confidence interval being just slightly below 65% (it was 64.5%), and this likely due to the smaller number of patients included in the PP sample, these results meet the pre-defined measures of success.

7.4.1.2 Secondary Efficacy Analyses

During the double-blind phase of the protocol (first 182 days), a critical secondary endpoint was to evaluate total testosterone C_{max} . The individual total testosterone C_{max} values were to be in the following ranges:

- $C_{max} \leq 1500$ ng/dL in $\geq 85\%$ of the subjects
- C_{max} between 1800-2500 ng/dL in $\leq 5\%$ of the subjects
- $C_{max} > 2500$ ng/dL in none of the subjects

For the first criterion, in the FA sample, $\geq 88.8\%$ of subjects on testosterone treatment had C_{max} values ≤ 1500 ng/dL. This results meets the first requirement. By individual PK days:

- On Day 14, 3.3% of subjects had a serum testosterone level > 1500 ng/dL.
- On Day 56, 2.7% of subjects had a serum testosterone level > 1500 ng/dL.
- On Day 112, 11.2% of subjects had a serum testosterone level > 1500 ng/dL.
- On Day 182, 8.3% of subjects had a serum testosterone level > 1500 ng/dL.

For the second criterion, in the FA Sample, 3.0% (22/741) of all C_{max} observations were in the range of 1800-2500 ng/dL, when considering the four PK days combined. By individual PK day, the percentage of subjects on testosterone treatment with C_{max} values from 1800 - 2500 ng/dL was:

- 4/175 (2.3%) on Day 14,
- 1/165 (0.6%) on Day 56,
- 10/179 (5.5%) on Day 112, and

- 6/165 (3.6%) on Day 182.

For the third criterion, there were to be no subjects with a C_{max} for serum testosterone >2500 ng/dL. However, within the 182 day double-blind period there actually 10 subjects with C_{max} > 2500 ng/dL. Each of these 10 outlier cases was reviewed in great detail by the Sponsor and in the primary medical officer's review. Herein, the reader is provided with a narrative summary and reviewer's comment for each of these patients:

1) Subject 003-008: The patient is 52 years old. The subject had a testosterone concentration of 3270 ng/dL at Baseline (assessed via LC-MS/MS at (b) (4)) prior to any scheduled drug administration. This subject's Baseline total testosterone concentration was re-assessed by RIA a (b) (4) and was found to be 631 ng/dL, markedly lower than the (b) (4) result. The subject's C_{avg} on Day 56 was 271 ng/dL and on Day 182 was 345 ng/dL. The subject's highest serum testosterone level during the 4 PK days was 915 ng/dL. The DHT/T ratio at the time of elevation was 0.006 which is non-physiologic and indicative of artifact or contamination.

Reviewer's Comment: This case is excluded from further consideration on the basis of blood sample contamination or artifact. In addition, the sample of relevance was actually a Baseline sample, prior to any study drug administration.

2) Subject 039-009: The patient is a 65 year old male. This patient had a single occurrence of a testosterone concentration of >2500 ng/dL of 3750 ng/dL at 1 hour Post dose on Day 56 while taking a dose of 5 g of testosterone gel 1.62%. The serum testosterone concentrations at 0.5 hours and 2 hours Post dose were 184 and 343 ng/dL respectively. The C_{avg} for Day 182 was 497 ng/dL and for Day 112 was 614 ng/dL. The precipitous drop in serum testosterone from 1 hour to the 2 hour time point (change of 3407 ng/dL) is not consistent with the testosterone half-life identified in previous work.

Reviewer's Comment: This case is excluded from further consideration on the basis of blood sample contamination or artifact. It is unlikely that the 1 hr serum T concentration could be 3750ng/dL when the 0.5 hour and 2 hour serum T concentration were 184 and 343 ng/dL, respectively.

3) Subject 012-008: The patient is a 58 year old male. The subject had a single occurrence of a testosterone concentration >2500 ng/dL of 4430 ng/dL at 2 hours Post dose on Day 182 while on a dose of 5 gm of testosterone gel 1.62% . At 1-hour post- dose and 6 hours post-dose samples concentrations were 771 ng/dL and 641 ng/dL, respectively. It is of note that on Day 56, the patient had testosterone concentrations of 1080 ng/dL at 4 hours Post dose, 1810 ng/dL at 8 hours Post dose, and 1030 ng/dL at 24 hours Post dose. On Day 112, testosterone concentrations were reported as 1230 ng/dL at 0.5 hours Post dose, 1050 ng/dL at 1 hour Post dose, 1440 ng/dL at 2 hours Post dose, 1310 ng/dL at 4 hours post dose, 1740 ng/dL at 8 hours Post dose, and 1200 ng/dL at 24 hours Post dose. C_{avg} on Days 112 and 182 were 1160 and 927 ng/mL, respectively. The subject was diagnosed with prostate cancer in the Open-Label period.

Reviewer's Comment: This subject had testosterone concentration of 4430 ng/dL an Day 182 bracketed by 2 eugonadal testosterone concentrations at 1 hour and 4 hours post dose. This case is excluded from further consideration/analysis on the basis of blood sample contamination or artifact.

4) Subject 005-028: The patient is a 46 year old male. The subject had a testosterone concentration of 3867 ng/dL at Day 28, a non- PK day (as assessed by RIA at (b) (4)), while assigned to a testosterone gel 1.62% dose of 3.75 g/day. The subject's total testosterone concentration assessed via LC-MS/MS

at (b) (4) on Day 28 was 1030 ng/dL. This was a predose sample. At Day 112 and Day 182 the C_{avg} was 595 and 440 ng/dL respectively. At Day 14, the testosterone gel 1.62% dose was reduced to 1.25 g/day. On PK day other than Day 14, the only value above 1000 ng/dL was 1130 ng/dL 0.5 hours Post dose on Day 56.

Reviewer's Comment: This case is excluded from further consideration on the basis of blood sample contamination or artifact. The RIA and LCMS assay results differed significantly for the same sample. The subject had no other significant T values.

5) Subject 044-005: The patient is 47 year old male. The subject had a testosterone concentration of 2850 ng/dL (LC-MS/MS at (b) (4)) at Predose on Day 14 while assigned to a 3.75 g dose of testosterone gel 1.62%. The subject's testosterone concentration on Day 14 assessed by RIA at (b) (4) was 1363 ng/dL. On Day 14, the testosterone concentrations at 0.5 hours Post dose were 1100 ng/dL, at 1 hour Post dose 725 ng/dL. The ratio of DHT/testosterone at Predose was 0.0677. The subject was titrated down to a dose of 1.25 g testosterone gel 1.62% on Days 56 and 182. The patient's C_{av} on Days 56 and 182 were 228 ng/dL and 320 ng/dL respectively. It is of note that on PK Days 112 and 56, the highest testosterone concentrations (for that day) occurred predose at approximately 6:30 am and were 424 and 527 ng/dL respectively.

Reviewer's Comment: This case is excluded from further consideration on the basis of blood sample contamination or artifact. The RIA and LCMS assay results differed significantly for the same sample. The other samples assayed on that same day were acceptable. The patient had no other significant T values.

6) Subject 007-006: The patient is a 41 year old male. At 8 hours Post dose on Day 112 while on a dose of 5.00 g of testosterone gel 1.62% the serum testosterone concentration was 2550 ng/dL. On Day 112 the Predose, 4 hour, and 12 hour testosterone concentrations were 268 ng/dL, 881 ng/dL, and 1760 ng/dL respectively. On Day 112, the C_{avg} was 1160 ng/dL and at Day 182 it was 772 ng/dL.

Reviewer's Comment: Comments on this particular case are provided below.

7) Subject 058-006: The patient is a 62 year old male. While on dose of 5.0 g testosterone gel 1.62%, on Day 112, a testosterone concentration of 2510 ng/dL was reported 2 hours Post dose. The Predose, 0.5 hour, 1 hour, and 4 hour testosterone concentrations were 1300, 1910, "cancelled", and 764 ng/dL respectively. The C_{avg} on Day 182 was 599 ng/dL and on Day 112, it was 801 ng/dL.

Reviewer's Comment: The hour 2 sample on Day 112 is higher than the hour 4 sample. The 1 hour sample was "cancelled". Additional comments on this particular case are provided below.

8) Subject 067-001: The patient is a 49 year old male. On Day 112 while on a 3.75 g daily dose of testosterone gel 1.62%, a Predose testosterone concentration of 2730 ng/mL was reported. The testosterone concentrations on the same day at other time points were:

Table 6: Subject 067-001 Testosterone Concentrations (ng/dL) in S176.3.104

Time	Day 56	Day 112	Day 182
Predose	562	2730	356
0.5 h	1220	1810	311
1h	866	1770	814
2 h	1440	1700	514

4 h	405	988	629
8 h	432	1600	739
12 h	473	2420	406
24h	360	846	237

The C_{avg} was 464 ng/dL on Day 182 and 519 ng/dL on Day 56. Both of these days were times where dose compliance was being recorded. The patient's compliance history is as follows:

- Visit 3 (Day 14) Compliance-108%
- Visit 4 (Day 28) Compliance-77%
- Visit 5 (Day 42) Compliance-86%
- Visit 6 (Day 56) Compliance-84%
- Visit 7 (Day 84) Compliance-114%
- Visit 8 (Day 112) Compliance 119% (Visit where testosterone was noted >2500 ng/dL)
- Visit 9 (Day 146) Compliance-126%
- Visit 10 Compliance-98%.

Reviewer's Comment: The elevated testosterone concentrations might be secondary to the patient using more than the prescribed amount of testosterone gel 1.62%. This case will not be evaluated further. There is no indication in narrative as to whether this was voluntary non-compliance, as opposed to other causes such as dispensing device malfunction, lack of proper instruction, etc.

9) **Subject 015-005:** The patient is a 57 year old male. On Day 14, while on a testosterone gel 1.62% dose of 2.5 g, the Predose testosterone concentration was 3290 ng/dL. The testosterone concentrations on Day 14 are shown below:

Table 7: Subject 015-005 Testosterone Concentrations (ng/dL) in S176.3.104

Time	Day 14 Testosterone (ng/mL)
Predose	3290
0.5 h	1880
1h	2000
2 h	1890
4 h	1370
8 h	1050
12 h	148
24h	207

Source: Listing 40, S176.3.104

On Days 56, 112 and 118 while on testosterone gel 1.62% 3.75 g, despite the increased dose compared to Day 14, the testosterone concentrations were in the eugonadal range except for a testosterone

concentration of 1040 ng/dL on Day 56 0.5 hours Post dose. The Sponsor suspects that the subject may have dosed with testosterone gel 1.62% prior to coming to the clinic on Day 14. The C_{avg} testosterone concentrations on Day 56 and 182 were 331 and 537 ng/dL, respectively.

Reviewer's Comment: A question of "overcompliance" is raised. Comments on this particular case are provided below.

10) Subject 049-008: The patient is a 71 year old male. This subject had a total of two occurrences of a testosterone concentration >2500 ng/dL on two different study days (Days 14 and 56). The subject was initially titrated down per protocol after Day 14, but later required to be titrated up per protocol after Day 42. On Day 14, while on a dose of testosterone gel 1.62% 2.5 g, at 0.5 hours Post dose the testosterone concentration was 3200 ng/dL. On Day 56, while on a dose of testosterone gel 1.62% 2.5 g, at 0.5 hours Post-dose the testosterone concentration was 2810 ng/dL. Below are the testosterone concentrations for both PK days' timepoints:

Table 8: Subject 049-008 Testosterone Concentrations (ng/dL) in S176.3.104

Time	Day 14 Testosterone	Day 56 Testosterone
Predose	1760	2080
0.5 h	3200	2810
1h	1760	685
2 h	cancelled	494
4 h	1710	416
8 h	985	320
12 h	811	400
24h	456	418

Source: Listing 40, S176.3.104

The C_{avg} for Days 112 and 182 were 925 ng/dL and 322 ng/dL, respectively. The Sponsor states that prior to the Day 56 Visit, the subject noted swimming and applying the study gel afterwards at approximately 15:00 hours. The subject then dosed again at 8:00 am the morning of his Day 56 visit. They suspect that a similar circumstance occurred before the Day 14 Visit (postulated as increased skin hydration and inappropriate interval between gel doses).

Reviewer's Comment: A question of "overcompliance" is raised. Comments on this particular case are provided below.

Taken together, of the ten patients with testosterone concentrations above 2500 ng/dL, 5 were adjudicated as being related to sample contamination or artifact and one (1) had documented "overcompliance"; that is, applying a larger dose than assigned.

In the remaining 4 patients with testosterone concentrations above 2500 ng/dL:

- There was a question of overdosage ("overcompliance") in Subjects 015-005 and 049-008. Of note, these same subjects (015-005 and 049-008) had testosterone concentrations above 2500 ng/dL at baseline or 0.5 hours post dose. Following dosing, their testosterone concentrations actually declined over the next 4 hours. This finding appears to support possible overdosage prior to the blood draw in both cases, as suspected by history.

- Patient 058-006 had a testosterone concentration of 2510 ng/dL at 2 hours post-dose on Day 112. The pre-dose, 1 hour and 4 hour post dose concentrations were 1300, “cancelled”, and 764 ng/dL, which show that the 2 hour sample is higher than the 4 hour sample.
- Subject 007-006 had a testosterone of 2500 ng/dL at 8 hours post dose. The testosterone concentrations at 4 hours and 12 hours were 881 and 1760 ng/dL respectively.

Overall, then, in these subjects, these events were sporadic, isolated, and non-recurrent. There were no concentrations of testosterone >2500 ng/dL in the Open-label period.

In terms of other secondary endpoints, there were only three that were significantly different compared to placebo at Day 182. These were serum LH, serum FSH, and Type 1 Cross-Linked C-Telopeptide. The decreases from baseline in serum LH and serum FSH were expected in the testosterone-treated group. It is of note that there were no differences noted in markers of inflammation, hypercoagulable tendency, lipids, or bone turnover with the exception of Type 1 Cross-Linked C Telopeptide.

Efficacy-Related Information Submitted in the CR

Complete study reports were submitted for two new studies, as follows:

- *Protocol S176.1.010 (Study 010)*: This was a crossover study comparing relative bioavailability of the 4-site and rotating (Phase 3) application methods.

The results of this study were intended to demonstrate comparability of systemic testosterone exposures between the new “4-site” application method (for 5 gm) and the Phase 3, “rotating” method (3 days abdomen and 4 days arms/shoulders). (b) (4)

- *Protocol S176.1.011 (Study 011)*: This was a transfer assessment study, using just the arms/shoulders application site.

The results of this study were intended to show that a simple t-shirt barrier effectively mitigated transfer when using the arms/shoulders-only site (for 5 gm). Based on bioequivalence of the arms/shoulders-only method to the rotating, Phase 3 method, as shown previously in Study 007, the Sponsor believed that the results of this study could support use of the “arms/shoulders-only” application method in labeling. In fact, it is the arms/shoulders-only method which was ultimately determined to be the final labeled method.

(b) (4)

The Division conducted a detailed review of both studies (assessing both dosing pathways) and decided that the better method was the arms/shoulders-only and that only a single method was appropriate

(b) (4) This part of the memo summarizes that data and the rationale that led to our decision.

Study 011 showed convincingly that a t-shirt barrier effectively mitigates transfer when the arms/shoulders-only site is used, as follows:

Twelve couples participated in this transfer assessment study. Pharmacokinetic analyses were conducted only in female subjects. The mean baseline testosterone (Day -1) concentration across all female subjects ranged from 5.9 -63.6 ng/dL over the 24-hour Baseline measurement period. The mean testosterone concentrations across all female subjects on Day 1 (the period following forced contact with dosed males) ranged from 6.8 -74.5 ng/dL across the measurement period. Thus, there was little difference between mean testosterone concentrations at baseline compared to on Day 1 after forced contact separated only by a simple t-shirt. The mean PK parameters for the 12 female subjects at baseline and on Day 1 are summarized below:

Table 9: Summary of PK Parameters for Total Testosterone; N=12 females, in S176.1.011

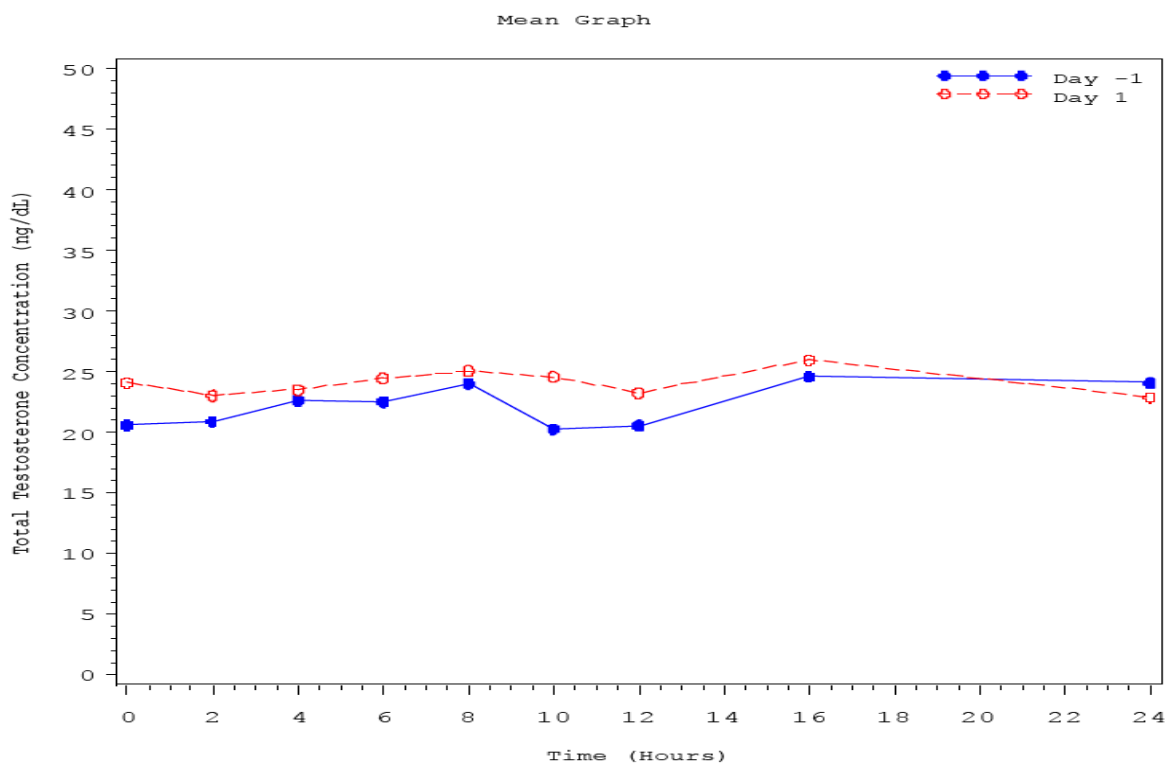
Parameter	Mean± SD		
	Day -1	Day 1	Baseline-adjusted
C _{max} (ng/dL)	26.4±18.1	29.5±20.3	7.6±5.8
C _{avg} (ng/dL)	22.8±16.1	24.2±18.0	1.5±3.2
T _{max} (h)*	16.0 (0.0-24.0)	9.0 (0.0-24.0)	5.0 (0.0-24.0)
AUC ₀₋₂₄ (ng.h/dL)	546.4±387.2	581.4±430.8	35.0±77.7

*Tmax shown as median

Source: Table 7.4.2-1 of S176.1.011 Study Report

The figure below depicts the mean total testosterone concentrations in females in S176.1.011 at Baseline and on Day 1. The figure depicts little difference in exposure between the days.

Figure 2: Mean Female Total Testosterone Concentrations in S176.1.011



Source: Copy Figure 7.4.1.1-1, S176.1.011 Study Report.

The table below provides mean testosterone concentrations for the 12 female participants at Baseline and on Day 1 at each timepoint when blood was sampled. Very little difference is again noted between Baseline and Day 1 at any given timepoint.

Table 10: Female Mean Testosterone Concentrations at Sampling Times in S176.1.011

Sampling Time (hr)		0	2	4	6	8	10	12	16	24	48
		Testosterone Concentrations (ng/dL)									
Female Subjects N=12	Day-1	20.59	20.90	22.64	22.53	24.02	20.27	20.55	24.58	24.08	
	Day 1	24.08	23.04	23.52	24.45	25.06	24.56	23.25	26.00	22.90	27.72

Source: Tables 10.2.1.2 and 10.2.1.1, S176.1.011 Study Report.

Based on this information, both the Clinical Pharmacology and Clinical review teams were of the opinion that a simple t-shirt barrier effectively mitigated transfer in this situation, concluding that when a t-shirt was used to cover the site of application, mean testosterone Cavg and Cmax in female subjects increased by 6% and 11%, respectively, compared to mean baseline testosterone concentrations.

In regard to systemic testosterone concentrations with the arms/shoulders-only method compared to the rotating method of Phase 3, Study 007 provided data from a direct comparison, as follows.

The total T exposure from the arms/shoulders-only application method (treatment “B”: upper arms/shoulder for 7 days) was found to be bioequivalent to the total T exposure from the rotating , Phase 3, application method (treatment “C”; abdomen for 3 days and upper arms/shoulders for 4 days), which was the application method recommended in the pivotal phase 3 study (see Table 11).

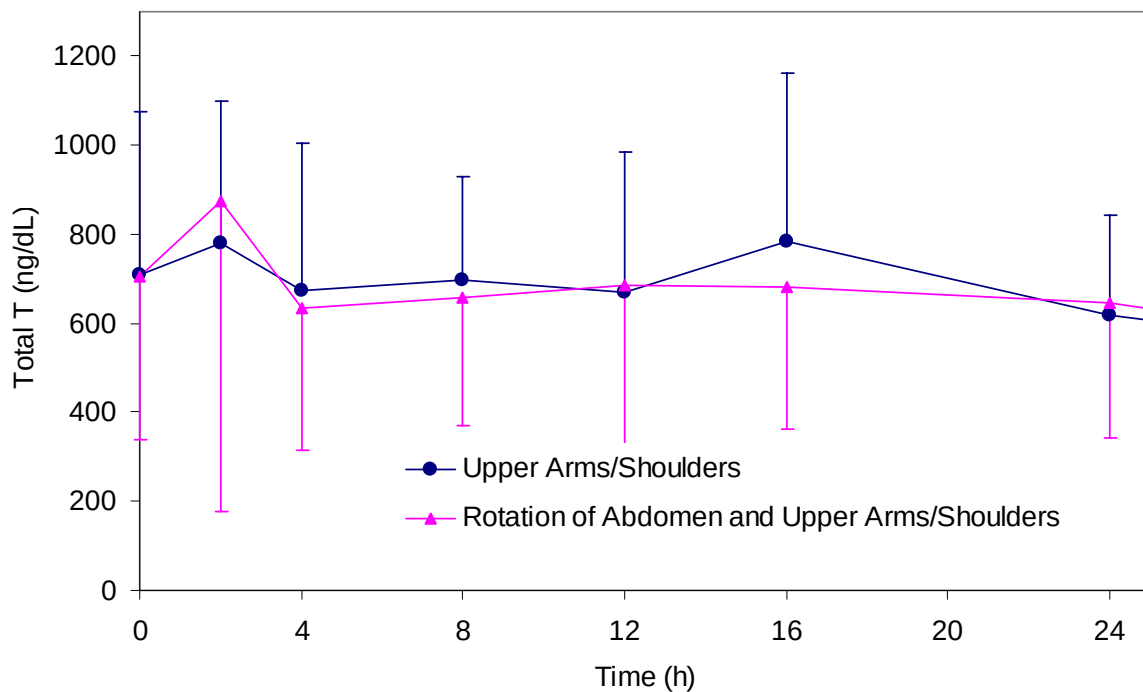
Table 11 : Mean PK Parameters of Total T on Day 7 – Exposure Comparison with Androgel 1.62% 5.0 g; Upper Arms/Shoulders Once Daily for 7 Days vs. Abdomen Once Daily for 3 Days and Upper Arms/Shoulders Once Daily for 4 Days; S176.1.007

	Treatment	N	Geometric mean	Geometric mean ratio (B/C)	90% CI
$C_{\max}$ (ng/dL)	C	33	942	1.06	0.94 – 1.20
	B	33	1000		
AUC_{0-24} (ng·hr/dL)	C	33	15400	1.04	0.95 – 1.14
	B	33	16000		
C_{avg} (ng/dL)	C	33	642	1.04	0.95 – 1.14
	B	33	666		

*Results for treatment A (once daily application of Androgel 1.62% 5.0 g to abdomen for 7 days) are not shown here.

Figure 3 depicts the similarity in total testosterone concentrations between the arms/shoulders-only method and the rotating method in Study 176.1.011.

Figure 3: Mean ($\pm$ SD) Serum Total T Concentrations on Day 7 in Patients Following AndroGel 1.62% Once-Daily Application of 81 mg of Testosterone (N=33) for 7 Days in Study



Finally, the data from Study 007 showed similarity in the irritation potential between arms/shoulders-only and the rotating methods.

Taken together, these data provide strong support for use of the arms/shoulders-only method for AndroGel 1.62%. The Sponsor agreed and the labeled was adjusted accordingly.

In regard to **Study 010**, which contained a comparison of the “4-site method” to the “rotating” method employed in Phase 3, it became clear that the 4-site method actually was associated with lower testosterone concentrations compared to the Phase 3 method. This new application method (treatment “B” in the table below) was associated with 16 to 27% lower total T exposure compared to the Phase 3 application method (treatment “A” in the table below).

Table 12: Statistical Comparison of PK Parameters of Total T on Day 7 – Exposure Comparison with AndroGel 1.62% 5.0 g – Rotating Method (Treatment “A” =Abdomen Once Daily for 3 Days

and Upper Arms/Shoulders Once Daily for 4 Days) versus “4-site’ Method (Treatment “B” = Both Upper Arms/Shoulders and Abdomen Once Daily for 7 Days) in S176.1.010

	Treatment	N	Geometric mean	Geometric mean ratio (B/A)	90% CI
C _{max} (ng/dL)	A	62	1095	0.73	0.66 – 0.81
	B	62	803		
AUC ₀₋₂₄ (ng·hr/dL)	A	62	13459	0.84	0.78 – 0.90
	B	62	11256		
C _{avg} (ng/dL)	A	62	561	0.84	0.78 – 0.90
	B	62	469		

Thus, the “4-site” application method was deemed not acceptable due to the lower T exposure which could lead to lower efficacy.

(b) (4)

The CR contained efficacy data from the open-label period (from Days 183 to 364) of S176.3.104. On Days 266 and 364, the proportion of responders, as defined by C_{avg} within the normal range, for the Continuing Active Androgel 1.62% group, who comprised actively treated for the entire year, was 78.4 and 77.9%, respectively. These results support the efficacy of Androgel 1.62% in patients treated for up to 1 year.

Table 13: Number and Percentage of Subjects Achieving Target Range for T C_{avg} by Day and Treatment in the Full Analysis Sample; Open-Label; S176.3.104

Study Day	Continuing Active Androgel 1.62%		Formerly Placebo		Total	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
266	109/139 (78.4)	(70.6, 84.9)	18/26 (69.2)	(48.2, 85.7)	127/165 (77.0)	(69.8, 83.2)
364	106/136 (77.9)	(70.0, 84.6)	20/23 (87.0)	(66.4, 97.2)	126/159 (79.2)	(72.1, 85.3)

Additional information concerning the percentages of responders using the per-protocol C_{max} definitions may be found in Section 2 of this review, as well as in the Medical Officer’s review and Clinical Pharmacology review of the CR. These data from secondary endpoints support the long-term efficacy of AndroGel 1.62%.

7.4.2 Overall Assessment of Efficacy

AndroGel 1.62%, in once daily doses of 1.25 g, 2.5 g, 3.75 g, and 5 g (determined by titration) was found to be efficacious in the treatment of male hypogonadism as measured by the primary endpoint. Two of three critical secondary endpoints were achieved. The third critical efficacy endpoint, testosterone C_{max} >2500 ng/dL in none of the subjects, was not achieved. The ten subjects not achieving this endpoint were studied carefully, and 5 of these could be eliminated due to sample contamination or artifact, and 1 due to “overcompliance”. In the other 4 cases, overdosage was possible in 2. There was no clear evidence of an adverse

clinical androgen effect related to any of the high testosterone concentrations. Overall, the medical officer and I conclude that these sporadic events do not signal a safety risk, and the product is considered efficacious.

In addition, the CR provided evidence that a t-shirt effectively mitigated transfer when the arms/shoulders-only application method was used (in Study 010). Since the arms/shoulders-only method was found to be bioequivalent to the Phase 3 rotating method (in Study 007), and was comparable for irritation potential, it is deemed acceptable and appropriate for the label to describe the arms/shoulders-only method in the Dosage & Administration data, with PK data from Study 007 included in the label to “link” the efficacy demonstrated in the Phase 3 Study 104 (for the rotating method) to the arms/shoulders-only method.

(b) (4)

8. Safety

8.1 SAFETY FINDINGS

The safety data provided in the original NDA were derived from the Phase 1 transfer, washing and skin irritation studies S176.1.003, S176.1.004, S176.1.008, S176.1.009, the integrated Phase 1 studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and most importantly, the 182 day double-blind period of the Phase 3 Study S176.3.104. The 120-Day Safety Update to the Original NDA contained safety data from the 6-month, open-label extension in Study S176.3.104

The CR contained additional safety data from the Phase 1 studies S176.1.010 (comparative bioavailability) and S176.1.011 (transfer). Postmarketing Safety Updates were also submitted for the Sponsor’s approved and related product AndroGel 1%.

In total, the original NDA contained safety data from 801 subjects exposed to AndroGel 1.62%. In the single Phase 3 Study, S176.3.104, a total of 234 patients were exposed to T-Gel 1.62% for a mean of 151.9 days. A total of 191 subjects participated in the 182-Day Open Label Period with a total of 161 subjects completing that study.

The majority of data on clinical adverse events was derived from the single Phase 3 study and its open-label extension phase.

8.1.1 Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events

No deaths occurred in the Phase 1 integrated studies or in the Phase 3 double-blind protocol. No deaths occurred in the 182-Day Open-Label Period.

In regard to serious adverse events, in the integrated Phase 1 studies, one subject in the 6.25 g dose group had a cardiac disorder reported (atrial fibrillation and supraventricular arrhythmias) and a second subject experienced right lower leg superficial and deep perivasvascular

dermatitis with eosinophilia. Both events were unrelated to the study drug in the investigator's opinion. In both cases, the patients recovered.

A total of 6 serious adverse events (SAEs) were reported in the Double-Blind period of the Phase 3 Study S176.3.104 by five subjects in the testosterone gel 1.62% group and these included (by preferred term): myocardial infarction, tachycardia, back pain, pituitary tumor, radicular pain and malignant hypertension. One subject (Subject 3104-044-003; 3.75 g testosterone gel 1.62%) reported two events: back pain and radicular pain. The clinical investigator considered the malignant hypertension event as "possibly related" (hematocrit was also increased in this patient) although this patient entered the trial was poorly controlled hypertension and an elevated hematocrit. The myocardial infarction was judged to be "unlikely related." A retinal detachment was the only SAE reported by a subject in the placebo group.

A total of 4 SAEs were reported in the 182-Day Open-Label Period. Subject 012-08 experienced prostate cancer on Day 314 and was discontinued. This subject had had a testosterone in excess of 2500 ng/dL in the double-blind study period. A prostate nodule was noted during a study-related digital exam (DRE) and subsequent biopsy diagnosed prostate cancer. This SAE was captured with a start date of Day 314. Subject 013-04 reported non-cardiac chest pain on Day 260 with resolution on Day 261 and completed the study. Subject 033-01 reported atrial fibrillation on Day 197 with recovery on Day 199. He completed the study. Subject 058-02 experienced an acute gastrointestinal hemorrhage on Day 296 with resolution of Day 299. He completed the study.

Overall, in the placebo-controlled, Phase 3 study, 25 of 234 patients treated with testosterone gel 1.62% withdrew due to an adverse event. 0 of 40 placebo patients withdrew due an adverse event. There were no TEAEs leading to study termination due to skin irritation.

The only adverse event leading to discontinuation that occurred in more than one subject in the testosterone gel 1.62% group (18/234, 7.7 % versus no subject in the placebo group) was the event of "*increased PSA*." Most of the subjects who discontinued due to increased PSA, discontinued because they met only the per-protocol criterion of change from baseline $>0.75\text{ng/mL}$. Four other subjects had a PSA value $>4\text{ ng/mL}$, these subjects had $\text{PSA} \leq 4.0\text{ ng/mL}$ upon repeat testing.

In the Open-Label Safety Extension (Day 183-Day 364), 9 patients discontinued secondary to an adverse event. One subject discontinued secondary to the adverse event of prostate cancer and is discussed in narratives of SAEs. Six subjects discontinued due to PSA changes meeting the pre-specified discontinuation criteria. Two subjects discontinued for hematocrit meeting the pre-specified discontinuation criteria.

The reader is referred to the next section (8.1.2 Other Adverse Events) for discussion of specific targeted adverse events, including increased hematocrit, increased serum PSA, prostate cancer, and hypertension. These events were targeted as they have been previously reported for testosterone replacement therapy. This section also includes information

concerning the potential for transfer of testosterone to another individual, a particular concern for testosterone gel products.

8.1.2 Other Adverse Events

Overall Adverse Events

Data from the Phase 3, double-blind study and the integrated Phase 1 studies are presented in the tables that follow. The most common treatment emergent adverse events were: PSA elevations, upper respiratory infections, back pain, headache, insomnia, hypertension, contact dermatitis, diarrhea, nasopharyngitis and myalgia.

In the controlled, Phase 3 study, the most common ($\geq 2\%$ in the testosterone gel 1.62% groups) adverse events by preferred term were: increased PSA (23/234, 9.8% versus no subject), upper respiratory infection (11/234, 4.7% versus no subject), back pain (7/234, 3.0% versus no subject), headache (7/234, 3% versus no subject), insomnia (7/234, 3.0% versus 1/40, 2.5%), hypertension (6/243, 2.6% versus no subject), and diarrhea, nasopharyngitis, myalgia, and dermatitis contact (5/234, 2.1% versus no subject for each PT). The six events of hypertension did not include the event of malignant hypertension.

Pre-specified criteria for abnormal PSA values were set in the protocol (> 4.0 ng/mL and /or change from Baseline > 0.75 ng/mL) for discontinuation of subjects. The incidence of increased PSA across the testosterone gel 1.62% groups was: 1.25 g: 1/17 (5.9%), 2.5 g: 2/60 (3.3%), 3.75 g: 10/66 (15.2%), 5.0 g: 10/91 (11.0%). Across all the testosterone gel 1.62% groups 7/209 (3.3%) subjects had a PSA value > 4.0 ng/mL.

Adverse reactions reported in at least 2% of patients in a treatment group and more frequently in testosterone-treated patients than in placebo-treated patients are shown in the following table.

Table 14: Common Adverse Events ($> 2\%$ for T-gel 1.62% and greater than placebo) for the Double-Blind Phase 3 Study (Safety Population)

SOC Preferred Term	Placebo N=40 n(%)	T-Gel 1.62% N=234 n (%)
Subjects with ≥ 1 TEAE	15(37.5)	130(55.6)
PSA increased	0(0.0)	20(9.8)
Upper Respiratory Infection	0(0.0)	11(4.7)
Back Pain	0(0.0)	7(3.0)
Headache	2(5.0)	7(3.0)
Insomnia	1(2.5)	7(3.0)
Hypertension	0(0.0)	6(2.6)
Dermatitis Contact	0(0.0)	5(2.1)
Diarrhea	0(0.0)	5(2.1)
Nasopharyngitis	0(0.0)	5(2.1)
Myalgia	0(0.0)	5(2.1)

Source: Clinical Study Report S176.3.104, Table 22, page 144.

Of note, there was no pattern of increasing incidence of single preferred terms with higher serum testosterone concentration category (see the medical officer's review).

Skin-related adverse events were very infrequently reported in the Phase 3 study, accounting for <2% of all reported AEs. No patient discontinued the Phase 3 study due to a skin-related adverse event.

In the open-label period, the incidence and categories of AEs reported were comparable to those noted in the double-blind period.

Overall, of the 147 subjects in the integrated Phase 1 studies (as above), 105 subjects (71.4%) experienced at least one AE. The most frequently reported AEs were headache, back pain, myalgias, and skin-related AE. The skin-related AEs were as follows: application site papules (10.9%), application site excoriation (5.4%), application site dermatitis (4.8%), application site erythema (4.8%), dry skin (6.1%) and acne (4.8%). All skin application site –related AEs were mild and did not lead to discontinuation.

Laboratory and vital signs data from the Phase 3 study demonstrated the expected findings for testosterone replacement therapy without unexpected findings:

- In the testosterone-treated groups, 4.8% of patients had a shift in hemoglobin from normal at baseline to high at endpoint versus none for placebo. There was a similar shift for hematocrit, and a total of 5 subjects had hematocrit >54%. One of these subjects discontinued per protocol on Day 86. Four subjects had elevations of hematocrit >54% in the open-label extension and were also discontinued.
- A total of 34 subjects in the Phase 3 controlled study had a serum PSA post-baseline that was >4.0 ng/dL and/or an increase in serum PSA from Baseline >0.75 ng/mL. A total of 7 subjects (3.3%) had a PSA post-baseline >4.0 ng/mL, while 33 subjects (15.8%) had an increase in PSA from baseline > 0.75 ng/mL, and 6/209 subjects (2.9%) met both criteria. A total of 17 subjects discontinued from the study during the double-blind phase due to an AE of “increased PSA.” Four of the subjects who discontinued had maximum PSA levels between 1 and 1.4 ng/mL, while two subjects had maximum PSA levels between 2 and 2.8 ng/mL. Of the remaining subjects with higher PSA levels, four subjects discontinued with PSA >4 ng/mL, but these subjects had PSA ≤4.0 ng/mL upon repeat testing.
- In the double-blind period of the Phase 3 study, there were no clinically meaningful differences between the testosterone gel 1.62% groups compared with the placebo group in mean changes from baseline at any timepoint for any vital sign and no important differences across dose groups were noted in the mean changes from baseline.

Targeted Adverse Events

Based upon the known safety issues for testosterone and testosterone gel, the primary medical officer targeted several areas for special safety review. These included: increased hemoglobin and hematocrit, increased serum PSA/prostate cancer, hypertension, increased serum testosterone levels, problems with compliance using medication, and secondary exposure (referred to as “transfer”) to others. For most of these issues, the reader is referred to the original medical officer’s review on pages 70-73. The transfer issue is described in the original medical officer’s review on page 113 - 118 and again in the medical officer’s CR review.

Briefly, **for the non-transfer issues:**

1) Testosterone is known to stimulate erythropoiesis and can increase hemoglobin and hematocrit. In Study S176.3.104, a modest increase in mean hematocrit was observed overall for the testosterone gel 1.62% groups compared with placebo. Several incidents of “markedly high” hematocrit (defined in the protocol) were reported in subjects who had been receiving study medication for 12 or more weeks, and the majority of the discontinuations due to increased hematocrit occurred in the open-label period of the study. Androgen class labeling instructs prescribers to monitor hemoglobin and hematocrit.

2) Testosterone is known to increase serum PSA. In Study S176.3.104, the mean change from baseline in serum PSA at endpoint was 0.14 ng/mL for the testosterone gel 1.62% group versus -0.12ng/mL for the placebo group. A total of 45 subjects reported PSA values on one occasion or more that met exclusion criteria for discontinuation in Study S176.3.104 (either an increase from baseline of 0.75 ng/mL or a value of > 4ng/mL at any time point): twenty-nine subjects in the double-blind period (0/40 placebo) and 12 subjects in the open-label period. Of these 45 patients, 27 were discontinued. A total of 9 subjects reported a PSA value >4.0 ng/ml (7 in the double-blind and 2 in the open-label periods). PSA results are described in the Adverse Reactions section of the labeling.

3) It is not known whether replacement of T in men with hypogonadism increases the risk of prostate cancer. This potential risk and the need for monitoring of serum PSA and digital rectal examination is shown in androgen class labeling. Prostate cancer occurred in one patient in this program, a 58 year-old subject (012-08). The patient had a past history of BPH and had stopped taking Avodart 26 July 2006. His first dose of testosterone gel 1.62% was (b) (6). At Day 279 a prostatic nodule was palpated and biopsies revealed prostate carcinoma in the side of the prostate contralateral to the nodule. On Day 182, this subject had testosterone concentration of 4430 ng/dL at 2 hours post-dose. His Caverages at Day 112 and 182 were 1160 and 927 ng/dL, respectively. His testosterone concentrations in the Open-Label Period were eugonadal. His PSA at baseline was 1.5 ng/mL, at Day 182 was 1.8 ng/mL, and at Day 279 was 2.3 ng/mL. The increase in PSA was not reported as an AE. The involved portions of the 2 positive biopsy core were described as “1% containing Gleason’s score 3+3 prostate adenocarcinoma.” While this patient may have had higher than average testosterone exposure on Day 182, no statement can be made about causality to his prostate cancer. Nonetheless, the case of prostate cancer is listed in labeling as an adverse reaction occurring in the clinical studies of AndroGel 1.62%.

4) Hypertension is a known potential adverse reaction to testosterone. Testosterone can increase fluid retention and red blood cell mass, potentially increasing blood pressure. A total of 13 subjects experienced the adverse event of “hypertension” while enrolled in Study S176.3.104 versus none in the placebo group: 6 subjects in the double-blind period only, 5 subjects in the open-label period only and 2 subjects in both periods. One of the six subjects in the double-blind period experienced malignant hypertension. This patient had poorly controlled, serious hypertension at baseline. The labeling for AndroGel 1.62% will include the adverse event term hypertension and its incidence of reporting in the controlled trial.

5) Compliance can be a problem in men taking testosterone every day for a lifetime. Compliance can be less than or more than appropriate. In S176.3.104, two patients with serum testosterone levels > 2500 ng/dL may have either used more than the recommended dose of testosterone gel 1.62% or used testosterone gel 1.62% more frequently than once daily. Sponsor has found throughout the testosterone gel 1.62% patient population that approximately 4% exhibited compliance > 80%. (b) (4)

For the transfer issue:

Secondary exposure to testosterone may occur from the product transferring from the user to a child or to another adult. In order to determine the potential for this problem and to assess whether a simple clothing barrier prevents such transfer, the Sponsor conducted several transfer assessment studies, including Study S176.1.003 (Study 003), S176.1.008 (Study 008), S176.1.009 (Study 009), and S176.1.011 (Study 011).

Study S176.1.003 is described in detail in the medical officer’s original NDA review on p113 - 114. This study assessed the transfer potential from male user to female partner when the maximum dose (5 gm) was applied to the abdomen only. The study tested direct skin contact with and without a t-shirt. 16 couples participated. The results of the study showed:

- A doubling of mean serum testosterone in Group A (direct contact at 2 hours).
- Covering the site of application prior to contact in Group B reduced the amount of exposure by 40-48% in the non-dose females compared to Group B; thus, a T-shirt did not effectively prevent transfer of a 5 gm dose when applied to the abdomen only.

Based upon the results of this study, showing lack of effective blockage of transfer by a simple clothing barrier, the Sponsor proceeded to conduct a second transfer study, Study S176.1.008 (Study 008).

Study S176.1.008 is described in detail in the medical officer’s original NDA review on p114 - 118. This study assessed the transfer potential from male user to female partner when half the maximum dose (2.5 gm) was applied to the abdomen only. For the 2.5 gm dose, the study tested direct skin contact with and without a t-shirt (Groups A and B, respectively).

The study also assessed the transfer potential of a 5 gm dose applied to the abdomen when the site was washed prior to contact at 2 hours post-dosing. For this objective, the study tested direct contact with and washout site washing (Groups C and D, respectively).

Finally, the study also assessed the transfer potential of a 5 gm dose when applied to the arms/shoulders only (Group E) and to the abdomen only (Group F) without any t-shirt barrier.

In brief, the results from this second transfer showed the following:

- A simple T-shirt barrier largely eliminated transfer for the dose of 2.5 gm.
- Washing the transfer site prior to direct skin contact (Group D) substantially limited the transfer of testosterone when used at a dose of 5 gm.
- Testosterone transfer was higher for the bare upper arms/shoulders contact compared to the bare abdomen contact.

Based on the finding that a simple t-shirt effectively mitigated transfer of a 2.5 gm dose, Sponsor proceeded to a third transfer study, Study S176.1.009, that assessed the transfer potential when 2.5 gm was applied to 4 anatomic sites (both arms/shoulders and both sides of the abdomen).

Study S176.1.009 is described in detail in the medical officer's Amendment review of the original NDA, on p16 -29. In this transfer assessment study, 12 couples participated. Males applied 5 gm gel to the upper arms/shoulders and abdomen as follows: 1.25 g applied to the left upper arm/shoulder, 1.25 g applied to the right upper arm/shoulder, 1.25 g applied to the left abdomen and 1.2 g applied to the right abdomen. The assessment was conducted with the use of the t-shirt to determine if transfer could be effectively mitigated.

The results showed that a simple T-shirt barrier effectively prevented transfer when using this new "4-site" application method for the 5 gm dose.

Therefore, Study S176.1.009 provided evidence that applying 5gm of AndroGel 1.62% to 4 anatomic sites (and similarly 3.75 gm gel to 3 anatomic sites), was a satisfactory method for an effective clothing barrier in mitigating transfer to others through physical contact.

However, it was still necessary to link the application site method derived from this study to the application method used in the Phase 3 Study S176.3.104 (the "rotating method"). The Sponsor did submit some evidence to this end as part of a major Clinical amendment to the original NDA, and this information was reviewed by the team (see pp 30-39 of the MO's review of the Clinical Amendment of the original). In short, this information was found insufficient to support comparability of the new method to the Phase 3 method. Therefore, a CR action was taken based upon lack of sufficient evidence to link the new application method to the Phase 3 method. In the CR, Sponsor submitted a final report for Study 010, which compared the systemic testosterone concentrations between the new "4-site" method and the Phase 3 "rotating" method. The results showed an approximate 20% lower exposure with the new method compared to the Phase 3 method.

Also as part of the CR, the Sponsor submitted a final study report for a fourth transfer assessment study, S176.1.011, which assessed transfer potential of the 5 gm dose when applied to the arms/shoulders only.

Study S176.1.011 is described in detail in the medical officer's CR review, on p47-66 and in this CDTL memo on p25-26. In this study, 12 couples participated. The dose tested was 5 gm to the arms/shoulders – only and transfer potential was assessed with a t-shirt in place,

The results showed convincingly that a t-shirt barrier effectively mitigated transfer when the arms/shoulders-only site was used.

With a t-shirt in place, mean testosterone Cavg and Cmax in female subjects increased by 6% and 11%, respectively, following contact with male users compared to mean baseline testosterone concentrations.

In addition, the results from Study 007 showed that systemic testosterone concentrations were bioequivalent when comparing the arms/shoulders-only site and the Phase 3, “rotating” method.

8.1.3 Postmarketing Safety Findings

There is ample postmarketing experience with the product's predecessor AndroGel 1%. AndroGel 1% was approved in 2000 for the same indication. A crude estimate of the number of patients exposed to AndroGel® 1% was calculated by the Sponsor as approximately (b) (4) patients or roughly 1.13 million patient years of treatment with AndroGel® 1% for the period February 2000 to September 2008. Thus, there are sufficient postmarketing safety data to state the known and potential postmarketing risks.

For a more detailed account of postmarketing experience, the reader is referred to the medical officer's review of the original NDA on p 147-159, and CR on p 108-117.

The major postmarketing issues (in brief) include: potential risk of prostate cancer, the unknown cardiovascular safety profile in aging males, thromboembolic events, erythrocytosis and possible stroke, misuse of the product, and potential transfer to children and women.

Of these, the most recent development has been the awareness by FDA of a small number of children (n=10-20) in whom testosterone appeared to have transferred from the male adult user to the child, with resultant androgen effects on the young females. Clitoral reduction surgery was needed in at least one case, and in several young females, bone age was reported to be modestly advanced. In response to these reports, the Agency worked with the two Sponsors of the testosterone gels to develop a Boxed Warning on the product labeling as well as a new Medication Guide to better inform users and to reduce behaviors and use practices that may have led to some of these cases. This Risk Evaluation and Mitigation Strategy (REMS) carries over completely to the AndroGel 1.62% NDA.

There are no new safety signals from the medical officer's recent review of the Postmarketing experience for AndroGel 1%.

8.1.4 Overall Assessment of Safety Findings

The safety profile and adverse events associated with AndroGel 1.62% are essentially the same as for AndroGel 1%. The issue of testosterone transfer potential for AndroGel 1.62% has been effectively mitigated by the Sponsor through use of the arms/shoulders-only application site and t-shirt barrier. The linkage of systemic exposures between the arms/shoulders-only application method and the Phase 3, "rotating" method allows approval of the product with the arms/shoulders-only application method in labeling and thus, acceptable resolution of the vexing transfer issue for this new topical testosterone product. The labeling will state that the Dosage & Administration of the new product, AndroGel 1.62% is different than that for AndroGel 1%, the old product.

In terms of the safety results from the clinical studies conducted for this NDA, nothing else has been detected that precludes approval. The data show the expected effects of a testosterone gel including: increased hemoglobin and hematocrit, increased PSA, several cases of increased blood pressure/hypertension, a single report of prostate cancer, lower urinary tract symptoms, acne, and mild skin inflammation. As part of the original NDA, the medical officer carefully reviewed 10 individual cases of supraphysiological testosterone concentrations and found them to be artifactual in 6 cases, related to likely overdose in 2 cases, and for unknown reason, though isolated and sporadic in 2 cases. These results alone do not preclude approval. The medical officer also detected several cases of supraphysiological testosterone concentrations among the CR data, but in these cases, the patients were all treated upfront with the maximum dose (5 gm), not with the lower dose (2.5 gm) and proper titration. Therefore, in our opinion, these cases also do not serve to preclude approval.

Finally, the labeling has been successfully negotiated with Sponsor, including the package insert, the Medication Guide and the container/carton labeling. The REMS associated with the Medication Guide is also acceptable.

9. Advisory Committee Meeting

An Advisory Committee was not held for this application. AndroGel 1.62% is a stronger strength of the already approved AndroGel 1%.

10. Pediatrics

(b) (4)

The Division was subsequently informed (on August 26, 2009) that a

determination had been made by PeRC that this application does not trigger PREA requirements.

11. Other Relevant Regulatory Issues

Division of Drug Advertising, Marketing and Communication (DDMAC)

A consultation regarding labeling for the new indication was requested and completed by DDMAC. In their final consult report dated April 14, 2011, Janice Maniwang and Beth Carr provided comments on various sections of the label, including Highlights, Dosage and Administration (D &A), Contraindications, Adverse Reactions, Clinical Pharmacology, Clinical Studies, the Patient Counseling. The DDMAC team also provided several comments on the Medication Guide, as well as one comment for the container/carton labeling.

All the DDMAC comments and recommendations were carefully considered and most were addressed through internal discussions amongst the primary review team and successful negotiations with Sponsor. However, several DDMAC recommendations were not taken, based on the differing overall recommendations made by the review team members. For example:

- In the Highlights and D&A sections, there is a bolded statement that the Dosage and Administration for AndroGel 1% is different than the Dosage and Administration for AndroGel 1.62%. DDMAC felt this statement was not clear and lacked context. However, the review team, including the Division of Medication Errors Prevention and Assessment (DMEPA), decided that this was an important, clear statement for labeling and it was kept without revision.
- DDMAC stated that the label should convey why the abdomen should not be used, as opposed to simply stipulating that the arms/shoulders only be used and the abdomen, chest, genitals, and other parts of the body not be used for application. The review team addressed this particular DDMAC recommendation by adding the data from the abdomen transfer study which showed some degree of transfer from the abdomen (with a 5 gm dose) despite a simple t-shirt barrier.
- DDMAC recommended to remove a sentence regarding the signs and symptoms of male hypogonadism. This sentence was deemed important for product use by the Clinical reviewers and was retained.
- On the carton label, there is a statement that “AndroGel® is a clear, colorless gel that provides transdermal delivery of testosterone through the skin of the shoulder or upper arm.” DDMAC considered this statement promotional and thus requiring of fair balance on the carton. The review team, including representatives from DMEPA, deemed this statement to be accurate and highly important for safe use of the product and thus, it was retained.

Division of Scientific Investigation (DSI)

Clinical site inspections by the Division of Scientific Investigation were not requested. However, at the request of the Division of Pharmacology III, DSI audited the analytical

portion of Phase 3 study 104. The analytical portion of the study was conducted at (b) (4)
(b) (4) The final DSI memorandum, dated November 9, 2009, stated:

“Following the above inspection, DSI recommends that the analytical portion of study S176.3.104 is acceptable for review.”

The reader should be aware that despite accepting the data for review, DSI did issue a Form 483 (b) (4), which included 3 deficiencies, as follows:

1. “*Integration parameters*” for dihydrotestosterone (DHT) were not all the same for the DHT assay in 10 bioanalytical runs. However, DSI stated that this did not affect the runs acceptability.
2.
 - a. “*Audit trails*” were not available in “*Analyst*” software for two bioanalytical runs. However, electronic data were available for one of these two runs; and for the other, an audit trail was available for a repeat injection of the same run.
 - b. The “*audit trail*” did not capture “*modification*” of one sample for testosterone and one sample for estradiol. However, these modifications were captured in the prints of the chromatograms in the study file.
3. There was an error in Table 8 of the analytical report for reported results of 4 samples. However, the correct results for these same 4 samples were provided in Table 20 of the same analytical report.

Financial Disclosure

Financial disclosures were submitted for the investigators in the pivotal Phase 3 study 104 and for the eight (8) Phase 1 studies submitted in the original NDA. A total of 77 investigators provided disclosures and none had relevant any relevant financial disclosure information to declare. There was no missing financial disclosure information for investigators in the studies noted.

Office of Surveillance and Epidemiology: Division of Risk Management (DRISK)

The Division of Risk Management (DRISK) provided separate consultations regarding their review of the Medication Guide and the Sponsor’s proposed Risk Evaluation and Mitigation Strategy (REMS).

DRISK REMS Review

On April 11, 2011, Shawna Hutchins and Claudia Karwoski of DRISK provided a final consult regarding the Sponsor’s proposed Risk Evaluation and Mitigation Strategy (REMS). The Sponsor submitted the proposed REMS on January 15, 2010.

DRISK concurred that a REMS was necessary, but it would consist only of the Medication Guide and follow-up assessment as for all other transdermal testosterone gel and solution products. DRISK offered a number of editorial revisions to the REMS document itself, as well as the following comments:

- DRISK offered minor edits to the goal of the REMS.
- DRISK found the Medication Guide distribution plan to be acceptable.
- DRISK found the proposed timetable of submissions (18 months, 3 years and 7 years) to be acceptable.
-  (b) (4).
- DRISK acknowledged Sponsor's commitment to submit the "KAB" survey methodology to FDA at least 90 days before actually administering the surveys.

The Sponsor accepted all the changes proposed by DRISK for the REMS and returned the revised document on April 13, 2010. On April 13, 2011, the Deputy Director for Safety in DRUP found the revised REMS acceptable.

DRISK Medication Guide Review

On April 11, 2011, Shawna Hutchins and LaShawn Griffiths of DRISK provided a final consult regarding the Sponsor's proposed Medication Guide. DRISK pointed out that their review of the Medication Guide was based on the "substantially complete" PI that was forwarded to them on March 29, 2011. DRISK provided a number of edits to the Medication Guide, all of which were conveyed to Sponsor, and were ultimately agreed upon by Sponsor.

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

On March 3, 2011, Latoya (Shene) Toombs, Irene Chang and Carol Holquist from DMEPA provided a final review of the carton/container labeling, the PI and the Medication Guide from the Medications Errors perspective. DMEPA also reviewed the Sponsor's planned Education and Communication Plan.

The review notes that on February 3, 2011, a teleconference was held with Sponsor to convey concerns regarding presentation of the strength of the product. At the teleconference, DMEPA and DRUP recommended that the AndroGel 1.62% labeling be revised in accordance with the recently approved products, Axiron and Fortesta, so that the strength is expressed in milligrams of testosterone per pump actuation. The Sponsor agreed fully with this recommendation and committed to submit revised labeling. In addition, the Sponsor was informed that the descriptors "1%" and "1.62%" could continue to follow the tradename "Androgel" so that the two products could be easily differentiated.

The Sponsor did subsequently submit revised labeling and it was reviewed in full by DMEPA. DMEPA provided comments and recommendations for revisions to the insert labeling, the Medication Guide and the container/carton labeling. Through successful internal discussions and external negotiations with Sponsor, all DMEPA issues were resolved and final labeling was acceptable to DMEPA.

DMEPA also reviewed the Sponsor's proposal for an education and communication plan. The target audience is largely healthcare professionals and the goal is to educate physicians and

pharmacists on how to correctly prescribe and dispense the two strengths of AndroGel. DMEPA found the plan to be “comprehensive to introduced the AndroGel 1.62% product overall”. DMEPA stressed that the plan should emphasize the new strength presentation (milligrams of testosterone) and the application site differences between AndroGel 1% and AndroGel 1.62%.

Office of Compliance

On December 7, 2009, the Office of Compliance provided an “Acceptable” recommendation via EES.

Controlled Substances Staff (CSS)

In their final review of the original NDA, dated August 19, 2009, James Tolliver, Silvia Calderon and Michael Klein of CSS confirmed that AndroGel 1.62% is in Schedule III of the Controlled Substances Act (not the Anabolic Steroids Control Act). CSS also provided specific recommendations for revisions to Section 9 of the proposed label (Drug Abuse and Dependence). The revisions include information that anabolic steroids, such as testosterone, are reported to be abused. CSS stated that while drug dependence has not be documented in individuals using therapeutic doses for approved indications, dependence has been observed in some individuals using high doses of anabolic steroids.

In their final review of the CR, dated April 4, 2011, James Tolliver, Silvia Calderon and Michael Klein of CSS stated:

“Based on reviews of material submitted in the new application and of the updated scientific and medical literature, the CSS scientific review and recommendations for labeling changes provided in the consult review, dated August 19, 2009, remain the same.

The labeling recommendations from CSS were conveyed to Sponsor during the labeling negotiations and all CSS recommendations were implemented.

12. Labeling

Labeling discussions were not held with Sponsor during the original NDA.

Labeling discussions were commenced towards the latter part of the CR review cycle and were successful in producing a Package Insert and Medication Guide acceptable to all members of the FDA review team and the Sponsor.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that this new drug application be Approved.

The CR deficiency has been adequately addressed through the use of the arms/shoulders-only method of dose application, including data showing that a t-shirt effectively mitigates transfer from that application site (Study 011), and data showing bioequivalence for serum testosterone concentrations between the arms/shoulders-only method of application and the Phase 3, “rotating” application method (Study 007).

13.2 Risk Benefit Assessment

The risk/benefit assessment for Androgel 1.62% is consistent with all previously approved topical testosterone products.

In terms of *efficacy*, this product, which is a more concentrated, lower volume version of the already approved AndroGel 1%, has been shown to adequately replace serum testosterone (in Study 104). The dosing regimen calls for a fairly low starting dose (40.5 mg testosterone – or 2.5 gm of gel) with two sequential dose-titration points at Days 14 and 28 after the initial dose. The dose can either be adjusted down (to 20.25 mg testosterone) or upward (to 60.75 mg or 81 mg testosterone) based on the single, trough serum total T concentration. The labeling describes this regimen clearly.

The use of the arms/shoulders method was shown to be bioequivalent to the “rotating” method used in Phase 3. In addition, the PK measurements in Phase 3 were always conducted when the patient was using the arms/shoulders-only method. Therefore, the efficacy shown in Phase 3 is well linked to the arms/shoulders-only (labeled) dose application method.

In terms of key *safety* issues, these are also all consistent with previously approved topical testosterone products.

The main review issue for this application was the transfer potential risk. Initial transfer assessment studies demonstrated that a t-shirt did not adequately mitigate transfer of the highest dose (5 gm gel) when using the abdomen-only application site (in Study 003). Therefore, alternative methods were proposed to resolve this concern. Shower skin washing of the site appeared effective in preventing transfer (in Study 009) and was proposed by the Sponsor, but the Division was concerned that this method was not feasible in a real-world setting. The Sponsor subsequently considered the use of a 4-site application method for the 5 gm dose since it was known that a t-shirt was an effective barrier to transfer at doses up to 2.5 gm (in Study 008). However, the 4-site application method was subsequently shown to provide only approximately 80% of the serum testosterone concentrations associated with the Phase 3, “rotating” method (in Study 010). Finally, the issue was resolved through demonstration that a t-shirt effectively mitigated transfer when the 5 gm dose was applied to arms/shoulders-only (in Study 011).

In regard to general safety issues, the NDA provides evidence of well-known testosterone-related pharmacological adverse effects, and these effects unto themselves would not preclude approval. These reactions include: increased hemoglobin and hematocrit, increased PSA,

several cases of hypertension, a single report of prostate cancer, mood changes, lower urinary tract symptoms, and mild skin inflammation (observed in Phase 1 predominantly).

Finally, the labeling has been successfully negotiated with Sponsor, including the package insert, the Medication Guide and container/carton labeling. The labeling makes it clear that the Dosage & Administration for Androgel 1.62% is different than for AndroGel 1%. The REMS, which pertains to the potential risk of secondary exposure to children and women is acceptable.

13.3 Recommendation for Postmarketing Risk Management Activities

All postmarketing risk management requirements and activities that apply to the currently approved testosterone gels also apply to AndroGel 1.62%

13.4 Recommendation for other Postmarketing Study Commitments

The Sponsor has committed to conduct a hand-washing study as a postmarketing requirement. The study will assess the amount of testosterone remaining on a user's hands after application of the dose, then after hand-washing. The Sponsor has committed to specific dates to submit the final study protocol, complete the study, and submit a final study report.

13.5 Recommended Comments to Applicant

There are no additional comments for Sponsor at this time.

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

/s/

MARK S HIRSCH
04/28/2011

GEORGE S BENSON
04/28/2011