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APPLICATION NUMBER:

22309Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Complete Response Submission
Application Number(s)	22-309
Priority or Standard	Standard
Submit Date(s)	October 25, 2010
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PDUFA Goal Date	April 29, 2010
Reviewer Name(s)	Roger Wiederhorn Medical Officer, DRUP Mark Hirsch Medical Team Leader, DRUP
Review Completion Date	April 19, 2011
Established Name	testosterone gel 1.62%
(Proposed) Trade Name	AndroGel 1.62%
Therapeutic Class	androgen
Applicant	Abbott Products Inc. 901 Sawyer Road Marietta, Georgia 30062
Formulation(s)	1.62% testosterone gel - topical
Dosing Regimen	20.25 mg to 81 mg once daily

Indication(s)	Testosterone replacement therapy in adult males
Intended Population(s)	Primary and secondary hypogonadism (congenital or acquired)

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1 Recommendations/Risk Benefit Assessment

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.

(b) (4)

1.2 Risk Benefit Assessment

A thorough and comprehensive review of sNDA 22-309 was carried out. 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. This claim is that AndroGel 1.62% (testosterone gel 1.62%) achieves eugonadal testosterone concentrations in hypogonadal men. 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 (C_{max} >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. No significant discernible differences in the safety profile based on dose or serum testosterone concentrations were detected.

The single pivotal study, S176.3.104, was a double-blind, placebo-controlled, 182-day protocol with a 182-day safety extension. 234 hypogonadal men received testosterone gel 1.62% and 40

patients received placebo. Predetermined testosterone concentrations were achieved at Day 112 (the efficacy endpoint).

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.

The data support the new adequate directions for use, including the data to describe a safe and effective dose.

1.3 Recommendations for Postmarket Risk Management Activities

A Medication Guide will be dispensed with each AndroGel (testosterone gel) 1.62% prescription in accordance with 21 CFR 208.24. The container and carton labels will include an instruction alerting the pharmacist to provide the Medication Guide to each person to whom the product is dispensed. Abbott will submit REMS Assessments to FDA by 18 months, 3 years, and 7 years from the date of the approval of the REMS.

1.4 Recommendations for Postmarket Studies/Clinical Trials

A study to evaluate the wash-off of AndroGel 1.62% from the hands will be conducted as a postmarketing (Phase 4) commitment. Sponsor has already submitted a protocol for this study (Study S176.1.012) entitled, "An Evaluation of the Effect of Hand Washing on the Amount of Residual Testosterone on the Hands after Application of Testosterone Gel 1.62%".

2 Introduction and Regulatory Background

2.1 Product Information

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 canister (b) (4) pump canister, capable of dispensing 75 gm of gel), which consists of a (b) (4) plastic canister with an airless pump dispenser. Each pump delivers 20.25 mg of testosterone (1.25 gm of gel). Four pumps are therefore required for the highest daily dose of 81 mg of testosterone (5 gm 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 (b) (4) sodium hydroxide (b) (4) and purified water (b) (4)

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

The proposed initial dose of the drug product is 20.25 mg of testosterone (2.5 gm gel) daily topically applied to the upper arms and shoulders. In the Phase 3 study, the gel was applied to the arms/shoulders and abdomen sites on a rotating basis. Based upon the complete response, doses above 40.5 mg of testosterone (≥3.75 gm gel) daily are to be applied exclusively to the upper arms/ shoulders to mitigate transfer to others through direct contact. The arms/shoulders method provides comparable exposure to arms/shoulder and abdomen rotating method. The arms/shoulders only method has also been shown to be relatively non-irritating.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Available Testosterone Formulations for the Proposed Indication

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Source: Bhasin S, Cunningham G, et. al., 2006: Testosterone Therapy in Adult Men With Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline: J of Clin Endocrin and Metab 9 (16): 1995-2010

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety in the product is testosterone. Testosterone in gel form is available in the United States in several formulations. Currently AndroGel is marketed as a 1% formulation. The Sponsor crudely estimates that approximately (b) (4) (or roughly 1.13 million patient years of treatment with AndroGel 1%) used AndroGel in the 28 February 2000 - 27 February 2008 cumulative post-marketing period. An estimated (b) (4) (~236,470 patient years) used testosterone gel 1% during the period of 28 February 2008 to 27 February 2009. In the period between 28 February 2009 and 27 February 2010, an estimated (b) (4) patients (~281,306 patient years) used testosterone gel 1%.

The following is relevant to the AndroGel 1% US experience, as provided by Sponsor:

Contraindications to the use of testosterone in men are breast or known or suspected prostate cancer. Pregnant or breast feeding women should not be exposed to exogenous testosterone. Testosterone may cause fetal harm.

Warnings and Precautions: 1) Patients with benign enlargement of the prostate (BPH) treated with androgen are at an increased risk for worsening of signs and symptoms of BPH. 2) Application site should be covered and hands washed to avoid transfer to others. 3) AndroGel is not indicated in women due to a lack of controlled evaluations and potential virilizing. 4) Exogenous administration of androgens may lead to azoospermia. 5) Edema may be a complication in patients with preexisting cardiac, renal or hepatic disease. 6) Gynecomastia or breast enlargement may develop. 7) Sleep apnea may occur in those with risk factors 7) Monitoring of serum testosterone, prostate specific antigen, hemoglobin, hematocrit, liver function tests and lipids periodically is recommended while using the product. 8) Alcohol based gels are flammable until dry.

The most common Adverse Reactions (incidence greater $\geq$ 5%) are acne, application site reaction, abnormal lab tests (including increased prostate specific antigen [PSA], elevated hemoglobin/hematocrit, and change in serum lipids) and prostatic disorders.

Drug Interactions: 1) Androgens may decrease blood sugar, and therefore insulin requirement in diabetic patients. 2) Use of testosterone with ACTH or corticosteroids may result in increased fluid retention. 3) Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants.

Use in Specific Populations: 1) Pregnancy: AndroGel may cause teratogenic effects. AndroGel should not be used in pregnant women. 2) Nursing mothers should not use AndroGel. 3) The safety and efficacy of AndroGel in males < 18 years has not been established. 4) There have not been sufficient numbers of geriatric patients involved in controlled clinical studies to determine whether efficacy in those > 65 differs from younger subjects. Additionally there is insufficient

long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease and prostate cancer. 5) No formal studies were conducted involving patients with renal or hepatic insufficiencies.

2.4 Important Safety Issues with Consideration to Related Drugs

The important potential safety issues with testosterone therapy include[1]:

- Cardiovascular disease
- Lipid alterations
- Erythrocytosis
- Fluid Retention
- Benign prostatic hypertrophy (BPH)
- Prostate cancer
- Hepatotoxicity
- Sleep apnea
- Gynecomastia
- Acne or oily skin
- Application site irritation
- Drug interactions: insulin, ACTH, oral anticoagulants, cyclosporine
- Testicular atrophy or infertility
- Potential for transfer of testosterone by skin contact to partners and children.
- Supraphysiological testosterone levels.

Appropriate monitoring during testosterone replacement therapy includes: At baseline – 1) Laboratory assessments of serum testosterone, serum PSA, hemoglobin/hematocrit, serum lipids, and serum liver enzymes. 2) Physical exam to include weight, blood pressure, skin status and rectal examination to assess prostate. Voiding symptoms can be assessed by history or by the International Prostate Symptom Score. Any history of sleep apnea should be obtained. Appropriate follow-up to assess changes in any of the above parameters should also be performed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is a second cycle review, based on a Complete Response action issued on March 12, 2010.

1 Rhoden E L and Morgentaler A, 2004, Risks of Testosterone-Replacement Therapy and Recommendations for Monitoring, N Eng J Med; 350: 482-92

On February 11, 2009, the original NDA for this product was submitted to FDA. One of the major review issues for this NDA in the first review cycle was limiting the potential for secondary exposure to testosterone by inadvertent transfer of gel to children and females.

Original studies conducted by Sponsor to assess the potential for transfer (from the abdominal application sites) did not appear to demonstrate adequate protection from transfer by a simple t-short. Therefore, the Sponsor proposed the use of both a t-shirt *and* shower skin washing of the application sites before physical contact with others was anticipated. The Division was not in agreement with this method, and instead recommended that a simpler, more feasible method of preventing transfer should be achieved. To that end, in a teleconference on September 25, 2009, the Sponsor suggested that the higher doses (60.75 mg of testosterone and 81 mg of testosterone in 3.75 gm and 5 gm of gel, respectively) could be "spread out"across 3 or 4 application sites, so as to limit the volume at each site and thus lessen the potential for transfer through a t-shirt. The Division stated that this strategy seemed reasonable and was a potential pathway to resolve the review issue.

On October 16, 2009, the Division received SDN 206 to the AndroGel IND (IND# 50,377). The document contained preliminary results from Study S176.1.009 (Study 009), entitled "An Open-Label, Study of Serum Testosterone Levels in Non-Dosed Females with Secondary Exposure to Testosterone Gel 1.62%." This study further characterized the transfer potential of the product. This time, evaluations were made to assess secondary exposure from dosed males to non-dosed females with a simple t-shirt barrier after application of 5 grams of gel to both the upper arms/shoulders *and* abdomen, bilaterally (use of 4 anatomic sites to "spread out" the larger volume of gel).

On November 10, 2009, the Sponsor submitted a supplement to the NDA itself (SDN 012) which contained preliminary results from this study, along with a rationale document outlining a justification why the application scheme used in Study 009 (higher doses spread out along 3 or 4 anatomic sites) should not adversely impact safety or efficacy conclusions from the previously completed pivotal, Phase 3 study S176.3.104 (Study 104).

The results of Protocol S176.1.009, on their face, with preliminary statistical comparisons, appeared to show no statistically significant differences between Baseline (Day -1) and Day 1 for serum testosterone concentrations in females after skin contact with treated males. Comparisons of baseline to Day 1 C_{av}, AUC_{0-24}, or C_{max} appeared to show that with four site application of 5 g of testosterone gel 1.62% in the male, a t-shirt barrier effectively blocked testosterone transfer to an unclothed female.

Despite the results of this new transfer study, which appeared to resolve the major review issue, the Division was concerned that revising the application site strategy from the one used in Phase 3 to the new "3- of 4-site application" strategy for the higher doses could result in changes in testosterone exposure, which was the primary efficacy endpoint in Study 104. In response to this concern, on November 25, 2009, the Sponsor submitted another NDA amendment. This amendment contained: 1) Solvay's response to six questions posed by the Division, 2) a letter to the FDA from the Principal Investigator for the AndroGel 1.62% pivotal study (Study 104), and

3) various attachment documents related to an assessment of comparability between the 4 anatomic sites and 2 anatomic sites application techniques.

It was the Division's judgment that all this information (in the amendment submitted on November 25, 2009), taken together, constituted a major clinical amendment that could change the outcome of the review and therefore, a 90 day extension of the PDUFA goal date was granted.

On January 15, 2009, the Sponsor submitted the final report of Study 009, the "4-site" transfer study. While the results of Study 009 appeared to show that with the four site application of 5 g of testosterone gel 1.62% in the male, a t-shirt barrier effectively blocked testosterone transfer to an unclothed female, there remained the concern that the new dosing recommendation was not used in the Phase 3 study. In response to this concern, the Sponsor provided data from patients who mistakenly applied the higher doses (60.75 mg of testosterone [3.75 gm of gel] and 81 mg of testosterone [5 gm of gel]) to 3 and 4 application sites. The data included serum testosterone concentrations from these patients, which the Sponsor used to support comparability of exposure between the new application method and the Phase 3 method. The Division was not convinced that this information was sufficient to support a link from the Phase 3 application site method to the new method. The Division was concerned that the new data came from a group of protocol violators, who were not pre-defined in the protocol, and in whom supervision appeared to be inadequate during the study. In addition, the analysis of testosterone concentrations from these patients was "post-hoc". The Clinical Pharmacology review team agreed that this information was not sufficient to link the Phase 3 data to the new application method. The Division recommended that a Phase 1, relative bioavailability study would be a reasonable way to bridge the 4 site application to the 2 site application technique for a dose of 5 gm.

Therefore, based upon the unresolved deficiency, on March 12, 2010, a **Complete Response** action was taken**.** The CR letter stated that this action was based on the findings that studies conducted to assess whether testosterone can transfer to others showed that a T-shirt did not adequately block transfer of a 5gm dose. Since a T-shirt was not a completely effective means of blocking transfer, the proposed label emphasized washing the application site prior to anticipated physical contact (b) (4). Relying principally on washing the application site (in the shower) prior to physical contact with others to prevent transfer of testosterone was considered problematic (and not feasible) in terms of patient compliance. Other simpler, more feasible means, in addition to shower skin washing of the skin application site prior to physical contact, were needed to prevent testosterone transfer to others. The CR letter stated that a **Complete Response** to this unresolved safety concern would entail generating data to show a satisfactory method for the clothing barrier technique. This might require modification in the method(s) of application of larger doses of testosterone gel 1.62% (e.g., "spreading out" the larger doses to both the abdomen and the arms/shoulders). If the dosing method is changed (e.g. spreading the larger dose out onto both sides of the abdomen and both arms/shoulders), then the CR letter stated that appropriate PK data to demonstrate testosterone concentrations comparable to those obtained in Study S176.3.104 (where the dosing schema was abdomen *or* arms/shoulders) would be required.

On April 29, 2010, a Type A meeting was held to discuss the content of the Complete Response letter and what additional studies were planned to formulate a Complete Response. The Sponsor proposed to conduct a comparative bioavailability study (Protocol S176.1.010 [Study 010]) to characterize the pharmacokinetic parameters of AUC and Cmax for total observed serum testosterone concentration at steady- state for the two dosing regimens (application to 4 anatomic sites [right and left upper arms and shoulders] versus the reference [application rotating between abdomen and upper arms/shoulders]). Agreement was not reached concerning a specific, pre-defined, difference between primary parameters of C_{max} and AUC that would constitute acceptable comparative bioavailability. The Division stated that this would be a review issue.

At the time of the Type A meeting, the Sponsor also proposed to conduct a second study, S176.1.011 (Study 011), which would evaluate the transfer potential for the gel when healthy males applied 2.5 grams to each upper arm/shoulder area (total dose 5 grams) and then covered with a t-shirt (the "arms/shoulders"-only method). The Division agreed that if this study showed no transfer at 2 hours post dose and after 15 minutes of supervised skin contact with a non-dosed female, it would accept this final study report in the NDA as a Complete Response to the deficiency in the Complete Response letter. The Division reasoned that the arms/shoulders-only method was a method allowed in the Phase 3 study. In fact, arms/shoulders-only was required as the application method prior to each of the 24-hour PK assessments in the Phase 3 study. In addition, there was data available from an already completed Phase 1 study (Study 007) showing highly comparable exposure between the arm/shoulders-only method and 3- or 4-site method.

The Sponsor also agreed at the April 29, 2010, Type A meeting to assess the potential for skin irritation of the new application method (4-site) in Study 010 using the same scale as that utilized in the Phase 3 Study 104. The Sponsor further agreed to submit the final study report for Study S176.3.104 in the CR. The Sponsor was also asked to submit in the CR the PSUR updating and covering the worldwide experience on the safety of AndroGel 1% (AndroGel 1.62% is not currently marketed anywhere).

Subsequent to the Type A meeting, additional communications took place between Sponsor and Division concerning the CR. For example, on June 18, 2010 and July 12, 2010, the Division conveyed comments and responses to Sponsor's questions from NDA submissions dated May 27, 2010 and June 21, 2010, respectively. These Sponsor's questions and Division's responses/comments dealt with regulatory strategy for the CR submission. The reader is referred to these documents in DARRTS for details.

At a subsequent teleconference on September 8, 2010, the Sponsor agreed to perform a hand washing study as a post-marketing commitment.

On October 29, 2010, the Sponsor submitted the Complete Response. To address the deficiency identified in the Complete Response letter, Abbott has submitted the results of two clinical studies in the current submission:

1) Study S176.1.010 (Study 010) entitled "*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."

2) Study S176.1.011 (Study 011) entitled "*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.*"

In addition, they have submitted a reissued report for the Phase III pivotal safety and efficacy study S176.3.104 which now contains the data from the 6- month open-label period of the study.

The results of study S176.1.009 (Study 009) entitled "*An Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-Dosed Females after Secondary Exposure to Testosterone Gel 1.62%*" are incorporated into the Module 2 summaries. This report was previously submitted to the NDA on 15 January 2010 and was reviewed during the 3-month clock extension during the first review cycle. Finally, the Sponsor has also submitted a protocol for a hand washing study, S176.1.012 (Study 012), as discussed with them during the September 8, 2010 teleconference.

The Sponsor offers two pathways for resolving the CR. The first is through the use of 3- and 4-sites of application for the higher doses of 60.75 mg of testosterone and 81 mg of testosterone. The second is through an "arms/shoulders"-only application site method. They believe both are viable pathways to approval.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is of good quality and no concerns have been raised about the integrity of the processes that were used by Sponsor to generate this submission.

3.2 Compliance with Good Clinical Practices

The Sponsor appears to have been compliant with Good Clinical Practices (GCP).

3.3 Financial Disclosures

Form FDA 3454 signed 29 September 2010 was provided in the submission. Financial disclosures were submitted for the principal investigators in Protocols S176.1.001, S176.1.002,

S176.1.003, S176.1.004, S176.1.005, S176.1.006, S176.1.007, S176.1.008, S176.1.009, S176.1.010, S176.1.011, and the pivotal Phase 3 study S176.3.104.

A total of 88 investigators (all from all protocols and study sites) had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54, 2(a)], proprietary interest in the covered product or significant equity interest in the Sponsor of the covered product [21 CFR 54.2(b)], significant payments of other sorts from the Sponsor of the covered study [12 CFR 54.2(f)]. There was no missing financial disclosure information for investigators in the above listed studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry review team provided Sponsor with comments on their container/carton labeling on March 7, 2011. The Chemistry review team also provided revisions to the proposed Package Insert and these were sent to Sponsor on March 29, 2011. A final labeling review from Chemistry is pending. Aside from labeling, there are no new chemistry issues since the original NDA submission of February 11, 2009.

4.2 Clinical Microbiology

The Microbiology consult for this application was completed October 28, 2009. Dr. Mello recommended Approval. There were no recommendations on Phase 4 Commitments and/or Agreements. There were no deficiencies. However, Dr. Mello requested that a comment is requested to be sent to the Sponsor stating that 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 any time during its shelf life. The comment was conveyed to Sponsor on November 30, 2009 and the NDA was amended accordingly.

4.3 Preclinical Pharmacology/Toxicology

There are no pending Pharmacology/Toxicology issues for this application. The Pharmacology Toxicology review is completed. Nonclinical data support Approval of AndroGel 1.62% solution for topical testosterone replacement in hypogonadal men, There are no new issues noted since the previous review of the 11 February 2009 NDA submission. Several minor Nonclinical labeling comments were conveyed to Sponsor comments and Sponsor accepted these entirely.

4.4 Clinical Pharmacology

At the January 20, 2011, Mid-Cycle meeting, Clinical Pharmacology presented their analysis regarding comparability of exposure to testosterone with application of 5 g testosterone gel 1.62% to either 4 sites (both arms/shoulders and both sides of the abdomen) versus 2 sites (both arms/shoulders) as compared to the results in S176.3.104, the pivotal study. It was their conclusion that the 4 site method of application would result in an 18% lower exposure based on AUC while the 2 site method would result in a 2-3% higher exposure. Further, a t-shirt appeared to mitigate transfer acceptably when the product was applied to the arms/shoulders. It was therefore recommended by Clinical Pharmacology, to provide comparable exposure to testosterone with a new application method, that both the 3.75 gm and the 5 g dose of testosterone gel 1.62% be applied to both upper arms and shoulders. The Clinical team agreed and thus. The approved method of application will be arms/shoulders for all doses.

4.4.1 Mechanism of Action

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.

4.4.2 Pharmacodynamics

While several clinical endpoints are measured in clinical trials (e.g., erectile function and libido questionnaires, mood profiles, body composition indices, and bone mineral density), there are no currently agreed upon primary clinical endpoints for Phase 3 studies of testosterone replacement. Therefore, for this NDA and for all previous testosterone replacement applications, the primary efficacy endpoints are pharmacokinetic (i. e., the attainment of testosterone concentrations in the eugonadal range).

4.4.3 Pharmacokinetics

Reviewer's Comment: The Pharmacokinetics of the product are shown in great detail in later parts of this review and also will be prominent in the Clinical Pharmacology review.

Herein, the Sponsor's overall summary of the Pharmacokinetics is provided in brief. Overall, the reviewer agrees with this assessment by Sponsor.

AndroGel 1.62% delivers physiologic amounts of testosterone that produces circulating testosterone concentrations that approximate normal levels (3000-1000 ng/dL) seen in healthy men. The product provides continuous transdermal delivery of testosterone for 24 hours following once daily administration. The skin serves as a reservoir for the sustained release of testosterone into the circulation. Up to 8.5 % of the dose of AndroGel 1.62% applied to the skin surface (of either the shoulders/upper arms or abdomen) is absorbed into systemic circulation and results in testosterone concentrations in the eugonadal range. Testosterone exposure is 30-40% lower when applied to the abdomen compared to the shoulders/upper arms.

All doses tested (1.25, 2.5, 3.75, and 5 g) provide continuous transdermal delivery of testosterone for 24 hours. A clinical study conducted in hypogonadal males has shown that with one application of the 2.5 g starting dose of AndroGel 1.62% mean testosterone concentrations rise to within normal levels by 2 hours after application and remain within the normal range for the remainder of the 24-hour period. Eighty percent of hypogonadal patients receiving the 2.5 g dose had C_{av} values within the eugonadal range on Day 1. On repeated daily application, mean testosterone concentrations are maintained within the normal range at all dose levels. Serum concentrations approximate the steady-state level by the end of the first 24 hours of dosing.

When AndroGel 1.62% is discontinued, serum testosterone levels return to approximately baseline levels within 48-72 hours after administration of the last dose.

Circulating testosterone is primarily bound to sex hormone-binding (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG), 2% remains unbound (free) and the rest is bound to albumin and other proteins.

There is considerable variation in the half-life of testosterone as reported in the literature ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The two major metabolites of testosterone are dihydrotestosterone (DHT) and estradiol.

Dihydrotestosterone concentrations increased with increasing testosterone concentrations during AndroGel 1.62% treatment. After 182 days of treatment in adult males, mean DHT concentrations were mostly within the eugonadal range for the 1.25, 2.5, and 5 g doses, but were 5-30% above the normal range for the 3.75 g dose group. The mean steady-state DHT/testosterone (DHT/T) ratio during 182 days of AndroGel 1.62% treatment typically remained within normal limits.

Following multiple dosing, mean estradiol concentrations were generally within the normal range for all doses tested.

In regard to the metabolism of AndroGel 1.62%, the information on DHT and estradiol has been summarized above and additional details are shown in the body of this review. Previous studies

have shown that about 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucoronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs mainly in the liver.

5 Sources of Clinical Data

In total, the original NDA contains safety data from 785 subjects exposed to AndroGel 1.62%. The safety data was derived from Phase 1 studies S176.1.003, S176.1.004, S176.1.008 (which were not integrated into the overall safety analysis), and Phase 1 studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104 (which were integrated into an overall safety analysis). By prior agreement, the safety data from the open-label period of Study S176.3.104 was submitted with the 120-Day Safety Update. 382 hypogonadal males are included in the integrated safety base, and 307 healthy males and 96 females (females participated in the "transfer" studies) are included in the non-integrated safety data base.

The single efficacy 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 (168 T-Gel [71.8%] and 28 [70.0%] placebo). In the Open-Label Period of Study S176.3.104, 219 patients were allocated to treatment. Of these 219 patients, 24 patients had been on placebo in the double blind period. 185 patients completed the study and of these 161 patients had received testosterone gel 1.62% in the double blind period.

Two additional studies are submitted in this submission as part of the Sponsor's Complete Response:

- Study S176.1.010: "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 phase 1 study involving 62 hypogonadal males to assess the effects of multiple doses of 5 g of T gel 1.62% (on PK and bioavailability) applied daily to either arms/shoulders only or arms/shoulders and abdomen on a rotational basis to hypogonadal males.

- Study S176.1.011: "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 phase 1 study involving 12 couples to assess the mitigation of secondary exposure by use of a standard t-shirt when AndroGel 1.62% was applied to the arms/shoulders only.

In addition, a revised Clinical Study Report (CSR) for the Phase III pivotal efficacy study (S176.3.104) is provided. In addition to data from the 6-month double-blind period of the study, the revised report now also contains findings from the 6-month open-label extension period of the study. (b) (4)

5.1 Tables of Studies/Clinical Trials

Table 2: Summary of Clinical Studies with AndroGel 1.62%

Type of Study	Objective	Design	Test Product	Duration of Treatment	Enrolled Completed Age Range
Phase I Clinical Pharmacology				(total days of exposure)	Hypogonadal Males
S176.1.001	Bioavailability (BA) and Multiple Dose Pharmacokinetics (PK)	Randomized, Open label, parallel	Testosterone (T)gel: to abdomen for each dose level of 1.25, 2.50 and 3.75	Daily, 5 days at each dose level (20 days)	38 enrolled 36 completed Age: 26-72 yo
S176.1.002	Single and Multiple Dose PK (*Dose-Ranging*)	Randomized, Open label, parallel	T gel 1.62%; 1.25 g, 2.50 g, 5.00 g or 6.25 g. Abdomen, upper arm/shoulders (rotation)	Daily for 14 Days	56 51 27-69 yo
S176.1.005	Multiple dose PK/BA *with/without Post dose skin washing*	Randomized, Open-label, three-way crossover	T gel 1.62%; 5.00 g upper arm/shoulders	Daily, 7 days at each dose level (21 days)	24 17 34-77 yo
S176.1.006	Multiple dose PK/BA *with/without moisturizer or sunscreen*	Randomized, Open-label, three-way crossover	T gel 1.62%; 2.50 g upper arm/shoulders	Daily, 7 days at each dose level (21 days)	18 15 31-60 yo
S176.1.007	Singe and Multiple Dose PK/BA (*Differences between application sites*)	Randomized, open-label, three-way crossover	T gel 1.62% 5.00 g, Abdomen, upper arms/shoulders+ both sites in rotation	Daily, 5 day washout between Treatments (31 days)	36 32 29-73 yo

S176.1.010 **Submitted in Complete Response**	Multiple Dose PK/BA (*Differences between application sites*)	Randomized, open-label, two-way crossover	T gel 1.62% 5.00 g, Abdomen 3 days, then upper arms/shoulders for 4 days vs. 7 days to arms/shoulders	Daily, 7 days each arm: 7 day washout between arms	62 Males 62 29-74 yo

Healthy Subjects					Healthy Subjects
S176.1.003	PK of female subjects *after contact with partner dosed with T gel*	Randomized, open-label	Males: T gel 1.62% 5.00 g Females: 15 minutes of contact time; no direct dose	(7 days)	96 (48 couples) 47 M, 48 F; 18-65 yo
S176.1.004	*Skin sensitization Skin irritation* of 1.62% T gel in males	Randomized, double-blind, placebo controlled	T gel 1.62%; 100 mg gel/3.14 cm^2 patch	(6 weeks): three phases: 21d induction, 12-17 day rest, and 5d rechallenge	235 214 18-79 yo
S176.1.008	PK eval of dose, *post dose washing, and application site transfer* - dosed male to non-dosed female	Randomized, open-label, parallel group	Males: T gel 1.62%; 2.5 or 5.00 g, 2 single daily doses to abdomen or shoulders/arms: Females: 15 minute contact time: no direct dose	(2 days), separated by 1-week washout period	48 (24 couples) 48 (24 couples) 18-59 yo
S176.1.009	PK of female subjects *after contact with partner dosed with T gel*	Open-label	Males: T gel 1.62% 5 g single dose to both arms/shoulders+ both sides abdomen	Single dose	26 (13 couples) 24 12 (couples) See Report 24-50 yo F 23-52 yo M

S176.1.011 **Submitted in Complete Response**	Single dose female PK after contact with partner dosed with 1.62% T gel	Open-label	Males: T gel 1.62% 5 g single dose to both arms/shoulders	Single dose	24 (12 couples) 26-59 yo F 29-52 yo M
Phase 3 Single Study	HYPOGONADAL MALES				
S176.3.104 **Open-Label Extension Submitted in Complete Response**	PK evaluation of % of patients in eugonadal range with AndroGel 1.62%	Randomized, Double-Blinded, Placebo Controlled.	Males: T gel 1.62%; 1.25, 2.50, 3.75, 5.00, placebo, g, daily	182 days: followed by 182 day open label safety study	274 196 45-64 yo (majority of patients)

yo= years old

5.2 Review Strategy

For the original NDA submission, Study S176.3.104 was by prior agreement the only Phase 3 pivotal efficacy study. The results of the total testosterone pharmacokinetic variables, C_{av} and C_{max} were analyzed. The Open-Label period of S176.3.104 was analyzed in this Complete Response review to determine maintenance of efficacy at 364 days. The major emphasis for safety evaluation of AndroGel 1.62% was placed on the safety data in Study S176.3.104, which was analyzed by DRUP as part of the review of the original application. Additional safety data was derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008, and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104 (all previously analyzed as part of the original application) as well as the Open-Label period of S173.3.104. The data from the integrated safety studies were analyzed separately by the Sponsor by prior agreement. The pharmacokinetic variables were separately and jointly reviewed by pharmacology and clinical divisions.

The 120 Day Safety-Update, containing the additional safety data from the Phase 3 study 104, was received and the data was incorporated into this NDA review.

In the original NDA review, particular attention was directed to two safety issues: 1) the potential risk of secondary exposure to testosterone through inadvertent transfer from men using the product and 2) testosterone concentrations in excess of 2500 ng/dL in hypogonadal men using the product . In this review of the Complete Response, attention will directed to four issues: 1) reliable and feasible means to mitigate the potential for secondary exposure 2) potential for skin irritation using different methods of application 3) comparability of exposure with different methods of testosterone gel 1.62% application 4) maintenance of efficacy at 364 days of testosterone gel 1.62% application.

The review strategy for this Complete Response submission was as follows:

- To review in detail the two new Phase 1 studies submitted in the CR – these are: Study S176.1.010 (*comparative bioavailability of 4 sites versus 2 sites of application for the 5 gm dose*), and Study S176.1.011 (*transfer potential of arms/shoulders only for the 5 gm dose*). The results of these studies will be analyzed with respect to resolving the issues noted in the Complete Response letter.
- To review the protocol for Study 176.1.012, a hand washing study. The Sponsor intends to perform this study as a post-marketing requirement.
- To review the complete study report for the Phase 3 study S176.3.104, which now includes efficacy and safety data for the 6-month open-label extension. (b) (4) (b) (4)
- To review the PSUR covering the recent worldwide experience on the safety of AndroGel 1%.
- To review the proposed product labeling, including the Medication Guide.
- To review the proposed REMS

5.3 Discussion of Newly Submitted Individual Studies/Clinical Trials

5.3.1 Study S 176.1.010: "A Multiple Dose Pharmacokinetic and Comparative Bioavailability Study of Testosterone Absorption after Administration of 5.00 g Testosterone Gel 1.62% to the Upper Arms/ Shoulders using an Application Site Rotation or a Combination of Application Sites in Hypogonadal Males"

Design and Conduct of Study S176.1.010

Basic Design:

The primary study objectives were:

- To determine the multiple dose PK of testosterone after administration of 5.00 g testosterone gel 1.62% in hypogonadal males.
- To determine the relative bioavailability of observed testosterone concentrations after administration of 5.00 g testosterone gel 1.62% using an application site rotation between the upper arms/shoulders and abdomen or a combination of the upper arms/shoulders and abdomen application sites.

There are no secondary objectives listed.

Reviewer's Comment: Study S176.1.009, submitted in the original application, showed that when 5.00 g testosterone gel 1.62% was applied to a combination of the right and left upper arms/shoulders as well as the right and left sides of the abdomen (four sites) in the

male, testosterone transfer to the female was effectively mitigated when the male wore a t-shirt. The current study is a bridging study to show that the four site application method in the males provides comparable testosterone exposure, in the male, as compared to the two site application method.

The safety objectives were to monitor and evaluate the safety of the subjects throughout the study.

This was a single center, open-label, randomized, two treatment, two periods, crossover study in sixty-two (62) hypogonadal male volunteers (aged 18-80 years). The total duration of the study was 24 days. Subjects who consented to participate in this study and met the inclusion/exclusion criteria underwent two sequential treatment periods in randomized order. There was a one week washout between treatments.

The statistical determination of sample size requirement concluded that 60 subjects would provide reasonable power to characterize the relative bioavailability of the different application regimens being investigated.

The test product was testosterone gel 1.62%, 5 g of gel, containing 81 mg testosterone.

The two treatments were as follows:

- Treatment A: Once daily application of testosterone gel 1.62% to the abdomen for 3 days (2.5 g to each the right and left sides of the abdomen) followed by application to the upper arms/shoulders (2.5 g to each the right and left upper arm/shoulder) for 4 days. The total daily gel dose was 5.00 g (81 mg of testosterone). This was a recommended dosing regimen in the pivotal Phase 3 study.
- Treatment B: Once daily application of testosterone gel 1.62% to a combination of the upper arms/shoulders and abdomen for 7 days. The total daily gel dose was 5.00 g (81 mg of testosterone) consisting of 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 left abdomen and 1.25 g applied to the right abdomen.

Reviewer's Comments:

1. *Treatment A is a two site (arms/shoulders vs abdomen) rotational application method that is characteristic of the methods of testosterone gel application in the Phase 3 study.*
2. *This study design is typical of a Phase 1 study to assess bioavailability between treatments.*
3. *The 7 day washout period is reasonable and the Sponsor anticipated no carry-over effects.*

Dose Rationale: Spreading the 5 gm dose (highest dose in the pivotal Study S176.3.004) out onto 4 anatomic sites is one way to mitigate skin transfer to testosterone in combination with a t-shirt barrier. Study S176.1.009 evaluated this technique. The 5 gm dose of gel (81 mg of

testosterone) utilized in Study S176.1.010 is the same dose that was used in Study S176.1.009. This study is a bridging PK study to determine if Treatment A and B exhibit comparable bioavailability.

Safety Parameters and Endpoints: All adverse events were listed by subject, with both the reported and coded (preferred) term indicated. Adverse events that occurred after the first dose of study medication on Day 1 through post treatment assessment were considered as on-treatment period. Treatment-emergent adverse events (TEAEs) were identified as AEs that started or worsened in severity on or after the first study drug administration, and within 30 days of the last study drug administration. Events were counted once per subject per PT and once per subject per SOC for each treatment. Only treatment emergent AEs were reported but, in the listings, all occurrences of AEs were presented.

Vital signs, including changes from baseline were summarized. Laboratory variables, including changes from baseline were summarized. At screening and end of study or early termination, a fasting blood sample was drawn for standard hematology, (white blood cells [WBC], red blood cells [RBC], hemoglobin, hematocrit, platelet count, and WBC differential count) and serum biochemistry (sodium-potassium, chloride, creatinine, blood urea nitrogen [BUN], glucose, cholesterol, triglycerides, , high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL], very-low-density lipoprotein cholesterol [VLDL], total protein, albumin, calcium, phosphorus, uric acid, total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], gamma-glutamyl transferase [GGT] and alkaline phosphatase). A urine sample was collected for urinalysis (pH, glucose, protein, ketones, and blood). These laboratory results are listed.

Vital signs, including changes from baseline were summarized. Laboratory variables, including changes from baseline were summarized. Pharmacokinetic measurements were obtained from the patients for total testosterone, DHT, and estradiol at the following times:

- Day -1 and Day 14 (baseline) at: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours with respect to the projected time of testosterone gel 1.62% dose administration
- Days 7 and 21 at: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours with respect to the projected time of testosterone gel 1.62% dose administration
- Days 5, 6, 19, at predose

Table 3: Study Flow Chart

	Days												
	-23 to -2	-2	-1	1-4	5-6	7	8	13	14	15-18	19-20	21	22 or Early Terminiation
Screening	X												
Medical History	X												
Physical Examination[1]	X												
Height and BMI	X												
DRE and IPSS	X												
CBC, Clinical Chemistry, and Urinalysis	X												
Testosterone for Inclusion	X												
PSA (collect prior to DRE)	X												
Viral Screen	X												
Drug and Alcohol Test	X	X						X					
12 Lead ECG	X												
Admit to Clinic		X						X					
Vital Signs (BP, Pulse, Temp)	X	X	X	X	X	X	X	X	X	X	X	X	X
Application Site Evaluation/ Scale			X	X	X	X	X	X	X	X	X	X	X
Dose			X	X	X	X			X	X	X	X	
PK Blood Sample			X[2]		X[4]	X[3]	X[3]	X[2]			X[4]	X[3]	X
Baseline/ Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge from Clinic							X[5]						X[6]
Study Completion													X

[1]Including Weight

[2]At 0,1,2,3,4,6,8,10,12,16 and 24 hours relative to the projected time of study drug administration on subsequent days.

[3]At 0,1,2,3,4,6,8,10,12,16 and 24 post-dose on Days 7 and 21.

[4]At Pre-dose.

[5]Discharge from Clinic after collection of 24 hour sample and dose application.

[6]Discharge from clinic on the morning of Day 22 after post-study assessments are complete.

Source: Scanned Copy, 9.1 Study Flow Chart, page 21, Statistical Analysis Plan S176.1.010 Study Report.

Inclusion Criteria:

1. Documentation of written informed consent was received.
2. Male subjects 18-80 years of age, inclusive.

3. Serum testosterone <300 ng/dL. Documented lab result was obtained during screening visit, within 6 weeks of Day -2 for subjects not currently on androgen replacement therapy, or following washout of androgen replacement therapy.
4. Subjects naïve to androgen replacement; or washout of 16 weeks following intramuscular androgen injections; or washout of 4 week following topical or buccal androgens; or 3 weeks following oral androgens.
5. Subjects had a Body Mass Index (BMI) of 20-35 kg/m^2 inclusive.
6. In the opinion of the investigator the subject was determined otherwise healthy by vital signs, medical history, physical exam, electrocardiogram (ECG), and laboratory examination (hematology, clinical chemistry, and urinalysis).

Exclusion Criteria:

1. Participants in any investigational drug trial within the previous thirty (30) days.
2. Receipt of any prescription medication within 21 days prior to Day -2 of the study or receipt of non-prescription (over the counter [OTC] medication within 7 days of Day -2 without Sponsor approval. Volunteers on a stable medication regimen (>3 months) for hypertension, hyperlipidemia, hyperlipemia, blood glucose control, or other conditions were evaluated on a case by case basis.
3. Blood or plasma donation within the sixty (60) days previous to Day 2.
4. Volunteers with any clinical/biochemical impairment of liver function or receipt of known hepatic enzyme inducing or inhibitory agents within sixty (60) days prior to Day -2.
5. Use of any drug with a half-life greater than 24 hours in the past 6 months prior to Day-2 without Sponsor approval.
6. Volunteers who were smokers or ex-smokers who had quit smoking for a period of less than 12 months prior to Day -2.
7. Consumption of caffeine containing products or beverages in excess of 5 cups/cans of coffee, tea, or cola per day, or any consumption of caffeine containing products or beverages within 24 hours of Day -2 (caffeine containing products was not to be allowed during each study period).
8. Findings of any kind of lesions (e. g. ulcer, erosion, lichenification, crust, inflammation) on the skin surface of the of the application site during physical examination (small tattoos were acceptable).
9. Previous history of, or current or suspected, prostate or breast cancer.
10. Untreated prolactinoma.
11. Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
12. Previous history of, or current or suspected, eczema or psoriasis.
13. Abnormal digital rectal examination (DRE) defined as presence of nodule or induration.
14. International Prostate Symptom Score (IPSS) > 15.
15. Baseline prostate specific antigen (PSA) > 2.5 ng/mL. If the subject had documentation of a negative prostate biopsy within the past six months, a PSA of 2.6 – 3.74 ng/mL was allowed.
16. Positive screen for alcohol or drugs of abuse.

17. Positive human immunodeficiency virus (HIV) or Hepatitis B/C.
18. Hematocrit > 48% or hemoglobin > 16 g/dL.
19. Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.

Statistical Considerations:

Sample size calculation: Based on data from a previous study that assessed testosterone concentrations when AndroGel 1.62% was applied to the upper arms/shoulders compared to the abdomen (S176.1.007), assuming a mean C_{avg} of 700 ng/dL and standard deviation of 347 ng/dL, 60 subjects were determined to give 90% power to detect a 30% difference between application sites at the two-sided 0.05 significance level. A total of 62 hypogonadal male subjects were enrolled to allow for at least 60 subjects to complete the full trial.

Reviewer's Comment: In a 17 July 2010 advice letter, the Division stated "Rather than agreeing to any 'success criteria', we prefer to review the entirety of the data from S176.1.010 upon submission of the study report in the Complete Response (CR). The focus of our review will be the ratio of the geometric mean AC and Cmax for the two treatment regimens, and the 90% confidence intervals for that ratio."

Statistical Analysis Plan: The protocol stated that the default summary statistics for plasma concentrations and PK parameters was the number of observations (n), mean, SD, minimum (Min), median, maximum (Max), coefficient of variation (CV), and geometric mean.

The statistical objectives of this study were to evaluate the comparative bioavailability of observed testosterone after administration of 5.00 g testosterone gel 1.62% when applied using a rotation or using combination of both the upper arms/shoulders and the abdomen after multiple dosing. Relative bioavailability comparisons were based on ratios of $AUC_{0\text{-}24,}$ C_{avg}, and C_{max}. The reference treatment for comparison is Treatment A since it was a recommended dosing regimen in Phase 3.

Descriptive statistics (n, mean, SD, CV, median, geometric mean, Min, Max) were provided for each treatment group for C_{max}, $C_{trough,}$ C_{avg}, $AUC_{0\text{-}24,}$ peak to trough fluctuation index, and relative bioavailability for both observed and baseline-adjusted testosterone. Two-sided 90% confidence intervals were calculated for each parameter.

Comparisons of Treatment B to reference Treatment A were made for both observed and baseline-adjusted testosterone within the framework of a linear mixed effects model with treatment, period, and sequence as fixed effects and subject within sequence as random effect. Parameters were log-transformed prior to analysis, and for the baseline-adjusted parameters, the log-transformed baseline value was included in the model as a covariate. A non-parametric analysis was performed if the assumption of the parametric approach was not supported by the data. Inter and intra-subject CV and 90% confidence intervals for the ratios of test versus reference were provided.

A listing was produced with testosterone and DHT results. The ratio of DHT to testosterone was presented. All testosterone concentrations greater than 1000 ng/dL, and greater than 2500 ng/dL, were "flagged". A summary table was produced that summarizes the number of subjects with concentrations greater than 1000 ng/dL and greater than 2500 ng/dL.

Interim Analysis: Not applicable.

Safety: The safety sample was used for the analysis of the safety and tolerability data. AEs were reported on a per-subject basis, i. e. counting subjects rather than events. This meant that if a subject suffered the same AEs repeatedly during the applicable study period, the event was counted only once for that period. If a subject suffered the same AE more than once, the event was assigned the worst severity. Only treatment emergent AEs (TEAEs) were reported. In the listings, however, all occurrences of the AEs were presented.

Vital signs, including changes from baseline were summarized. Laboratory variables, including changes from baseline were summarized. Safety testosterone and hematocrit laboratory values were listed.

Non-standard safety data were collected in the following categories:

- Digital rectal examination
- International Prostate Symptom Score
- Application site evaluation at Day -1 and each day prior to administration of study drug.

Safety Considerations

The risks of multiple doses of testosterone in hypogonadal males was reviewed in the original NDA and found to be safe. The dose used in this protocol is the maximal dose for approval.

Application sites were assessed during the protocol

Study Results

Pharmacokinetic

A total of 62 hypogonadal male subjects were enrolled in this study and were allocated to treatment. All 62 subjects completed the study per protocol and none were prematurely withdrawn from the study as a result of AEs, lost to follow-up, withdrawal of consent, administrative reasons or protocol violations. All subjects were included the PK evaluations.

Two subjects on Day 1 only applied one 1.25 g gel dose incorrectly. All other dose administrations were correct for these subjects and Sponsor expects these two minor events did not affect the multiple dose pharmacokinetics on Day 7.

Overall the subjects enrolled in the study had a mean age of 47.4 years (range 29-74), mean height of 1.7 m (range 1.6-1.9) and mean weight of 84.1 kg (range 61.1-117.3). 57 subjects

(91.9%) were classified as White and 5 subjects (8.1%) were classified as Black (African Heritage or African American). 56 (90.3%) subjects were of Hispanic or Latino ethnicity.

The mean baseline (Day-1/Day14) concentrations of observed testosterone ranged from 263-371 ng/dL for Treatment A and 262-338 ng/dL for treatment B, representing values just below or at the lower end of the eugonadal range of 300-1000 ng/dL. Mean observed testosterone trough (pre-dose) concentrations on Days 5, 6, and 7 of each treatment period were 646, 681 and 834 ng/dL for Treatment A (Phase 3 method) and 517, 537 and 651ng/dL for Treatment B (4-site method). Visual inspection of the range of trough concentrations pre-dose on Days 5, 6, 7 suggest in the Sponsor's opinion that steady state testosterone concentrations were achieved by the 5th day of treatment administration.

Table 4: Mean (SD) Testosterone Pharmacokinetic Parameters

	Observed				**Baseline Adjusted**			
	Treatment A		**Treatment B**		**Treatment A**		**Treatment B**	
	n		**n**		**n**		**n**	
C_{max}(ng/dL)	62	*1283(817*)	62	866(369)	60	1000(833)	58	578(380)
AUC_{0-24} (ng*hr.dL)	62	14433 (5880)	62	11817 (3981)	60	7891 (5578)	58	5270(3647)
C_{avg} (ng/dL)	62	601(245)	62	496(166)	60	329(232)	58	220(152)

Note: negative concentrations were treated as missing and subjects with more than half of all concentrations negative for a given treatment are not included in the summary.
Source: Adapted from Table 6 of S176.1.010 Study report, page 46.

> *Reviewer's Comment: Treatment A (Phase 3 method) is associated with a higher C_{max} and AUC compared to Treatment B (4-site method).*

The numbers of subjects who had observed testosterone concentrations exceeding 1000 ng/dl or 2500 ng/dL after start of treatment are presented in Table 19. Sponsor points out that this study was conducted using the highest planned clinical dose of 5.00 g of testosterone gel 1.62% under fixed dose conditions, without the intended up-titration from a lower starting dose . See table below:

Table 5: Number of Subjects with Testosterone Concentrations Greater than 1000 ng/dL or Greater than 2500 ng/dL on Treatment in Study S176.1.010 (81 mg fixed dose)

	Number of Subjects (%)	
Treatment	**>1000 ng/dL (N=62)**	**>2500 ng/dL (N=62)**
A	31(50)	7(11)
B	21(34)	0

Source; Table 5 of S176.1.010 Study report, page 44.

Mean baseline (Day-1/Day14) concentrations of observed DHT ranged from 20.5 to 26.9 ng/dL (normal reference range 11.2-95.5 ng/dL) and estradiol concentrations ranged from 16.3 to 24.0 pg/mL (normal reference range 10-40 pg/mL). Concentrations of DHT ranged from 68.5 to 122.0 ng/dL and 64.2 to 103.0 ng/dL) after Treatment A and Treatment B, respectively. Concentrations of estradiol ranged from 23.6 to 38.8 pg/mL and 24.7 to 35.9 pg/mL after treatment A and Treatment B, respectively. Mean observed DHT and estradiol concentration-time profiles after treatment with testosterone gel 1.62% followed the same general pattern as the testosterone concentration data.

Table 6: Individual Testosterone and Dihydrotestosterone Concentrations in Patients with T>2500 ng/dL in Study S176.1.010 (81 mg fixed dose)

Subject (Dose Sequence)	Day of Occurrence T>2500	Hour° and Concentration (ng/dL)	DHT (ng/dL)	DHT/T Ratio
27525(A/B)	7	Predose 3340 1° -3240 8° -2290	242 383 216	0.072 0.012 0.080
27528(A/B)	7	1°-3370	358	0.106
27531(A/B)	7	1°-2780	240	0.086
27554(A/B)	7	3°-4010 8°-3500	246 158	0.064 0.045
27614(A/B)	7	3°-2920	186	0.064
27523(B/A)	21	2°-2530	128	0.051
27524(B/A)	21	Predose-3300	267	0.081

Source: S176.1.010 Study Report, Listing 12.2.6.1

Reviewer's Comment: It is to be noted that all patients were given the highest to be marketed dose without titration in protocol S176.1.010. This is the likely reason for these sporadic, transient elevations of testosterone concentrations.

Table 7: Predose Testosterone Concentrations in Patients with T>2500

Study Day **(Dose Sequence)**	-1	5	6	7	14	19	20	21
Patient	Predose Testosterone Concentrations							
27525 (A/B)	267	1570	1370	3340*	131	759	1490	696
27528 (A/B)	386	811	668	1230*	302	895	637	930
27531 (A/B)	296	1070	686	829*	225	613	519	695
27554 (A/B)	316	448	359	1770*	324	476	1080	524
27614 (A/B)	283	375	415	499*	180	365	383	1110
27523 (B/A)	363	732	665	860	348	922	1070	852*
27524 (B/A)	236	948	1050	714	198	759	1490	3330*

(*=Day of T >2500 ng/dL); Source: Source: S176.1.009 Study Report, Listing 12.2.6.1

Table 8: Comparison of Baseline-Adjusted Testosterone Pharmacokinetic Parameters-ANCOVA

Parameter	Analyte	Treatment	n	Comparison		
				Geo LS Mean	Ratio (%)	90% CI
AUC_{0-24} ng*hr/dL	Observed Testosterone (ANOVA) [terms for treatment, period, sequence with subject as random effect]	A	62	13459	0.836	0.781, 0.895
		B	62	11256		
C_{avg} (ng/dL)		A	62	561	0.836	0.781, 0.895
		B	62	469		
C_{max} (ng/dL)		A	62	1095	0.733	0.663, 0.812
		B	62	803		
AUC_{0-24} ng*hr/dL	Baseline-Adjusted Testosterone (ANOVA)* [terms for treatment, period, sequence with subject as random effect]	A	60	6092	0.672	0.565, 0.800
		B	58	4094		
C_{av} (ng/dL)		A	60	254	0.672	0.565, 0.800
		B	58	171		
C_{max} (ng/dL)		A	60	752	0.627	0.533, 0.737
		B	58	471		
AUC_{0-24} ng*hr/dL	Baseline-Adjusted Testosterone (ANOVA)* [terms for treatment, period, sequence with subject as random effect, log baseline PK as covariate]	A	62	13461	0.836	0.782, 0.894
		B	62	11255		
C_{av} (ng/dL)		A	62	561	0.836	0.782, 0.894
		B	62	469		
C_{max} (ng/dL)		A	62	1095	0.734	0.663, 0.812
		B	62	803		

* negative concentrations were treated as missing and subjects with more than half of all concentrations negative for a given treatment are not included in the summary.
Sources: Tables 10.1.2.3.3, 10.1.2.3.4, and 10.1.2.3.5, S176.1.010 Study Report, pages 131-133.

Reviewer's Comments:

1. *In most cases, the predose testosterone level rose throughout either treatment sequence, but more so in Treatment A*
2. *There does not appear to be a carryover effect from the previous treatment regimen.*
3. *In response to a 16 December 2009 FDA Request for Information, in commenting upon the seven subjects with total testosterone concentrations in excess of 2500 ng/dL, the Sponsor points out that these values were sporadic and not sustained. More importantly, these values did not occur under actual use conditions under which patients would start at the 2.5 g dose of AndroGel 1.62% and then undergo monitoring and titration to an individualized dose level.*
4. *Three of 62 subjects in Treatment Group B (4-site method) had a Cavg below 300 ng/dL on Day - these values were 295,291, and 288 ng/dL, respectively. Source Table 10.1.2.3.1 page 119 of 1187 Protocol S176.1.010).*

An additional analysis was performed by the reviewer to ascertain the number of patients in whom testosterone concentrations were below 300 ng/dL and 200 ng/dL respectively, after receiving 7 days of testosterone replacement. The two Treatments A and B were compared. Pre-dose and 24 hours post-dose were not utilized in the comparison.

Table 9: Patients with Low Testosterone Concentrations on 7th Day of Treatment

Treatment A		Treatment B	
Number of Patients with One or More Testosterone Concentrations Below Stated Limit			
<200 ng/dL	<300 ng/dL	<200 ng/dL	<300 ng/dL
2	21	2	34
Number of Patients with Two or More Testosterone Concentrations Below Stated Limit			
1	14	1	22

Source: Study Report S176.1.010 Listing 12.2.6.1 (adapted from)

Reviewer's Comment: In addition, there were five patients, by my count who had five or more testosterone concentrations below 300 ng/dL on the 7th day of Treatment B (4-site method) and one in Treatment A (Phase 3 method). Treatment B has a lower AUC and C_{max}.

Table 20 illustrates the PK analyses of the study results. The Sponsor reaches the following conclusions:

- Both application methods, combination of the abdomen and upper arms/shoulders (Treatment B – the "4-site" method), or a rotation from the abdomen to upper arms shoulders (Treatment A – the Phase 3 method), at a fixed 5 gm testosterone Gel 1.62% dose (81 mg of testosterone), resulted in mean testosterone C_{avg} and C_{max} values within or just above the eugonadal range of 300-1000 ng/dL.
- Based on the statistical comparisons, application of Androgel 1.62% to a combination of the upper arms/shoulders and abdomen (Treatment B) results in 16% lower C_{avg} and 27% lower C_{max} compared to application of gel with rotation from the abdomen to the upper arms shoulders (Treatment A).
- Given the present phase I study design, the wide eugonadal therapeutic range, and titration that will occur in clinical practice, these study results support dosing testosterone gel 1.62% using either a combination or rotation method of gel application.

Reviewer's Comment: Despite the approximately 20% reduction in exposure for the new 4-site method compared to the Phase 3 method, the results are close enough for me to conclude that the two application methods result in" comparable" exposure to testosterone. Based on this overall lower exposure, Treatment B had no elevations of testosterone in excess of 2500 ng/dL, fewer elevations above 1000 ng/dL, and some testosterone concentrations below 300 ng/dL. The Clinical Pharmacology review team has expressed concern regarding

the 20% overall lower exposure for the new 4-site method compared to the Phase 3 method.

Safety

All 62 hypogonadal male subjects enrolled in this study received study medication according to the planned dosing schedule.

No deaths or SAEs occurred during the course of the study. The proportion of subjects with non-serious TEAEs was the same for both study treatments (27% [17 of 62 subjects]). No subjects were discontinued due to a study-related TEAE.

Table 10: Overview of Adverse Events

Category	Number of Subjects (%)	
	Treatment A (N=62)	Treatment B (N=62)
Deaths	0	0
Subjects with a least one SAE	0	0
Subjects with a least one TEAE	17 (27)	17 (27)
Subjects with TEAE Leading to Termination	0	0
Subjects with at least one severe TEAE	0	0
Subjects without TEAE	45 (73)	45 (73)

Source: Adapted from Table 8, S176.1.010 Study Report, page 50

No individual TEAE occurred in ≥5% of subjects for either Treatment A or Treatment B. Gastrointestinal disorder TEAEs were the most frequent non-serious TEAEs reported in 11 subjects (18%) across both treatments. Non-serious gastrointestinal disorder TEAEs included diarrhea (4 subjects, 6.5%), constipation (2 subjects, 3%), nausea (2 subjects, 3%), and in 1 subject each abdominal discomfort, toothache, and dry mouth (2%) across both treatments. Other non-serious TEAEs reported most frequently were skin and subcutaneous tissue disorders (9 subjects, 14.5%), general disorders and administrative site conditions (6 subjects, 9.6%) and headaches (4 subjects, 6.5%) for both treatments combined. The majority of non-serious TEAEs reported during the course of this study were mild in severity. Three subjects experienced events of moderate severity.

Table 11: Display of Adverse Events Occurring in More Than One Patient (HLT and PLT)

HLT PT	A (N=62) n (%) Events	B (N=62) n (%) Events
Subjects with at Least One TEAE	17 (27.4%) 28	17 (27.4) 29
GI Motility and Defecation	4 (6.5) 5	2 (3.2) 2
Diarrhea	2 (3.2) 3	2 (3.2) 2
Constipation	2 (3.2) 2	2 (3.2) 2
GI Signs and Symptoms	3 (4.8) 3	0
Abd. Discomfort	3 (3.2) 2	0
Epidermal/Dermal Conditions	1 (1.6) 1	5 (8.1) 8
Erythema	1 (1.6) 1	1 (1.6) 1
Dermatitis	0	1 (1.6) 1
Pruritis	0	1 (1.6) 1
Rash Papular	0	1 (1.6) 1
Skin Irritation	0	1 (1.6) 1
Skin Appendage Conditions	3 (4.8) 3	0
Acne	1 (1.6) 1	0
Alopecia	1 (1.6) 1	0
Hyperhydrosis	1 (1.6) 1	0
Headaches	2 (3.2) 3	2 (3.2) 4
Headache	2 (3.2) 3	2 (3.2) 4

Source: Table 10.1.3.1.2, S176.1.010 Study Report, pages 140-143.

Application site assessments using a protocol-specified scale were performed pre-dose on Days -1 to 21 and on Day 22/Early Termination. The Sponsor reports treatment-emergent AEs related to application site assessments were recorded for 3 (4.8%) subjects receiving Treatment B. All three subjects developed one or more papules at the administration site. No TEAEs were reported for Treatment A. The application site evaluation terms were as follows:

Irritation-numeric grades:

0. No evidence of irritation.
1. Minimal erythema, barely perceptible
2. Moderate erythema, readily visible or minimal edema or minimal papular response
3. Erythema and papules
4. Definite edema
5. Erythema, edema, and papules

6. Vesicular eruption
7. Strong reaction spreading beyond test site

Irritation letter grades:

A. Slight glazed appearance
B. Marked glazing
C. Glazing with peeling and cracking
F. Glazing with fissures
G. Film of dried serous exudates covering all or portion of the patch site
H. Small petechial erosions and/or scabs

No patient in either Appendix 12, Listing 12.2.4.9 and Appendix 12.2.7, Listing 12.2.7.1 had an application site assessment that required a letter grade.

A summary chart of application site findings was constructed by the reviewer (see Table 25 below). Any subject with abnormal application site findings on Day -1 was omitted. To be included in this list, a subject had to have a finding occur twice in the same treatment period. The most severe level of irritation was used. If an individual had a similar level of irritation in both treatment periods, then the first treatment was listed as the inciting treatment. If the severity of irritation decreased from the first treatment to the second treatment, then the first treatment was considered causal. If the converse occurred, only the level of irritation in the first treatment period was listed. See table below:

Table 12: Tabulation of Application Site Irritative Events

Subject	Attributed Treatment	Irritation Location	Grade
27527	A	All four sites	1
27545	B	All four sites	1
27546	B	All four sites	1
27551	A	All four sites	1
27559	B	All four sites	1
27564	B	R, L upper arms/shoulders	1
27565	B	R, L abdomen	1
27568	B	R, L abdomen	1
27552	B	All four sites	1
27550	B	All four sites	2
27556	B	All four sites	2

Source: Listing 12.2.4.9 Application Site Evaluation, S176.1.010 Study Report.

Reviewer's Comment: For those patients who made this list, all but 2 had Grade 1 erythema. Case 27550 had an irritative grade 2 skin finding only on 1 site (upper arm shoulder) on Days 16 through 19. On Days 20 and 21 and 22 the findings at that site

were 0, 1, 0 respectively, demonstrating resolution of the erythema with continued use. Case 27566 had an irritative finding of grade 2 at all four sites on Days 4, 5, 6, 7, and 8. On Days 14 through 20, this subject had an irritative grade of 1 at all sites, but Day 21 the irritative grade noted was zero at all sites. Thus, there is only one subject in this study with possible skin irritation. In Study S176.1.009 (N=235), a formal contact sensitization and irritation study, only 2 subjects were noted to have a mild skin rash. This reviewer's conclusion for that study was "Testosterone Gel 1.62% appears to have no sensitization potential and minimal irritation potential as compared to placebo. However, rash was reported in 2 patients and "rash" should be included in labeling." The results from Study S176.1.010 do not alter that recommendation.

Clinical Laboratory Evaluation: There were no overall trends in hematology, blood chemistry, or urinalysis values that were judged to be clinically important.

Five patients entered the study with hematocrits below the normal limit (normal 42-54% for males). There was no report of a hematocrit above 54%. At study termination, all hematocrits in these 5 patients were still below the normal limit. Their were no other laboratory abnormalities in these subjects to implicate a process that could account for the lowered baseline hematocrits in these 5 subjects except for Subject 27524 who entered the study with an eosinophil count of 16% and at end of study the eosinophil count was 18%. The hematocrit results for these 5 subjects are presented in the table below:

Table 13: Summary of Abnormal Hematocrit Assessments

Subject	Treatment Sequence	Baseline Value	Abnormal Value/Day
27524	B/A	41.4%	36.8%/Day 22 EOS
27529	B/A	38.3%	36.3%/Day 22 EOS
27536	A/B	39.9%	36.7%/Day 22 EOS
27538	A/B	36.6%	36.6%/Day 22 EOS
27565	A/B	38.7%	36.3%/Day 22 EOS

* EOS=end of Study; Source: Adapted from Table 9, S176.1.010 Study Report, page 55.

Subject 27525 entered the study with a uric acid of 10.9 mg/dL and at end of study the uric acid was 9.6 mg/dL. There were no noted changes in liver chemistries, serum albumin levels or EGFR in this subject during the study.

Subject 27569 at end of study [Day 22] reported a GGT of 126 U/L (baseline was 74 U/L). The normal range for GGT is 1-94 U/L. An unscheduled Day 27 GGT was 106 U/L. The subject had no abnormalities or increases of bilirubin, alkaline phosphatase, aspartate amino transferase, alanine aminotransferase, or ALT.

There was a total of 7 patients with minor laboratory abnormalities in this study. None of the 7 patients with laboratory abnormalities had an explanatory finding in their medical history.

Reviewer's Comment: These abnormalities do not need further evaluation.

Vital Signs: With respect to the blood pressure, there was no conclusive trend noted during the Study. Table 23 (below) was derived from a summary of vital signs. Blood pressure summary analysis did not take into account which treatment came first (to detect a carryover effect) as there was a 7-day washout period between treatment arms. After completion of each treatment arm a pulse increase was noted (Treatment A 3.7 bpm [SD 8.6] and Treatment B 5.9 bpm [SD 8.4]).

Table 14: Summary of Blood Pressure (mmHg)

Visit	Statistics	Treatment A (N=62)	Treatment B (N=62)
Baseline (Day1/Day15)	n Mean (SD) Systolic/*Diastolic*	62 **122**(14.2)/***81.0****(7.4)*	62 **120.9**(14.1)/*80.**9**(7.0)*
Change from Baseline	Mean (SD) Change from Baseline Systolic/*Diastolic*	n=62 for all baseline comparisons	
Day 2/ Day 16		**0.6** (8.8)/***0.1*** *(6.2)*	**3.1** (12.1)/***0.6*** *(6.0)*
Day 3/ Day 17		**0.8** (9.9)/***1.0*** *(6.1)*	**2.1** (9.7)/***0.8*** *(6.2)*
Day 4/ Day 18		**2.1** (9.4)/***0.8*** *(6.4)*	**1.0** (11.8)/***-0.2*** *(6.7)*
Day 5/ Day 19		**0.0** (9.8)/***-0.3*** *(6.2)*	**0.9** (11.0)/***-0.5*** *(7.0)*
Day 6/ Day 20		**-0.4** (9.8)/***0.5*** *(6.3)*	**0.8** (11.5)/***-0.8*** *(6.4)*
Day 7/ Day 21		**-1.2** (10.6)/***0.5*** *(6.2)*	**-1.5** (13.3)/***-0.7*** *(6.8)*
Day 8/ Day 22		**-0.1** (11.6)/***1.0*** *(7.1)*	**2.1** (14.1)/***-0.6*** *(7.2)*

Source: Adapted from Table 10.1.3.3.1, S176.1.010 Study Report, page 249.

Three subjects experienced markedly abnormal vital signs values during the study. Narratives are below:

Subject 27539: This 54-year old Hispanic/Latino White male was randomly assigned to treatment sequence A/B. He received the Phase 3 method in the first period Days 1-7 and the 4-site method in the second period (Days 15-21). On Day 5, the subject experienced an increase in sitting DBP (increased from 94 mmHg at Baseline to 114 mmHg on Day 5) that met the criteria for markedly abnormal vital signs. At a subsequent unscheduled assessment on Day 5 (that same day), the subject's sitting DBP was 90 mmHg (below baseline) and remained below the baseline level throughout the completion of Treatment A. No medical history of hypertension was reported and no AE related to the markedly abnormal DBP was recorded.

Subject 27606: This 57-year old Hispanic/Latino White male was randomly assigned to treatment sequence B/A. He received the "4-site method" in the first period (Days 1-7) and

the Phase 3 method in the second (Days 15-21). The subject experienced increases in sitting SBP and sitting DBP at an unscheduled assessment on Day 15 (SBP increased from 111 mmHg at Baseline to 187 mmHg on Day 15; DBP increased from 83 mmHg at Baseline to 111 mmHg on Day 15). The scheduled Day 15 blood pressure measurement (at 06:16) was 168/109 mmHg. A subsequent recheck at 07:20 on the same day was normal (111/83 mmHg). The further recheck at 16:35 on the same day was again elevated (187/111 mmHg); these blood pressure changes met the criteria for markedly abnormal vital signs. At the next scheduled blood pressure assessment (the next day -Day 16, 07:20), the subject's SBP and DBP measurements were 118 mmHg and 84 mmHg, respectively, and remained near baseline levels through the completion of Treatment A. No medical history of hypertension was reported and no AEs related to the markedly abnormal SBP and DBP were recorded.

Subject 27545: This 52-year old non-Hispanic/Latino White male was randomly assigned to treatment sequence B/A. He received the "4-site method" in the first period (on Days 1-7) and the 4-site method in the second period (Days 15-21). On Day 6, the subject experienced an increase in body temperature (increased from 36.4°C at Baseline to 38.5°C on Day 6) that met the criteria for markedly abnormal vital signs. At the next scheduled temperature assessment (the next day, Day 7), the subject's body temperature was 36.2°C. No AE related to markedly abnormal body temperature was recorded.

> *Reviewer's Comment: I have no comments for Subject 27539 (one time elevation of DBP which upon repeat was not verified) or Subject 27545 (one time temperature elevation) further. Subject 27606 had elevated blood pressures on Day 15 and subsequent return to baseline the next day. It is not clear that this is a drug-related adverse event. Still, increase in blood pressure (possibly related to fluid retention) is a known potential adverse reaction of testosterone replacement therapy and is appropriately described in the proposed product label for AndroGel 1.62%.*

Electrocardiograms: ECGs were collected at Screening (Baseline) and study exit. The results are depicted in the table below:

Table 15: Overall Safety ECG Assessment

Visit	A/B (N=31)	B/A (N=31)	All Subjects (N=62)
	n (%)		
Screening	31	31	62
Normal	14 (42.5)	15(48.4)	29 (46.8)
Abnormal CS	0	0	0
Abnormal NCS	17 (54.8)	17 (54.8)	34 (54.8)
Day 22/EOS	31	31	62
Normal	22 (71.0)	23 (73.2)	45 (72.6)
Abnormal CS	0	0	0
Abnormal NCS	9 (29.0)	8 (25.8)	17 (27.4)

CS=deemed clinically significant by investigator, NCS=deemed not clinically significant by investigator
Source: Adaption Table 10.1.3.4.1, S176.1.010 study report, page 262.

One subject, 27546, randomly assigned to treatment sequence A/B, experienced sinus rhythm with first degree AV block at study exit. Subject 27606, randomly assigned to treatment sequence B/A, experienced a non-specific T-wave abnormality at study exit. Subject 27562, a 50-year old non-Hispanic/Latino Black male, randomly assigned to treatment sequence A/B, received Testosterone Gel 1.62% (5.00 g) on Days 1-7 and Days 15-21. The subject experienced what was described as a low voltage QRS, inferior infarction at study exit. The observation was not considered clinically significant by the investigator.

Reviewer's Comment: The possible low voltage QRS, inferior infarction at study exit (Subject 27562) is the only ECG abnormality of concern to this reviewer. There are no supporting enzyme or clinical data and no repeat ECGs to very that this is indeed a true finding or document evolution of ECG changes. In addition, safety data from S176.3.104, do not indicate an increased ECG safety risk. I would not pursue these results further.

Physical Examinations: There were no clinically significant digital rectal examinations (DREs) throughout the study. One subject (27605 randomized to treatment B/A) had a normal DRE at Screening, but an abnormal, non-clinically significant DRE at study exit ("mildly enlarged prostate"). At a follow-up recheck (Day 51) the subject's DRE was normal. There were no discernible trends in the PSA or abnormal PSAs noted.

Both increases and decreases in the International Prostate Symptom Score (IPSS) from Baseline to post treatment were observed, with most increases being of a magnitude of 1-2 points. One subject (27526) had an increase in IPSS from 1 to 11. No AEs related to IPSS results were reported.

Sponsor's Safety Conclusions:

Testosterone gel 1.62% appeared to be safe and well tolerated in this population of hypogonadal males when administered as a once daily fixed dose of 5 gm (81 mg of testosterone) applied to the abdomen for 3 day followed by arms shoulders for 4 days or a combination of the abdomen and upper arms/shoulders for 7 days.

No deaths, SAEs, or discontinuations due to AEs occurred during this study. Individual TEAE occurred in fewer than 5% of subjects for both treatments. The most common SOCs for the TEAEs were gastrointestinal, skin and subcutaneous tissue disorders, general disorders and administrative site conditions, and nervous system disorders. No trends or clinically significant changes were noted in clinical laboratory data, vital sign data, DRE results, or IPSS data.

Reviewer's Comment: I agree with the Sponsor's safety conclusions. Treatment B (the "4-site" method) provides systemic testosterone exposures of approximately 80% of

Treatment A (the method used in the pivotal study S176.3.104). (b) (4) (b) (4) (b) (4) *Clinical Pharmacology is uncomfortable with the dropoff in exposure with Treatment B.* (b) (4) (b) (4) *The Sponosor responded by agreeing that that confusion could arise for patients. They propose basing dosing and administration instructions on the arms/shoulders method alone. They have submitted* (b) (4) *labeling to that effect which is under final review. I find the Sponsor's decision appropriate and acceptable.*

5.3.3 Protocol S176.1.011: 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.

Design and Conduct of Study S176.1.011

Basic Design:

The primary study objectives were:
To determine the pharmacokinetics of total testosterone concentrations in female subjects after a single episode of skin contact with a male partner dosed with testosterone gel 1.62% (5 g) to the upper arms/shoulders only.
To evaluate testosterone transfer from males dosed with testosterone gel 1.62% (5 g) to non-dosed female subjects when contact with the upper arms/shoulders application site occurred at 2 hours postdose with a t-shirt barrier.

Secondary objectives:

Not applicable

Reviewer's Comment: The primary objective of this study was to show that a t-shirt barrier effectively blocks the transfer of testosterone to a female partner after a single episode of skin contact, when the male applied 5 g of testosterone gel 1.62% to both upper arms and shoulders (2 anatomic sites). The arms/shoulder only method was allowed in the pivotal Phase 3 study, S176.3.104. In addition the pharmacokinetics of this method were shown to be virtually identical to a rotating arms/shoulder and abdomen method (which was the recommended Phase 3 method) in the Phase 1 study S176.1.007. The primary objective and rationale for the study are acceptable and sound.

This study was a single center, single dose, open-label study in healthy male and female volunteers. Twelve (12) male-female couples who consented to participate in this study and met

the inclusion/exclusion criteria were enrolled in the study. All male-female couples enrolled underwent the same dose and skin contact procedures.

The test product was AndroGel 1.62%, 5 g of gel, containing 81 mg of testosterone.

On Study Day 1, all male subjects received an application of testosterone gel. Two hours following gel application to the male subjects, 15 minutes of supervised skin contact of the application sites occurred between the dosed female and the non-dosed female partner as described below:

Males: Application of testosterone gel to the upper arms/shoulders (2.5 g of gel applied to each the left and right upper/arm shoulder for a total dose of 5 g.

Dosing was to occur in 1.25 g gel increments. 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 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 and including the back of the arm, spread over the maximum surface area without reapplying gel to the previously dosed areas. The fourth 1.25 g was to be applied to the opposite upper arm as described above without reapplying gel to the previously dosed areas.

Females: Skin contact with application site at 2 hours post dose; male wearing a t-shirt. The t-shirt to be used was a 100% cotton long-sleeved t-shirt that fully covered the application sites. Female subjects were given a tube top to wear to expose the shoulders and arms. Male subjects were given a long-sleeved 100% cotton t-shirt to wear that fully covered the application site.

Each couple engaged in a total of 15 minutes of contact in a vertical position. Female subjects were instructed to rub their hands, wrists, arms, and shoulders up and down the arms and shoulders of their male partner during the contact period. One minute periods of alternating active rubbing and resting of the female's arms on the male's shoulders were to occur until the 15 minute time period was complete. After contact, female subjects waited at least 5 minutes prior to putting clothes over the exposed area. Female subjects thoroughly washed their hands with soap and water immediately after skin contact was complete. Female subjects were not to shower or bathe until 24 hours after the contact period. The antecubital region of the female's arms was covered during the contact period to prevent potential blood sample contamination.

Female subjects were confined to the study site Days -2 to 3 for a total of approximately 5 days and 4 nights throughout the course of the study. Male subjects were confined to the study site Days -1 to 1 for a total of approximately 2 days and 1 night throughout the course of the study.

Serum testosterone concentrations were used to calculate C_{max}, T_{max}, T_{min}, $AUC_{0-24,}$ and C_{min} on Days -1 and 1.

Dose Rationale: As in Study S167.1.009 5 gm (81 mg of testosterone, the largest to-be-marketed dose) was utilized. This method was allowed in the pivotal Phase 3 study S176.3.104. The PK

of this method was measured in Study S176.1.007 and was found virtually identical to the rotating method (arms/shoulder and abdomen) recommended in the Phase 3 study. Therefore if a T-shirt barrier largely mitigates transfer from male to female, this study by itself will satisfy the data requirement stipulated in the COMPLETE RESPONSE action.

Safety Parameters and Endpoints: Separate male and female safety samples were used for the analysis of the safety and tolerability data. AEs were reported on a per-subject basis, i. e. counting subjects rather than events for the applicable period. If the event occurred more than once in the applicable period, the event was assigned the worst severity, the closest relationship to the study drug, and the earliest starting date. Only treatment-emergent AEs were reported, but in the listings, all occurrences of AEs were presented.

Vital signs, including changes from baseline were summarized. Laboratory variables, including changes from baseline were summarized. Safety testosterone and hematocrit laboratory values were listed.

Pharmacokinetic measurements from female subjects only were done for determination of total testosterone, estradiol, and dihydrotestosterone at the following times:

- Day-1 (baseline) at 0, 2, 4, 6, 8, 10, 12, 16 hours with respect to the planned end time of skin contact on subsequent days.
- Day 1 at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 16, 24 and 48 hours after the end of skin contact

Inclusion and Exclusion Criteria:

Inclusion Criteria
Males

1. Documentation of written informed consent.
2. Male subjects 18-80 years of age, inclusive
3. Subjects with a Body Mass Index of 20-35 kg/m^2, inclusive.
4. In the opinion of the investigator, the subject is determined to be in good health as determined by vital signs, medical history, physical exam, ECG, and laboratory examination (hematology, clinical chemistry, and urinalysis).
5. Negative hepatitis B/C and HIV.

Females

1. Documentation of written informed consent.
2. Female subjects 18-80 years of age, inclusive.
3. In the opinion of the investigator, the subject is determined to be in good health as determined by vital signs, medical history, physical exam, ECG, and laboratory examination (hematology, clinical chemistry, and urinalysis).
4. Subjects with a Body Mass Index of 20-30 kg/m^2, inclusive.

5. Subjects with a screening testosterone in the normal range, as specified by the normal range at the testing facility.
6. Negative hepatitis B/C and HIV.

Exclusion Criteria

Male

1. Positive screen for alcohol or drugs of abuse.
2. Subject with a hematocrit >48%.
3. Previous history of, or current or suspected, prostate or breast cancer.
4. Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
5. Findings of any kind of skin lesions on the skin surface of the upper arms/shoulders and abdomen during physical examination (small tattoos are acceptable).
6. Participants in any investigational drug trial within the previous 30 days.
7. Receipt of any prescription medication within 21 days prior to Day -2 of the study or receipt of non-prescription (OTC) medication within 7 days of Day-2 without sponsor approval.
8. Subjects who smoked or used other nicotine products within the past 12 months.
9. Consumption of caffeine-containing products in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day -2 (caffeine-containing products were not allowed during each study period).
10. Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.
11. Baseline Prostate Specific Antigen (PSA) > 2.5 ng/mL. If the subject has documentation of a negative prostate biopsy within the past six months, a PSA of 2.6-3.74 ng/mL will be allowed.
12. Abnormal digital rectal examination (DE) defined as presence of nodule or induration.
13. Untreated prolactinoma.
14. Previous history of, or current or suspected, eczema or psoriasis.

Female

1. Subjects who are pregnant or lactating.
2. Subjects of child-bearing potential who are not using an acceptable method of birth control. Barrier methods of birth control (i. e., diaphragm/condom with spermicide) are acceptable for study participation. Oral or implanted contraceptives are unacceptable methods of birth control for study participation. Female subjects who are surgically sterile are enrolled.
3. Previous history of, or current or suspected, hirsutism.
4. Participants in any investigational drug trial within the previous 30 days.
5. Positive screen for alcohol or drugs of abuse.
6. Receipt of any prescription medication within 21 days prior to entry into the study, or receipt of non-prescription medication or herbal products within 7 days of study commencement without sponsor approval.
7. Blood or plasma donation within the 60 days prior to study entry.

8. Subjects with any clinical/biochemical impairment of liver function or receipt of known hepatic enzyme inducing or inhibitory agents within 90 days prior to entry into study.
9. Use of any drug with a half-life greater than 24 hours in the past 12 months without sponsor approval.
10. Subjects who smoked or used other nicotine products within the past 12 months.
11. Consumption of caffeine-containing products in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day -2 (caffeine-containing products were not allowed during each study period).
12. Findings of any kind of skin lesions on the skin surface of the upper arms/shoulders and abdomen during physical examination (small tattoos are acceptable).
13. Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.
14. Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
15. Previous history of, or current or suspected, eczema or psoriasis.

Reviewer's Comment: The eligibility criteria are reasonable.

Table 16: Female and Male Schedule of Assessments

Female Subjects

Assessment	Days					
	-23 to -2	-2	-1	1	2	3 or Early Termination
Screening	X					
Medical History	X					
Physical Examination, including weight	X					X
Height and BMI	X					
CBC, Clinical Chemistry, Urinalysis	X					X
Testosterone for Inclusion	X					
Viral Screen	X					
Serum β-HCG	X	X				X
Drug and Alcohol Test	X	X				
12 Lead ECG	X					X
Record Date Last Menstrual Period		X				
Admit to Clinic		X				
Vital Signs (BP, pulse, temp)	X	X	X	X	X	X
Contact Site Evaluation			X	X	X	X
Skin Contact with Male Partner				X		
PK Blood Sample			X[1]	X[2]	X[3]	X[2]
Baseline/Adverse Event Recording	X	X	X	X	X	X
Record Concomitant Medication	X	X	X	X	X	X
Discharge from Clinic						X[4]
Study Completion						X

[1]At 0, 2, 4, 6, 8, 10, 12, and 16 hours relative to the projected time of skin contact on Day 1.
[2]At 0 (predose), 2, 4, 6, 8, 10, 12, 16, 24, and 48 hours after end of skin contact on Day 1.
[3]Continued blood sampling from Day 1.
[4]Females were to be discharged from the clinic on Day 3 after the post-study assessments were complete.

Male Subjects

Assessment	Days		
	-23 to -2	-1	1 or Early Termination
Screening	X		
Medical History	X		
Physical Examination, including weight	X		X
Height and BMI	X		
CBC, Clinical Chemistry, Urinalysis	X		X
PSA	X		X
DRE	X		
Viral Screen	X		
Drug and Alcohol Test	X	X	
12 Lead ECG	X		X
Admit to Clinic		X	
Vital Signs (BP, pulse, temp)	X	X	X
Application Site Evaluation		X	X
Dose Application			X
Skin Contact with Female Partner			X
Baseline/Adverse Event Recording	X	X	X
Record Concomitant Medication	X	X	X
Discharge from Clinic			X[1]
Study Completion			X

[1]Males were to be discharged from the clinic on Day 1 after all dosing and skin contact study procedures and post study assessments were complete.

Source: Copy of Table 5.5.1.4-1, Study Report S176.1.011, pages 24-25.

Statistical Considerations:

Sample size calculation: The Sponsor estimated that a sample size of 12 couples would give 80% power to detect a change from baseline in the serum testosterone of non-dosed females, given that the true mean difference is 9 ng/dL with a standard deviation of 10 ng/dL (based on the results from the S176.1.003 study), using a paired t-test.

Statistical analysis plan: The protocol stated that the default summary statistics for quantitative and ordinal variables would be the number of observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) for subjects with data. Any other summary statistics would be described on an individual basis. For qualitative variables, per category the numbers and frequencies of subjects with non-missing data (n, %) would be the default summary presentation, and if appropriate and present, the number of missing values.

The safety sample would consist of all subjects who had exposure to at least one dose of study medication. The pharmacokinetic (PK) sample would consist of all subjects included in the safety sample and who had sufficient bioanalytical assessments to calculate a complete set of the primary pharmacokinetic parameters. The following PK parameters were calculated:

- C_{trough} = observed predose serum concentration, representing the troughs
- C_{min} = the lowest concentration observed during the 24-hour dosing interval
- C_{max} = observed maximum serum concentration
- T_{max} = time to reach maximum observed serum concentration
- T_{min} = time of minimum observed serum concentration
- $AUC_{(0-24)}$ = area under the serum concentration-time curve from zero to 24 hours
- C_{avg} = the time-averaged concentration over the dosing interval: $AUC_{(0-24)}/24$
- PTF = peak trough fluctuation: C_{max}- C_{min}/ C_{av}

The objective was to assess within treatment differences in $AUC_{(0-24)}$, C_{avg}, and C_{max} pharmacokinetic parameters for total testosterone between baseline (Day-1) and Day 1. Comparisons to baseline was the primary analysis. Two- sided 90% confidence intervals were calculated for each parameter.

Interim analysis: Not applicable

Safety Considerations: The risks of a single dose of testosterone in healthy eugonadal males were considered minimal. The risk of transfer to a female partner was considered small, and even if such was to occur, testosterone is rapidly metabolized and would not be expected to be of harm in this single dose study, especially in women who are surgically sterilized or using an acceptable form of contraception. In a previous transfer study (S176.1.003), which included treatment arms of direct male to female skin contact, as well as contact with the male wearing a t-shirt barrier, there were only rare occurrences of testosterone levels above the normal range for female subjects. The most frequent TEAEs were headache, dyspepsia, and dizziness. There were no withdrawals due to AEs and there were no SAEs or deaths. This previous study required males to apply testosterone gel 1.62% daily for 7 days, compared to a single day for the current study S176.1.011.

Study Results

The Sponsor made one change to their planned analyses when they concluded that Day 1, 12 hour samples from female subjects 27579 and 27581 had been switched. 10, 12 and 16 hours of these subject's Day 1 serum samples were analyzed for gamma glutamyl transpeptidase (GGTP). The GGTP results from these samples along with the results at screening and the end of the study, indicated that the samples had been switched. This investigation was conducted by the Quality Assurance group of Cetero Research-Miami. The database was corrected so that the primary pharmacokinetic and statistical analysis used a dataset in the corrected form. The Sponsor also included an "as is" analysis in Appendix 12.1.9.3.

Reviewer's Comment: This correction is acceptable. The results of the "as is" analysis were also reviewed. I will base my analysis on the corrected database.

Disposition: A total of 12 couples (24 subjects consisting of 12 males and 12 females) were enrolled in the study. No subjects discontinued from the study.

Protocol Deviations: No protocol deviations occurred pertaining to:

- Inclusion/exclusion criteria
- Protocol deviations
- Conduct of the study
- Pharmacokinetic sample deviations - except for the switching of Day 1, 12 hour serum samples between female subjects 27579 and 27581.

Demographics: A summary of demographic data is presented below:

Table 17: Subject Demographics Protocol S176.1.011

Gender	**N**	**Mean Age (range)**	**Mean BMI (kg/m^2)**
Males	12	41.9 (29-52)	28.35
Females	12	40.3 (21-59)	26.26

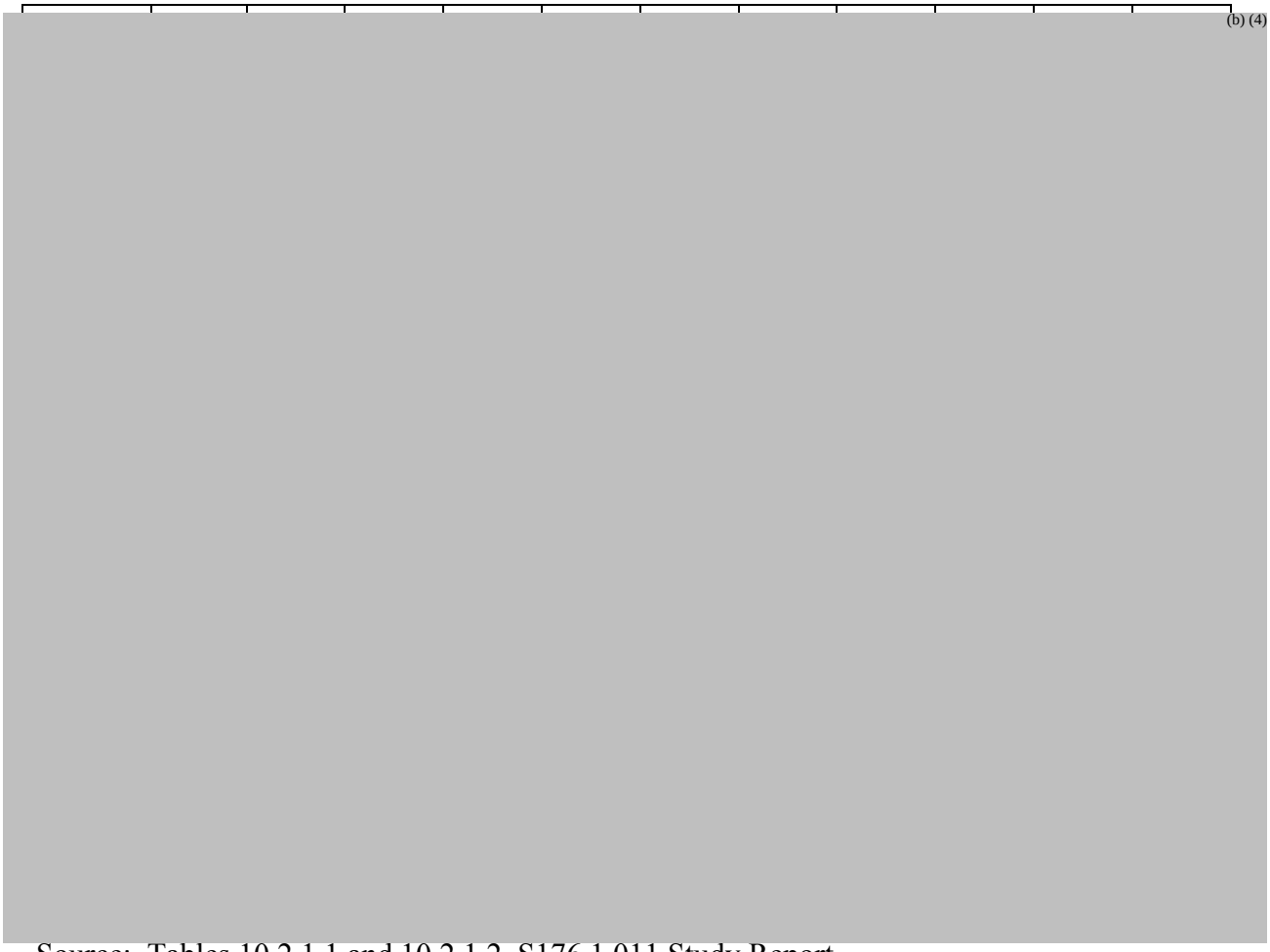
Source: Adapted from Table 10.1.2, S176.1.011 Study Report

All females were white, Hispanic. 10 of 12 males were white, Hispanic or Latino and 2 of 12 males were black/ African American, Hispanic or Latino.

Pharmacokinetic Results:

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. Individual testosterone concentrations for each female subject are provided in the table below:

Table 18: Testosterone Concentrations in Female Partners of Men Dosed with Androgel 1.62% 5 gm (81 mg of testosterone) on the Upper Arms/Shoulders – Times Shown are the Hours Post Contact



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

Table 19: Selected Individual Pharmacokinetic Parameters for Day-1 and Day 1 (Individual Female Subjects) S176.1.011

Subject N=12	**T_{max} Day-1**	**T_{max} Day 1**	**C_{max} Day-1**	**C_{max} Day 1**	**AUC/C_{avg} Day-1**	**AUC/C_{avg} Day 1**
	(h)		**ng/dL**		**h*ng/dL**	
27571	16.0	16.0	56.3	58.9	1182.6/49.3	1172.6/48.9
27572	24.0	16.0	63.6	74.5	1371.4/57.1	1615.88/67.3
27573	24.0	0.0	32.4	32.4	673.5/28.1	676.5/28.2
27574	16.0	16.0	13.0	10.9	265.9/11.1	236.7/9.9
27575	8.0	8.0	36.3	40.9	746.6/31.1	800.7/33.4
27576	4.0	8.0	21.2	19.5	419.7/17.5	403.7/16.8
27577	24.0	4.0	13.1	15.9	280.0/11.7	320.4/13.4
27578	24.0	10.0	28.0	30.1	543.2/22.6	529.3/22.1
27579	16.0	24.0	8.4	9.8	177.1/7.4	197.9/8.2
27580	16.0	16.0	9.4	10.1	192.4/8.0	219.1/9.1
27581	24.0	0.0	18.6	18.6	401.2/16.7	383.0/16.0
27582	0.0	6.0	15.5	32.0	302.9/12.6	420.6/17.5
Mean	16.3	10.3	26.4	29.5	546.4/22.8	581.4/24.2

Source: Tables 10.2.2.1 and 10.2.2.2, S176.1.011 Study Report.

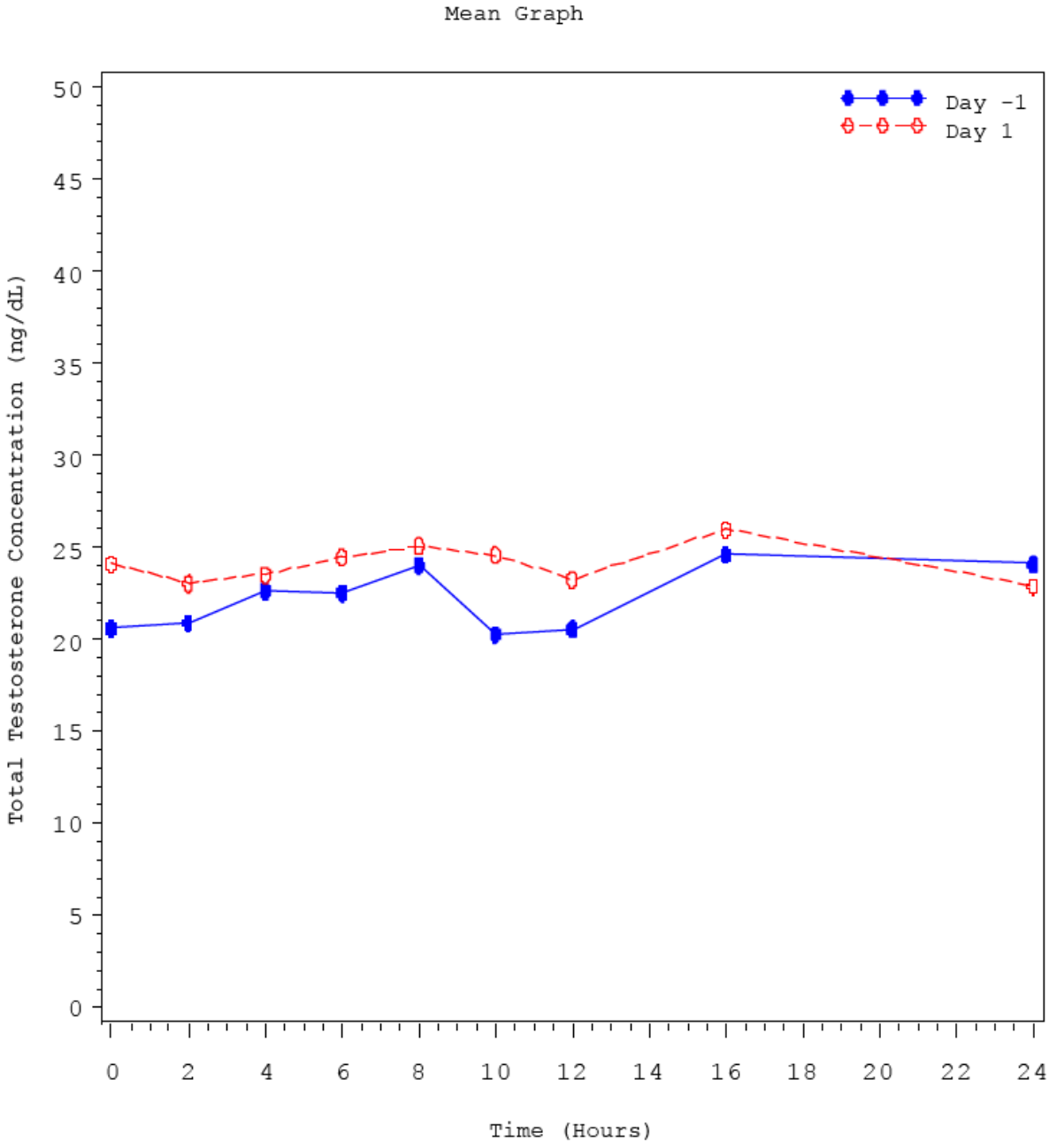
Table 20: Summary of PK Parameters for Total Testosterone; N=12 females

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

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

The figure below shows mean total testosterone concentrations in females in S176.1.011:

Figure 1: Mean Female Total Testosterone Concentrations



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

Table 21: 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 of S176.1.011 Study Report.

The Sponsor observes that the mean pharmacokinetic parameters for C_{min}, C_{max} and C_{avg} were similar between baseline (Day-1) and Day 1 after skin contact. The largest increase in C_{avg} for an individual subject was 10.2 ng/dL (in Subject 27572). This subject's pre-dose concentration (Hour 0) was increased by 11.7ng/dL between Day -1 and Day 1. This increase was observed at Hour 0 on Day 1; this is, prior to any skin contact. This increase remained consistent throughout the 24 h measurement period on Day 1. It is notable that there were changes in serum testosterone in the same patient even on Day -1, prior to any skin contact with men using AndroGel 1.62%. The largest fluctuations in serum testosterone on Day -1 within a given subject were 22.0 ng/dL, 14.5 ng/dL and 13.8 dL in subjects 27571, 27572, and 27575, respectively.

The largest increases from Day -1 to Day 1 in C_{max} were 15.5 ng/dL (Subject 27572) and 19.3 ng/dL (Subject 27582). The Sponsor states that the increased C_{max} for subject 27572 is related to the pre-dose increase observed prior to skin contact procedures (as described in the previous paragraph). The C_{max} for Subject 27582 occurred at 6 hours post-contact. However the remaining concentrations in this subject's profile on Day 1 were similar to baseline (Day -1). All concentrations for these two subjects, and all subjects in the study, remained in the normal female range for testosterone defined by the Sponsor as 0 to 90 ng/dL. The Sponsor attributes some of the variation noted to circadian and menstrual cycles. Therefore, they believe that individual time points may not be the best indication of transfer/exposure and that AUC or C_{avg} may be a better means of evaluating exposure and transfer over time.

The Sponsor has also calculated confidence intervals for the difference between the pharmacokinetic parameters calculated for total testosterone concentrations on Day -1 and Day 1. All p-values were non-statistically significant. Furthermore, the 95% CI for all parameters contained zero (which may signify no difference).

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}, $AUC_{0-24,}$ 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.

Safety Evaluations:

Twenty-four (24) subjects were included in the safety sample. There were no deaths in this study. There were no serious adverse events reported in this study. There were no adverse events reported in this study.

Clinical Laboratory Evaluation:

No clinically significant changes in the clinical laboratory measurements over the course of the study were reported which could be reasonably associated with the test product under investigation.

No female or male subjects had abnormal total testosterone levels either at Screening or at end of study.

The test that had the highest number of abnormal values in females overall at either screening or end of study was urinalysis. At baseline, 2 subjects (16.7%) had abnormal results and 10 subjects (83.4%) had normal results. At the end of the study, 4 subjects (33.4%) had abnormal results and 8 subjects (66.7%) had normal results.

The test that had the highest number of abnormal values in males overall at either screening or end of study was serum cholesterol concentration. At baseline, 6 subjects (50%) had values above the normal range and 6 subjects (50%) had values within the normal range. At the end of the study, 7 subjects (58.3%) had values above the normal range and 5 subjects (41.7%) had values within the normal range. PSA results for all subjects were within the normal range at screening and at the end of study. The largest change in PSA was for Subject 27594; the baseline concentration was 0.8 ng/mL, and this decreased to 0.5 ng/mL at the end of the study.

There were no biochemistry, hematology, or urinalysis results that were judged to be clinically significant.

Vital Signs:

There were no out of range measurements for any of the female subjects. Male Subject 27593 had a high systolic blood pressure at screening (161 mmHg); the measurement was repeated and the subsequent result (143 mmHg) was within the normal range. At study exit, systolic blood pressure was again high (164 mmHg); the repeated result was again high (176 mmHg), however, no further repeat measurements were taken. The diastolic blood pressure for male Subject 7597 was high (93 mmHg) at screening; the measurement was repeated and the result was within the normal range.

Physical Exam:

There were no abnormal findings or changes noted in the DRE at Screening or end of study. One subject was noted to have external hemorrhoids.

Electrocardiograms:

Of 7 subjects with abnormal results at Screening (first degree AV block [n=3], incomplete RBBB [n=2], sinus bradycardia [n=11], and sinus bradycardia/first degree AV block [n=1]), 5 of these same subjects had the same abnormal result at the end of the study. Two of subjects with first degree AV block at screen had normal ECGs at exit and one subject with a normal ECG at screen developed sinus arrhythmia at exit.

Application Site:

There were no application site abnormalities that changed or emerged after drug application or skin contact in either male or female subjects.

> *Reviewer's Comment: The arms/shoulder application method is the one that Clinical Pharmacology has concluded is the preferred method in terms of comparable exposure to testosterone when compared to the efficacy results for the "rotating" method use in the phase 3 study. This comparability of exposure was demonstrated in Study S176.1.007. A concern was raised by Clinical Pharmacology, based on the results of Study S176.1.007 with regard to application site irritation. Table 13 from the Clinical Study report for S176.1.007 appears to show a modestly increased incidence of application site papules and application site dermatitis for the arms/shoulders method of application (treatment B) compared to the Phase 3 rotating method (treatment C). A scanned copy of this table is presented below as part of my review of this issue:*

Table 22: Summary of Application Site Treatment Emergent Adverse Events by Treatment Groups S176.1.007

Preferred Term	All Subjects n=36	Treatment A n=34	Treatment B n=34	Treatment C n=34
Application site excoriation	7 (19.4%)	5 (14.7%)	1 (2.9%)	2 (5.9%)
Application site papules	5 (13.9%)	0	4 (11.8%)	1 (2.9%)
Application site dermatitis	4 (11.1%)	2 (5.9%)	3 (8.8%)	0
Application site dryness	3 (8.3%)	2 (5.9%)	1 (2.9%)	0
Application site erythema	2 (5.6%)	1 (2.9%)	1 (2.9%)	1 (2.9%)
Application site nodule	2 (5.6%)	1 (2.9%)	1 (2.9%)	0
Application site bruising	1 (2.8%)	0	1 (2.9%)	0
Application site pruritus	1 (2.8%)	0	1 (2.9%)	0
Application site reaction	1 (2.8%)	0	0	1 (2.9%)

Notes: Treatment A= once daily application of 5.00 g testosterone gel 1.62% to the abdomen for 7 days.
Treatment B = once daily application of 5.00 g testosterone gel 1.62% to the upper arms/shoulders for 7 days.
Treatment C = once daily application of 5.00 g testosterone gel 1.62% to the abdomen for 3 days, followed by application to the upper arms/shoulders for 4 days.
Four subjects did not complete the study thus, n=34.

Source: Table 13, Clinical Study Report S176.1.007, page 61.

It is to be noted that S176.1.007 was a PK crossover study and not designed as a skin irritation study. While the skin application sites were assessed prior to each administration of the study drug by either the investigator or a qualified designee, no guidelines were provided and it was left to the investigator to "record the findings as appropriate."

Utilizing Appendix 12.2.7 of the study report, the following table was constructed:

Table 23: General Disorders and Administrative Site Conditions S167.1.004

Treatment A (n=34)	SUBID	AE MedDRA Preferred Term	AE Literal Term	Severity	Relationship To Study Drug
Application site excoriation	26810	Excoriation	Excoriation	mild	probable
	26811	Excoriation	Excoriations	mild	unrelated
	26822	Excoriation		mild	unrelated
	26822	Excoriation	Excoriation	mild	probable
	26825	Excoriation	Excoriations	mild	unrelated
	26825	Excoriation		mild	unrelated
	26835	Excoriation	Excoriation	mild	probable
Application site papules					
Application site dermatitis	26813	Dermatitis	Dermatitis	mild	probable
	26825	Dermatitis		mild	probable
Application site dryness	26813	Dryness	Xerosis	mild	probable
	26831	Dryness	Xerosis	mild	probable
Application site erythema	26822	Erythema	Erythema	mild	probable
Application site nodule	26835	Nodule	Nodule	mild	unrelated
Application site pruritus	26806	Pruritis	Proritus	mild	probable
Application site reaction					
Treatment B (n=34)					
Application site excoriation	26808	Excoriation	Excoriations	mild	probable
Application site papules	26809	Papules		mild	unrelated
	26811	Papules	Papules	mild	probable
	26814	Papules	Papule	mild	unrelated
	26815	Papules	Papule	mild	unrelated
	26818	Papules	Papule	mild	unrelated
Application site dermatitis	26811	Dermatitis	Dermatitis	mild	probable
	26838	Dermatitis	Dermatitis	mild	probable
	26838	Dermatitis	Dermatitis	mild	possible
	26838	Dermatitis	Dermatitis	mild	probable
	26825	Dermatitis	Dermatitis	mild	probable
Application site dryness	26832	Dryness		mild	probable
Application site erythema	26822	Erythema	Erythema	mild	probable
	26809	Erythema	Erythema	mild	unrelated
Application site nodule					
Application site pruritus					
Application site reaction					
Treatment C (n=34)					
Application site excoriation	26822	Excoriation	Excoriation	mild	probable
	26824	Excoriation	Excoriation	mild	probable
Application site papules	26822	Papules	Papule	mild	probable
Application site dermatitis					
Application site dryness					
Application site erythema	26809	Erythema		mild	probable
Application site nodule					
Application site pruritis					
Application site reaction					

Source: Appendix 12.2.7 S176.1.004 Study Report SUBID=subject ID

In some cases, the same adverse event was reported twice in the same treatment period on a different day. In Table 36 above, I have reported it the number of times it appeared in Listing 12.2.7.1. Several patients had more than one AE on the same day and therefore they can appear more than once in each treatment period. The totals may therefore not equal those in Table 13 of the study report.

There are many AEs shown in Table 36 that in the opinion of the investigator are unrelated to the study drug. Most notable are those of a single papule reported by the investigator which was then coded as "papules" as the preferred term. There are also single papules coded as preferred term "papules" which the investigator did attribute to the study drug.

In addition, there are patients who were noted to have an AE on a skin site different from the skin site being treated. This was recorded as an AE for the treatment arm they were in when the skin site finding was noted and the AE was attributed to the current treatment. Below are listed the AEs that occurred at skin sites not currently being treated, along with the randomization code for the individual patient:

Subject 26813 (Randomization B-A-C): While on treatment A (abdomen) developed dermatitis to bilateral upper arms/shoulders application site.

Subject 26822 (A-C-B): While on treatment B (arms/shoulder) developed left upper quadrant erythema.

Subject 26825 (B-C-A): While on treatment B (arms/shoulders) developed right lower quadrant dermatitis. While on treatment A (abdomen) developed dermatitis of bilateral arms. The subject was also noted on 2 occasions to have excoriations of the left upper arm while on treatment A (abdomen).

Subject 26835 (B-C-A): While on treatment A (abdomen) was noted to have nodule on the back and excoriation of the right upper back and shoulder on separate days.

Subject 26838 (A-B-C): While on treatment B (arms/shoulders) was noted to have dermatitis of the mid abdomen.

Subject 26811 (C-A-B): While on treatment B (arms/shoulders) developed 3 erythematous papules on the right upper quadrant of the abdomen. While on treatment A (abdomen) developed 4 excoriations of the left upper shoulder application site. While on treatment B (arms/shoulders) developed dermatitis of the right upper quadrant of the abdomen.

> *Reviewer's Comment: These examples, in my opinion, indicate that despite a washout period between treatment arms, there is likely some carry-over effect rendering a conclusion about which treatment has the least site reactions problematic at best.*

The table below shows the incidence of administrative site conditions, eliminating conditions judged unrelated by the investigator, occurrence of a single papule, and conditions occurring on sites not being currently treated.

Table 24: Adjudicated Administrative Site Conditions from Study S176.1.007

	SUBID	AE MedDRA	AE Literal	Severity	Related to Study
		Preferred	Term		Drug
Treatment A (n=34)		Term			
Application site excoriation	26810	Excoriation	Excoriation	mild	probable
	26822	Excoriation	Excoriation	mild	probable
Application site dryness	26813	Dryness	Xerosis	mild	probable
	26831	Dryness	Xerosis	mild	probable
Application site erythema	26822	Erythema	Erythema	mild	probable
Application site pruritus	26806	Pruritis	Pruritis	mild	probable
Treatment B (n=34)					
Application site excoriation	26808	Excoriation	Excoriations	mild	probable
Application site dermatitis	26838	Dermatitis	Dermatitis	mild	probable
Application site dryness	26832	Dryness		mild	probable
Treatment C (n=34)					
Application site excoriation	26822	Excoriation	Excoriation	mild	probable
	26824	Excoriation	Excoriation	mild	probable
Application site papules	26822	Papules	Papule	mild	probable
Application site erythema	26809	Erythema		mild	probable

With respect to treatment B, three of the papule cases were judged unrelated, one was a single papule, and one was on a skin site not being treated in Arm B. With respect to dermatitis in Treatment B, 3 of the 4 cases occurred on skin sites not being treated in Treatment B.

> *Reviewer's Comment: My conclusion is that treatment B is no more irritating than the other treatment arms. None of the treatments are particularly irritating.*

It is also relevant to note here the results of Study S176.1.004, a "classical", cumulative irritation and sensitization study (21 consecutive days of irritation assessment, followed by a washout phase and then single dose sensitization phase). It contained a detailed scoring guide and blinded assessment. Four separate treatments were applied to the arms/shoulders including: positive control, saline control, excipients only, and AndroGel 1.62%. For the skin area being tested, the dosing was greater than 6-fold the expected exposure with normal application. 214 patients were exposed to all 23 days of treatment. This study has already been reviewed in the original NDA review.

The study results are depicted in the table below:

Table 25: Arms Shoulders Application Site Scores in Study S176.1.004

	Scores					**Total**
	0.0	**0.5**	**1.0**	**1.5**	**>1.5**	**Sites**
Testosterone Gel 1.62%	1021	868	35	2	0	1926
Placebo Gel	1283	622	21	0	0	1926
Positive Irritant Control	179	1217	511	1	63	1971
Low Irritant Control (NS)	578	1177	1177	3	39	1956

NS=normal saline
Source: Table 7, Clinical Study Report S176.1.004, page 38.

The irritation potential for each treatment was determined by the scores obtained during the induction phase. Irritation was graded as follows: 0-no evidence of irritation, 1-minimal erythema, 2-definite erythema, 3-erythema and papules, 4- definite edema, 5-erythema edema and papules, 6-vesicular eruption, and 7-strong reaction extending beyond test site.

> *Reviewer's Comment: This study is quite convincing of the lack of irritation potential for the product.*

Finally, it is also notable that the Phase 3 study did not absolutely require a rotating application method, it was only recommended as an option. Therefore, it is reasonable to assume that many patients used arms/shoulders application frequently and possibly some exclusively. A total of 91 hypogonadal men used the 5 gm dose of testosterone gel 1.62% (81 of testosterone) during the phase 3 study. There were 40 placebo patients in the phase 3 study. 1 patient in the 5 gm dose group reported application site pruritis as the sole administrative and application site AE versus none for the placebo group in the pivotal study. Aside from pruritis, there was no real application site irritation noted for the 5 gm dose.

> *Reviewer's Comment: I am convinced that AndroGel 1.62% is not irritating to the arms/shoulders when applied repeatedly.*

Reviewer's Overall Safety Comment for Study S176.1.011: Overall, the study treatment was well-tolerated by the male and female subjects, and no safety concerns were identified. The arms/shoulders method of application of the 5 gm dose of AndroGel 1.62% in conjunction with a t-shirt barrier effectively mitigates transfer of testosterone to a female partner. In addition, this method of application is not irritating to the skin of the arm/shoulders with repeated dosing.

5.3.4 Protocol S176.3.104: Open-Label Efficacy Amendment (b) (4) (b) (4)

The analysis and results of this efficacy amendment are discussed in Sections 6.1.1, 6.1.2, 6.1.3, 6.1.4, 6.1.5, 6.1.6, 6.1.7 6.1.9 and 7.2.1.

6 Review of Efficacy

Efficacy Summary

The primary efficacy variable for Study S176.3.104 was the percentage of subjects with total testosterone C_{avg} within the normal range on Day 112. C_{avg} results were required to fall with the normal range of 300-1000 ng/dL, with success being defined as ≥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 C_{avg} values within the target range, which met the criteria for efficacy.

The key secondary efficacy success criteria required the individual C_{max} results to be within the following ranges:

- ≤1500 ng/dL in ≥85% of the subjects,
- between 1800-2500 in ≤5% of the subjects, and
- >2500 in none of the subjects.

(b) (4)

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 C_{avg} 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 C_{max} 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 C_{max} 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 C_{max} 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 C_{max} 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 C_{max} >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)

(b) (4)

Initially, the Sponsor had considered a new method of application which would use 4 skin sites for the highest dose (81 mg of testosterone). The question arose as to the comparable efficacy (comparable testosterone exposure) between this new method and the rotating method use in pivotal study S176.3.104. This question was explored in Study S176.1.010. The two methods are shown below:

- Treatment A: Once daily application of testosterone gel 1.62% to the abdomen for 3 days (2.5 g to each the right and left sides of the abdomen) followed by application to the upper arms/shoulders (2.5 g to each the right and left upper arm/shoulder) for 4 days. The total daily gel dose was 5.00 g (81 mg of testosterone).

- Treatment B: Once daily application of testosterone gel 1.62% to a combination of the upper arms/shoulders and abdomen for 7 days. The total daily gel dose was 5.00 g (81 mg of testosterone), consisting of 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 left abdomen and 1.25 g applied to the right abdomen.

Both application methods resulted in mean testosterone C_{avg} and C_{max} values within or just above the eugonadal range. Based on the statistical comparisons, application of 81 mg of testosterone in AndroGel 1.62% to a combination of the upper arms/shoulders and abdomen (Treatment B) resulted in a 16% lower C_{avg} and 27% lower C_{max} compared to application of gel with rotation from the abdomen to the upper arms shoulders (Treatment A). Treatment B had no elevations of total testosterone concentrations above 2500 ng/dL as compared to treatment A which had 7 (11%) subjects with sporadic total testosterone concentrations above 2500 ng/dL. On the other hand, treatment B had more patients with a tendency to have one or more testosterone concentrations below either 300ng/mL or 200ng/mL.

Reviewer's Comments:

1. *The most likely reason for the sporadic high concentrations of serum T in Study S176.1.010 was that the study was not dose titrated to main testosterone concentrations within the normal range, but rather the maximum dose was given as the starting dose and continued for 7 days.*

2. Despite the approximate 20% lower exposure using the new "4-site" method compared to the Phase 3 method, some would consider these exposure results to be "close enough" to each other to conclude that the two application methods treatment A and B in S176.1.010 result in comparable exposure to testosterone. However, a previous study (S176.1.007) has shown that the arms/shoulders-only method provides virtually identical exposure to the Phase 3 rotating method and a recent study (S176.1.011) shows that a t-shirt effectively mitigates transfer when using the arms/shoulders-only method. Taken together, the evidence is more

convincing in support of the use of the arms/shoulders only method over the "4-site" method.

The remainder of this section provides an overview of the efficacy results from the double-blind period of Study S176.3.104 and a more detailed review of the results from the Open-Label period. For additional details regarding the double-blind period results, the reader is referred to the prior Clinical review for the original application.

6.1 Indication

The proposed indication for AndroGel® 1.62% is for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism [congenital or acquired] or hypogonadotrophic hypogonadism [congenital or acquired].

6.1.1 Methods

In support of this application, the original NDA contained efficacy results from one Phase 3 (S176.3.104, double-blind phase) study. The Division agreed at the EOP2 Meeting, 18 October 2006, that a single Phase 3 study evaluating the safety and efficacy of testosterone gel 1.62% would be sufficient to file the application for review. This review of efficacy is based on review of Protocol S176.3.104. Of note, additional multiple-dose pharmacokinetic data for testosterone 1.62% was collected in several Phase 1 studies, including the dose-ranging study S176.1.002.

In Study S176.3.104, 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 collected in the study up to and including Day 182. A Final Integrated Clinical Study Report including data from Baseline through the end of the Study (Day 364) was included in the 120 day Safety Update to the Original NDA. By prior agreement, a revised Clinical Study Report (CSR) for the entire Phase 3, pivotal, efficacy study (S176.3.104) was submitted. In addition to data from the 6 month double-blind period of S176.3.104 that were previously reviewed, the revised report now contains findings from the 6 month open-label extension period of the study. (b) (4)

(b) (4)

The efficacy of testosterone gel 1.62% in males with primary or secondary hypogonadism is determined by the pharmacokinetic (PK) profile in this population.

For reader ready reference, the efficacy conclusion for the six month double-blinded pivotal study is presented below:

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. 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, 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. Analysis of variables that might imply androgen effects was conducted. Overall, the reviewer concluded that the remaining sporadic events did not signal a safety risk. Additionally, there were no subjects in the 182 day Safety Extension with a testosterone concentration of 2500 ng/dL or above.

6.1.2 Demographics

The demographics of the hypogonadal men in the open-label portion of S176.3.104 are summarized in the table below:

Table 26: Demographics of Hypogonadal Patients in Phase 3 Safety Sample for the Open-Label Period in S.176.3.104. (Shown by dose being taken upon entering the open-label period).

	Statistic		T-Gel			
		Formerly Placebo N=26	1.25 g N=11	2.5g N=35	3.75g N=39	5.0g N=85
Age (years)	Mean	52.9	53.8	52.2	54.6	52.3
<45	n (%)	5(19.2)	2(18.2)	5(14.3)	8(20.5)	15(17.6)
45-54	n (%)	6(23.1)	5(45.5)	14(40.0)	12(30.8)	35(41.2)
55-64	n (%)	9(34.6)	1(9.1)	12(34.3)	12(30.8)	28(23.9)
>=65	n (%)	6(23.1)	3(27.3)	4(11.4)	7(17.9)	7(8.2)
Ethnicity						
Hispanic/Latino	n (%)	1	0	5	0	4
Other	n (%)	25	11	35	39	81
Race						
American Indian or Alaska Native	n (%)	0	0	1		1
Asian	n (%)	0	0	0	0	4
Black	n (%)	2	1	1	6	12
Hawaiian/Pacific	n (%)	2	0	0	0	0
White	n (%)	24	10	33	33	68
Other		0	0	0	0	0

*some subjects indicated more than one racial background
Source: Clinical Study Report: S176.3.104 Amendment #1: Table 2.0.0.1: pages 30-31.

Reviewer's Comment: The demographics of patients in the S176.3.104 double- blind protocol and the open-label phase were similar. The mean age in the open-label period for the full analysis data set was 55.8 years for those patients formerly on placebo versus 52.9 years for those patients formerly on AndroGel 1.62 %.

The majority of subjects had some reported medical history (185/191, 96.8%). The most common medical history conditions (≥ 10% for preferred term) included: hypertension, hypogonadism, erectile dysfunction, hypercholesterolemia, seasonal allergy, gastroesophageal reflux disease, hyperlipidemia, diabetes mellitus non-insulin dependent, drug hypersensitivity and depression.

The table below summarizes additional baseline characteristics for the Open-Label Period in Study S176.3.104:

Table 27: Other Baseline Characteristics for the Open-Label Period-Study S176.3.104

	Formerly Placebo (N=26)	T-Gel 1.62% (N=170)
	Mean values	Mean Values
Height (m)	1.8	1.9
Weight (kg)	98.1	99.6
Waist Circumference (cm)	104.9	105.5
Hip Circumference (cm)	107.7	108.0
Waist to Hip Ratio	0.98	0.97
BMI (kg/m^2)	31.0	31.2
Sitting SBP (mmHg)	129.5	130.2
Sitting DBP (mmHg)	78.2	80.1
Sitting Pulse (bpm)	74.0	71.1
Percent Free PSA (%)	24.1	25.3

Source: Source: Clinical Study Report: S176.3.104 Amendment #1: Table 22, page 48

Reviewer's Comment: The baseline parameters in Table 36 are similar to those reported for the double-blind period of the study and to the Safety Sample of the open-label period. Overall the patients entering the open-label period of the study exhibit no significant demographic differences from the patients in the double-blind period of the study.

6.1.3 Subject Disposition

A total of 191 subjects were allocated to treatment for the open-label period; 163 of these patients had formerly received active treatment during the double-blind period. Based on subject's last titrated dose, allocation to testosterone gel 1.62% treatment in the open-label period was as follows: 15 subjects to 1.25 gm (20.25 mg testosterone), 41 subjects to 2.5 gm (40.5 mg testosterone), 43 subjects to 3.75 gm (60.75 mg testosterone), and 92 subjects to 5 gm (81 mg testosterone). Of the 191 subjects allocated to treatment in the open-label period, 15.7%

(30/191) eventually discontinued from study. In the double-blind period of Study S176.3.104, 70% of placebo subjects and 71.8% of subjects on active treatment had completed the study.

Overall, the most common reasons for discontinuation in the open-label period were adverse events (17/191. 8.9% [versus 9.1% in the double-blind period]) and withdrawal of consent (6/191, 3.1% [versus 9.1% in the double-blind period]). The percentage of subjects who withdrew consent was higher in the subjects who entered the double-blind period taking 1.25 gm group (1.25 gm: 2/15, 13.3%; 2.5 gm: 2/41, 4.9%; 3.75 gm: 0/43; 5 gm: 2/92). The percentage of subjects who discontinued due to an AE was lower in patients who entered the open-label period taking 2.5 gm and 5 gm (1.25 gm: 2/15, 13.3%; 2.5 gm: 3/41, 7.3%; 3.75 gm: 5/43, 11.6%; 5 gm: 7/92, 7.6%). The most common AE leading to discontinuation was PSA increased, which was pre-specified in the protocol as a discontinuation criterion.

Reviewer's Comment: No clear trend over time is apparent for AEs or discontinuations either in comparison to the double-blind period or by visit.

Table 28: Summary of Subject Disposition for the Open-Label Period-Study S176.3.104

	Formerly Placebo	T Gel				
		Total	1.25 g	2.5 g	3.75 g	5.0 g
	N=28	N=191	N=15	N=41	N=43	N=92
Subjects	n(%)					
Completed	24(85.7)	161(84.3)	10(66.7)	33 (80.5)	37 (86.0)	81(88.0)
Terminated prematurely	4(14.3)	30(15.7)	5(33.3)	8(19.5)	6(14.0)	11(12.0)
Reasons for Premature Termination						
AE	2(7.1)	17(8.9)	2(13.3)	3(7.3)	5(11.6)	7(7.6)
Efficacy Lack	0	2(1.0)	0	1(2.4)	0	1(1.1)
Lost to Follow-up	1(3.6)	2(1.0)	0	1(2.4)	0	1(1.1)
Withdrew Consent	1(3.6)	6(3.1)	2(13.3%)	2(4.9)	0	1(1.1)
Administrative	0	1(0.5)	0	0	0	1(1.1)
Protocol Violation	0	2(1.0)	1(6.7)	1(2.4)	0	0

Source: Table 17, Summary of Clinical Efficacy, S176.3.104 Amendment#1, page 41.

The mean duration of exposure to the study gel for all subjects was 319.7 days. For subjects who received placebo during the double-blind period of the study, the mean duration of exposure to the study gel was 171.4 days. The cumulative duration of exposure to study drug for the majority of subjects was >44-52 weeks (67/191, 35.1%) or >52 weeks (72/191, 37.7%). For

subjects who received placebo during the double-blind period of the the study, the cumulative duration of exposure for the majority of subjects was >20-26 weeks (16/28, 57.1%).

No increases or decreases in testosterone gel 1.62% dose were made after Day 266. Based on subjects' last titrated dose during the open-label period, allocation to testosterone gel 1.62% treatment was as follows: 15 subjects to 1.25 gm, 41 subjects to 2.5 gm, 43 subjects to 3.75 gm and 92 subjects to 5 gm.

Overall mean compliance for the full analysis sample was similar for the patients previously taking testosterone gel 1.62% and those taking placebo (94.29% versus 97.70%). No meaningful differences in mean compliance were observed across the testosterone gel 1.62% dose groups, except for a greater percentage of subjects who were taking 1.25 gm and 2.5 gm with >120% compliance compared with the other two testosterone gel 1.62% groups (1.25 g: 3/11, 27.3%; 2.5 gm: 4/35, 11.4%, 3.75 gm: 2/39, 5.1%; 5 gm: 1/85, 1.2%).

Table 29: Compliance to Study Medication-Full Analysis Sample-182-Day Open-Label Period

	Placebo	T Gel				
	Formerly	Total	1.25 g	2.5 g	3.75 g	5.0 g
	N=26	N=170	N=11	N=35	N=39	N=85
	n					
Overall Compliance	26	170	11	35	39	85
Overall Compliance n(%)						
<80	4(15.4)	27(15.9)	1(9.1)	5(14.3)	8(20.5)	13(15.3)
80-120	19(73.1)	133(78.2)	7(63.6)	26(74.3)	29(74.4)	71(83.5)
120	3(11.5)	10(5.9)	3(27.3)	4(11.4)	2(5.1)	1(1.2)

Source: Table 2.3.0.1, CSR S176.3.104 Amendment#1, page 64

Major protocol deviations included compliance <80% or > 120% (20.7% for Continuing Active versus 28.6 % for Formerly Placebo), and pharmacokinetic sample out of Day 364 window (12.0% for Continuing Active versus 21.4% for Formerly Placebo).

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable for the double-blind portion of the study was total testosterone C_{avg} on Day 112. C_{avg} results were required to fall within the normal range of 300-1000 ng/dL, with success being defined as ≥75% of subjects on active treatment within the normal serum testosterone concentration range (300-1000ng/dL) on this day. Additionally the lower bound of the 95% CI was to be not less than 65% based on the Day 112 results. As stated in the in the November 2, 2009, Medical Officer's NDA review, the primary efficacy endpoints were achieved for the double-blind period.

The primary efficacy variable for the open-label part of the study was total testosterone C_{avg} on Day 364. C_{avg} results were required to fall within the normal range of 300-1000 ng/dL, with success being defined as ≥75% of subjects on active treatment within the normal serum

testosterone concentration range (300-1000ng/dL) on this day. Additionally the lower bound of the 95% CI was to be not less than 65% based on the Day 364 results.

On Day 364 in the Continuing Active testosterone treatment group, 77.9% of subjects had C_{avg} values within the target range with the lower bound of the 95% CI not being <65% for primary efficacy (95% CI 70.0%-84.6%).

On PK days, Days 266 and 365, the PK sampling times were 0, 0.5, 1, 2, 4, 8, 12, and 24 hours.

Table 30 : Number and Percentage of Patients Achieving Target Range for Average Total Testosterone Concentration (C_{avg}) by Day and Treatment-FA Sample-182-Day Open-Label Period

Study Day	Total Testosterone C_{avg} (ng/dL)	Continuing Active		Formerly Placebo		Combined	
			95% CI		95% CI		95% CI
		n/N	Interval	n/N	Interval	n/N	Interval
			(%)		(%)		(%)
266	<300	25/139		6/26		31/165	
	300-1000	109/139	(70.6,84.9)	18/26	(48.2,85.7)	127/165	(69.8,83.2)
	>1000	5/139		2/26		7/165	
364	<300	28/136		2/23		30/159	
	300-1000	106/136	(70.0,84.6)	20/23	(66.4,97.2)	126/159	(72.1,85.3)
	>1000	2/136		1/23		3/159	

Source: Table 11.1.2.1, Clinical Study Report S176.3.104, page 1653.

In the continuing active treatment group in the Open Label Period at treatment Day266, 1 subject taking 1.25 gm per day had concentrations of total testosterone > 1000 ng/dL. The C_{avg} for this subject was 1160 ng/dL. 1 subject taking 2.5 gm per had concentrations of total testosterone > 1000 ng/dL on Day 266. The C_{avg} for this subject was 1090 ng/dL. 2 subjects taking 3.75 gm per day had concentrations of total testosterone > 1000 ng/dL on day 266. The C_{avg} for these subjects were 1180 and 1100ng/dL. 1 subject taking 5.0 gm per day treatment group had concentrations of total testosterone > 1000 ng/dL on Day 266. The C_{avg} for this subject was 1270 ng/dL.

Table 31: Subjects with Testosterone C_{avg} > 1000 ng/dL at Day 364

Nominal Time (h)	0	0.5	1	2	4	8	12	24
Subject: 042/015				Day 266: Dose 2.5 g				
	589	558	466	487	493	614	1870	473
				Day 364: Dose 1.25 g				
	587	446	590	829	819	1210	Cancelled	1010
Subject 028/031:				Day 266: Dose 5 g				
	1070	1320	1250	Cancelled	1270	779	2120	489
				Day 364: Dose 3.75				
	1630	1840	1650	1430	1650	961	944	889

Source: Listing 35.1, Clinical Study Report S176.3.104 page 17

In addition, there were 10 patients with testosterone values in excess of 1000 ng/dL at Day 364.

> *Reviewer's Comment: In most, if not all, of the few patients in the Open-Label period with a C_{avg} testosterone concentration of >1000 ng/dL, the trough testosterone concentration was above normal (in excess of 1000 ng/dL) which could easily be detected by a clinician, and with titration as recommended by labeling, this finding can be mitigated. There is maintenance of efficacy out to Day 364, as the Primary Efficacy Endpoint is achieved at 1 year.*

6.1.5 Analysis of Secondary Endpoints(s)

A Critical Secondary Efficacy Endpoint was to evaluate total testosterone C_{max} values during the first 182 Day of the study and this endpoint was also evaluated for the Open-Label Period. The individual Cmax values were to be in the following ranges:

- Cmax ≤ 1500 ng/dL in ≥85% of the subjects
- Cmax between 1800-2500 in ≤5% of the subjects
- Cmax >2500 ng/dL in none of the subjects

Table 32: Number and Percentage of Patients Achieving C_{max} Ranges by Day for Continuing Active Testosterone Gel Treatment for the Open-Label Period

		Continuing Active Testosterone gel 1.62% n/N (%)		
Study Population (sample)	**Study Day**	**≤1500 ng/dL**	**1800-2500ng/dL**	**>2500 ng/dL**
Full Analysis	Overall	258/275 (93.8)	9/275 (3.3)	0/275 (0.0)
	266	131/139 (94.2)	5/139 (3.6)	0/130 (0.0)
	364	127/136 (93.4)	4/136 (2.9)	0/136 (0.0)
Efficacy	Overall	250/267 (93.6)	9/267 (3.4)	0/267 (0.0)
	266	123/131 (93.9)	5/131 (3.8)	0/131 (0.0)
	364	127/136 (93.4)	4/136 (2.9)	0/136 (0.0)
Per Protocol	Overall	135/145 (93.1)	5/145 (3.4)	0/145 (0.0)
	266	69/74 (93.2)	4/74 (5.4)	0/74 (0.0)
	364	66.7 (93.0)	1/71 (1.4)	0/71 (0.0)

Source: Table 30, Summary of Clinical Efficacy S176.3.104, page 60.

Reviewer's Comment: With respect to the Critical Secondary Endpoint, all goals were achieved except at Day 266 in the Per Protocol Sample, where 5.4% of patients were in the 1800 -2500 ng/dL for total testosterone concentration (allowed up to 5%). At Day 364, that value was 1/71 (1.4%). It is my overall opinion that the Critical Secondary Endpoint was met for Efficacy in the Open-Label period.

6.1.6 Other Endpoints

Dihydrotestosterone (DHT): For the Continuing Active Testosterone treatment group, DHT levels were within the eugonadal reference range (11.2-95.5 ng/dL) on both Day 266 and Day 364. The mean (SD) DHT/T ratios for the Continuing Active testosterone gel 1.62% group was 0.1781(0.0683) with 95% prediction intervals of 0.0809-0.343. This value is within the normal range (0.074-0.330).

Reviewer's Comment: Serum DHT concentrations increased as serum testosterone concentrations increased. The mean DHT/T ratio was approximately 17-18% with 95% CI 8% - 34%. This is acceptable.

E2 (Estradiol): Mean E2 concentrations generally paralleled changes seen in testosterone concentrations. The mean concentration profiles for E2 for all doses were generally within the normal range of 10-40 pg/mL for Day 266 and Day 364.

LH (Luteinizing Hormone): The LH levels decreased significantly from Baseline on Day 266 and Day 363 with testosterone treatment for both Continuing Active and Formerly Placebo groups. A near-significant correlation between C_{avg} of testosterone and the decrease in LH was observed. The decrease in LH was significant at all age groups.

FSH (Follicle Stimulating Hormone): The FSH levels decreased significantly from Baseline on Day 266 and Day 363 with testosterone treatment for both Continuing Active and Formerly Placebo groups. A significant correlation between C_{avg} of testosterone and the decrease in FSH was observed. The decrease in FSH was significant at all age groups.

Inflammatory Markers: The levels of interleukin 10 (IL-10) decreased significantly from Baseline on Day 364 in the Continuing Active group and on Day 266 for the Formerly Placebo group. A significant correlation correlation between C_{avg} of testosterone and decrease in IL-10 was observed. No significant changes were noted with TNF-alpha, IL-6, and HS-CRP.

MMP-9 (Matrix Metalloprotease-9): The levels of MMP-9 decreased significantly from Baseline for the Continuing Active group on both day 266 and 364 but not for the Formerly Placebo group. . A significant correlation correlation between C_{avg} of testosterone and decrease in MMP-9 was observed.

Fibrinogen and D-Dimer: Fibrinogen in both the presence and absence of concomitant therapy decreased significantly from Baseline on Day 266 and Day 364 for the Continuing Active group. No significant differences were noted for D-dimer.

Waist to Hip Ratio: The waist-to-hip ratio values did not change significantly with testosterone treatment for both treatment groups.

Bone Specific Acid Phosphatase and Type 1 Cross-linked C Telopeptide: There were no significant changes noted for bone specific acid phosphatase at Day 365. C telopeptide decreased significantly from baseline on Day 266 and Day 364 for the Continuing Active group but not for the Formerly Placebo group.

> *Reviewer's Comment: Many of these secondary endpoints are exploratory but they seem to show no alarming trends for long term testosterone replacement in hypogonadal men. In addition, there were favorable changes with regard to inflammatory markers, fibrinogen, and bone formation markers.*

6.1.7 Subpopulations

Analysis of C_{avg} data was conducted to evaluate whether age and race had any influence on achieving target range average total testosterone concentrations in the Open-Label Period. The summarization by race and age did not show any apparent differences in achieving target range Cavg concentrations. However, no definitive conclusions could be made since no statistical

testing was done. No clear trends were seen when race and age groups were compared within the Continuing Active and Formerly Placebo groups.

Subgroup analyses of Cavg by BMI showed no clear trends.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The clinical information in this **COMPLETE RESPONSE** validates the dosing recommendations reviewed in the November 2, 2009 NDA review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Sponsor has shown that the achievement of the primary efficacy endpoint and the critical secondary efficacy endpoints persists at Day 364 without evidence of tolerance effects. See Overall Summary of Efficacy.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The original NDA review (finalized November 2, 2009), contained safety data from 785 subjects exposed to AndroGel 1.62%. That safety data was derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008, and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104. By prior agreement, the safety data from the open-label period of Study S176.3.104 was submitted with the 120-Day Safety Update to the original NDA. The data in this Complte Response was received and reviewed and provides no new safety signals compared to the data in the original NDA. A total of 382 hypogonadal males were included in the integrated safety data base, and 307 healthy males and 96 females are included in the non-integrated safety data base.

An additional 62 males in non-integrated phase 1 study, S176.1.010 were exposed to AndroGel 1.62% 5 gm daily for a total of 14 days (two courses of 7 day exposure separated by a 7 day washout period).

Including Studies S 176.1.009, S176.1.010 and S176.1.011, a total of 429 unique hypogonadal male subjects and 322 healthy unique male subjects received AndroGel 1.62%. In addition, 89 unique healthy female subjects participated in “transfer” studies of AndroGel 1.62%. Within

these studies there were no deaths or non-fatal SAEs. There were three adverse events in Study S176.1.010 denoted in the study reports as "markedly abnormal vital signs". Two of these events were blood pressure elevations and one was a temperature elevation. All of these events were noted on only one day and spontaneously resolved without intervention.

This Safety Summary considers safety issues as they pertain to the data provided to address a COMPLETE RESPONSE to the issues noted in the original NDA application. The reader is referred to the Medical Officer's Review of the original NDA for detailed information concerning safety results from the original application. Additionally, Appendix 9.8 of this document provides a summary discussion of the more general safety issues related to AndroGel 1.62% as considered in the original NDA submission.

Transfer:
This Safety Summary considers the findings of Studies S176.1.009 and S176.1.011 as they pertain to the safety issue of transfer or potential secondary exposure to women and children after testosterone gel 1.62% skin application in males. Overall, transfer is effectively mitigated by a t-shirt using either the 4-site application method or the arms/shoulders-only method for doses of 5gm. Utilizing AUC comparisons of female exposure to testosterone when the males applies testosterone gel 1.62% to four application sites (S176.1.009) or to two application sites (S176.1.011), the AUC is increased by 1.7 % in Study S176.1.009 and by 6.9% in Study S176.1.011, respectively. This may in part reflect normal variation in serum testosterone concentrations in women. The Sponsor has elected to base dosing and administration instructions on the 2 site (arm/shoulders-only) application method. I concur with this recommendation. A more detailed discussion of this issue is contained in Appendix 9.8.

Sporadic Testosterone Levels > 2500 ng/dL:
As part of a bridging study to document comparable exposure to testosterone when hypogonadal males administer 5 gm of testosterone gel 1.62% once a day, the Sponsor performed Study S176.1.010 which assessed the patient testosterone exposure utilizing the 4-site and rotating application methods. Both methods allowed patients to attain eugonadal levels of testosterone concentration. In that study, in Treatment A (3 days of abdominal application of 5 g of testosterone gel 1.62% followed by 4 days of application of the same dose to both arms/shoulders), which was the method used in the phase 3 study, several testosterone concentrations in excess of 2500 ng/dL occurred (7 patients). The Sponsor points out that these values did not occur under actual use conditions under which patients would start at the 2.5 gm dose of AndroGel 1.62% and then undergo monitoring and titration to an individualized dose level. In this study, the highest dose was administered initially and for 7 consecutive days. The Sponsor also points out that these values were sporadic and not sustained. I concur with the Sponsor's comments on this issue.

Application Site Irritation:

In Study S176.1.010, the application sites of testosterone gel 1.62% were assessed using a protocol specified scale just prior to dosing on Days -1 to 21 and on Day 22/Early Termination. Only one subject was noted with possible skin irritation. In Study S176.1.004 (N=235), which

was a classical skin irritation and contact sensitization study and employed the arms/shoulders only method of application, only 2 subjects were noted to have a mild skin rash. Almost all scores for skin erythema were zero (none) or 1 (mild). In this study, no sensitization potential and only minimal irritation potential was observed as compared to placebo. AndroGel 1.62% is largely non-irritating. The percentages of patients reported skin-related AEs in Study S176.3.104 is reported in the labeling, as is "rash" as part of the Post Approval Experience for AndroGel 1%.

Hand Washing:
In the Complete Response, the Sponsor submitted a protocol for Study S176.1.012, a studyto determine the effect of hand washing on removal of testosterone from the hands after they are used to apply AndroGel 1.62%. This study will be performed as a post-approval requirement. The study is well designed and meets preliminary guidelines we communicated to the Sponsor.

In summary, the safety and tolerability of AndroGel 1.62% is quite reasonable, and consistent with all other testosterone replacement products. The few events of testosterone elevations >2500 ng/dL in Study S176.1.010 are almost certainly related to the initiation of the highest dose and continued use of the highest dose for 7 days. The labeling for the drug will recommend to initiate therapy with one half that dose and check serum testosterone concentrations at Days 14 and 28 to determine whether dose adjustment is needed. Both the arms/shoulders only method and the 4 site-application method in association with a male t shirt barrier effectively mitigates male to female testosterone transfer. The arms/shoulders-only method is not associated with skin site irritation. There is no issue from the safety standpoint that precludes approval.

7.1 Methods

The safety of AndroGel 1.62% in the pivotal study S176.3.104 and the Phase 1 and Phase 2 studies was reviewed as part of the original NDA application. That review was finalized on November 2, 2009. The safety data for that review was derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008 (transfer, washing and skin irritation studies), and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182-day double-blind period of the Phase 3 Study S176.3.104. The original MO's review also included a brief review of the preliminary safety data from the Open-Label Period of Study S176.3.104. By prior agreement the Sponsor has submitted an amended study report for Study S176.3.104 to incorporate the findings in the Open-Label Period. This current review of safety will evaluate any new safety findings that are noted in the amended study report for S176.3.104, and the safety findings and safety implications of Studies S176.1.009, S176.1.010, and S176.1.011. The only new studies submitted with this Complete Response were S176.1.010, and S176.1.011, and these have been reviewed in detail in Section 5.3 above. A summary of the Review of Safety from the sNDA of November 2, 2009, is provided as an appendix for ready reader reference.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review of safety will evaluate any new safety findings that are noted in the amended study report for S176.3.104, and the safety findings and safety implications of Studies S176.1.009, S176.1.010, and S176.1.011. The only new studies submitted with this Complete Response were S176.1.010, and S176.1.011, and these have been reviewed in detail in Section 5.3 above. The review will consist of the following item:

- New safety findings noted in the Amended Final Study Report for S176.3.104,
- Study S176.1.009 (although the study report for this transfer study was submitted in the original NDA),
- Study S176.1.010,
- Study S176.1.011,
- The 7th (2008) and 8th (2009) Annual Post-Marketing Safety Updates (PSURs) for Androgel 1%.

7.1.2 Categorization of Adverse Events

The adverse events were analyzed in the following categories:

- Deaths
- Other serious adverse events
- Dropouts
- Adverse events associated with dropouts
- Other significant adverse events
- Testosterone concentrations >2500 ng/dL

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data will not be pooled for the cohorts to be considered in this safety analysis.

7.2 Adequacy of Safety Assessments

The Medical Officer's Review of the original NDA was finalized on November 2, 2009. That review contained safety data from 785 subjects exposed to AndroGel 1.62%. That safety data was derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008, and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182-day, double-blind period of the Phase 3 Study S176.3.104. By prior agreement, the preliminary safety data from the open-label period of Study S176.3.104 was submitted with the 120-Day Safety Update to the original NDA. The data in this Update was received and reviewed and provide no new safety signals compared to the data in the original NDA. For the current review, 382 hypogonadal males are included in the integrated safety data base, and 307 healthy males and 96 females are included in the non-integrated safety data base.

In this Complete Response, in the Phase 1 integrated studies, a total of 172 hypogonadal men were exposed to any dose of T-Gel 1.62 %. 10 men (6.8%) were exposed for 0-7 days, 54 men (36.7%) for 8-14 days, 42 men (28.6%) for 15-21 days, 8 men (5.4%) for 22-28 days and 33 men (22.4%) for greater than 28 days. When analyzed by individual dose, 24 subjects were exposed to 1.25 gm for a mean of 9.1 days, 40 subjects were exposed daily to 2.5 gm for a mean of 14.1 days, 22 subjects were exposed to 3.75 gm for a mean of 9.5 days, 72 subjects were exposed to 5.0 gm for a mean of 21.8 days and 11 subjects were exposed to 6.25 gm for a mean of 13.5 days.

An additional 62 males in the non-integrated phase 1 study, S176.1.010 were exposed to AndroGel 1.62% 5 gm daily for a total of 14 days (two courses of 7 day exposure separated by a 7 day washout period).

In this Complete Response, a total of 429 unique hypogonadal male subjects, 322 healthy unique male subjects received AndroGel 1.62%, in addition 89 unique healthy female subjects who participated in Phase 1 'transfer" studies.

In the single Phase 3 Study, S176.3.104, 234 patients were exposed to T-Gel 1.62 % for a mean of 151.9 days. The cumulative duration of exposure to different doses of testosterone gel 1.62% group and placebo was similar at each 4-week interval. The mean exposure to 2.5 gm was lower as it was the starting dose from which subjects were titrated based on pre-determined testosterone concentrations. A total of 191 subjects participated in the 182-Day Open Label Period with a total of 161 subjects completing the study. The mean duration of exposure to the study drug (gel) for all subjects in the Open-Label Period was 319.7 days, and for the formerly placebo patients in the Open-Label Period it was 171.4 days. The cumulative duration of exposure to study drug for the majority of subjects was >44-52 weeks (67/191, 35.1%) or >52 weeks (72/191, 37.7%). For subjects who received placebo during the double-blind period of the study, the cumulative duration of exposure to study drug for the majority of subjects was 20-26 weeks (16/28, 57.1%).

> *Reviewer's Comment: The extent of exposure in Study S176.3.104 was more than required for assessment of safety of a testosterone replacement product.*

In the open-label period of Study S176.3.104, no increases or decreases in testosterone gel 1.62% were made after Day 266. The allocation of subjects among dose groups for the 170 subjects receiving testosterone gel 1.62% at Day 266 was as follows: 1.25 gm: 11 subjects, 6.5%; 2.5 gm: 35 subjects, 20.6%; 3.75 gm: 39 subjects, 22.9%, 5 gm: 85 subjects, 50%.

A total of 405 hypogonadal men were exposed to the to-be-marketed drug. 172 hypogonadal males were exposed to the to-be-marketed drug in the integrated Phase I trials. Of these men, 36.7% were exposed for a mean of 8-14 day and 22.4% for greater than 28 days.

In the non-integrated Phase 1 studies, 235 healthy men were exposed to testosterone gel 1.62% for a total of 26 days in a sensitization and skin irritation study, 48 healthy males and females were exposed to 5 gm of testosterone gel 1.62% daily for 7 days applied to the male only in a

"transfer" study, and 24 healthy males and females were exposed to 2 days of exposure to testosterone gel 1.62% (one dose each of 2.5 gm or 5 gm) applied to the male only to evaluate post dose washing and its effect on transfer of testosterone gel. In non-integrated transfer studies S176.1.009 and S176.1.011, a total of 24 healthy males and 24 healthy females were exposed to a single 5 gm dose of AndroGel 1.62%.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 191 subjects participated in the 182-Day Open Label Period with a total of 161 subjects completing the study. The mean duration of exposure to the study drug (gel) for all subjects in the Open-Label Period was 319.7 days, and for the formerly placebo patients in the Open-Label Period it was 171.4 days. The cumulative duration of exposure to study drug for the majority of subjects was >44-52 weeks (67/191, 35.1%) or >52 weeks (72/191, 37.7%). For subjects who received placebo during the double-blind period of the study, the cumulative duration of exposure to study drug for the majority of subjects was 20-26 weeks (16/28, 57.1%).

In the open-label period of Study S176.3.104, no increases or decreases in testosterone gel 1.62% were made after Day 266. The allocation of subjects among dose groups for the 170 subjects receiving testosterone gel 1.62% at Day 266 was as follows: 1.25 gm: 11 subjects, 6.5%; 2.5 gm: 35 subjects, 20.6%; 3.75 gm: 39 subjects, 22.9%, 5 gm: 85 subjects, 50%.

> *Reviewer's Comment: The overall exposure and doses/durations are adequate for safety evaluations*,

Section 6.1.2 contains a discussion of the demographics of population studied in S176.3.104.

> *Reviewer's Comment: The demographics of the study population are appropriate for the target population.*

7.2.2 Explorations for Dose Response

There were no explorations for dose response in the **COMPLETE RESPONSE.** However, there were Phase 2, clinical dose-ranging investigations submitted and reviewed as part of the original NDA application.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or *in vitro* testing was performed.

7.2.4 Routine Clinical Testing

The routine clinical safety testing that was conducted as part of Study S176.3.104 and in the reminder of the drug development program was comprehensive and appropriate for the product. The reader is referred to the MO's original review and to Appendix 6 of this review. The safety assessments included: collecting clinical AEs, clinical laboratory measurements (hematology, chemistry, urinalysis, lipid parameters, PSA, vital signs, physical examination (including digital rectal exam [DRE]), ECG, International Prostate Symptom Score (IPSS-1), application site evaluation, skin assessments, and investigation for the potential transfer of testosterone through skin contact.

7.2.5 Metabolic, Clearance, and Interaction Workup

The following information is available from the approved AndroGel® 1% label and was submitted in this NDA application in support of testosterone metabolism, clearance and interactions:

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10-100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major metabolites of testosterone are E2 and DHT.

Testosterone is primarily cleared by metabolic processes in the liver, skin, genital, and other tissues. This metabolism includes conversion to the active metabolite DHT by 5α-reductases in the skin and liver and to E2 by aromatase complexes (CYP19) found in the liver, fat, and testes. Transdermal delivery of testosterone bypasses the extensive first-pass metabolism in the liver.

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucoronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

It is not anticipated that there will be any differences in the excretion of testosterone for testosterone gel 1.62% compared to previously approved products. Therefore, no additional information in this regard is needed from the testosterone gel 1.62% development program. However, data from two Phase 1 studies in the AndroGel 1.62% development program showed that serum testosterone concentrations returned to Baseline levels by not more than 48-72 hours after the last topical application of testosterone gel 1.62% (Studies S176.1.005 and S176.1.007).

Drug interactions were not addressed specifically in the testosterone gel 1.62% development program, they are not needed. The following potential drug interactions are based on testosterone class labeling:

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

- Corticosteroids: The current use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.
- Oral Anticoagulants: Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The clinical adverse events observed for Androgel 1.62% in the course of the development program are consistent with those observed for Androgel 1% and generally consistent with the entire class of testosterone replacement therapies. The adverse events reported for both AndroGel 1.62% and AndroGel 1% include the following :

Nasopharyngitis, Upper Respiratory Tract Infection, Hemoglobin Increased, Blood Triglycerides increased, PSA increased*, Pain in extremity, Back Pain, Shoulder Pain, Arthritis, Dry Skin, Erythema, Rash Erythematous, Fatigue, Nausea, Vomiting, Diarrhea, Headache, Dizziness, Dyspnea, Hypertension, Hyperlipidemia, Depression, Neprolithiasis, Acne, and Gynecomastia.

The reported incidence of selected clinical adverse events for AndroGel 1.62% from the double-blind period of Study S176.3.104 are shown in Table 46 below.

Table 33: Selected Clinical Adverse Events forTestosterone Gel 1.62% from Study S176.3.014

	Testosterone gel 1.62% All Doses (N=234)	Placebo (N=40)
Patients discontinuing due to AE	25 (10.7%)	0
Patients with ≥ 1 TEAE	130 (55.6%)	15 (37.5%)
Nasopharyngitis	5 (2.1%)	0
Upper Respiratory Tract Infection	11 (4.7%)	0
Hemoglobin increased	1 (4%)	0
Blood Triglycerides increased	1 (0.4%)	0
PSA increased*	23 (9.8%)	0
Pain in extremity	1 (0.4%)	1 (2.5%)
Back Pain	7 (3.0%)	0
Shoulder Pain	0	0
Arthritis	0	0
Dry Skin	1 (0.4%)	0
Erythema	2 (0.9%)	0
Rash Erythematous	0	0
Fatigue	3 (3%)	1 (2.5%)
Nausea	0	0
Vomiting	1 (0.4)	0
Diarrhea	5 (1.0%)	0
Headache	7 (3.0%)	2 (5.0%)
Dizziness	3 (3.0%)	0
Dyspnea	0	0
Hypertension	6 (2.6%)	0

Hyperlipidemia	2 (0.9%)	0
Depression	0	0
Neprolithiasis	1 (0.4%)	0
Acne	2 (0.9%)	0
Gynecomastia	1 (0.4%)	1 (2.5%)
Subjects with ≥ 1 "Related" TEAE	47 (20.1)	3 (7.5%)

Source: adapted from Table 15, 2.5 Clinical Overview, page 58, of original NDA submission, February 11, 2009.

> ** Reviewer's Comment: Regarding "PSA increase" as a clinical adverse event, there were strict PSA-based discontinuation criteria in Study S176.3.104 which served to increase the reported incidence of "PSA increase" as a clinical adverse event in S176.3.104.*

In addition to the selected events in Table 46, three (3) of 291 patients receiving testosterone gel 1.62% also reported anger or aggression as an adverse event. Three (3) of 291 patients receiving testosterone gel 1.62% reported edema and 3 patients reported liver test abnormalities as an adverse in the 182 double- blind period of S176.3.104. No testosterone gel 1.62% patient reported decreased urinary flow or nocturia as an AE.

> *Reviewer's Comment:The testosterone gel 1.62% AE profile is consistent with similar approved drugs in its class. No new signals or patterns were noted or observed.*

7.3 Major Safety Results

This discussion deals with Studies S176.1.009, S176.1.010, and S176.1.011. For a discussion of previous protocols submitted and reviewed for this sNDA the reader is referred to the Medical Officer's review of the original NDA, finalized on November 2, 2009 and the brief Summary of Safety in Appendix 8 of this review.

7.3.1 Deaths

There were no deaths in Studies S176.1.009, S176.1.010, and S176.1.011.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events in Studies S176.1.009, S176.1.010, and S176.1.011.

7.3.3 Dropouts and/or Discontinuations

In Study S176.1.009, male subject 27474 was found to have hypertension at baseline. He and his partner (subject 27417) were replaced prior to any dosing. There were no dropouts or discontinuations in Studies S176.1.010 or S176.1.011.

7.3.4 Significant Adverse Events

Two patients in Study S176.1.010 experienced blood pressure levels coded as "markedly abnormal" on Study Day 5 (one patient) and Study Day 15 (one patient) while receiving 5 gm of AndroGel 1.62% on that day. Narratives for these two patients are provided here:

> Subject 27539: This 54-year old Hispanic/Latino White male was randomly assigned to treatment sequence A/B. He received the Phase 3 method in the first period Days 1-7 and the 4-site method in the second period (Days 15-21). On Day 5, the subject experienced an increase in sitting DBP (increased from 94 mmHg at Baseline to 114 mmHg on Day 5) that met the criteria for markedly abnormal vital signs. At a subsequent unscheduled assessment on Day 5 (that same day), the subject's sitting DBP was 90 mmHg (below baseline) and remained below the baseline level throughout the completion of Treatment A. No medical history of hypertension was reported and no AE related to the markedly abnormal DBP was recorded.
>
> Subject 27606: This 57-year old Hispanic/Latino White male was randomly assigned to treatment sequence B/A. He received the "4-site method" in the first period (Days 1-7) and the Phase 3 method in the second (Days 15-21). The subject experienced increases in sitting SBP and sitting DBP at an unscheduled assessment on Day 15 (SBP increased from 111 mmHg at Baseline to 187 mmHg on Day 15; DBP increased from 83 mmHg at Baseline to 111 mmHg on Day 15). The scheduled Day 15 blood pressure measurement (at 06:16) was 168/109 mmHg. A subsequent recheck at 07:20 on the same day was normal (111/83 mmHg). The further recheck at 16:35 on the same day was again elevated (187/111 mmHg); these blood pressure changes met the criteria for markedly abnormal vital signs. At the next scheduled blood pressure assessment (the next day -Day 16, 07:20), the subject's SBP and DBP measurements were 118 mmHg and 84 mmHg, respectively, and remained near baseline levels through the completion of Treatment A. No medical history of hypertension was reported and no AEs related to the markedly abnormal SBP and DBP were recorded.

One patient in Study S176.1.010, experienced an elevation of the body temperature on Day 6 to 38.5 ° C while receiving 5 gm of AndroGel 1.62%. On Day 7 (the last day of 7 day dosing cycle), the temperature was 36.2 ° C.

Both of these adverse events are discussed in greater detail within the discussion of Study S176.1.010 in Section 5.3.1 of this review.

> *Reviewer's Comment: I have no comments for Subject 27539 (one time elevation of DBP which upon repeat was not verified) or Subject 27545 (one time temperature elevation) further. Subject 27606 had elevated blood pressures on Day 15 and subsequent return to*

baseline the next day. It is not clear that this is a drug-related adverse event. Still, increase in blood pressure (possibly related to fluid retention) is a known potential adverse reaction of testosterone replacement therapy and is appropriately described in the proposed product label for AndroGel 1.62%.

7.3.5 Submission Specific Primary Safety Concerns

The studies in the Complete Response submission do not reveal any additional safety concerns. The safety issues addressed in the review of the original NDA submission are summarized in Appendix 8 of this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase III Study**:** Data from the Phase III double-blind study and the integrated Phase I 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.

Table 34: Common Treatment -emergent Adverse Events (>2% for T-Gel 1.62% and greater than for placebo) for the Double-blind Phase III 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 (2 February 2009 NDA submission), Table 22, page 144.
**PSA increased was codified by strict per-protocol discontinuation criteria based on relatively small increases in serum PSA (>0.75 ng/mL) or serum PSA > 4 ng/mL.*

The most common TEAEs by category (SOC) for the testosterone gel 1.62% groups compared with placebo were Infections and Infestations (37/234, 15.8% versus 5/40, 12.5%) and Investigations 34.234, 14.5% versus no subject). The most common (≥2% in the testosterone gel 1.62% groups) TEAEs by preferred term (PT) 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 an event of malignant hypertension in a patient with pre-existing hypertension.

There were pre-specified criteria for abnormal PSA values 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 gm: 1/17, 5.9%; 2.5 gm: 2/60, 3.3%; 3.75 gm: 10/66, 15.2%; 5.0 gm: 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.

The incidence of "hypertension" reported as a clinical adverse event across the testosterone gel 1.62% groups was 1.25 gm: 1/17, 5.9%; 2.5 gm: 0/60; 3.75 gm: 1/66, 1.5%; 5.0 gm 4/91, 4.4%.

No other clinically relevant differences in incidences of TEAEs were noted across dose groups of testosterone gel 1.62%

> *Reviewer's Comment: It is notable that diarrhea and upper respiratory conditions are also reported more commonly in the active treatment group compared to placebo in the AndroGel® 1% label and thus, may be treatment related. These events are reflected in the proposed testosterone gel 1.62% product label. PSA elevations are most likely treatment related and are also presented in labeling. It is not clear that that the hypertension cases are clearly hypertension, nor whether there is a definitive drug-related signal. Nevertheless, this AE will be listed in the label and is a possible AE to testosterone replacement therapy. There was no indication that application site pruritis and dermatitis increased with increased testosterone concentrations. No patient discontinued because of an application site TEAE.*

The proportion of subjects with at least one TEAE ranged from 52.5% to 80.0% across serum testosterone concentration categories (≤ 1500 ng/dL: 96/183, 52.5%; 1501 to 1800 ng/dL: 9/16, 56.3%; 1800 to ≤ 25000 ng/dL: 17/25, 68.0%; >2500 ng/dL: 8/10, 80.0%). There was no pattern of increasing incidence of single preferred terms with higher serum testosterone concentration category.

Table 35: Incidence of TEAEs by Highest Measured Testosterone Concentration Category for Events that Occurred in at Least One Subject in the >2500 ng/dL Category (Safety Sample Testosterone gel 1.62% Group)

Preferred Term	T≤2500 N=224	T>2500 N=10
Subjects with at least one AE	n (%) 122(54.5)	n (%) 9(90.0)
Toothache	0	1(10.0)
PSA Increased	22(9.8)	1(10.0)
Weight Increased	1(0.4)	1(10.0)
Mood Swings	0	1(10.0)
Libido Increased	0	1(10.0)
Nephrolithiasis	0	1(10.0)
Nipple Disorder	0	1(10.0)
Erectile Dysfunction	1	1(10.0)
Erection Increased	0	1(10.0)
Testicular Pain	1(0.4)	1(10.0)
Acne	1(0.4)	1(10.0)
Hypotension	1(0.4)	1(10.0)

Source: Clinical Study Report S176.3.104 (sNDA submission 11 February 2009), Table 23, Page 148

Table 36: TEAEs by Testosterone (ng/dL) C_{max} and Body System (Safety Sample)

Primary SOC (Disorder)	≤1500 T level N=183	1501-<1800 N=16	1800-≤2500 N=25	>2500 N=10
Pt with at least one AE	N (%) 96(52.5)	N (%) 9(56.3)	N (%) 17(68.0)	N (%) 8(80.0)
Cardiac	3(1.6)	0	2(8.0)	0
Endocrine	1(0.5)	0	0	0
Eye	0	0	1(4.0)	0
Gastrointestinal	8(4.4)	0	0	1(10.0)
General and Site Conditions	15(8.2)	0	0	0
Immune System	4(2.2)	0	0	0
Infections Infestations	31(16.9)	1(6.3)	4(16.0)	1(10.0)
Injury, Poisoning, Procedural Complications	12(6.6)	1(6.3)	3(12.0)	0
Investigations	27(14.8)	1(6.3)	4(16.0)	2(20.0)
Metabolism Nutrition	1(0.5)	3(18.8)	3(12.0)	0
Musculoskeletal Connective Tissue	11(6.0)	3(18.8)	6(24.0)	0
Nervous System	8(4.4)	2(12.5)	3(12.0)	0
Psychiatric	8(4.4)	2(12.5)	2(8.0)	2(20.0)
Renal, Urinary	1(0.5)	0	0	1(10.0)
Reproductive, Breast	5(2.7)	1(6.3)	0	1(10.0)
Respiratory, Thoracic, Mediastinal	7(3.8)	2(12.5)	1(4.0)	0
Skin, SubQ	13(7.1)	2(12.5)	0	1(10.0)
Vascular	0	1(6.3)	0	0

Source: Clinical Study Report S176.3.104 (sNDA Submission 11 February 2009); Table 3.17.0, page 1830

Reviewer's Comment: The number of reports in the higher exposure groups are too small to make meaningful comparisons to the other groups, other than to state that the TEAE rate in subjects with testosterone levels >1500 ng/dL(n=34) is 66.7% versus 52.5% for men with testosterone levels <1500 ng/dL.

In the Open-Label Safety Extension the TEAEs occurring in ≥5% of subjects are displayed in the table below:

Table 37: Open-Label Safety Extension TEAEs occurring in 5% or more of Subjects

Term (HLT) Statistic n (%)	Formerly Placebo N=28	T-Gel 1.62% Total N=191	T-Gel 1.62% 1.25 gm N=15	T-Gel 1.62% 2.5 gm N=41	T-Gel 1.62% 3.75 gm N=43	T-Gel 1.62% 5.0 gm N=92
Diarrhea	1(3.6)	2(1.0)	2(13.3)	0	0	0
Asthenia	0	3(1.6)	1(6.7)	0	1(2.3)	1(1.1)
Viral infection	2(7.1)	3(1.6)	0	0	1(2.3)	2(2.2)
Lower Respiratory Infection	1(3.6)	5(2.6)	1(6.7)	1(2.4)	1(2.3)	2(2.2)
Upper Respiratory Infection	2(7.1)	18 (9.4)	0	2(4.9)	4 (9.3)	12(13.0)
PSA increased	3(10.7)	10(5.2)	2(13.3)	3(7.3)	1(2.3)	4(4.3)
Triglyceride increased	0	2 (1.0)	1 (6.7)	0	0	1 (1.1)
Sexual Desire Disorders	0	2 (1.0)	1 (6.7)	0	0	1(1.1)
Skin Rashes, Eruptions	0	1 (0.5)	1 (6.7)	0	0	0

Source: 120 Day Safety Update to sNDA Submission 11 February 2009): Tables 3.2.0 and 3.1.0

Reviewer's Comments:

1. *The incidence and categories of AEs in the Open-Label Period appear comparable to those noted in the double blind period. No new safety concerns are engendered by this list of AEs.*
2. *The distribution of C_{max} values of testosterone for the subjects in the safety extension is as follows: ≤ 2500 ng/dL N=179, ≤ 1500 N=158, 1501≤ 1800 ng/dL N=9, 1800 ≤ 2500 ng/dL N=12, and > 2500 ng/dL N=0. Upon review of Table 3.17.3, it is my opinion that there was not a disproportionate number of AEs associated with higher C_{max} testosterone concentrations.*
3. *There were no new findings to add to common adverse events from Studies S176.1.009, S176.1.010, and S176.1.011.*

7.4.2 Laboratory Findings

In the open-label period of Study S176.3.104, the summary of "marked abnormalities" (as per the protocol definitions) show that for each parameter, the percentage of subjects in the testosterone gel 1.62% Total group (subjects who had formerly received active treatment during the double-blind period) with "marked abnormalities" was <2% except for: Hct >0.54% (3/163, 2.0%), serum GGT≥100 U/L (3/163, 2.0%), and serum triglycerides ≥5.6mmol/L (1/163, 4.6%). No subject met the criterion for elevated liver function for discontinuation (3X ULN if confirmed by repeat blood test) in the double-blind or open label periods. PSA increased is discussed in detail in the Medical Officer's review of the original NDA (finalized November 2, 2009) and briefly summarized in Appendix 8 of this review.

In Study S176.3.009, no significant changes in the clinical laboratory measurements of the course of the study occurred which could be reasonably associated with the test product under investigation. Total testosterone levels in female subjects on Day -1 (Baseline) ranged from 7.03 ng/dL to 50.0 ng/dL (normal range 0-90 ng/dL). On Day 1 (the day of skin contact) the testosterone range was 7.2 ng/dL to 43.5 ng/dL.

In Study S176.3.011, no significant changes in the clinical laboratory measurements of the course of the study occurred which could be reasonably associated with the test product under investigation. Total testosterone levels in female subjects at Day -1 (Baseline) ranged from 6.04 ng/dL to 63.60 ng/dL (normal range 0-90 ng/dL). On Day 1 (the day of skin contact) the testosterone range was 7.51 ng/dL to 74.50 ng/dL.

In Study S176.1.010, seven subjects experienced laboratory values that met the criteria to meet the per-protocol definition of "markedly abnormal" laboratory criteria, as follows:

Five patients *entered the study* with hematocrits below the normal limit (normal 42-54% for males). There was no report of a hematocrit above 54% during the study. At study termination their hematocrits were still below the normal limit. Their were no other laboratory abnormalities in these subjects to implicate a process that could account for the lowered hematocrit except for Subject 27524 who entered the study with an eosinophil count of 16% and at end of study the eosinophil count was 18%. Their hematocrit results are presented in the table below:

Table 38: Summary of Abnormal Hematocrit Assessments

Subject	Treatment Sequence	Baseline Value	Abnormal Value/Day
27524	B/A	41.4%	36.8%/Day 22 EOS
27529	B/A	38.3%	36.3%/Day 22 EOS
27536	A/B	39.9%	36.7%/Day 22 EOS
27538	A/B	36.6%	36.6%/Day 22 EOS
27565	A/B	38.7%	36.3%/Day 22 EOS

* EOS=end of Study; Source: Adapted from Table 9, S176.1.010 Study Report, page 55.

Subject 27525 entered the study with a uric acid of 10.9 mg/dL and at end of study the uric acid was 9.6 mg/dL. There were no noted changes in liver chemistries, serum albumin levels or EGFR during the study.

Subject 27569 at end of study [Day 22] reported a GGT of 126 U/L (baseline was 74 U/L). The normal range for GGT is 1-94 U/L. An unscheduled Day 27 GGT was 106 U/L. The subject had no abnormalities or increases of bilirubin, alkaline phosphatase, aspartate amino transferase, alanine aminotransferase, or ALT.

All 7 patients with laboratory abnormalities did not have an explanatory finding in their medical history.

7.4.3 Vital Signs

In the Open-Label Period of Study S176.3.104, the were no clinically meaningful changes from baseline at any timepoint for vital signs, and no important differences across dose groups were noted in the mean change from Baseline. In the 182 Day Open Label Safety Extension, the average weight gain per subject was -0.22 kg (Baseline [Day 182] to endpoint [Day 364]). The sitting systolic blood pressure increased on average 0.1 mmHg per subject. The sitting diastolic blood pressure changed from Baseline at endpoint -1.3 mmHg. Sitting pulse changed from Baseline at endpoint -0.3 bpm.

Table 39: "Marked Abnormalities" of Vital Signs in the 182 Day Open-Label Safety Period Extension by Per-Protocol Definitions

Statistic n(%)	Formerly Placebo N=28	T gel 1.25 gm N=15	T gel 2.5 gm N=41	T gel 3.75 gm N=43	T gel 5.0 gm N=92
Weight					
>7%↓	2 (7.1)	0	6 (15.0)	2 (4.9)	9 (10.1)
>7%↑	2 (7.1)	1 (7.1)	1 (2.5)	3 (7.3)	7 (7.9)
Systolic BP					
bsl≤90&↓≥20	0	2 (1.1)	0	1 (2.5)	1 (1.1)
bsl≥180&↑≥20	0	2 (1.1)	0	1 (2.5)	1 (1.1)
Diastolic BP					
bsl<50&↓≥15	0	0	0	0	1 (1.1)
bsl≥105&↑≥15	0	0	1 (2.5)	0	1 (1.1)
Pulse (bpm)					
bsl≤50&↓≥15	0	0	1 (2.5)	0	1 (1.1)
bsl≥120&↑≥15	0	0	0	0	0

*bsl=Baseline
Source: Table 5.1.0 120 Day Safety Update, Page 2364

Reviewer's Comment: There are no discernible trends of concern in this data. The small numbers in each treatment group may preclude noting any differences with respect to dose.

In Study S176.1.009, there were no vital signs that were out-of-range over the course of the study for either the female or male subjects who were enrolled in the study.

In Study S176.1.011, there were no out of range measurements for any of the female subjects. Two male subjects had out-of-range results. Subject 1011-27593 had high systolic blood pressure at screening (161 mmHg); the measurement was repeated and the subsequent result was again high (143 mmHg); the repeated result was again high (176 mmHg). The diastolic blood pressure for male subject 1011-27597 was high (93 mmHg) at screening; the measurement was repeated and the result (85 mmHg) was within the normal range.

In Study S176.1.010, no clinically important trends were noted in mean change-from baseline vital sign data. Three subjects (Subjects 27539, 27606 and 27545) had "markedly abnormal" vital signs values during the study as per protocol definitions. Narratives and reviewer's comment for these three patients have been provided twice previously in this review and will not be repeated here.

7.4.4 Electrocardiograms (ECGs)

Across all studies in the testosterone gel 1.62% development program, there were no clinically significant changes from Baseline in ECG findings.

7.4.5 Special Safety Studies/Clinical Trials

Transfer Studies

Studies S176.1.009 and S176.1.011 were submitted in this **COMPLETE RESPONSE** to evaluate alternative application methods of AndroGel 1.62% as a means of decreasing testosterone transfer to a female by skin contact to a male partner using a t-shirt barrier who had applied 5 g of AndroGel 1.62% either to both arms/shoulders or to both arms/shoulders and both sides of the abdomen. It appears that both methods, the 4-site method and the arms/shoulders method adequately mitigate testosterone transfer.

Skin Irritation

The Sponsor conducted a dedicated cumulative skin irritation and sensitization study as well as two studies dedicated to the issue of transfer in the originally submitted NDA. The reader is referred to the Medical Officer's original NDA review as well as a brief summary in Appendix 9.5.

In Study S176.1.010, the new bioavailability study comparing 4-site to rotating application methods, the application sites of testosterone gel 1.62% were assessed using a protocol specified scale prior to dosing on Days -1 to 21 and on Day 22/Early Termination.

Treatment emergent AEs related to application sites were recorded for 3 (4.8%) subjects receiving Treatment B (4-site method -1.25 g both upper arms/shoulders and both sides of abdomen daily for 7 days). All three subjects developed one or more papules at the administration site. No TEAEs were reported for Treatment A (rotating method - 2.5 g to each side of abdomen for 3 days followed by 2.5 g to each arms/shoulders daily for 4 days).

In this study, the scales used for application site evaluations were as follows:

Irritation-numeric grades:

0. No evidence of irritation.
1. Minimal erythema, barely perceptible
2. Moderate erythema, readily visible or minimal edema or minimal papular response
3. Erythema and papules
4. Definite edema
5. Erythema, edema, and papules
6. Vesicular eruption
7. Strong reaction spreading beyond test site

Irritation letter grades:

D. Slight glazed appearance
E. Marked glazing
F. Glazing with peeling and cracking
F. Glazing with fissures
G. Film of dried serous exudates covering all or portion of the patch site
H. Small petechial erosions and/or scabs

No patient in this study was assigned a letter grade (reference Appendix 12, Listing 12.2.4.9 and Appendix 12.2.7, Listing 12.2.7.1).

A summary chart of application site findings was constructed by the reviewer. Any subject with abnormal application site findings on Day -1 was omitted. To qualify as an application site AE for this chart, the finding had to occur twice in the same treatment period. The most severe level of irritation was used. If an individual had a similar level of irritation, then the first treatment was listed as the inciting treatment. If the severity of irritation decreased from the first treatment to the second treatment, then the first treatment was considered causal. If the converse occurred, only the level of irritation in the first treatment period was listed. See table below:

Table 40: Tabulation of Application Site Irritative Events

Subject	Attributed Treatment	Irritation Location	Grade
27527	A	All four sites	1
27545	B	All four sites	1
27546	B	All four sites	1
27551	A	All four sites	1
27559	B	All four sites	1
27564	B	R, L upper arms/shoulders	1
27565	B	R, L abdomen	1
27568	B	R, L abdomen	1
27552	B	All four sites	1
27550	B	All four sites	2
27556	B	All four sites	2

Source: Listing 12.2.4.9 Application Site Evaluation, S176.1.010 Study Report and Table 25 in this current review.

Reviewer's Comment: For those patients who made this list, all but 2 had Grade 1 erythema. Case 27550 had an irritative grade 2 skin finding only on 1 (site upper arm shoulder) on Days 16 through 19. On Days 20 and 21 and 22 the findings at that site were 0, 1, 0 respectively. Case 27566 had an irritative finding of grade 2 at all four sites on Days 4, 5, 6, 7, and 8. On Days 14 through 20, this subject had an irritative grade of 1 at all sites, but Day 21 the irritative grade noted was zero at all sites. Thus, there is only one subject in this study with possible skin irritation. In Study S176.1.009 (N=235), a formal contact sensitization and irritation study, only 2 subjects were noted to have a mild skin rash. This reviewer's conclusion for that study was "Testosterone Gel 1.62% appears to have no sensitization potential and minimal irritation potential as compared to placebo." The results from Study S176.1.010 do not alter that recommendation.

7.4.6 Immunogenicity

For the assessment of immunogenicity potential, the Sponsor conducted a dedicated cumulative skin irritation and contact sensitization study, showing no evidence of sensitization. The reviewer also analyzed Table 3.1.1, Incidence of TEAE's Safety Sample, on page 1698 of the Clinical Study Report S176.3.104, for this issue.

Under the Primary MedDRA SOC General Disorders and Administrative Site Conditions, 1 testosterone gel 1.62% 1.25 g subject reported "application site hypersensitivity" and 1 testosterone gel 1.62% 5.0 g subject reported "application site pruritis".

Under the Primary MedDRA SOC Immune System Disorders, 1 subject receiving testosterone gel 1.62% 3.75 g reported "allergy to an arthropod bite", and 3 subjects receiving testosterone gel 1.62% 5.0 g reported "seasonal allergy".

Under the Primary MedDRA SOC Respiratory, Thoracic, and Mediastinal Disorders, 1 subject receiving testosterone gel 1.62% 5 g reported breathing abnormalities and 1 subject reported wheezing. In addition, one subject each in the placebo group, testosterone gel 1.62% 1.25 g, group, and testosterone gel 1.62% 5 g group reported pharyngolaryngeal pain. One subject receiving testosterone gel 1.62% 2.5 g reported throat irritation.

Under the Primary MedDRA SOC Skin and Subcutaneous Tissue Disorders, skin-related AEs reported in the phase 3 study Study 104 are listed in the table below:

Table 41: Skin Adverse Events S176.3.104

Preferred Term	Placebo	Testosterone gel 1.62% by Final Dose			
Statistic n (%)	N=40	1.25 g N=40	2.5 g N=58	3.75 g N=66	5.0 g N=91
Acne	0	1(5.9)	0	0	1 (1.1)
Heat Rash	0	0	0	0	1 (1.1)
Dermatitis	0	0	1 (1.7)	0	0
Dermatitis Contact	0	1 (5.9)	0	4 (6.1)	0
Skin Irritation	0	0	0	0	1 (1.1)
Drug Eruption	0	0	0	0	1 (1.1)
Erythema	0	0	1 (1.7)	0	1 (1.1)
Pruritis	0	0	0	0	1 (1.1)
Rash Papular	0	0	0	1 (1.5)	1 (1.1)

Source: Table 3.1.0, Clinical Study Report S176.3.104, Page 1693.

No subject discontinued from Study S176.3.104 for site reactions or dermatologic AEs

The entire clinical study report was searched for the terms angioedema, anaphylaxis, urticaria, hives, generalized skin rash, pharyngeal edema and laryngeal edema with no reports found.

Reviewer's Comments:

1. *While there were several reports of mild application site reactions and dermatitis, there were no clinically or statistically significant differences in mean scores at any timepoint between testosterone gel 1.62% and placebo groups for the skin irritation assessments.*
2. *There appears to be no evidence of major systemic immunologic or allergic phenomena secondary to testosterone gel 1.62% in Protocol S176.3.104.*

In Study S176.1.010, there was only 1 subject with possible application site irritation (see Section 7.4.5).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No clinically significant trend attributing the frequency of adverse events to the testosterone gel 1.62% dose was found.

7.5.2 Time Dependency for Adverse Events

Table 42: Time Dependency Adverse Events S176.3.104

Assessment Statistic n (%)	Testosterone gel 1.62% Double-Blind Period N=234	Testosterone gel 1.62% Open-Label Period N=191
	Mean Exposure=151.9 Days	Mean Exposure 319.7 Days
Deaths	0	0
Serious Adverse Events	5 (2.1)	4 (2.1)
Discontinuations Due to TEAE	25 (10.7)	9 (4.7)
TEAEs	130 (55.6)	79 (41.4)
Application Site Hypersensitivity	1 (0.4)	1 (0.5)
PSA either > 4.0 and/or increase of >0.75 ng/	34 (14.9)	12 (6.3)
PSA Discontinuation	17 (7.3)	6 (3.1)
Hematocrit > 54%	5 (2.1)	4 (2.6)
Hematocrit Discontinuation	1 (0.4)	4 (2.1)

Sources: Clinical Study Report S176.3.104: Table 3.0.0 page 1691: Listing 18, Pages 2961-2994 and S176.3.104 120 Day Safety Update Table 3.1.0 Pages 2293-2303: Table 29 of the 2 November 2009 NDA review.

Reviewer's Comment: There does not appear to be a time dependency noted for adverse events.

7.5.3 Drug-Demographic Interactions

Based on the low incidences of markedly abnormal clinical laboratory and vital signs values and the small number of subjects in the placebo group, no between-treatment comparisons can be made based on subgroup analysis for age (<45 years N=40; 45-54 years N=90; 55-64 years N=69; ≥ 65 years N=8) and race (white, non-white).

Safety analyses by extrinsic factors show that there were no clear patterns across the number of hours after dose application subjects washed their skin (two, six, or 10 hours Post dose), the presence or absence of moisturizer lotion or sunscreen, or across three difference administration site schedules. Secondary to the small sample sizes for some categories and the low incidence of markedly abnormal clinical laboratory and vital signs, Sponsor states no definitive conclusions can be drawn.

7.5.4 Drug-Disease Interactions

There were no clinically or statistically differences in least- squares (LS) mean change from Baseline at each timepoint between the testosterone gel 1.62% and placebo groups in the IPSS Total Score. The LS mean change from Baseline at Endpoint was 0.8 in the testosterone gel 1.62% and 0.3 in the placebo group.

Reviewer's Comment: Testosterone is known to increase the PSA in males. A concern is that this rise of PSA may indicate increase of prostate volume and lead to increasing voiding symptoms and urinary retention; however, only a modest increase of the IPSS was noted in patients receiving testosterone gel 1.62%, and there were no reported urinary retention events in Study S176.3.104.

7.5.5 Drug-Drug Interactions

In Study S176.1.006, Testosterone gel (2.5 g dose: 40.5 mg testosterone) was applied once daily to the upper arms/shoulders for 7 days, either alone or 1 hour before application of 6.0 g of moisturizer lotion or 6.0 g of sunscreen. Testosterone pharmacokinetic parameters $AUC_{0-24,}$ C_{avg} and C_{max} were calculated on Day 7 and compared between treatments. It was found that application of moisturizer lotion 1 hour after application of 2.5 g testosterone gel 1.62% once daily to the same skin site increased bioavailability of testosterone by 14% and 17% increase in AUC_{0-24} and C_{max}, respectively, compared to testosterone gel 1.62% alone. Application of sunscreen under similar circumstances had no effect on overall exposure (AUC_{0-24}) of testosterone, but increased C_{max} by 13% compared to testosterone gel 1.62% administered alone. Individual and mean concentrations of C_{av} and C_{max} values were within the eugonadal range (300-1000 ng/dL) for all three treatments.

No other drug-drug interaction studies have been conducted for testosterone gel 1.62%. The following information is available from the approved AndroGel 1% label:

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

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

Oral Anticoagulants: Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

The Sponsor adds in their submission the following additional interactions that have been reported in the literature:

Bupropion: Use of systemic steroids concomitantly with bupropion has been reported to lower the seizure threshold. The prescribing information for Wellbutrin® and Zyban® recommends minimizing the potential for occurrence by not exceeding the prescribed dose of buproprion, increasing the dose gradually, and/or using divided doses when applicable.

Cyclosporine: Concomitant administration of cyclosporine and anabolic steroids may result in increased cyclosporine blood levels and toxicity. It is recommended that such combinations be avoided, or if concomitant administration is necessary, that circulating cyclosporine levels be monitored and cyclosporine dosage be adjusted as appropriate, and the patients be monitored for signs of increased cyclosporine toxicity (such as renal dysfunction or neurotoxicity).

Dehydroepiandrosterone (DHEA): Concomitant use of DHEA with testosterone is reported to result in an increased risk for androgenic and hepatic side-effects. The effect appears to be dose-dependent, and at doses commonly used by body builders (e.g. 1000 mg), androgenic effects are likely. It is recommended that concomitant use of DHEA be avoided.

Paclitaxel: Testosterone has been reported to inhibit the metabolism of paclitaxel (via inhibition of CYP2C8) to its primary metabolite 6α-hydroxypaclitaxel *in vitro*, and may also alter the pharmacokinetics of paclitaxel *in vivo.* The prescribing information for TAXOL® recommends that caution be exercised with the concomitant use of paclitaxel and CYP2C8 inhibitors such as testosterone. Patients should be monitored for increased adverse effects due to paclitaxel toxicity including bone marrow suppression, myalgia/arthralgia, nausea/vomiting, and mucositis. Dose adjustment of either medication may be required.

Reviewer's Comment: These reports from the literature are of interest and in some cases do appear in product labeling (e.g., buproprion and paclitaxel). The reviewer does not deem it necessary to add these to the AndroGel 1.62% label at this time.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

At the current time, I am not aware of any evidence of the carcinogenicity of AndroGel® or testosterone gel 1.62%. There is also is no definitive evidence that testosterone replacement in

general is causative of prostate cancer, although large studies in geriatric males at risk of prostate cancer have not been conducted .

As of 8 August 2007, a total of 22 cases of nonprostatic malignancies involving patients taking AndroGel® 1% were identified in the Sponsor's database. There were 18 different types of malignancies and no one malignancy was reported more than twice. From 2004 to 2007, there was a modest increase in the number of malignancies in Solvay's postmarketing database from zero cases in 2004 to three in 2005, five in 2006 and seven in 2007. All seven cases reported in 2007 were from different cancer sites and the patient either had a duration of testosterone therapy of less than one year, and previous history of cancer and tumors, and reported risks factors for cancer. No specific trend of a specific cancer site was detected.

Of the 22 cases of nonprostatic malignancies, two were pituitary tumors, one was a meningioma in a formerly resected pituitary tumor site, two were breast cancer at 5 and 6 weeks of AndroGel® therapy and may represent the same case, two were recurrent testicular cancer and one was testicular seminoma.

7.6.2 Human Reproduction and Pregnancy Data

Testosterone gel 1.62% is not intended for use by, and should not be used by pregnant or lactating women. The clinical safety data is related only to the treatment of males with testosterone gel 1.62% and therefore, safety information is not available, nor applicable, for use in pregnancy and lactation. It is not known how much testosterone transfers into human milk. Exposure of the fetus to androgens may result in varying degrees of virilization.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of AndroGel 1.62% in males <18 years old has not been established. Improper use may result in premature closure of the epiphyses.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The labeling for approved testosterone products describes one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels up to 11,400 ng/dL and had a cerebrovascular accident. This case also appears in the Investigator Brochure Testosterone gel 1.62%. Edition No. IB-176.01, 22 September 2009. Treatment of overdosage would consist of discontinuation of testosterone gel 1.62%, washing the application site with soap and water, and appropriate symptomatic and supportive care. Data from two Phase I studies have shown that serum testosterone concentrations return to approximately Baseline levels by 48-72 hours after the last topical application of testosterone gel 1.62%.

Testosterone gel 1.62% contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act. Oral ingestion of testosterone gel 1.62% should not result in

clinically significant serum testosterone concentrations due to excessive first-pass metabolism. Pump weight verification data in Study S176.3.104 did not appear to contain evidence of consistent drug overuse.

No information on testosterone withdrawal or rebound is available from the testosterone gel 1.62% development program or in the approved AndroGel 1% label.

7.7 Additional Submissions

During an 8 September 2010 teleconference, Abbott agreed to perform a hand washing study as a Post-Marketing Requirement (PMR). A proposed protocol for this study was included in the Complete Response submission and is summarized herein.

7.7.1 Study S176.1.012 An Evaluation of the Effect of Hand Washing on the Amount of Residual Testosterone on the Hands after Application of Testosterone Gel 1.62%

Study Objectives

The primary objective is to assess the amount of residual testosterone on the hands of healthy male subjects with and without hand washing following application of testosterone gel 1.62%.

Study Design

(b) (4)

washing (Treatment A). This will be assessed using the left hand, right hand, and the total sum from both hands. The primary description will be based on the data from both hands totaled.

The sample size is based on clinical judgment and is believed to be sufficient to satisfy the objectives. Sixteen (16) subjects will be allocated allowing two potential dropouts.

Reviewer's Comment: The study appears adequately designed to achieve the stated objective. From the Clinical perspective, there are no changes recommended at this time. Additional comments will be requested from Clinical Pharmacology and Biometrics review teams.

8 Postmarket Experience

Testosterone gel 1.62% is not currently marketed. However, extensive post-marketing safety information is available for AndroGel® (testosterone gel) 1% which is approved and marketed internationally in 65 countries. The safety findings noted in testosterone gel 1.62% Phase I-III clinical studies appear similar and consistent with testosterone 1% and this class of drug. As part of the **COMPLETE RESPONSE,** sponsor was asked to update the reports of post marketing experience for AndroGel 1%. They have submitted post-marketing safety update reports (PSURs) for the years 2009 and 2010, and a "bridge" report to cover the period from the end of the lock period for the 2010 report (27 February 2010) to the cut point of 31 August 2010.

This section will update the previous Postmarket Experience section from the Medical Officer's original sNDA review placed in DARRTS November 2, 2009. Only new findings and potential safety signals will be discussed.

An estimated (b) (4) patients (~236,470 patient-years) were exposed to testosterone gel 1% during the period of 28 February 2008 to 27 February 2009. A crude estimate of the number of patients exposed to AndroGel® was calculated by the Sponsor which resulted in an estimate of approximately (b) (4) patients or roughly 1.13 million patient years of treatment with AndroGel® for the 28 February 2000-27 September 2008 cumulative post-marketing review period. In the period between 28 February 2009 and 27 February 2010, an estimated (b) (4) patients (~281,306 patient years) were exposed to testosterone gel 1%.

Reviewer's Comment: The use of AndroGel 1% over the last two years is large (approximately (b) (4) patients and (b) (4) patients in 2009 and 2010, respectively).

During the period 28 February 2008 to 27 February 2009 (7th Periodic Safety Update for AndroGel 1%), of the estimated (b) (4) users, a total of 170 serious, and unlisted non-serious spontaneous adverse event reports (ICSRs) were received from healthcare professionals, of which 42 events were regarded as serious. Most ICSRs were received spontaneously from the market (99.4 %) followed by health authority reports (3 %), respectively (reports may be received from more than one source).

In the 7th Periodic Safety Update, 839 medically unconfirmed reports from consumers or other non-healthcare professionals were received; 22 serious and 817 non-serious.

> *Reviewer's Comment: The consumer/non-health care professional reports do not provide any additional safety information, not already encompassed by the healthcare provider reports.*

During the period from 28 February 2009 and 27 February 2010 (8th Periodic Safety Update for AndroGel 1%), of the estimated (b) (4) users, a total of 144 serious and unlisted nonserious spontaneous adverse event reports (ICSRs) were received from healthcare professional. Of these 36 reports were regarded as serious. Most ICSRs were received spontaneously from the market (94%) followed by the literature (3.5%), clinical studies (2.8%), and health authorities (2.1%), respectively (reports may be received from more than one source).

In the 8th Periodic Safety Update, eight hundred and one medically unconfirmed reports from consumers or other non-healthcare professionals were received, 42 were serious and 759 were nonserious.

> *Reviewer's Comment: The consumer/non-health care professional reports do not provide any additional safety information, not already encompassed by the healthcare provider reports.*

For AndroGel 1%, the 'bridge" report – the PSUR update from the end of the lock period for the 2010 report (27 February 2010) to the cut point of 31 August 2010 - did not reveal important new safety information.

According to Sponsor's submission, in the 7th PSUR the potential safety signals of idiopathic thrombocytopenic purpura (ITP) and secondary exposure were identified and analyzed. It was concluded that no further safety action other than routine monitoring was warranted. In the 8th PSUR, the potential safety signals of pancreatitis and myocardial infarction were identified and analyzed and the Sponsor concluded that no further safety action other than routine pharmacovigilance activities is warranted.

> *Reviewer's Comment: With regard to the potential safety risk of myocardial infarction and testosterone replacement, the Division of Reproductive and Urologic Products (DRUP) recently consulted the Division of Epidemiology (DEPI) to analyze and provide comment on 3 systematic reviews from the literature concerning cardiovascular effects of testosterone replacement therapy in hypogonadal men. The consult was completed on December 6, 2010. 58 individual studies were identified from among the three systematic reviews. 34 individual studies were selected as satisfactory for review. The conclusion from DEPI, based on their review of these studies, was that the overall cardiovascular risk associated with testosterone replacement therapy (TRT) and associated with placebo are comparable and do not support an association between TRT and increased risk of cardiovascular events in men.*

Summarized below are updates to several potential safety issues identified by Sponsor in previous safety updates and these issues have previously been reviewed by the Medical Officer in his review of the original NDA, finalized on November 2, 2009:

Experience with Drug-Drug Interactions: During the more than 8-year post-marketing review period of Androgel 1% from 28 February 2000 through 27 September 2008, 30 postmarketing reports mentioned a possible drug interaction: all were non serious. The Periodic Safety Update Reports, Drug Interactions, 2000-2008 were reviewed. No new safety signals were detected and no new safety actions were undertaken by Sponsor re: drug interactions. In the 7th PSUR reporting period, there were four reports of possible drug interaction. In the 8th PSUR, one possible nonserious drug-drug interaction was reported. The ADRs the patients experienced were either listed for testosterone (e. g. fluctuating testosterone levels) or were events related to their underlying conditions.

Experience with Overdose: During the more than 8-year post-marketing review period of Androgel 1% from 28 February 2000 through 27 September 2008, there was one report of suspected overdose. This has been previously reviewed in the original NDA review, November 2, 2009. In the review period covered in the 7th PSUR there were no reports of overdose. In the 8th PSUR, one accidental overdose was reported which was nonserious.

Drug Abuse or Misuse: During the more than 8-year post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, there were eight postmarketing reports of adverse events in users who may have been abusing or purposefully misusing AndroGel 1%. These were several non-serious reports reviewed in the sNDA review, November 2, 2009. In the 7th PSUR, eleven cases were reported. None of these reports constitute a serious public health threat. No new safety signals were detected. In the 8th PSUR, twelve cases were coded as drug abuse or misuse, two of them were serious:

- *GR-SOLVAY-00202004473*: This is a literature report involving a 29-year old male who experienced pulmonary peliosis with a fatal outcome, likely related to the abuse and misuse of androgenic steroids over a long period of time.

- *US-SOLVAY-00209002403*: This consumer report concerned a 51-year-old female who was exposed to testosterone gel 1% by her husband without her knowledge.

The remaining 8 cases involved men who independently altered their prescribed dose frequency, dose or application site.

Experience During Pregnancy or Lactation: During the more than 8-year post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, there were 18 postmarketing reports of possible AndroGel exposure during pregnancy. In the 7th PSUR reporting period, there were no reports of testosterone gel 1% being taken during pregnancy or lactation. In the 8th PSUR reporting period, there was one case report:

- US-SOLVAY-00209006500: Patient is a 38 year-old female who became pregnant while her husband (the reporter) was being treated with testosterone gel 1%, 5g daily. No other event was reported in this patient. At the time of the reporting, the husband continued to use testosterone gel 1%, and the consumer was still pregnant.

Children: During the post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, a total of 11 adverse events were reported in children who were being treated with AndroGel 1% and another 26 postmarketing adverse events were received for AndroGel 1% with possible inadvertent AndroGel exposure in children (≤17 years old).

Reviewer's Comment: The reader should be aware that many, and perhaps all, of the cases of inadvertent exposure had been previously reviewed in great detail by the review teams in DRUP, DMEP, PMHS, and OSE prior to the sNDA. This multi-Divisional review led to extensive labeling changes and a Medication Guide.

During the 7th Periodic Safety reporting period, there were five case reports of secondary exposure, and two cases of adolescent use. In one of the two adolescent cases, AndroGel 1% was prescribed to a 17 year-old male for testosterone replacement and while using AndroGel 1%, the patient ingested carnitine, which imparted a fish-like odor to his breath. In the second case, a 12 year-old male with Crohn's disease, was prescribed testosterone gel 1% for delayed puberty. The patient developed fatigue.

In the 8th PSUR reporting period, there were 10 reports of testosterone gel 1% being used in children/adolescents. 9 of these cases involved potential secondary exposure. The 10th case involved a 12 year-old male with no pituitary function who was being treated with testosterone gel 1% as replacement therapy. In association with 1.25 g of testosterone gel every other day in the morning, he developed nausea and a few episodes of vomiting. The patient remained on medication with resolution of vomiting and nausea ongoing. The nausea seemed to get better as the day went on.

The Sponsor observes that, overall, no changes in reaction frequency or pattern of secondary exposure have been observed during the period covered. A boxed warning that a risk of secondary exposure of testosterone to others, (b) (4) (b) (4) The Sponsor feels no further action is necessary.

Reviewer's Comment: I concur.

Women: During the post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, a total of 190 post-marketing reports involving females were received by the Sponsor. Of these, 57 females reported using AndroGel outside the labeled indications. The remaining 137 reports involved possible inadvertent secondary exposure.

Reviewer's Comment: Most, perhaps all, of these adult female cases were reviewed by a DRUP Medical Officer in the context of the DRUP/OSE secondary exposure review. According to the medical officer's review, perhaps one case contained sufficient information to raise a concern regarding secondary exposure to an adult woman with any clinical sequalae.

In the 7th PSUR reporting period, there were a total of 30 post-marketing reports involving females received by Sponsor. Six involved off-label use of testosterone gel 1%. 24 reports were regarding women who may have experienced accidental/secondary exposure through contact with their partners. The majority of the reports reflected androgenic signs or symptoms (e.g. virilism). One case is of interest and is presented below in brief:

- US-SOLVAY-00209000227: This is a consumer report regarding a 47 year-old female who reported breast cancer approximately two years after her husband began testosterone gel 1% treatment. She reported her husband slept in a t-shirt, but suspected secondary exposure by means of doing the laundry. No additional information is received.

  Reviewer's Comment: The Sponsor points out that this is the first case of breast cancer reported to be associated with secondary exposure to testosterone gel 1%. With the paucity of information provided in this case, they conclude no new safety signal is indicated. I agree.

In the 8th PSUR reporting period, there were a total of 46 ADR reports involving women who received testosterone gel 1% during the review period. 7 of theses ADRs were serious. Of the remaining 39 ADRs, 38 involved possible secondary exposure to testosterone gel 1% and 1 case was a health care professional report involving an adult female using testosterone gel 1% 1.25 g daily for low libido and very low testosterone. In this woman, one month after starting testosterone gel 1% therapy, an orange discoloration of the skin of the palms, soles of feet and chest was noted. On the day of reporting, the testosterone gel 1% therapy was ongoing.

The seven serious cases are discussed briefly below:

- *CA-SOLVAY-00309007781*: Patient is a 49 year-old female who experienced fatigue, loss of libido and medication residue ("white powdery film on skin after it dried") while being treated with testosterone gel 1% for an unknown indication.

- *US-SOLVAY-00209003373 and US-SOLVAY-00209003374*: These two cases (reported by the same consumer) involved young girls, two and four years old, who experienced enlarged clitoris after possible secondary exposure to testosterone gel 1% through contact with their father.

- *US-SOLVAY-00209002682*: A consumer stated that about the "same time" he began using testosterone gel 1%, his wife developed a cough. His wife developed the cough prior to starting lisinopril for hypertension and was later switched to losartan. The

husband reported compliance with all drug use instructions, and also noted that his wife did not handle his clothing that had been in contact with testosterone gel 1%. A chest x-ray revealed pneumonia. The event responded to therapy and therapy with testosterone gel 1% is ongoing.

- *CA-SOLVAY-00309003048*: This is a consumer report concerning a female of unknown age who experienced an eye hemorrhage approximately 3 months after her husband started using testosterone gel 1% for an unknown indication. She had never had this happen before nor did it happen again after her husband discontinued the medication. She was unsure if she ever had and skin contact with her husband or even if she had any exposure to the testosterone gel 1%. The consumer had experienced breast cancer with mastectomy previously and was concerned about testosterone transfer to her. The Sponsor points out that an eye hemorrhage (such as a subconjunctival hemorrhage) can occur among other reasons spontaneously, from eye rubbing, from vigorous cough or straining, from high blood pressure and in conjunction with an underlying bleeding disorder.

- *US-SOLVAY-00209002403*: This consumer report concerned a 51 year-old female whose husband, without her knowledge, was exposing her to testosterone gel 1%, 2.5g, to possibly increase her sexual desire. One day after the first dose, which had been placed on her leg and thigh, she experienced urticaria (hives) on different parts of her body, but not where the testosterone gel 1% had been applied. The wife self treated with diphenhydramine and prednisone tablets with hive resolution. The hives returned the next day and in emergency she received an injection of hydroxyzine pamoate and a prednisone dose pack.

- *CA-SOLVAY-00309007481*: This case was provided by the Canadian Health Authority and concerns a female patient of unknown age treated with testosterone gel 1%, 2.5g/packet, unknown daily dose, unknown date for unknown indication. After a therapy duration of four months, the patient experienced aggression, anorgasmia, dizziness, drug dispensing error, dyspnea, dysuria, hair growth abnormal, hypertension, irritability and oropharyngeal pain. Attempts to obtain additional information have been unsuccessful.

  Reviewer's Comment: These seven serious events do not create a new safety signal and adequate information is currently available in the AndroGel 1% labeling regarding use in women and potential transfer of testosterone. The majority of ADRs were mild in nature and most reflect known adverse effects of testosterone gel. A previous review of adult cases by DRUP and OSE failed to demonstrate a clear association of commonly reported AEs to inadvertent exposure, while some pediatric cases appeared to have evidence of inadvertent (secondary) exposure.

Elderly: During the post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, from an estimated total of (b) (4) treated patients, there were

658 reports received by the Sponsor involving patients with known ages of 65 years or older, of which 61 (9.3%) met the serious criteria.

During the 7th PSUR reference period, among an estimated (b) (4) treated patients, a total of 177 (16%) ADR reports originated from cases with reported ages ≥ 65 years. During the 8th PSUR reporting period, among an estimated (b) (4) treated patients, a total of 176 (16%) ADR reports, originated from cases ages ≥ 65. Of these 176, nine were assessed as serious.

The most common ADRs reported spontaneously by this population are consistent with those reported overall for the product and consistent with background conditions observed in the elderly population. The serious ADRs that were reported are not uncommon in an elderly population with underlying medical conditions. No specific risk or safety issue to the subpopulation of elderly patients was detected.

Effects on Long Term Treatment: During the post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, the longest duration of treatment overall was eight years. 400 reports were received by the Sponsor in patients with known durations of treatment longer than one year, with 61 categorized as serious.

During the 7th PSUR reference period, a total of 104 ADR reports were received involving patients with a known duration of treatment exceeding one year (range one to eight years). Twelve reports were assessed as serious. With the exception of prostate cancer (n=2) none were reported more than once. Breast cancer was reported in a female. Of the nonserious ADRs, the most commonly reported were conditions commonly observed in the patient population.

During the reporting period covered by the 8th PSUR, a total of 126 ADR reports were received involving patients with known duration of treatment exceeding one year. Nineteen reports were assessed as serious. Of these 19 reports in long-term users, only polycythemia (n=2), myocardial infarction (n=3), pancreatitis (n=2), and prostate cancer (n=3) were reported more than once. The Sponsor states that labeling addresses the potential effects of testosterone on the prostate (e.g., worsening of BP and unknown relationship to the development of prostate cancer) . No change to the labeling recommendations regarding prostate cancer is indicated based on the results in this review period. No new safety signal was identified.

Deaths: In the 7th PSUR, two deaths are reported:

- *US-SOLVAY-00208001214*: This physician report regards a 55-year old male who died due to a myocardial infarction. The patient had a history of smoking and the physician assessed causality with testosterone gel 1% as possible. No additional information was provided.

- *US-SOLVAY-00209000862*: This physician report involved a 40 year old male patient with a long history of depression and paraplegia who committed suicide after being prescribed testosterone gel 1%, dose unknown for low testosterone. The patient reported difficulties with applying AndroGel 1% and conveyed interest to switching to patch

therapy in a phone call to the physician. Four days after the call the physician was informed that on an unspecified day the patient had committed suicide. The patient was on an unknown concomitant antidepressant medication.

In the 8th PSUR, there were five cases with the outcome of death:

- *US-SOLVAY-00210000159*: This physician report describes a mid-fifty year old male with a history of hyperlipidemia, diabetes mellitus, and erectile dysfunction who experienced a fatal myocardial infarction and had taken 17 months of AndroGel 1% therapy. The report states that there was no prior history of coronary artery disease and a negative evaluation for coronary artery disease two to two and half years prior to the acute event. Two week prior to the fatal event he was assessed by his physician and "everything seemed okay."

- *US-SOLVAY-00310000680*: This is a physician report regarding a male patient in his 50's with a history of hyperlipidemia, diabetes (about 59 years duration), and erectile dysfunction of unknown duration. Approximately one year after starting testosterone gel at an unknown dose for erectile dysfunction (reported off label use), the patient had a fatal myocardial infarction. The patient had a negative evaluation for coronary artery disease two and a half years prior to the fatal event.

  Reviewer's Comment: There is a strong suspicion on the part of the Sponsor that these first two cases are one and the same.

- *US-SOLVAY-00209007000*: This study report describes a 63 year old male subject who participated in the "TOM" trial, which was entitled 'Effects of Testosterone Replacement on Atherosclerosis Progression in Older Men with Low Testosterone Levels'. Medical history was significant for diabetes type II (22 years duration), hypertension (22 years duration), and allergy (not further specified). He was on 24 different concomitant medications. The patient was dead in his bed after missing his scheduled 27 months' visit. No further information was provided.

- *US-SOLVAY-00209003609*: This physician report provided via a company sales representative concerned a male treated with testosterone gel 1%, 7.5 g daily for an unknown duration and indication. In June, 2009, the patient committed suicide as claimed by his family. Attempts to gain additional information were unsuccessful.

- *GR-SOLVAY-00209004473*: This literature report describes a 29 year old male body builder (medical history unknown) who was treated with testosterone gel (dose, duration, and indication unknown). He was found dead at home. The autopsy results suggest pulmonary peliosis and proximal cause of death was internal hemorrhage (chest cavity) and circulatory collapse. Blood and urine toxicology analysis revealed the presence of nandrolone and its metabolites and a testosterone/epitestosterone ratio suggesting testosterone abuse.

There were no reported deaths in the "Bridge Report" created to cover the period from the end of the lock period for the 2010 report (27 Feb 2010) to the cut point of 31 August 2010.

Reviewer's Comments:

1. *There appears to be one case of MI in a 59 year old male with hyperlipidemia, >50 year history of diabetes and erectile dysfunction. Background conditions may well have played a role this patient's MI. There is also one case from the published "TOM trial", in which doses above the normal range were administered to elderly, debilitated men. These two cases do not suggest a signal for myocardial infarction. Nonetheless, the potential risk of MI was recently evaluated by the Division of Epidemiology (DEPI) – and is discussed iabove. It was their conclusion that the overall cardiovascular risk associated with testosterone replacement therapy (TRT) compared to placebo are comparable and do not support an association between TRT and increased risk of cardiovascular events in men.*
2. *The case of suicide in a paraplegic with a long history of depression is also considered to be confounded by the background conditions. Nonetheless, "depression" is included the product labeling under* ***Post Marketing Experience.***
3. *No new safety signal is generated by these deaths.*

Anaphylactic Reaction: There are two reports of possible anaphylactic reaction:

- *SOLV00209004559*: In the 8th PSUR, a consumer report concerns a 52 year old man with Klinefelter's Syndrome who experienced flushing across the neck, top of the shoulders and upper chest, tightness in the chest and difficulty breathing while being treated with AndroGel. Androgel was started on an unknown date in 2002 on a flexible dosing schedule of 15 gm (three packets) daily for two consecutive days then 10 gm (two packets) daily for one day and then repeating the dosing schedule on a continuous basis. On 2 August 2009, the consumer experienced flushing across his neck, the top of his shoulders and his upper chest after he applied AndroGel. The flushing occurred within seconds and caused the skin on his neck, top of his shoulders and upper chest to turn purple in color with blotches of varying degrees of purple. The consumer also experienced tightness in his chest and some difficulty in breathing when he experienced flushing. The adverse events resolved in two or three minutes. He experienced the adverse events every day since 2 August 2010. The consumer noted that he usually applied AndroGel to his shoulders and or/abdomen and that he experienced the reported events even when he applied AndroGel to his abdomen only. As of 12 August 2009, the consumer continued to use AndroGel and experienced the adverse events. The patient has a past history of an anaphylactic reaction to a testosterone injection. The date of the MedWatch Report is 4 April 2010. The Suspect Adverse Drug Reaction Report has been obtained and reviewed.

- *US-SOLVAY-00210003329*: In the "Bridge Report" created to cover the period from the end of the lock period for the 2010 report (27 Feb 2010) to the cut point of 31 August 2010, is a line listing under Serious-Immune System Disorders for "Systemic reaction to

Androgel/Anaphylactic reaction." This is a physican report involving a patient with a history of a cutaneous reaction to AndroGel and experienced "a systemic reaction of AndroGel". It was unknown whether the treatment with AndroGel and the reported adverse events were ongoing at the time of the report. There is no description of the reaction or information relating to first dose to onset and outcome of event. There is no dosage information or stop date. The Suspect Adverse Reaction has been obtained and review.

An additional case report is of note:

- US-SOLVAY-00209002403 8th PSUR:This consumer report concerned a 51 year-old female whose husband, without her knowledge, was exposing her to testosterone gel 1%, 2.5g, to possibly increase her sexual desire. One day after the first dose, which had been placed on her leg and thigh, she experienced urticaria (hives) on different parts of her body, but not where the testosterone gel 1% had been applied. The wife self treated with diphenhydramine and prednisone tablets with hive resolution. The hives returned the next day and in emergency she received an injection of hydroxyzine pamoate and a prednisone dose pack.

Reviewer's Comment: AndroGel is not indicated for use in women (US-SOLVAY-00209002403) this is indicated in the label. In the Klinefelter's case, AndroGel was used by a patient with a known allergy to testosterone. AndroGel is contraindicated in men with known hypersensitivity to any of its ingredients. In the final case of a "systemic reaction to AndroGel" (US-SOLVAY-00210003329) the report does not contain enough information to make any conclusion as to the nature of the event and relation to AndroGel use. Based on these cases, I suggest no labeling changes at this time.

Prescription Errors/Medication Errors: During the post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, there were 32 non-serious reports of medication errors. The majority (n=15) of reports involved men who intentionally applied AndroGel to not recommended areas (e. g. genitals). There were three reports of oral administration. There were 12 reports of incorrect use. All ADRs were non serious and most were listed events.

During the 7th PSUR reference period, a total of 32 ADRs were coded involving prescription or medication errors. None of the errors or resulting ADRs were assessed as serious. 19 reports deal with incorrect dose, including intentional drug misuse (9), incorrect dose (4), inappropriate schedule (4), underdose (1), and wrong technique. There were 13 reports of incorrect administration, including drug administered at inappropriate site (9), accidental exposure (eyes, mouth, 2), incorrect route (oral, 1) and drug administration error (1). With the exception of three reports, all were patient errors.

During the reporting period covered by the 8th PSUR, a total of 32 ADRs were coded involving prescription or medication errors. Two reports were discussed as serious (CA-SOLVA-00309007481 and US-SOLVAY-00209002403): both occurred in women and were previously discussed. 19 of the errors can be classified as incorrect dose, including intentional drug misuse (11), incorrect dose (4), accidental overdose (1), inappropriate schedule (1), drug dispensing error (1), and wrong technique (1). There were 13 reports of incorrect administration including drug administered at wrong site (10), accidental exposure (penis: 1), and incorrect route (injection: 1, oral 1). With one exception (CA-SOLVAY-00309007481) all were patient errors.

9 Appendices

9.1 Literature Review/References

No specific literature reports were reviewed as part of the review of this Clinical Response.

9.2 Labeling Recommendations

The labeling reviews have encompassed the Full Prescribing Information (FPI), the Medication Guide, and the container and carton. The Division of Risk Management (DRISK) contributed to the review of the Medication Guide, while the Division of Medication Error Prevention and Analysis (DMEPA) provided a reviewer of the container/carton labeling as well as the FPI and Medication Guide.

One of the major labeling issues that was resolved during this review cycle centered on how to describe the product and the dose. In a final DMEPA review, completed on 2 March 2011, it was stated:

A. **General Comments**

(b) (4)

(b) (4)

9.3 Advisory Committee Meeting

No Advisory Committee meeting was held for this application.

9.4 Previous Phase 1 Studies

In this section, an overview of the previously performed Phase 1 studies submitted to sNDA 22309 is provided for ready reader reference. These studies were reviewed as part of the original NDA and the additional detail may be found in the reviewer's original NDA review.

Study S176.1.1001: The Multiple Dose Pharmacokinetics and Comparative Bioavailability of Testosterone After Administration of 1.25, 2.5, and 3.75 g Dose Levels of Investigational Testosterone Hydro-Alcoholic Gel Formulations in Hypogonadal Male Volunteers.

This Phase 1 single site US study had as its objectives the following:

- To determine the multiple dose pharmacokinetics and comparative bioavailability of testosterone after administration of testosterone gel (T-gel) in three different strengths, at three different doses: 1.25 g, 2.5 g, and 3.75 g,
- To compare the pharmacokinetics of three new T-gel formulations with the currently marketed AndroGel® product (AndroGel 1%) and to determine which of the new T-gel dose strengths and which dose levels met the following criteria:
    - The proportion of subjects with observed maximum total testosterone concentrations (C_{max}) >1000 ng/dL after investigational T-gel administration was less than the proportion observed after reference treatment
    - The proportion of subjects with an average total testosterone serum concentration (C_{avg}) and/or the lowest concentration observed over the 24-hour dosing interval (C_{min}) within the normal eugonadal range of 300 to 1000 ng/dL and/or within 80% of 650 ng/dL (range of 520 to 780 ng/dL) and was equal to or greater than the proportion observed after reference treatment.
    - The proportion of individual total testosterone concentrations during each 24-hour profile within 300 to 1000 ng/dL was greater than or equal to the proportion observed after reference treatment.
    - Compared with the reference product, similar or higher average total testosterone serum concentration (C_{av}) was observed with a lower mass of gel;
- To assess the dose proportionality of T-gel over the dose range of 1.25 to 3.75 g for each of the three different strengths;
- To monitor and evaluate the safety of the subjects throughout the study.

A total of 38 healthy hypogonadal male subjects were enrolled in the study. 36 subjects completed the protocol and 2 subjects prematurely withdrew consent after having received at least one dose of medication. Both subjects were randomly assigned to Treatment C and received a total of 5 once daily doses (1.25 g of gel dose) of 1.62% T-gel prior to withdrawal. Both subjects completed end of study procedures.

Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

The study drug was applied topically to the abdomen once daily for 5 days at dose levels of 1.25g (15.3, 30.4 and 45.8 mg testosterone), 2.50 g (17.8, 35.5, and 53.3 mg testosterone), and 3.75 g (20.3, 40.5, and 60.8 mg testosterone) of gel. The mg of testosterone cited above represents the 1.22%, 1.42%, and 1.62% formulations respectively. The duration of treatment was approximately 23 days. The reference therapy was AndroGel® (1.00%, 5.00 g, of gel [50 mg testosterone]).

Pharmacokinetic blood samples were collected on Day-1 at -24 and -12 hours relative to the projected time of gel application on Day1: at predose on Days 1, 3, 4, 8, 9, 13, 14, 18, and 19: and at predose, and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post dose on Days 5, 10, 15, and 20. Plasma concentrations of total testosterone, dihydrotestosterone, and estradiol were determined. The following PK parameters were determined using noncompartmental methods: observed predose concentration (C_{trough}), lowest serum concentration observed during the 24-hour dosing interval (C_{min}), observed maximum serum concentration (C_{max}), time of minimum observed concentration (t_{min}), time to reach maximum observed serum concentration(t_{max}), area under the serum concentration- time curve from aero to 24 hours (AUC_{0-24}), time-averaged concentration over the dosing interval, determined by $AUC_{0-24}/24(C_{av})$ and peak trough fluctuation (PTF).

Results and Conclusions for Study S176.1.1001: On the fifth day of treatment at each dose level, mean observed and baseline-adjusted testosterone concentrations were relatively constant over the 24-hour dosing interval. Mean concentrations peaked at approximately 4 hours, and some doses showed a second peak at 12 to 16 hours. Mean observed testosterone concentrations were above the lower limit of the eugonadal range (>300ng/dL) at most time points for all gel doses in Treatment A (1.22% T-gel) and for the 2.50 g and 3.75 g doses in Treatment C (1.62% T-gel). For treatment B (1.42% T-gel) doses, mean testosterone concentrations varied above and below the lower limit of the eugonadal range. The following are additional specific conclusions from this study:

- Topical application of 1.22%, 1.42%, and 1.62% T-gel at dose levels of 1.25, 2.50 and 3.75 g to the abdomen for 5 days provided mean C_{av} testosterone levels within or just below the eugonadal ranges (300 to 1000 ng/dL) and was comparable to 5.00 g of the reference 1% AndroGel® 1% product. There were no statistical differences in exposure within treatment groups or across dose levels and gel strengths.

- Statistical analysis of steady state was inconclusive. Graphical assessment of mean and median trough concentrations suggested steady state was achieved by the third day of dosing for all treatments.

- Dose proportionality or linearity in testosterone exposure, based on AUC_{0-24} and Cmax, and was not demonstrated for any gel strength.

- Mean concentration-time profiles of Treatments A, B, and C at the 2.50 and 3.75 g dose levels were comparable to the reference (AndroGel 1%, 5.00g), but of the three T-gel strengths evaluated , the 1.62% strength was the most comparable to AndroGel®1 % (5.00 g). As a consequence, the Sponsor moved forward with the 1.62% formulation because it showed the most comparable exposure to Androgel 1% and because it had the lowest volume.

Safety for Study S176.1.1001: Safety for this protocol is also discussed within the Phase 1 integrated safety analysis in Section 7 of this review. No serious adverse events or deaths were reported during this study. No subjects were prematurely withdrawn from the study due to AEs.

"Markedly abnormal vital signs" as defined by the protocol were observed in the following four subjects:

- Subject 24704, a 41 year-old white male assigned to Treatment A (1.22% testosterone gel administered on Days 1 to 15 plus the reference treatment on Day 16 to 20), experienced a decrease in weight that met the criteria for markedly abnormal vital signs. At termination, the subject's weight was 67 kg (baseline value: 88.6kg), an overall loss of 21.6 kg.
- Subject 24710, a 56 year-old white male assigned to Treatment A (1.22% testosterone gel administered on Days 1 to 15 plus the reference treatment on Day 16 to 20), experienced an increase in body temperature of 101.7^{o} F (baseline value: 98^{o} F) at an unscheduled assessment on 28 October 2005, one day prior to resuming the study Day 6 dosing. Two additional markedly abnormal temperature readings of 101.1^{o}F were noted on Day 6 assessments (scheduled and unscheduled). No related AE's were noted and the subject's body temperature returned to normal levels on Day 7.
- Subject 24725, a 71 year old white male assigned to Treatment B (1.42% testosterone gel administered on Day 1 to 10 and 16 to 20 plus the reference treatment on Days 11 to 15), experienced a high systolic blood pressure of 195 mmHg (baseline value: 175 mmHg) at an unscheduled visit on Day 2. No subsequent assessments met the criteria for markedly abnormal values. No related AEs were noted; however, a medical history of hypertension was noted that was ongoing at study entry.
- Subject 24741, a 58 year-old white male assigned to Treatment C (1.62% testosterone gel administered on Days 1 to 10 and 16 to 20 plus the reference treatment on Days 11 to 15), experienced a total of 14 pulse rate values that met the markedly abnormal criteria. Abnormal assessments were observed throughout the study form Day 4 through unscheduled assessments at termination and ranged from 120 to 132 bpm. No related AEs were noted and no follow-up was deemed necessary by the investigator.

Reviewer's Comment: These individual lab values provide no specific reason for concern.

Study S176.1.002: 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.

This Phase 1 single-site US study had the following as its objectives:

- To determine the single and multiple dose pharmacokinetics of testosterone gel (T-gel) at doses of 1.25 g (20.3 mg T), 2.50 g (40.5 mg T), 3.75 g (60.8 mg T), and 6.25 g (101.3 mg T).
- To assess the dose proportionality and accumulation of testosterone 1.62% over the dose range of 1.24 g (20.3 mg T) to 6.25 g (101.3 mg T).
- To monitor and evaluate the safety of subjects throughout the study.

The study was an open-label, single and multiple-dose, parallel group study in hypogonadal male subjects. Subjects were administered 1.25 g, 2.5 g, 3.75 g, 5.00 g, or 6.25 g of T-gel 1.62% once daily for 14 days. The dose was dependent on group randomization. The site of application was rotated over the 14 day treatment period. Study drug was applied to the shoulder/upper arm on Days 1, 2, 5 to 9, and 12 to 14 and applied to the abdomen on Days 3, 4, 10, and 11. The duration of treatment was 17 days, not including the screening period. Subjects were confined to the clinic for the entire 17 day period. Serial blood samples for measurement of serum testosterone, dihydrotestosterone, and estradiol concentrations were collected at baseline (Day -1), and following single dosing (Day 1) and multiple dosing (Day 14). A total of 56 hypogonadal male subjects were enrolled in this study and received at least one dose of medication. A total of 51 subjects completed the study according to the protocol. Three subjects were prematurely withdrawn from the study due to high testosterone levels and two subjects withdrew due to adverse events (AEs).

Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

Pharmacokinetic blood samples were collected for determination of total testosterone, dihydrotestosterone, and estradiol at the following timepoints:

Day-1 (Baseline): predose, and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 16 hours relative to the projected time of gel application on subsequent study days;
Day 1: predose, and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 16 hours post dose;
Days 2 to 13; predose; and
Day 14: predose, and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours post dose.

Serum levels of total testosterone, dihydrotestosterone, and estradiol were determined and used to calculate observed and baseline-adjusted maximum serum concentration (C_{max}), lowest serum concentration (C_{min}), predose serum concentration on Day 14 (C_{trough}), time-averaged concentration over the dosing interval, determined by AUC_{0-24}/tau (C_{av}), time to reach maximum observed serum concentration(t_{max}), time of minimum concentration (t_{min}), area under the serum concentration- time curve over the 24- hour dosing interval (AUC_{0-24}), peak to trough fluctuation (PTF), and the accumulation interval.

Results and Conclusions for Study S176.1.002:
Following single doses (Day 1), mean observed testosterone concentrations showed a continuous increase up to 8 hours post dose for all dose groups, after which concentration remained consistent and within the eugonadal range (300 to 1000 ng/dL) for the remainder of the 24-hour dosing interval.

Following multiple dosing (Day 14), mean observed testosterone concentrations were relatively consistent and were within the eugonadal range over the entire 24-dosing interval for all dose groups. Mean observed C_{max} was within the eugonadal range for all treatments on Day 1. On

Day 14, mean C_{max} was within the eugonadal range for the 1.25g, 2.5 g, and 3.75 g doses, but was just above the limit for the 5.00 and 6.25 g doses.

$AUC_{0\text{-}24\ and}$ C_{max} values for testosterone showed a generally linear, dose-related increase in exposure of the 1.25 to 5.00 g dose range on Day 1 and over the entire dose range (1.25 to 6.25 g) on Day 14.

Steady state concentrations were achieved by Day 2 by analysis of mean and median trough concentrations but not by statistical analysis.

No accumulation of testosterone was seen at the 1.25 g and 2.50 g doses, and <2-fold accumulation was seen at the 3.75 g to 6.25 g doses, following multiple dosing for 14 days.

> *Reviewer's Comment: Based on the single and multiple dose pharmacokinetics and concentration-time profiles, all 1.62% T-gel levels (1.25 to 6.25 g) evaluated in this study were considered by Sponsor to be evaluable for further clinical development.*

Safety for Study S176.1.002: Five subjects experienced clinically out of range laboratory values, as defined by the protocol, but in no case was testosterone listed as out of range. 3 subjects were withdrawn from the study due to predose testosterone levels that exceeded protocol-specified limits (>900 ng/dL) on Days 3, 6, and 9. Two subjects were withdrawn from the study due to an AE of hypertension:

- Subject 25802, a 67-old White male assigned to receive 5 gm of 1.62% T-gel and received doses on Day 1 and Day 2. He experienced an AE of hypertension (exacerbation of predose condition) prior to dosing on Day 3 and was prematurely withdrawn from the study. Screening blood pressure was 162/74 mm Hg with two repeat values of 154/74 mm Hg and 149/71 mm Hg, respectively. The maximum blood pressure observed was 175 mm Hg on Day 3. The patient was on no concomitant medications.
- Subject 25817, a 67 year-old White male receiving 5 gm of 1.62% T-gel on Days 1 through 3 experienced an AE of hypertension (exacerbation of predose condition) that continued throughout dosing, and was prematurely withdrawn prior to dosing on Day 4. Screening blood pressure was 162/74 with two repeat values of 154/74 mm Hg and 149/71 mm Hg, respectively. The maximum blood pressure observed was 175/176 mm Hg on Day 3. No concomitant medications were administered.

There were no deaths or serious adverse events. The most frequent treatment-emergent adverse events overall (reported by ≥4 subjects) were application site papules (9/56, 16.1%), hypertension (8/56, 14.3%), acne (6/56, 10.7%), hematoma (4/56, 7.1%) and headache (4/56, 7.1%).

Three subjects experienced "markedly abnormal vital signs", as defined in the protocol:

- Subject 25793, a 58 year-old white male randomized to treatment A (1.25 testosterone gel 1.62%), experienced a high pulse rate of 126 bpm on Day 5 (baseline value: 87 bpm). At an unscheduled assessment on Day 5, this value was noted as 123 bpm, which also

met markedly abnormal criteria. An AE of mild tachycardia was noted. No action was taken and subject recovered.

- Subject 25797, a 59 year-old white male, randomized to treatment C (3.75 g testosterone gel 1.62%), experienced an increase in weight that met criterion for markedly abnormal vital sign values. At termination, the subject's weight was 95.9 kg (baseline value: 89.5 kg); an overall gain of 6.4 kg.
- Subject 25802, a 67 year-old white male, randomized to Treatment D (5.00 g testosterone gel 1.62%) experienced a high systolic blood pressure of 186 mmHg on Day 3 (baseline value: 144 mmHg). Additionally, this subject experienced high systolic blood pressure values of 191 mmHg, 189 mmHg, and 185 mmHg at subsequent unscheduled sequential assessments on Day 3. No markedly abnormal diastolic blood pressures were observed in this subject. This subject also experienced high pulse rates of 123 and 120 bpm (baseline value: 93 bpm) at unscheduled assessments on Day 3. Relevant medical history for the subject included a diagnosis of hypertension at screening. An AE of hypertension was noted post dose and the subject was terminated from the study on Day 4 due to the AE of hypertension.

Reviewer's Comment: The study supported the continued development of the 1.25 gm to 6.25 gm doses of AndroGel 1.62%. The two events of increased blood pressure (coded as "hypertension") may have been related to pre-dose conditions coupled with higher doses of Androgel 1.62% without preceding titration.

Study S176.1.005: A Randomized, Open-Label, Three-Way Crossover Pharmacokinetic Study to Evaluate the Effects of Skin Washing After Administration of Testosterone Gel 1.62% in Hypogonadal Males.

This Phase 1 single-site US study had as its objectives:

- To determine the multiple dose pharmacokinetics of testosterone after administration of 5gm testosterone gel 1.62% in hypogonadal males with and without post dose skin washing;
- To evaluate any changes in the systemic absorption of testosterone after administration of 5gm testosterone gel 1.62% when the application site is not washed for 24 hours post dose and when skin washing occurred at 2 hours, 6 hours, or 10 hours post dose; and
- To assess whether residual testosterone remained on the application site post skin washing.

Twenty-four hypogonadal male subjects were enrolled and 17 subjects completed the study. The subjects received 5 gm testosterone gel 1.62% applied topically once daily in the morning to the shoulders/upper arms for 7 days during each of the three consecutive treatment periods, for a total of 21 days of dosing. Serum was obtained for measurement of testosterone, dihydrotestosterone, and estradiol to allow pharmacokinetic (PK) assessments. Six subjects were prematurely discontinued for increased serum T (testosterone concentrations >900 ng/dL as specified in the protocol and determined by clinical safety laboratory results obtained from the

local laboratory), and 1 subject was discontinued due to a serious adverse event (SAE) of atrial fibrillation. A total of 24 subjects participated in both the PK and safety analysis.
Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

Within 30 minutes prior to the targeted time of dose application, subjects showered and washed the application site with commercially available Ivory Bar Soap and water. Subjects were not allowed to remain in the shower for longer than 10 minutes. The designated area for gel application was to be thoroughly dried. Each subject received 5.00 g testosterone gel 1.62% applied topically once daily in the morning for 7 days for three consecutive treatment periods for a total of 21 days. There was no washout period between periods. On the seventh day of dosing of each treatment period, depending on randomization, skin washing of the drug application site with Ivory soap and water occurred in the shower with a lather time of approximately 2 minutes followed by a thorough rinse. The application site was then thoroughly dried (page 20 of Study Report S176.1.1005). The washing occurred at the following times:

- Treatment A: 2 hours post dose
- Treatment B: 6 hours post dose
- Treatment C: 10 hours post dose

Tape stripping procedures were conducted on the sixth and seventh day of each treatment period to evaluate the presence of any residual testosterone remaining in the stratum corneum with or without washing.

The subjects were confined to the clinic for the entire period of the study which was 27 days. Reference therapy was when 5.00 g testosterone gel 1.62% was applied and no washing was conducted. This was conducted on the sixth day of dosing of each treatment period.

Pharmacokinetics testing was conducted as follows:

- Day-1 (Baseline): 0, 2, 4, 6, 8, 12, 16, and 24 hours with respect to the projected time of dose administration;
- Days 6, 13, and 20 (Day 6 of each treatment period): 0, 2, 4, 6, 8, 12, 16, and 24 hours post dose;
- Days 7, 14, and 21 (Day 7 of each treatment period): 0, 2, 4, 6, 8, 12, 16, and 24 hours post dose;
- Day 21 at 48, 72, and 96 hours post dose; and
- Days 4, 5, 11, 12, and 19: post dose.

Time to reach steady state was assessed using observed trough concentrations of testosterone. To assess the effect of skin washing within each treatment, the observed and baseline-adjusted testosterone PK parameters, AUC_{0-24}, C_{max} and C_{av} were compared to those without washing using contrasts within a linear mixed model for each analyte/parameter. Application without washing served as the reference treatment.

Results and conclusions for Study S176.1.005: Overall, mean observed testosterone concentrations were relatively lower on Day 7 (with post dose skin washing) than Day 6 (without post dose skin washing) when the skin was washed at 2 and 6 hours post-dose, but not with skin washing at 10 hours post dose.

For Treatment A (washing at 2 hours after dose application), mean observed testosterone concentrations remained within the eugonadal range (300-100ng/dL) over the entire 24-hour dosing interval for both treatment Days 6 and 7. For treatment B (washing at 6 hours after dose application) and C (washing at 10 hours after application) , mean observed testosterone concentrations were generally contained with the eugonadal range for the majority of timepoints. For treatments A and B, skin washing at 2 and 6 hours post dose, respectively, caused a small statistically significant decrease in bioavailability compared to when there was no post dose wash. AUC_{0-24} decreased by 14% on average for Treatment A and 10 % on average for Treatment B. No effect of skin washing was observed for AUC0-24 in Treatment C. Skin washing had no effect on C_{max} for any treatment.

> *Reviewer's Comment: It is notable that washing after 2 hours lowered AUC by only approximately 14%, and there was no effect of washing at Hour 6 and Hour 10. Therefore, the label will state that washing can take place at 2 hours or later after dosing with AndroGel 1.62%.*

Of note, four of the 24 subjects (17%) had at least one observed testosterone concentration >2500 ng/dL. Steady state concentrations of testosterone generally occurred by Day 4 for Treatment B, Day 5 for Treatment A and Day 6 for Treatment C. The observed serum testosterone concentrations above 2500 ng/dL are listed in a Study Appendix as: Subject 26333-serum testosterone level of 2830 ng/dL, Subject 26338-serum testosterone level of 3950 ng/dL, Subject 26341-serum testosterone levels of 2960 ng/dL, 3020 ng/dL, 3240 ng/dL, and Subject 26345-serum testosterone level of 3230 ng/dL.

Table 44: Numbers of Subjects with concentrations Exceeding 2500 ng/dL

Treatment	Before Skin Washing	After Skin Washing	Total
A	2(8)	1(4)	2(8)
B	0	1(4)	1(4)
C	1(4)	0	1(4)
Total			4(17)

Source: Table 6: Clinical Study Report S176.1.1005, page 43

> *Reviewer's Comment: This protocol did not include dose titration based on serum testosterone levels and therefore from a clinical standpoint the elevated testosterone levels in several patients are notable but not considered a major safety concern.*

Utilizing tape stripping, it was determined that the amount of testosterone at the application site was significantly decreased after post dose skin washing. Compared to no post dose skin washing, the amount of testosterone recovered was decreased by 84.0% (2 hr washing), 87.2% (6 hr washing), and 81.3% (10 hr washing) after post dose skin washing in total (strips 1-10; surface and deeper skin layer combined) for Treatments A, B, C, respectively. Based on skin stripping results, the amount of testosterone remaining on the skin of the application site decreased with skin washing 2-10 hours post dose.

The conclusions of the study are:

- Application site washing at 2 and 6 hours post dose after administration of testosterone gel 1.62% caused a slight decrease in AUC_{0-24} and C_{avg} but not C_{max}. Application site washing at 10 hours post dose had no effect on AUC_{0-24}, C_{av}, or C_{max}.
- Steady-state conditions were achieved for testosterone concentrations after 4-6 days of once daily application of testosterone gel 1.62%.
- Upon discontinuation of testosterone gel l.62%, serum testosterone levels returned to baseline with 48 hours.

There were no deaths during the course of this study.

Subject 26326 discontinued from the study on Day 20 due to an SAE of atrial fibrillation. This subject is a 77 year-year old white male assigned to treatment sequence C, B, A. Screening blood pressure and pulse rate were 143/92 mmHg and 63 bpm respectively, and Day-1 blood pressure and pulse rate were 168/99 mmHg and 62 bpm respectively. On Day 20, approximately 9.5 hours following administration of study medication, the subject complained of "heart flutter and fullness of chest" shortly after eating dinner. In the emergency room, blood pressure and pulse were 148/83 and 147 bpm. ECGs revealed atrial fibrillation which responded to intravenous diltiazem and procainamide. The atrial fibrillation persisted for 9 hours and then resolved. The subject's medical history is positive of obesity, hypertension, hyperlipidemia, allergic rhinitis, intermittent acid reflux, insomnia, esophageal ulcer, and intermittent constipation. The patient had reported experiencing five to six episodes of "heart racing" over the last 3 years that were of short duration and usually at night. However, the subject had not reported these events to his physician. The subject was receiving lisinopril 30 mg daily upon entry into study. There had been no caffeine consumption for 3 weeks.

Subject 26328 experienced an overall weight decrease of 9.1 kg and exited the study on Day 25. His baseline weight was 92.8 kg and exit weight was 83.7 kg. He received testosterone gel 1.62% (5.00 g) on Days 1-21 and was assigned treatment sequence A, C, B. No AE related to the markedly abnormal decrease in weight was recorded.

<u>Study S176.1.1006: A Randomized, Open-Label, Three-Way Crossover, and Multiple Dose Pharmacokinetic Study of the Effect of Moisturizer Lotion or Sunscreen Application on the Serum Levels of Testosterone in Hypogonadal Males Administered Testosterone Gel 1.62%.</u>

This US single center Phase 1 study had as its objectives:

- To determine the multiple dose pharmacokinetics of testosterone after administration of 2.5 g testosterone gel 1.62% in hypogonadal males with and without moisturizer lotion or sunscreen;
- To determine the effect of concomitant application of moisturizer lotion or sunscreen on the absorption of testosterone in hypogonadal males administered daily applications of 2.5 g testosterone gel 1.62%.

A total of 18 hypogonadal male subjects were enrolled in this study and received at least one dose of study medication. A total of 15 subjects completed the study per protocol. Three subjects were prematurely discontinued from the study; 1 subject withdrew due to a predose testosterone >900 ng/dL as specified in the protocol, and 2 subjects withdrew consent. A total of 18 subjects were included in both the pharmacokinetic (PK) and safety analyses.

The duration of the study was 24 days, not including the screening period. There were four confinement periods consisting of 2 nights each. When not confined to clinic, subjects returned to the clinic on an outpatient basis for dosing purposes and PK sample collection.

Each subject underwent three sequential treatment periods in randomized order. There was no washout period between treatments. The three treatments were as follows:

Treatment A: once daily application of 2.5 g testosterone gel 1.62% applied to the upper arms/shoulders for 7 days. Each day, 1 hour after testosterone gel administration, a 6.0 g application of moisturizer lotion, Lubriderm Daily Moisture Lotion, was applied to the same application site.

Treatment B: once daily application of 2.50 g of testosterone gel 1.62% applied to the upper arms/shoulders for 7 days. Each day, 1 hour after testosterone gel administration, a 6.0 g application of sunscreen, Coppertone Spectra3 UVA/UVB Sunblock Lotion SPF 50, was applied to the same application site.

Treatment C: once daily application of 2.50 g testosterone gel 1.62% applied to upper arms/shoulders for 7 days. (Reference therapy)

Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

Pharmacokinetic whole blood samples were collected for determination of total testosterone, dihydrotestosterone, and estradiol at the following times:

- Day -1 (Baseline): 0, 2, 4, 6, 8, 12, 16, and 24 hours with respect to the projected time of dose administration;
- Days 7, 14, and 21: 0, 2, 4, 6, 8, 12, 16, and 24 hours post dose testosterone gel 1.62% application;

- Days 2-6, 9-13, and 16-20: predose.

Maximum observed serum concentration (C_{max}), area under the serum concentration-time curve from time zero to 24 hours post dose ($_{AUC0-24}$), the lowest concentration observed during the 24-hour dosing interval (C_{min}), average serum concentration (t_{min}), and peak to trough fluctuation (PTF) were calculated for observed and baseline-adjusted testosterone. In addition, observed post dose (trough) serum concentrations (C_{trough}) were determined. Concentration-time data were summarized using descriptive statistics for dihydrotestosterone and estradiol.

Results and conclusions: Mean observed C_{max} and C_{av} values for all treatments were within the eugonadal range. Additionally, no individual subjects had C_{max} or C_{avg} values for any treatment above the upper limit of the eugonadal range (>1000 ng/dL).

The conclusions of this study are:

- Application of moisturizer lotion 1 hour after application of 2.5 g testosterone gel 1.62% once daily for 7 days to the same skin site increased the bioavailability of testosterone modestly (14% and 17% increase in AUC_{0-24} and C_{max}, respectively) compared to testosterone gel 1.62% administered alone.
- Application of sunscreen 1 hour after application of 2.5 g testosterone gel 1.62% once daily for 7 days to the same skin site had no effect on overall exposure (AUC_{0-24}) of testosterone, but increased C_{max} by 13% compared to testosterone gel 1.62% administered alone.
- Individual and mean C_{avg} and mean C_{max} values were with the eugonadal range (300-1000ng/dL) following application of 2.5 g testosterone gel 1.62% with or without subsequent application of moisturizer lotion or sunscreen q hour post dose for 7 days within each treatment period, across 21 days of consecutive dosing.
- Graphical assessment and statistical analysis indicate that with once daily application, steady state was achieved by Day 2 for all treatments.

A total of 4 subjects (22.2%) exposed to the study medication reported at least one treatment emergent adverse event (TEAE). The most frequent non-serious TEAE overall was headache (2/18, 11.1%). One subject (1/18, 11.1%) reported an upper respiratory tract infection, and one subject (1/18, 11.1%) reported worsening of erectile dysfunction which was an ongoing baseline medical condition. There were no application site assessments noted during the study, and no subjects reported application site TEAEs. The frequency of non-serious TEAEs was similar across treatment groups. One subject (subject 26750) discontinued from the study due to a predose testosterone level of 1064 ng/dL on Day 18 which was above the protocol-specified limit of 900 ng/dL. No deaths or SAEs occurred during the course of this study. No subjects discontinued from the study due to AEs. This study is included in the integrated Phase 1 safety summary within Section of this review.

Two subjects experienced “markedly abnormal vital sign values” as defined in the protocol:

- Subject 26758, a 36-year old white male randomly assigned to treatment sequence B, A, C, experienced a decrease in pulse rate exceeding guidelines for markedly abnormal (≤

50 bpm and ≥15 bpm change from baseline). At Day 6, the subject's pulse rate was 50 bpm (Baseline value: 76 bpm); an overall decrease of 26 bpm. Systolic and diastolic blood pressures at the time of the decreased pulse rate were 111 mmHg and 51 mmHg, respectively. At the time of the abnormal pulse rate, the subject was receiving Treatment B (2.5 g testosterone gel 1.62% followed by 6.0 g of sunscreen 1 hour post dose). On Day 7 through study termination (Day 22), the subject's pulse rate values ranged from 52-69 bpm.

- Subject 26760, a 60 year-old white male randomly assigned to treatment sequence A, B, C, experienced an increase in diastolic blood pressure that met the criterion for markedly abnormal vital sign values (≥105 mmHg and ≥15 mmHg increase from baseline). At Day 16, the subject's diastolic blood pressure was 107 mmHg (Baseline value: 90 mmHg0; an overall increase of 17 mmHg. Systolic blood pressure and pulse rate at the time of increased diastolic blood pressure were 146 mmHg (an increase of 22 mmHg from Baseline) and 89 bpm (a decrease of 4 bpm from Baseline), respectively. At the time of the abnormal diastolic blood pressure, the subject was receiving Treatment C (2.5 g testosterone gel 1.62%).

Study S176.1.007: A Single and Multiple Dose Pharmacokinetic and Comparative Bioavailability Study of Testosterone Absorption after Administration of Testosterone Gel 1.62% to the Abdomen, Upper Arms/Shoulders or via a Rotation Schedule in Hypogonadal Males

This single center Phase 1 US study had as its objectives:

- To determine single and multiple dose pharmacokinetics of testosterone after administration of testosterone gel 1.62% in hypogonadal males; and
- To determine the relative bioavailability of testosterone after administration of 5gm testosterone gel 1.62% to the abdomen, upper arms/shoulders, and to a rotating schedule of these two application sites.

A total of 36 hypogonadal male subjects were enrolled in the study and received at least one dose of study medication. A total of 32 subjects completed the study according to the protocol. Two subjects were prematurely discontinued from the study due to administrative reasons (predose testosterone >900 ng/dL as specified in the protocol and determined by clinical safety laboratory results obtained from the local laboratory); 1 subject withdrew consent due to a family emergency; and 1 subject withdrew to a serious adverse event (SAE) of dermatitis on the lower leg. A total of 36 subjects were included in both the PK and safety analyses.

Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

Hypogonadal male volunteers received 5.00 g of testosterone gel 1.62% once daily for each of three 7-day treatment regimens. There was a 5-day washout period between the 3 treatments which consisted of the following:

Treatment A: Once daily application of 5.00 g testosterone gel 1.62% to the abdomen, for 7 days.
Treatment B: Once daily application of 5.00 g testosterone gel 1.62% to the upper arms/shoulders for 7 days.
Treatment C: Once daily application of 5.00 g testosterone gel 1.62% to the abdomen for 3 days, followed by application to the upper arms/shoulders for 4 days

The total duration of the study was 36 days, not including the Screening period. Subjects were confined to the clinic for the entire study period.

Pharmacokinetic whole blood samples were collected for determination of total testosterone, dihydrotestosterone, and estradiol at the following times:

- Day -1 (Baseline): 0, 2, 4, 6, 8, 12, 16, and 24 hours with respect to the projected time of dose administration;
- Days 1, 12, and 23 (Treatment Day 1): 0, 2, 4, 8, 12, 16, and 24 hours post dose;
- Days 7, 18, and 29 (Treatment Day 7): 0, 2, 4, 8, 12, 16, 24, 48, 72, and 120 hours post dose; and
- Days 3-6, 14-17, 25-28 (Treatment Days 3-6): predose (trough).

Maximum observed serum concentration (C_{max}), area under the serum concentration-time curve from time zero to 24 hours post dose($_{AUC0-24}$), the lowest concentration observed during the 24-hour dosing interval (C_{min}), average concentration over the dosing interval over a 24-hour period (Cav), time to reach maximum observed serum concentration (t_{max}), time of minimum observed serum concentration (t_{min}), peak to trough fluctuation (PTF), accumulation ratio, and relative bioavailability were calculated for observed and baseline-adjusted testosterone. Concentration-time data were summarized using descriptive statistics for dihydrotestosterone and estradiol.

Results and Conclusions for Study S176.1.007: Following treatment with testosterone gel 1.62%, mean observed concentrations were within the eugonadal range (300-1000 ng/dL) after 2 hours post dose on Treatment Day 1 and over the 24-hour dosing interval on Treatment Day 7 for all treatments. Twenty-five subjects had testosterone concentrations >1000 ng/dL after testosterone gel application. Of these, one had concentrations >2500 ng/dL.

Table 45: Numbers of Subjects with Testosterone Concentrations >1000 or 2500 ng/dL While on Treatment

Treatment	Numbers of Subjects (%)	
	>1000 ng/dL	>2500 ng/dL
A	7(19)	0(0)
B	21(58)	0(0)
C	17(47)	1(3)[a]
Total Across Treatments	25(69)	1(3)

[a] A concentration of 4160 ng/dL in Subject 26832 on Treatment Day 7 (upper arms/shoulders) at 2 hours post dose.
Source: Clinical Study Report S176.1.007, page 43.

> *Reviewer's Comment: Because of the nature of the study, dose titration could not occur as it did in the Phase 3 protocol. Therefore, the single patient with markedly elevated serum T is not considered a major safety concern. In regard to outliers, see the reviewer's assessment of the dose-titration Phase 3 study.*

On Treatment Day 1, mean observed testosterone concentrations were higher for Treatment B (upper arms/shoulders application) compared to Treatment A (abdomen application) and as compared to Treatment C (rotation application-abdomen 3 days followed by upper arms/shoulder 4 days). Treatments A and C had similar mean concentrations on Day 1. On Treatment Day 7, mean concentrations were lower for Treatment A (abdomen) compared to Treatments B (arm/shoulders) and C (rotating schedule). Treatments B (arms/shoulders) and C (rotation application) provided similar mean testosterone concentrations on Day 7.

After multiple dosing, steady-state conditions were achieved by Treatment Day 2 for both Treatments A and B. For Treatment C (rotating), trough concentrations showed a shift after treatment Day 4, which reflected the change in application site (from abdomen to upper arms/shoulders). After the last application of testosterone gel 1.62%, mean observed testosterone concentrations returned to baseline levels by 48 hours post dose on Treatment Day 7 for Treatment A, and 72 hours post dose for Treatments B and C.

The conclusions of this study are:

- Single and multiple dose application of testosterone gel 1.62% applied to the abdomen provided approximately 30-40% lower bioavailability compared to upper arm/shoulder application.
- A rotation application schedule, where 5 gm testosterone gel 1.62% was applied for 3 day to the abdomen followed by 4 days to the upper arms/shoulder, provided comparable bioavailability to abdominal application on Day 1 and comparable bioavailability to upper arm/shoulder application on Day 7.
- Steady-state testosterone concentrations were achieved within 2 days when testosterone gel 1.62% was applied solely to the abdomen or upper arms/shoulders once daily for 7 days.

- After the last dose of testosterone gel 1.62% was applied, testosterone concentrations returned to baseline levels within 48 hours after abdomen application and within 72 hours after upper arms/shoulders and rotation application.

Reviewer's comment: The data from this study show that arm/shoulders and a "rotating schedule" (3 days abdomen than 4 days arms/shoulders) provide comparable exposure. The abdominal site provides 30-40% less exposure.

There were no deaths in the study. A total of 31 subjects (86.1%) exposed to study medication reported at least one treatment emergent adverse event (TEAE) throughout the course of the study. One serious, TEAE of dermatitis was reported during the study (see narrative below). Application site TEAEs were among the most frequent TEAEs (reported in ≥ subjects). These included application site excoriation (7/36, 19.4%), application site papules (5/36, 13.9%) and application site dermatitis (4/36, 11.1%). Other non-serious TEAEs reported most frequently were dry skin (8/36, 22.2%), arthropod bite (5/36, 13.9%), and pruritus and headache (each reported in 4/36, [11.1%] of subjects).

Reviewer's Comment: The reader is referred to earlier sections of this review regarding the reviewer's more detailed analysis of the application site reactions in this study. Based upon more detailed review, it was concluded that the arms/shoulders only method was not more irritating than the rotating application method in this study.

Subject 26827 is a 55 year-old white male randomly assigned to treatment sequence C, A, B, received testosterone gel 1.62% on the abdomen on Days 1-3 and on the shoulder/upper arm on Days 4-7. On 15 March 20007 (Day 6), Subject 26827 noted a "red skin patch" on his "lower front leg". The sub-investigator assessed the subject at 3.5 hours post dose on 16 March 2007 (Day 7) and found a right lower lateral anterior leg erythema, characterized as "rough feeling" and of "smooth appearance". A biopsy was ordered and the subject received concomitant treatment with transdermal hydrocortisone cream. The subject was discontinued from the study at Day 7. The SAE of dermatitis was moderate in severity and considered unrelated to the study medication according to the investigator. When the subject returned to the study site on 26 March 2007 to complete the biopsy, he reported the use of OTC hydrocortisone cream twice daily (BID) since study withdrawal. An assessment of the subject by the sub-investigator revealed a continued slight erythema with "no scale and no component." The biopsy results showed superficial and deep perivascular dermatitis and eosinophilia, consistent with a dermal hypersensitivity reaction and a periodic acid-Schiff (PAS) stain negative for fungi. At a post-study follow-up call on 2 April 2007, the subject reported discontinuing the use of hydrocortisone cream on 25 March 2007 and the SAE of dermatitis has resolved on 28 March 2007. The subject had a relevant medical history of dermatitis and erythema to the lower right leg with a corresponding onset of September 2006 and December 2006, respectively. The subject reported previous treatment for dermatitis with antibacterial and antifungal ointments beginning in October 2006, and treatment for erythema with hydrocortisone as needed and OTC skin lotion since 02 December 2006. At Screening, the subject reported both events as having been resolved on 1 February 2007.

The following 8 subjects experienced "markedly abnormal vital signs" as defined in the protocol:

- Subject 26807 is a 51 year- old white male, randomly assigned to treatment sequence C, B, A, received testosterone gel 1.62% (5 gm) on Days 1-7, 12-18 and 23-29. At the first assessment performed on Day-2, the subjects SBP was 168 mmHg; and his corresponding DBP was 122 mmHg (Baseline value 107 mmHg), which met the criteria for markedly abnormal vital signs. At a subsequent unscheduled assessment on Day-2, the subject experienced high blood pressure values of 180 mmHg (Baseline value 138 mmHg) for SBP and 128 mmHg for DBP. These values also met the criteria for markedly abnormal vital signs.

Reviewer's Comment: No past medical history of hypertension was reported.

- Subject 26182, a 50 year-old black male, randomly assigned to treatment sequence A, B, C, received testosterone gel 1.62% (5 gm) on Days 1-4; however was discontinued from the study on Day 4 due to a testosterone level >900 ng/dL obtained from the clinical safety laboratory results, as specified in the protocol. The subject experienced a decrease in weight that met the criterion for markedly abnormal vital sign values (≥ 7% decrease from Baseline). At the termination assessment (Day 5), the subject's weight was 88.7 kg (Baseline value: 96.4 kg); an overall decrease of 7.7 kg.

- Subject 26819, a 58 year-old white male, randomly assigned to treatment sequence B, A, C, received testosterone gel 1.62% (5 gm) on Days 1-7, 12-18, and 23-29. The subject experienced a decrease in weight that met the criteria for markedly abnormal vital sign values (≥ 7% decrease from Baseline). At study exit (Day 34), the subject's weight was 90.0 kg (Baseline value: 97.6 kg); an overall decrease of 7.6 kg.

- Subject 26825, a 51 year-old white male, randomly assigned to treatment sequence B, C, A, received testosterone gel 1.62% (5 gm) on Days 1-7, 12-18 and 23-29. The subject experienced a high DBP of 105 mmHg at an unscheduled assessment on Day -2 (Baseline value: 80 mmHg). This met the criteria for markedly abnormal vital signs.

Reviewer's Comment: No past medical history of hypertension was reported.

- Subject 26826, a 56 year-old white male, randomly assigned to treatment sequence B, A, C, received testosterone gel 1.62% (5 gm) on Days 1-7, 12-18, and 23-29. The subject experienced a high DBP of 108 mm Hg on Day -2 (Baseline value: 89 mmHg). This met the criteria for markedly abnormal vital signs.

Reviewer's Comment: No past medical history of hypertension was reported.

- Subject 26830, a 36 year-old white male randomly assigned to treatment sequence A, C, B, received testosterone gel 1.62% (5 gm) on Day 1-7, 12-18, and 23-29. The subject experienced a high DBP of 126 mmHg on Day 11 (Baseline value: 80 mmHg). This met the criteria for markedly abnormal vital signs.

- Subject 26835. a 49 year-old white male, randomly assigned to treatment sequence B, C, A, received testosterone gel 1.62% (5.00 g) on Days 1-7, 12-18 and 23-29. The subject experienced a high DBP of 107 mmHg on Day 31 (Baseline value: 92 mmHg). This met the criteria for markedly abnormal vital signs. No medical history of hypertension was reported.

- Subject 26840, a 57 year-old white male, randomly assigned to treatment sequence B, A, C, received testosterone gel 1.62% (5.00 g) on Days 1-7, 12-18, and 23-29. The subject experienced a decrease in weight that met the criterion for markedly abnormal vital sign values (≥ 7% decrease from Baseline). At study exit (Day 34), the subject's weight was 72.2 kg (Baseline value: 79.3 kg); an overall decrease of 7.1 kg.

Table 46: Sponsor's Standards For the Identification of "Markedly Abnormal Vital Signs"

Variable	Unit	Markedly Low	Markedly High
SBP	mmHG	Value = 90 and 20 mmHg decrease from Baseline	Value = 180 and 20 mmHg increase from Baseline
DBP	mmHg	Value = 50 and 15 mmHg decrease from Baseline	Value = 120 and 15 mmHg increase from Baseline
Pulse	bpm	Value = 50 and 15 bpm decrease from baseline	Value = 120 and 15 bpm increase from baseline
Weight	Kg	= 7% decrease from Baseline	= 7% increase from Baseline
Temperature	^{o}F	NA	Value =101.0 and =2.0 increase from Baseline

Source: Analysis Plan for Study S176.1.007: page 29, Table 17.2.3

9.5 Skin Transfer and Irritation Studies

Skin Transfer Studies

Several transfers studies were conducted and submitted as part of the original NDA. These are summarized herein:

S176.1.003 was a single center, open label, randomized, single and multiple exposures, parallel group study in healthy male and female couples. Each male-female couple was randomized to one of three treatment groups. Each group consisted of 16 couples. The pharmacokinetic objectives of the study were 1) to determine the pharmacokinetics of total testosterone

concentrations in female subjects after single and multiple episodes of skin contact with a male partner dosed with testosterone gel 1.62%, and to 2) to evaluate skin-to-skin testosterone transfer from males dosed with testosterone gel 1.62% to non-dosed female subjects when direct contact occurred 2 hours or 12 hours post-dose and when contact occurred with a t-shirt at 2 hours post dose (the three treatment groups). The testosterone gel was applied to the abdomen and each couple engaged in abdomen to abdomen contact in the vertical position for 15 minutes daily. The drug dose used in the study was 5 g of testosterone gel 1.62% applied once a day.

There were three treatment groups:

- Treatment A: Direct skin contact occurred two hours post dose (no t-shirt)
- Treatment B: Skin contact occurred two hours post dose with the male wearing a t-shirt
- Treatment C: Direct skin contact occurred 12 hours post dose (no t-shirt)

Blood samples for measurement of serum testosterone, DHT, and estradiol concentrations were collected from female subjects only at the following times: serially over a 24-hour period on Day-1 (baseline), serially over the 24-hour period following the end of contact on Days 1 and 7, and at 48 hours after end of contact on Day 7.

Results: PK was performed only on the female subjects. The baseline testosterone concentrations were similar across all treatment groups (20.1-29.3 ng/dL [normal range 8-75 ng/dL]). Based on the concentration- time profiles, mean observed testosterone concentrations increased from baseline yet remained within the normal range (for females) on Days 1 and 7 for all treatments except for direct skin contact 2 hours post-dose, where the normal range was exceeded. In treatment A at 16 hours post skin contact on Day 1, the testosterone average level was 81.5 ng/dL ng/L with an SD of 31.2 ng/dL. On Day 7 in Treatment A at 16 hours post skin contact, the average testosterone level was 65.2 ng/dL with an SD of 25.1 ng/dL. The Time 0 average testosterone concentration was 47.0 ng/dL on Day 7. The mean C_{avg} for observed testosterone was within the normal female range after single and multiple episodes of skin contact except for Day 1 of treatment A at 16 hours (81.5 ng/dL). This demonstrates clear evidence of transfer when 15 minutes of unprotected skin rubbing transpired in Treatment Group A - which notably used no barrier.

There was variation amongst the subjects as is reflected in the standard deviations of 31.2 ng/dL at 16 hours on Day 1 and 25.1 ng/dL on Day 7 at 16 hours in Treatment A subjects. In Treatment B, the standard deviations ranged from 11.6 to 19.0.

Covering the site of application on the male partner prior to post dose contact reduced the amount of exposure by 40-48% according to the Sponsor, as seen in Treatment Group B. The mean C_{max} remained within the normal range for adult women. Accumulation of testosterone was minimal in females after daily skin contact for 7 days. Mean testosterone concentrations in females returned to baseline levels 48 hours after last skin contact with a dose male partner.

Table 47: Study S176.1.003 Average Testosterone (ng/dL) Concentrations by Treatment for Female Subjects

Treat-ment	Study Day	Nominal Time (h)									
		0	2	4	6	8	10	12	16	24	48
A	-1	20.1	22.6	23.6	24.9	25.8	23.1	24.0	28.9	24.6	NA
	1	24.6	36.4	45.2	56.6	47.4	60.2	57.8	81.5	46.2	NA
	7	47.0	52.9	68.0	68.5	60.4	61.0	64.2	65.2	53.3	34.0
B	-1	23.1	23.0	23.1	24.1	24.1	22.8	24.2	26.3	23.8	NA
	1	23.8	31.6	39.8	38.9	36.0	37.6	36.0	46.2	35.3	NA
	7	39.5	36.8	38.1	38.0	37.1	34.6	35.0	47.3	33.1	26.3
C	-1	22.3	23.0	26.9	29.3	27.5	29.0	28.4	27.7	21.3	NA
	1	21.3	43.8	44.1	66.3	74.7	69.6	68.6	55.2	57.4	NA
	7	32.3	51.6	47.0	48.5	55.5	55.4	52.2	48.6	41.5	30.4

NA=not applicable Source: Clinical Study Report S176.1.003 Table 10.2.1

Reviewer's Comment: In this study, covering the site of application reduced the exposure in women compared to not covering the site. However, a T-shirt barrier still permitted some testosterone exposure in females. By my calculation, the amount of transfer could be reduced by as much as 60% by a T-shirt. Based on this study, which showed the inability to fully mitigate transfer with a t-shirt, the Sponsor was asked to re-consider the means by which transfer could be effectively mitigated. They eventually decided upon the arms/shoulder only application method, which had a comparable efficacy to the rotating application method, but a t-shirt effectively mitigated transfer from the arms/shoulders.

Study S176.1.008 was a randomized, open-label, parallel group study to evaluate the effects of a 2.5 gm dose (with/without a T-shirt), post-application washing, and application site on the transfer potential of testosterone gel 1.62% from dosed males to a non-dosed partner. Contact time was 15 minutes. 24 healthy male-female couples participated. The study objectives were:

- To evaluate skin-to-skin testosterone transfer potential from males dosed with gel to non-dosed female subjects using a dose of 2.5 g gel, when contact occurred 2 hours post dose with and without a t-shirt.
- To evaluate skin-to-skin testosterone transfer potential from males dosed with 5.0 g gel to non-dosed female subjects when direct contact occurred 2 hours post dose with and without post dose washing.
- To evaluate skin-to-skin testosterone transfer potential from males dosed with 5.0 g gel to non-dosed female subjects when direct contact occurred 2 hours post dose after application to upper arms/shoulders or abdomen of males with the corresponding site in females.

Each treatment group was composed of eight couples, for a total of 24 couples. Within each treatment group, subjects received two single dose/exposure treatments in randomized order. Within 1 hour prior to the targeted time of dose application, male subjects showered and washed

the application site with soap and water. Subjects were not allowed to remain in the shower for longer than 10 minutes. The designated area for gel application was to be thoroughly dried. Each dosing day included 15 minutes of supervised skin contact between the dosed male and his non-dosed female partner. Dose application and subsequent skin contact occurred on Days 1 and 8 of the study (7 day washout period). The three treatment groups were the following:

- **Treatment Group I: Treatment A**: Male subject-2.5 gm testosterone gel 1.62% (40.5 mg testosterone) applied to the abdomen. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt). **Treatment B**: Male subject-2.5 gm testosterone gel 1.62% (40.5 mg testosterone) applied to the abdomen. Contact with female-contact occurred 2 hours post dose with the male wearing a t-shirt.
- **Treatment Group II: Treatment C**: Male subject-5.00 g testosterone gel 1.62% (81 mg testosterone) applied to the abdomen. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt). **Treatment D:** Treatment Male subject-5.00 testosterone gel 1.62% (81 mg testosterone) applied to the abdomen. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt) after washing of the male application site. Washing of the application prior to contact is described on page 22 of Clinical Study Report S176.1.1008 as "*male subjects showered and thoroughly washed the application site with soap and water 15 minutes prior to the scheduled contact time. The abdomen was thoroughly dried.*" No further detail is provided about washing duration or technique.
- **Treatment Group III: Treatment E**: Male subject-5.0 g testosterone gel 1.62% (81 mg testosterone) applied to the upper arms/shoulders. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt). **Treatment F**: Male subject-5.0 g testosterone gel 1.62% (81 mg testosterone) applied to the abdomen. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt).

Results: Mean baseline testosterone concentrations (females only) were within the normal range for all groups (16.2-30.3 ng/dL). Mean observed testosterone concentrations increased above baseline for all treatments except for abdomen-abdomen contact 2 hours post dose (2.5 gm) with the male wearing a t-shirt. Observed testosterone concentrations returned to approximate baseline levels at or before 48 hours following the last contact for all treatments.

A T-shirt barrier largely eliminated population mean transfer in this study for the 2.5 g testosterone gel 1.62% dose. However, two subjects, 27403 and 27419, had small baseline-adjusted testosterone increases (17.4 and 13.8 ng/dL at the maximum), as well as a few other testosterone increases over baseline in excess of 10 ng/dL but less than maximum. In addition, Subject 27398 had negative values (lower than baseline) throughout the entire collection period.

> *Reviewer's Comment: There is a wide amount of variability in female testosterone levels. One cause of variability is cyclic variation of testosterone. If the sample size is adequate, this variation (both up and down) would be expected to even out. In future protocols, females should be studied at the same time in their menstrual cycle or be postmenopausal to decrease this type of variability. Despite two subjects (#27403 and #27419) with small*

increases above baseline, I concur that a T-shirt barrier largely eliminated population mean transfer in this study for the 2.5 g testosterone gel 1.62% dose.

Table 48: Protocol S176.1.1008: Baseline Adjusted Testosterone (ng/dL) Treatment B (T-Shirt Barrier)

	Nominal Time (h)									
Subject	0	2	4	6	8	10	12	16	24	48
27398	-21.2	-21.0	-18.1	-22.6	-14.8	-18.7	-14.3	-17.2	-2.20	-4.60
27400	0.40	-2.50	-2.30	-0.70	-10.1	2.50	-4.30	2.30	-40.3	-43.3
27403	14.8	0.80	12.3	**17.4**	16.9	4.70	14.2	11.0	-19.6	-18.8
27407	-0.10	-0.20	0.80	0.00	-0.10	1.80	6.40	8.70	3.80	2.80
27410	-1.80	-2.10	-0.60	6.40	2.60	0.20	4.20	-3.70	3.60	1.30
27412	-5.00	-1.40	3.30	0.70	1.90	-1.50	-4.90	6.80	2.50	5.10
27415	1.80	0.50	4.20	1.10	3.70	2.40	7.70	1.40	1.90	1.40
27419	9.60	1.60	**13.8**	11.2	8.60	7.70	4.40	2.00	-29.7	-35.7

Source: Adapted from Table 10.2.7: Clinical Study Report S176.1.1008, page 118

Washing the transfer site prior to direct skin contact (Group D) substantially limited the transfer of testosterone - AUC_{0-24} and C_{avg} were comparable to baseline and C_{max} was only slightly increased. Nonetheless, there were still two subjects, 27405 and 27411 with increases from baseline (perhaps showing evidence for skin transfer of testosterone versus normal background variability) and 4 subjects, 27399, 27402, 27404, 27417 with lesser and modest increases from baseline in serum testosterone.

Table 49: Protocol S176.1.008: Baseline Adjusted Testosterone (ng/dL) Treatment D (Site Washing)

	Nominal Time (h)									
Subject	0	2	4	6	8	10	12	16	24	48
27399	0.400	8.40	4.00	2.90	1.30	4.90	3.50	3.70	2.60	3.50
27402	0.00	6.00	5.00	4.80	7.40	7.30	0.60	-4.30	1.80	-1.30
27404	4.60	3.90	3.80	-1.00	3.80	2.60	6.10	-0.80	-5.50	-4.20
27405	12.3	8.70	12.3	11.0	**13.4**	6.90	1.30	10.2	-6.80	-10.8
27411	21.3	**16.9**	2.90	7.60	-1.50	1.30	-4.00	1.60	0.70	-4.90
27413	-3.30	0.80	0.10	2.00	1.50	0.10	-0.90	0.10	1.20	3.30
27416	1.10	-1.00	-0.90	-1.50	-1.10	0.50	0.30	2.30	-6.00	-4.90
27417	11.3	5.30	0.10	-1.40	2.40	2.00	0.60	3.30	-12.2	3.30

Source: Adapted from Table 10.2.7: Clinical Study Report S176.1.1008, page 120

Reviewer's Comment: The current data appears to support the conclusion that skin washing prior to physical contact largely eliminates risk of transfer of testosterone gel 1.62% to the female partner, but even within the study there were two individuals with increases in testosterone from baseline. Whether these increases signify transfer or

reflect normal background variability is unknown. Significant variability of female testosterone levels and cyclic variation to testosterone concentrations provide possible explanations for individuals with very modest testosterone increases.

It is notable that the technique of washing the application site used in Protocol S176.1.008 included a shower and soap and water lathering of the application site.

The Clinical Pharmacology team finds that washing the site prior to contact precludes transfer and this method can be used as one type of precaution for transfer.

After direct application to upper arms/shoulders (Group E) or abdomen (Group F) and skin-to-skin contact of a female with the corresponding application site on a male partner dosed within 5.0 gm of testosterone gel 1.62 %, an increase in testosterone was observed with the normal range for both contact sites however, mean C_{max} increased above the upper limit of normal following upper/shoulder contact.

Table 50: Study S176.1.008 Average Serum Concentrations (ng/dL) of Testosterone by Treatment for Female Subjects

Treat-ment	Nominal Time (h)									
	0	2	4	6	8	10	12	16	24	48
A	32.1	24.3	32.3	36.9	24.8	31.5	43.1	24.3	23.7	39.6
B	20.6	17.0	21.2	20.9	21.6	19.2	20.3	21.5	21.5	20.0
Baseline	20.8	20.0	19.5	19.2	20.5	19.3	18.7	20.0	31.5	
C	23.1	31.1	26.3	28.1	26.2	26.3	29.1	22.7	21.8	21.6
D	20.8	21.4	18.7	19.0	19.0	18.6	16.4	17.3	17.4	18.4
Baseline	14.9	15.2	15.9	15.4	15.8	15.0	16.4	15.5	20.4	
E	52.2	80.4	60.8	50.1	67.0	57.3	54.5	61.0	42.1	54.0
F	32.6	36.1	42.1	37.8	31.8	43.7	41.2	44.0	36.5	32.7
Baseline	13.3	13.7	15.0	14.0	16.0	15.2	14.6	14.4	39.1	

Source: Clinical Study S176.1.008, Table 10.2.4, Table 10.2.1 Baseline is Day -1 for the two groups above each baseline row.

Reviewer's Comment: In this study and in Stud 003, it appears that the female exposure to testosterone due to secondary exposure, can be mitigated by coverage of the application site for the 2.5 gm dose, but the t-shirt did not prevent transfer at the abdominal site for the 5gm dose. Therefore, the Sponsor conducted an additional transfer study (Study 011 described in an earlier section of this review) and in fact, transfer from the arms/shoulder site was effectively mitigated by a t-shirt in that study.

Skin Sensitization and Skin Irritation Study

Study S176.1.004 was a double-blind, randomized, placebo controlled study to evaluate the sensitization and irritation potential of repeat applications of testosterone gel 1.62 % in healthy

male subjects. This was a double-blinded study using a randomized design where each subject received all test articles. The study was performed in the US. The subjects in the study during the induction phase applied a skin patch (3.14 cm^2) to separate sites on the upper outer arm which contained Testosterone Gel 1.62 % 100mg. This amount of testosterone is 5 fold higher than the highest clinical dose in Study S176.3.004. The patch was applied every 48-72 hours for a total of 9 applications. Skin reactions to the patch were recorded. A rest phase of 12-17 days occurred during which no patches were applied. In the following challenge phase, the skin patches were applied to sites on the upper back for 48 hours. These sites were then evaluated 30 minutes and 48 hours after patch removal. If a rechallenge was necessary, it was conducted 3-4 weeks following the final evaluation of the challenge phase.

235 men were enrolled and 214 men completed the protocol. Four subjects were lost to follow-up. Six subjects were dropped due to non-compliance, and 2 subjects were discontinued due to a nonserious AE of rash. There were 4 test articles used:

a. Testosterone gel 1.62%
b. Placebo gel
c. Positive irritant control
d. Low irritant control

The irritation potential for each patch was determined by the scores obtained during the induction phase. Irritation was graded as follows: 0-no evidence of irritation, 1-minimal erythema, 2-definite erythema, 3-erythema and papules, 4- definite edema, 5-erythema edema and papules, 6-vesicular eruption, and 7-strong reaction extending beyond test site

Sensitization reaction was evaluated as follows: inflammatory responses were graded: 0-no visible reaction or erythema, 0.5-slight confluent or patchy erythema, 1 mild reaction-macular erythema, 2-moderate reaction-macular erythema, 3-strong to severe reaction-macular erythema.

Results: No serious adverse events or deaths occurred during the study. Fifty-one subjects (51/235, 21.7%) reported 97 nonserious events over the course of the study. The most common AE was headache (20 events in 13 subjects, 5.5%).

The following (2) subjects discontinued from study participation due to the nonserious AEs of rash:

- Subject 26625, a 20 year-old Caucasian male assigned to random sequence A, C, D, B experienced a nonserious AE of rash of moderate intensity considered probable in relationship to treatments. The rash occurred one day after last exposure to test articles and resolved with topical and oral therapy. The subject was exposed a total of 18 days at the time concomitant topical hydrocortisone acetate was administered.
- Subject 26626, a 38 year-old White male randomly assigned to sequence C, B, A, D experienced a non serious AE of rash on the right arm and chest that was considered unlikely related to treatments. He received topical clobetasol ointment. He was exposed to the test articles for a total of 16 days at the time the concomitant medication was administered.

Three subjects experienced application site pruritis comprising 4 non-serious AEs that were attributed to the treatments by the investigator on a probable basis. The Sponsor concluded that there we no findings of patch irritation of clinical relevance. There was no evidence that Testosterone gel 1.62% produced sensitization as results during the challenge phase were similar to placebo gel. The Sponsor also concluded that Testosterone Gel 1.62% produced very mild irritation (all irritation scores<2, and 98% of scores were either 0 or 0.5 [similar to placebo]).

No trends or clinically significant changes were noted in clinical laboratory data, vital sign data, or physical examinations.

Reviewer's Comment: Testosterone Gel 1.62% appears to have no sensitization potential and minimal irritation potential as compared to placebo. However, rash was reported in 2 patients. The term "rash" is included in labeling.

Table 15: TEAEs in Study S176.1.104

System Organ Class	Preferred Term	Total (N=235)
Total Number TEAEs		141
Patients with ≥ TEAE		68(29%)
		n (%)
Ear and Labyrinth	Ear discomfort	1(0.4)
	Ear pain	3(1.3)
Eye Disorders	Ocular hyperemia	2(0.9)
Gastrointestinal Disorders	Abdominal pain	1(0.4)
	Abdominal Pain upper	5(2.1)
	Constipation	1(0.4)
	Dyspepsia	1(0.4)
	Nausea	3(1.3)
	Retching	1(0.4)
	Toothache	3(1.3)
	Vomiting	1(0.4)
Gen Disorders, Administration site	Applic site pruritis	3(1.3)
	Fatigue	1(0.4)
	Irritability	2(0.9)
	Pyrexia	2(0.9)
Infections, Infestations	Conjunctivitis	1(0.4)
	Herpes Simplex	1(0.4)
	Influenza	1(0.4)
	Lower respiratory	1(0.4)
	Nasopharyngitis	7(3.0)
Injury, Poisoning, Procedural Complications	Arthropod bite	1(0.4)
	Hand fracture	1(0.4)
	Joint dislocation	1(0.4)
	Sunburn	3(1.3)

Metabolism, Nutrition	Anorexia	1(0.4)
	Dehydration	1(0.4)
Musculoskeletal Connective	Arthralgia	1(0.4)
	Back pain	2(0.9)
	Myalgia	3(1.3)
	Musculoskeletal pain	1(0.4)
	Neck pain	1(0.4)
	Pain extremity	1(0.4)
Nervous System Disorders	Headache	19(8.1)
	Lethargy	1(0.4)
	Syncope	3(1.3)
Psychiatric Disorders	Insomnia	2(0.9)
Respiratory, Thoracic, Mediastinal Disorders	Cough	9(3.8)
	Dysphonia	1(0.4)
	Epistaxis	1(0.4)
	Secretions increased (upper airway)	1(0.4)
	Nasal congestion	2(0.9)
	Nasal discomfort	1(0.4)
	Pharyngolaryngeal pain	6(2.9)
	Rhinitis allergic	1(0.4)
	Rhinorrhea	11(4.7)
Skin, Subcutaneous	Pruritis	1(0.4)
	Rash	3(1.3)
Vascular Disorders	Dizziness	1(0.4)
	Flushing	1(0.4)
	Hot flush	1(0.4)

Source: S176.1.004 (b) (4) Study M/ R06-1122, Table 10.3.1, page 645

Reviewer's Comment: These subjects received five times the testosterone dose of patients using 5 gm of Androgel 1.62%. Aside from the 3 patients in whom syncope was reported, the TEAEs are quite benign. The incidence of syncope was evaluated further in the pivotal study results. Subject 051-02 (receiving testosterone gel 1.62% 2.5g) in Protocol S176.3.104 experienced syncope during the pharmacokinetic sampling period on Day 14 and was discontinued. A total of 3 subjects receiving testosterone gel 1.62% (1-2.5g, 2-5.0 g) experienced syncope during the double blind period versus none for placebo. Dizziness occurred in 3 subjects receiving testosterone gel 1.62 %(1-2.5 g and 2-5.0 g) and in no placebo subjects. Syncope is not known to be an adverse reaction to testosterone, nor does this experience indicate syncope to be an adverse reaction to AndroGel.

9.6 Brief Summary of Study S176.3.104: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Testosterone Gel 1.62% for the Treatment of Hypogonadal Men

Reviewer's Comment: This section contains an overview of the Phase 3 pivotal study 104. A detailed analysis of Safety and Efficacy of this Phase 3 study as it pertains to the Complete Response is provided in Sections 6 and 7 of this review. In addition, a more detailed review may be found in the Medical Officer's review of the original NDA.

Study S176.3.104 was a multi-center, 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.

Patients were included if:

- They were males, 18-80 years of age.
- Had 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:
- Had 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.
- Had average serum testosterone concentration of <300 ng/dL determined from two laboratory specimens collected at the same visit, 30 (=/- five) minutes apart between the hours of 6:00 a. m. and 10:00 a. m.
- Were naïve to androgen replacement or had undergone a washout of 12 weeks following intramuscular androgen injections; four weeks following topical or buccal androgens; and 3 weeks following oral androgens.
- Had intact skin surfaces at the gel application sites.
- They had no significant medical conditions that would be adversely impacted by testosterone replacement were eligible for study inclusion.

Patients were excluded if they met any of the following criteria:

1. Low serum testosterone concentrations secondary to causes other than primary or secondary hypogonadism (congenital or acquired).
2. Previous history of, current, or suspected prostate or breast cancer
3. IPSS-1 score >15 points.
4. Abnormal finding on DRE of the prostate as determined by the investigator. Prostate enlargement by itself was not an exclusion criterion.
5. PSA > 2.5 ng/mL or 2.6-3.74 ng/mL without a negative biopsy within the past 6 months with pathology report available for principal investigator's review (this exclusion criterion was modified to PSA>1.25 ng/mL for men on the 5-α reductase inhibitors finasteride or dutasteride).
6. Body Mass Index (BMI) less than 18 or greater than 40 kg/m^2.

7. Untreated prolactinoma.
8. Currently seeking fertility or seeking fertility within one year of trial participation.
9. Poorly controlled diabetes defined a hemoglobin A1C (HgbA1c) >9.
10. History of Human Immunodeficiency Virus (HIV) infection.
11. Multiple sclerosis (MS) or other degenerative central nervous system (CNS) diseases, or spinal cord injury.
12. History, current, or suspected, obstructive sleep apnea.
13. Findings of any kind of skin lesions on the surface of the application site during the physical examination (small tattoos were acceptable).
14. Generalized skin disease that may affect absorption of investigational gel (e. g., psoriasis or eczema).
15. Clinically significant neurological, hematological, autoimmune, endocrine, cardiovascular, liver, renal, gastrointestinal, pulmonary, or infectious diseases that would interfere with the subject's participation or compromise the subject's safety in the study, as determined by the investigator.
16. History, suspicion, or current evidence of drug or alcohol abuse within the previous 12 months.
17. History of heart failure (New York Heart Association [NYHA] Class III or greater).
18. Known skin intolerance to alcohol or allergy to any of the ingredients of testosterone gel 1.62%.
19. Subjects with sitting systolic blood pressure (SBP) >160 mmHg or <90 mmHg, or sitting diastolic blood pressure (DBP) > 100 mmHg or <60 mmHg.
20. Hemoglobin (HGB) >16.0 g/dL, hematocrit (Hct) >48%, serum albumin <3.5 g/dL, fasting blood glucose >300 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) >2X ULN (upper limit of normal).
21. Using any over-the-counter (OTC) steroid preparations or derivatives (e.g., dehydroepiandrosterone [DHEA]).

Subjects were discontinued for the following reasons:

- For any subject during the study with an increase in PSA >0.75 ng/dL from baseline, a repeat test was performed. If the average of the two measurements confirmed a change from baseline <0.75 ng/mL, the subject was allowed to continue in the study. If the change was confirmed to be > 0.75 ng/mL, the subject was discontinued and early termination assessments were completed. Men treated with 5-α reductase inhibitors had PSA change from baseline discontinuation criteria half the values of men not taking 5-α reductase inhibitors (i.e., PSA change from baseline >0.37 ng/mL).
- If a subject had an absolute PSA value of >4.0 ng/mL post-baseline, a repeat test was performed. If the average of the two measurements was ≤4.0ng/mL, the subject was allowed to continue in the study. If the average of the two measurements was >4.0 ng/mL, the subject had to be discontinued. Men treated with a 5-α reductase inhibitors had absolute discontinuation thresholds half the values of men not taking 5-α reductase inhibitors (i. e., rise to >2.0 ng/mL).
- If a DRE abnormality was noted (e.g., nodule or induration).

- If SGOT or SGPT were >3X ULN; the subject had to be discontinued following a repeat confirmatory test.
- If the Hct was >54%, the subject was to be discontinued and early termination assessments completed.
- If a serum testosterone concentration > 2500 ng/dL was observed, the unblinded Quintiles clinical reviewer had the authority to intervene with subjects proceeding in the study.

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, see Table 4) and placebo administered over a period of 182 days. 224 subjects were planned. 274 subjects (testosterone gel 1.62%: 234 subjects, placebo: 40 subjects) were randomized and analyzed for safety; 206 subjects (testosterone gel 1.62%: 179; placebo 27 subjects) 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 3 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 by the investigator 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 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.

Subjects were advised of the following precautions:

- Study drug should not be applied prior to study visits.

- Study drug should be applied using proper application technique
- There is a potential for dermal transfer to another person when vigorous skin-to-skin contact is made.
- Study drug should be properly stored.
- Study drug should not be applied to scrotum

At 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.

The Safety Sample consisted of all subjects who were allocated to the Treatment Sample and had at least one dose of study medication administered. Three patient populations were used in the analysis of efficacy: 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, the Efficacy Sample consisted of all subjects included in the FA Sample and had any efficacy data for Day 112 (the primary timepoint), and 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. Only available parameters were used for all analytes. LOCF was used only for secondary endpoints.

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 NDA presents data collected in the study up to and including Day 182. By prior agreement, a Final Integrated Clinical Study Report including data from Baseline through the end of the Study (Day 364) was included in the 120 day Safety Update.

Table 3: Pre-specified Testosterone Gel 1.62% Dose Titration Criteria

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 %

Table 4: Doses Administered

Gel Strength	Gel Dose (g)	T Dose (mg) Applied	Number of Pump Actuations
1.62%	1.25	20.3	1
1.62%	2.50	40.5	2
1.62%	3.75	60.8	3
1.62%	5.00	81.0	4

Source: adapted from Table 2, Clinical Study Report S1763104, 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. Success in the study was defined as ≥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:

- Cmax ≤1500 ng/dL in ≥85% of the subjects
- Cmax between 1800-2500 ng/dL in ≤5% of the subjects
- Cmax >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.

The schedule of events, including safety measures, were obtained as outlined in the table below:

Table 51: Schedule of Events Study S176.3.1004

Evaluations	Screening A / B	Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Days (Weeks)	Days -14 / -7	Day 1	Day 14 (Week 2)	Day 28 (Week 4)	Day 42 (Week 6)	Day 56 (Week 8)	Day 84 (Week 12)	Day 112 (Week 16)	Day 140 (Week 20)	Day 182 (Week 26)
Informed consent	X / -									
Inclusion/Exclusion	- / X	X								X
Baseline/Assessment for Open-Label Phase										X
Demographics, Medical History	X / -									
Height, Weight, BMI, and Waist-to-Hip Ratio	- / X							X		X
Physical Exam (includes breast)	- / X						X			X
Urology Exam (DRE) [a]	- / X						X			X
Vital Signs	- / X	X	X	X	X	X	X	X	X	X
12-Lead ECG	- / X									X
IPSS-1	- / X						X			X
Screening Testosterone and PSA	X[b] / -									
Complete blood count, Clinical Chemistry, Urinalysis	- / X	X[b]								X[b]
Percent Free PSA		X					X			X
Prolactin (b) (4)	- / X									
Safety or Titration Lab (Testosterone)		X	X	X	X	X	X	X	X	X
Safety Labs (PSA, HCT, HGB, SGOT, SGPT, Lipids)	- / X	X					X			X
Sex Steroid Labs (testosterone, DHT, E2)		X	X[g]	X	X	X[g]	X	X[g]	X	X[g]
Predose SHBG		X	X	X	X	X	X	X	X	X
PK Blood Sample[c]			X			X		X		X
PD Blood Sample (predose) [d]		X					X			X
SF-36		X						X		
Site Application Assessment		X	X	X	X	X	X	X	X	X
Randomization IVRS		X								
Dispense Medication [f]		X	X[f]	X[f]	X[f]	X	X	X	X	X
Collect Medication			X	X	X	X	X	X	X	X
Baseline/AE Recording	X / X	X	X	X	X	X	X	X	X	X
Record Concomitant Medication	X / X	X	X	X	X	X	X	X	X	X

Evaluations	Visit 10	Visit 10a	Visit 10b	Visit 11	Visit 12	Visit 13	Visit 14 [a]
Days (Weeks)	Day 182 (Wk 26)	Day 196 (Wk 28)	Day 210 (Wk 30)	Day 224 (Wk 32)	Day 266 (Wk 38)	Day 308 (Wk 44)	Day 364 (Wk 52)
Informed consent							
Inclusion/Exclusion	X						
Baseline/Assessment for Open-Label Phase	X						
Demographics, Medical History							
Height, Weight, BMI, and Waist-to-Hip Ratio	X						X
Physical Exam (includes breast)	X				X		X
Urology Exam (DRE) [e]	X				X		X
Vital Signs	X			X	X	X	X
12-Lead ECG	X						X
IPSS-1	X				X		X
Screening Testosterone and PSA							
Complete blood count, Clinical Chemistry, Urinalysis	X[b]						X
Percent Free PSA	X				X		X
Prolactin (b) (4)							
Safety or Titration Lab (Testosterone)	X	X	X	X	X	X	X
Safety Labs (PSA, HCT, HGB, SGOT, SGPT, Lipids)	X				X		X
Sex Steroid Labs (testosterone, DHT, E2)	X[g]			X	X[g]	X	X[g]
Predose SHBG	X			X	X	X	X
PK Blood Sample[c]	X				X		X
PD Blood Sample (predose) [d]	X				X		X
SF-36							X
Site Application Assessment	X			X	X	X	X
Randomization IVRS							
Dispense Medication [f]	X			X	X	X	
Collect Medication	X			X	X	X	X
Baseline/AE Recording	X	X	X	X	X	X	X
Record Concomitant Medication	X			X	X	X	X

9.7 Summary of Efficacy: Double-Blind Period of Pivotal Study S176.3.104

The primary efficacy variable for Study S176.3.104 was the percentage of subjects with total testosterone C_{avg} within the normal range on Day 112. C_{avg} results were required to fall with the normal range of 300-1000 ng/dL, with success being defined as ≥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 C_{avg} values within the target range, which met the criteria for efficacy.

The key secondary efficacy success criteria required the individual Cmax results to be within the following ranges:

- ≤1500 ng/dL in ≥85% of the subjects
- between 1800-2500 in ≤5% of the subjects and
- >2500 in none of the subjects.

In the FA sample, 93.9% (696/741) of C_{max} observations were ≤1500 ng/dL when considering all four PK days combined. Analyzed for each PK day, the percentage of subjects on testosterone treatment with C_{max} values ≤1500 ng/dL was 96.7% (203/210) on Day 14; 97.3% (178/183) on Day 56; 88.8% (159/179) on Day 112; and 92.3% (156/169) on Day 182.

Overall 3.0% (22/741) of C_{max} observations were in the range of 1800-2500 ng/dL when considering all four PK days combined in the FA sample. Analyzed for each PK day, the percentage of subjects on testosterone treatment with C_{max} values from 1800-2500 ng/dL was 2.4% (5/210) on Day 14; 0.5% (1/183) on Day 56; 5.6% (10/179) on Day 112; and 3.6%(6/169) on Day 182.

A total of 10/234 subjects had a total of 11 testosterone concentrations >2500 ng/dL in the double-blind phase of Study S176.3.104. The testosterone concentrations that exceeded the 2500 ng/dL threshold in Study S176.3.104 were rare, sporadic, and inconsistent. Five of the 10 subjects with serum testosterone concentrations > 2500 ng/dL were eliminated on the basis of sample contamination or artifact and 1 of the 10 subjects was eliminated on the basis of taking more than the prescribed test item dose ("overcompliance"). In the four remaining patients, overdosage was possible in two cases. The four patients in whom sample contamination was not clear and overdosage was not definite were compared to the overall study population receiving testosterone gel 1.62% (in a dose specific manner where possible) with respect to changes in secondary efficacy variables, weight, BMI, hemoglobin, hematocrit, cholesterol, HDL, estradiol and dihydrotestosterone. No indication of increased testosterone dose effect was noted.

There were no subjects in the 182 day Safety Extension with a testosterone concentration of 2500 ng/dL or above.

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. 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. However, when the ten subjects not achieving this endpoint were analyzed, 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. Analysis of variables that might imply androgen effects was conducted. Overall, it was concluded that these sporadic events did not signal a safety risk.

9.8 Summary of Safety: sNDA 22309 Review, November 2, 2009

The studies performed by the Sponsor were adequate to assess the safety of testosterone gel 1.62%. 785 subjects were exposed to testosterone gel 1.62%. The duration of exposure in 191 subjects was 1 year. No patient deaths were reported in any of the studies. The adverse event profile was similar to other drugs in its class. (See Section 2.4 Important Safety Issues With Consideration to Related Drugs). With respect to SAEs, there appeared to be no repetitive

occurrence pattern, there was an overall lack of attribution of any SAE to the study drug. There was one case in which "polycythemia" and "malignant hypertension" was reported in a patient, but this patient had marginally-controlled, serious hypertension at baseline and a baseline hematocrit of 46-47%. The adverse events reported in this patient are considered to be confounded by his serious background conditions, which included marginally controlled, serious hypertension and baseline polycythemia. Rises of PSA was the most frequent reason for study withdrawal, but these were likely a consequence of the strict definitions of PSA increase employed in the pivotal study. Increased hematocrit was also reported as an adverse event in several patients. In the double-blind period, the remaining reasons for premature study termination occurred as single events. No new trends were noted in the open-label period.

The following are key safety issues identified during the review and the overall means of addressing these issues:

Transfer Issue
There are postmarketing reports of accidental secondary exposure to testosterone in children from adults using different testosterone gels. Any testosterone transfer to pre-pubertal children is of concern as these could have developmental effects. Therefore the issue of transfer was investigated rigorously for this product in this application.

In two skin transfer studies from the original NDA, it was determined that a t-shirt could prevent transfer when using the 2.5 gm dose, but not when 5 gm was applied to the abdomen. The Sponsor originally proposed that soap and water washing of the application site, coupled with a t-shirt barrier, would be an effective precaution. It was known from Phase 1 Studies 003 and 008 conducted as part of the original NDA that skin washing with soap and water removed 84% of 5 gm of testosterone gel 1.62% on the skin at 2 hours post dose with similar results at 6 and 10 hours (87.2% and 81.3% respectively) (Study S173.1.1005). Despite this information, the Division insisted that Sponsor determine a method that could prevent transfer using a simple t-shirt. Thus, the Sponsor conducted an additional transfer study (Study 011) which demonstrated that a t-shirt effectively mitigated transfer when the highest maximum dose (5 gm) was applied to the arms/shoulders. Since the arms/shoulders method provides nearly identical exposure to the rotating application method recommended in Phase 3, then the arms/shoulders application was determined to be a safe and effective application method which could be used with a t-shirt to effectively mitigate the risk of transfer.

Sporadic Testosterone Levels >2500 ng/dL
In Study S176.3.104 an increase in serum testosterone concentration was reported in 10 patients receiving testosterone gel 1.62% in the double-blind period and in no patients in the open-label period. Six of these patients were eliminated from further consideration secondary to: 1) a lower testosterone concentration upon repeat testing of the same serum sample (3 subjects, 631, 1363 and 1150 ng/dL of testosterone respectively), 2) a single isolated testosterone concentration spike with eugonadal values immediately prior to and after the time of the spike (2 subjects) 3) documented over compliance (1 subject). Of the four patients with testosterone concentrations above 2500 ng/dL in the double-blind period

- Subjects 015-005 and 049-008 had testosterone concentrations above 2500 ng/dL at baseline or at 0.5 hours post dose. Following dosing, their testosterone concentrations actually declined over the next 4 hours.
- 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 ng/dL, cancelled, and 764 ng/dL.

  Reviewer's Comment: These three subjects would have had their testosterone dose titrated downward by following the product label. For unknown reasons Subject 015-005 (Day 14) did not have the testosterone dose titrated downward.

- 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.

In all these 4 subjects, the elevated serum T events were sporadic, well circumscribed and non-recurrent. There were no concentrations of testosterone >2500 ng/dL reported in the Open-label period.

The four subjects described above were studied for evidence of overall excess testosterone exposure or clinical detrimental effects. The values for DHT and estradiol for these subjects were within the 95% CI for the general study patient population. Serum DHT, estradiol and LH did not show changes of an increased testosterone response in these 4 patients. Serum FSH appeared higher in these 4 patients compared to other patients, but the significance of this finding is unknown. "Increased testosterone response" as manifested by changes in weight, BMI, hemoglobin, hematocrit, PSA, BP systolic, BP diastolic, cholesterol, and HDL were not demonstrated in the double-blind period for these 4 subjects. However, one of these 4 subjects did discontinue treatment secondary to an elevated PSA on Day 204 (058-06).

Based upon a cursory review of the approved product labeling, the overall exposures to testosterone between AndroGel 1% and AndroGel 1.62% appear comparable. In light of 1) the fact that AndroGel 1.62% met all other pharmacokinetic endpoints which documented a eugonadal testosterone concentration except for the sporadic, short-lived occurrence of testosterone concentration > 2500 ng/dL in a few subjects, 2) the achievement of supranormal testosterone concentrations of short duration with injectable androgen administration for many years without ill-effect, and 3) general comparability of exposure between AndroGel 1% and AndroGel 1.62%, the four subjects described above do not provide enough evidence in my opinion to preclude approval of this NDA.

In summary, the events of elevations of testosterone >2500 ng/dL are sporadic, non-recurrent and do not appear to be associated with increased morbidity. From a safety standpoint, I see no reason why these events should preclude approval. It is also important to note, that recommendations for periodic assessment of testosterone concentrations and appropriate dose adjustment will be present in the final product label.

Increased Hematocrit

Testosterone is known to increase red blood cell production. In some patients, hematocrit can increase with testosterone replacement therapy. Currently approved testosterone labeling advises periodic measurements of hematocrit. In Study S176.3.104, an increase in mean hematotcrit was observed overall for the testosterone gel 1.62% groups compared with placebo (Endpoint: 0.026 V/V versus -0.003 V/V). All of the incidents of "markedly abnormal" elevated hematocrits (by criteria defined in the study protocol) were reported in subjects who had been receiving study medication for 12 or more weeks at the time when the event occurred, and the majority of the discontinuations due to increased hematocrit occurred in the open-label period of the study. In the double-blind period of S176.3.104, the incidence of the adverse event of "hematocrit increased" was 2/234 (0.9%) in the testosterone gel 1.62% group, while no subject in the placebo group (0/40) reported the event. In the open-label period, the incidence of hematocrit increased was 4/191 (2.1%). One subject, on the last day of the double-blind period had a single markedly high hematocrit which was not reported. There is insufficient data to show an association of this AE and testosterone gel 1.62% dose level. Correlation between "hematocrit increased" and serum testosterone concentration is also difficult as 5 of 7 subjects with "markedly high hematocrit" had serum concentrations > 1000 ng/dL during the double-blind portion of the study, but no clinically significant increases of hematocrit were noted in the 10 subjects in Study S176.3.104 with total serum concentrations >2500 ng/dL. There were no thromboembolic events noted in these patients. No new safety signal or change in pattern was detected for this adverse event in this NDA. This AE is appropriately labeled in the proposed product label.

Prostate Cancer

It is not known whether replacement of T in men with hypogonadism increases the risk of prostate cancer. Currently, there is no evidence in published literature or from controlled clinical trials to draw this conclusion. Nonetheless, this potential risk and the recommendation to monitor PSA and digitial rectal examination is shown in testosterone replacement product labeling. In this NDA, prostate cancer occurred in one patient, a 58 year-old man (subject 012-08). The patient had a past history of BPH and had stopped taking Avodart on July 26, 2006 prior to his first dose of Androgel 1.62% in the clinical trial, which occurred on (b) (6). At Day 279 of the trial, a prostatic nodule was palpated and biopsies revealed prostate carcinoma in the contralateral prostate side to the nodule. On Day 182, this subject had a testosterone concentration of 4430 ng/dL 2 hours post-dose. His C_{avg} on Days 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 and at Day 182 was 1.8 ng/mL. The PSA at Day 279 was 2.3 ng/mL. The increase in PSA was not reported as a clinical AE. The involved portions of the 2 positive biopsy core were 1% containing Gleason's score 3+3 prostate adenocarcinoma. While this patient may have had higher than average testosterone exposure, no statement can be made about causality to his prostate cancer. Nonetheless, prostate cancer does appear as a possible adverse event in product labeling, and this case will be listed as and adverse reaction in the appropriate section of labeling.

Hypertension
Increased blood pressure, possibly related to fluid retention, is a potential adverse reaction to testosterone. Testosterone can increase fluid retention and red blood cell mass, both could potentially increase 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. Two of the subjects in the double-blind period were not receiving study drug at the time of the event and were removed from this analysis. One of the six subjects in the double-blind period experienced malignant hypertension, but this patient had marginally controlled, serious hypertension and a hematocrit of 47% at baseline. Therefore, the independent effect of testosterone replacement therapy on hypertension in this patient is unknown. The proportion of patients with an AE of "hypertension" roughly paralleled the proportion of subjects in each dose group and there appearred to be no correlation of these events with serum testosterone concentrations or with other laboratory values. The majority of subjects with hypertension as an AE had pre-existing hypertension (7/11). There did not appear to be an increase of the AE of hypertension related to increasing duration of exposure to testosterone gel 1.62%. There were no discernible study population trends regarding blood pressure. This AE is appropriately described in the proposed product label for AndroGel 1.62%. No further action is recommended**.**

Increased PSA:
Testosterone replacement can increase serum PSA. It is clear that small changes from baseline in serum PSA connote harm. The Sponsor used a strict set of criteria to define "PSA increased" in these studies. Subjects were included in Study S176.3.104 if the PSA was <2.5 ng/dL. They were excluded if the PSA became > 4.0 ng/dL or the PSA increase from Baseline was >0.75 ng/dl (average of 2 determinations). A total of 45 subjects reported PSA values on one occasion or more that met exclusion criteria for PSA velocity in Study S176.3.104. 29/234 in the double-blind period (versus 0/40 placebo) and 12/191 subjects in the open-label period. Of these 45 patients, 27 were discontinued. 9 subjects in Study S176.3.104 reported a PSA value >4.0ng/ml (7 in the double-blind and 2 in the open-label periods). Of these 9 subjects, 5 were discontinued. 81% (38/47) of the subjects for whom elevations met the PSA elevation criteria or were reported as an adverse event reported a decrease in PSA after initial elevated value, and 16 subjects (34%) had final PSA values within 10% of the subject's baseline. Increases in serum PSA that qualified as an AE were not correlated with age, race, testosterone gel 1.62% dose, serum testosterone concentration nor time of exposure. In the study population of S176.3.104, the mean change from Baseline in serum PSA at Endpoint was 0.14 ng/mL in the testosterone gel 1.62% group versus -0.12ng/ML in the placebo group. This AE is appropriately described in the proposed product label for AndroGel 1.62%. No Further action is recommended.

Compliance:
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 that approximately 4% of patients in the Androgel 1.62% efficacy clinical trials exhibited compliance > 80%. (b) (4)

(b) (4)

This labeling and Medication Guide will also be implemented for AndroGel 1.62%.

Correlation of Adverse Events with Peak Testosterone Concentrations:
The Sponsor performed a thorough analysis of adverse events by peak testosterone levels. While there is a possible trend of increased AEs in subjects with higher peak testosterone concentrations, in the majority of patients the serum testosterone concentrations were in the eugonadal range prior to the AE. It did not appear that subjects with an isolated peak testosterone concentrations above 1500 ng/dL had a greater overall exposure to testosterone throughout the study than patients who did not. The number of subjects in the groups with testosterone > 1500 ng/dL was too small to document a new safety finding or trend.

> *Reviewer's Comment: In this reviewer's opinion, these safety issues have been adequately addressed. The Sponsor has provided an acceptable means of application (arms/shoulders only), in which transfer can be effectively mitigated by a t-shirt and is provides comparable exposure to the rotating application method recommended in Phase 3. The reported adverse reactions are consistent with and not apparently worse than those reported for all other testosterone replacement products and these are acceptably described in product labeling.*

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

/s/

A R WIEDERHORN
04/20/2011

MARK S HIRSCH
04/20/2011
I concur.

NDA 22309: SDN 29 (Ser. 28)

Medical Officer's Memorandum: Clinical Review Issues Noted at Time of Filing of Complete Response

Date Submitted:	October 25, 2010
PDUFA Goal Date:	April 29, 2010
Date Memo Completed:	
Product:	AndroGel (testosterone gel) 1.62%
Dose and Route:	1.25 gm – 5 gm, once daily by topical application
Indication:	For replacement therapy in males for conditions Associated with a deficiency or absence of endogenous Testosterone (Primary hypogonadism [congenital or Acquired] or hypogonadotrophic hypogonadism [congenital or acquired]

Summary

This review assesses whether this COMPLETE RESPONSE (CR) contains information capable of resolving the CR from the clinical perspective. This document also serves as the basis for communication to Sponsor for potential Clinical Review issues identified during the initial review period.

Conclusion

Following a preliminary review of the major components of this COMPLETE RESPONSE submission, this submission appears to contain information capable of resolving the CR from a Clinical perspective. In addition, the Clinical review team has several Clinical comments for Sponsor (see final section of this memo).

Background (in Brief):

AndroGel 1.62% is a topical gel testosterone product which is to be used for once a day dosing for the treatment of conditions associated with a deficiency or absence of endogenous testosterone. On February 11, 2009, the Sponsor submitted to the Division NDA 22-309. While suitable efficacy was demonstrated, the final recommendation, on March 12, 2010, was that NDA 22-309 be **NOT APPROVED** at that time, and that a **Complete Response** action be taken**.** Studies conducted to assess whether testosterone can transfer to others showed that a T-shirt does not adequately block transfer of a 5gm

dose when applied to both sides of the abdomen (b) (4) [redacted]. The Clinical review team believed that relying principally on washing the application site (in the shower) prior to physical contact with others to prevent transfer of testosterone was problematic in terms of patient compliance. The Clinical review team believed that a simpler, more feasible means, in addition to shower skin washing of the skin application site prior to physical contact, was needed to prevent testosterone transfer to others. The information originally provided by the Sponsor showed that a T-shirt did block transfer at the 2.5gm dose, but the T-shirt barrier did not adequately block testosterone transfer at the 5 gram testosterone gel dosage (abdomen site). A **COMPLETE RESPONSE** action to this unresolved safety concern was advised by the Clinical review team, and we provided the opinion that a CR would entail generating data to show a satisfactory method for the clothing barrier technique. This might require modification in the method(s) of application of larger doses of testosterone gel 1.62% (e.g., application of 2.5gm on the abdomen and 2.5gm on the arms/shoulders). If the dosing method was to be changed (e.g. spreading the larger doses [3.75 gm and 5 gm] out onto both sides of the abdomen and both arms/shoulders), then appropriate PK data to demonstrate testosterone concentrations comparable to those obtained in Study S176.3.104 (where the dosing schema was abdomen *or* arms/shoulders) would also be required.

Prior to the **COMPLETE RESPONSE** action (March 12, 2010) taken by the Division, on January 15, 2009, the Sponsor submitted the final report of Study S176.1.009 which was designed to demonstrate that with 4 site application of AndroGel 1.62 %, transfer of testosterone to others through physical contact was largely prevented by a simple clothing barrier.

The review of Study S176.1.009 was essentially divided into two parts:

1. Did protocol S176.1.009 provide information suitable to conclude that 4 site male anatomic application of 5.0 gm of AndroGel 1.62% when combined with a male T-shirt barrier largely blocked the transfer of testosterone to the bare skin of a female partner when vigorous and prolonged contact occurs?

2. If protocol S176.1.009 did provide suitable information to confirm that transfer was largely blocked by the 4-site application and simple clothing barrier techniques utilized, then was there suitable PK information documenting comparable testosterone exposure in males using the 2 anatomic site versus the 4 anatomic site application method for the 5.0 gm dose of AndroGel 1.62%?

The results of Protocol S176.1.009, with preliminary statistical comparisons, appeared to show no statistically significant differences between Baseline (Day -1) and Day 1 for testosterone concentrations in females after skin contact with males who had applied the product using the 4-anatomic site technique. The data for C_{av}, AUC_{0-24}, and C_{max}

indicated that with the four site application of 5 g of testosterone gel 1.62% in the male, a t-shirt barrier effectively blocked testosterone transfer to an unclothed female.

However, in addressing the second part of this issue, the Phase 3 subgroup that Sponsor used to justify the new dosing recommendation did not apply AndroGel 1.62% in a uniform non-sporadic manner throughout the Phase 3 study, Protocol S176.3.004. The Clinical review team believed that this constituted a post-hoc analysis of a not prespecified group of protocol violators who in addition were not adequately supervised as per protocol. In addition, it was believed that the bioavailability comparisons referring to AndroGel 1% (a different product) were not applicable for reasons stated in the Clinical Pharmacology review. It was the opinion of the Clinical review team and the Office of Clinical Pharmacology that the level of evidence provided in support of the dosing change with regard to comparable exposure to testosterone using AndroGel 1.62% at two sites versus four sites for the 5 g dose was not acceptable and further information was needed to bridge the gap. We stated to Sponsor that a Phase 1, relative bioavailability study would be a reasonable way to bridge the 4 site application to the 2 site application technique for a dose of 5 gm. A COMPLETE RESPONSE action was taken by the Division.

On April 29, 2010, a Type A meeting was held with Sponsor, at which time the content of the Complete Response Letter and what additional studies were planned to formulate a Complete Response was discussed. A Comparative Bioavailability Study (Protocol S176.1.010) was proposed which was intended to characterize the pharmacokinetic parameters of AUC and Cmax for total observed testosterone at steady- state for the two 5 gm dosing regimens as outlined in the Division's complete response letter (application to 4 anatomic sites [right and left upper arms and shoulders] versus the reference [application rotating between abdomen and upper arms/shoulders]). The applicant agreed to present the treatment mean ratios of PK parameters and associated 90% CI for both baseline-corrected and uncorrected total testosterone. A separate 24-hour baseline was to be obtained for each of the treatment periods. Agreement was not reached concerning the acceptable difference between primary parameters of Cmax and AUC that would constitute comparative bioavailability. This would be a review issue.

At the Type A meeting, the Sponsor also proposed a second study, Protocol S176.1.011, which was intended to evaluate the transfer potential for testosterone when healthy males applied 2.5 grams to each upper arm/shoulder area (for a total dose of 5 grams) and then covered the arms/shoulders with a t-shirt. The Division agreed that if this study showed effective blockade to transfer at 2 hours post dose and after 15 minutes of supervised skin contact with a non-dosed female, then we could accept this final study report in the NDA as a complete response to the deficiency in the **COMPLETE RESPONSE** letter.

At the Type A meeting, the Applicant also agreed to assess skin irritation of the new application method used in Protocol S176.1.010 using the same scale as utilized in the pivotal study S176.3.104.

At the Type A meeting, the Applicant requested to submit the final study report for Study S176.3.1004 in the CR. This would include both efficacy and safety results. The Sponsor was also asked to submit in the CR the PSUR covering the worldwide experience on the safety of AndroGel 1% (AndroGel 1.62% is not currently marketed anywhere in the world).

Finally, at a teleconference on 8 September 2010, the Sponsor agreed that the CR would include a brief synopsis of a hand washing study protocol to be conducted under a post-marketing requirement (PMR).

Filing Submission Content and Analysis

The submission contains the following elements:

- Study Report for Protocol S176.1.009: *"An Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-Dosed Females after Secondary Exposure to Testosterone Gel 1.62%."* This is the 4-site, T-shirt study. This study was previously reviewed with a conclusion that the 4-site application of 5 gm largely and acceptably mitigated transfer.

- Study Report for Protocol S176.1.010: *"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). Based on a cursory review, the two regimens appear to show comparable bioavailability, although the 4-site regimen shows slightly lower, but still eugonadal testosterone concentrations. (b) (4)

  This study also contains assessments of skin irritation as requested by the Division and the Office of Clinical Pharmacology.

  Of note, seven subjects in this study (all in the rotating [Phase III] regimen) exhibited at least one testosterone level greater than 2500 ng/dL. (Note: All patients in this study were treated with the 5 gm dose and the to-be-marketed regimen is to start at 2.5 gm and up-titrate as needed).

- Study Report for Protocol S176.1.011: *"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 is the arms/shoulders T-shirt study. The reviewer has not conducted a thorough review yet, but preliminarily this study appears to demonstrate that a T-shirt largely blocks transfer of 5mg when applied

to the arms/shoulders. Nevertheless, based on a cursory review of the individual patient response graphs and T concentration data, there may be a few more patients in this study compared to the 4-site T-shirt study in whom the T concentrations increased modestly from baseline despite a T-shirt.

- Complete Study Report for Protocol S176.3.104. This was the original Phase III pivotal study but now includes data for the 6 – month open-label extension period. Changes made to the previous report were not highlighted. A highlighted version showing all changes to the original study report has been requested. Cursory inspection reveals no new real issues. (b) (4).

- PSURs for AndroGel 1% for 2009 and 2010 plus a bridging report to current submission date: These reports are in the same form as previous PSURs and are adequate for review. AndroGel 1.62% is not marketed anywhere in the world.

- Full Protocol for A Postmarketing Requirement (PMR) Study: This is the hand-washing study. 16 male subjects will apply 5 gm (maximum dose) to upper arms/shoulders using hands. Subjects either wash hands by a designated method (Treatment A: *Wash*) or not (Treatment B: *No Wash*) in a crossover fashion and sampling occurs 2 min after application. Hands will be wiped with 3 ethanol dampened gauze pads (palm, fingers, and back of hand). Data for both hands will be totaled. This protocol follows the Division's general recommendations and is meant to fulfill a post-marketing requirement.

- (b) (4)

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- Proposed REMS (including Medication Guide and follow-up assessment plan)

- Revised IB

- Required CRFs from the 6-month, open-label safety extension of the pivotal Phase III study S176.3.1004 are present as are the CRFs for patients with at least one testosterone concentration greater than 2500 ng/dL in Study 176.1.010.

Reviewer's Comment: The Sponsor has complied with all requirements enumerated in the April 29, 2010, teleconference. The applicant appears to have submitted the requested items necessary for responding to the Complete

Response. The items are in appropriate form and format to allow for an adequate review.

Review Issues and Requests for Additional Information

The following are review issues and requests for additional information from Sponsor. These should be conveyed to Sponsor in a regulatory letter:

1. (b) (4)

2. Seven subjects in the relative bioavailability Study S176.1.010 (all in the rotating regimen) exhibited at least one testosterone level greater than 2500 ng/dL. These patients were all dosed up-front with the highest dose (5 gm). This is a review issue.

3. There may be a few more patients in the arms/shoulders transfer study (Study S176.1011) compared to the 4-site transfer study (Study S176.1.009) in whom the T concentrations increased very modestly from baseline despite a T-shirt. This is a review issue. Please provide a comparative analysis of data from these two transfer studies, including your impression of whether the 4-site T-shirt method is more preventative of secondary exposure compared to the arms/shoulders T-shirt method.

4. (b) (4)

5. The complete study report for Study S176.3.104 does not highlight changes made to the previous report. Please provide a version that highlights the changes from the previous report.

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

/s/

A R WIEDERHORN
12/07/2010

MARK S HIRSCH
12/07/2010
I concur.

IND 50,377 Serial Number 168 (SDN 214) – *New Protocol*
NDA 22-309 Sequence 0026 (SDN 27) – *Sponsor's Proposed Approach to Resolution of Complete Hold*

Medical Officer's Memorandum: New Protocol and Sponsor's Proposed Approach to Resolution of Complete Response Deficiency

Date Submitted:	IND 50, 377: Serial 186 (SDN 214), May 14, 2010 NDA 22-309: Sequence 0026 (SDN 27), May 27 2010
Date Received:	IND 50, 377: Serial 186 (SDN 214), May 17, 2010 NDA 22-309: Sequence 0026 (SDN 27), May 28 2010
Date Memo Completed:	
Product:	AndroGel (testosterone gel) 1.62%
Dose and Route:	1.25 gm – 5 gm, once daily, by topical application
Indication:	For replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone (primary hypogonadism [congenital or acquired] or hypogonadotropic hypogonadism [congenital or acquired])
Reviewer:	A. Roger Wiederhorn MD Division of Reproductive and Urologic Products (DRUP) Mark S. Hirsch MD, Medical Team Leader, DRUP

Background

On March 12, 2010, a Complete Response (CR) letter was issued for NDA 22-309.

In this NDA, the main safety issue was the lack of a simple clothing barrier to prevent secondary exposure of testosterone to females and children who would be in close, physical contact to the user of AndroGel 1.62%. Results from a "transfer study", wherein a total of 5 gm of gel was applied to both sides of the male abdomen and 15 minutes of skin-to-skin contact was required, appeared to demonstrate transfer of some testosterone from the male user to a female partner despite the male user wearing a t-shirt. The

Sponsor responded by demonstrating that transfer was largely mitigated by a t-shirt when the 5 g dose of AndroGel 1.62% was applied to 4 different anatomic sites, including both arms/shoulders and both sides of the abdomen (not just the abdomen alone). Unfortunately, this "4 site" application method differed from the application method used in the Phase 3 Study S176.3.104, in which 5 gm were applied to either both shoulders/upper arms *or* both sides of the abdomen, on a rotating basis, but not to both. The Sponsor was asked to "link" the 4-site method to the Phase 3 method, so that DRUP would be assured that the methods provided comparable efficacy. The Sponsor provided efficacy information from "non-compliant" patients in the Phase 3 study, who erroneously used the 4-site method, rather than the Phase 3 method. However, the Division did not agree that the information provided by the Sponsor to support comparability of testosterone concentrations associated with the new 4-site application method and those associated with the Phase 3 method was sufficient. The Complete Response letter stated that the Sponsor should:

"Conduct and provide a complete report for a steady-state, 2-way crossover, comparative bioavailability study of AndroGel 1.62% in hypogonadal males, evaluating the following two regimens:

1. Application of a 5 gm dose to 2 anatomic sites utilizing the upper arms/shoulders or abdomen on a rotating basis, as per the instructions for use in the Phase 3 Study S176.3.104, versus
2. Application of a 5 gm dose to 4 anatomic sites utilizing both upper arms/shoulders and both sides of the abdomen, as per the instructions for use in Study S176.1.009."

On March 16, 2010, the Sponsor requested a Type A, Post-Action meeting. This combined meeting request/meeting package contained a full clinical study protocol for Study S176.1.010, a proposed comparative bioavailability study comparing the new 4-sire regimen, to the Phase 3 regimen (as requested in the CR letter). The meeting package also contained a protocol *synopsis* for Study S176.1.011, a transfer study employing a dose of 5 gm to the arms/shoulders only. The Sponsor's questions to FDA concerned the design and conduct of the comparative bioavailability study S176.1.010, as well as the potential for the new transfer study S176.1.011 to resolve the CR deficiency on its own.

On April 29, 2010, a Type A, Post-Action meeting was held. The reader is referred to the final meeting minutes dated May 27, 2010 for details. Of note, the Division and Sponsor did not agree upon an acceptable difference in testosterone exposures between the new 4-site method and the Phase 3 method. The Division also asked Sponsor to further clarify the role of the new transfer Study S176.1.011 in the Complete Response.

On May 14, 2010, in Serial Submission 168 to IND #50,377, the Sponsor submitted a final new protocol for Study S176.1.010, the comparative bioavailability study (new 4-site method versus the Phase 3 method).

On May 27, 2010, in Sequence 026 Submission to NDA 22-309, the Sponsor submitted:
1) A proposed approach to approval of AndroGel 1.62%, including the role of new transfer study S176.1.011, and
2) A rationale for "success criteria" in the comparative bioavailability study S176.1.010.

On June 18, 2010, the Division conveyed comments related to the May 27, 2010 submission. We conveyed our agreement that new transfer study S176.1.011 could resolve the CR. We also conveyed a continued lack of agreement with the proposed success criteria for Study S176.1.010. The reader is referred to the letter for additional details.

On June 21, 2010, the Sponsor requested clarification of our June 18, 2010 regulatory letter. The Sponsor requested to know whether we had already drawn conclusions from the submitted headline results from the new transfer study S176.1.011 (which was completed), and why we didn't agree with the proposed success criteria for the comparative bioavailability study S176.1.010.

On July 13, 2010, the Division conveyed another regulatory letter with responses to the June 21, 2010 questions from Sponsor. The Division stated that we had no yet drawn conclusions from the new transfer study S176.1011 headline results, and that our major concern regarding the proposed success criteria was that the proposed % difference between application methods allowed for a substantive difference between the two treatment groups which could result in very high, potentially unsafe upper confidence limits for mean testosterone exposure. The reader is referred to the letter for additional details.

Thus, the Sponsor is exploring several options to resolve the CR issue. One method proposed by the Sponsor is through a demonstration that a t-shirt largely mitigates transfer when 5 gm is applied to the arms/shoulders only. Thus, they conducted new transfer Study S176.1.011. The arms/shoulders only method used in the new transfer study would fall within the application method used in the Phase 3 study S176.3.104. The new transfer study evaluated the transfer potential for the 1.62% testosterone gel when healthy males applied 2.5 grams to each upper arm/shoulder area (total dose 5 gm) and then covered the application site with a t-shirt. At two hours post-dose, 15 minutes of supervised skin contact occurred with a non-dosed female.

The purpose of this memo is two-fold:
1) To review the Sponsor's proposed approach to resolution of the CR and their rationale for the currently proposed "success criteria" for the comparative bioavailability study protocol (Study S176.1.010)), submitted on May 17, 2010.
2) To review the new comparative bioavailability study protocol (Study S176.1.010), submitted on May 14, 2010 (and ongoing).

Since the new transfer study Study S 176.1.011 has been completed, "headline results" are discussed in this memo. The reader should also be aware that first dosing for the comparative bioavailability Study S 176.1.010 occurred 19 May 2010, and this study may

already be completed. This memorandum will discuss these two studies and their effect in resolving the deficiency noted in the CR letter.

Medical Officer's Review

Sponsor's Proposed Approach to Resolution of the CR and Their Rationale for the Currently Proposed "Success Criteria" for the Comparative Bioavailability Study protocol (Study S176.1.010) – submitted on May 27, 2010 as Sequence 0026 to NDA 22-309

Part 1: Sponsor's Proposed Approach to Approval of AndroGel 1.62% (to Resolve the CR)

The Sponsor has conducted two clinical studies to address the deficiency in the AndroGel 1.62% application. The studies are:

- **Study S176.1.010** "A Multiple Dose Pharmacokinetic and Comparative Bioavailability Study of Testosterone Absorption after Administration of 5 g Testosterone Gel l.62% to the Upper Arms/ Shoulders using an Application Site Rotation or a Combination of Application Sites in Hypogonadal Males."
  This study will determine the relative bioavailability of observed and baseline-adjusted testosterone after administration of 5 g Testosterone Gel 1.62% using an application site rotation between the upper arms/shoulders and abdomen or combination of the upper arms/shoulders and abdomen application sites. The first dosing for this study occurred 19 May 2010. The protocol for this study was submitted to the FDA (SDN 214 IND 50,377) May 14, 2010 and received by the FDA 17 May 2010. This protocol is reviewed later in this memorandum.

- **Study S176.1.011** "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 study evaluated the potential for testosterone transfer from 12 males dosed on each upper arm/shoulder with Testosterone Gel 1.62% (5 g) to non-dosed female subjects when contact with the upper arms/shoulders application site occurs at 2 hours post-dose with a T-shirt barrier. Dosing and contact for all subjects for this study took place on 5 May 2010 (12 male female couples). Headline results from this trial are discussed herein.

Headline Results from the new Transfer Study, S176.1.011

In their presentation of headline results, the Sponsor presents differences in C_{av} and C_{max} between Day -1 and Day 1 for female subjects in Study S176.1.011. Day -1 is baseline and Day 1 represents T concentrations after supervised contact with a male using AndroGel 1.62% and wearing a t-shirt. The differences in means between Day -1 and

Day 1 is < 4 ng/dL for each parameter. The mean percent change from Baseline (Day -1) to Day 1 is 19% for C_{max} and 7% for both C_{av} and AUC_{0-24}.

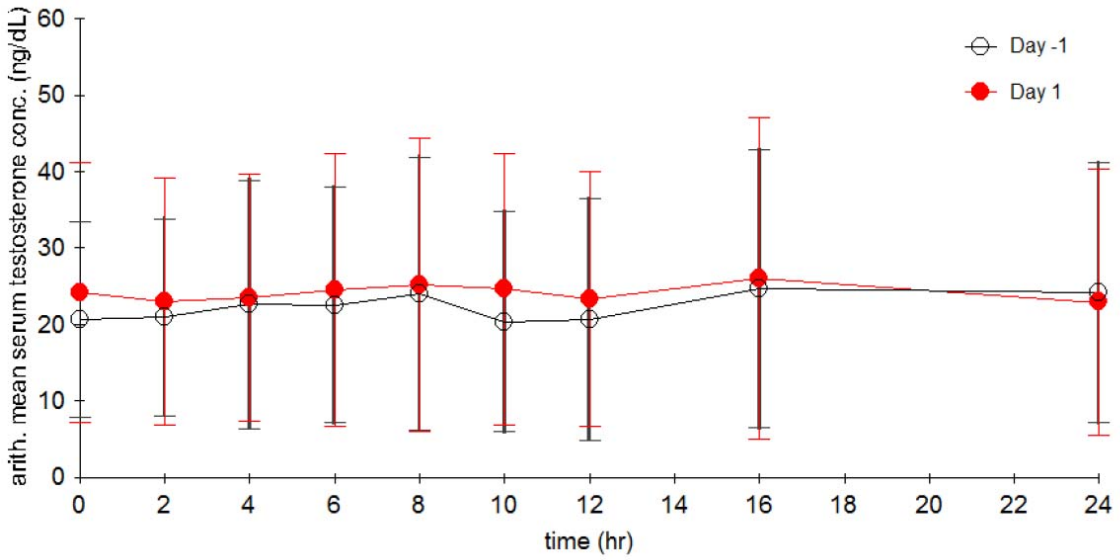
Table 1: Differences in C_{av} and C_{max} between Day-1 and Day 1 for female subjects in Study S176.1.011

	Cmax (ng/dL)				Cav (ng/dL)			
	Day -1	Day 1	Difference	% Change	Day -1	Day 1	Difference	% Change
Mean	26.3	29.9	3.6	19.2	22.8	24.2	1.4	7.3
Median	19.9	24.8	2.4	7.3	17.1	17.2	0.6	3.9
SD	18.1	19.9	5.5	36.2	16.1	17.9	3.3	14.9

Source: Table 1: Copy of page 2 in Sequence 0026 submission to NDA 22-309

The Sponsor also presents a graphic illustration of the mean changes in testosterone concentration for female subjects as a time profile for Day -1 and Day 1. The mean baseline testosterone concentrations are approximately 20 ng/dL for Day -1 and approximately 23 ng/dL for Day 1. The increases in testosterone concentrations overtime are minimal when comparing Day -1 and Day 1 as shown in the figure below:

Figure 1: Mean Testosterone Concentration-Time Profile for Day -1 and Day 1



Source: Figure 1: Copy of Figure 1 on page 2 of Sequence 0026 submission to NDA 22-309

The differences between Day -1 and Day 1 in C_{av} and C_{max} by individual subject are presented in Table 2 below:

Table 2: Differences in C_{av} and C_{max} by subject

Subject	Cmax (ng/dL)				Cav (ng/dL)			
	Day -1	Day 1	Difference	% Change	Day -1	Day 1	Difference	% Change
27571	56.3	58.9	2.6	4.6	49.3	48.8	-0.5	-1.0
27572	63.6	74.5	10.9	17.1	57.1	67.3	10.2	17.9
27573	32.4	32.4	0	0.0	28.1	28.2	0.1	0.4
27574	13	10.9	-2.1	-16.2	11.1	9.86	-1.24	-11.2
27575	36.6	40.9	4.3	11.7	31.1	33.4	2.3	7.4
27576	21.2	19.5	-1.7	-8.0	17.5	16.8	-0.7	-4.0
27577	13.1	15.9	2.8	21.4	11.7	13.4	1.7	14.5
27578	28	30.1	2.1	7.5	22.6	22.1	-0.5	-2.2
27579	8.42	15	6.58	78.1	7.38	9.09	1.71	23.2
27580	9.43	10.1	0.67	7.1	8.01	9.13	1.12	14.0
27581	18.6	18.6	0	0.0	16.7	15	-1.7	-10.2
27582	15.5	32	16.5	106.5	12.6	17.5	4.9	38.9
Mean	**26.3**	**29.9**	**3.6**	**19.2**	**22.8**	**24.2**	**1.4**	**7.3**
Median	**19.9**	**24.8**	**2.4**	**7.3**	**17.1**	**17.2**	**0.6**	**3.9**
SD	**18.1**	**19.9**	**5.5**	**36.2**	**16.1**	**17.9**	**3.3**	**14.9**

Source: Copy of Table 4 on page 17 of Sequence 0026 submission to NDA 22-309

The largest increase in C_{av} for an individual subject was 10.2 ng/dL (Subject #27572). This subject's predose concentration was increased approximately 12 ng/dL between Day -1 and Day 1. According to the Sponsor, the Day 1 increase in C_{av} for this subject can be explained by an increase noted prior to contact with the male user on Day 1. This subject also had the only reported testosterone concentration in the protocol above the upper limit of the normal female range (81.2 ng/dL, on Day 1 at 3 hours).

The largest increases in Cmax were 10.9 ng/dL (Subject #27572) and 16.5 ng/dL (Subject #27582). The increased Cmax for Subject #27572 may be related to an increase prior to skin contact procedures. The Cmax for Subject #27582 occurred at the 6 hour post contact timepoint. However, the remaining concentrations in this subject's testosterone PK profile on Day 1 were similar to her Baseline (Day-1) concentrations for all other post contact timepoints. All concentrations for these two subjects remained in the normal female range for testosterone (8-75 ng/dL).

The Sponsor next compares the ratios of C_{av}, AUC_{0-24}, and C_{max} For Day1 and Day-1 as shown in Table 3 below:

Table 3: Comparison of Ratios for Day1/Day-1 for Study S176.1.011

Parameter	Ratio Day 1/Day -1	90% CI	95% CI
Cav	1.064	0.992, 1.141	0.976, 1.159
AUC0-24	1.065	0.993, 1.142	0.977, 1.160
Cmax	1.151	1.006, 1.318	0.976, 1.358

Source: Copy of Table 2 on page 3 of Sequence 0026 submission to NDA 22-309

The C_{av} and AUC_{0-24} point estimate ratios for Day 1/Day-1 and the 90% and 95% confidence limits, in the Sponsor's opinion, were not significantly different between the two days.

> *Reviewer's Comment: These headline results appear to show that the ratios for Day 1/Day-1 for C_{av}, AUC_{0-24}, and C_{max} fall within a CI limit of 80 to 125 % (bioequivalence limits). The 95% CI for C_{avg} and AUC_{0-24} also appear to fall within 80 to 125% and are close to falling within that limit for C_{max}. However, a comparison between groups for a strict evaluation of bioequivalence is not by ratio but rather by CI for the geometric means of the two regimens.*

Estradiol concentrations in the pharmacokinetic samples were also measured (and will be included in the CSR in the CR), the Sponsor concluded that the 12 hour blood sample on Day 1 may have been switched between Subjects #27579 and #27581 at the clinical site. No other compliance or biopharmaceutics issues were identified. The Sponsor is continuing to investigate this matter. Additional pharmacokinetic/statistical analysis was subsequently conducted in which the 12 h samples for the affected subjects were treated as missing, or as if the testosterone concentrations had also been switched. The Sponsor states that the results of both these analyses show that there is no change with regard to statistical conclusions. The Sponsor presents their reanalysis with the Day 1, 12 hour testosterone concentrations excluded for Subjects #27579 and #27581 as shown in Table 4 below:

Table 4: Comparison of Ratios for Day1/Day -1, 12 hour concentrations on Day 1 excluded for 27579 and 27581

Parameter	Ratio Day 1/Day -1	90% CI	95% CI
Cav	1.061	0.996, 1.131	0.982, 1.147
AUC0-24	1.062	0.997, 1.131	0.983, 1.148
Cmax	1.111	0.990, 1.246	0.965, 1.279

Ratios and CI are based on the ln-transformed data

Source: Copy of Table 6 on page 19 of Sequence 0026 submission to NDA 22-309

> *Reviewer's Comment: When the study results are submitted in their entirety and our comprehensive review is conducted as part of the Response to CR, we will assess the effect of this issue (purported erroneous switching of the 12 hour estradiol samples between Subjects #27579 and #27581) on the overall conclusions.*

The preliminary safety results suggest that no subjects (0/24) exposed to the study drug directly or through skin contact reported any adverse events throughout the course of this single-dose transfer study. There were no withdrawals due to AEs, no serious adverse events (SAEs) and no deaths reported in the headline results. There were no clinically significant abnormalities reported amongst the headline results for vital signs, application site evaluations, clinical laboratory parameters or ECG evaluations.

> ***Reviewer's Overall Comments in Regard to the Headline Results from the new Transfer Study S176.1.011****: If the headline results are confirmed by the review team's thorough analysis of the data in the CR, it would appear that a T-shirt barrier effectively blocks testosterone transfer when a 5 g dose of Testosterone Gel 1.62% is applied to both arms/shoulders. This result alone, if found to be accurate upon analysis of all data, would address the CR deficiency in the AndroGel 1.62% application.*

Part 2: Sponsor's Proposed "Success Criteria" for the Ongoing Comprative Bioavailability Study S176.1.010 and Supporting Rationale (Including a Brief Review of the Study Protocol)

Brief Review of the Study Protocol for Ongoing Study S176.1.010, entitled, "*A Multiple Dose Pharmacokinetic and Comparative Bioavailability Study of Testosterone Absorption after Administration of 5 g Testosterone Gel l.62% to the Upper Arms/ Shoulders using an Application Site Rotation or a Combination of Application Sites in Hypogonadal Males*".

The first dosing for this study occurred on May 19, 2010. The objectives of this study were:

- To determine the multiple dose testosterone pharmacokinetics after administration of 5 g of Testosterone Gel 1.62% in hypogonadal males.
- To determine the relative bioavailability of observed testosterone after administration of 5 g Testosterone Gel 1.62% using an application site rotation between the upper arms/shoulders and abdomen versus a combination of the upper arms/shoulders and abdomen application sites.

The study was an open-label, randomized, two period, two treatment, crossover study in hypogonadal male volunteers, and it was to be conducted at one or more centers in the US. Forty subjects were to be enrolled to allow at least 36 subjects to complete the treatment.

Two treatments were to be administered as follows:

- Treatment A: Once daily application of Testosterone Gel 1.62% to the abdomen for 3 days (2.5 g to each the right and left sides of the abdomen) followed by application to the upper arms/shoulders (2.5 g to each the right and left upper arm/shoulder) for 4 days. The total daily gel dose would be 5 g.

Reviewer's Comment: This is the reference therapy and is representative of dosing used in the Phase 3 Study S176.3.104.

- Treatment B: Once daily application of Testosterone Gel 1.62% to a combination of the upper arms/shoulders and abdomen for 7 days. The total daily gel dose would be 5 g consisting of 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 1.25 g applied to the right abdomen.

Reviewer's Comment: This is the new "4-site" application method.

The inclusion criteria included:

- Documentation of written informed consent
- Male subjects, 18-80 years of age, inclusive
- Serum testosterone < 300 ng/dL. Documented lab result showing hypogonadism may be obtained during screening visit, within 6 weeks of Day-2 for subjects not currently on androgen replacement therapy, or following washout of androgen replacement therapy in subjects currently on androgen replacement therapy.
- Subjects naïve to androgen replacement, or washout of 16 weeks following intramuscular androgen injections; 4 weeks following topical or buccal androgens; and 3 weeks following oral androgens.
- Subjects with Body Mass Index (BMI) of 20-35 kg/m^2, inclusive.
- In the opinion of the investigator, the subject is determined to be in good health as determined by vital signs, medical history, physical exam, ECG, and laboratory examination (hematology, clinical chemistry, and urinalysis).

The exclusion criteria included:

- Participants in any investigational drug trial within the previous 30 days.
- Receipt of any prescription medication within 21 days prior to Day -2 of the study, or receipt of non-prescription (OTC) medication within 7 days of Day -2 without sponsor approval. Volunteers on a stable medication regimen (>3 months) for hypertension, hyperlipidemia, blood glucose control, or other conditions will be evaluated on a case by case basis.
- Blood or plasma donation within the 60 days prior to study entry.
- Subjects with any clinical-biochemical impairment of liver function or receipt of known hepatic enzyme inducing or inhibitory agents within 60 days prior to Day -2.
- Use of any drug with a half-life greater than 24 hours in the past 6 months without Sponsor approval.
- Volunteers who are smokers or ex-smokers who have quit smoking for a period of less than 12 months prior to Day -2.
- Consumption of caffeine-containing products or beverages in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day-2 (caffeine-containing products were not allowed during each study period).

- Findings of any kind of lesions (e. g. ulcer, erosion, lichenification, crust, inflammation) on the skin surface of the upper arms/shoulders during physical examination (small tattoos are acceptable).
- Previous history of, or current or suspected, prostate or breast cancer.
- Untreated prolactinoma.
- Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
- Previous history of, or current or suspected, prostate or breast cancer.
- Abnormal digital rectal examination (DRE) defined as presence of nodule or induration. Prostate enlargement consistent with BPH is not itself an exclusion criteria.
- International Prostate Symptom Score (IPSS) > 15.
- Baseline Prostate Specific Antigen (PSA) >2.5 ng/mL. If the subject has documentation of a negative prostate biopsy within the past six months, a PSA of 2.6 – 3.74 ng/mL will be allowed.
- Positive screen for alcohol or drugs of abuse.
- Positive HIV or Hepatitis B/C.
- Hematocrit > 48% or hemoglobin >16 g/dL.
- Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.

The Criteria for Evaluation included:

Pharmacokinetics: Whole blood samples (6 mL) would be collected for determination of total testosterone, dihydrotestosterone, and estradiol for the following times:

Day -1 and Day 14 (baseline for Periods 1 and 2, respectively) at: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours with respect to the projected time of administration.

Days 7 and 21 (endpoints for Periods 1 and 2, respectively) at: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post dose administration.

Days 5, 6, 19, 20 at: predose.

C_{max}, C_{av}, T_{max}, and AUC_{0-24} will be calculated for observed and baseline-adjusted testosterone.

Safety: Screening assessments included medical history, vital signs, 12 lead ECG, physical examination (including weight and height), clinical laboratory determinations (including testosterone and PSA measurement), DRE and IPSS. Final assessments included physical examination (including weight), vital signs, 12-lead ECG, clinical laboratory determinations (including PSA measurement), DRE and IPSS, and application site evaluation. Throughout the study vital signs, application site evaluation, adverse events and concomitant medications were to be monitored.

The Statistical Methods included the following:

For pharmacokinetic analyses: The statistical objectives of this study were to evaluate the comparative bioavailability of observed testosterone after administration of 5 g Testosterone Gel 1.62% when applied using a rotation between the upper arms/shoulders and abdomen ("Treatment A") versus using a combination of both the upper arms/shoulders and the abdomen after multiple dosing ("Treatment B"). Relative bioavailability comparisons were to be based on ratios of C_{max} and AUC_{0-24}. The reference treatment for comparison is Treatment A.

Comparisons of Treatment B to reference Treatment A would be made for both observed and baseline- adjusted testosterone within the framework of a linear mixed effects model with treatment, period, and sequence as fixed effects and subject within sequence as random effect. A separate baseline was to be determined for each treatment period. Assessment parameters were to be log-transformed prior to analysis, and for the baseline adjusted parameters, the log-transformed baseline value would be included in the model as a covariate. A non-parametric analysis would be performed if the assumption of the parametric approach was not supported by the data. Inter and intra subject CVs and 90% confidence intervals for the ratios of test: reference would be provided.

Sample size: Based on data from a previous Solvay study that assessed application site pharmacokinetics of the upper arms/shoulders compared to the abdomen (Study S176.1.007), assuming a mean C_{av} of 700 ng/dL and standard deviation of 347 ng/dL, then 34 subjects would give 90% power to detect a 40% difference between application sites and 80% power to detect a 35% difference at the two-sided 0.05 significance level. Thus, the Sponsor stated that 36 subjects would provide reasonable power to characterize the relative bioavailability of the different application regimens. The Sponsor planned to enroll 40 male hypogonadal male subjects with the expectation that at least 36 subjects would complete the full trial.

Sponsor's Proposed "Success Criteria": The Sponsor proposes the following "success criteria", and rationale for those success criteria:

- *Sponsor's Proposed Success Criteria*: The two methods of drug application (upper arms/shoulders versus upper arms/shoulders and abdomen) would be considered "similar" if the observed ratio of AUC of testosterone for the test method versus the reference method (T/R) was within a range of **0.7 to 1.43** and the ratio of observed C_{max} of testosterone for the T/R was within a range of **0.65 to 1.54**. The Sponsor stated that the point estimates for the ratios would be based on the geometric means of the relevant pharmacokinetic (PK) parameters.

- The Sponsor stated that to achieve a study with higher power would require a large number of hypogonadal males that may not be feasible to assemble for a phase 1 confinement bioavailability study (e.g., upwards of 85 subjects to detect a difference smaller than 40%). The Sponsor further stated that if the true

difference between reference and test treatments turns out to be "small", then sizing the study to achieve sufficient power to detect a difference < 40% would be irrelevant.

- Information supporting the *Sponsor's Rationale for the Proposed Success Criteria* included the following:
    - Study S176.1.007 demonstrated a 40% difference in bioavailability when comparing application of the product to both the right and left upper arms and shoulders versus application to both left and right abdominal application. Nonetheless, it was acceptable in the Phase 3 study to use either the arms/shoulders or the abdomen on any given day (a rotation between arms/shoulder and abdomen was encouraged).

    - Study UMD-96-012 showed a 20 to 30% difference in testosterone levels when comparing 4 application sites versus 1 application site for AndroGel 1%, and the Division considered this difference clinically irrelevant in NDA 21-015 for AndroGel 1%.

    - The Sponsor cites a wide therapeutic index for testosterone.

    - The Sponsor cites the ability to titrate the dose of AndroGel 1.62%.

    - The Sponsor cites the high coefficient of variation for testosterone results observed in the pivotal Phase 3 Study S176.3.104 for AndroGel 1.62%.

Reviewer's Comment: At the April 29 teleconference, both Clinical and Clinical Pharmacology review teams expressed the concern that the Sponsor's proposed T/R ratios (their proposed "success criteria") for both AUC (0.7 to 1.43) and Cmax (0.65 to 1.54) were too broad. The major concern regarding these proposed "success criteria" was that the proposed % difference between application methods allowed for a substantive difference between the two treatment groups which could result in very high, potentially unsafe upper confidence limits for mean testosterone exposure. None of the information provided by Sponsor to support their proposed success criteria (open bullet items above) resolve this concern. Ultimately, the Division will need to review the entirety of the data from Study S176.1.010, including data on testosterone "outliers" and make a decision as to whether the two treatment show "comparable" bioavailability.

***Reviewers Overall Comments in Regard to the Comparative Bioavailability Study S176.1.010**: The study is ongoing now and is safe to proceed. In general, the study is appropriately designed to achieve its objectives. A larger sample size would have provided appropriate power to detect a difference between groups of < 40%. The Clinical and Clinical Pharmacology review teams do not agree with the Sponsor's proposed "success criteria" for this study because the proposed % difference between application methods allowed for a substantive difference between the two treatment groups which could result in very high, potentially*

unsafe upper confidence limits for mean testosterone exposure. This lack of agreement had been conveyed to the Sponsor on several occasions, both via teleconference and via regulatory letter.

Sponsor's Proposed Approach to Resolution of the Complete Response Deficiency

It is not yet entirely clear the exact strategy that Sponsor will use to resolve the CR deficiency. The Sponsor proposes to provide the following major pieces of Information as part of their Complete Response submission:

- A final study report for the new transfer study S176.1.011.
- Either a final study report, or just the safety data, from the comparative bioavailability study S176.1.010
- A final study report for S176.3.104, including the open-label extension part of this Phase 3 study
- Updated PSUR(s) for the AndroGel 1% product.

Reviewer's Comment: At the April 29, 2010 teleconference, the Division noted that there appear to be two different pathways that the applicant was proposing to take to resolve the CR deficiency:
1) Resolving the CR with the results from the new transfer Study S176.1.011, on their own, or
2) Resolving the CR using data from the comparative bioavailability Study S176.1.010 to link the mew 4-site application method to the Phase 3 rotating (2-site) method.
The Division recommended that the Sponsor should decide which pathway to take prior to submission of the CR, and make that clear in the CR submission. It would appear that the Applicant has chosen to use both studies, with S176.1.011 as the primary study to resolve the CR deficiency, and S176.1.010 as a "backup".

ADDENDUM

As described in the Background section of this memo, the Division conveyed a general advice letters to Sponsor on June 18, 2010 and on July 13, 2010. The Background section of this memo describes the Division's comments in those letters. The reader is referred to those letters for details.

In brief, the letters conveyed the following major points:

- The S176.1.011 transfer study could serve as the primary pathway to approval based upon the proposition that a method of application exists (arms/shoulders only) which fulfills the efficacy requirement and also might allow for use of a t-shirt barrier to prevent transfer. This decision was not based upon a review of the study's headline results.

- The Division cannot currently agree that the headline study data from S176.1.01 demonstrate prevention of transfer. That will be a review matter.

- Rather than agreeing to any "success criteria", the Division prefers to review the entirety of the data from S176.1.011 upon submission of the study report in the Complete Response (CR). The focus of the Division's review will be the ratio of the geometric mean AUC and Cmax for the two treatment regimens, and the 90% confidence limits for that ratio. The major concern of the Division is that the proposed % difference allows for substantive difference between the two major treatment regimens for mean exposure (AUC and Cmax), which could result in very high, potentially unsafe, upper confidence limits.

- In the event that the Division does ultimately agree that the new transfer S176.1.011 shows no evidence of transfer, then S176.1.010 would become more of a safety study. The Division considers it a reasonable approach to provide the final report for new transfer Study S176.1.011 in the CR as a primary pathway forward for approval, and the report for study S176.1.010 in the CR as a pathway forward in the event that S176.1.011, after our review, is believed to demonstrate transfer. If the Sponsor decides to respond to the CR using the data from new transfer Study S176.1.011 as the *only* pathway forward, then the Sponsor still must submit safety results from S176.1.010 as part of the CR.

Recommended Regulatory Action:

The responses to follow-up questions in Abbott's May 27 submission were conveyed to the Sponsor in a General Advice Letter 12 July 2010. Therefore no further regulatory action is indicated. This memo is being filed to document the events that followed the NDA action and preceded the submission of the CR.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-50377	ORIG-1	ABBOTT PRODUCTS INC	ANDROGEL (TESTOSTERONE)
NDA-22309	GI-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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

/s/

A R WIEDERHORN
08/04/2010

MARK S HIRSCH
08/05/2010
I concur.

Summary Review for Regulatory Action

Date	March 11, 2010
From	George S. Benson, MD
Subject	Division Deputy Director Summary Review
NDA/BLA # **Supplement #**	22-309
Applicant Name	Solvay Pharmaceuticals, Inc.
Date of Submission	February 11, 2009
PDUFA Goal Date	March 12, 2009 (following three month extension)
Proprietary Name / **Established (USAN) Name**	AndroGel 1.62% Testosterone gel
Dosage Forms / Strength	Multi-dose pump which delivers 1.25 grams of testosterone gel with each depression
Proposed Indication(s)	Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Action	Complete response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Roger Wiederhorn, MD
Statistical Review	Mahboob Sobhan, Ph. D.
Pharmacology Toxicology Review	Jeffrey Bray, Ph.D. Lynnda Reid, Ph.D.
CMC Review	Hitesh Shroff, Ph.D. Donna Christner, Ph.D. Moo Jhong Rhee, Ph.D.
Microbiology Review	Robert Mello, Ph.D. Bryan Riley, Ph.D.
Clinical Pharmacology Review	Sandhya Apparaju, PhD Myong Jin Kim, PharmD Edward D. Bashaw, PharmD
DDMAC	Janice Maniwang, PharmD, M.B.A. Carrie Newcomer, PharmD
DSI	Xikui Chen, Ph.D. C.T. Viswanathan, Ph.D. Martin Yau, Ph.D.
CDTL Review	Mark Hirsch, MD
OSE/DMEPA	Lori Cantin, RPh Kristina Arnwine, PharmD Denise Toyer, PharmD Carol Holquist, RPh Maria Wasilik
OSE/DRISK	(REMS) Shawna Hutchins, BSN,RN Claudia Karwoski, PharmD (Medguide) Melissa Hulett, MSBA,BSN,RN LaShawn Griffiths, MSHS-PH, BSN,RN Mary Willy, Ph.D.
OCS	James Tolliver, Ph.D. Silvia Calderon, Ph.D. Michael Klein, Ph.D. Corrine Moody
Project Management Staff	Jeannie Roule Jennifer Mercier

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction
2. Background
3. Chemistry, Manufacturing, and Controls
4. Nonclinical Pharmacology/Toxicology
5. Clinical Pharmacology/Biopharmaceutics
6. Clinical Microbiology
7. Efficacy – Clinical/Statistical
8. Safety
9. Advisory Committee Meeting
10. Pediatrics
11. Other Relevant Regulatory Issues
12. Labeling
13. Decision/Action/Risk Benefit

1. Introduction

AndroGel (testosterone gel) 1% was approved (NDA 21-015) for the indication of testosterone "replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone" in February, 2000. NDA 22-309 for AndroGel 1.62% (testosterone gel 1.62%) was submitted on February 11, 2009. This new formulation has a lower volume of application and (b) (4) compared to Androgel 1%.

Two testosterone gels, AndroGel 1% and Testim, are currently approved for testosterone replacement therapy in men. A variety of other dosage forms and routes of administration of testosterone including intramuscular injection, testosterone implants, buccal tablets, and transdermal patches are also approved for this indication.

The transfer of testosterone gel products from patients to others (particularly children) has been recognized as a significant safety concern. An Advisory Committee meeting regarding this issue was held on June 23, 2009. Both AndroGel 1% and Testim currently have black box warnings and Medication Guides relating to the increased awareness of secondary exposure of children to testosterone gels.

Because the initial "transfer study" demonstrated that AndroGel 1.62% (at the 5 gram dose) could be transferred to others through clothing, the sponsor submitted an additional transfer study utilizing additional application sites. In addition, data were submitted which the sponsor believes demonstrated that the testosterone pharmacokinetics (PK) were comparable between the original two site application regimen and a new three and four site application regimen. A three month review extension was granted to allow review of these additional data.

This review focuses on the single primary Phase 3 study (S176.3.104) as well as the Phase 1 studies which deal with the drug transfer issue and the comparability of testosterone PK when multiple application sites are utilized.

2. Background

All studies for AndroGel 1.62% were conducted under IND #50,377 which was the original AndroGel 1% IND. The opening study for AndroGel 1.62% was a Phase 1 multiple dose pharmacokinetic study which was submitted by the Sponsor on August 25, 2005.

The Division agreed at the EOP2 Meeting on October 18, 2006, that a single Phase 3 study evaluating the efficacy and safety testosterone gel 1.62% (in addition to the Phase 1 safety studies) would be sufficient for NDA submission.

(b) (4) also served as the laboratory for most of the Phase 1 studies and the Phase 3 (S176.3.104) study evaluating the safety and efficacy of AndroGel 1.62% in hypogonadal men. Analytes specifically affected included testosterone, dihydrotestosterone, estradiol, and sex hormone-binding globulin.

A meeting between the Division and Solvay was held on August 13, 2008, to discuss the (b) (4) issue as it related to the analytes for the AndroGel 1.62% trials. 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 (b) (4) (b) (4).

A Pre-NDA meeting was held on January 21, 2008, and NDA 22-309 was submitted on February 11, 2009. During review of the phase 1 "transfer studies," it was noted that a T-shirt adequately blocked transfer of the 2.5 g dose, but not the 5g dose, applied to two sites on the abdomen. The sponsor subsequently submitted data from an additional "transfer study" utilizing 4 sites (5.0 g dose applied to 2 abdominal and 2 shoulder sites) and additional data which the sponsor believes demonstrate PK comparability between

applying 5 g of the gel to either 2 abdominal sites or 4 sites (2 abdominal and 2 shoulder). A three month PDUFA goal date extension was granted to allow review of these additional data. The new PDUFA goal date is March 12, 2010.

3. CMC/Device

The CMC reviewer concluded that "This NDA has now provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities are in compliance with cGMP. Labels/labeling have required information. Therefore, from the CMC perspective, this NDA is recommended for "Approval."

"The Office of Compliance has completed site inspections of all facilities and issued an overall "Acceptable" recommendation."

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer concluded that "nonclinical data support approval."

Comment: I agree with the pharmacology/toxicology reviewer that, other than completing labeling, there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Following initial review of clinical pharmacology data (including efficacy data from phase 3 study S176.3.104 as well as transfer and washoff studies 1.003, 1.008, and 1.005), the clinical pharmacology review team concluded that "NDA 22-309 is acceptable from a Clinical Pharmacology perspective provided an agreement can be reached with the sponsor with respect to the labeling language."

Study 1.003 had demonstrated that clothing (T-shirt) did not adequately block transfer of the 5.0 gram dose applied to two abdominal sites to a female partner. Study 1.008 demonstrated that washing the application site (via showering) did prevent transfer. The clinical review team did not believe that the transfer risk could be adequately labeled and, therefore, adequately mitigated by requiring showering prior to contact with others because they believe that this is an unrealistic expectation. These concerns were communicated to the sponsor in a teleconference held with the Division on October 1, 2009. In this meeting, the sponsor expressed their interest in conducting a new transfer study to evaluate whether spreading out the gel on multiple sites (i.e. both upper arms/shoulders and both sides of abdomen, instead of either site alone) would minimize transfer potential. The Division acknowledged the sponsor's proposal but also noted that even if the new application instructions proved successful in preventing transfer further information may be needed to link the existing safety and efficacy data derived from trial

S176.3.104 to the new mode of administration (3 or 4 site administration versus 1 or 2 sites).

On November 9 and December 8, 2009, the Division received the November 6 and 24, 2009, major amendments to this application which contained additional clinical and clinical pharmacology safety information pertaining to a new transfer study and rationale associated with the applicability of completed clinical trial data to the new dosing instructions.

The additional transfer study (1.009) showed that the transfer risk was mitigated by applying the 5.0 gram dose to four sites (both sides of the abdomen and both shoulders/arms) (b) (4) The question of comparability of testosterone serum levels between 2 site versus 3 or 4 site application was raised. The sponsor submitted PK data from protocol violators in phase 3 study S176.3.104 who applied the testosterone gel to multiple sites. The sponsor believes that these data support the comparability of testosterone serum levels whether a given dose of the drug is applied to 2, 3, or 4 sites.

In addition to transfer study 1.009, the potential for transfer of testosterone from men using testosterone 1.62% gel to non-dosed female partners was evaluated in two phase 1 studies (1.003 and 1.008). In addition, the effect of washing on removing residual testosterone on the skin was evaluated in study 1.005 using tape stripping analysis. These transfer and "wash off" studies are further discussed below.

Study 1.003:

This study was an open-label study of healthy male and female couples (16 couples per treatment cohort). In each treatment cohort, each man applied 5.0 g testosterone gel 1.625 to his abdomen once daily for seven days.

Three treatment cohorts were studied:

A. Direct skin contact of male and female occurred two hours post-dose (no t-shirt covering application site).
B. Contact occurred two hours post-dose with the male wearing a t-shirt
C. Direct skin contact of male and female occurred twelve hours post-dose (no t-shirt covering application site).

Serum testosterone levels over a 24 hour period for PK assessment were obtained from each female at baseline (Day -1) and beginning at the end of the 15 minute contact period on Day 1 and Day 7. No PK data were obtained from the male partners.

The mean testosterone PK parameters in the female partners are shown in Table 1.

Table 1: Mean (% CV) observed testosterone pharmacokinetic parameters in female volunteers in each of the treatment groups and days of transfer evaluation study S176.1.003

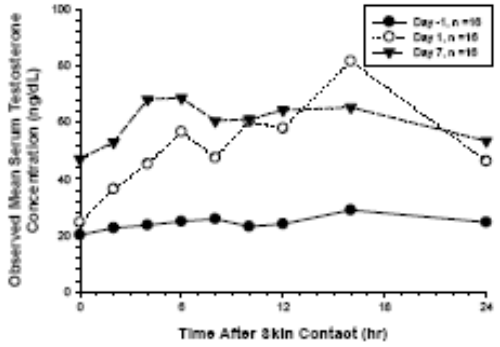
		Trt A	Trt B	Trt C
C_{max}	Day -1	30.75 (39 %)	29.7 (57.5 %)	32.6 (65 %)
	Day 1	77.7 (44 %)	49.2 (68.5%)	85 (75 %)
	Day 7	88.1 (41 %)	51.4 (66 %)	68.6 (66 %)
C_{avg}	Day -1	25.5 (39%)	23.8 (57.6%)	26.2 (62 %)
	Day 1	52.8 (47 %)	34.4 (57.2%)	62.4 (71 %)
	Day 7	61.7 (33.5 %)	38.9 (60 %)	50 (69 %)
AUC	Day -1	611 (39 %)	573 (57 %)	631 (62 %)
	Day 1	1245 (47%)	812 (57 %)	1475 (71 %)
	Day 7	1454 (34 %)	918 (60 %)	1174 (69 %)

A: direct contact at 2h post-dose; B: contact at 2 h post-dose /T-shirt on male; C: direct contact at 12 h post-dose

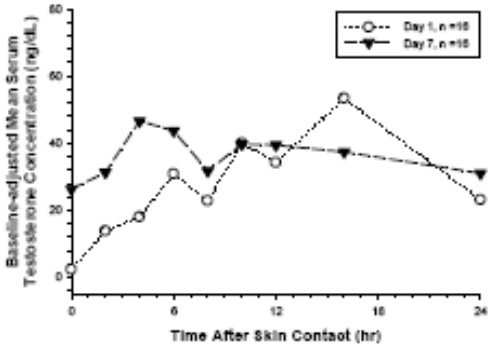
Figure 1 summarizes the observed and baseline-adjusted testosterone concentration-time profiles within the three treatment groups:

Figure 1. Observed and baseline-adjusted testosterone concentration-time profiles within the three treatment groups.

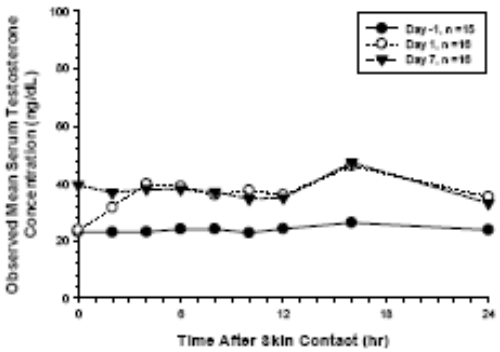
Treatment A, Observed



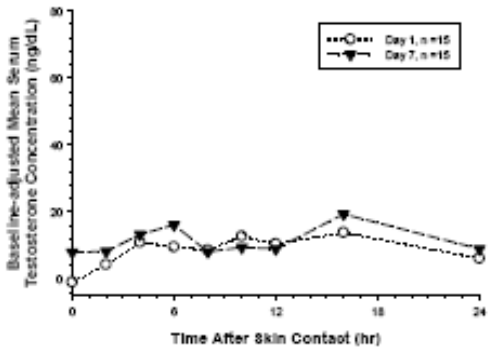
Treatment A, Baseline-adjusted



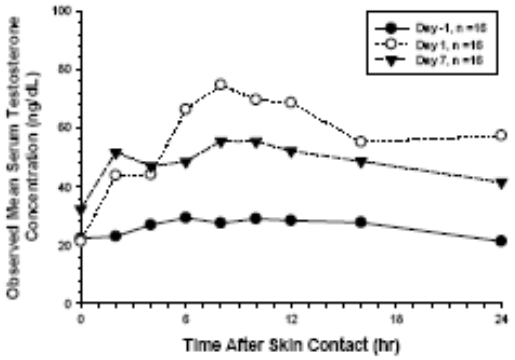
Treatment B, Observed



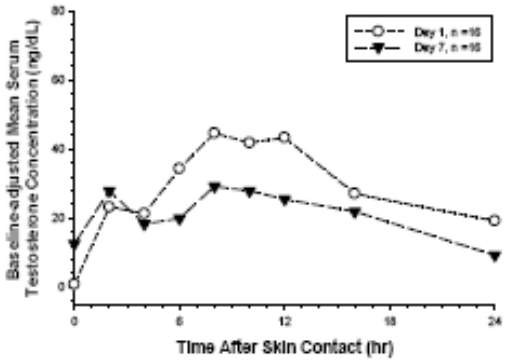
Treatment B, Baseline-adjusted



Treatment C, Observed



Treatment C, Baseline-adjusted



Treatment A: Direct skin contact occurred 2 hours postdose (no t-shirt), Treatment B: Skin contact occurred 2 hours postdose (with the male wearing a t-shirt), Treatment C: Direct skin contact occurred 12 hours postdose (no t-shirt).

Supporting documentation: Table 10.2.1 and Table 10.2.4.

Figure 1. Arithmetic Mean Observed and Baseline-adjusted Testosterone Serum Concentration versus Time Profiles on Linear Scales for each Treatment

Female subjects in Treatment A (direct skin-to-skin contact at 2h post-dose) and Treatment C (direct skin-to-skin contact at 12 h post-dose) had an approximate 2.0 to 2.7-fold increase from their baseline C_{avg} on Days 1 and 7. Female subjects in treatment B (2 h contact /with t-shirt on male) had a 1.6 to 2.0-fold increase from baseline C_{avg} observed for Days 1 and 7.

Of the thirteen women in Group B, 11 had increases in serum testosterone levels over baseline. Two had a >2-fold increase and one had a >3-fold increase.

The clinical pharmacology reviewer concluded that "Significant partner-to-partner transfer of testosterone occurs from AndroGel 1.62 % gel (abdominal application of 5.0 g gel dose equivalent to 81 mg testosterone) as evident from a statistically significant increase from baseline in systemic testosterone concentrations in non-dosed females. Covering the application site with clothing reduced the magnitude of transfer in such individuals but did not eliminate it completely.

Patients should be advised of this risk. Cautionary language should be included in the product labeling to communicate this risk to physicians/patients and appropriate precautions to minimize transfer should be taken (e.g. hand-washing after dose application, covering of the application site with clothing, avoiding direct contact with the product or with the drug application site in dosed individuals, washing of the drug application site if a direct contact is anticipated, etc). A combination of such measures may be needed to minimize transfer."

Study 1.008:

This trial was a randomized, open-label, parallel group study to evaluate the effects of dose, post-dose washing, and application site on the transfer potential of testosterone gel 1.62% from dosed males to a non-dosed female partner.

24 healthy couples (or 48 total subjects; 24 male, 24 female) were randomized to one of the three treatment groups (I, II, III). Within each treatment group, subjects received two single dose/exposure treatments in a randomized order. Each single dose/contact was separated by a 1-week washout period. Dose application and subsequent skin contact occurred on Days 1 and 8 of the study.

- Group **I** *[2.5 g dose; Trt **A:** direct skin contact at 2h post-dose; Trt **B:** contact at 2h post-dose with clothing barrier to cover application site]*
- Group **II** *[5.0 g dose; Trt **C:** direct skin contact at 2 h post-dose**;** Trt **D:** direct skin contact at 2h post-dose after the male showered]*
- Group **III** *[5.0 g dose; Trt **E:** direct skin contact at 2 h post-dose-gel applied to shoulders/upper arms; Trt **F:** direct skin contact at 2h- gel applied to abdomen]*

Each couple engaged in a total of 15 minutes of contact. Male subjects in Treatment B were given a 100% cotton t-shirt to wear that fully covered the abdomen. For Treatment D only, male subjects showered and thoroughly washed the application site with soap and

water 15 minutes prior to the scheduled contact time. Blood samples for serum analyses of testosterone were collected at various time points on day -1, day 1 and day 8 and results are shown in Table 2.

Table 2: Observed PK parameters of testosterone across all groups

Observed testosterone PK Mean (SD)	C_{max} ng/dL	C_{avg} ng/dL	AUC_{0-24} ng.h/dL
Group I- Baseline	35.96 (18.1)	21.6 (8.2)	519 (197)
Trt A	44.65 (24.6)	27.7 (12.8)	666 (309)
Trt B	24.03 (7.42)	20.6 (8.0)	495 (191)
Group II- Baseline	20.96 (7.26)	16.4 (4.2)	393 (101)
Trt C	36.6 (16.1)	25.3 (8.7)	606 (208)
Trt D	24.2 (9.13)	18.2 (5.9)	436 (142)
Group III- Baseline	39.7 (37.08)	18.5 (10.3)	445 (247)
Trt E	103.6 (29.4)	56.3 (17.2)	1350 (413)
Trt F	57.5 (34.3)	38.9 (26.6)	933 (640)

Group I: 2.5g, abdomen; Trt A: direct contact at 2h; Trt B: contact at 2 h with T-shirt on male
Group II: 5 g, abdomen; Trt C: direct contact at 2 h; Trt D: direct contact at 2h after male washing
Group III: 5 g, two sites; Trt E: direct contact at 2 h; gel on shoulders; Trt F: direct contact at 2h; gel on abdomen]

The "fold-increase" over baseline in the female partners is shown in Table 3.

Table 3: Fold changes in testosterone exposure over baseline in female subjects [mean (range)] in the various treatment groups of transfer evaluation study 1.008

Mean fold-changes (Range)	Group I		Group II		Group III	
	Trt A	Trt B	Trt C	Trt D	Trt E	Trt F
C_{max}	1.26	0.80	1.86	1.17	5.01	2.21
	[0.9-1.58]	[0.37-1.36]	[0.89-3.27]	[0.96-1.91]	[1.0-11.07]	[0.77-7.97]
C_{avg}	1.32	1.00	1.61	1.09	6.15	2.48
	[0.7-1.73]	[0.51-1.27]	[0.91-2.78]	[0.95-1.32]	[1.65-23.9]	[1.06-5.55]

Group I: 2.5g, abdomen; Trt A: direct contact at 2h; Trt B: contact at 2 h with T-shirt on male
Group II: 5 g, abdomen; Trt C: direct contact at 2 h; Trt D: direct contact at 2h after male washing
Group III: 5 g, two sites; Trt E: direct contact at 2 h; gel on shoulders; Trt F: direct contact at 2h; gel on abdomen]

Individual fold-changes from baseline are shown in Table 4.

Table 4: Individual fold-changes from baseline across various treatment groups

Fold changes over baseline in various PK parameters						
	Group I		Group II		Group III	
	Trt A	Trt B	Trt C	Trt D	Trt E	Trt F
C_{max}	0.90	0.51	2.57	1.33	2.27	1.87
	1.22	0.37	1.37	1.07	10.52	7.97
	1.48	0.69	3.27	1.00	5.57	1.91
	1.58	1.36	1.70	0.96	1.00	0.77
	1.15	0.91	1.12	1.91	11.07	1.48
	1.03	0.98	2.71	1.15	1.29	1.23
	1.51	1.15	1.34	0.96	3.42	1.23
	1.21	0.46	0.89	1.01	4.97	1.28
Average	1.26	0.80	1.87	1.17	5.01	2.22
C_{avg}	0.70	0.51	1.83	1.22	4.18	4.52
	1.54	0.72	1.34	1.08	10.38	5.55
	1.73	1.20	2.78	0.98	2.21	1.27
	1.53	1.27	1.55	1.32	2.22	1.75
	0.90	1.02	1.04	1.17	23.92	2.66
	1.09	1.11	2.22	1.04	1.65	1.81
	1.39	1.20	1.26	0.95	1.74	1.06
	1.68	1.00	0.91	0.99	2.94	1.26
Average	1.32	1.00	1.62	1.10	6.15	2.49

Group I: 2.5g, abdomen; Trt A: direct contact at 2h; Trt B: contact at 2 h with T-shirt on male
Group II: 5 g, abdomen; Trt C: direct contact at 2 h; Trt D: direct contact at 2h after male washing
Group III: 5 g, two sites; Trt E: direct contact at 2 h; gel on shoulders; Trt F: direct contact at 2h; gel on abdomen]

In treatment B (2.5 g; male T-shirt), small increases in C_{avg} over baseline were still apparent in few of the individuals (4 out of 8 individuals; ranging 11 % – 27%). Similar trends were seen with C_{max}. In treatment group D (5.0 g; direct contact after washing application site), 4 out of 8 individuals still had an increase in Cavg over baseline ranging from 4 % to 33 %. Similar trends were seen with C_{max}.

The clinical pharmacology reviewer concluded the following:

Group I: Results from this group suggest that clothing to cover the application site may aid in minimizing the overall transfer at the 2.5 g dose level, although it may not completely eliminate transfer to non-dosed individuals.

Group II: Overall washing of the application site prior to contact appears to minimize (but not completely eliminate) transfer to non-dosed individuals. Use of washing in conjunction with clothing to cover the application site may further reduce the degree of

transfer to non-dosed individuals. The washing protocol in this study included soap and water and sponsor notes that use of a wash-cloth could have potentially removed more of the drug from the application site. Patient instructions could potentially incorporate this as an additional measure to mitigate transfer.

Group III: Results from this group demonstrate that transfer potential to non-dosed individuals upon direct skin contact is significant for testosterone 1.62 % gel formulation regardless of the site of application. Appropriate precautionary measures should be used to minimize transfer.

Study 1.005:

Study 1.005 was a randomized, open-label, three-way crossover pharmacokinetic study to evaluate the effects of skin washing after administration of testosterone gel.

This was a single center, open-label, randomized, three-way crossover study in 24 hypogonadal male volunteers. 5.0 g testosterone gel 1.62% (81 mg testosterone) was applied topically once daily in the morning to the shoulders/upper arms for 7 days during each of three consecutive treatment periods, for a total of 21 days of dosing. There was no washout period between treatment periods. On the seventh dosing day of each treatment period, skin washing with soap and water occurred at the following times:

Treatment A: 2 hours post-dose
Treatment B: 6 hours post-dose
Treatment C: 10 hours post-dose

The skin washing occurred in the shower using commercially available Ivory Bar soap and water on the shoulder/upper arms with a soap lather time of approximately 2 minutes followed by a thorough rinse. The site of application was then thoroughly dried. Tape stripping procedures were conducted at 30 minutes after the projected or actual wash time on the sixth (control) and seventh (washed) days of each treatment period to evaluate the presence of any residual testosterone remaining in the stratum corneum with or without washing. For tape stripping, at the same skin site 10 strips total were applied and removed. The drug was extracted from the 10 strips in two samples. The first sample contained strips 1-3 and the second sample contained strips 4-10.

The clinical pharmacology reviewer concluded that the results of this study suggest that while washing of the application site resulted in removal of at least 80 % of residual testosterone from the application site, the systemic absorption of testosterone was not markedly affected. Thus skin application sites can be allowed to be washed at or after 2 hours post-dose during clinical use. While tape stripping results showed that residual testosterone on the skin can be removed (by at least 80 %) by washing the site with soap and water, washing did not completely remove all traces of drug from the skin.

Conclusions on the transfer potential from Androgel 1.62 %:

- Results from studies S176.1.003, S176.1.005 and S176.1.008 suggest that significant secondary exposure of testosterone in non-dosed individuals (e.g. females, children) can occur when direct skin-to-skin contact with the Androgel 1.62 % application site occurs.
- Clothing barrier reduces but does not eliminate transfer and thereby secondary exposure. Therefore, clothing alone shouldn't be used as a sole means of transfer minimization.
- Washing with soap and water was effective in removing most of the residual testosterone from the skin and by far appears to be the most effective way to minimize transfer (combining the results from studies S176.1.005 and S176.1.008). Sponsor notes in a subsequent correspondence (09/17/09) to the division that use of a washcloth, rather than using only soap and water, may potentially remove additional testosterone from the surface of the skin due to desquamation of the outer layers of the skin. Although this was not evaluated clinically, use of a washcloth may be incorporated as an additional measure to avoid transfer. Patients should however avoid sharing washcloths with their spouses or other family members.
- Washing coupled with a clothing barrier to cover the application site would likely have the most benefit in the clinical setting to prevent transfer. Washing at or after 2 h post-dose been shown not to adversely influence the systemic exposure in the male patient and therefore will not compromise efficacy. However, patients should be advised to wash at any time post-dose if contact with non-dosed individuals is anticipated and unavoidable.
- If direct contact does occur by accident, it is important that the contact site is immediately and thoroughly washed with soap and water to minimize systemic absorption. Data from S176.1.008 suggests that transfer and thereby secondary exposure to non-dosed individuals occurs very rapidly as evidenced by high systemic T levels at time 0 in group C, which marks the end of the 15-minute contact session.

The sponsor submitted the results of a new transfer study (S176.1.009) as well as a rationale document justifying the absence of a formal bridging study linking the revised dosing instructions to those employed in the phase 3 program for AndroGel 1.62 % gel. These two items constituted the primary components of this major NDA amendment.

Results of the new transfer study indicate that when contact occurred in the presence of a clothing barrier with males who applied the 5.0 g over all four skin sites (2 sides of abdomen and both shoulders/arms), fold-increase in testosterone Cavg in females on day 1 was 1.06 (i.e. 6 % over baseline). The range of absolute increases in C_{avg} in these females was 0.23 – 3.9 ng/dL. Mean increases in C_{max} were 1.08 on average (i.e. 8 % over baseline). The individual with the highest C_{max} change over baseline was subject # 27445 who showed a net increase in C_{max} over baseline of 16 ng/dL. This was a one-time occurrence in this individual in whom the remaining concentrations were identical to those in her baseline.

The results from the new transfer study S176.1.009 suggest that the testosterone transfer to non-dosed females was largely mitigated when contact occurred with a T-shirt barrier on a male who applied a 5.0 g dose of the 1.62 % gel formulation to 4 different application sites (both upper arms/shoulders and both sides of abdomen).

The Office of Clinical Pharmacology recommendation for NDA 22309 is as follows:

> "The Office of Clinical Pharmacology has reviewed the original NDA submitted on 02/11/2009, as well as major amendment related submissions for NDA 22-309 [AndroGel® (Testosterone gel) 1.62 %]. The information contained within NDA 22-309 is **not acceptable** for approval from a Clinical Pharmacology perspective. Based on the review of the major amendments submitted on 11/06/2009, 11/24/2009, 12/03/2009, 12/11/2009, 12/23/2009, and 01/15/2010, the sponsor has not provided adequate evidence to justify that the safety and efficacy of the drug would remain unchanged under the proposed new conditions of use.

- The proposed revisions to the application instructions for AndroGel 1.62 % gel require the use of both shoulders/upper arms as well as the abdominal sites for the two higher doses (i.e. three sites and four sites, respectively for the 3.75 g and 5.0 g doses). While this regimen has been demonstrated to mitigate transfer to non-dosed individuals, this is different from the phase 3 clinical trial (S176.3.104), in which dose was applied to either shoulders/upper arms or abdomen but not to both at the same time (i.e. two sites). The potential impact of this increased surface area of gel application with the use of additional application sites (relative to phase 3 usage) on the pharmacokinetics (PK) is unknown for the new 1.62 % formulation.

- The proposal to use limited PK information from a subgroup of phase 3 patients who had deviated from the protocol and have documented sporadic use of the gel onto multiple application sites is considered as inadequate evidence in this regard and sets a low standard for approval.

- Additionally, skin safety (irritation) data following continuous once daily application to multiple sites is not available from the completed clinical trials for Androgel 1.62 % formulation. The proposed new application instructions require use of all four sites (at the 5.0 g dose) on a daily basis and therefore wouldn't allow rotation of sites to minimize irritation potential. The impact of these changes to the overall patient convenience and compliance is not known. Furthermore, increased skin irritation can also impact the dermal absorption of testosterone which the current data cannot support.

Action items to resolve deficiency:

In order to bridge the phase 3 clinical trial findings to the revised dose application instructions, the sponsor should conduct the following study:

- A steady-state, 2-way crossover, comparative bioavailability study of AndroGel 1.62 % gel (5.0 g dose) in hypogonadal male patients, evaluating the following two regimens:

    - Dose application over 2 sites to upper arms/shoulders or abdomen via rotation (per phase 3 clinical trial usage)

    vs.

    - Dose application over 4 sites to both upper arm/shoulders and both sides of abdomen (per revised application instructions)."

The Division Director for Division of Clinical Pharmacology 3, Office of Clinical Pharmacology concurred with the clinical pharmacology reviewer and the clinical pharmacology team leader on the final recommendation as well as the action items recommended to resolve the deficiencies.

In addition, the following Summary of Important Clinical Pharmacology and Biopharmaceutics Findings is included in the clinical pharmacology review.

- The original NDA for AndroGel 1.62 % testosterone gel formulation was submitted on February 11, 2009. During the review cycle it was evident that interpersonal transfer potential was significant for the gel even in presence of a clothing barrier. In an attempt to assuage the Division's concern in this regard, the sponsor conducted a new transfer study (S176.1.009) employing revised dosing instructions aimed at minimizing drug amount at any one skin site so as to mitigate transfer. A 5.0 g dose of the gel was distributed over multiple skin sites of the male subjects (both upper arms/shoulders and both sides of the abdomen, "four sites") in this study as opposed to the completed clinical program for AndroGel 1.62 % gel where drug was applied to either upper arms/shoulders or abdomen but not to both sites at once.
- The results from this new phase 1 transfer study S176.1.009 as well as a supporting document justifying the absence of a formal bridging study linking the revised dosing instructions to those employed in the phase 3 program for AndroGel 1.62 % gel, constituted the primary components of this major NDA amendment.
- Results of the new transfer study (S176.1.009) indicate that when contact occurred in presence of a clothing barrier with males who applied the 5.0 g dose over all four skin sites, mean (range) fold-increase in average testosterone concentration over 24 hour period (Cavg) in females on day 1 was 1.06 (range, 0.78-1.21 fold) (i.e. 6 % over baseline). The range of absolute increases in C_{avg} in these females was 0.23 – 3.9 ng/dL. Mean increase in C_{max} was 1.08 (range, 0.67-1.74) (i.e. 8 % over baseline). The individual with the highest C_{max} change over baseline was # 27445 who showed a net increase in C_{max} over baseline of 16 ng/dL. This was a one-time occurrence in this individual in whom the remaining concentrations were identical to those in her baseline.
- The results from the new transfer study S176.1.009 suggest that the testosterone transfer to non-dosed females was largely mitigated when contact occurred with a

T-shirt barrier on male who applied a 5.0 g dose of the 1.62 % gel formulation to 4 different application sites (both upper arms/shoulders and both sides of the abdomen).

- (b) (4)

(b) (4)

- While dosing over multiple sites appears to mitigate transfer, no PK (efficacy) or safety data are currently available from continuous once daily application of the 1.62 % gel to multiple application sites (both sides of upper arms/shoulders and abdomen, without rotation).
- No formal 'bridging' study was conducted to justify the applicability of the phase 3 clinical trial data (where only 2 sites were used for spreading out the 3.75 g or 5.0 g doses), to the newly proposed regimen involving use of multiple application sites despite the doubling of the application surface area with use of two additional sites. The potential impact of this increased surface area of gel application with the use of two additional application sites (relative to phase 3 usage) on PK is unknown for the new 1.62 % formulation.
- Skin safety (irritation) data following continuous once daily application to all four sites is also not available from the completed clinical trials. The proposed new application instructions require use of all four sites (at the 5.0 g dose) on a daily basis and therefore wouldn't allow rotation of sites to minimize irritation potential.
- Data were presented by the sponsor for a small group of phase 3 patients (n=41) who were identified by the case report forms to have applied the drug to multiple application sites (three or four sites) on few occasions during the study period. This data were found to be inadequate evidence due to several reasons:
    - data originates from a group of phase 3 patients who had deviated from the protocol (i.e. in using four sites instead of the protocol stipulated two site usage) and therefore use of such data for revising dosing instructions for clinical use is questionable and sets a low standard for drug approval.

    - multiple site usage was sporadic in these patients over the 180 day study period, with only 6 patients reporting more than one occasion of documented multiple site usage on PK days (i.e. on days 56, 112 or 182).
    - during the review it was identified that several of the patients did not apply the gel per the revised dosing table shown above (17 out of 41 patients). Additionally, the degree of supervision by the clinic staff for those in clinic doses couldn't be confirmed by the sponsor.
- Owing to the absence of a formal study to bridge the revised dosing instructions to the existing phase 3 clinical trial data and due to the deficiencies identified with the data presented in lieu of such a study, the Office of Clinical Pharmacology finds the clinical pharmacology information submitted in the major amendment for NDA 22-309 **not acceptable** for approval. The sponsor has not provided adequate evidence to show that the safety of the formulation remains unaffected under the proposed new conditions of use.

The results of study S176.1.009 and the sponsor's rationale for the comparability of testosterone PK applied to 2 versus 3 or 4 sites were also reviewed by the primary medical officer and the cross-discipline team leader (CDTL).

The primary medical officer "agrees with the Office of Clinical Pharmacology that the data supporting NDA 22-309 are not acceptable. The reviewer recommends that the application should receive a **Complete Response** action at this time."

The CDTL notes that "I strongly concur with the Clinical Pharmacology decision regarding the need for additional pharmacokinetic data to link the newly proposed application method as in Study 176.1.009 to the Phase 3 study S176.3.104."

Comment: I agree with the clinical pharmacology and clinical reviewers that the issue of testosterone transfer potential and the sponsor's revised dosing regimen to mitigate transfer at the 3.75 and 5.0 gram doses currently preclude approval of NDA 22-309. Specifically, testosterone PK data are inadequate to conclude that the testosterone exposures obtained with the use of the 4 site application method (for 5 gm) or the use of the 3 site application method (for 3.75 gm) are comparable to the data obtained in the primary phase 3 study where drug was applied to 2 sites (arm/shoulders on the days when PK measurements were performed). Knowing the comparability of testosterone with the various dosing regimens is particularly important because testosterone PK data served as the primary efficacy endpoint and as the most important safety surrogate marker in the single primary trial S176.3.104.

6. Clinical Microbiology

The Microbiology review concluded that "this application is recommended for approval from microbiology product quality standpoint." The reviewer recommended that the following comment, which is not a deficiency, be communicated to the 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 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."

7. Clinical/Statistical-Efficacy

A single phase 3 efficacy trial (S176.3.104), supported by multiple phase 1 studies, was submitted. This was a multi-center (53 United States sites), randomized, double-blind, placebo-controlled study of testosterone gel 1.62% for the indication testosterone replacement therapy in hypogonadal men.

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. Two hundred seventy-four subjects (testosterone gel 1.62%: 234 subjects, placebo: 40 subjects) were randomized and analyzed for safety; 206 subjects (testosterone gel 1.62%: 179; placebo 27 subjects) 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 5 below). No dose was to be titrated below 1.25 g, or above 5.0 g, during the study. Sham titrations occurred in placebo-treated subjects. Subjects were maintained at their respective Day 42 (Week 6) dose until Day 182 (Week 26).

Table 5: Pre-specified Testosterone Gel 1.62% Dose Titration Criteria

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 %

Key inclusion criteria included:

- 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 visit, 30 (=/- five) minutes apart between the hours of 6:00 a. m. and 10:00 a. m.
- naïve to androgen replacement or had undergone a washout of 12 weeks following intramuscular androgen injections; four weeks following topical or buccal androgens; and 3 weeks following oral androgens.

Key exclusion criteria included:

- previous history of, current, or suspected prostate or breast cancer
- IPSS-1 score >15 points.
- abnormal finding on DRE of the prostate as determined by the investigator. Prostate enlargement by itself was not an exclusion criterion.
- PSA > 2.5 ng/mL or 2.6-3.74 ng/mL without a negative biopsy within the past 6 months with pathology report available for principal investigator's review (this exclusion criterion was modified to PSA>1.25 ng/mL for men on the 5-α reductase inhibitors finasteride or dutasteride).
- Body Mass Index (BMI) less than 18 or greater than 40 kg/m^2.
- hemoglobin (HGB) >16.0 g/dL, hematocrit (Hct) >48%, serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) >2X ULN (upper limit of normal).

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 by the investigator 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 the 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 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.

At 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.

Demographics: The phase III study population in trial S176.3.104 appears to be similar to that of other approved testosterone replacement products. Mean baseline concentrations of total testosterone were similar in the testosterone gel 1.62% (282 ng/dL) and the placebo group (294 ng/dL). Subject 046-06 had Klinefelter's Syndrome. There were no patients with the diagnosis of Kallmann's Syndrome entered into the study.

Patient Disposition: 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 (168 T-Gel [71.8% of randomized] and 28 [70.0% of randomized] placebo). The most common last titrated dose was 5.00 g testosterone gel 1.62%. Similar percentages of placebo and T-Gel patients discontinued from the study groups. The most common AE leading to discontinuation was increased PSA which was prespecified as a discontinuation criteria and will be discussed in the Safety section of this review. Patient disposition is shown in Table 6.

Table 6: Consented Subject Disposition S176.3.104-182 Day Pivotal Period

Subjects	Placebo N=40	T-Gel 1.25g N=17	T-Gel 2.5g N=60	T-Gel 3.75g N=66	T-Gel 5.0g N=91	Total T-Gel N=234
	n (%)					
Completed	28(70.0)	12 (70.6)	35(58.3)	50(75.8)	71(78)	168(71.8)
Premature Terminate	12(30.0)	5(29.4)	25(41.7)	16(24.2)	20(22.0)	66(28.2)
Reasons						
Adv event	0	1(5.9)	6(10.0)	8(12.1)	10(11.0)	25(9.1)
Lack of Efficacy	0	1(5.9)	0	1(1.5)	0	2(0.7)
Lost to Follow-up	2(5.0)	0	3(5.0)	0	2(2.2)	7(2.6)
Withdrew Consent	8(20.0)	1(5.9)	10(16.7)	4(6.1)	4(4.4)	27(9.9)
Admin	1(2.5)	0	1(1.7)	1(1.5)	3(3.3)	6(2.2)
Protocol Violation	1(2.2)	1(11.8)	5(8.3)	2(3.0)	1(1.1)	11(4.0)

Note: Treatment groups are based on subject's last titrated dose.
Source: Clinical Study Report S176.3.104 adapted from Table 1.0.0: page 184

Comment: The majority of subjects were titrated to the 3.75 and 5.0 g doses. This information is important when considering the sponsor's new dosing regimen of utilizing 3 and 4 sites for the two highest doses.

The primary efficacy endpoint was the percentage of subjects with serum testosterone C_{avg} within the normal range of 300-1000 ng/dL at Day 112. Success in the study was defined as ≥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.

An important secondary safety endpoint was to evaluate total testosterone C_{max} values during the first 182 Days of the study. The individual total testosterone C_{max} 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

Results:

On Day 112, 81.6% of subjects on testosterone treatment (95% CI of 75.1% -87.0%) had C_{av} values within the target range, which met the criteria for efficacy. (See Table 7.)

Table 7. Percentage of Patients Achieving Target Testosterone Concentration (FA)

		T-Gel	T-Gel	Placebo	
Study Day	Total T(Cav) ng/DL	n/N (%)	95% CI	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

Statistical review: Following review of primary study S176.3.104, the statistical reviewer concluded that "the results support the efficacy of T-Gel 1.62% in providing adequate

testosterone replacement (as shown by C_{avg} in the normal range in more than 81% of the patients) therapy 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."

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 full analysis sample, $\geq$88.8% of subjects on testosterone treatment had C_{max} values $\leq$1500 ng/dL. For the second criterion, in the full analysis 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. 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 10 subjects with $C_{max} > 2500$ ng/dL. Each of these 10 outlier cases was reviewed in detail by the Sponsor, the primary medical officer (pages 53-60 of primary medical officer review), and the cross-discipline team leader (pages 21-26 of the CDTL review).

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 large dose than assigned.

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

- There was a question of overdosage ("overcompliance") in Subjects 015-005 and 049-008. These 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 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 samples.

- 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.

Efficacy summary:

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 important secondary endpoints were achieved. The third important secondary endpoint, testosterone C_{max} >2500 ng/dL in none of the subjects, was not achieved. The ten subjects not achieving this endpoint were examined in depth, 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 two. There was no clear evidence of an androgen effect related to any of the high testosterone concentrations. Overall, the primary medical officer and the cross discipline team leader concluded that these sporadic events did not pose a safety risk and that the product is considered efficacious. I agree.

The impact of the new dosing regimen proposed by the sponsor to mitigate the potential for drug transfer to others on testosterone PK is not known. The use of 4 sites (rather than 2 sites) for the two highest doses may alter testosterone absorption pharmacokinetics. Prior to approval, the sponsor will be asked to perform a study to bridge the phase 3 clinical trial findings to the revised dose application instructions. The following study design will be recommended:

- A steady-state, 2-way crossover, comparative bioavailability study of AndroGel 1.62 % gel (5.0 g dose) in hypogonadal male patients, evaluating the following two regimens:

    - Dose application over 2 sites to upper arms/shoulders or abdomen via rotation (per phase 3 clinical trial usage)

    versus

    - Dose application over 4 sites to both upper arm/shoulders and both sides of abdomen (per revised application instructions).

8. Safety

The safety data are derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008, S176.1.009 (transfer, washing and skin irritation studies), and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104.

In total, the NDA contains 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 adverse events is derived from the single Phase 3 study and its open-label extension phase.

Deaths:

No deaths occurred in the Phase I integrated studies or in the Phase III double-blind protocol.
No deaths occurred in the 182 day Open-Label Period.

Serious adverse events (SAEs):

In regard to serious adverse events, in the integrated Phase I 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, in the investigator's opinion, were unrelated to the study drug. In both cases the patients recovered.

A total of 6 SAEs were reported in the double-blind period of the Phase 3 Study S176.3.104. Five subjects were in the testosterone gel 1.62% group and one was in the placebo group. The five patients in the testosterone gel group experienced 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 "possibly related" (hematocrit was also increased in this patient) and the myocardial infarction as" 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 a 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.

Study discontinuation:

Overall, in the placebo-controlled, Phase 3 study, 25 of 234 patients treated with testosterone gel 1.62% withdrew due to an adverse event. None of 40 placebo patients withdrew due an adverse event. There were no AEs leading to study discontinuation 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 criterion of change from baseline

>0.75ng/mL. Four other subjects had a PSA value >4 ng/mL, these subjects had PSA ≤ 4.0 ng/mL upon repeat testing.

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

Overall adverse events:

In the controlled Phase 3 study, the most common (≥2% in the testosterone gel 1.62% groups and greater than in the placebo control group) 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 preferred term. The six events of hypertension did not include the event of malignant hypertension.

There were pre-specified criteria for abnormal PSA values 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 drug treated than in placebo patients are shown in Table 8.

Table 8: Common Adverse Events (>2% for T-gel 1.62% and greater than placebo) for the Double-Blind Phase III 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.

Skin-related adverse events were 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, 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:

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 group, 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 time point for any vital sign.

The primary medical officer and CDTL reviewed several safety issues which are known to be associated with testosterone replacement therapy:

1) Testosterone is known to stimulate erythropoeisis and can increase hemoglobin and hematocrit. In Study S176.3.104, a modest increase in mean hematotcrit was observed overall for the testosterone gel 1.62% groups compared with placebo. Several incidents of markedly high hematocrit were reported in subjects who had been receiving study medication for 12 or more weeks. 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 -0.12 ng/mL for the placebo group. A total of 45 subjects reported PSA values on one or more occasions 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 > 4 ng/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). Any future labeling for AndroGel 1.62% should include these PSA results and recommend PSA monitoring.

3) It is not known whether replacement of testosterone 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 are included in androgen class labeling. Prostate cancer occurred in one patient in this drug development program, a 58 year-old subject (012-08). The patient had a past history of BPH and had stopped taking Avodart on July 26, 2006. His first dose of testosterone gel 1.62% was on (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 a testosterone serum level of 4430 ng/dL at 2 hours post-dose. His $C_{averages}$ 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 cores 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, this event should be described in product labeling.

4) Hypertension is a known potential adverse event associated with testosterone therapy. 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 marginally controlled hypertension at baseline.

Safety overview:

The safety profile and adverse events associated with AndroGel 1.62% are essentially the same as for AndroGel 1% except for the issue of testosterone transfer. Studies dealing with the potential transfer of AndroGel 1.62% are further discussed in the Clinical Pharmacology section of this review.

The first two transfer studies conducted by the Sponsor (S176.1.003 and S176.1.008) showed that a simple T-shirt was not a fully effective barrier to transfer for the 5gm dose but was an effective barrier for the lower 2.5 gm dose. Thus, the volume of gel at a given application site was shown to play some role in penetration through a T-shirt barrier. In an attempt to mitigate the transfer at the higher dose, the sponsor re-configured the application method by spreading the 5 gm dose out onto both arms/shoulders and both sides of the abdomen, resulting in 1.25 gm on each of 4 anatomic sites. This method was studied in a third transfer study (S176.1.009) and this change resulted in a T-shirt acting as an effective barrier to transfer.

The new method of application, despite being useful for the effective T-shirt barrier, is, however, different from the method of application used in the primary phase 3 trial S176.3.104. The long-term impact on systemic exposure of spreading the gel out onto a larger surface area (4 sites, versus 2 sites [arms/shoulders only]) has not been well characterized. The sponsor provided data from approximately 20-40 subjects who erroneously and sporadically applied testosterone in the Phase 3 study to more application sites than recommended and these data were thought by the sponsor to demonstrate comparability of serum testosterone levels in the 2 versus 3 or 4 site application schemes. However, the medical and clinical pharmacology review teams do not agree that these comparability data are sufficient to link the new application method to the substantial evidence of safety and efficacy from Phase 3 trial S176.3.104.

I agree with the medical and clinical pharmacology review teams that this NDA application cannot be approved at this time. The Sponsor will need to demonstrate that exposures to testosterone are comparable when one applies the gel as 5 gm over both arms/shoulder & both sides of the abdomen versus when one applies 5 gm of the gel just to the arms/shoulders or just to the abdomen.

In terms of the safety results from the clinical studies conducted for this NDA submission, there are no other issues which preclude approval. The data show the expected effects of a testosterone gel including increased hemoglobin and hematocrit, increased PSA, a single report of prostate cancer, lower urinary tract symptoms, acne, and skin inflammation, among other conditions. The medical officer and CDTL carefully reviewed 10 individual cases of supraphysiological testosterone concentrations and found them to be artifactural 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.

If this NDA is ultimately approved, labeling will need to be completed, including the package insert, the Medication Guide, and container/carton labeling. The REMS associated with the Medication Guide will also need to be addressed.

9. Advisory Committee Meeting

No advisory committee was convened to discuss the approval of Androgel 1.62%. There are currently two approved testosterone gel preparations (Androgel 1% and Testim). An Advisory Committee was held on June 23, 2009, to discuss the transfer potential of testosterone gels from patients to others, particularly children. The Advisory Committee agreed with the Division's plans to require labeling revisions (including a black box warning) and a Medication Guide for Androgel 1% and Testim. If approved, the same labeling and a Medication Guide dealing with the potential transfer of testosterone to others will be applied to Androgel 1.62%.

10. Pediatrics

The sponsor requested a full waiver of pediatric studies (b) (4) this NDA application does not trigger PREA requirements.

11. Other Relevant Regulatory Issues

A. Division of Scientific Investigations (DSI)

Clinical site inspections by the DSI were not requested. At the request of the Division of Clinical Pharmacology III, DSI audited the analytical portion of the primary clinical trial S176.3.104. The analytical portion of the study was conducted at (b) (4) (b) (4) The DSI (November 9, 2009) "recommends that the analytical portion of study S176.3.104 is acceptable for review."

B. Compliance

Compliance (December 7, 2009) determined that the inspections of the drug substance and drug product manufacturing and testing operations are acceptable.

C. Office of Surveillance and Epidemiology

i. Division of Medication Error Prevention and Analysis (DMEPA) :

A draft review of container/carton and package insert labeling was received. These issues will be re-evaluated at the time of a complete response submission.

ii. Division of Risk Management (DRISK)

DRISK will address the MedGuide during the next review cycle. The consultation stated "we will defer our review of the Medication Guide until such time as the review Division plans to address labeling. Please send us a consult request at that time."

D. Division of Drug Marketing, Advertising and Communication (DDMAC)

DDMAC provided comments on the originally submitted Package Insert (PI) and Medication Guide and will be consulted again at the time of submission of a Complete Response.

E. Controlled Substance Staff (CSS)

The Controlled Substance Staff recommended revised labeling under Section 9 in the label ("Drug Abuse and Dependence" section). The recommended changes (specifically dealing with abuse, addiction, and dependence) will be conveyed to the sponsor during the next review cycle when labeling discussions are held.

F. Financial Disclosure

Form FDA 3454 signed June 26, 2008, was provided in the submission. Financial disclosures were submitted for the principal investigators in Protocols S176.1.001, S176.1.002, S176.1.003, S176.1.004, S176.1.005, S176.1.006, S176.1.007, S176.1.008, and the pivotal Phase 3 study S176.3.104.

A total of 77 investigators (all from all protocols and study sites) had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54, 2(a)], proprietary interest in the covered product or significant equity interest in the Sponsor of the covered product [21 CFR 54.2(b)], significant payments of other sorts from the Sponsor of the covered study [12 CFR 54.2(f)]. There was no missing financial disclosure information for investigators in the above listed studies.

12. Labeling

Because of the Complete Response action, labeling and labeling negotiations with the sponsor were not completed. The revised method of application to prevent drug transfer to others (3 or 4 anatomical site applications rather than 2 for the higher Androgel 1.62% doses) is a major reason for the Complete Response action.

The Division of Medication Error Prevention and Analysis (DMEPA) found the tradename AndroGel 1.62% acceptable after reviewing the sponsor's proposed education and communication plan and found "the plan acceptable based on new information submitted by the Applicant on November 6, 2009."

If approved, AndroGel 1.62% labeling would be consistent with the two previously approved testosterone gel products with respect to transfer potential (particularly to children). This labeling would include a black box warning.

The Division of Risk Management (DRISK) deferred review of the Medication Guide until a time when physician labeling is substantially complete.

A consultation from the Controlled Substance Staff (CSS) recommended changes to the Drug Abuse and Dependency portion (Section 9) of the label. These recommendations will be considered/incorporated into the final labeling if AndroGel 1.62% is approved during a subsequent review cycle.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

I do not think that NDA 22-309, with the data submitted, can be approved at this time and a Complete Response action will be taken. The primary reason for this action is the lack of data to support a pharmacokinetic link to bridge the newly proposed application method as in Study 176.1.009 to the efficacy and safety data provided in Phase 3 study S176.3.104.

This decision is in keeping with the recommendations of the clinical pharmacology reviewer, the clinical pharmacology team leader, the Division Director of the Division of Clinical Pharmacology 3, the primary medical officer, and the cross-discipline team leader (CDTL).

The clinical pharmacology review team wrote:

"Owing to the absence of a formal study to bridge the revised dosing instructions to the existing phase 3 clinical trial data and due to the deficiencies identified with the data presented in lieu of such a study, the Office of Clinical Pharmacology finds the clinical pharmacology information submitted in the major amendment for NDA 22-309 **not acceptable** for approval. The sponsor has not provided adequate evidence to show that the safety of the formulation remains unaffected under the proposed new conditions of use."

The primary medical officer "agrees with the Office of Clinical Pharmacology that the data supporting NDA 22-309 are not acceptable. The reviewer recommends that the application should receive a **Complete Response** action at this time."

The CDTL notes that "I strongly concur with the Clinical Pharmacology decision regarding the need for additional pharmacokinetic data to link the newly proposed application method as in Study 176.1.009 to the Phase 3 study S176.3.104."

- **Risk Benefit Assessment**

The issue of testosterone transfer potential and the sponsor's revised dosing regimen to preclude transfer at the 3.75 and 5.0 gram doses currently preclude approval of NDA 22-309. Specifically, testosterone PK data are inadequate to conclude that the testosterone exposures obtained with the use of the 4 site application method (for 5 gm) or the use of the 3 site application method (for 3.75 gm) are comparable to the PK data obtained in the primary phase 3 study where drug was applied to 2 sites (arm/shoulders on the days when PK measurements were performed). Knowing the comparability of testosterone is particularly important because testosterone PK data served as the primary efficacy endpoint and as the most important safety surrogate marker in the single primary trial S176.3.104. I agree with the clinical pharmacology and clinical reviewers that an additional study is needed. Specifically, a Phase 1, multiple-dose, relative bioavailability study comparing the testosterone exposures obtained with use of the 4-anatomic site application method (for 5 gm) versus the Phase 3, per-protocol 2-site method (rotating method, with arms/shoulders used on the PK day). I agree with the CDTL that "it would be prudent to conduct application site irritation assessments during this trial to compare application site irritation between the 2 methodologies."

The remainder of the data submitted in this NDA demonstrate that the product provides acceptable testosterone exposure when used at titrated doses of 1.25 gm to 5 gm, as per the Phase 3 dosing and administration instructions. The requisite percentage of patients met the C_{avg} criteria, and, in addition, two of the three required C_{max} criteria were met. In the 10 individual cases where C_{max} was > 2500 ng/dL, 5 cases can be ascribed to artifact, 1 case was likely to have been an artifact, and 2 cases were probably related to excessive dosing. In the two cases where no reason for the supraphysiologic concentration was obvious, the incident was isolated and sporadic, without clear clinical consequence. I agree with the primary medical officer and the CDTL that these results alone should not preclude approval.

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, a single report of prostate cancer, lower urinary tract symptoms, and skin inflammation (predominantly seen in phase 1 studies). All of these events can be adequately labeled.

If, following a Complete Response submission, the product is found to be approvable, labeling will need to be completed, including the package insert, the Medication Guide and container/carton labeling. The REMS, which pertains to the potential risk of secondary exposure to children and women (and includes a Medication Guide), will also need to be completed.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

A complete response action will be taken. The REMS (including the Medication Guide) and labeling will be re-evaluated and reviewed at the time of a Complete Response submission. The REMS and Medication Guide will be consistent with that required for the other two approved testosterone gels.

- **Recommendation for other Postmarketing Requirements and Commitments**

Currently, it does not appear that any postmarketing requirement or commitment (other than REMS activities) are needed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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

/s/

GEORGE S BENSON
03/11/2010

Cross-Discipline Team Leader Memo

Date	March 8, 2009
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	22-309
Applicant	Solvay Pharmaceuticals Inc.
Date of Submission	February 11, 2009
PDUFA Goal Date	March 12, 2009
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:	***Complete Response***

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 (AndroGel 1% and Testim 1%), 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 Solvay Pharmaceuticals, the same Sponsor as for this application. The Sponsor estimates that approximately (b) (4) patients have used AndroGel 1% since its approval in February, 2000.

The Sponsor now proposes 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) 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 to skin of the upper arms and shoulders, and abdomen. 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, 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.

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) plastic canister with a pump dispenser. Each pump delivers 1.25gm of gel Four pump actuations are therefore required for the highest daily dose of 5gm.

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

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

(b) (4)

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, 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*" (Protocol S176.1.001). 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 (which would allow lower gel volumes).

The next study protocol submitted was a Phase 1, dose-ranging trial, 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*" (Protocol S176.1.002). This study showed generally linear, dose-related increases in exposure from the 1.25 gm to 6.25 gm doses 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.

(b) (4)

(b) (4)

served as a laboratory for most of the Phase 1 studies and the Phase 3 (S176.3.104) study evaluating the safety and efficacy of AndroGel 1.62% in hypogonadal men. Analytes specifically affected include testosterone, dihydrotestosterone, estradiol, and sex hormone-binding globulin.

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 (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 (b) (4) (b) (4)

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

The following notable events have transpired since receipt of the 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 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, 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.

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 a major clinical amendment received within 3 months of the original goal date.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, A. Roger Wiederhorn, stated in his first review, dated November 2, 2009:

*"Recommendation on Regulatory Action: It is recommended NDA 22-309 be **NOT APPROVED** at this time, and that a **Complete Response** action be taken. Studies conducted to assess whether testosterone can transfer to others have shown that a T-shirt does not adequately block transfer of a 5gm dose.* (b) (4) [redacted] *The reviewer believes that other simpler, more feasible means, in addition to shower skin washing of the skin application site prior to physical contact, is needed to prevent testosterone transfer to others.*

*Currently, the information provided by the Sponsor shows that a T-shirt does block transfer at the 2.5gm dose, but the T-shirt barrier does not adequately block testosterone transfer at the 5 gram testosterone gel dosage. A **COMPLETE RESPONSE** to this unresolved safety concern would entail generating data to show a satisfactory method for the clothing barrier technique. This might require modification in the method(s) of application of larger doses of testosterone gel 1.62% (e.g., application of 2.5gm on the abdomen and 2.5gm on the arms/shoulders). If the dosing method is changed (e.g. spreading the larger dose out onto both sides of the abdomen and both arms/shoulders), then appropriate PK data to demonstrate testosterone concentrations comparable to those obtained in Study S176.3.104 (where the dosing schema was abdomen or arms/shoulders) will also be required."*

Dr. Wiederhorn further concluded:

"The Sponsor's submission and amendments do not allow for labeling that will permit acceptably safe use of testosterone gel 1.62% with respect to the issue of issue of transfer of testosterone by direct skin contact from treated male to others (including females and more importantly, children). With respect to the T-shirt barrier, the discrepancy between results for the 2.5 g and 5 gm doses poses a significant barrier to adequate labeling for the transfer issue. Additional studies are needed to acceptably mitigate the risk of testosterone transfer using a clothing barrier. These studies could evaluate the type of clothing barrier, time of contact after testosterone gel 1.62% application, and the use of multiple sites of application for larger doses of testosterone gel 1.62%.

Other than for the transfer issue, the data support adequate directions for use, including the data to describe a safe and effective dose."

Additionally:

"*…should the transfer issue related to a clothing barrier be acceptably resolved, a postmarketing Risk Evaluation and Mitigation Strategy (REMS) will still be necessary to address the overall transfer risk. This will include a Medication Guide, and other educational efforts to patients, prescribers and health care professionals. The Sponsor is aware of the ultimate need for this REMS and has submitted a proposal already.*"

It is important to point out that Dr. Wiederhorn's final conclusions pre-date the Sponsor's submissions of November 5, and November 24, 2009. In these submissions, the Sponsor provided preliminary "headline" data from a third transfer study (S176.1.009), a proposal to revise the application site regimen from the Phase 3 rotating regimen to a 3- or 4-site application regimen (for doses in excess of 2.5 gm), and a Rationale with accompanying data in support of the new 3- or 4-site application regimen. The Sponsor believes that the results of this third transfer study show that a t-shirt effectively blocks transfer at a dose of 5 gm, when the dose is spread out onto 4 sites, rather than limited to 2 sites. The Sponsor further believes that a subgroup analysis of the Phase 3 study S176.3.104 shows that a 3- or 4-site application regimen provides comparable testosterone exposure to the Phase 3 rotating regimen. The Clinical and Clinical Pharmacology teams conducted an overview-type review of these November submissions. Dr. Wiederhorn and I found the headline results from the third transfer study S176.1.1009 to be promising in terms of prevention of transfer to others. However, we were concerned that the data submitted in support of exposure comparability between the 3- or 4-site regimens and the rotating regimen appeared insufficient to assure comparability between the Phase 3 regimen and the new regimen from Study 009. The data are from a small number of patients, who did not use the 3- or 4-site regimen uniformly nor consistently.

On December 10, 2009, the PDUFA clock was extended by 3 months, allowing us to review the final study report for the third transfer study 009, as well as the Sponsor's argument relevant to comparability of exposure between the Phase 3, rotating (arms/shoulders and abdomen) application method (5 gm spread over 2 application sites) to the newly proposed application method (5 gm spread out over 4 application sites, including both arms/sholders and both sides of the abdomen).

In his final Addendum review of the major Clinical amendment dated March 8, 2010, Dr. Wiederhorn concluded:

1. "*It is this reviewer's opinion that Study S176.1.009 has provided evidence that applying 5gm of AndroGel 1.62% to 4 anatomic sites (and similarly, by inference, 3.75 gm gel to 3 anatomic sites), is a satisfactory method for an effective simple clothing barrier in mitigating transfer to others through physical contact*.
2. *Sponsor has failed to provide suitable PK information documenting comparable testosterone exposure in males using the 2 anatomic sites versus the 4 anatomic site application method for the 5.0 gm dose of AndroGel 1.62% or for the 3 site application method for the 3.75 gm dose of AndroGel 1.62%.*"

Dr. Wiederhorn provided the following recommendation for regulatory action

"*The medical reviewer agrees with the Office of Clinical Pharmacology that the data supporting NDA 22-309 is not acceptable. The reviewer recommends that the application receive a Complete Response action at this time. Current data and studies submitted are not sufficient in providing suitable PK information documenting comparable testosterone exposure in males using the 2 anatomic site versus the 4 anatomic site application method for the 5.0 gm dose of AndroGel 1.62% or for the 3 site application method for the 3.75 gm dose of AndroGel 1.62%. A COMPLETE RESPONSE to this unresolved safety concern would entail generating data to show comparable testosterone exposure in males using the 2 anatomic site application scheme as in Phase 3 to the 4 anatomic site application method*

used in transfer study 009 for the 5.0 gm dose of AndroGel 1.62% or for the 3 site application method for the 3.75 gm dose of AndroGel 1.62%."

I concur with Dr. Wiederhorn's conclusions and final recommendation. The Sponsor will need to provide clear information to support exposure comparability between the 3- and 4-site application regimen (used in transfer study 009) and the rotating regimen (used in the Phase 3 study 104). The optimal way to obtain such information would be to conduct a Phase 1, two-way, cross-over study comparing testosterone exposure between the two regimens.

3. CMC/Device

The Chemistry Review team, Hitesh Shroff and Moo Jhong Rhee, made the following recommendation in their first review dated October 27, 2009:

> *"The Microbiology consult review has not been completed yet, so the assurance of the purity of the drug is still pending. The Office of Compliance has not made a final overall 'Acceptable' recommendation for all facilities listed in the application."*
>
> *Therefore, until these issues are resolved, this application is not recommended for approval from the CMC perspective.*"

Subsequent to the completion of this first CMC review, the Microbiology issue was resolved. 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, 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 conveyed to Sponsor on November 24, 2009, and was formally accepted by Sponsor on November 25, 2009.

On December 7, 2010, just prior to the December 10, 2010, PDUFA clock extension, the Office of Compliance provided a final Acceptable recommendation for this application in the EES system. The inspection of (b) (4), a backup quality control site in (b) (4), had taken place on (b) (4), but the EES was updated only on December 7, 2009.

Drs. Shroff and Rhee provided a final Chemistry review on January 4, 2010, which stated the following:

> "*This NDA has now provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities are in compliance with cGMP. Labels/labeling have required information. Therefore, from the CMC perspective, this NDA is recommended for Approval.*"

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Reviewers, Jeffrey Bray and Lynnda Reid, made the following recommendation in their final review dated August 7, 2009:

> "*Nonclinical data support approval.*"

There were no recommendations for additional nonclinical studies. The main nonclinical labeling recommendation was to add statements to Section 13 (Nonclinical Toxicology) regarding carcinogenesis, mutagenesis, and fertility.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review team of Sandhya Apparaju and Myong-Jin Kim conveyed two Clinical Pharmacology reviews, the first one finalized on October 26, 2009,and the second one conveyed to the Clinical review team in draft form on February 24, 2010 and finalized on March 7, 2010. In their review of the original NDA, Clinical Pharmacology made the following recommendation:

> *"NDA 22-309 is acceptable from a Clinical Pharmacology perspective provided an agreement can be reached with the sponsor with respect to the labeling language."*

Drs. Apparaju and Kim also commented upon the Division of Scientific Investigation (DSI) audit of the (b) (4), which was not yet final at the time they had completed their original Clinical Pharmacology review. The DSI audit was subsequently completed and the data were found acceptable for use in review (see DSI section below)

At the time of their original review, the issue that required most attention was potential for testosterone transfer (see the Special Safety Issue section below). The Sponsor had conducted two transfer studies, Studies S176.1.003 and S.176.1.008, which revealed that a simple clothing barrier was not sufficient to preclude secondary exposure (transfer) of AndroGel 1.62% to others. However, Study S176.1.008 did demonstrate that the application sites could be washed after 2 hours, and that the washing effect was sufficient to allow contact with others. At the time, the Clinical Pharmacology review team strongly advised labeling that would instruct men to wash their application sites when any contact was expected with others, be it unclothed *or* clothed contact. The team advised that the label note that a T-shirt was not a sufficient barrier and that washing prior to any contact was required. The Clinical Pharmacology review team proposed significant labeling changes to enact this type of precaution.

However, the Clinical review team did not agree that this precaution was clinically feasible and initiated discussions with the Sponsor to encourage another means of precluding transfer. The Sponsor subsequently conducted a third transfer study, S176.1.009, which spread the 5 gm dose out onto 4 anatomic application sites (both shoulders/arms & both sides of the abdomen) and this method appeared to allow effective use of a simple T-shirt barrier to preclude transfer.

When the NDA PDUFA clock was extended to accommodate the major clinical amendment that contained (at least in part) the report for Study S176.1.009, the Clinical Pharmacology review team agreed to re-consider their recommended precautions for transfer in light of the

new transfer study results. A second Clinical Pharmacology review was written by the same team and was provided to the Clinical team on February 24, 2010 and finalized on March 4, 2010. In this second review, Drs Apparaju and Kim, recommended the following:

> *"The information contained within NDA 22-309 is not acceptable for approval from a Clinical Pharmacology perspective. Based on the review of the major amendments (and dates provided), the sponsor has not provided adequate evidence to justify that the safety and efficacy of the drug would remain unchanged under the proposed new conditions of use."*

Dr. Apparaju and Kim provide the following explanation for this decision:

> "*The proposed revisions to the application instructions for AndroGel 1.62% gel require the use of both shoulders/upper arms as well as the abdominal sites for the two higher doses (three and four sites, respectively, for the 3.75 g and 5.0 g doses). While this regimen has been demonstrated to mitigate transfer to non-dosed individuals, this is different from the phase 3 clinical trial (S176.3.104), in which dose was applied to either shoulders/upper arms or abdomen but not to both at the same time (i.e. two sites). The potential impact of this increased surface area of gel application with the use of additional application sites (relative to phase 3 usage) on the pharmacokinetics (PK) is unknown for the new 1.62 % formulation."*

Dr. Apparaju and Kim provided this comment on the Sponsor's submission of limited data from approximately 20-40 subjects in the Phase 3 trial who sporadically and rarely used more than the per-protocol application sites to apply gel:

> "*The proposal to use limited pharmacokinetic information from a subgroup of phase 3 patients who'd (sic) deviated from the protocol and have documented sporadic use of the gel onto multiple application sites is considered as inadequate evidence in this regard and sets a very low standard for approval.*"

The Clinical Pharmacology final review also provided the following comment pertaining to skin irritation:

> "*Additionally, skin safety (irritation) data following continuous once daily application to multiple sites is not available from the completed clinical trials for AndroGel 1.62% formulation. The proposed new application instructions require use of all four sites (at the 5.0 g dose) on a daily basis and therefore wouldn't allow rotation of sites to minimize irritation potential. The impact of these changes to the overall patient convenience and compliance is not known. Furthermore, increased skin irritation can also impact the dermal absorption of testosterone which the current data cannot support.*"

The Clinical Pharmacology final review recommended the following action item to resolve the NDA deficiency:

"A steady-state, 2-way crossover, comparative bioavailability study of AndroGel 1.62% gel (5.0 g dose) in hypogonadal male patients, evaluating the following two regimens:

- Dose application over 2 sites to upper arms/shoulders or abdomen via rotation (per phase 3 clinical trial usage),

vs.

- Dose application over 4 sites to both upper arms/shoulders and both sides of abdomen (per revised application instructions)."

I strongly concur with the Clinical Pharmacology decision regarding the need for additional pharmacokinetic data to link the newly proposed application method as in Study 176.1.009 to the Phase 3 study S.1.176.3.104. However, it is not entirely clear to me why additional studies or investigations are needed relevant to skin irritation, as the AndroGel 1.62% was very well tolerated in Phase 3, with little, if any, evidence of irritation over 6 continuous months of use. With this in mind, I believe that it is unlikely that the new method of application will be clinically meaningfully irritating. Nonetheless, for certainty, it is not unreasonable for application site irritation to be assessed in the multiple-dose, relative bioavailability study which will be required as part of the Complete Response.

In terms of the information submitted in the Clinical amendment, Clinical Pharmacology had the following comments (comments derived from the final Clinical Pharmacology review, section entitled "*Summary of Important Clinical Pharmacology and Biopharmaceutics Findings.*"):

- The results from the new transfer study S176.1.009 suggest that the testosterone transfer to non-dosed females was largely mitigated when contact occurred with a T-shirt barrier on male who applied a 5.0 g dose of the 1.62 % gel formulation to 4 different application sites (both upper arms/shoulders and both sides of abdomen).
- (b) (4)
  :

  (b) (4)
- While dosing over multiple sites appeared to mitigate transfer, no PK (efficacy) or safety data were available from continuous once daily application of the 1.62 % gel to

multiple application sites (both sides of upper arms/shoulders and abdomen, without rotation).

- No formal 'bridging' study was conducted to justify the applicability of the phase 3 clinical trial data (where only 2 sites were used for spreading out the 3.75 g or 5.0 g doses), to the newly proposed regimen involving use of multiple application sites despite the doubling of the application surface area with use of two additional sites. The potential impact of this increased surface area of gel application with the use of two additional application sites (relative to phase 3 usage) on PK is unknown for the new 1.62 % formulation.
- Skin safety (irritation) data following continuous once daily application to all four sites were also not available from the completed clinical trials. The proposed new application instructions require use of all four sites (at the 5.0 g dose) on a daily basis and therefore wouldn't allow rotation of sites to minimize irritation potential.
- Data were presented by the sponsor for a small group of phase 3 patients (n=41) who were identified by the case report forms to have applied the drug to multiple application sites (three or four sites) on few occasions during the study period. These data were found to be inadequate evidence due to several reasons:
    - The data originate from a group of phase 3 patients who deviated from the protocol (i.e. in using four sites instead of the protocol stipulated two site usage) and therefore use of such data for revising dosing instructions for clinical use is questionable and sets a low standard for drug approval.
    - Multiple site usage was sporadic in these patients over the 180 day study period, with only 6 patients reporting more than one occasion of documented multiple site usage on PK days.
    - During the review it was identified that several of the patients did not apply the gel per the revised dosing table shown above (17 out of 41 patients). Additionally, the degree of supervision by the clinic staff for those in clinic doses couldn't be confirmed by the sponsor.

Taken together, Clinical Pharmacology had the following conclusion:

> "*Owing to the absence of a formal study to bridge the revised dosing instructions to the existing phase 3 clinical trial data and due to the deficiencies identified with the data presented in lieu of such a study, the Office of Clinical Pharmacology finds the clinical pharmacology information submitted in the major amendment for NDA 22-309 not acceptable for approval. The sponsor has not provided adequate evidence to show that the safety of the formulation remains unaffected under the proposed new conditions of use.*"

I concur with the Clinical Pharmacology conclusion, their rationale for the conclusion, and their recommendation for action to resolve the NDA deficiency.

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. Examples of such acceptance criteria are shown in the following table*:"

Parameter	*Acceptance Criteria*
Total aerobic count	NMT 100 CFU/gm
Total Yeast & Mold	NMT 10 CFU/gm
S. aureus	Absent/1 gm
P. aeruginosa	Absent/ 1gm

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 this NDA include 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 (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 asses 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)

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/m^2.
- 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 NDA presented data 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.

Table 1: Pre-specified Testosterone Gel 1.62% Dose Titration Criteria

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

Table 2: Doses Administered

Gel Strength	Gel Dose (g)	T Dose (mg) Applied	Number of Pump Actuations
1.62%	1.25	20.3	1
1.62%	2.50	40.5	2
1.62%	3.75	60.8	3
1.62%	5.00	81.0	4

Source: adapted from Table 2, Clinical Study Report S1763104, 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 ≥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:

- Cmax ≤1500 ng/dL in ≥85% of the subjects
- Cmax between 1800-2500 ng/dL in ≤5% of the subjects
- Cmax >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: Demographics of Hypogonadal Patients in Phase III 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: pages228

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 (168 T-Gel [71.8% of randomized] and

28 [70.0% of randomized] placebo). 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 Discontination		
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 ≥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 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

		T-Gel	T-Gel	Placebo	
Study Day	Total T(Cav) ng/DL	n/N (%)	95% CI	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 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 (± SD) daily testosterone concentration of 561 (± 259) ng/dL on Day 112 (n= 179), and 536 (± 236) ng/dL on Day 182 (n= 169).

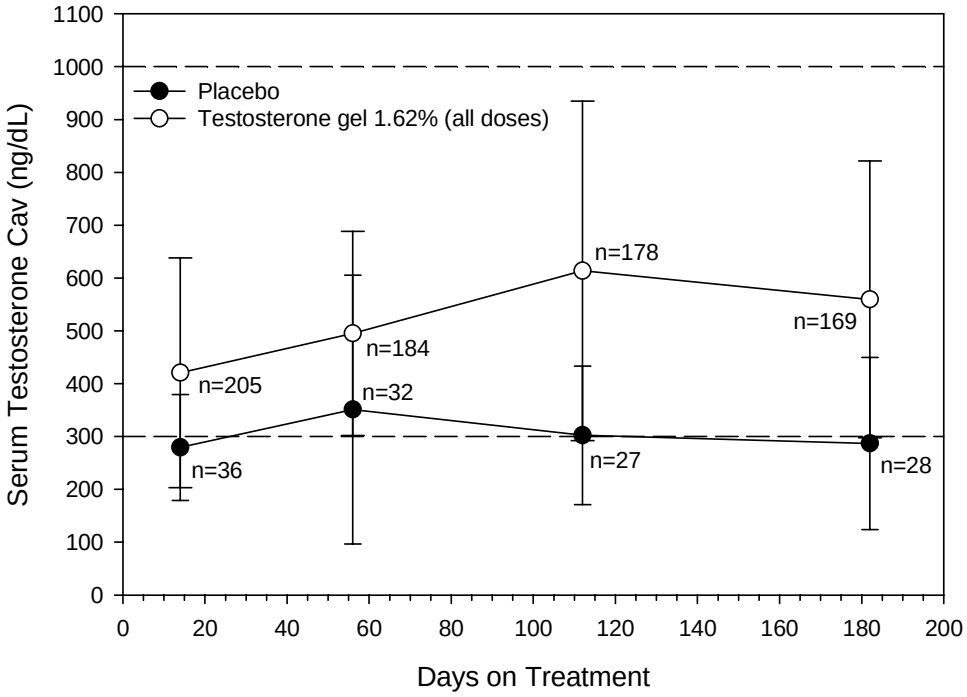


Figure 1: Mean (SD) Steady-State Testosterone C_{avg} Values in Patients on Once-Daily AndroGel 1.62% Therapy

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 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 Cavg in the normal range in more than 81% of patients without exceeding Cmax 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 subject had serum testosterone C_{max} values 1500 - 2500 ng/dL, and 2 had values > 2500 ng/dL. In actuality, 10 subjects had serum testosterone Cmax values values > 2500 ng/dL. Each of these subjects is described individually below.

7.4.1.2 Secondary Efficacy Analysis

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, ≥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 brief summary:

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 re-assessed by RIA at (b) (4) was 631 ng/dL, markedly lower than the (b) (4) result. The subject's C_{av} on Day 56 was 271 ng/dL and at 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_{av} 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_{av} 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_{av} 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_{av} 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_{av} 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)

Time	Day 56	Day112	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_{av} was 464 ng/dL on Day 182 and 519 ng/dL on Day 56. Both of these days were times where dose compliance was noted. The patient's compliance history coupled with symptoms 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 (Day146) Compliance-126%
- Visit 10 Compliance-98%.

Reviewer's Comment: The testosterone concentrations are 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/mL)

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 $C_{av\ testosterone}$ 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/mL)

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_{av} for Days 112 and 182 are 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. 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/d:

- 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 samples.

- 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

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

8. Safety

8.1 SAFETY FINDINGS

The safety data are derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008, S176.1.009 (transfer, washing and skin irritation studies), and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104.

In total, the NDA contains 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 adverse events is 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 I integrated studies or in the Phase III double-blind protocol. No deaths occurred in the 182-Day Open-Label Period.

In regard to serious adverse events, in the integrated Phase I 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 (TESAEs) 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 included (PT): 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 investigators considered the malignant hypertension "possibly related" (hematocrit was also increased in this patient) and the myocardial infarction as "unlikely related." A retinal detachment was the only TESAE 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 criterion of change from baseline >0.75ng/mL. Four other subjects had a PSA value>4 ng/mL, these subjects had PSA ≤ 4.0ng/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 III double-blind study and the integrated Phase I 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 (≥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.

There were pre-specified criteria for abnormal PSA values 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 9: Common Adverse Events (>2% for T-gel 1.62% and greater than placebo) for the Double-Blind Phase III 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 medical officer's review on pages 70-73. The transfer issue is described in the medical officer's review on page 113 - 118 and again in the medical officer's Addendum review.

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

1) Testosterone is known to stimulate erythropoeisis and can increase hemoglobin and hematocrit. In Study S176.3.104, a modest increase in mean hematotcrit was observed overall for the testosterone gel 1.62% groups compared with placebo. Several incidents of markedly high hematocrit 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). Any future labeling for AndroGel 1.62% will need to show these PSA results and explain the need for PSA monitoring.

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) (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, it would be prudent to describe this event in product labeling.

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 marginally controlled, serious hypertension at baseline. The future labeling for AndroGel 1.62% should describe this result in conjunction with the androgen class labeling for this issue.

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 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 first conducted Study S176.1.003. This study is described in detail in the medical officer's original NDA review p113 -114.

Study S176.1.003 included 16 couples randomized to 3 groups - **Group A**: direct skin contact 2 hours after dosing of a male with 5 gm, **Group B**: skin contact 2 hours after dosing of the

male with 5 gm but accompanied by donning of a long-sleeve, cotton T-shirt, and **Group C**: direct skin contact after dosing of a male with 5 gm after 12 hours. During each treatment period, couples were mandated to undergo 15 minutes of bound rubbing of abdomens (the site of gel application) prior to dosing and on each of 7 days of dosing. 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, but a T-shirt did not effectively prevent transfer.
- There was still evidence of transfer in Group C (direct contact at 12 hours) albeit less than in Group A.

The average concentrations in on-dosed women by treatment group, at nominal times after dosing in Study S176.1.003, is shown in the table below.

Table 10: Study S176.1.003 Average Testosterone (ng/dL) Concentrations by Treatment for Female Subjects

Treat-ment	Study Day	Nominal Time (h)									
		0	2	4	6	8	10	12	16	24	48
A	-1	20.1	22.6	23.6	24.9	25.8	23.1	24.0	28.9	24.6	NA
	1	24.6	36.4	45.2	56.6	47.4	60.2	57.8	81.5	46.2	NA
	7	47.0	52.9	68.0	68.5	60.4	61.0	64.2	65.2	53.3	34.0
B	-1	23.1	23.0	23.1	24.1	24.1	22.8	24.2	26.3	23.8	NA
	1	23.8	31.6	39.8	38.9	36.0	37.6	36.0	46.2	35.3	NA
	7	39.5	36.8	38.1	38.0	37.1	34.6	35.0	47.3	33.1	26.3
C	-1	22.3	23.0	26.9	29.3	27.5	29.0	28.4	27.7	21.3	NA
	1	21.3	43.8	44.1	66.3	74.7	69.6	68.6	55.2	57.4	NA
	7	32.3	51.6	47.0	48.5	55.5	55.4	52.2	48.6	41.5	30.4

NA=not applicable Source: Clinical Study Report S176.1.003 Table 10.2.1

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. This study is described in detail in the medical officer's original NDA review p114 -118.

In Study S176.1.008, the Sponsor sought to evaluate the transfer potential of a dose of 2.5 gm with and without a shirt, to evaluate the transfer potential of 5 gm with and without post-dose washing of the application site, and to evaluate the transfer potential of application of 5 gm to the arms/shoulders, as opposed to the abdomen as used for all other groups.

During each treatment group, couples were again required to make 15 minutes of bound abdomen –to abdomen contact, except in the case of Group E, which rubbed arms/shoulders. For the washing groups, men were required to take a thorough shower. The groups were as follows:

Group A: 2.5 gm applied to the abdomen. Direct contact with female 2 hours post dose.

Group B: 2.5 gm applied to the abdomen. Contact with female 2 hours post dose with the male wearing a t-shirt.

Group C: 5 gm applied to the abdomen. Direct contact with female 2 hours post dose.

Group D: 5 gm applied to the abdomen. Direct contact with female-2 hours post dose after washing of the male application site.

Group E: 5 gm applied to the upper arms/shoulders. Direct contact with female 2 hours post dose.

Group F: 5.0 gm applied to the abdomen. Direct contact with female- 2 hours post dose.

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 upper arms/shoulders contact compared to the abdomen.

The table below shows the post-contact, serum testosterone concentrations from each non-dosed females in Group B, in whom a T-shirt barrier blocked transfer of 2.5 gm.

Table 11: Protocol S176.1.1008: Baseline Adjusted Testosterone (ng/dL) Treatment B (T-Shirt Barrier)

	Nominal Time (h)									
Subject	0	2	4	6	8	10	12	16	24	48
27398	-21.2	-21.0	-18.1	-22.6	-14.8	-18.7	-14.3	-17.2	-2.20	-4.60
27400	0.40	-2.50	-2.30	-0.70	-10.1	2.50	-4.30	2.30	-40.3	-43.3
27403	14.8	0.80	12.3	17.4	16.9	4.70	14.2	11.0	-19.6	-18.8
27407	-0.10	-0.20	0.80	0.00	-0.10	1.80	6.40	8.70	3.80	2.80
27410	-1.80	-2.10	-0.60	6.40	2.60	0.20	4.20	-3.70	3.60	1.30
27412	-5.00	-1.40	3.30	0.70	1.90	-1.50	-4.90	6.80	2.50	5.10
27415	1.80	0.50	4.20	1.10	3.70	2.40	7.70	1.40	1.90	1.40
27419	9.60	1.60	13.8	11.2	8.60	7.70	4.40	2.00	-29.7	-35.7

Source: Adapted from Table 10.2.7: Clinical Study Report S176.1.1008, page 118

The next table shows the post-contact serum testosterone concentrations from each non-dose female in Group D, in whom 2-hour post-dose showering by male users successfully precluded transfer.

Table 12: Protocol S176.1.008: Baseline Adjusted Testosterone (ng/dL) Treatment D (Site Washing)

	Nominal Time (h)									
Subject	0	2	4	6	8	10	12	16	24	48
27399	0.400	8.40	4.00	2.90	1.30	4.90	3.50	3.70	2.60	3.50
27402	0.00	6.00	5.00	4.80	7.40	7.30	0.60	-4.30	1.80	-1.30
27404	4.60	3.90	3.80	-1.00	3.80	2.60	6.10	-0.80	-5.50	-4.20
27405	12.3	8.70	12.3	11.0	13.4	6.90	1.30	10.2	-6.80	-10.8
27411	21.3	16.9	2.90	7.60	-1.50	1.30	-4.00	1.60	0.70	-4.90
27413	-3.30	0.80	0.10	2.00	1.50	0.10	-0.90	0.10	1.20	3.30
27416	1.10	-1.00	-0.90	-1.50	-1.10	0.50	0.30	2.30	-6.00	-4.90
27417	11.3	5.30	0.10	-1.40	2.40	2.00	0.60	3.30	-12.2	3.30

Source: Adapted from Table 10.2.7: Clinical Study Report S176.1.1008, page 120

Finally, the Sponsor proceeded to conduct a third and final transfer study, Study S176.1.1009 to demonstrate that application of 5 gm, spread out onto 4 anatomic sites (both arms/shoulders and both sides of the abdomen) would allow for a simple T-shirt to effectively block transfer of the maximum to-be-approved dose. The results of this study constituted a large part of the major Clinical amendment that served to extend the PDUFA clock.

This study is described in detail in the medical officer's Amendment review p16 -29.

Study S176.1.1009 was a single center, single-dose, open-label study conducted in 12 male-female couples. 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. Two hours after dosing, 15 minutes of supervised bound contact took place between the men and women with the man wearing a long-sleeve T-shirt. The objective was determine whether the T-shirt effectively prevented transfer when using this new 4-anatomic site application regimen. The means to demonstrate this was to compare pre-dose serum T concerntrations to post-dose T concentrations in each woman and for the group.

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

The mean baseline testosterone (Day -1) concentration across all female subjects ranged from 6.3-57.3 ng/dL over the 24-hour Baseline measurement period. The mean testosterone concentrations across all subjects on Day 1 (the period following forced contact with dosed males) ranged from 6.3-43.5 ng/dL across the measurement period.

The next table shows the post-contact serum testosterone concentrations from each non-dose female in this study:

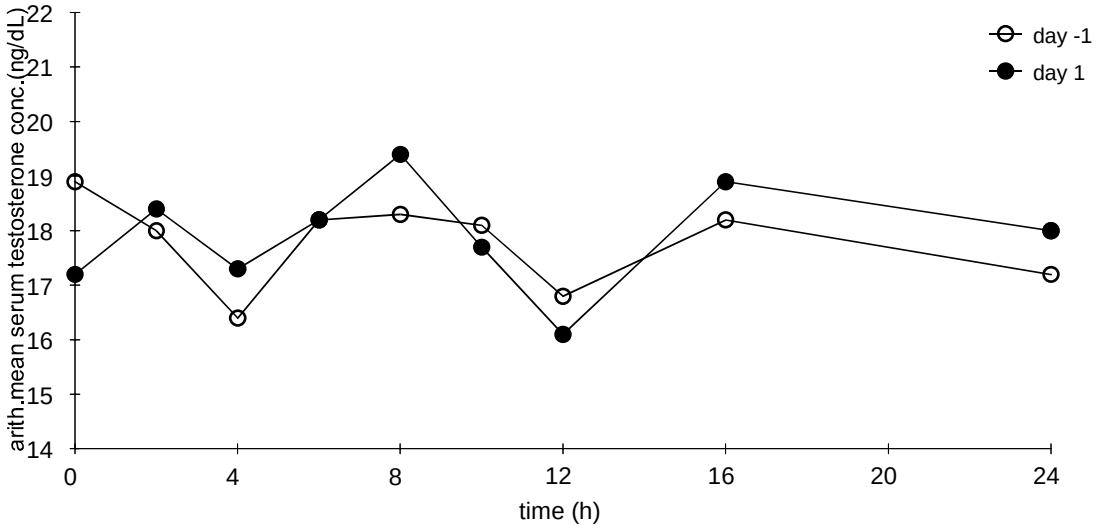
Table 13: Individual Female Subject Testosterone Concentrations (ng/dL)

(b) (4)

Source: Appendix II. Individual Subject Testosterone Concentrations, Summary Headline Results Report, pages 64-69 and Table 14.2.1.1., Table 14.2.1.2, December 11, 2009, amendment, SDN 18, Final Study Report S176.1.009 Tables 14.2.1.1, 14.2.1.2 January 15, 2010 amendment, SDN 19.

Figure 2 below shows the mean testosterone concentration profile for the female group on Day -1 and Day 1. The profiles virtually overlap.

Figure 2. Mean Testosterone Concentration-Time Profile for Day -1 and Day 1



Source: Copy of Figure 1, Preliminary Headline Results, page 7.

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

The next step in resolving the potential transfer problem for AndroGel 1.62% is to link the application site method derived from this study (Study S176.1.009), a method that allows safe use of a simple clothing barrier, to the method used in the Phase 3 Study S176.3.104. In the Phase 3 study, on each PK day, patients were supposed to apply their dose only to the arms/shoulders, and not to the arms/shoulders & abdomen nor to the abdomen alone. Throughout the Phase 3 study, patients were instructed to use the arms/shoulders, with the allowance that a rotating method was acceptable with 4 days use of arm/shoulders and 3 days abdomen, but not both at the same time. The issue that faces the review team and the Sponsor is that the new method of application that allows use of an effective clothing barrier was not used in Phase 3. Therefore, the evidence for comparability is needed. The Sponsor submitted some evidence to this end as part of the major Clinical amendment, and this information was reviewed by the medical officer (pp 30-39 of the MO's review of the Clinical Amendment) and by the Clinical Pharmacologist. In short, this information was found insufficient to support comparability of the new method to the Phase 3 method. The reader is referred to the Clinical Pharmacology section of this memo for details.

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 a 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 pp 147-159.

The major postmarketing issues (in brief) include: potential risk of prostate cancer, the unknown cardiovascular safety profile in aging males, thromboembolic events, erythrocystosis 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) will also carry over completely to the AndroGel 1.62% NDA at the time of some future approval.

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% except for the issue of testosterone transfer.

The first two transfer studies conducted by Sponsor (S176.1.003 and S176.1.008) showed that a simple T-shirt was not a fully effective barrier to transfer for the 5gm dose but was an effective barrier at the lower 2.5 gm dose. Thus, the volume of gel at a given application site was shown to play some role in penetration through a simple T-shirt barrier. In response to this circumstance, the Sponsor re-configured the application method by spreading the 5 gm dose out onto both arms/shoulders and both sides of the abdomen, resulting in 1.25 gm on each of 4 anatomic sites. This method was studied in a third transfer study (S176.1.009) and the switch resulted in a T-shirt acting as an effective barrier to transfer.

Unfortunately, the new method of application, despite being useful for the effective T-shirt barrier, was not the same as the Phase 3 method of application. The long-term impact on systemic exposure of spreading the gel out onto a larger surface area (4 sites, versus 2 sites [arms/shoulders only] has not been well characterized. The Sponsor provided data from approximately 20-40 subjects who erroneously and sporadically applied testosterone in the Phase 3 study to more application sites than recommended and these data were touted as demonstrating comparability to the new T-shirt useful method. However, the medical officer and clinical pharmacology team do not agree that these comparability data are sufficient to link

the new method to the substantial evidence of safety and efficacy from Phase 3. In fact, on its face the data appear to show at least a 20% increase in exposure with the new method.

Therefore, this application cannot be approved at this time. The Sponsor will need to demonstrate that exposures to testosterone are comparable when one applies the gel as 5 gm over both arms/shoulder & both sides of the abdomen versus when one applies 5 gm of the gel just to the arms/shoulders.

In terms of the safety results from the clinical studies conducted from this NDA, nothing else precludes approval. The data show the expected effects of a testosterone gel included increased hemoglobin and hematocrit, increased PSA, a single report of prostate cancer, lower urinary tract symptoms, acne, skin inflammation, among other conditions. The medical officer carefully reviewed 10 individual cases of supraphysiological testosterone concentrations and found them to be artifictural 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.

Finally, at such time as the product is ready for approval, then labeling will need to be completed, including the package insert, the Medication Guide and container/carton labeling. The REMS associated with the Medication Guide will also need to be completed.

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

The Applicant requested a full waiver of pediatric studies. (b) (4) 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 her final consult report dated October 6, 2009, Janice Maniwang provided comments on various sections of the label, including Highlights, Indications and Usage, Dosage and Administration, Warnings and Precautions, Clinical Pharmacology, Clinical Studies, the Patient Counseling section.

Since the application is to receive a Complete Response action based upon unresolved Safety concerns, labeling was not conveyed to Sponsor. The DDMAC comments and

recommendations will be incorporated into the labeling at such time as the safety issue is resolved, and labeling discussions ensue.

Of note, many of the DDMAC comments are related to the issue of secondary exposure of AndroGel to others (especially children and women), and subsequent to the DDMAC review, the Sponsor submitted revised labeling which accounted for this issue.

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 to (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 was 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 chromotograms 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)

On November 10, 2009, 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 September 2, 2009. DRISK commented that they took into consideration the approved AndroGel 1% REMS in reviewing the REMS proposed for this new 1.62% gel.

DRISK offered some minor editorial revisions to the REMS document itself, as well as the following comments:

- DRISK generally concurred with the parts of the REMS, including a Medication Guide and a Timetable for Submission of Assessments.
- DRISK found the goal of the REMS to be acceptable.
- DRISK found the Medication Guide distribution plan to be generally 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.

On February 26, 2010, Melissa Hulett and Mary Willy of DRISK provided a final consult regarding the Sponsor's proposed Medication Guide. The consult, in its entirety, stated:

> "*The Division of Reproductive and Urologic Products (DRUP) requested that the Division of Risk Management review proposed patient labeling for New Drug Application (NDA) 22-309 submitted by Unimed Pharmaceuticals for AndroGel 1.62% (testosterone gel).*
>
> *DRUP does not plan to address labeling during this review cycle; therefore, we will defer our review of the Medication Guide until such time as the review Division plans to address labeling. Please send us a consult request at that time.* "

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

On November 3, 2009, Jeannie Roule, the Project Manager for DRUP for this NDA finalized a memo describing why there was not a formal DMEPA review of the tradename AndroGel 1.62%.

The memo from Ms. Roule contains an April 13, 2009 eMAIL from Lori Cantin, Safety Evaluatory in DMEPA relevant to review of the trade name AndroGel. The eMAIL from Lori Cantin was sent directly to Sponsor and stated:

> "*We will review the (trade)name as it pertains to the labels and labeling, however, a specific tradename review will not be conducted based on the information you have submitted*."

On March 3, 2010, Lori Cantin and Kristine Arnwime of DMEPA provided a draft review of container/carton and package insert labeling relevant to medication errors. DMEPA also provided comments on the Sponsor's proposed "education and communication plan."

In regard to labeling, DMEPA had several comments and recommendations. For the container and carton, DMEPA stated:

- The product strengths (1% and 1.62%) are not displayed with sufficient prominence, particularly for the 1% product. Increase the prominence of the product strength for the AndroGel 1% product on the container label and carton labeling in order to highlight this information and further differentiate the 1% and 1.62% products.
- The intended space for the bearing of the required expiration date is not specified on the proposed labels and labeling. 21 CFR 201.17 requires that the expiration date appear on the immediate container and carton label. C. Ensure that the expiration date appears on the immediate container label and carton labeling as required by 21 CFR 201.17.
- The NDC number is displayed at the bottom of the principal display panel of the carton labeling and is not displayed on the immediate container label's principal display panel. Per 21CFR 207.35(b)(3)(i), if the NDC number is shown on a drug label, it shall be placed in the top third of the principal display panel of the immediate container and of any outside container or wrapper. The NDC number is also displayed as part of the bar-code symbol. If the NDC number is to appear as part of the bar-code symbol, it must be displayed prominently on both the immediate container and on any outside container or wrapper, as required by regulation. DMEPA defered to the Office of New Drug Quality Assessment to determine the correct placement and presentation for the NDC number.
- Based on the new information submitted in an amendment on November 6, 2009, the dosing table on the container label and carton labeling should be revised to reflect the number of application sites required for each dose.
- DMEPA recommended that the container/carton labeling be revised to add a statement to inform healthcare providers of the actual amount of testosterone delivered for each actuation. For example, "Each actuation delivers XXXX of testosterone."

For the package insert, DMEPA stated:

- In Section 2 (DOSAGE AND ADMINISTRATION) of the Full Prescribing Information, Table 2 does not specify that the dosing information is for the 1.62% product. Although the package insert is specific to the AndroGel 1.62% product, adding the strength of the product to the table header will increase clarity and decrease the potential for errors when prescribing, particularly if the package insert labeling is accessed via the internet. DMEPA recommended that the header for Table 2 in Section 2 (DOSAGE AND ADMINISTRATION) of the Full Prescribing Information include the strength of the product in order to improve clarity and minimize the potential for errors when prescribing.

In regard to the proposed "education and communication plan" materials, DMEPA had the following comments:

- The Applicant's proposed education and communication plan is acceptable if revised to include the new information regarding the recommended number of application sites for each prescribed dose of Androgel.

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 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. The labeling recommendations from CSS will be conveyed to Sponsor during the next cycle review when labeling discussions are held.

12. Labeling

Internal labeling discussions were initiated for this NDA but were not completed as the decision was made that the application would receive a Complete Response action. Additional information was needed to demonstrate comparability of the 4-anatomic site application technique for 5gm testosterone gel used in the most recent transfer study 009 to the 2-anatomic site (arms/shoulders or rotating arms/shoulders & abdomen) application site technique used in the Phase 3 study, 104. Labeling discussions were not held with Sponsor.

Labeling discussions will re-initiate once sufficient information has been received to demonstrate that the application method that allows for use of a simple clothing barrier compares adequately to the application method used in Phase 3.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that this new drug application receive a Complete Response.

The application lacks sufficient information to link the revised skin site application method that was used in Study S176.1.009 to the skin site application method that was used in the Phase 3 Study S176.3.104. Therefore, it is not possible to determine that the proposed new method of application, which allows use of a T-shirt as a simple barrier to transfer, conveys the same risks and benefits as the method of application used in Phase 3 to generate the substantial safety and efficacy data that supports this application.

13.2 Risk Benefit Assessment

I believe that it is not possible to draw a final conclusion about risks and benefits of AndroGel 1.62% because the information needed to do so is lacking.

As summarized in various section of this memo, a key issue for this product is the risk of secondary exposure ("transfer") to non-dosed children and women. In order to preclude such transfer, the current thinking on this issue is that a simple clothing barrier (a T-shirt, for example) is essential. The Sponsor did successfully demonstrate that a simple clothing barrier can prevent transfer of even the maximum 5 gm dose, **if** the product is applied to the body in portions of 1.25 gm to each bodily application site. Thus, if 5 gm will be used, then the patient should apply 1.25 gm to the left arm/shoulder, 1.25 gm to the right arm/shoulder, 1.25 gm to the left side of the abdomen and 1.25 gm to the right side of the abdomen. Similarly, if the patient will be applying 3.75 gm, then he should use 3 bodily sites: both arms/shoulders and one side iof the abdomen. This is a reasonable dose and administration method. However, thiis is **not** the method used in the pivotal Phase 3 study (S176.3.104). In the Phase 3 study, patients used a "rotating" application site methodology; that is, they used the arms/shoulders for several days, followed by the abdomen for several days, but not both arms/shoulders & abdomen simultaneously. In fact, on all days where efficacy was assessed (referred to as "PK days"), patients were supposed to use just the arms/shoulders.

In order to link the new recommended method (we shall refer to that method as the "4-anatomic site" method) to the Phase 3 method, the Sponsor submitted data from 41 patients in the Phase 3 study who did not adhere to the per-protocol application method. These patients did not apply gel just to the arms/shoulders on the PK days as per the protocol. Instead, they used a variety of application methods, including, but not limited to: 5gm to 4 anatomic sites, 3.75g to 3 anatomic sites, 5 gm to 3 anatomic sites, and 3.75 gm to 4 anatomic sites. It was unexpected that these protocol violations occurred at all since dosing on PK days was supposed to take place under the direct supervision of the investigator. According to the Sponsor, however, supervision on the PK days was not universal, and in fact, for these 41 subjects, supervision of dosing was admitted to be suboptimal. Of the 41 patients who constitute this subgroup (constituting 66 individual events of misapplication), case report forms show that 17 of them applied gel in a manner inconsistent with the currently proposed 4-anatomic site, to-be-marketed, administration method. Therefore, the Clinical Pharmacology team believes, and the Clinical team concurs, that data from these 17 patients cannot reasonably be included in any analysis. Based on the Clinical Pharmacology review, I identified 23 individual patients comprising this subgroup, of whom 17 patients provided just one pharmacokinetic profile, 4 patients provided 2 pharmacokinetic profiles, and 2 patients provided a single pharmacokinetic profile. It is not clear how these 23 patients actually applied the product throughout the entire study, just that they applied it incorrectly on these specific PK days.

I agree with the Clinical Pharmacology review team and medical officer that such limited and isolated data from a small group of protocol violators cannot serve to bridge the testosterone exposures associated with the new administration technique to the testosterone exposures observed using the Phase 3 technique with the degree of confidence needed for product

approval in this circumstance. Testosterone exposure is crucial, because it serves as the primary efficacy endpoint and as the most important safety surrogate marker.

I concur with Clinical Pharmacology that an additional study is needed, specifically, a Phase 1, multiple-dose, relative bioavailability study comparing the testosterone exposures obtained with use of the 4-anatomic site application method (for 5 gm) versus the Phase 3, per-protocol method (rotating method, with arms/shoulders used on the PK day). It would be prudent to conduct application site irritation assessments during this trial to compare application site irritation between the 2 methodologies.

Therefore, I find there to be a major unresolved issue which requires data from an additional clinical study. The NDA cannot be approved and a Complete Response letter should be issued.

In regard to the rest of the data submitted in this NDA, I conclude that the Phase 3 study demonstrates that the product provides acceptable testosterone exposure when used at titrated doses of 1.25 gm to 5 gm, as per the Phase 3 dosing and topical administration instructions. The requisite percentage of patients met the $C_{average}$ criteria, and in addition two of the three required $C_{maximum}$ criteria were met. In the 10 individual cases where $C_{maximum}$ was > 2500 ng/dL, 5 cases can be ascribed to artifact, 1 cases was likely to have been an artifact, and 2 cases were probably related to excessive dosing. In the two cases where no reason for the supraphysiologic concentration was obvious, the incident was isolated and sporadic, without clear clinical consequence. In fact, all 10 such events were isolated and sporadic. Therefore, I do not believe that these results alone should preclude approval.

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, a single report of prostate cancer, lower urinary tract symptoms, skin inflammation (in Phase 1 predominantly), among other conditions.

Finally, at such time as the product is ready for approval, then labeling will need to be completed, including the package insert, the Medication Guide and container/carton labeling. The REMS, which pertains to the potential risk of secondary exposure to children and women (and includes a Medication Guide) will also need to be completed.

13.3 Recommendation for Postmarketing Risk Management Activities

At the time of final approval, all postmarketing risk management requirement and activities that apply to the approved testosterone gels should be applied to AndroGel 1.62%

13.4 Recommendation for other Postmarketing Study Commitments

Currently, there do not appear to be a need for any postmarketing study commitments, aside from those already incorporated into the anticipated REMS.

13.5 Recommended Comments to Applicant

It is recommended that in advance of conducting the study, the Sponsor should discuss with the Division a draft protocol for a multiple, dose, Phase 1, relative bioavailability study. The

objective of this study should be to demonstrate that the method of skin site application that was used in Study S176.1.009 is comparable in terms of systemic testosterone exposure to the skin site application method that was used in the Phase 3 Study S176.3.104.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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
03/08/2010

GEORGE S BENSON
03/09/2010

Medical Officer's Review of Major Amendment to NDA

Application Type	NDA
Application Number(s)	22-309
Priority or Standard	Standard
Submit Date(s)	February 11, 2009
Received Date(s)	February 11, 2009
PDUFA Goal Date	December 12, 2009
PDUFA Goal Date after Major Clinical Amendment	March 12, 2010
Reviewer Name(s)	Roger Wiederhorn, Medical Officer DRUP Mark Hirsch, Team Leader, DRUP
Review Completion Date	
Established Name	Testosterone gel
(Proposed) Trade Name	AndroGel 1.62%
Therapeutic Class	Androgen
Applicant	Solvay Pharmaceuticals Inc. 901 Sawyer Road Marietta, Georgia 30062
Formulation(s)	1.62% testosterone gel
Dosing Regimen	2.5 g once daily
Indication(s)	Androgen replacement therapy in adult males
Intended Population(s)	Primary and secondary

hypogonadism (congenital or acquired)

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Appendices

Introduction AndroGel 1.62% Major Amendment

Introduction:

Prior to the Sponsor's submission of a major Clinical amendment on November 25, 2009, the Clinical review team had voiced continued safety concerns related to the potential for transfer of AndroGel 1.62% despite a simple clothing barrier. Therefore, the original Clinical review recommendation was for the application to be **Not Approved**. The issue that precluded approval was as follows:

Studies conducted to assess whether testosterone could transfer to others did not show that a T-shirt was sufficiently effective in blocking transfer of a 5 gm dose. (b) (4) The Clinical reviewers believed that relying principally on washing the application site (and studies had been conducted with washing in the shower) prior to physical contact with others to prevent transfer of testosterone was problematic in terms of patient compliance. The Clinical reviewer believed that other simpler, more feasible means, other than shower skin washing of the skin application site prior to physical contact, was needed to prevent testosterone transfer to others. The information provided by the Sponsor in the NDA submission showed that a simple T-shirt blocked transfer at the 2.5gm dose, but the T-shirt barrier did not adequately block testosterone transfer at the 5 gram testosterone gel dosage.

It was the Clinical reviewer's opinion that a proper response to this unresolved safety concern would entail generating data to show a satisfactory method for a simple clothing barrier technique. The Clinical reviewer believed that this might require modification in the method(s) of application of larger doses of testosterone gel 1.62% (e.g., application of 2.5gm on the abdomen and 2.5gm on the arms/shoulders – 4 anatomic sites). The Clinical reviewer was aware that if the dosing method was changed (e.g. spreading the larger dose out onto both sides of the abdomen and both arms/shoulders), then information would need to be submitted to demonstrate testosterone concentrations comparable to those obtained in Study S176.3.104 where the dosing schema was abdomen *or* arms/shoulders (2 anatomic sites).

The concern regarding inadequate prevention of testosterone transfer at the 5 gram testosterone gel dosage using a simple T-shirt barrier was communicated to the Sponsor on several occasions during the review. The Sponsor responded to an Information Request (in Supporting Document Number [SDN] 11, dated August 28, 2009) with a consideration of spreading out the gel application to four sites for the 5 gram dosage to increase the efficiency of T-shirt prevention of testosterone transfer. This was also mentioned in a telephone communication on September 25, 2009.

On October 16, 2009, the Division received SDN 206 to the AndroGel IND (IND# 50,377). The document contained preliminary results from Study S176.1.009 (Study 009), entitled "An Open-Label, Study of Serum Testosterone Levels in Non-Dosed Females with Secondary Exposure to Testosterone Gel 1.62%." This study further characterized the transfer potential of the 1.62% testosterone gel formulation. Evaluations were made to assess secondary exposure from dosed males to non-dosed females with a simple t-shirt barrier after application of 5 grams to the upper arms/shoulders and abdomen, bilaterally (4 anatomic sites). (The final study report was submitted on January 15, 2010).

On November 5, 2009, by email and on November 10 by EDR submission, the Sponsor submitted SDN 012 which contained:

- A Cover Letter
- An Executive Summary
- Preliminary Headline Results Report for protocol S176.1.009: "An Open-Label, Study of Serum Testosterone Levels in Non-Dosed Females Secondary Exposure to Testosterone Gel 1.62%"
- A Rationale document outlining supportive justifications regarding why the application scheme used in S176.1.009 to prevent transfer through a t-shirt (4 anatomic sites) should not adversely impact safety or efficacy conclusions from the previously completed pivotal, Phase 3 study S176.3.104,
- Rationale Table
- Proposed Revised Labeling
- Proposed Revised Medication Guide

The results of Protocol S176.1.009, on their face, with preliminary statistical comparisons, appeared to show no statistically significant differences between Baseline (Day -1) and Day 1 for serum testosterone concentrations in females after skin contact with treated males. Comparisons of baseline to Day 1 C_{av}, AUC_{0-24}, or C_{max} indicated that with four site application of 5 g of testosterone gel 1.62% in the male, a t-shirt barrier effectively blocks testosterone transfer to an unclothed female.

The Sponsor submitted an NDA amendment on November 25, 2009. This amendment contained: 1) Solvay's response to six questions posed by the Division, 2) a letter to the FDA from the Principal Investigator for the AndroGel 1.62% pivotal Phase III Study [S176.3.004], Dr Joel Kauffman, and 3) the attachments noted in the table below (related to an assessment of comparability between 4 anatomic sites and 2 anatomic site application technique):

Table 1: Appendices to Clinical Amendment

Appendix	Document Title	File Name
1	S176.3.104 Study Protocol	s1763104-prot-or-amend.pdf
2	S176.3.104 Procedural Guidance Document	Solvay-S1763104-Procedural Guidance Document-2Mar07.pdf
3	Listing of Subjects Who Dosed Multiple Application Sites	PK dose collection.rtf
4	Application Site Details from the eCRF for Titration Visits	Titration Day CRFs.doc
5	Application Site Details from the eCRF for PK Visits	CRF capture.doc
6	SAS data transport file that contains 3 datasets: bothdays.sas7bdat, dayof.sas7bdat, and predoset.sas7bdat. Data Definitions Word document that contains a printout of bothdays.sas7bdat and dayof.sas7bdat.	Fdareqst.xpt; Data definitions.doc Fdareq.doc
7	Concentration Profiles for all Applicable Subjects	Cp profiles FDA request.pdf
8	Word document that contains a printout of predoset.sas7bdat	FDARequestNov19Part2.doc

Source: Copied from cover letter, Response to Information Request for NDA 22-309, 24 November 2009.

It was the Division's judgment that all this information, taken together, constituted a major clinical amendment that could change the outcome of the review and therefore, a 90 day extension of the PDUFA goal date was granted.

On January 15, 2009, the Sponsor submitted the final report of Study S176.1.009 which was designed to demonstrate that with 4 site application of AndroGel 1.62 %, transfer of

testosterone to others through physical contact is largely prevented by a simple clothing barrier.

The review of this major Clinical amendment is essentially divided into two parts:

1. Does protocol S176.1.009 provide information suitable to conclude that 4 site male anatomic application of 5.0 gm of AndroGel 1.62% when combined with a male T-shirt barrier largely blocks the transfer of testosterone to the bare skin of a female partner when vigorous and prolonged contact occurs?

2. If protocol S176.1.009 does provide suitable information to confirm that transfer is largely blocked by the 4-site application and simple clothing barrier techniques utilized, then is there suitable PK information documenting comparable testosterone exposure in males using the 2 anatomic site versus the 4 anatomic site application method for the 5.0 gm dose of AndroGel 1.62%?

Executive Summary AndroGel 1.62% Major Amendment

Part 1: Study S176.1.009

S716.1.009 was a single center, single dose, open-label study in healthy male and female volunteers. Twelve (12) male-female couples were enrolled into the study. The purpose of the study was to evaluate skin-to-skin testosterone transfer from males using four site dosing of Testosterone Gel 1.62% (5 g) to non-dosed female subjects when contact with the application sites, upper arms/shoulders and abdomen occurs at 2 hours post-dose with a t-shirt barrier. The 5 g dose of Testosterone Gel 1.62% utilized in study S176.1.009 is the same dose that was utilized in study S176.1.003 in which a t-shirt barrier prevented approximately 50-60% of testosterone transfer when 5 g of Testosterone Gel 1.62% was applied to both sides of the male abdomen (2 anatomic sites).

Pharmacokinetic analyses were conducted only in female subjects. The mean testosterone (Day -1) baseline concentrations across all female subjects ranged from 6.3-57.3 ng/dL over the 24-hour Baseline measurement period. The mean testosterone concentrations across all subjects on Day 1 (the period following forced contact with AndroGel 1.62% dosed males) ranged from 6.31-43.5 ng/dL across the measurement period. All concentrations at Baseline and after skin contact were in the eugonadal female range (where a normal range is 8-75 ng/dL for a female population aged 18 to 61 years).

The median difference between Baseline (Day -1) and Day 1 for AUC_{0-24}, C_{avg}, and C_{max} for total testosterone in females was 33.985 ng-hr/dL, 1.42 ng/dL and 1.6 ng/dL, respectively. The 95% confidence interval for the difference between baseline (Day -1) and endpoint (Day 1) included zero for all three parameters, indicating that there was no significant differences from baseline. Transfer of testosterone to female subjects was largely prevented with a t-shirt barrier when males applied 5 g of testosterone gel 1.62% to four application sites (both upper arms/shoulders, both sides of the abdomen), sufficient to mitigate the risk of testosterone to others through physical contact.

It is this reviewer's opinion that Study S176.1.009 has provided evidence that applying 5 gm of AndroGel 1.62% to 4 anatomic sites (and similarly, by inference, 3.75 gm gel to 3 anatomic sites), is a satisfactory method for an effective clothing barrier in mitigating transfer to others through physical contact. It therefore is reasonable to proceed to the second part of the major amendment review.

Part 2: PK Evidence of Comparable Male Exposure to Testosterone between 2 Site and 4 Site Application of 5 gm of AndroGel 1.62%.

For a complete narrative of the events and submissions leading to the Division's decision to review the information that Sponsor submitted, the reader is referred to the introductory material in this executive summary. Included in this portion of the medical officer's Addendum is information to enhance the reader's understanding of the situation.

On 05 November 2009, in SDN 12, the Sponsor submitted a rationale document outlining justifications why the application scheme used in S176.1.009 to prevent transfer through a t-shirt (the 4 anatomic sites application technique) should not adversely impact safety or efficacy conclusions from the previously completed pivotal, Phase 3 study S176.3.104. After reviewing this rationale document, Clinical Pharmacology submitted the following questions to the Sponsor in an Information Request dated 18 November 2009:

1. You report that a subgroup of patients in Phase 3 has applied the testosterone 1.62 % gel to both abdomen & shoulders/upper arms on visit days (titration and PK-days).

   Per the Phase 3 study report included in NDA 22-309, patients were advised that "*study drug NOT be applied prior to study visits*" and that on PK days subjects apply the study gel "*at the clinic under direct supervision of study staff*".

   We therefore assume that dose application in those patients who used multiple application sites was also done in the clinic under supervision. In this regard, we request that you provide narratives/descriptions of the supervised dose application procedures for this subgroup of individuals, for each of the PK and titration days.

   This will be an important piece of information in our consideration of whether data obtained from this subgroup of patients would be a good representation of the multiple sites of application employed in your new transfer study S176.1.009 and proposed for use in your revised labeling included in your submission dated, November 5, 2009.

   If dosing to multiple sites in any or all of these individuals did not occur in the clinic under staff supervision and hence narratives are not available, comment on whether other records are available from those doses that can describe the method and sites of application. Any such records should be included in your response.

2. Comment as to why dosing to multiple application sites was employed in these patients and whether that was recorded as a protocol violation.

3. Provide a listing of the following information for all patients on each PK day who had applied dose to 3 or 4 application sites: Patient ID, PK day, dose, number and description of the application sites, whether dosing occurred at clinic, and PK parameters. Submit this information also for patients who used multiple sites of application on both the day before and on the day of PK. Also include plasma concentration-time profile data for these individuals. For subjects who applied dose to multiple application sites prior to a titration day provide a listing of their pre-dose concentrations. Please provide this information in SAS transport file format.

4. Comment on whether each of the patients in this subgroup was a responder or non-responder per final efficacy analyses (Day 112). Comment on whether

any of these subjects were included in the list of testosterone outliers and whether this is attributable to the use of multiple drug application sites.

5. Submit the final study report for the new transfer study S176.1.009.

6. Clarify the volume of gel for each 1.25 g pump actuation.

The Sponsor subsequently submitted a study report for Study S176.1.009, the 4-anatomic site transfer study, as well as responses to the Clinical Pharmacology request. Taken together, the Division decided that this information constituted a major clinical amendment that could change the outcome of the review and therefore, a 90 day extension of the PDUFA goal date was granted. Part 2 of this executive summary considers the Sponsor's responses relative to the comparability assessment of testosterone concentrations in men using the 4-anatomic site technique (as in transfer Study 009) versus the 2-anatomic site technique (as in the Phase 3 Study 104).

The Sponsor provides several reasons why the new 4-anatomic site application technique can be bridged to the Phase 3 results. The Sponsor's strongest argument is that some patients in Phase 3 erroneously used the 4-anatomic site technique on at least one PK day during the Phase 3 study. Data from these "protocol violators" is available and can be used to compare efficacy between the 4-anatomic site technique and the per-protocol 2-anatomic site technique. Additional arguments were also provided, including the following:

In their 05 November 2009 rationale document outlining justifications why the application scheme used in S176.1.009 to prevent transfer through a t-shirt (4 anatomic sites) should not adversely impact safety or efficacy conclusions from the previously completed pivotal, Phase 3 study S176.3.104, the Sponsor cites the results of Protocol UMD-96-012 for AndroGel 1% (NDA 21-015) which compared the testosterone exposure of subjects applying 10 g of AndroGel 1% to the left arm and left shoulder to subjects applying the same amount of AndroGel 1% to both arms and shoulders and both sides of the abdomen. By Sponsor's calculation, this resulted in application of AndroGel 1% to an area four times greater than the single site. The C_{av} was 23% higher with the four site application of AndroGel 1% compared to the one site application. The Sponsor concludes that with surface areas differing by 4-fold only a 20-30% difference in serum concentrations was noted with AndroGel 1%. The Sponsor further postulates that differences in testosterone levels when comparing application of AndroGel 1.62% to two sites compared to four are expected to be less than the differences observed in the AndroGel 1% Study which compared one site versus four sites. The limited data presented for AndroGel 1.62% suggests that exposure to testosterone increases with 4 site application versus one or two sites. Further, AndroGel 1 % and AndroGel 1.62% may not be the same in terms of absorption per application surface area.

Although pivotal Phase III protocol for AndroGel 1.62% (S176.3.104) specified the application of gel to the arms/shoulder on PK days, the Sponsor states that the data collected indicate a small subset of participants applied the gel to multiple sites on the

day of and/or the day before PK visits. It is stated on Page 26 of the NDA submission that on days where 24-hour PK sampling was conducted, subjects applied the study gel to the upper arms/shoulders at the clinic under direct supervision of the study staff. However, as per the electronic CRFs, there were subjects who applied AndroGel 1.62% to the abdomen, and to both the arms/shoulders and abdomen on PK days. The table below illustrates the number of patients who used each site of application.

Table 1: Number of Subjects Who Employed the Abdomen, Arm/Shoulder, and Abdomen + Arm/Shoulders Application Sites on PK Day in Study 104

PK Day	Application Site		
	Abdomen	Arm/Shoulder	Abdomen and Arm/Shoulder
14	26	142	2
56	12	131	22
112	8	153	18
182	8	139	18

Source: Appendix 5 of November 24, 2009, submission.

The Sponsor provided a comparative analysis of testosterone concentrations in patients using multiple sites versus those using the per-protocol 2 sites (shown in Table 2 below). This exploratory analysis suggests that there may be a difference of as much as 20%, or more, with regard to testosterone exposure with 2 site versus 3 or 4 site application of AndroGel 1.62% on PK days 112 (efficacy endpoint) and 182. Based upon the evidence provided and this exploratory relative bioavailability analysis, it would be problematic to assume comparable T concentrations between the 4-anatomic site regimen used in Study 009 and the per-protocol regimen in the Phase 3 study 104.

Table2: PK Results Based on Application Site on PK Day

Application Site/PK Day	**Mean C_{av}**	**Mean C_{max}**	**Mean AUC**
Day 56			
Abdomen	522.8	745.3	12550
Arm/Shoulder	458.9	725	11020
Arm/Shoulder/Abd	459.4	665.3	11030
Day 112			
Abdomen	502.3	759.4	12040
Arm/Shoulder	556	834.2	13350
Arm/Shoulder/Abd	628.7	975.2	15100
Day 182			
Abdomen	427.4	622.6	10280
Arm/Shoulder	533.4	802.7	12810
Arm/Shoulder/Abd	607.3	934	14570

Source: Tables 12.4.6 to 12.4.8, Module 5.4-Rationale Table, SDN 13. The values above are for all AndroGel 1.62% doses and reflect sporadic 3 and 4 site application, not uniform application.

In their 30 November 2009 amendment, the Sponsor documents 66 individual incidents where patients in the Phase 3 Study 104 applied AndroGel 1.62% to more than the recommended anatomic sites. In 41 unique patients, one or more incidents of application of AndroGel 1.62% occurred in the 3.75 g and 5.0 g dose groups on PK Days 56, 112 and 182.

In their final review, page 3, the Clinical Pharmacology review team concluded:

> "The Office of Clinical Pharmacology has reviewed the original NDA submitted on 02/11/2009, as well as major amendment related submissions for NDA 22-309 [AndroGel® (Testosterone gel) 1.62 %]. The information contained within NDA 22-309 is **not acceptable** for approval from a Clinical Pharmacology perspective. Based on the review of the major amendments submitted on 11/06/2009, 11/24/2009, 12/03/2009, 12/11/2009, 12/23/2009, and 01/15/2010, the sponsor has not provided adequate evidence to justify that the safety and efficacy of the drug would remain unchanged under the proposed new conditions of use.

- The proposed revisions to the application instructions for AndroGel 1.62 % gel require the use of both shoulders/upper arms as well as the abdominal sites for the two higher doses (i.e. three sites and four sites, respectively for the 3.75 g and 5.0 g doses). While this regimen has been demonstrated to mitigate transfer to non-dosed individuals, this is different from the phase 3 clinical trial (S176.3.104), in which dose was applied to either shoulders/upper arms or abdomen but not to both at the same time (i.e. two sites). The potential impact of this increased surface area of gel application with the use of additional application sites (relative

to phase 3 usage) on the pharmacokinetics (PK) is unknown for the new 1.62 % formulation.

- The proposal to use limited PK information from a subgroup of phase 3 patients who'd deviated from the protocol and have documented sporadic use of the gel onto multiple application sites is considered as inadequate evidence in this regard and sets a low standard for approval."

Reviewer's Overall Findings and Conclusions for Major Amendment

1. It is this reviewer's opinion that Study S176.1.009 has provided evidence that applying 5gm of AndroGel 1.62% to 4 anatomic sites (and similarly, by inference, 3.75 gm gel to 3 anatomic sites), is a satisfactory method for an effective simple clothing barrier in mitigating transfer to others through physical contact.

2. Sponsor has failed to provide suitable PK information documenting comparable testosterone exposure in males using the 2 anatomic sites versus the 4 anatomic site application method for the 5.0 gm dose of AndroGel 1.62% or for the 3 site application method for the 3.75 gm dose of AndroGel 1.62%.

Recommendation on Regulatory Action

The medical reviewer agrees with the Office of Clinical Pharmacology that the data supporting NDA 22-309 is not acceptable. The reviewer recommends that the application should receive a **Complete Response** action at this time**.** Current data and studies submitted are not sufficient in providing suitable PK information documenting comparable testosterone exposure in males using the 2 anatomic site versus the 4 anatomic site application method for the 5.0 gm dose of AndroGel 1.62% or for the 3 site application method for the 3.75 gm dose of AndroGel 1.62%. A **COMPLETE RESPONSE** to this unresolved safety concern would entail generating data to show comparable testosterone exposure in males using the 2 anatomic site application scheme as in Phase 3 to the 4 anatomic site application method used in transfer study 009 for the 5.0 gm dose of AndroGel 1.62% or for the 3 site application method for the 3.75 gm dose of AndroGel 1.62%.

Appendix I: Protocol S176.1.009

1. Executive Summary:

The purpose of this part of the Addendum review is to determine whether Study S176.1.009 (Study 009) generated sufficient data to show that application of 5 grams of AndroGel 1.62% to 4 anatomic sites combined with a simple t-shirt barrier largely blocks transfer to an unclothed female. Previous studies had demonstrated a small amount of transfer to a female partner despite a t-shirt barrier when 5 grams of AndroGel 1.62% was applied to just 2 anatomic sites. This was an unresolved Clinical safety concern for NDA 22309. Prior to the NDA goal date, the Sponsor submitted preliminary data from Study 009, which they believed resolved the concern by spreading the highest dose out onto 4 anatomic sites. The final study report was submitted on January 15, 2010. It is this reviewer's opinion that Study S176.1.009 resolves the safety concern as it has generated data to showing a satisfactory method for the application site/clothing barrier technique.

Since the new "4-site" method will become the to-be-marketed use, we asked that Sponsor provide evidence that testosterone concentrations will be comparable between the new "4-site" method and the old "2-site" method used in Phase 3. Analysis of the Sponsor's "comparability" data, between males using this new application technique and males using the per-protocol, Phase 3 technique will be reviewed separately.

2. Background:

The reader is referred to the original Clinical review, which provided a recommendation that NDA 22-309 for AndroGel 1.62% be **NOT APPROVED** and that a **Complete Response** action be taken. The issue that precluded approval was as follows:

Studies conducted to assess whether testosterone could transfer to others did not show that a T-shirt was sufficiently effectively in blocking transfer of a 5gm dose. Since the Sponsor acknowledged that a T-shirt was not a completely effective means of blocking transfer, the proposed label emphasized washing the application site prior to anticipated physical contact as the principal risk mitigation strategy for transfer. The Clinical reviewers believed that relying principally on washing the application site (in the shower) prior to physical contact with others to prevent transfer of testosterone was problematic in terms of patient compliance. The Clinical reviewer believed that other simpler, more feasible means, other than shower skin washing of the skin application site prior to physical contact, was needed to prevent testosterone transfer to others. The information provided by the Sponsor in the NDA submission showed that a simple T-shirt blocked transfer at the 2.5gm dose, but the T-shirt barrier did not adequately block testosterone transfer at the 5 gram testosterone gel dosage. It was the Clinical reviewer's opinion that a **COMPLETE RESPONSE** to this unresolved safety concern would entail generating data to show a satisfactory method for a clothing barrier technique. The Clinical reviewer believed that this might require modification in the method(s) of application of larger doses of testosterone gel 1.62% (e.g., application of 2.5gm on the abdomen and 2.5gm on the arms/shoulders – 4 anatomic sites). The Clinical reviewer was

aware that if the dosing method was changed (e.g. spreading the larger dose out onto both sides of the abdomen and both arms/shoulders), then appropriate PK data would need to be submitted to demonstrate testosterone concentrations comparable to those obtained in Study S176.3.104 where the dosing schema was abdomen *or* arms/shoulders (2 anatomic sites).

The concern regarding inadequate prevention of testosterone transfer at the 5 gram testosterone gel dosage using a simple T-shirt barrier was communicated to the Sponsor on several occasions during the review. The Sponsor responded to an Information Request (in Supporting Document Number [SDN] 11, dated August 28, 2009) with a consideration of spreading out the gel application to four sites for the 5 gram dosage to increase the efficiency of T-shirt prevention of testosterone transfer. This was also mentioned in a telephone communication on September 25, 2009.

On October 16, 2009, the Division received SDN 206 to the AndroGel IND (IND# 50,377). The document contained preliminary results from Study S176.1.009 (Study 009), entitled "An Open-Label, Study of Serum Testosterone Levels in Non-Dosed Females with Secondary Exposure to Testosterone Gel 1.62%." This study further characterized the transfer potential of the 1.62% testosterone gel formulation. Evaluations were made to assess secondary exposure from dosed males to non-dosed females with a simple t-shirt barrier after application of 5 grams to the upper arms/shoulders and abdomen, bilaterally (4 anatomic sites).

On November 5, 2009, by email and on November 10 by EDR submission, the Sponsor submitted SDN 012 which contained:

- A Cover Letter
- An Executive Summary
- Preliminary Headline Results Report for protocol S176.1.009: "An Open-Label, Study of Serum Testosterone Levels in Non-Dosed Females Secondary Exposure to Testosterone Gel 1.62%"
- A Rationale document outlining supportive justifications regarding why the application scheme used in S176.1.009 to prevent transfer through a t-shirt (4 anatomic sites) should not adversely impact safety or efficacy conclusions from the previously completed pivotal, Phase 3 study S176.3.104,
- Rationale Table
- Proposed Revised Labeling
- Proposed Revised Medication Guide

The results of Protocol S176.1.009, on their face, with preliminary statistical comparisons, appeared to show no statistically significant differences between Baseline (Day -1) and Day 1 after skin contact for C_{av}, AUC_{0-24}, or C_{max} indicating that with four site application of 5 g of testosterone gel 1.62% in the male, a t-shirt barrier effectively blocks testosterone transfer to an unclothed female.

The Sponsor's justifications why the 4 site application scheme used in S176.1.009 provide testosterone concentrations comparable to those observed in the Phase 3 study,

which employed a 2-site application scheme, are considered in Appendix 2 of this review.

On January 15, 2009, the Sponsor submitted the final report for transfer Study S176.1.009 which was designed to demonstrate that with 4 site application of AndroGel 1.62 %, transfer of testosterone to others through physical contact is largely prevented by a simple t-shirt barrier. The medical officer's review of Study S176.1.009 is provided here.

3. Study S176.1.009: An Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62%.

Design and Conduct of Study S176.1.009

Basic Design:
The primary study objectives were:

- To determine the pharmacokinetics of total testosterone concentrations in female subjects after a single episode of skin contact with a male partner dosed with Testosterone Gel 1.62% (5 g) applied to both arms and shoulders and the right and left abdomen (four site application).
- To evaluate skin-to-skin testosterone transfer from males using four site dosing of Testosterone Gel 1.62% (5 g) to non-dosed female subjects when contact with the application sites, upper arms/shoulders and abdomen occurs at 2 hours post-dose with a t-shirt barrier.

There are no secondary objectives listed.

> *Reviewer's Comment: The primary objective of this study was to show that a t-shirt barrier effectively blocks the transfer of testosterone to a female partner after a single episode of skin contact, when the male applied 5 gm to both sides of the abdomen and both arms/shoulders (4 anatomic sites). The primary objective is appropriate in this circumstance.*

The safety objectives were to monitor and evaluate the safety of the subjects throughout the study.

This was a single center, single dose, open-label study in healthy male and female volunteers. Twelve (12) male-female couples who provided consent to participate in this study and met the inclusion/exclusion criteria would be enrolled into the study. All male-female couples enrolled would undergo the same dose and skin contact procedures.

The test product was Testosterone Gel 1.62%, 5 g of gel, containing 81 mg testosterone.

On Study Day 1 all male subjects received an application of testosterone gel. Two hours following gel application to the male subjects, 15 minutes of supervised skin contact of

the application sites occurred between the dosed female and the non-dosed female partner as described below:

Males-Application of testosterone gel to the upper arms/shoulders and abdomen (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).

Dose application for each male subject occurred under the supervision of the clinical staff. Within one hour prior to the targeted time of dose application, male subjects showered and washed the application site with soap and water. Subjects were not to remain in the shower for longer than 10 minutes. The designated area for gel application was thoroughly dried.

Females- Skin contact with application site at 2 hours post dose; male wearing a t-shirt. The t-shirt to be used was a 100% cotton long-sleeved t-shirt that fully covered the application sites.

Female subjects showered within 30 minutes prior to the contact time and the abdomen and shoulder/arms were thoroughly dried. Female subjects were given a tube top to wear to expose the shoulders/arms and abdomen.

Each couple engaged in a total of 15 minutes of contact in a vertical position. A waistband was placed around the couple to ensure maximum contact. During the contact session, the couples swayed their abdomens in opposing directions (left/right)
for a duration of 1 minute starting at the beginning of minute 2, 5, 8, 11, and 14. In addition, the female continuously kept her arms resting on the male's shoulders, and for a duration of 1 minute starting at the beginning of minute 3, 6, 9 12, and 15, female subjects were instructed to rub their hands, wrists, arms, and shoulders up and down the arms and shoulders of their male partner. After contact, female subjects waited at least 5 minutes prior to putting clothes over the exposed area. Female subjects thoroughly washed their hands with soap and water immediately after skin contact was complete. Female subjects were not to shower or bathe until 24 hours after the contact period. The antecubital region of the female's arms was covered during the contact period to prevent potential blood sample contamination.

> *Reviewer's Comment: The treatment techniques in this transfer study are similar to the previously conducted transfer studies, S176.1.003 and S176.1.008. While these study techniques are somewhat contrived and exaggerate the degree of contact between dosed males and non-dosed females, they are considered appropriate in this circumstance because they serve to represent an extreme "worst-case" scenario.*

Dose Rationale: Spreading the 5gm (highest) dose out onto 4 anatomic sites was discussed by the Sponsor as a possible method to mitigate skin transfer of testosterone in combination with a t-shirt barrier. The 5 g dose of Testosterone Gel 1.62% to be utilized in study S176.1.009 is the same dose that was utilized in study S176.1.003 in which a t-

shirt barrier prevented approximately 50-60% of testosterone transfer when 5 g of Testosterone Gel 1.62% was applied to both sides of the male abdomen (2 anatomic sites).

> *Reviewer's Comment: The 4-anatomic site method is reasonable to investigate and the 5 g dose of Testosterone Gel 1.62%, as 5 g is the highest proposed dose. If the t-shirt successfully blocks testosterone transfer after 4 site application, the Sponsor proposes to recommend 3 site dosing of the 3.75 g Testosterone Gel 1.62% treatment without formal transfer testing. I feel this is reasonable.*

Safety Parameters and Endpoints: Separate male and female safety samples were used for the analysis of the safety and tolerability data. AEs were reported on a per-subject basis, i. e. counting subjects rather than events for the applicable period. If the event occurred more than once in the applicable period, the event was assigned the worst severity, the closest relationship to the study drug, and the earliest starting date. Only treatment emergent AEs were reported, but in the listings, all occurrences of AEs were presented.

Vital signs, including changes from baseline were summarized. Laboratory variables, including changes from baseline were summarized. Safety testosterone and hematocrit laboratory values were listed.

Pharmacokinetic measurements from female subjects only were done for determination of total testosterone, estradiol, and dihydrotestosterone at the following times:

- Day-1 (baseline) at 0, 2, 4, 6, 8, 10, 12, 16 hours with respect to the planned end time of skin contact on subsequent days.
- Day 1 at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 16, 24 and 48 hours after the end of skin contact

Table 2: Female Assessments

Female Subjects

Assessment	Days															
	-23 to -2	-2	-1	1	2	~~3~~	~~6~~	~~7~~	~~8~~	~~9~~	~~10~~	~~13~~	~~14~~	~~15~~	~~16~~	*3* ~~17~~ or Early Termination
Screening	X					-		-	-	-	-		-	-	-	
Medical History	X					-		-	-	-	-		-	-	-	
Physical Examination, including weight	X					-		-	-	-	-		-	-	-	X
Height and BMI	X					-		-	-	-	-		-	-	-	
CBC, Clinical Chemistry, Urinalysis	X					-		-	-	-	-		-	-	-	X
Testosterone for Inclusion	X					-		-	-	-	-		-	-	-	
Viral Screen	X					-		-	-	-	-		-	-	-	
Serum β-HCG	X	X				-	~~X~~	~~X~~	-	-	-	~~X~~	~~X~~	-	-	X
Drug and Alcohol Test	X	X				-	~~X~~	~~X~~	-	-	-	~~X~~	~~X~~	-	-	
12 Lead ECG	X					-		-	-	-	-		-	-	-	X
Record Date Last Menstrual Period		X				-		-	-	-	-		-	-	-	
Admit to Clinic		X				-	~~X~~	~~X~~	-	-	-	~~X~~	~~X~~	-	-	
Vital Signs (BP, pulse, temp)	X	X	X	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
Contact Site Evaluation			X	X	X	~~X~~		~~X~~	~~X~~	~~X~~	-		~~X~~	~~X~~	~~X~~	X
Skin Contact with Male Partner				X		-		-	~~X~~	-	-		-	~~X~~	-	
PK Blood Sample			X[1]	X[2]	X[2]	~~X~~[2]		~~X~~[4]	~~X~~[2]	~~X~~[2]	~~X~~[2]		~~X~~[4]	~~X~~[2]	~~X~~[2]	X[2]
Baseline/Adverse Event Recording	X	X	X	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
Record Concomitant Medication	X	X	X	X	X	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
Discharge from Clinic						~~X~~[3]		-	-	-	~~X~~[3]		-	-	-	X[4,3]
Study Completion						-		-	-	-	-		-	-	-	X

[1]At 0, 2, 4, 6, 8, 10, 12, and 16 hours relative to the projected time of skin contact on ***Day 1*** ~~subsequent days~~.
[2]At 0, 2, 4, 6, 8, 10, 12, 16, 24, and 48 hours after end of skin contact on Days ~~1, 8 and 15~~.
[3]Females will be discharged from the clinic on Days 3 ***after the post-study assessments are complete*** ~~and 10 after study assessments are complete~~.

Source: Copied from Page 36 of protocol submission

Table 2: Male Assessments

Male Subjects

Assessment	Days						
	-23 to -2	-1	1	~~7~~	~~8~~	~~14~~	*1* ~~15~~ or Early Termination
Screening	X		-	-	-	-	
Medical History	X		-	-	-	-	
Physical Examination, including weight	X		-	-	-	-	X
Height and BMI	X		-	-	-	-	
CBC, Clinical Chemistry, Urinalysis	X		-	-	-	-	X
PSA	X		-	-	-	-	X
DRE	X		-	-	-	-	~~X~~
Viral Screen	X		-	-	-	-	
Drug and Alcohol Test	X	X	-	~~X~~	-	~~X~~	
12 Lead ECG	X		-	-	-	-	X
Admit to Clinic		X	-	~~X~~	-	~~X~~	
Vital Signs (BP, pulse, temp)	X	X	~~X~~	~~X~~	~~X~~	~~X~~	X
Application Site Evaluation		X	~~X~~	~~X~~	~~X~~	~~X~~	X
Dose Application			~~X~~	-	~~X~~	-	X
Skin Contact with Female Partner			~~X~~	-	~~X~~	-	X
Baseline/Adverse Event Recording	X	X	~~X~~	~~X~~	~~X~~	~~X~~	X
Record Concomitant Medication	X	X	~~X~~	~~X~~	~~X~~	~~X~~	X
Discharge from Clinic			~~X~~[1]	-	~~X~~[1]	-	X[2,1]
Study Completion			-	-	-	-	X

[1]Males will be discharged from the clinic on Days 1 ***after post study assessments are complete*** ~~and 8 after study assessments are complete~~.
[2]~~Males will be discharged from the clinic on Day 15 after study assessments are complete.~~

Source: Copied from page 37 of protocol submission

Reviewer's Comment: The safety parameters, endpoints and assessments appear appropriate.

Inclusion and Exclusion Criteria:

Inclusion Criteria

Males

1. Documentation of written informed consent.
2. Male subjects 18-80 years of age, inclusive
3. Subjects with a Body Mass Index of 20-35 kg/m^2, inclusive.
4. In the opinion of the investigator, the subject is determined to be in good health as determined by vital signs, medical history, physical exam, ECG, and laboratory examination (hematology, clinical chemistry, and urinalysis).
5. Negative hepatitis B/C and HIV.

Females

1. Documentation of written informed consent.
2. Female subjects 18-80 years of age, inclusive.
3. In the opinion of the investigator, the subject is determined to be in good health as determined by vital signs, medical history, physical exam, ECG, and laboratory examination (hematology, clinical chemistry, and urinalysis).
4. Subjects with a Body Mass Index of 20-30 kg/m^2, inclusive.
5. Subjects with a screening testosterone in the normal range, as specified by the normal range at the testing facility.
6. Negative hepatitis B/C and HIV.

Exclusion Criteria

Male

1. Positive screen for alcohol or drugs of abuse.
2. Subject with a hematocrit >48%.
3. Previous history of, or current or suspected, prostate or breast cancer.
4. Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
5. Findings of any kind of skin lesions on the skin surface of the upper arms/shoulders and abdomen during physical examination (small tattoos are acceptable).
6. Participants in any investigational drug trial within the previous 30 days.
7. Receipt of any prescription medication within 21 days prior to Day -2 of the study or receipt of non-prescription (OTC) medication within 7 days of Day-2 without sponsor approval.
8. Subjects who smoked or used other nicotine products within the past 12 months.
9. Consumption of caffeine-containing products in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day -2 (caffeine-containing products were not allowed during each study period).

10. Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.
11. Baseline Prostate Specific Antigen (PSA) > 2.5 ng/mL. If the subject has documentation of a negative prostate biopsy within the past six months, a PSA of 2.6-3.74 ng/mL will be allowed.
12. Abnormal digital rectal examination (DE) defined as presence of nodule or induration.
13. Untreated prolactinoma.
14. Previous history of, or current or suspected, eczema or psoriasis.

Female

1. Subjects who are pregnant or lactating.
2. Subjects of child-bearing potential who are not using an acceptable method of birth control. Barrier methods of birth control (i. e., diaphragm/condom with spermicide) are acceptable for study participation. Oral or implanted contraceptives are unacceptable methods of birth control for study participation. Female subjects who are surgically sterile are enrolled.
3. Previous history of, or current or suspected, hirsutism.
4. Participants in any investigational drug trial within the previous 30 days.
5. Positive screen for alcohol or drugs of abuse.
6. Receipt of any prescription medication within 21 days prior to entry into the study, or receipt of non-prescription medication or herbal products within 7 days of study commencement without sponsor approval.
7. Blood or plasma donation within the 60 days prior to study entry.
8. Subjects with any clinical/biochemical impairment of liver function or receipt of known hepatic enzyme inducing or inhibitory agents within 90 days prior to entry into study.
9. Use of any drug with a half-life greater than 24 hours in the past 12 months without sponsor approval.
10. Subjects who smoked or used other nicotine products within the past 12 months.
11. Consumption of caffeine-containing products in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day -2 (caffeine-containing products were not allowed during each study period).
12. Findings of any kind of skin lesions on the skin surface of the upper arms/shoulders and abdomen during physical examination (small tattoos are acceptable).
13. Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.
14. Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
15. Previous history of, or current or suspected, eczema or psoriasis.

Reviewer's Comment: The eligibility criteria are reasonable.

Statistical Considerations:

Sample size calculation: The Sponsor estimated that a sample size of 12 couples would give 80% power to detect a change from baseline in the serum testosterone of non-dosed females, given that the true mean difference is 9 ng/dL with a standard deviation of 10 ng/dL (based on the results from the S176.1.003 study), using a paired t-test.

Statistical analysis plan: The protocol stated that the default summary statistics for quantitative and ordinal variables would be the number of observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) for subjects with data. Any other summary statistics would be described on an individual basis. For qualitative variables, per category the numbers and frequencies of subjects with non-missing data (n, %) would be the default summary presentation, and if appropriate and present, the number of missing values.

The safety sample would consist of all subjects who had exposure to at least one dose of study medication. The pharmacokinetic (PK) sample would consist of all subjects included in the safety sample and who had sufficient bioanalytical assessments to calculate a complete set of the primary pharmacokinetic parameters. The following PK parameters were calculated:

- C_{trough} = observed predose serum concentration, representing the troughs
- C_{min} = the lowest concentration observed during the 24-hour dosing interval
- C_{max} = observed maximum serum concentration
- T_{max} = time to reach maximum observed serum concentration
- T_{min} = time of minimum observed serum concentration
- $AUC_{(0-24)}$ = area under the serum concentration-time curve from zero to 24 hours
- C_{av} = the time=averaged concentration over the dosing interval, determined by $AUC_{(0-24)}/24$
- PTF = peak trough fluctuation, determined by $(C_{max}- C_{min}/ C_{av})$

The objective was to assess within treatment differences in $AUC_{(0-24)}$, C_{av}, and C_{max} pharmacokinetic parameters for total testosterone between baseline (Day-1) and Day 1. Comparisons to baseline was the primary analysis. Two- sided 90% confidence intervals were calculated for each parameter.

Interim analysis: Not applicable

Safety Considerations: The risks of a single dose of testosterone in healthy eugonadal males were considered minimal. The risk of transfer to a female partner was considered small, and even if such was to occur, testosterone is rapidly metabolized and would not be expected to be of harm in this single dose study, especially in women who are surgically sterilized or using an acceptable form of contraception. In a previous transfer study (S176.1.003), which included treatment arms of direct male to female skin contact, as well as contact with the male wearing a t-shirt barrier, there were only rare occurrences of testosterone levels above the normal range for female subjects. The most frequent TEAEs were headache, dyspepsia, and dizziness. There were no withdrawals due to AEs

and there were no SAEs or deaths. This previous study required males to apply testosterone gel 1.62% daily for 7 days, compared to a single day for Study 009.

> *Reviewer's Comment: I expect the TEAEs in this study to be similar in type and less than the 20.8% incidence for both male and female subjects noted in study S176.1.003 as there is only one male application of testosterone gel as opposed to daily application for seven days. Further, the dose is being spread out onto 4 application sites, lessening the already small risk of transfer to female subjects.*

Study Results:

Disposition of Subjects and Demographics: A total of 12 male-female subjects were enrolled into the study, completed the single dose and contact period, and completed the study according to the protocol. Subjects 27474 (male) and 27447 (female) were replaced by stand-by Subjects 27448 (male) and 27457 (female) prior to dosing as the male partner had hypertension prior to dosing.

Table 3. Subject Demographics

Gender	N	Age	BMI (kg/m^2)
Males	12	46 (23-59)	27 (21-31)
Females	12	41 (24-50)	25 (21-30)

Source: Table 1 of Preliminary Headline Results Report, 5 November 2009, page 2.

One female was 50 years-old, 3 female subjects were 45-49 years-old, 2 female subjects were 40-44 years-old, 6 female subjects were 30-39 years-old, and one subject was 24 years old.

Female subject 27449 had her last menstrual period in 2003 and female subject's last menstrual period was 24 July 2007. All other female subjects had their last menstrual period within 30 days of Day -1. There was no attempt to standardize the episode of skin contact with a male dosed with AndroGel 1.62% with respect to the female's menstrual cycle (Listing 16.2.6.1).

Female subject 27446 underwent bilateral ovarian cystectomy in 2001. It is of note that this subject on Day-1 had the highest serum concentrations of total testosterone at all PK sampling time periods time periods amongst the 12 female subjects. On Day 1 Female subject 27446 also had the highest serum concentrations of total testosterone at all PK sampling time periods except the 8 hour sampling time. Female subject 27446 had a BMI of 21.7, had no abnormalities noted on physical examination, was normotensive, and had normal blood glucose and serum cholesterol. In the Final Study Report there is no additional history.

> *Reviewer's Comment: In light of no additional history justifying removal of this subject, I would not suggest analyzing the data with this subject excluded.*

Table 4: Ethnicity

Gender	N	White Not Hispanic or Latino	White Hispanic or Latino	Black	Asian
Males	12	0(0.0%)	11 (91.7%)	1 (8.3%)	0 (0.0%)
Females	12	0(0.0%)	11 (91.7%)	1 (8.3%)	0 (0.0%)

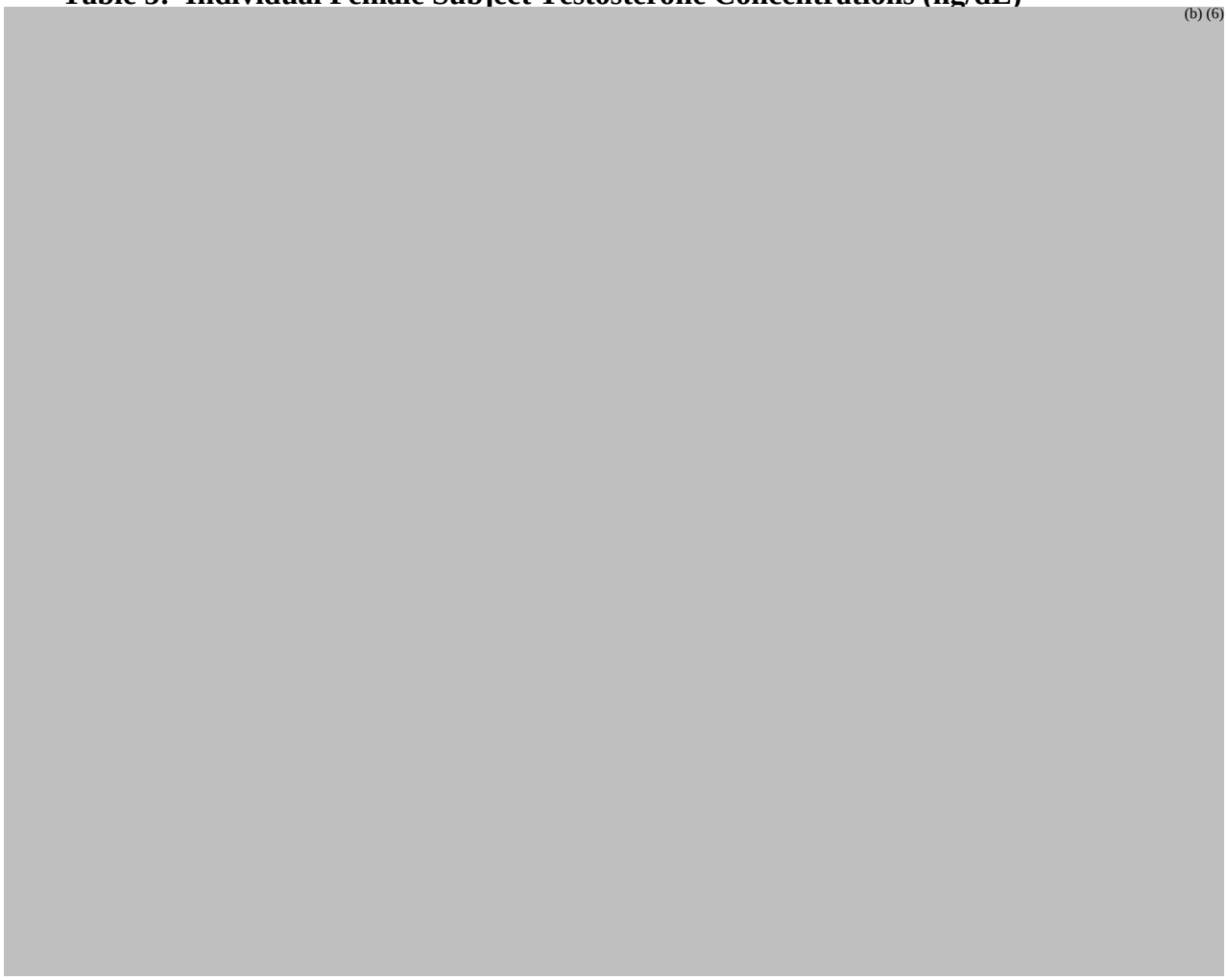
Source: Table 2 of Preliminary Headline Results Report, 5 November 2009, page 2.

Pharmacokinetic Results:

Pharmacokinetic analyses were conducted only in female subjects. The mean baseline testosterone (Day -1) concentration across all female subjects ranged from 6.3-57.3 ng/dL over the 24-hour Baseline measurement period. The mean testosterone concentrations across all subjects on Day 1 (the period following forced contact with dosed males) ranged from 6.3-43.5 ng/dL across the measurement period. All concentrations at Baseline and after skin contact were in the eugonadal female range (where a normal range is 8-75 ng/dL for a female population aged 18 to 61 years). Individual testosterone concentrations for each female subject are provided in the table below:

Table 5: Individual Female Subject Testosterone Concentrations (ng/dL)

(b) (6)



Headline Results Report, pages 64-69 and Table 14.2.1.1., Table 14.2.1.2, December 11, 2009, amendment, SDN 18, Final Study Report S176.1.009 Tables 14.2.1.1, 14.2.1.2 January 15, 2010 amendment, SDN 19.

Reviewer's Comment: Table 5 demonstrates no notable increase from baseline for any of 9 sampling timepoints in any of the 12 female subjects.

Selected individual testosterone pharmacokinetic summarized parameters for Day-1 and Day 1 for each of the female subjects are shown in the table below:

Table 6: Selected Individual Pharmacokinetic Parameters for Day – 1 and Day 1 (Individual Female Subjects)

Subject N=12	**T_{max} Day-1**	**T_{max} Day 1**	**C_{max} Day-1**	**C_{max} Day 1**	**AUC/C_{av} Day-1**	**AUC/C_{av} Day 1**
	(h)		**ng/dL**		**h*ng/dL**	
27445	2.00	8.00	21.5	37.5	430/17.9	484/20.2
27446	0.00	6.00	57.3	43.5	1067/44.5	831/34.6
27448	24.0	16.0	24.6	28.5	528/22.0	611/25.5
27449	24.0	24.0	9.29	9.31	175/7.28	193/8.04
27450	16.0	6.00	21.1	25.9	436/18.2	539/22.0
27451	16.0	8.00	16.3	16.5	324/13.5	362/15.1
27452	0.00	24.0	14.5	16.0	310/12.9	315/13.1
27453	8.0	24.0	34.5	23.2	607/25.3	530/22.1
27454	10.0	8.00	17.6	21.8	369/15.4	428/17.8
27455	6.0	8.00	13.4	12.3	267/11.1	230/9.60
27456	2.0	6.00	11.8	12.3	235/9.77	264/11.0
27457	24.0	10.0	16.9	19.0	348/14.5	410/17.1
Mean	11.0	12.3	21.6	22.2	425/17.69	432/18.01

Source: Table 3 and 4, Preliminary Headline Results, pages 6, 7 and Table 14.2.2.1., Table 14.2.2.2, December 11, 2009, amendment, SDN 18.

Reviewer's Comment: Table 6 demonstrates no post-contact PK parameters of concern in any subject.

In a few of the female subjects, Tmax was as delayed as 16 to 24 hours. For reference, mean Day 1 pharmacokinetic parameters for serum total testosterone in adult men administered AndroGel 1.62% in study S176.1.002 are shown in the table below:

Table 7: T_{max} in PK Study S176.1.002

Day 1	**Male Topical Dose of AndroGel 1.62%**				
	1.25 g	**2.5 g**	**3.75 g**	**5.0 g**	**6.25 g**
T_{max} h	12.0	10.0	10.0	12.0	16.0

Source: Table 12, Pharmacology Review of NDA 22-309, page 23.

Reviewer's Comment: Using the observed T_{max} after a single application of AndroGel 1.62% in dosed male subjects as a qualitative guide, in my opinion, there does not appear to be a shift in the time of occurrence of T_{max} after dosing that would indicate significant absorption by the female after skin contact with a dosed male partner. In previous transfer studies, peak testosterone concentrations occurred largely between 10 and 12 hours post contact.

It is also of interest to assess key pharmacokinetic parameters as baseline-adjusted values, and these are shown in the table below.

Table 8: Summary of Selected PK Parameters - Baseline Adjusted Total Testosterone (Individual Female Subjects)

Subject	C_{max} ng/dL	C_{av} ng/dL	AUC-24 ng*h/dL
27445	20.80	2.11	50.70
27446	-0.60	-9.82	-235.70
27448	9.80	3.31	79.53
27449	2.27	0.54	13.04
27450	10.60	3.85	92.30
27451	3.80	1.55	37.27
27452	3.30	0.22	5.22
27453	2.40	-3.25	-78.10
27454	6.90	2.27	54.51
27455	0.80	-1.56	-37.44
27456	3.00	1.06	25.45
27457	4.90	2.55	61.32
Mean	5.66	0.24	5.68

Source: Table 14.2.2.3., December 11, 2009, Amendment, SDN 18.

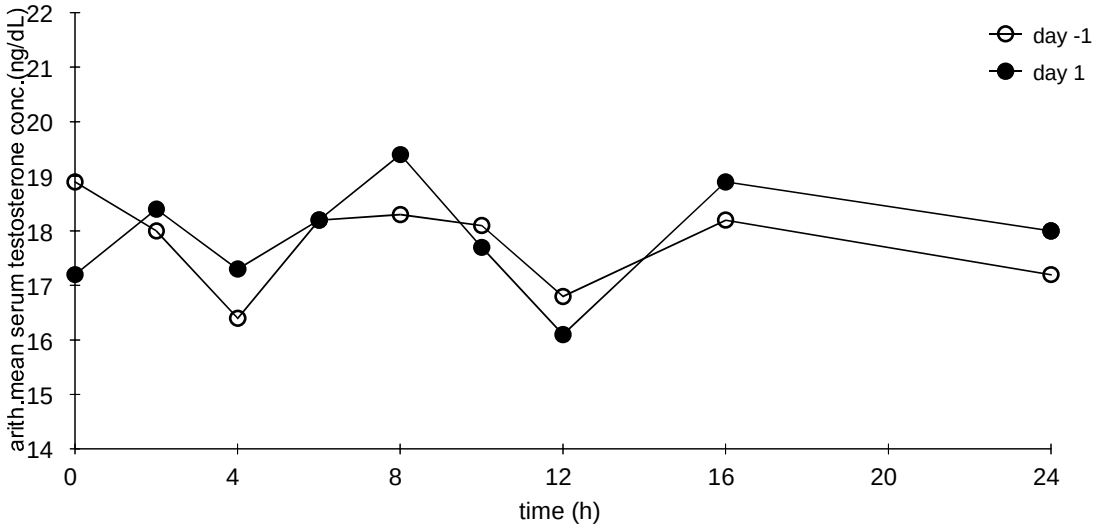
Table 9: Comparison Between Baseline (Day -1) and Endpoint (Day 1) for Key Total Testosterone PK Parameters

Parameter	Mean Difference Between Days	Median Difference Between Days	95% CI for Median Difference	P-value
Cav	0.34 ng/dL	1.42 ng/dL	(-80.00, 1599.99)	0.3013
AUC0-τ	8 h*ng/dL	33.99 h*ng/dL	(-3.33, 6.67)	0.3013
Cmax	0.59 ng/dL	1.6 ng/dL	(-4.60, 7.30)	0.3013

Source: Copy of Table 5, Preliminary Headline Results, page 7 and Table14.2.3, December 11, 2009, amendment, SDN 18.

Reviewer's Comment: Based on the data presented in Tables 5, 6, 8, 9 and Figure 1, the mean pharmacokinetic parameters for $C_{av,\ AUC\ 0\text{-}24}$, and C_{max} are similar between baseline (Day-1) and Day 1 after skin contact. The difference in means is < 1 ng/dL for C_{av} and C_{max} and represents a 1.92% and 2.69% increase for the mean Baseline (Day-1) for $C_{av\ and}$ C_{max} respectively. The largest increase in C_{av} for an individual subject was 3.90 ng/dL (Subject #27450). The largest increase in C_{max} for an individual was 16 ng/dL (Subject #27445); however the remaining concentrations in this subject's profile were similar to Day -1. The final report for Protocol S176.1.009, submitted January 15, 2010 reveals the same findings as the preliminary "headline"results submitted on November 5, 2009.

Figure 1. Mean Testosterone Concentration-Time Profile for Day -1 and Day 1



Source: Copy of Figure 1, Preliminary Headline Results, page 7.

Reviewer's Comments:

1. *The Day -1 and Day 1 concentration-time curves shown in Figure 1 are virtually overlapping.*
2. *In my opinion, the information derived from the data from study S176.1.009 shows that with 4 site application of 5 g of testosterone gel 1.62%, a t-shirt largely blocks the transfer of testosterone, sufficient to mitigate the risk of testosterone to others through physical contact.*

Safety Results: There were no deaths nor serious adverse events reported. There were no adverse events in males. In 4/24 subjects (4 females), at least one adverse event (AE) was reported throughout the course of the study and these AEs are shown in the table below:

Table 10: Adverse Events protocol S176.1.009

Subject	Adverse Event	Severity	Treatment	Resolved
27448	Headache	Mild	None	Yes
27449	Constipation	Mild	Prune Juice	Yes
27449	Headache	Mild	None	Yes
27456	Constipation	Mild	Prune Juice	Yes
27457	Constipation	Mild	Prune Juice	No

Source: Table 6, Preliminary Headline Results, Page 8.

There were no clinically significant abnormalities observed for vital signs, application site evaluations, clinical laboratory parameters or ECG evaluations in this study.

4. Reviewer's Overall Conclusions in Regard to Transfer Study 009:

The median difference between Baseline (Day -1) and Day 1 for AUC_{0-24}, C_{avg}, and C_{max} for total testosterone in females was 33.985 ng-hr/dL, 1.42 ng/dL and 1.6 ng/dL, respectively. The 95% confidence interval for the difference between baseline (Day -1) and endpoint (Day 1) included zero for all three parameters, indicating that there was no significant differences from baseline. Transfer of testosterone to female subjects was largely prevented with a t-shirt barrier when males applied 5 g of testosterone gel 1.62% to four application sites (both upper arms/shoulders, both sides of the abdomen), sufficient to mitigate the risk of testosterone to others through physical contact.

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

In their final review on page 5, the Office of Clinical Pharmacology similarly concluded: "*The results from the new transfer study S176.1.009 suggest that the testosterone transfer to non-dosed females was largely mitigated when contact occurred with a T-shirt barrier on male who applied a 5.0 g dose of the 1.62 % gel formulation to 4 different application sites (both upper arms/shoulders and both sides of abdomen).*"

Appendix II: Bridging Data for Comparable Exposure

1. Executive Summary:

The purpose of this part of the Addendum review is to determine whether the application of the 5.0 gm dose of AndroGel 1.62% to 4 anatomic sites provides comparable exposure to testosterone in the male as compared to the application of 5.0 gm of AndroGel 1.62% to 2 anatomic sites.

Previous transfer studies had demonstrated that a t-shirt was not fully effective as a barrier to transfer to a female partner when 5 grams of AndroGel 1.62% was applied to just 2 anatomic sites. This was a continuing Clinical safety concern for NDA 22-309. Prior to the NDA goal date, the Sponsor submitted a preliminary report from Study 009, which they believed resolved the concern by spreading the highest dose out onto 4 anatomic sites. The final study report was submitted on January 15, 2010. It is this reviewer's opinion that Study S176.1.009 provides sufficient data to show that a t-shirt is a satisfactory method to prevent transfer when 5 grams of AndroGel 1.62% is applied to 4 anatomic sites, rather than just 2 anatomic sites.

(b) (4)

we asked that Sponsor provide evidence that testosterone concentrations will be comparable between the new "4-site" method and the old "2-site" method used in Phase 3. The comparability data that the Sponsor provided consisted of instances in Protocol S176.3.004, the pivotal Phase 3 study, in which protocol instructions were not followed and AndroGel 1.62% was applied to 3 or 4 anatomic sites when it should have been applied to just 2 anatomic sites.

In a 30 November 2009 amendment to the NDA, the Sponsor identified 41 unique patients who had one or more incidents of multisite application of AndroGel 1.62% which occurred in the 3.75 g and 5.0 g dose groups on PK Days 56, 112 and 182. The multisite use was sporadic and not consistent between patients nor within the same patient. The Clinical Pharmacology review team conducted a detailed review of the data from 41 patients, and upon eliminating some of these patients from further consideration and considering the quality of the data presented, they concluded that the level of evidence provided is not sufficient to draw the conclusion of comparability of exposure to testosterone in males applying AndroGel 1.62% 5.0 gm to 2 versus 4 anatomic sites. This clinical reviewer concurs with the Clinical Pharmacology conclusion.

2. Background:

The reader is referred to the original Clinical review, which provided a recommendation that NDA 22-309 for AndroGel 1.62% be **NOT APPROVED** based upon the Clinical concern related to the lack of a demonstrated simple clothing barrier to transfer. (b) (4)

(b) (4)

The Clinical reviewer believed that other simpler, more feasible means, other than washing of the skin application site prior to physical contact, was needed to prevent testosterone transfer to others.

The information provided by the Sponsor in the original NDA submission showed that a simple T-shirt blocked transfer at the 2.5gm dose, but the T-shirt barrier did not adequately block testosterone transfer at the 5 gram testosterone gel dosage. It was the Clinical reviewer's opinion that a means to address this persistent safety concern would be for the Sponsor to show a satisfactory method for a clothing barrier technique. The Clinical reviewer believed that this might require modification in the method(s) of application of larger doses of testosterone gel 1.62% (e.g., application of 2.5gm on the abdomen and 2.5gm on the arms/shoulders – 4 anatomic sites). The Clinical reviewer was aware that if the dosing method was changed (e.g. spreading the larger dose out onto both sides of the abdomen and both arms/shoulders), then it would be necessary to show comparability of testosterone concentrations when using the new 4-site application technique to the testosterone concentrations obtained in Study S176.3.104 where the dosing schema was abdomen *or* arms/shoulders (2 anatomic sites).

The concern regarding inadequate prevention of testosterone transfer at the 5 gram testosterone gel dosage using a simple T-shirt barrier was communicated to the Sponsor on several occasions during the review. The Sponsor responded to an Information Request (in Supporting Document Number [SDN] 11, dated August 28, 2009) with a consideration of spreading out the gel application to four sites for the 5 gram dosage to increase the efficiency of T-shirt prevention of testosterone transfer. This was also mentioned in a telephone communication on September 25, 2009.

On October 16, 2009, the Division received SDN 206 to the AndroGel IND (IND# 50,377). The document contained preliminary results from Study S176.1.009 (Study 009), entitled "An Open-Label, Study of Serum Testosterone Levels in Non-Dosed Females Secondary Exposure to Testosterone Gel 1.62%." This study further characterized the transfer potential of the 1.62% testosterone gel formulation. Evaluations were made to assess secondary exposure from dosed males to non-dosed females with a simple t-shirt barrier after application of 5 grams to the upper arms/shoulders and abdomen, bilaterally (4 anatomic sites).

On November 5, 2009, by email and on November 10 by EDR submission, the Sponsor submitted SDN 012 which contained:

- A Cover Letter
- An Executive Summary
- Preliminary Headline Results Report for protocol S176.1.009: "An Open-Label, Study of Serum Testosterone Levels in Non-Dosed Females Secondary Exposure to Testosterone Gel 1.62%"
- A Rationale document outlining supportive justifications regarding why the application scheme used in S176.1.009 to prevent transfer through a t-shirt (4

anatomic sites) should not adversely impact safety or efficacy conclusions from the previously completed pivotal, Phase 3 study S176.3.104,
- Rationale Table
- Proposed Revised Labeling
- Proposed Revised Medication Guide

The results of Protocol S176.1.009, on their face, with preliminary statistical comparisons, appeared to show no statistically significant differences between Baseline (Day -1) and Day 1 for testosterone concentrations in females after skin contact with males who had applied the product using the 4-anatomic site technique. The data for C_{av}, AUC_{0-24}, and C_{max} indicated that with the four site application of 5 g of testosterone gel 1.62% in the male, a t-shirt barrier effectively blocks testosterone transfer to an unclothed female.

On November 18, 2009, the Division conveyed an Information Request to Sponsor containing the following specific requests:

1. You report that a subgroup of patients in Phase 3 has applied the testosterone 1.62 % gel to both abdomen & shoulders/upper arms on visit days (titration and PK-days).

   Per the Phase 3 study report included in NDA 22-309, patients were advised that "*study drug NOT be applied prior to study visits*" and that on PK days subjects apply the study gel "*at the clinic under direct supervision of study staff*".

   We therefore assume that dose application in those patients who used multiple application sites was also done in the clinic under supervision. In this regard, we request that you provide narratives/descriptions of the supervised dose application procedures for this subgroup of individuals, for each of the PK and titration days.

   This will be an important piece of information in our consideration of whether data obtained from this subgroup of patients would be a good representation of the multiple sites of application employed in your new transfer study S176.1.009 and proposed for use in your revised labeling included in your submission dated, November 5, 2009.

   If dosing to multiple sites in any or all of these individuals did not occur in the clinic under staff supervision and hence narratives are not available, comment on whether other records are available from those doses that can describe the method and sites of application. Any such records should be included in your response.

2. Comment as to why dosing to multiple application sites was employed in these patients and whether that was recorded as a protocol violation.

3. Provide a listing of the following information for all patients on each PK day who had applied dose to 3 or 4 application sites: Patient ID, PK day, dose, number and description of the application sites, whether dosing occurred at

clinic, and PK parameters. Submit this information also for patients who used multiple sites of application on both the day before and on the day of PK. Also include plasma concentration-time profile data for these individuals. For subjects who applied dose to multiple application sites prior to a titration day provide a listing of their pre-dose concentrations. Please provide this information in SAS transport file format.

4. Comment on whether each of the patients in this subgroup was a responder or non-responder per final efficacy analyses (Day 112). Comment on whether any of these subjects were included in the list of testosterone outliers and whether this is attributable to the use of multiple drug application sites.

5. Submit the final study report for the new transfer study S176.1.009.

6. Clarify the volume of gel for each 1.25 g pump actuation.

The Sponsor submitted an NDA amendment by email November 25, 2009 and received in EDR on November 30, 2009. This amendment contained: 1) Solvay's response to the six questions posed by the Division, 2) a letter to the FDA from the Principal Investigator for the AndroGel 1.62% pivotal Phase III Study [S176.3.004], Dr Joel Kauffman, and 3) the attachments noted in the table below (related to the comparability assessment):

Table 1: Appendices to Clinical Amendment (November 30, 2009)

Appendix	Document Title	File Name
1	S176.3.104 Study Protocol	s1763104-prot-or-amend.pdf
2	S176.3.104 Procedural Guidance Document	Solvay-S1763104-Procedural Guidance Document-2Mar07.pdf
3	Listing of Subjects Who Dosed Multiple Application Sites	PK dose collection.rtf
4	Application Site Details from the eCRF for Titration Visits	Titration Day CRFs.doc
5	Application Site Details from the eCRF for PK Visits	CRF capture.doc
6	SAS data transport file that contains 3 datasets: bothdays.sas7bdat, dayof.sas7bdat, and predoset.sas7bdat. Data Definitions Word document that contains a printout of bothdays.sas7bdat and dayof.sas7bdat.	Fdareqst.xpt; Data definitions.doc Fdareq.doc
7	Concentration Profiles for all Applicable Subjects	Cp profiles FDA request.pdf
8	Word document that contains a printout of predoset.sas7bdat	FDARequestNov19Part2.doc

Source: Copied from cover letter, Response to Information Request for NDA 22-309, 24 November 2009.

A teleconference between the Division and Solvay occurred 01 December 2009. In this conference, clarification was obtained that verification of multiple application of AndroGel 1.62% in Protocol S176.3.004 was documented in the electronic case report form and was primary source data.

This part of the review concerns the PK data presented by the Sponsor relating to testosterone exposure in males applying AndroGel 1.62% on 3 or more sites in Study S176.3.104 (these subjects may be viewed as protocol violators). The Sponsor seeks to use the information derived from these subjects to demonstrate comparable testosterone exposure of this new 4-site application technique to the 2 site application technique which was used by the vast majority of patients who used 3.75 g and 5 g doses of AndroGel 1.62% in the single, pivotal, Phase 3 study. The key point of analysis is whether the data is sufficient to assure comparable testosterone exposure to the per protocol results.

3. Submission Review:

An assessment of Protocol S176.1.009 is included as Appendix I in this Addendum review, and therefore, the results of that study will not be reiterated here. In brief, the investigation was a single center, single dose, open-label study in twelve (12) healthy male-female couples. The primary study objective was:

- To evaluate skin-to-skin testosterone transfer from males dosed with Testosterone Gel 1.62% (5 g) to non-dosed female subjects when contact with the application sites, upper arms/shoulders and abdomen occurred at 2 hours postdose with a t-shirt barrier using the four site application technique of male dosing.

Protocol S176.1.009 was well-designed, with appropriate inclusion and exclusion criteria, standard contact techniques, PK sampling points, PK analysis and safety monitoring to safely achieve the stated primary study objective. The final study report was submitted on January 15, 2009, and has been reviewed in Appendix I of this Addendum review.

> *Reviewer's Comment: Transfer of testosterone to female subjects was largely prevented with a t-shirt barrier when males applied 5 g of testosterone gel 1.62% to four application sites (both upper arms/shoulders, both sides of the abdomen).*
>
> *It is this reviewer's opinion that Study S176.1.009 has generated data showing a satisfactory method for the clothing barrier technique*

In their November 5, 2009, submission, the Sponsor also put forth supportive justifications regarding why the application scheme used in the new transfer study (S176.1.009) should not adversely impact safety or efficacy conclusions from Phase 3. Their arguments include:

1) *Comparisons of the current situation to AndroGel 1%*: Protocol UMD-96-012 in the AndroGel 1% NDA (NDA 21-015) compared the testosterone exposure of subjects applying 10 g of AndroGel 1% to just the left arm and left shoulder to subjects applying the same amount of AndroGel 1% to both arms and shoulders and both sides of the abdomen. By Sponsor's calculation, this resulted in application of AndroGel 1% to an area four times greater than the single site (L arm/shoulder). The C_{av} was 23% higher with the four site application of AndroGel 1% compared to one site. The Sponsor concludes that with surface areas differing by 4-fold only a 20-30% difference in serum T concentrations was noted with AndroGel 1%. The Sponsor

postulates that differences in testosterone concentrations when comparing application of AndroGel 1.62% to two sites compared to four should be less than the differences observed in the AndroGel 1% Study which compared one site to four sites.

In their final review, page 15, the Office of Clinical Pharmacology (OCP) provided comments concerning this specific justification. In this regard, OCP stated:

- The approved 1 % formulation also requires a larger volume of gel compared to the 1.62 % formulation. The impact of distributing a smaller volume of gel containing a [redacted] (b) (4) and active ingredients on the absorption and PK (safety and efficacy) is not known.

- While the statistical analyses of the Phase 1 study that evaluated PK differences with surface area of application for the AndroGel 1 % product (UMD-96-012; sample size of n= 9) concluded absence of significant differences, nevertheless there was ~25 % increase in Cavg for 4-sites vs. 1-site.

- It should also be noted that the earlier program for the 1 % formulation did not rely on (Phase 1) data alone to allow multiple-site application during clinical use. Instead, the Phase 3 study of AndroGel 1% included use of multiple application sites for the two higher doses (7.5 g and 10 g) and thus safety/efficacy as well titration success using this regimen was well established. In contrast, the current clinical program for the 1.62 % gel formulation did not allow simultaneous use of multiple sites in any of its clinical studies.

- While the 1 % and 1.62 % formulations are qualitatively similar, there are quantitative differences, the effect of which on drug absorption and PK is not known. [redacted] (b) (4)

  Reviewer's Comment: We concur with these observations and conclusions from the Clinical Pharmacology review. It is not clear that the AndroGel 1% experience can be directly applied to AndroGel 1.62%. The limited PK data presented for AndroGel 1.62% suggests that exposure to testosterone increases with 4 site application versus one or two sites. Therefore, AndroGel 1 % and AndroGel 1.62% may not be the same in terms of absorption versus application site surface area.

2) *Data from Phase 3 multisite users*: Although the Phase 3 protocol for AndroGel 1.62%, Study S176.3.104, specified the application of gel to the arms/shoulders on PK days, the Sponsor states that the data collected indicate that a small subset of participants applied 3.75 gm or 5 gm of the gel to multiple sites on the day of and/or on the day before PK visits. It is stated on Page 26 of the NDA submission that on days where 24-hour PK sampling was conducted, subjects were supposed to apply the study gel to the upper arms/shoulders at the clinic under direct supervision of the

study staff. However, according to the Sponsor, there were subjects who either applied the gel to the abdomen alone, or in addition to applying the gel to the arms/shoulders, also applied their assigned dose of 3.75 gm or 5gm AndroGel 1.62% to the abdomen on PK days.

In their 30 November 2009 amendment, the Sponsor documents 66 individual incidents of protocol violations relating to application of AndroGel 1.62% to more than the recommended application sites. In 41 unique patients, one or more such incidents occurred in the 3.75 g and 5.0 g dose groups on PK Days 56, 112 and 182.

The table below illustrates the extent of these protocol violations.

Table 2: Number of Subjects who Applied AndroGel 1.62% to Each Application Site on PK Days (includes protocol violators who used multiple sites)

PK Day	Application Site		
	Abdomen	Arm/Shoulder	Abdomen and Arm/Shoulder
14	26	142	2
56	12	131	22
112	8	153	18
182	8	139	18

Source: Appendix 5 of November 24, 2009, submission.

The Sponsor also presented an analysis of serum T concentrations on each PK day based on application sites from Table 2. The table below illustrates the results from this analysis on the PK days (Days 56, 112, and 182). Of note, Day 112 is considered the primary efficacy timepoint.

Table 3: PK Results By Application Site on PK Day

Application Site/PK Day	**Mean C_{av}**	**Mean C_{max}**	**Mean AUC**
Day 56			
Abdomen	522.8	745.3	12550
Arm/Shoulder	458.9	725	11020
Arm/Shoulder/Abd	459.4	665.3	11030
Day 112			
Abdomen	502.3	759.4	12040
Arm/Shoulder	556	834.2	13350
Arm/Shoulder/Abd	628.7	975.2	15100
Day 182			
Abdomen	427.4	622.6	10280
Arm/Shoulder	533.4	802.7	12810
Arm/Shoulder/Abd	607.3	934	14570

Source: Tables 12.4.6 to 12.4.8, Module 5.4-Rationale Table, SDN 13.

In their final review of the major amendment, page 14 and 15, the Office of Clinical Pharmacology (OCP) had the following observations and conclusions concerning this specific justification:

- While dosing over multiple sites appears to mitigate transfer, no PK (efficacy) or safety data is currently available from continuous once daily application of the 1.62 % gel to multiple application sites (both sides of upper arms/shoulders and abdomen, without rotation).

- Available PK data from multiple site usage is from a subgroup of Phase 3 patients who deviated from the study protocol with respect to site(s) of application. The use of multiple sites in these individuals was not prospectively planned and was not adequately controlled.

- In addition, per CRF documentation, several of these patients (17 out of 41) did not use multiple application sites as intended in the proposed revised dosing instructions. Some patients either employed multiple sites where it was not required (e.g. for a 1.25 g or 2.5 g dose) or used it incorrectly (i.e. 3 sites for a 5.0 g dose or 4 sites for a 3.75 g doses of gel). The relevance of such data is therefore questionable.

- The degree of supervision during dose application on multiple sites in this subgroup could not be confirmed by the Sponsor even for in-house dosing on visit days. Hence, adherence by the individuals in this subgroup to the proposed new dosing instructions (e.g. consistent application of 1.25 g of gel per each site) can not be confirmed.

- Use of multiple application sites was also sporadic in this subgroup with no evidence of consistent use over time; most patients had documented use of multiple sites only once during the 180 day study period. Since consistent daily use is not documented, the impact of earlier daily doses (possibly using different sites of application) on PK profiles resulting from multiple-site usage is not known.

- From a regulatory perspective, use of this subgroup data requires post-hoc analyses of phase 3 information from a subgroup; Use of such data for revising dose application instructions for the entire patient population is questionable

  Reviewer's Comment: I concur with these observations and conclusions from Clinical Pharmacology review. If the results shown in Table 3 are taken at face value, they appear to show an approximate increase of >15% in mean Cav and Cmax for arms/shoulder/abdomen over arms/shoulders alone. The reviewer continues to have concerns as to the specific technique used in applying the gel to the anatomic sites. This subgroup of patients (who could be viewed as protocol violators) was identified by review of eCRF listings. The Sponsor has previously acknowledged that direct observation of the AndroGel 1.62% application was not always conducted by investigators, as called for in the protocol.

In their final review of the major amendment page 15, the Clinical Pharmacology team concludes:

> *"…the expectation that the Phase 3 clinical trial reflects the conditions of clinical usage is not met due to the proposed revisions to the application regimen. The level of evidence provided in support of the change is not acceptable and further information is needed to bridge the gap.*"
>
> *Reviewer's Comment: I concur with the above conclusion of Clinical Pharmacology.*

4. Reviewer's Overall Conclusions in Regard to Comparability of Exposure Between the 4-Site Application Technique as in Study 009 and the 2-Site Technique, as in the Phase 3 Study 104

In their final review of the major amendment, page 13, the Office of Clinical Pharmacology concludes:

> "*No formal 'bridging' study was conducted to justify the applicability of the phase 3 clinical trial data to the newly proposed regimen involving use of multiple application sites.*"

OCP further stated on page 13:

> (b) (4) *In addition, Sponsor presents PK data from a small group of phase 3 patients who had deviated from the protocol by applying drug to multiple sites.*"

The Phase 3 subgroup that Sponsor uses to justify the new dosing recommendation did not apply AndroGel 1.62% in a uniform non-sporadic manner throughout the Phase 3 study, Protocol S176.3.004. This constitutes post-hoc analysis of a not prespecified group of protocol violators who in addition were not adequately supervised as per protocol. In addition, the bioavailability comparisons referring to AndroGel 1% results are not applicable for reasons stated in the Clinical Pharmacology review. Therefore, the reviewer concurs with the Office of Clinical Pharmacology that the level of evidence provided in support of the dosing change with regard to comparable exposure to testosterone using AndroGel 1.62% at two sites versus four sites for the 5 g dose is not acceptable and further information is needed to bridge the gap. A Phase 1, relative bioavailability study would be a reasonable way to bridge the 4 site application to the 2 site application technique for a dose of 5 gm.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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

/s/

A R WIEDERHORN
03/08/2010

MARK S HIRSCH
03/08/2010
I concur.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-309
Priority or Standard	Standard
Submit Date(s)	February 11, 2009
Received Date(s)	February 11, 2009
PDUFA Goal Date	December 12, 2009
Reviewer Name(s)	Roger Wiederhorn, Medical Officer DRUP Mark Hirsch, Team Leader, DRUP
Review Completion Date	
Established Name	Testosterone gel
(Proposed) Trade Name	AndroGel 1.62%
Therapeutic Class	Androgen
Applicant	Solvay Pharmaceuticals Inc. 901 Sawyer Road Marietta, Georgia 30062
Formulation(s)	1.62% testosterone gel
Dosing Regimen	2.5 g once daily
Indication(s)	Androgen replacement therapy in adult males
Intended Population(s)	Primary and secondary hypogonadism (congenital or acquired)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended NDA 22-309 be **NOT APPROVED** at this time, and that a **Complete Response** action be taken**.** Studies conducted to assess whether testosterone can transfer to others have shown that a T-shirt does not adequately block transfer of a 5gm dose. Since a T-shirt is not a completely effective means of blocking transfer, the proposed label emphasizes washing the application site prior to anticipated physical contact as the principal risk mitigation strategy for transfer. Relying principally on washing the application site (in the shower) prior to physical contact with others to prevent transfer of testosterone is considered problematic in terms of patient compliance. The reviewer believes that other simpler, more feasible means, in addition to shower skin washing of the skin application site prior to physical contact, is needed to prevent testosterone transfer to others. Currently, the information provided by the Sponsor shows that a T-shirt does block transfer at the 2.5gm dose, but the T-shirt barrier does not adequately block testosterone transfer at the 5 gram testosterone gel dosage. A **COMPLETE RESPONSE** to this unresolved safety concern would entail generating data to show a satisfactory method for the clothing barrier technique. This might require modification in the method(s) of application of larger doses of testosterone gel 1.62% (e.g., application of 2.5gm on the abdomen and 2.5gm on the arms/shoulders). If the dosing method is changed (e.g. spreading the larger dose out onto both sides of the abdomen and both arms/shoulders), then appropriate PK data to demonstrate testosterone concentrations comparable to those obtained in Study S176.3.104 (where the dosing schema was abdomen *or* arms/shoulders) will also be required.

1.2 Risk Benefit Assessment

A thorough and comprehensive review of sNDA 21-368 was carried out. 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. This claim is that AndroGel 1.62% (testosterone gel 1.62%) achieves eugonadal testosterone concentrations in hypogonadal men. 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 (C_{max} >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 "overcompliant" 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 presented a safety risk. Four daily doses of AndroGel 1.62% were evaluated: 1.25 g; 2.5 g (starting dose); 3.75 g; and 5 g. Titration of dose is based upon serum testosterone concentrations. All doses were

utilized by patients. No significant discernible differences in the safety profile based on dose or serum testosterone concentrations were detected.

The single pivotal study, S176.3.104, was a double-blind placebo-controlled 182 day long protocol with a 182 day safety extension. 234 hypogonadal men received testosterone gel 1.62% and 40 patients received placebo. Predetermined testosterone concentrations were achieved at Day 112 (the efficacy endpoint).

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 are sporadically high testosterone concentrations and transfer risk. The sporadically high testosterone concentrations do not appear to be 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 is an ongoing and unresolved safety concern.

The Sponsor's submission and amendments do not allow for labeling that will permit acceptably safe use of testosterone gel 1.62% with respect to the issue of issue of transfer of testosterone by direct skin contact from treated male to others (including females and more importantly, children). With respect to the T-shirt barrier, the discrepancy between results for the 2.5 g and 5 gm doses poses a significant barrier to adequate labeling for the transfer issue. Additional studies are needed to acceptably mitigate the risk of testosterone transfer using a clothing barrier. These studies could evaluate the type of clothing barrier, time of contact after testosterone gel 1.62% application, and the use of multiple sites of application for larger doses of testosterone gel 1.62%.

Other than for the transfer issue, the data support adequate directions for use, including the data to describe a safe and effective dose.

1.3 Recommendations for Postmarket Risk Management Activities

NDA approval is not recommended, therefore, no Postmarket Risk Management Activities are recommended at this time. However, should the transfer issue related to a clothing barrier be acceptably resolved, a postmarketing Risk Evaluation and Mitigation Strategy (REMS) will still be necessary to address the overall transfer risk. This will include a Medication Guide, and other educational efforts to patients, prescribers and health care professionals. The Sponsor is aware of the ultimate need for this REMS and has submitted a proposal already.

1.4 Recommendations for Postmarket Studies/Clinical Trials

NDA approval is not recommended, therefore, no Postmarket Studies are recommended at this time. The need for postmarket studies will be reconsidered once the transfer issue related to a clothing barrier has been acceptably addressed.

2 Introduction and Regulatory Background

2.1 Product Information

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 (b) (4), capable of dispensing 75 g of gel), which consists of a (b) (4) plastic canister with an airless pump dispenser. Each pump delivers 1.25gm of gel. Four pumps are therefore required for the highest daily dose of 5gm.

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

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

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Available Testosterone Formulations for the Proposed Indications

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Source: Bhasin S, Cunningham G, et. al., 2006: Testosterone Therapy in Adult Men With Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline: J of Clin Endocrin and Metab 9 (16): 1995-2010

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety in the product is testosterone. Testosterone in gel form is available in the United States in several formulations. Currently AndroGel is marketed as a 1% formulation. The Sponsor crudely estimates that approximately (b) (4) (or roughly 1.13 million patient years of treatment with AndroGel 1%) have taken AndroGel in the 28 February 2000 - 27 February 2008 cumulative post-marketing period. The following is relevant to the AndroGel 1% US experience, as provided by Sponsor:

Contraindications to the use of testosterone in men are breast or known or suspected prostate cancer. Pregnant or breast feeding women should not be exposed to exogenous testosterone. Testosterone may cause fetal harm.

Warnings and Precautions: 1) Patients with benign enlargement of the prostate (BPH) treated with androgen are at an increased risk for worsening of signs and symptoms of BPH. 2) Application site should be covered and hands washed to avoid transfer to others, 3) AndroGel is not indicated in women due to a lack of controlled evaluations and potential virilizing. 4) Exogenous administration of androgens may lead to azoospermia. 5) Edema may be a complication in patients with preexisting cardiac, renal or hepatic disease. 6) Gynecomastia or breast enlargement may develop. 7) Sleep apnea may occur in those with risk factors 7) Monitoring of serum testosterone, prostate specific antigen, hemoglobin, hematocrit, liver function tests and lipids periodically is recommended while using the product. 8) Alcohol based gels are flammable until dry.

The most common Adverse Reactions (incidence greater ≥ 5%) are acne, application site reaction, abnormal lab tests, and prostatic disorders.

Drug Interactions: 1) Androgens may decrease blood sugar, and therefore insulin requirement in diabetic patients. 2) Use of testosterone with ACTH or corticosteroids may result in increased fluid retention. 3) Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants.

Use in Specific Populations: 1) Pregnancy: AndroGel may cause teratogenic effects. AndroGel should not be used in pregnant women. 2) Nursing mothers should not use AndroGel. 3) The safety and efficacy of AndroGel in males < 18 years has not been established. 4) There have not been sufficient numbers of geriatric patients involved in controlled clinical studies to determine whether efficacy in those > 65 differs from younger subjects. Additionally there is insufficient long-term safety data in geriatric patients to assess the potential risks of cardiovascular disease and prostate cancer. 5) No formal studies were conducted involving patients with renal or hepatic insufficiencies.

2.4 Important Safety Issues with Consideration to Related Drugs

The important potential safety issues with testosterone therapy include[1]:

- Cardiovascular Disease
- Lipid Alterations
- Erythrocytosis
- Fluid Retention
- Benign Prostatic Hypertrophy
- Prostate Cancer
- Hepatotoxicity
- Sleep Apnea
- Gynecomastia
- Acne or oily skin
- Application site irritation
- Drug interactions: Application site moisturizer lotion or sunscreen, insulin, ACTH, oral anticoagulants, cyclosporine, paclitaxel
- Testicular atrophy or infertility
- Potential for transfer of testosterone by skin contact to partners and children.
- Supranormal testosterone levels.

Appropriate monitoring during testosterone replacement therapy includes: At baseline – 1) Laboratory assessments of serum testosterone, serum PSA, hemoglobin/hematocrit, serum lipids, and serum liver enzymes. 2) Physical exam to include weight, blood pressure, skin status and rectal examination to assess prostate. Voiding symptoms can be assessed by history or by the

1 Rhoden E L and Morgentaler A, 2004, Risks of Testosterone-Replacement Therapy and Recommendations for Monitoring, N Eng J Med; 350: 482-92

International Prostate Symptoms Score. Any history of sleep apnea should be obtained. Appropriate follow-up to assess changes in any of the above parameters.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

AndroGel 1.62% is a topical gel testosterone product which is to be used for once a day dosing for the treatment of conditions associated with a deficiency or absence of endogenous testosterone. The Sponsor, Solvay Pharmaceuticals, Inc., also markets AndroGel 1% under NDA 21-015. The new product, AndroGel® (testosterone gel) 1.62%, (b) (4), reduced volume of application, (b) (4) compared to AndroGel 1%. The proposed starting dose of AndroGel® 1.62% is 2.5 gm (2 pump actuations) once daily. Dose adjustments are made in increments of 1.25 gm based upon trough serum testosterone determinations, in order to achieve and maintain serum testosterone levels in the normal range.

All studies for AndroGel 1.62% were conducted under IND #50,377 which was the original AndroGel 1% IND. The opening study for AndroGel 1.62% was a Phase 1 protocol, 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*" (Protocol S1761001) and was submitted by the Sponsor on August 25, 2005.

The Sponsor supports approval with one Phase 3 study (S176.3.104), supportive evidence from five Phase 1 safety studies in hypogonadal males (S176.1.001, S176.1.002, S176.1.005, S176.1.006 and S176.1.007), and safety results from three additional Phase 1 safety studies in eugonadal males (S176.1.003, S176.1.004, and S176.1.008). The Division agreed at the EOP2 Meeting on 18 October 2006 that a single Phase 3 study evaluating the efficacy and safety testosterone gel 1.62% would be sufficient to file the application for review.

At the 18 October 2006 EOP2 meeting, the Division agreed that at least 6 months data from the Phase 3 study should be submitted in the original NDA, and that the Division would accept the completed study report for S176.3.104, including the full 1 year of data, with the 4 month Safety Update. The Division also stated that it would not be necessary to integrate the safety data from the Phase 1 studies with the Phase 3 data.

At the Pre-NDA meeting on 21 January 2008, the Sponsor agreed not to submit the initial NDA until Study 176.1.008 (the second "transfer study") was completed and the study report would be included in the NDA submission. In addition, the Division voiced concerns regarding several patients with maximum serum T concentrations above 2500 ng/dL. The Sponsor has provided in their submission detailed analyses for each case of Cmax greater than 2500 ng/dL.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is of good quality and no concerns have been raised about the integrity of the processes that were used by Sponsor to generate this submission.

3.2 Compliance with Good Clinical Practices

The Sponsor appears to have been compliant with good clinical practices.

3.3 Financial Disclosures

Form FDA 3454 signed 26 June 2008 was provided in the submission. Financial disclosures were submitted for the principal investigators in Protocols S176.1.001, S176.1.002, S176.1.003, S176.1.004, S176.1.005, S176.1.006, S176.1.007, S176.1.008, and the pivotal Phase 3 study S176.3.104.

A total of 77 investigators (all from all protocols and study sites) had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54, 2(a)], proprietary interest in the covered product or significant equity interest in the Sponsor of the covered product [21 CFR 54.2(b)], significant payments of other sorts from the Sponsor of the covered study [12 CFR 54.2(f)]. There was no missing financial disclosure information for investigators in the above listed studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

At the time of the October 7, 2008, NDA review team "Wrap-up" meeting, Drs. Shroff and Christner stated that there were 2 outstanding CMC issues for this application.

> First, the CMC team was still waiting for a Microbiology consult. The microbiologist, Dr. Mello, informed the team that his review would be completed by October 29, 2009.
>
> Second, a facility inspection of (b) (4) was not yet conducted by Compliance. This facility serves as a backup quality control center. The inspection was scheduled for October 22 and 29, 2009.

At the time of completion of this MO's review, CMC review #1 had been completed (Oct 21, 2009) but these 2 issues were still outstanding.

4.2 Clinical Microbiology

The Microbiology consult for this application was completed Ocotber 28, 2009. Dr. Mello recommended Approval. There were no recommendations on Phase 4 Commitments and/or Agreements. There were no deficiencies. A comment is requested to be sent to the Sponsor stating that acceptance criteria for the microbiological quality of the drug product should be listed in Table 2 and Table 3, respectively, of the NDA submisiion Section 3.2.P.5.1, along with a statement that the drug product will comply with the acceptance criterial if tested at any time during its shelf life.

4.3 Preclinical Pharmacology/Toxicology

There are no pending Pharmacology/Toxicology issues for this application. The PharmTox review is completed. The pharmacologist, Dr. Bray, informed the team that there would be some revisions proposed for the Nonclinical parts of the proposed label.

4.4 Clinical Pharmacology

At the time of the October 7, 2008, NDA review team "Wrap-up" meeting, Drs. Apparaju and Kim stated that: 1) extensive revisions to the label would be proposed for the transfer issue, and 2) there was one outstanding Clinical Pharmacology issue. A Division of Scientific Investigation (DSI) inspection of (b) (4) was still not completed. (b) (4) was responsible for re-analysis all original serum samples that had been previously assayed by (b) (4). The inspection of (b) (4) was planned for (b) (4).

In their final review, dated October 26, 2009, the ClinPharm review team re-stated that the DSI inspection was still outstanding and re-emphasized the need for extensive labeling changes re: transfer. The review stated that if the DSI inspection was acceptable and the Sponsor made the ClinPharm recommended labeling changes, then the application would be acceptable from a ClinPharm perspective.

In regard to the labeling issue, Drs. Apparaju and Kim acknowledged that a T-shirt did not fully block transfer of testosterone from patient to others, therefore they agreed with Sponsor that the principal means to reduce the risk of transfer should be reliance on washing of the application sites prior to anticipated physicial contact. They acknowledged that the washing studies had used a shower as the means of "washing", but they stated that simple washing with a washcloth without a shower might be just as good as a shower. (b) (4)
.

On October 8, 2009, the Clinical and Clinical Pharmacology teams met to discuss the Clinical Pharmacology proposal for labeling revisions. Drs. Apparaju and Kim presented some revisions to the label, including to the Highlights section, the Boxed Warning, and the Warnings and Precautions section.

> *<u>Reviewer's Comment</u>: Currently, the reviewer does not agree with the Clinical Pharmacology proposals for labeling revisions.* (b) (4)
> (b) (4)
> .

In their final review, the Clinical Pharmacology team proposed extensive revisions to the PI to emphasize (b) (4)

4.4.1 Mechanism of Action

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.

4.4.2 Pharmacodynamics

While several clinical endpoints are measured in clinical trials (e.g., erectile function and libido questionnaires, mood profiles, body composition indices, and bone mineral density), there are no currently agreed upon pharmacodynamic primary endpoints for Phase 3 studies of testosterone replacement. Therefore, for this NDA and for all previous testosterone replacement applications, the primary efficacy endpoints are pharmacokinetic (i. e., the attainment of testosterone concentrations in the eugonadal range).

4.4.3 Pharmacokinetics

Reviewer's Comment: The Pharmacokinetics of the product are shown in great detail in later parts of this review and also will be prominent in the Clinical Pharmacologist's review. Herein, the Sponsor's overall summary of the Pharmacokinetics are provided in brief. Overall, the reviewer agrees with this assessment by Sponsor.

AndroGel 1.62% delivers physiologic amounts of testosterone that produces circulating testosterone concentrations that approximate normal levels (3000-1000 ng/dL) seen in healthy men. The product provides continuous transdermal delivery of testosterone for 24 hours following once daily administration. The skin serves as a reservoir for the sustained release of testosterone into the circulation. Up to 8.5 % of the dose of AndroGel 1.62% applied to the skin surface (of either the shoulders/upper arms or abdomen) is absorbed into systemic circulation and results in testosterone concentrations in the eugonadal range. Testosterone exposure is 30-40% lower when applied to the abdomen compared to the shoulders/upper arms.

All doses tested (1.25, 2.5, 3.75, and 5 g) provide continuous transdermal delivery of testosterone for 24 hours. A clinical study conducted in hypogonadal males has shown that with one application of the 2.5 g starting dose of AndroGel 1.62% mean testosterone concentrations rise to within normal levels by 2 hours after application and remain within the normal range for the remainder of the 24-hour period. Eighty percent of hypogonadal patients receiving the 2.5 g dose had C_{av} values within the eugonadal range on Day 1. On repeated daily application, mean testosterone concentrations are maintained within the normal range at all dose levels. Serum concentrations approximate the steady-state level by the end of the first 24 hours of dosing.

When AndroGel 1.62% is discontinued, serum testosterone levels return to approximately baseline levels within 48-72 hours after administration of the last dose.

Circulating testosterone is primarily bound to sex hormone-binding (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG), 2% remains unbound (free) and the rest is bound to albumin and other proteins.

There is considerable variation in the half-life of testosterone as reported in the literature ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The two major metabolites of testosterone are dihydrotestosterone (DHT) and estradiol.

Dihydrotestosterone concentrations increased with increasing testosterone concentrations during AndroGel 1.62% treatment. After 182 days of treatment in adult males, mean DHT concentrations were mostly within the eugonadal range for the 1.25, 2.5, and 5 g doses, but were 5-30% above the normal range for the 3.75 g dose group. The mean steady-state DHT/testosterone (DHT/T) ratio during 182 days of AndroGel 1.62% treatment typically remained within normal limits.

Following multiple dosing, mean estradiol concentrations were generally within the normal range for all doses tested.

In regard to the metabolism of AndroGel 1.62%, the information on DHT and estradiol has been summarized above and additional details are shown in the body of this review. Previous studies have shown that about 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucoronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs mainly in the liver.

5 Sources of Clinical Data

In total, the NDA contains safety data from 785 subjects exposed to AndroGel 1.62%. The safety data was derived from Phase 1 studies S176.1.003, S176.1.004, S176.1.008 (which were not integrated into the overall safety analysis), and Phase 1 studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104 (which were integrated into an overall safety analysis). By prior agreement, the safety data from the open-label period of Study S176.3.104 was submitted with the 120-Day Safety Update. 382 hypogonadal males are included in the integrated safety base, and 307 healthy males and 96 females are included in the non-integrated safety data base.

The single efficacy 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 (168 T-Gel [71.8%] and 28 [70.0%] placebo).

5.1 Tables of Studies/Clinical Trials

Table 2: Summary of Clinical Studies with AndroGel 1.62%

Type of Study	Objective	Design	Test Product	Duration of Treatment	Enrolled Completed Age Range
Phase I Clinical Pharmacology				(total days of exposure)	Hypogonadal Males
S176.1.001	Bioavailability (BA) and Multiple Dose Pharmacokinetics (PK)	Randomized, Open label, parallel	Testosterone (T)gel: to abdomen for each dose level of 1.25, 2.50 and 3.75	Daily, 5 days at each dose level (20 days)	38 enrolled 36 completed Age: 26-72 yrs
S176.1.002	Single and Multiple Dose PK (*Dose-Ranging*)	Randomized, Open label, parallel	T gel 1.62%; 1.25 g, 2.50 g, 5.00 g or 6.25 g. Abdomen, upper arm/shoulders (rotation)	Daily for 14 Days	56 51 27-69 yrs
S176.1.005	Multiple dose PK/BA with/without Post dose skin washing	Randomized, Open-label, three-way crossover	T gel 1.62%; 5.00 g upper arm/shoulders	Daily, 7 days at each dose level (21 days)	24 17 34-77 yrs
S176.1.006	Multiple dose PK/BA with/without moisturizer or sunscreen	Randomized, Open-label, three-way crossover	T gel 1.62%; 2.50 g upper arm/shoulders	Daily, 7 days at each dose level (21 days)	18 15 31-60 yrs
S176.1.007	Singe and Multiple Dose PK/BA (*Differences between application sites*)	Randomized, open-label, three-way crossover	T gel 1.62% 5.00 g, Abdomen, upper arms/shoulders+ both sites in rotation	Daily, 5 day washout between Treatments (31 days)	36 32 29-73 yrs

Healthy Subjects					Healthy Subjects
S176.1.003	PK of female subjects after contact with partner dosed with T gel	Randomized, open-label	Males: T gel 1.62% 5.00 g Females: 15 minutes of contact time; no direct dose	(7 days)	96 (48 couples) 47 M, 48 F; 18-65 yrs
S176.1.004	Skin sensitization Skin irritation of 1.62% T gel in males	Randomized, double-blind, placebo controlled	T gel 1.62%; 100 mg gel/3.14 cm^2 patch	(6 weeks): three phases: 21d induction, 12-17 day rest, and 5d rechallenge	235 214 18-79 yrs
S176.1.008	PK eval of dose, post dose washing, and application site transfer - dosed male to non-dosed female	Randomized, open-label, parallel group	Males: T gel 1.62%; 2.5 or 5.00 g, 2 single daily doses to abdomen or shoulders/arms: Females: 15 minute contact time: no direct dose	(2 days), separated by 1-week washout period	48 (24 couples) 48 (24 couples) 18-59 yrs
Phase 3 Single Study	HYPOGONADAL MALES				
S176.3.104	PK evaluation of % of patients in eugonadal range with AndroGel 1.62%	Randomized, Double-Blinded, Placebo Controlled.	Males: T gel 1.62%; 1.25, 2.50, 3.75, 5.00, placebo, g, daily	182 days: followed by 182 day open label safety study	274 196 45-64 (majority of patients)

5.2 Review Strategy

Study S176.3.104 was by prior agreement the only Phase 3 pivotal efficacy study. The results of the total testosterone pharmacokinetic variables, C_{av} and C_{max} were analyzed. The major emphasis for safety evaluation of AndroGel 1.62% was placed on the safety data in Study S176.3.104. Additional safety data was derived from non-integrated studies S176.1.003,

S176.1.004, S176.1.008, and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104. The data from the integrated safety studies was analyzed separately by the Sponsor by prior agreement. The pharmacokinetic variables were separately and jointly reviewed by pharmacology and clinical divisions.

The 120 Day Safety-Update, containing the additional safety data from the Phase 3 study 104, was received and the data was incorporated into this NDA review.

For this application, particular attention was directed to two safety issues: 1) the issue of testosterone transfer and 2) testosterone concentrations in excess of 2500 ng/dL.

After the filing review and March 31, 2009 filing meeting, the Division conveyed a number of review issues the Sponsor in the 74-Day letter, including requests for further analysis for the review issues of hypertension, syncope, elevated hematocrit, PSA increase, possible over-compliance, and the relationship of AEs to systemic exposure. Responses to these requests have also been received and incorporated into this NDA review.

At the July 13, 2009 Mid-Cycle Meeting, the transfer issue was again discussed in great detail. More intense scrutiny of this particular issue followed. The transfer issue was discussed again at the August 10, 2009, 6-month status meeting. Following the 6-month status meeting, the Division conveyed continued concerns regarding the transfer issue in an August 28, 2008 regulatory letter to Sponsor. The Sponsor responded to this letter on September 17, 2008 (Sequence No. 0011 to the NDA) and this submission was incorporated into the NDA review. The transfer issue was discussed again at the September 17, 2009, 7-month status meeting, as well as at a dedicated meeting with the Deputy Director on September 24, 2009. Finally, a teleconference was held with Sponsor on October 1, 2009.

5.3 Discussion of Individual Studies/Clinical Trials

Study S176.3.104:

> *Reviewer's Comment: This section contains an overview of the Phase 3 pivotal study 104. A detailed analysis of Safety and Efficacy of this Phase 3 study is provided in Sections 6 and 7 of this review.*

Study S176.3.104 was a multi-center, 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.

Patients were included if:

- They were males, 18-80 years of age.
- Had 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:

- Had 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.
- Had average serum testosterone concentration of <300 ng/dL determined from two laboratory specimens collected at the same visit, 30 (=/- five) minutes apart between the hours of 6:00 a. m. and 10:00 a. m.
- Were naïve to androgen replacement or had undergone a washout of 12 weeks following intramuscular androgen injections; four weeks following topical or buccal androgens; and 3 weeks following oral androgens.
- Had intact skin surfaces at the gel application sites.
- They had no significant medical conditions that would be adversely impacted by testosterone replacement were eligible for study inclusion.

Patients were excluded if they met any of the following criteria:

1. Low serum testosterone concentrations secondary to causes other than primary or secondary hypogonadism (congenital or acquired).
2. Previous history of, current, or suspected prostate or breast cancer
3. IPSS-1 score >15 points.
4. Abnormal finding on DRE of the prostate as determined by the investigator. Prostate enlargement by itself was not an exclusion criterion.
5. PSA > 2.5 ng/mL or 2.6-3.74 ng/mL without a negative biopsy within the past 6 months with pathology report available for principal investigator's review (this exclusion criterion was modified to PSA>1.25 ng/mL for men on the 5-α reductase inhibitors finasteride or dutasteride).
6. Body Mass Index (BMI) less than 18 or greater than 40 kg/m^2.
7. Untreated prolactinoma.
8. Currently seeking fertility or seeking fertility within one year of trial participation.
9. Poorly controlled diabetes defined a hemoglobin A1C (HgbA1c) >9.
10. History of Human Immunodeficiency Virus (HIV) infection.
11. Multiple sclerosis (MS) or other degenerative central nervous system (CNS) diseases, or spinal cord injury.
12. History, current, or suspected, obstructive sleep apnea.
13. Findings of any kind of skin lesions on the surface of the application site during the physical examination (small tattoos were acceptable).
14. Generalized skin disease that may affect absorption of investigational gel (e. g., psoriasis or eczema).
15. Clinically significant neurological, hematological, autoimmune, endocrine, cardiovascular, liver, renal, gastrointestinal, pulmonary, or infectious diseases that would interfere with the subject's participation or compromise the subject's safety in the study, as determined by the investigator.
16. History, suspicion, or current evidence of drug or alcohol abuse within the previous 12 months.

17. History of heart failure (New York Heart Association [NYHA] Class III or greater).
18. Known skin intolerance to alcohol or allergy to any of the ingredients of testosterone gel 1.62%.
19. Subjects with sitting systolic blood pressure (SBP) >160 mmHg or <90 mmHg, or sitting diastolic blood pressure (DBP) > 100 mmHg or <60 mmHg.
20. Hemoglobin (HGB) >16.0 g/dL, hematocrit (Hct) >48%, serum albumin <3.5 g/dL, fasting blood glucose >300 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) >2X ULN (upper limit of normal).
21. Using any over-the-counter (OTC) steroid preparations or derivatives (e.g., dehydroepiandrosterone [DHEA]).

Subjects were discontinued for the following reasons:

- For any subject during the study with an increase in PSA >0.75 ng/dL from baseline, a repeat test was performed. If the average of the two measurements confirmed a change from baseline <0.75 ng/mL, the subject was allowed to continue in the study. If the change was confirmed to be > 0.75 ng/mL, the subject was discontinued and early termination assessments were completed. Men treated with 5-α reductase inhibitors had PSA change from baseline discontinuation criteria half the values of men not taking 5-α reductase inhibitors (i.e., PSA change from baseline >0.37 ng/mL).
- If a subject had an absolute PSA value of >4.0 ng/mL post-baseline, a repeat test was performed. If the average of the two measurements was ≤4.0ng/mL, the subject was allowed to continue in the study. If the average of the two measurements was >4.0 ng/mL, the subject had to be discontinued. Men treated with a 5-α reductase inhibitors had absolute discontinuation thresholds half the values of men not taking 5-α reductase inhibitors (i. e., rise to >2.0 ng/mL).
- If a DRE abnormality was noted (e.g., nodule or induration).
- If SGOT or SGPT were >3X ULN; the subject had to be discontinued following a repeat confirmatory test.
- If the Hct was >54%, the subject was to be discontinued and early termination assessments completed.
- If a serum testosterone concentration > 2500 ng/dL was observed, the unblinded Quintiles clinical reviewer had the authority to intervene with subjects proceeding in the study.

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, see Table 4) and placebo administered over a period of 182 days. 224 subjects were planned. 274 subjects (testosterone gel 1.62%: 234 subjects, placebo: 40 subjects) were randomized and analyzed for safety; 206 subjects (testosterone gel 1.62%: 179; placebo 27 subjects) 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 3 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 by the investigator 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 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.

Subjects were advised of the following precautions:

- Study drug should not be applied prior to study visits.
- Study drug should be applied using proper application technique
- There is a potential for dermal transfer to another person when vigorous skin-to-skin contact is made.
- Study drug should be properly stored.
- Study drug should not be applied to scrotum

At 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.

The Safety Sample consisted of all subjects who were allocated to the Treatment Sample and had at least one dose of study medication administered. Three patient populations were used in the analysis of efficacy: 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, the Efficacy Sample consisted of all subjects included in the FA Sample and had any efficacy data for Day 112 (the primary timepoint), and 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. Only available parameters were used for all analytes. LOCF was used only for secondary endpoints.

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 NDA presents data collected in the study up to and including Day 182. By prior agreement, a Final Integrated Clinical Study Report including data from Baseline through the end of the Study (Day 364) was included in the 120 day Safety Update.

Table 3: Pre-specified Testosterone Gel 1.62% Dose Titration Criteria

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 %

Table 4: Doses Administered

Gel Strength	Gel Dose (g)	T Dose (mg) Applied	Number of Pump Actuations
1.62%	1.25	20.3	1
1.62%	2.50	40.5	2
1.62%	3.75	60.8	3
1.62%	5.00	81.0	4

Source: adapted from Table 2, Clinical Study Report S1763104, 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. Success in the study was defined as ≥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:

- Cmax ≤1500 ng/dL in ≥85% of the subjects
- Cmax between 1800-2500 ng/dL in ≤5% of the subjects
- Cmax >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.

The schedule of events, including safety measures, were obtained as outlined in the table below:

Table 3: Schedule of Events Study S176.3.1004

Evaluations	Screening A / B	Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Days (Weeks)	Days -14 / -7	Day 1	Day 14 (Week 2)	Day 28 (Week 4)	Day 42 (Week 6)	Day 56 (Week 8)	Day 84 (Week 12)	Day 112 (Week 16)	Day 140 (Week 20)	Day 182 (Week 26)
Informed consent	X / -									
Inclusion/Exclusion	- / X	X								X
Baseline/Assessment for Open-Label Phase										X
Demographics, Medical History	X / -									
Height, Weight, BMI, and Waist-to-Hip Ratio	- / X							X		X
Physical Exam (includes breast)	- / X						X			X
Urology Exam (DRE) [e]	- / X						X			X
Vital Signs	- / X	X	X	X	X	X	X	X	X	X
12-Lead ECG	- / X									X
IPSS-1	- / X						X			X
Screening Testosterone and PSA	X[b] / -									
Complete blood count, Clinical Chemistry, Urinalysis	- / X	X[b]								X[b]
Percent Free PSA (b) (4)		X					X			X
Prolactin	- / X									
Safety or Titration Lab (Testosterone)		X	X	X	X	X	X	X	X	X
Safety Labs (PSA, HCT, HGB, SGOT, SGPT, Lipids)	- / X	X					X			X
Sex Steroid Labs (testosterone, DHT, E2)		X	X[g]	X	X	X[g]	X	X[g]	X	X[g]
Predose SHBG		X	X	X	X	X	X	X	X	X
PK Blood Sample[c]			X			X		X		X
PD Blood Sample (predose) [d]		X					X			X
SF-36		X						X		
Site Application Assessment		X	X	X	X	X	X	X	X	X
Randomization IVRS		X								
Dispense Medication [f]		X	X[f]	X[f]	X[f]	X	X	X	X	X
Collect Medication			X	X	X	X	X	X	X	X
Baseline/AE Recording	X / X	X	X	X	X	X	X	X	X	X
Record Concomitant Medication	X / X	X	X	X	X	X	X	X	X	X

Evaluations	Visit 10	Visit 10a	Visit 10b	Visit 11	Visit 12	Visit 13	Visit 14 [a]
Days (Weeks)	Day 182 (Wk 26)	Day 196 (Wk 28)	Day 210 (Wk 30)	Day 224 (Wk 32)	Day 266 (Wk 38)	Day 308 (Wk 44)	Day 364 (Wk 52)
Informed consent							
Inclusion/Exclusion	X						
Baseline/Assessment for Open-Label Phase	X						
Demographics, Medical History							
Height, Weight, BMI, and Waist-to-Hip Ratio	X						X
Physical Exam (includes breast)	X				X		X
Urology Exam (DRE) [e]	X				X		X
Vital Signs	X			X	X	X	X
12-Lead ECG	X						X
IPSS-1	X				X		X
Screening Testosterone and PSA							
Complete blood count, Clinical Chemistry, Urinalysis	X[b]						X
Percent Free PSA	X				X		X
Prolactin (b) (4)							
Safety or Titration Lab (Testosterone)	X	X	X	X	X	X	X
Safety Labs (PSA, HCT, HGB, SGOT, SGPT, Lipids)	X				X		X
Sex Steroid Labs (testosterone, DHT, E2)	X[g]			X	X[g]	X	X[g]
Predose SHBG	X			X	X	X	X
PK Blood Sample[c]	X				X		X
PD Blood Sample (predose) [d]	X				X		X
SF-36							X
Site Application Assessment	X			X	X	X	X
Randomization IVRS							
Dispense Medication [f]	X			X	X	X	
Collect Medication	X			X	X	X	X
Baseline/AE Recording	X	X	X	X	X	X	X
Record Concomitant Medication	X			X	X	X	X

Source: Study Report S176.3.104, Table 3, pages 40 and 41.

Overview of the Phase 1 Studies

Reviewer's Comment: Herein, the reviewer provides an overview of the Phase 1 studies, including brief description of the study designs and study results. Safety information is provided in an integrated analysis within Section 7.

Study S176.1.1001: The Multiple Dose Pharmacokinetics and Comparative Bioavailability of Testosterone After Administration of 1.25, 2.5, and 3.75 g Dose Levels of Investigational Testosterone Hydro-Alcoholic Gel Formulations in Hypogonadal Male Volunteers.

This Phase 1 single site US study had as its objectives the following:

- To determine the multiple dose pharmacokinetics and comparative bioavailability of testosterone after administration of testosterone gel (T-gel) in three different strengths, at three different doses: 1.25 g, 2.5 g, and 3.75 g,
- To compare the pharmacokinetics of three new T-gel formulations with the currently marketed AndroGel® product (AndroGel 1%) and to determine which of the new T-gel dose strengths and which dose levels met the following criteria:

  - The proportion of subjects with observed maximum total testosterone concentrations (C_{max}) >1000 ng/dL after investigational T-gel administration was less than the proportion observed after reference treatment
  - The proportion of subjects with an average total testosterone serum concentration (C_{avg}) and/or the lowest concentration observed over the 24-hour dosing interval (C_{min}) within the normal eugonadal range of 300 to 1000 ng/dL and/or within 80% of 650 ng/dL (range of 520 to 780 ng/dL) and was equal to or greater than the proportion observed after reference treatment.
  - The proportion of individual total testosterone concentrations during each 24-hour profile within 300 to 1000 ng/dL was greater than or equal to the proportion observed after reference treatment.
  - Compared with the reference product, similar or higher average total testosterone serum concentration (C_{av}) was observed with a lower mass of gel;
- To assess the dose proportionality of T-gel over the dose range of 1.25 to 3.75 g for each of the three different strengths;
- To monitor and evaluate the safety of the subjects throughout the study.

A total of 38 healthy hypogonadal male subjects were enrolled in the study. 36 subjects completed the protocol and 2 subjects prematurely withdrew consent after having received at least one dose of medication. Both subjects were randomly assigned to Treatment C and received a total of 5 once daily doses (1.25 g of gel dose) of 1.62% T-gel prior to withdrawal. Both subjects completed end of study procedures.

Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

The study drug was applied topically to the abdomen once daily for 5 days at dose levels of 1.25g (15.3, 30.4 and 45.8 mg testosterone), 2.50 g (17.8, 35.5, and 53.3 mg testosterone), and 3.75 g (20.3, 40.5, and 60.8 mg testosterone) of gel. The mg of testosterone cited above represents the 1.22%, 1.42%, and 1.62% formulations respectively. The duration of treatment was approximately 23 days. The reference therapy was AndroGel® (1.00%, 5.00 g, of gel [50 mg testosterone]).

Pharmacokinetic blood samples were collected on Day-1 at -24 and -12 hours relative to the projected time of gel application on Day1: at predose on Days 1, 3, 4, 8, 9, 13, 14, 18, and 19: and at predose, and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post dose on Days 5, 10, 15, and 20. Plasma concentrations of total testosterone, dihydrotestosterone, and estradiol were determined. The following PK parameters were determined using noncompartmental methods: observed predose concentration (C_{trough}), lowest serum concentration observed during the 24-hour dosing interval (C_{min}), observed maximum serum concentration (C_{max}), time of minimum observed concentration (t_{min}), time to reach maximum observed serum concentration(t_{max}), area under the serum concentration- time curve from aero to 24 hours (AUC_{0-24}), time-averaged

concentration over the dosing interval, determined by $AUC_{0-24}/24(C_{av})$ and peak trough fluctuation (PTF).

Results and Conclusions for Study S176.1.1001: On the fifth day of treatment at each dose level, mean observed and baseline-adjusted testosterone concentrations were relatively constant over the 24-hour dosing interval. Mean concentrations peaked at approximately 4 hours, and some doses showed a second peak at 12 to 16 hours. Mean observed testosterone concentrations were above the lower limit of the eugonadal range (>300ng/dL) at most time points for all gel doses in Treatment A (1.22% T-gel) and for the 2.50 g and 3.75 g doses in Treatment C (1.62% T-gel). For treatment B (1.42% T-gel) doses, mean testosterone concentrations varied above and below the lower limit of the eugonadal range.

- Topical application of 1.22%, 1.42%, and 1.62% T-gel at dose levels of 1.25, 2.50 and 3.75 g to the abdomen for 5 days provided mean C_{av} testosterone levels within or just below the eugonadal ranges (300 to 1000 ng/dL) and was comparable to 5.00 g of the reference 1% AndroGel® 1% product. There were no statistical differences in exposure within treatment groups or across dose levels and gel strengths.
- Statistical analysis of steady state was inconclusive. Graphical assessment of mean and median trough concentrations suggested steady state was achieved by the third day of dosing for all treatments.
- Dose proportionality or linearity in testosterone exposure, based on AUC_{0-24} and Cmax, and was not demonstrated for any gel strength.
- Mean concentration-time profiles of Treatments A, B, and C at the 2.50 and 3.75 g dose levels were comparable to the reference (AndroGel 1%, 5.00g), but of the three T-gel strengths evaluated , the 1.62% strength was the most comparable to AndroGel®1 % (5.00 g).

Safety for Study S176.1.1001: Safety for this protocol is also discussed within the Phase 1 integrated safety analysis in Section 7 of this review. No serious adverse events or deaths were reported during this study. No subjects were prematurely withdrawn from the study due to AEs.

Markedly abnormal vital signs were observed in the following four subjects:

- Subject 24704, a 41 year-old white male assigned to Treatment A (1.22% testosterone gel administered on Days 1 to 15 plus the reference treatment on Day 16 to 20), experienced a decrease in weight that met the criteria for markedly abnormal vital signs. At termination, the subject's weight was 67 kg (baseline value: 88.6kg), an overall loss of 21.6 kg.
- Subject 24710, a 56 year-old white male assigned to Treatment A (1.22% testosterone gel administered on Days 1 to 15 plus the reference treatment on Day 16 to 20), experienced an increase in body temperature of 101.7^{o} F (baseline value: 98^{o} F) at an unscheduled assessment on 28 October 2005, one day prior to resuming the study Day 6 dosing. Two additional markedly abnormal temperature readings of 101.1^{o}F were noted

on Day 6 assessments (scheduled and unscheduled). No related AE's were noted and the subject's body temperature returned to normal levels on Day 7.

- Subject 24725, a 71 year old white male assigned to Treatment B (1.42% testosterone gel administered on Day 1 to 10 and 16 to 20 plus the reference treatment on Days 11 to 15), experienced a high systolic blood pressure of 195 mmHg (baseline value: 175 mmHg) at an unscheduled visit on Day 2. No subsequent assessments met the criteria for markedly abnormal values. No related AEs were noted; however, a medical history of hypertension was noted that was ongoing at study entry.

- Subject 24741, a 58 year-old white male assigned to Treatment C (1.62% testosterone gel administered on Days 1 to 10 and 16 to 20 plus the reference treatment on Days 11 to 15), experienced a total of 14 pulse rate values that met the markedly abnormal criteria. Abnormal assessments were observed throughout the study form Day 4 through unscheduled assessments at termination and ranged from 120 to 132 bpm. No related AEs were noted and no follow-up was deemed necessary by the investigator.

Reviewer's Comment: Based on the lack of differences in exposure between the 3 dose strengths, the Sponsor indicated that they would select the maximum strength (1.62%) for continued development, as it allowed for the lowest mass of gel.

Study S176.1.002: 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.

This Phase 1 single-site US study had the following as its objectives:

- To determine the single and multiple dose pharmacokinetics of testosterone gel (T-gel) at doses of 1.25 g (20.3 mg T), 2.50 g(40.5 mg T), 3.75 g (60.8 mg T), and 6.25 g (101.3 mg T).
- To assess the dose proportionality and accumulation of testosterone 1.6% over the dose range of 1.24 g (20.3 mg T) to 6.25 g (101.3 mg T).
- To monitor and evaluate the safety of subjects throughout the study.

The study was an open-label, single and multiple-dose, parallel group study in hypogonadal male subjects. Subjects were administered 1.25 g, 2.5 g, 3.75 g, 5.00 g, or 6.25 g of T-gel 1.62% once daily for 14 days. The dose was dependent on group randomization. The site of application was rotated over the 14 day treatment period. Study drug was applied to the shoulder/upper arm on Days 1, 2, 5 to 9, and 12 to 14 and applied to the abdomen on Days 3, 4, 10, and 11. The duration of treatment was 17 days, not including the screening period. Subjects were confined to the clinic for the entire 17 day period. Serial blood samples for measurement of serum testosterone, dihydrotestosterone, and estradiol concentrations were collected at baseline (Day -1), and following single dosing (Day 1) and multiple dosing (Day 14). A total of 56 hypogonadal male subjects were enrolled in this study and received at least one dose of medication. A total of 51 subjects completed the study according to the protocol. Three subjects

were prematurely withdrawn from the study due to high testosterone levels and two subjects withdrew due to adverse events (AEs).

Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

Pharmacokinetic blood samples were collected for determination of total testosterone, dihydrotestosterone, and estradiol at the following timepoints:
Day-1 (Baseline): predose, and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 16 hours relative to the projected time of gel application on subsequent study days;
Day 1: predose, and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 16 hours post dose;
Days 2 to 13; predose; and
Day 14: predose, and at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours post dose.

Serum levels of total testosterone, dihydrotestosterone, and estradiol were determined and used to calculate observed and baseline-adjusted maximum serum concentration (C_{max}), lowest serum concentration (C_{min}), predose serum concentration on Day 14 (C_{trough}), time-averaged concentration over the dosing interval, determined by AUC_{0-24}/tau (C_{av}), time to reach maximum observed serum concentration(t_{max}), time of minimum concentration (t_{min}), area under the serum concentration- time curve over the 24- hour dosing interval (AUC_{0-24}), peak to trough fluctuation (PTF), and the accumulation interval.

Results and Conclusions for Study S176.1.002:
Following single doses (Day 1), mean observed testosterone concentrations showed a continuous increase up to 8 hours post dose for all dose groups, after which concentration remained consistent and within the eugonadal range (300 to 1000 ng/dL) for the remainder of the 24-hour dosing interval.

Following multiple dosing (Day 14), mean observed testosterone concentrations were relatively consistent and were within the eugonadal range over the entire 24-dosing interval for all dose groups. Mean observed C_{max} was within the eugonadal range for all treatments on Day 1. On Day 14, mean C_{max} was within the eugonadal range for the 1.25g, 2.5 g, and 3.75 g doses, but was just above the limit for the 5.00 and 6.25 g doses.

$AUC_{0-24\ and}$ C_{max} values for testosterone showed a generally linear, dose-related increase in exposure of the 1.25 to 5.00 g dose range on Day 1 and over the entire dose range (1.25 to 6.25 g) on Day 14.

Steady state concentrations were achieved by Day 2 by analysis of mean and median trough concentrations but not by statistical analysis.

No accumulation of testosterone was seen at the 1.25 g and 2.50 g doses, and <2-fold accumulation was seen at the 3.75 g to 6.25 g doses, following multiple dosing for 14 days.

Based on the Single and multiple dose pharmacokinetics and concentration-time profiles, all 1.62% T-gel levels (1.25 to 6.25 g) evaluated in this study were considered by Sponsor to be evaluable for further clinical development.

Safety for Study S176.1.002: Five subjects experienced clinically out of range laboratory values but in no case was testosterone listed as out of range. 3 subjects were withdrawn from the study due to predose testosterone levels that exceeded protocol-specified limits (>900 ng/dL) on Days 3, 6, and 9. Two subjects were withdrawn from the study due to an AE of hypertension:

- Subject 25802, a 67-old White male assigned to receive 5.00 g of 1.62% T-gel and received doses on Day 1 and Day 2. He experienced an AE of hypertension (exacerbation of predose condition) prior to dosing on Day 3 and was prematurely withdrawn from the study. Screening blood pressure was 162/74 mm Hgwith two repeat values of 154/74 mm Hg and 149/71 mm Hg, respectively. The maximum blood pressure observed was 175 mm Hg on Day 3. The patient was on no concomitant medications.
- Subject 25817, a 67 year-old White male receiving 5.00 g of 1.62% T-gel on Days 1 through 3; however experienced an AE of hypertension (exacerbation of predose condition) that continued throughout dosing, and was prematurely withdrawn prior to dosing on Day 4. Screening blood pressure was 162/74 with two repeat values of 154/74 mm Hg and 149/71 mm Hg, respectively. The maximum blood pressure observed was 175/176 mm Hg on Day 3. No concomitant medications were administered.

There were no deaths or serious adverse events. The most frequent treatment-emergent adverse events overall (reported by ≥4 subjects) were application site papules (9/56, 16.1%), hypertension (8/56, 14.3%), acne (6/56, 10.7%), hematoma (4/56, 7.1%) and headache (4/56, 7.1%).

Three subjects experienced markedly abnormal vital signs during the study:

- Subject 25793, a 58 year-old white male randomized to treatment A (1.25 testosterone gel 1.62%), experienced a high pulse rate of 126 bpm on Day 5 (baseline value: 87 bpm). At an unscheduled assessment on Day 5, this value was noted as 123 bpm, which also met markedly abnormal criteria. An AE of mild tachycardia was noted. No action was taken and subject recovered.
- Subject 25797, a 59 year-old white male, randomized to treatment C (3.75 g testosterone gel 1.62%), experienced an increase in weight that met criterion for markedly abnormal vital sign values. At termination, the subject's weight was 95.9 kg (baseline value: 89.5 kg); an overall gain of 6.4 kg.
- Subject 25802, a 67 year-old white male, randomized to Treatment D (5.00 g testosterone gel 1.62%) experienced a high systolic blood pressure of 186 mmHg on Day 3 (baseline value: 144 mmHg). Additionally, this subject experienced high systolic blood pressure values of 191 mmHg, 189 mmHg, and 185 mmHg at subsequent unscheduled sequential assessments on Day 3. No markedly abnormal diastolic blood pressures were observed in this subject. This subject also experienced high pulse rates of 123 and 120 bpm (baseline value: 93 bpm) at unscheduled assessments on Day 3. Relevant medical history for the

subject included a diagnosis of hypertension at screening. An AE of hypertension was noted post dose and the subject was terminated from the study on Day 4 due to the AE of hypertension.

Safety for this protocol will also be discussed under the Phase 1 integrated safety analysis.

Study S176.1.005: A Randomized, Open-Label, Three-Way Crossover Pharmacokinetic Study to Evaluate the Effects of Skin Washing After Administration of Testosterone Gel 1.62% in Hypogonadal Males.

This Phase 1 single-site US study had as its objectives:

- To determine the multiple dose pharmacokinetics of testosterone after administration of 5gm testosterone gel 1.62% in hypogonadal males with and without post dose skin washing;
- To evaluate any changes in the systemic absorption of testosterone after administration of 5gm testosterone gel 1.62% when the application site is not washed for 24 hours post dose and when skin washing occurred at 2 hours, 6 hours, or 10 hours post dose; and
- To assess whether residual testosterone remained on the application site post skin washing.

Twenty-four hypogonadal male subjects were enrolled and 17 subjects completed the study. The subjects received 5.00 g testosterone gel 1.62% applied topically once daily in the morning to the shoulders/upper arms for 7 days during each of the three consecutive treatment periods, for a total of 21 days of dosing. Serum was obtained for measurement of testosterone, dihydrotestosterone, and estradiol to allow pharmacokinetic (PK) assessments. Six subjects were prematurely discontinued for increased serum T (testosterone concentrations >900 ng/dL as specified in the protocol and determined by clinical safety laboratory results obtained from the local laboratory), and 1 subject was discontinued due to a serious adverse event (SAE) of atrial fibrillation. A total of 24 subjects participated in both the PK and safety analysis.
Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

Within 30 minutes prior to the targeted time of dose application, subjects showered and washed the application site with commercially available Ivory Bar Soap and water. Subjects were not allowed to remain in the shower for longer than 10 minutes. The designated area for gel application was to be thoroughly dried. Each subject received 5.00 g testosterone gel 1.62% applied topically once daily in the morning for 7 days for three consecutive treatment periods for a total of 21 days. There was no washout period between periods. On the seventh day of dosing of each treatment period, depending on randomization, skin washing of the drug application site with Ivory soap and water occurred in the shower with a lather time of approximately 2 minutes followed by a thorough rinse. The application site was then thoroughly dried (page 20 of Study Report S176.1.1005). The washing occurred at the following times:

- Treatment A: 2 hours post dose

- Treatment B: 6 hours post dose
- Treatment C: 10 hours post dose

Tape stripping procedures were conducted on the sixth and seventh day of each treatment period to evaluate the presence of any residual testosterone remaining in the stratum corneum with or without washing.

The subjects were confined to the clinic for the entire period of the study which was 27 days. Reference therapy was when 5.00 g testosterone gel 1.62% was applied and no washing was conducted. This was conducted on the sixth day of dosing of each treatment period.

Pharmacokinetics testing was conducted as follows:

- Day-1 (Baseline): 0, 2, 4, 6, 8, 12, 16, and 24 hours with respect to the projected time of dose administration;
- Days 6, 13, and 20 (Day 6 of each treatment period): 0, 2, 4, 6, 8, 12, 16, and 24 hours post dose;
- Days 7, 14, and 21 (Day 7 of each treatment period): 0, 2, 4, 6, 8, 12, 16, and 24 hours post dose;
- Day 21 at 48, 72, and 96 hours post dose; and
- Days 4, 5, 11, 12, and 19: post dose.

Time to reach steady state was assessed using observed trough concentrations of testosterone. To assess the effect of skin washing within each treatment, the observed and baseline-adjusted testosterone PK parameters, AUC_{0-24}, C_{max} and C_{av} were compared to those without washing using contrasts within a linear mixed model for each analyte/parameter. Application without washing served as the reference treatment.

Results and conclusions for Study S176.1.005: Overall, mean observed testosterone concentrations were relatively lower on Day 7 (with post dose skin washing) than Day 6 (without post dose skin washing) when the skin was washed at 2 and 6 hours post-dose, but not with skin washing at 10 hours post dose.

For Treatment A (washing at 2 hours after dose application), mean observed testosterone concentrations remained within the eugonadal range (300-100ng/dL) over the entire 24-hour dosing interval for both treatment Days 6 and 7. For treatment B (washing at 6 hours after dose application) and C (washing at 10 hours after application) , mean observed testosterone concentrations were generally contained with the eugonadal range for the majority of timepoints. For treatments A and B, skin washing at 2 and 6 hours post dose, respectively, caused a small statistically significant decrease in bioavailability compared to when there was no post dose wash. AUC_{0-24} decreased by 14% on average for Treatment A and 10 % on average for Treatment B. No effect of skin washing was observed for AUC0-24 in Treatment C. Skin washing had no effect on C_{max} for any treatment.

Reviewer's Comment: It is notable that washing after 2 hours lowers AUC by approximately 14%. It is expected that washing even sooner than 2 hours after dose administration would lower T concentrations even more. This is of relevance to the transfer issue. If washing were to serve as the principal means of preventing gel transfer from bodily contact, than this would mean that washing at anytime up to 2 hours after application would be expected to reduce the efficacy of this product. If one is unable to wash due to deleterious effects on efficacy, this essentially precludes body contact with anyone for 2 hours after dosing of the product.

A total of 23 (96%) subjects had at least one observed testosterone concentration >1000 ng/dL, and 4 (17%) of the 24 subjects had at least one observed testosterone concentration >2500 ng/dL. Steady state concentrations of testosterone generally occurred by Day 4 for Treatment B, Day 5 for Treatment A and Day 6 for Treatment C. The patient case report forms provided for the patients with testosterone concentrations >2500 ng/dL do not state when these elevations occurred. The testosterone serum levels included in the case report forms for these 4 subjects show only serum T concentrations below 1000 ng/dL, except for a serum testosterone of 1026 ng/dL for subject 26333 on Day 11. The observed serum testosterone concentrations above 2500 ng/dL are listed in an Appendix as: Subject 26333-Serum testosterone level of 2830 ng/dL, Subject 26338-Serum testosterone level of 3950 ng/dL, Subject 26341-Serum testosterone levels of 2960 ng/dL, 3020 ng/dL, 3240 ng/dL, and Subject 26345-Serum testosterone level of 3230 ng/dL.

Table 4: Numbers of Subjects with concentrations Exceeding 1000 or 2500 ng/dL

Treatment	> 1000ng/dL			>2500 ng/dL		
	Number of Subjects (%)					
	Before Skin Washing	After Skin Washing	Total	Before Skin Washing	After Skin Washing	Total
A	16(67)	8(33)	17(71)	2(8)	1(4)	2(8)
B	20(83)	12(46)	20(83)	0	1(4)	1(4)
C	18(75)	9(38)	18(75)	1(4)	0	1(4)
Total			23(96)			4(17)

Source: Table 6: Clinical Study Report S176.1.1005, page 43

Utilizing tape stripping, it was determined that the amount of testosterone at the application site was significantly decreased after post dose skin washing. Compared to no post dose skin washing, the amount of testosterone recovered was decreased by 84.0% (2 hr washing), 87.2% (6 hr washing), and 81.3% (10 hr washing) after post dose skin washing in total (strips 1-10; surface and deeper skin layer combined) for Treatments A, B, C, respectively. Based on skin stripping results, the amount of testosterone remaining on the skin of the application site decreased with skin washing 2-10 hours post dose.

Reviewer's Comment: This protocol did not include dose titration based on serum testosterone levels and therefore from a clinical standpoint the elevated testosterone levels in several patients are notable but not considered a major safety concern.

The conclusions of the study are:

- Application site washing at 2 and 6 hours post dose after administration of testosterone gel 1.62% caused a slight decrease in AUC_{0-24} and C_{av} but not C_{max}. Application site washing at 10 hours post dose had no effect on AUC_{0-24}, C_{av}, or C_{max}.
- Steady-state conditions were achieved for testosterone concentrations after 4-6 days of once daily application of testosterone gel 1.62%.
- Upon discontinuation of testosterone gel l.62%, serum testosterone levels returned to baseline with 48 hours.

There were no deaths during the course of this study.

Subject 26326 discontinued from the study on Day 20 due to an SAE of atrial fibrillation. This subject is a 77 year-year old white male assigned to treatment sequence C, B, A. Screening blood pressure and pulse rate were 143/92 mmHg and 63 bpm respectively, and Day-1 blood pressure and pulse rate were 168/99 mmHg and 62 bpm respectively. On Day 20, approximately 9.5 hours following administration of study medication, the subject complained of "heart flutter and fullness of chest" shortly after eating dinner. In the emergency room, blood pressure and pulse were 148/83 and 147 bpm. ECGs revealed atrial fibrillation which responded to intravenous diltiazem and procainamide. The atrial fibrillation persisted for 9 hours and then resolved. The subject's medical history is positive of obesity, hypertension, hyperlipidemia, allergic rhinitis, intermittent acid reflux, insomnia, esophageal ulcer, and intermittent constipation. The patient had reported experiencing five to six episodes of "heart racing" over the last 3 years that were of short duration and usually at night. However, the subject had not reported these events to his physician. The subject was receiving lisinopril 30 mg daily upon entry into study. There had been no caffeine consumption for 3 weeks.

Subject 26328 experienced an overall weight decrease of 9.1 kg and exited the study on Day 25. His baseline weight was 92.8 kg and exit weight was 83.7 kg. He received testosterone gel 1.62% (5.00 g) on Days 1-21 and was assigned treatment sequence A, C, B. No AE related to the markedly abnormal decrease in weight was recorded.

<u>Study S176.1.1006: A Randomized, Open-Label, Three-Way Crossover, and Multiple Dose Pharmacokinetic Study of the Effect of Moisturizer Lotion or Sunscreen Application on the Serum Levels of Testosterone in Hypogonadal Males Administered Testosterone Gel 1.62%.</u>

This US single center Phase 1 study had as its objectives:

- To determine the multiple dose pharmacokinetics of testosterone after administration of 2.5 g testosterone gel 1.62% in hypogonadal males with and without moisturizer lotion or sunscreen;

- To determine the effect of concomitant application of moisturizer lotion or sunscreen on the absorption of testosterone in hypogonadal males administered daily applications of 2.5 g testosterone gel 1.62%.

A total of 18 hypogonadal male subjects were enrolled in this study and received at least one dose of study medication. A total of 15 subjects completed the study per protocol. Three subjects were prematurely discontinued from the study; 1 subject withdrew due to a predose testosterone >900 ng/dL as specified in the protocol, and 2 subjects withdrew consent. A total of 18 subjects were included in both the pharmacokinetic (PK) and safety analyses.

The duration of the study was 24 days, not including the screening period. There were four confinement periods consisting of 2 nights each. When not confined to clinic, subjects returned to the clinic on an outpatient basis for dosing purposes and PK sample collection.

Each subject underwent three sequential treatment periods in randomized order. There was no washout period between treatments. The three treatments were as follows:

Treatment A: once daily application of 2.5 g testosterone gel 1.62% applied to the upper arms/shoulders for 7 days. Each day, 1 hour after testosterone gel administration, a 6.0 g application of moisturizer lotion, Lubriderm Daily Moisture Lotion, was applied to the same application site.

Treatment B: once daily application of 2.50 g of testosterone gel 1.62% applied to the upper arms/shoulders for 7 days. Each day, 1 hour after testosterone gel administration, a 6.0 g application of sunscreen, Coppertone Spectra3 UVA/UVB Sunblock Lotion SPF 50, was applied to the same application site.

Treatment C: once daily application of 2.50 g testosterone gel 1.62% applied to upper arms/shoulders for 7 days. (Reference therapy)

Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

Pharmacokinetic whole blood samples were collected for determination of total testosterone, dihydrotestosterone, and estradiol at the following times:

- Day -1 (Baseline): 0, 2, 4, 6, 8, 12, 16, and 24 hours with respect to the projected time of dose administration;
- Days 7, 14, and 21: 0, 2, 4, 6, 8, 12, 16, and 24 hours post dose testosterone gel 1.62% application;
- Days 2-6, 9-13, and 16-20: predose.

Maximum observed serum concentration (C_{max}), area under the serum concentration-time curve from time zero to 24 hours post dose ($_{AUC0-24}$), the lowest concentration observed during the 24-

hour dosing interval (C_{min}), average serum concentration (t_{min}), and peak to trough fluctuation (PTF) were calculated for observed and baseline-adjusted testosterone. In addition, observed post dose (trough) serum concentrations (C_{trough}) were determined. Concentration-time data were summarized using descriptive statistics for dihydrotestosterone and estradiol.

Results and conclusions: Mean observed C_{max} and C_{av} values for all treatments were within the eugonadal range. Additionally, no individual subjects had C_{max} or C_{av} values for any treatment above the upper limit of the eugonadal range (>1000 ng/dL).

The conclusions of this study are:

- Application of moisturizer lotion 1 hour after application of 2.5 g testosterone gel 1.62% once daily for 7 days to the same skin site increased the bioavailability of testosterone modestly (14% and 17% increase in AUC_{0-24} and C_{max}, respectively) compared to testosterone gel 1.62% administered alone.
- Application of sunscreen 1 hour after application of 2.5 g testosterone gel 1.62% once daily for 7 days to the same skin site had no effect on overall exposure (AUC_{0-24}) of testosterone, but increased C_{max} by 13% compared to testosterone gel 1.62% administered alone.
- Individual and mean C_{av} and mean C_{max} values were with the eugonadal range (300-1000ng/dL) following application of 2.5 g testosterone gel 1.62% with or without subsequent application of moisturizer lotion or sunscreen q hour post dose for 7 days within each treatment period, across 21 days of consecutive dosing.
- Graphical assessment and statistical analysis indicate that with once daily application, steady state was achieved by Day 2 for all treatments.

A total of 4 subjects (22.2%) exposed to the study medication reported at least one treatment emergent adverse event (TEAE). The most frequent non-serious TEAE overall was headache (2/18, 11.1%). One subject (1/18, 11.1%) reported an upper respiratory tract infection, and one subject (1/18, 11.1%) reported worsening of erectile dysfunction which was an ongoing baseline medical condition. There were no application site assessments noted during the study, and no subjects reported application site TEAEs. The frequency of non-serious TEAEs was similar across treatment groups. One subject (subject 26750) discontinued from the study due to a predose testosterone level of 1064 ng/dL on Day 18 which was above the protocol-specified limit of 900 ng/dL. No deaths or SAEs occurred during the course of this study. No subjects discontinued from the study due to AEs. This study is included in the integrated Phase 1 safety summary within Section of this review.

Two subjects experienced markedly abnormal vital sign values during the study:

- Subject 26758, a 36-year old white male randomly assigned to treatment sequence B, A, C, experienced a decrease in pulse rate exceeding guidelines for markedly abnormal ($\leq$ 50 bpm and $\geq$15 bpm change from baseline). At Day 6, the subject's pulse rate was 50 bpm (Baseline value: 76 bpm); an overall decrease of 26 bpm. Systolic and diastolic blood pressures at the time of the decreased pulse rate were 111 mmHg and 51 mmHg, respectively. At the time of the abnormal pulse rate, the subject was receiving Treatment

B (2.5 g testosterone gel 1.62% followed by 6.0 g of sunscreen 1 hour post dose). On Day 7 through study termination (Day 22), the subject's pulse rate values ranged from 52-69 bpm. No AE related to the markedly abnormal decrease in pulse rate was noted.

- Subject 26760, a 60 year-old white male randomly assigned to treatment sequence A, B, C, experienced an increase in diastolic blood pressure that met the criterion for markedly abnormal vital sign values (≥105 mmHg and ≥15 mmHg increase from baseline). At Day 16, the subject's diastolic blood pressure was 107 mmHg (Baseline value: 90 mmHg0; an overall increase of 17 mmHg. Systolic blood pressure and pulse rate at the time of increased diastolic blood pressure were 146 mmHg (an increase of 22 mmHg from Baseline) and 89 bpm (a decrease of 4 bpm from Baseline), respectively. At the time of the abnormal diastolic blood pressure, the subject was receiving Treatment C (2.5 g testosterone gel 1.62%). No AE related to the markedly abnormal increase in diastolic blood pressure was noted.

Study S176.1.007: A Singe and Multiple Dose Pharmacokinetic and Comparative Bioavailability Study of Testosterone Absorption after Administration of Testosterone Gel 1.62% to the Abdomen, Upper Arms/Shoulders or via a Rotation Schedule in Hypogonadal Males

This single center Phase 1 US study had as its objectives:

- To determine single and multiple dose pharmacokinetics of testosterone after administration of testosterone gel 1.62% in hypogonadal males; and
- To determine the relative bioavailability of testosterone after administration of 5gm testosterone gel 1.62% to the abdomen, upper arms/shoulders, and to a rotating schedule of these two application sites.

A total of 36 hypogonadal male subjects were enrolled in the study and received at least one dose of study medication. A total of 32 subjects completed the study according to the protocol. Two subjects were prematurely discontinued from the study due to administrative reasons (predose testosterone >900 ng/dL as specified in the protocol and determined by clinical safety laboratory results obtained from the local laboratory); 1 subject withdrew consent due to a family emergency; and 1 subject withdrew to a serious adverse event (SAE) of dermatitis on the lower leg. A total of 36 subjects were included in both the PK and safety analyses.

Subjects were included in the study if they were hypogonadal males (serum testosterone < 300 ng/dL at screening), 18 to 75 years of age, had undergone a 3 to 6 week washout period appropriate to type of previous androgen replacement therapy (if applicable), and had a body mass index (BMI) of 20 to 35 kg/m^2 inclusive.

Hypogonadal male volunteers received 5.00 g of testosterone gel 1.62% once daily for each of three 7-day treatment regimens. There was a 5-day washout period between the 3 treatments which consisted of the following:

Treatment A: Once daily application of 5.00 g testosterone gel 1.62% to the abdomen, for 7 days.
Treatment B: Once daily application of 5.00 g testosterone gel 1.62% to the upper arms/shoulders for 7 days.
Treatment C: Once daily application of 5.00 g testosterone gel 1.62% to the abdomen for 3 days, followed by application to the upper arms/shoulders for 4 days

The total duration of the study was 36 days, not including the Screening period. Subjects were confined to the clinic for the entire study period.

Pharmacokinetic whole blood samples were collected for determination of total testosterone, dihydrotestosterone, and estradiol at the following times:

- Day -1 (Baseline): 0, 2, 4, 6, 8, 12, 16, and 24 hours with respect to the projected time of dose administration;
- Days 1, 12, and 23 (Treatment Day 1): 0, 2, 4, 8, 12, 16, and 24 hours post dose;
- Days 7, 18, and 29 (Treatment Day 7): 0, 2, 4, 8, 12, 16, 24, 48, 72, and 120 hours post dose; and
- Days 3-6, 14-17, 25-28 (Treatment Days 3-6): predose (trough).

Maximum observed serum concentration (C_{max}), area under the serum concentration-time curve from time zero to 24 hours post dose($_{AUC0-24}$), the lowest concentration observed during the 24-hour dosing interval (C_{min}), average concentration over the dosing interval over a 24-hour period (Cav), time to reach maximum observed serum concentration (t_{max}), time of minimum observed serum concentration (t_{min}), peak to trough fluctuation (PTF), accumulation ratio, and relative bioavailability were calculated for observed and baseline-adjusted testosterone. Concentration-time data were summarized using descriptive statistics for dihydrotestosterone and estradiol.

Results and Conclusions for Study S176.1.007: Following treatment with testosterone gel 1.62%, mean observed concentrations were within the eugonadal range (300-1000 ng/dL) after 2 hours post dose on Treatment Day 1 and over the 24-hour dosing interval on Treatment Day 7 for all treatments. Twenty-five subjects had testosterone concentrations >1000 ng/dL after testosterone gel application. Of these, one had concentrations >2500 ng/dL.

Table 5: Numbers of Subjects with Testosterone Concentrations >1000 or 2500 ng/dL While on Treatment

Treatment	Numbers of Subjects (%)	
	>1000 ng/dL	>2500 ng/dL
A	7(19)	0(0)
B	21(58)	0(0)
C	17(47)	1(3)[a]
Total Across Treatments	25(69)	1(3)

[a] A concentration of 4160 ng/dL in Subject 26832 on Treatment Day 7 (upper arms/shoulders) at 2 hours post dose.

Source: Clinical Study Report S176.1.007, page 43.

> *Reviewer's Comment: Because of the nature of the study, dose titration could not occur as it did in the Phase 3 protocol. Therefore, the single patient with markedly elevated serum T is not considered a major safety concern. In regard to outliers, see the reviewer's assessment of the dose-titration Phase 3 study.*

On Treatment Day 1, mean observed testosterone concentrations were higher for Treatment B (upper arms/shoulders application) compared to Treatment A (abdomen application) and as compared to Treatment C (rotation application-abdomen 3 days followed by upper arms/shoulder 4 days). Treatments A and C had similar mean concentrations on Day 1. On Treatment Day 7, mean concentrations were lower for Treatment A (abdomen) compared to Treatments B (arm/shoulders) and C (rotating schedule). Treatments B and C provided similar mean testosterone concentrations on Day 7.

After multiple dosing, steady-state conditions were achieved by Treatment Day 2 for both Treatments A and B. For Treatment C (rotating), trough concentrations showed a shift after treatment Day 4, which reflected the change in application site (from abdomen to upper arms/shoulders). After the last application of testosterone gel 1.62%, mean observed testosterone concentrations returned to baseline levels by 48 hours post dose on Treatment Day 7 for Treatment A, and 72 hours post dose for Treatments B and C.

The conclusions of this study are:

- Single and multiple dose application of testosterone gel 1.62% applied to the abdomen provided approximately 30-40% lower bioavailability compared to upper arm/shoulder application.
- A rotation application schedule, where 5.00 g testosterone gel 1.62% was applied for 3 day to the abdomen followed by 4 days to the upper arms/shoulder, provided comparable bioavailability to abdominal application of Day 1 and comparable bioavailability to upper arm/shoulder application of Day 7.
- Steady-state testosterone concentrations were achieved within 2 days when testosterone gel 1.62% was applied solely to the abdomen or upper arms/shoulders once daily for 7 days.
- After the last dose of testosterone gel 1.62% was applied, testosterone concentrations returned to baseline levels within 48 hours after abdomen application and within 72 hours after upper arms/shoulders and rotation application.

> *<u>Reviewer's comment</u>: The data from this study show that arm/shoulders and a "rotating schedule" (3 days abdomen than 4 days arms/shoulders) provides 30-40% more exposure than abdomen. Therefore the sites of application are not interchangeable. Since the Phase 3 study 104 was conducted using the rotating schedule and thus, there is very good, stand-alone pharmacokinetic data for the rotating schedule, the rotating schedule would be the appropriate one for labeling.*

There were no deaths in the study. A total of 31 subjects (86.1%) exposed to study medication reported at least one treatment emergent adverse event (TEAE) throughout the course of the study. One serious, TEAE of dermatitis was reported during the study (see narrative below). Application site TEAEs were among the most frequent TEAEs (reported in ≥ subjects). These included application site excoriation (7/36, 19.4%), application site papules (5/36, 13.9%) and application site dermatitis (4/36, 11.1%). Other non-serious TEAEs reported most frequently were dry skin (8/36, 22.2%), arthropod bite (5/36, 13.9%), and pruritus and headache (each reported in 4/36, [11.1%] of subjects).

Subject 26827 is a 55 year-old white male randomly assigned to treatment sequence C, A, B, received testosterone gel 1.62% on the abdomen on Days 1-3 and on the shoulder/upper arm on Days 4-7. On (b) (6) (Day 6), Subject 26827 noted a "red skin patch" on his "lower front leg". The sub-investigator assessed the subject at 3.5 hours post dose on (b) (6) (Day 7) and found a right lower lateral anterior leg erythema, characterized as "rough feeling" and of "smooth appearance". A biopsy was ordered and the subject received concomitant treatment with transdermal hydrocortisone cream. The subject was discontinued from the study at Day 7. The SAE of dermatitis was moderate in severity and considered unrelated to the study medication according to the investigator. When the subject returned to the study site on (b) (6) (b) (6) to complete the biopsy, he reported the use of OTC hydrocortisone cream twice daily (BID) since study withdrawal. An assessment of the subject by the sub-investigator revealed a continued slight erythema with "no scale and no component." The biopsy results showed superficial and deep perivascular dermatitis and eosinophilia, consistent with a dermal hypersensitivity reaction and a periodic acid-Schiff (PAS) stain negative for fungi. At a post-study follow-up call on 2 April 2007, the subject reported discontinuing the use of hydrocortisone cream on 25 March 2007 and the SAE of dermatitis has resolved on 28 March 2007. The subject had a relevant medical history of dermatitis and erythema to the lower right leg with a corresponding onset of September 2006 and December 2006, respectively. The subject reported treatment for dermatitis with antibacterial and antifungal ointments beginning in October 2006, and treatment for erythema with hydrocortisone as needed and OTC skin lotion since 02 December 2006. At Screening, the subject reported both events as having been resolved on 1 February 2007.

The following 8 subjects experienced markedly abnormal vital signs during the study:

- Subject 26807 is a 51 year- old white male, randomly assigned to treatment sequence C, B, A, received testosterone gel 1.62% (5.00 g) on Days 1-7, 12-18 and 23-29. At the first assessment performed on Day-2, the subjects SBP was 168 mmHg; and his corresponding DBP was 122 mmHg (Baseline value 107 mmHg), which met the criteria for markedly abnormal vital signs. At a subsequent unscheduled assessment on Day-2, the subject experienced high blood pressure values of 180 mmHg (Baseline value 138 mmHg) for SBP and 128 mmHg for DBP. These values also met the criteria for markedly abnormal vital signs. No medical history of hypertension was reported and no AEs related to the markedly abnormal blood pressure values were recorded.
- Subject 26182, a 50 year-old black male, randomly assigned to treatment sequence A, B, C, received testosterone gel 1.62% (5.00 g) on Days 1-4; however was discontinued from the study on Day 4 due to a testosterone level >900 ng/dL obtained from the clinical

safety laboratory results, as specified in the protocol. The subject experienced a decrease in weight that met the criterion for markedly abnormal vital sign values (≥ 7% decrease from Baseline). At the termination assessment (Day 5), the subject's weight was 88.7 kg (Baseline value: 96.4 kg); an overall decrease of 7.7 kg. No AE's related to the markedly abnormal decrease in weight was recorded.

- Subject 26819, a 58 year-old white male, randomly assigned to treatment sequence B, A, C, received testosterone gel 1.62% (5.00 g) on Days 1-7, 12-18, and 23-29. The subject experienced a decrease in weight that met the criteria for markedly abnormal vital sign values (≥ 7% decrease from Baseline). At study exit (Day 34), the subject's weight was 90.0 kg (Baseline value: 97.6 kg); an overall decrease of 7.6 kg. No AE related to the markedly abnormal increase in weight was recorded.
- Subject 26825, a 51 year-old white male, randomly assigned to treatment sequence B, C, A, received testosterone gel 1.62% (5.00 g) on Days 1-7, 12-18 and 23-29. The subject experienced a high DBP of 105 mmHg at an unscheduled assessment on Day -2 (Baseline value: 80 mmHg). This met the criteria for markedly abnormal vital signs. No medical history of hypertension was reported and no AE related to the markedly abnormal DBP value was recorded.
- Subject 26826, a 56 year-old white male, randomly assigned to treatment sequence B, A, C, received testosterone gel 1.62% (5.00 g) on Days 1-7, 12-18, and 23-29. The subject experienced a high DBP of 108 mm Hg on Day -2 (Baseline value: 89 mmHg). This met the criteria for markedly abnormal vital signs. No medical history of hypertension was reported and no AE related to the markedly abnormal DBP value was recorded.
- Subject 26830, a 36 year-old white male randomly assigned to treatment sequence A, C, B, received testosterone gel 1.62% (5.00 g) on Day 1-7, 12-18, and 23-29. The subject experienced a high DBP of 126 mmHg on Day 11 (Baseline value: 80 mmHg). This met the criteria for markedly abnormal vital signs. No AE related to the markedly abnormal DBP was recorded.
- Subject 26835. a 49 year-old white male, randomly assigned to treatment sequence B, C, A, received testosterone gel 1.62% (5.00 g) on Days 1-7, 12-18 and 23-29. The subject experienced a high DBP of 107 mmHg on Day 31 (Baseline value: 92 mmHg). This met the criteria for markedly abnormal vital signs. No medical history of hypertension was reported and no AE related to the markedly abnormal DBP value was recorded.
- Subject 26840, a 57 year-old white male, randomly assigned to treatment sequence B, A, C, received testosterone gel 1.62% (5.00 g) on Days 1-7, 12-18, and 23-29. The subject experienced a decrease in weight that met the criterion for markedly abnormal vital sign values (≥ 7% decrease from Baseline). At study exit (Day 34), the subject's weight was 72.2 kg (Baseline value: 79.3 kg); an overall decrease of 7.1 kg. No AE related to the markedly abnormal decrease in weight was recorded.

Table 6: Sponsor's Standards For the Identification of "Markedly Abnormal Vital Signs"

Variable	Unit	Markedly Low	Markedly High
SBP	mmHG	Value = 90 and 20 mmHg decrease from Baseline	Value = 180 and 20 mmHg increase from Baseline
DBP	mmHg	Value = 50 and 15 mmHg decrease from Baseline	Value = 120 and 15 mmHg increase from Baseline
Pulse	bpm	Value = 50 and 15 bpm decrease from baseline	Value = 120 and 15 bpm increase from baseline
Weight	Kg	= 7% decrease from Baseline	= 7% increase from Baseline
Temperature	^{o}F	NA	Value =101.0 and =2.0 increase from Baseline

Source: Analysis Plan for Study S176.1.007: page 29, Table 17.2.3

6 Review of Efficacy

Efficacy Summary

The primary efficacy variable for Study S176.3.104 was the percentage of subjects with total testosterone C_{av} within the normal range on Day 112. C_{av} results were required to fall with the normal range of 300-1000 ng/dL, with success being defined as ≥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 C_{av} values within the target range, which met the criteria for efficacy.

The key secondary efficacy success criteria required the individual Cmax results to be within the following ranges:

- ≤1500 ng/dL in ≥85% of the subjects
- between 1800-2500 in ≤5% of the subjects and
- >2500 in none of the subjects.

In the FA sample, 93.9% (696/741) of C_{max} observations were ≤1500 ng/dL when considering all four PK days combined. Analyzed for each PK day, the percentage of subjects on testosterone treatment with C_{max} values ≤1500 ng/dL was 96.7% (203/210) on Day 14; 97.3% (178/183) on Day 56; 88.8% (159/179) on Day 112; and 92.3% (156/169) on Day 182.

Overall 3.0% (22/741) of C_{max} observations were in the range of 1800-2500 ng/dL when considering all four PK days combined in the FA sample. Analyzed for each PK day, the percentage of subjects on testosterone treatment with C_{max} values from 1800-2500 ng/dL was 2.4% (5/210) on Day 14; 0.5% (1/183) on Day 56; 5.6% (10/179) on Day 112; and 3.6%(6/169) on Day 182.

A total of 10/234 subjects had a total of 11 testosterone concentrations >2500 ng/dL in the double-blind phase of Study S176.3.104. The testosterone concentrations that exceeded the 2500 ng/dL threshold in Study S176.3.104 were rare, sporadic, and inconsistent. Five of the 10 subjects were eliminated on the basis of sample contamination or artifact and 1 of the 10 subjects was eliminated on the basis of taking more than the prescribed test item dose ("overcompliance"). In the four remaining patients, overdosage was possible in two cases. The four patients in whom sample contamination was not clear and overdosage was not definite were compared to the overall study population receiving testosterone gel 1.62% (in a dose specific manner where possible) with respect to changes in secondary efficacy variables, weight, BMI, hemoglobin, hematocrit, cholesterol, HDL, estradiol and dihydrotestosterone. No indication of increased testosterone dose effect was noted.

There were no subjects in the 182 day Safety Extension with a testosterone concentration of 2500 ng/dL or above.

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. 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, 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. Analysis of variables that might imply androgen effects was conducted. Overall, I concluded that these sporadic events did not signal a safety risk.

6.1 Indication

The proposed indication for AndroGel® 1.62% is for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism [congenital or acquired] or hypogonadotrophic hypogonadism [congenital or acquired].

Examples of causative conditions or agents for primary (hypergonadotropic) hypogonadism include: 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.

Examples of causative conditions or agents for secondary (hypogonadotropic) hypogonadism include: idiopathic gonadotrophin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma or radiation.

6.1.1 Methods

In support of this application, the Sponsor provided efficacy results from one Phase 3 (S176.3.104, double-blind phase) study. The Division agreed at the EOP2 Meeting, 18 October 2006, that a single Phase 3 study evaluating the safety and efficacy of testosterone gel 1.62% would be sufficient to file the application for review. This review of efficacy is based on review of Protocol S176.3.104. Of note, additional multiple-dose pharmacokinetic data for testosterone 1.62% was collected in several Phase 1 studies, including the dose-ranging study S176.1.002.

The efficacy of testosterone gel 1.62% in males with primary or secondary hypogonadism is determined by the pharmacokinetic (PK) profile in this population.

6.1.2 Demographics

Table 7: Demographics of Hypogonadal Patients in Phase III 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: pages228

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). A smaller percentage of subjects in the testosterone gel 1.62% group were 55 to 64 years of age compared with the placebo group (67/124, 31.3%

versus 16/37, 43.2%). In the testosterone gel 1.62% group, the majority of subjects were in the 45-54 and 55-64 years age categories (83/214, 38.8% and 67/214, 31.3%). In the placebo group, the most common age category was 55-64 years (16/37, 43.2%). The majority of subject in the testosterone gel 1.62% groups and the placebo group were white (177/214, 82.7% versus 35/37, 94.6%) and not Hispanic or Latino (198/214, 92.5% versus 35/37, 94.6%).

Analysis of demographic data for the Safety Sample showed results consistent with the FA (Full Analysis) sample.

Table 8: Other Baseline Characteristics Full Analysis Sample Phase III Study

			T-Gel			
	Statistic	Placebo N=37	1.25 g N=17	2.5 g N=41	3.75 g N=65	5.0 g N=91
Height(m)	Mean (SD)	1.79(0.07) n=37	1.78(0.07) n=17	1.79(0.06) n=41	1.80(0.06) n=65	1.78(0.07) n=91
Weight(kg)	Mean (SD)	98.5(13.0) n=37	96.6(14.8) n=17	98.1(15.3) n=41	103.3(16.9) n=65	99.6(14.3) n=91
Waist (cm)	Mean (SD)	104.4(11.5) n=37	103.1(10.8) n=17	105.0(11.1) n=41	108.3(12.7) n=63	106.5(10.8) n=90
Hip Circum(cm)	Mean (SD)	107.6(9.5) n=37	105.1(12.6) n=17	107.3(7.9) n=41	110.3(11.3) n=63	108.9(9.3) n=90
Waist/Hip ratio	Mean (SD)	0.97(0.07) n=37	0.98(0.06) n=17	0.99(0.08) n=41	0.98(0.07) n=63	0.97(0.06) n=90
BMI ($kg/m^{2)}$	Mean (SD)	30.6(4.1) n=37	30.5(3.8) n=17	30.8(4.6) n=41	31.8(4.4) n=65	31.4(12.7) n=91
Sitting SBP (mmHg)	Mean (SD)	130.1(13.6) n=37	128.5(16.0) n=17	130.0(14.6) n=41	129.8(15.2) n=65	129.9(12.7) n=91
Sitting DBP (mmHg)	Mean (SD)	79.1(7.7) n=37	78.9(9.9) n=17	80.1(10.4) n=41	80.0(8.4) n=65	80.4(8.4) n=91
Sitting Pulse	Mean (SD)	73.4(14.3) n=37	73.4(9.9) n=17	71.4(12.0) n=41	71.0(9.4) n=65	24.8(12.3) n=91
% Free PSA	Mean (SD)	24.7(11.4) n=36	24.2(14.6) n=17	25.5(11.0) n=40	23.7(10.3) n=64	24.8(12.3) n=91

Source: Clinical Study Report: S176.3.104: Table 2.1.0: pages 231-232.

The mean waist-to-hip ratio, Body Mass Index, percent free PSA, and sitting SBP, DBP and pulse at Baseline were similar between treatment groups.

Mean baseline concentrations of total testosterone were similar in the testosterone gel 1.62% (282 ng/dL) and the placebo group (294 ng/dL). Similarly, the mean baseline DHT and E2 values were similar in the testosterone gel 1.62% group (DHT: 18.9 ng/dL and E2: 19.8 pg/mL) and placebo group (DHT: 22.0 ng/dL, E2: 19.4 pg/mL). The mean baseline values of serum PSA were similar in the testosterone gel 1.62% group (0.89 ug/L) and the placebo group (0.85 ug/L).

Subject 046-06 is diagnosed as Klinefelter's Syndrome. There are no patients with the diagnosis of Kalman's Syndrome in the protocol.

There was a slightly higher incidence of baseline eye disorder in the placebo group and the T-Gel group had a slightly higher incidence of ear and labyrinth disorders, as well as gastrointestinal-hepatobiliary disorders. The placebo group had a slightly higher incidence of use of drugs for peptic ulcer disease. The overall compliance for the Full Analysis Data set was 97.70 % for placebo and 94.29% for the T-Gel group.

Reviewer's Comment: The Phase III study population appears similar to those of other approved testosterone replacement products.

6.1.3 Subject Disposition

Table 9: Analysis Groups

	Placebo N=40	T-Gel N=234	Overall N=274
	n (%)		
Safety Sample	40(100.0)	234(100.0)	274(100.0)
Number Excluded	0	0	0
Reasons			
No Drug Taken	0	0	0
Full Analysis Sample	37(92.5)	214(91.5)	251(91.6)
Number Excluded	3(7.5)	20(8.5)	23(8.4)
Reasons			
No Drug Taken	0	0	0
No Postbaseline Efficacy Data	3(7.5)	20(8.5)	23(8.4)
Per Protocol Sample	27(67.5)	150(64.1)	177(64.6)
Number Excluded	13(32.5)	84(35.9)	97(35.4)
Reasons			
No Drug Taken	0	0	0
Major Protocol Violation	10(25.0)	72(30.8)	82(29.9)
No Postbaseline Efficacy Data	3(7.5)	20(8.5)	23(8.5)
Efficacy Sample	27(67.5)	179(76.5)	206(75.2)
Number Excluded	13(32.5)	55(23.5)	69(24.9)
Reasons			

No Drug Taken	0	0	0
No 112 Day Efficacy Data	13(32.5)	55(23.5)	68(24.8)

Source: Clinical Study Report: S176.3.104: Table 6: page 60.

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 (168 T-Gel [71.8% of randomized] and 28 [70.0% of randomized] placebo). The most common last titrated dose was 5.00 g testosterone gel 1.62%. Similar percentages of placebo and T-Gel patients discontinued from the study groups. The most common AE leading to discontinuation was increased PSA which was prespecified as a discontinuation criteria and will be discussed in the Safety section of this review.

Table 10: Consented Subject Disposition S176.3.104-182 Day Pivotal Period

Subjects	Placebo N=40	T-Gel 1.25g N=17	T-Gel 2.5g N=60	T-Gel 3.75g N=66	T-Gel 5.0g N=91	Total T-Gel N=234
	n (%)					
Completed	28(70.0)	12 (70.6)	35(58.3)	50(75.8)	71(78)	168(71.8)
Premature Terminate	12(30.0)	5(29.4)	25(41.7)	16(24.2)	20(22.0)	66(28.2)
Reasons						
Adv event	0	1(5.9)	6(10.0)	8(12.1)	10(11.0)	25(9.1)
Lack of Efficacy	0	1(5.9)	0	1(1.5)	0	2(0.7)
Lost to Follow-up	2(5.0)	0	3(5.0)	0	2(2.2)	7(2.6)
Withdrew Consent	8(20.0)	1(5.9)	10(16.7)	4(6.1)	4(4.4)	27(9.9)
Admin	1(2.5)	0	1(1.7)	1(1.5)	3(3.3)	6(2.2)
Protocol Violation	1(2.2)	1(11.8)	5(8.3)	2(3.0)	1(1.1)	11(4.0)

Note: Treatment groups are based on subject's last titrated dose.
Source: Clinical Study Report S176.3.104 adapted from Table 1.0.0: page 184

Reviewer's Comment: The protocol violations in all subjects allocated to treatment were either sampling time out of the window or lack of compliance (taking medication <80 or >120 %).

Table 11: Reason for Dropout by Visit Phase III Pivotal Study

	Day 14	Day 28	Day 42	Day 56	Day 84	Day112	Day140	Day182
T-Gel 1.62%	Statistic n (%)							
Number of subjects assessed	226 (96.6)	212 (90.6)	207 (88.5)	202 (86.3)	198 (84.8)	230 (83.9)	182 (77.8)	175 (74.8)
Number of subjects terminated	15(6.4)	5(2.1))	4(1.7)	4(1.7)	4(1.7)	5(1.8)	7(3.0)	7(2.6)
Reason	Statistic n (%)							
AE	3(1.3)	2(<1.0)	0	1(<1.0)	1(<1.0)	9(4.6)	5(2.7)	4(2.3)
Lack efficacy	1(<1.0)	0	1(<1.0)	0	0	0	0	0
Lost to follow-up	0	0	0	1(<1.0)	0	2(1.0)	0	0
Withdrew consent	4(1.8)	2(<1.0)	2(<1.0)	1(<1.0)	2(1.0)	2(1.0)	2(1.1)	0
Administrative	1(<1.0)	0	1(<1.0)	1(<1.0)	1(<1.0)	0	0	1(<1.0)
Protocol Violation	6.7(2.7)	1(<1.0)	0	0	0	0	0	2(1.1)
Missing	0	0	0	0	0	0	0	0
Placebo	Statistic n (%)							
Number of subjects assessed	39 (97.5)	38 (95.0)	37 (92.5)	35 (87.5)	32 (80.0)	32 (80.0)	28 (70.0)	28 (70.0)
Number of subjects terminated	1(2.5)	1(2.5)	1(2.5)	2(5.7)	1(2.5)	4(10.0)	0	0
Reason	Statistic n (%)							
AE	0	0	0	0	0	0	0	0
Lack efficacy	0	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	1(2.9)	0	0	0	0
Withdrew consent	1(2.6)	1(2.6)	1(2.7)	2(5.7)	0	3(9.4)	0	0
Administrative	0	0	0	0	1(3.1)	0	0	0
Protocol Violation	0	0	0	0	0	1(3.1)	0	0
Missing	0	0	0	0	0	0	0	0

Source: Clinical Study Report S176.3.104: Table 1.0.1: pages 188-194

Reviewer's Comment: The increased adverse events in the T-Gel 1.62% patients at Days 112 and 140 may reflect the AE of increased serum PSA.

The overall mean compliance for the FA Sample was similar for the testosterone gel 1.62% groups and the placebo group (94.29% versus 97.70%). Most subjects were in the 80-120% compliance category in the testosterone gel 1.62% groups and the placebo group (179/214, 83.6% versus 29/37, 78.4%). No meaningful differences in mean compliance were observed between treatment groups, or across the dose groups, except for a greater percentage of subjects

in the 1.25 g testosterone gel 1.62% (5/17, 29.4%) group with >120% compliance compared with the other three testosterone gel 1.62% groups (2.5 g 1/41, 2.4%; 3.75 g: 3/65, 4.6%; 5.0 g: no subject).

6.1.4 Analysis of Primary Endpoint(s)

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 ≥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%.

81.6% (95% CI of 75.1% to 87.0%) of subjects in the FA sample on testosterone treatment had C_{avg} values within the normal concentration range on Day 112.

Table 12: Percentage of Patients Achieving Target Testosterone Concentration (FA)

		T-Gel	T-Gel	Placebo	
Study Day	Total T(Cav) ng/DL	n/N (%)	95% CI	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

Reviewer's Comment: In my opinion, the Sponsor has achieved their Primary Efficacy Endpoint.

6.1.5 Analysis of Secondary Endpoints(s)

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} ≤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, HDL#, 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 linked C telopeptide), waist to hip ratio, and the SF-36.

Table 13: Number and Percentage of Patients Achieving Target Range for Cmax by Day and Treatment (Efficacy Sample)

Study Day	Total Testosterone C_{max} (ng/dL)	T-Gel 1.62%		Placebo	
		n/N (%)	95% CI	n/N (%)	95% CI
14	<=1500ng/dL	170/175 (97.5)	(93.5, 99.1)	27/27 (100.0)	(87.2, 100.0)
	1501-<1800	0/175 (0.0)		0/27 (0.0)	
	1800-2500	4/175 (2.3)		0/27 (0.0)	
	>2500	1/175 (0.6)		0/27 (0.0)	
56	<=1500ng/dL	160/165 (97.0)	(93.1, 99.0)	26/26 (100.0)	(86.8, 100.0)
	1501-<1800	1/165 (1.2)		0/26 (0.0)	
	1800-2500	1/165 (0.6)		0/26 (0.0)	
	>2500	1/165 (1.2)		0/26 (0.0)	
112	<=1500ng/dL	159/179 (88.8)	(83.3, 93.0)	26/27 (96.3)	(81.0, 99.9)
	1501-<1800	8/179 (4.5)		1/27 (3.7)	
	1800-2500	10/179 (5.5)		0/27 (0.0)	
	>2500	1/179 (1.1)		0/27 (0.0)	
182	<=1500ng/dL	152/165 (92.1)	(86.9, 95.7)	27/27 (100.0)	(87.2, 100.0)
	1501-<1800	6/165 (3.6)		0/27 (0.4)	
	1800-2500	6/165 (3.6)		0/27 (0.4)	
	>2500	1/165 (0.6)		0/27 (0.4)	

Source: Clinical Study Report S176.3.104: Table 11.2.4: page 409

In the full analysis sample, ≥88.8% of subjects on testosterone treatment had C_{max} values ≤1500 ng/dL, thus meeting the first secondary efficacy criteria:
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.

Overall, 3.0% (22/741) of C_{max} observations were in the range of 1800-2500 ng/dL when considering all four PK days combined in the FA sample. By PK day, the percentage of subjects on testosterone treatment with C_{max} values from 1800-2500 ng/dL was (5/21) on Day 14; 0.5% (1/183) on Day 56; 5.6% (10/179) on Day 112; and 3.6 % (6/169) on Day 182. This is a 3.0% overall C_{max} observation in the range of 1800-2500 ng/dL when considering all four PK days.

The third efficacy criteria was that there were to be no subjects with a C_{max} for serum testosterone >2500 ng/dL. Within the 182 day double-blind period there 10 subjects with C_{max} > 2500 ng/dL. They are presented below in Table 14.

Table 14: Serum Total Testosterone Concentrations >2500 ng/dL in Study S176.3.104

Subject Number	Dose (g/day)	Day	Timepoint After Dosing	Total Testosterone (ng/dL)	DHT (ng/dL)	DHT/T Ratio (95% interval)	E2 (pg/mL)	Comments Narrative Analysis	%Overall Compliance Gms/day at >2500 timepoint
Normal Range					11.2-99.5ng/dL	(0.074-0. 330)	<20 pg//mL		
	Cases of Suspected Blood Sample Contamination Influencing PK Profiles								
003-008	N/A Before drug	1	Baseline Day 1 (No active treatment yet)	3270	18	0.006	48	Handling error-repeat 631ng/dL	100.4 %
039-009	5.00	56	1 hour	3750	43	0.011	14	Blood Sample contamination	96.0% 5 5 gms/day
012-008	5.00	182	2 hour	4430	77	0.017	22	Blood Sample contamination	91.6% 2.8 gms/day
005-028	3.75	28	Pre-dose	3867	100	0.026	No value	Blood Sample contamination	112.6% 2.7 gms/day
044-005	2.50	14	Pre-dose	2850	193	0.068	No value	Handling error-repeat 1030ng/dL	79.9% 5.6 gms/day
	Cases of Acute Increases in Systemic Absorption Primarily Influencing PK Profiles								
007-006	5.00	112	8 hour	2550	137	0.054	16	Increased absorption from dermal compartment/ heat stress & Blood Sample contamination	93.7% 5 5 gms/day
058-006	5.00	112	2 hour	2510	237	0.094	43	Rare acute increase in systemic absorption – ? etiol	92.7% 5 2 gms/day
067-001	3.75	112	Pre-dose	2730	267	0.098	64	Higher than prescribed dosing	106.2% 3 3 gms/day
015-005	2.5	14	Pre-dose	3290	341	0.104	31	Suspected double dosing Day 14	92.0% 2 5 gms/day
049-008	2.50	56	0.5 hour	2810	354	0.126	35	Applied every 17h,skin hydration	87.7% 1.8 gms/day
049-008	2.50	14	0.5 hour	3200	414	0.129	17	Applied every 17h	2.8 gms/day

Source: 2.5 Clinical Overview of NDA submissions adapted from Table 8, page 39 and Listing 14 of Clinical Study Report S176.3.104.

Analysis by case of subjects with a testosterone concentration of >2500 ng/dL - more intensive consideration:

Subject 003-008: The patient is 52 years old and has had hypertension for 12 years and hyperlipidemia for 18 years. His concomitant medications include rosuvastatin, fenfibrate, and olmersartan. His baseline PSA was 0.5 ng/mL and at Day 182 was 0.5 ng/mL. There were no laboratory abnormalities. The subject had a testosterone concentration of 3270 ng/dL at Baseline

(assessed via LC-MS/MS a (b) (4) prior to any scheduled drug administration. This subject's Baseline total testosterone concentration re-assessed by RIA at (b) (4) was 631 ng/dL, markedly lower than the (b) (4) result. The subject's C_{av} on Day 56 was 271 ng/dL and at 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. The 95% prediction interval of the DHT/T ratio for subject in the testosterone gel 1.62% group observed over the whole study was 0.074-0.330.

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.

Subject 039-009: The patient is a 65 year old male with a history of hypertension, rosacea, and hypercholesterolemia. His concomitant medications include atorvastatin, acetylsalicylic acid, metronidazole (topical), multivitamins, fish oil, and vitamin C. His baseline PSA was 1.1 ng/mL and at Day 182 was 2.9 ng/mL. There were no abnormal rectal DRE findings. The PSA elevation (>0.75ng/mL) was not reported as an AE. A repeat PSA test result was pending at time of database lock of the double-blind portion of the study. This subject discontinued during the open-label portion of the study and no repeat PSA value could be obtained. There were no other laboratory abnormalities. 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 on a dose of 5.00 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_{av} 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.

Subject 012-008: The patient is a 58 year old male with a history of acne, muscle disorder, deafness, hypertension, hypercholesterolemia, nephrolithiasis, and rosacea. His concomitant medications include minocycline, lorsartan, amlodipine besylate with benazepril and simvastatin. During the double-blind portion of the protocol, he reported the adverse events of testicular pain, increased weight, and nephrolithiasis. His PSA at Baseline was 1.5 ng/mL and at Day 182 was 1.8 ng/mL. The DRE detected no abnormal findings. 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 5.00 g 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 (ng/dl) of 1080 at 4 hours Post dose, 1810 at 8 hours Post dose, and 1030 at 24 hours Post dose. On Day 112, testosterone concentrations (ng/dl) 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_{av} at Days 112 and 182 were 1160 and 927 ng/mL, respectively. The subject was diagnosed with prostate cancer in the Open-Label period.

Table 15: Subject 012-008 Testosterone Concentrations (ng/dL)

T-Gel Dose	***2.5 g***	***5 g***	***5 g***	***5 g***	***Open-Label Dose 5 g***		
Sampling Time	**PK Day 14**	**PK Day 56**	**PK Day 112**	**PK Day 182**	**Baseline**	**Day 243 Pre-dose**	**Day 279 Pre-dose**
0	311	706	739	816	234	618	626
0.5	187	631	1230	588			
1	367	903	1050	771			
2	349	864	1440	4430			
4	466	1080	1310	641			
8	248	1810	1740	772			
12	362	855	757	660			
24	520	1030	1200	705			

Source; Listing 40 Clinical Study Report S176.3.104, Listing 23 182-Day Open-Label Period S176.3.104

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.

Subject 005-028: The patient is a 46 year old male with a history of hypertension and osteoarthritis. His concomitant medications include olmesartan, celecoxib and a multivitamin. During the double-blind portion of the protocol, he reported the adverse events of acne and mood swings. The PSA was 2.5 ng/mL at Baseline and at Day 182 was 2.5 ng/mL. There were no markedly abnormal laboratory findings. 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_{av} 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.

Subject 044-005: The patient is 47 year old male with a history of intermittent tension headaches and hypogonadism (etiology not provided). His concomitant medication is acetaminophen for headaches. During the double-blind portion of the protocol, he reported the adverse event of erectile dysfunction for which he took Cialis 20 mg prn. The PSA was 0.5 ng/mL at Baseline at

Day 182 was 0.5 ng/mL. There were no DRE abnormalities. There were no markedly abnormal laboratory findings. 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.*

Subject 007-006: The patient is a 41 year old male with a history of hypertension and a 7 year history of testicular atrophy. His concomitant medication is amlopdipine/benazepril for hypertension. During the double-blind period he reported the adverse events of nasopharyngitis and toothache. The PSA at Baseline was 0.2 ng/mL and at Day 182 was 0.2 ng/mL. There were no markedly abnormal laboratory findings. 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. At Day 112 the C_{av} was 1160 ng/dL and at Day 182 it was 772 ng/dL.

> *Reviewer's Comment: Comments on this particular case are provided in a single Reviewer's Analysis on page 59.*

Subject 058-006: The patient is a 62 year old male with a history of asthma, atrial fibrillation and Barrett's esophagus. His concomitant medications include: esomeprazole, memetasone, clopidogrel, propafenone and diltiazem. The PSA at Baseline was 1.4 ng/mL and at Day 182 was 3.6 ng/mL with repeats of 3.3 ng/mL and 2.4 mL. The baseline DRE revealed an "enlarged 2+ prostate, not clinically significant and Day 182: no clinically significant abnormalities noted." There were no markedly abnormal laboratory findings. The PSA increase was the only adverse event reported for this subject. 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_{av} 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 in a single Reviewer's Analysis on page 59.*

Subject 067-001: The patient is a 49 year old male with a history of hypertension, GERD (gastro-esophageal reflux), hypercholesterolemia, obesity, palpitations, BPH (benign prostatic hypertrophy), seasonal allergies, and depression. The subject had a cyst removed from his right breast in 1999. His concomitant medications include: triamcinolone nasal spray, cetrizine, metoprolol, tamsulosin, escitalopram, phentermime, esomeprazole, rosuvastatin, Vitamin E, fish oil capsule, and vitamin B_6. On Day 63 and Day 72 the subject reported erection increased and libido increased. On Day 150, he experienced a nipple disorder (slight enlargement of both nipples) which was considered mild by the investigator. The PSA at baseline was 0.7 ng/mL and at Day 182, it was 0.5 ng/mL. The DRE had no abnormal findings. There were no markedly abnormal laboratory findings. 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 16: Subject 067-001 Testosterone Concentrations (ng/dL)

Time	Day 56	Day112	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_{av} was 464 ng/dL on Day 182 and 519 ng/dL on Day 56. Both of these days were times where dose compliance was noted. The patient's compliance history coupled with symptoms 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% (subject states that he is having constant erections and arousal; captured as AE's)
- Visit 7 (Day 84) Compliance-114% (all above complaints resolve)
- Visit 8 (Day 112) Compliance 119% (Visit where testosterone was noted >2500 ng/dL)
- Visit 9 (Day146) Compliance-126% (breast nipple enlargement noted as AE)
- Visit 10 Compliance-98.14% (withdrew consent).

Reviewer's Comment: The testosterone concentrations are 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.

Subject 015-005: The patient is a 57 year old male with no relevant past medical history. His concomitant medications include bismuth 1 tsp prn (diarrhea) and budesonide nasal spray for seasonal allergies. The Baseline PSA was 0.8 ng/mL, and at Day 182, the PSA was 0.4ng/mL. The DRE had no abnormal findings. There were no markedly abnormal laboratory findings. 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 17: Subject 015-005 Testosterone Concentrations (ng/mL)

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 $C_{av\ testosterone}$ 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 in a single Reviewer's Analysis on page 59*

Subject 049-008: The patient is a 71 year old male with a medical history of congestive heart failure, hypertension, coronary artery disease, GERD, osteopenia, osteoarthritis with left knee replacement, chronic back pain with lumbar fusion, depression, and gynecomastia (for 16 years). His concomitant medications include: lisinopril, furosemide, atenolol, atorvastatin, citalopram, diflunisal, ipratropium, and hydrocodone with acetaminophen. During the double-blind portion of the trial the adverse event of hypotension was reported. The Baseline PSA was 0.9 ng/mL and on Day 182 the PSA was 0.7 ng/mL. There were no markedly abnormal laboratory findings.

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 18 : Subject 049-008 Testosterone Concentrations (ng/mL)

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_{av} for Days 112 and 182 are 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. 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 (increased skin hydration and inappropriate interval between gel doses). High DHT levels support enhanced absorption and or inappropriate dose interval as opposed to contamination of specimens).

> *Reviewer's Comment: A question of "overcompliance" is raised. Comments on this particular case are provided in a single Reviewer's Analysis on page 59*

Reviewer's Analysis: 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 large dose than assigned.

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

- *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 samples.*

It is notable that even if the results for subjects 015-005, 049-008 and 058-006 were "real", these subjects would have had their testosterone dose titrated downward by instructions in the proposed product label.

- *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, well circumscribed and non-recurrent. There were no concentrations of testosterone >2500 ng/dL in the Open-label period.

6.1.6 Other Endpoints

The table below summarizes the differences between placebo and testosterone gel 1.62% patients for each of the secondary efficacy variables. The remainder of this section provides a brief overview of the results from these secondary endpoints. Of note, while some information may be gleaned from these results, all the secondary endpoints were considered exploratory. In addition, the results from secondary endpoints were used to conduct a safety analysis of the four outlier patients who had a testosterone concentration >2500 ng/dL where contamination or artifact were not clear and overdosage was not definite. This analysis is shown in Section 6.17 below.

Table 19: Secondary Efficacy Variables

Secondary Variable	Study Day	Testosterone Gel 1.62%		Placebo		Least Square Means		Pairwise Comparison		
			Mean	N	Mean	T-Gel	Placebo	Difference	95% CI	
SHBG(nmol/L)	84	193	-2.7	31	1.5	-3.5	1.9	-5.4	(-9.9, -0.9)	
	182	165	-0.7	28	0.1	-1.0	0.1	-1.2	(-5.9, 3.6)	
LH (IU/L)	84	194	-3.60	30	-0.05	-3.47	0.82	-4.29	(-5.87, -2.71)	<
	182	166	-3.48	26	-0.25	-3.50	0.92	-4.29	(-5.63, -3.34)	<
FSH(IU/L)	84	194	-4.56	30	-0.51	-4.39	0.77	-5.16	(-7.20, -3.13)	<
	182	166	-4.38	26	0.56	-4.09	1.84	-5.93	(-7.82, -4.04)	<
TNF-α(pg/mL)	84	186	-0.638	29	0.567	-1.432	2.149	-3.581	(-9.442, 2.280)	
	182	150	-0.446	24	-0.502	0.251	1.724	-1.472	(-6.575, 3.629)	
IL-6(ng/L)	84	189	-0.26	31	-0.79	-0.25	-0.41	0.17	(-1.0, 1.33)	
	182	162	0.30	26	-0.02	0.27	0.22	0.04	(-1.58, 1.67)	
IL-10(pg/mL)	84	145	-2.39	22	0.58	-2.08	0.88	-2.96	(-5.55, -0.37)	
	182	130	-2.95	19	-1.31	-2.44	-0.37	-2.07	(-5.53, 1.40)	
HS-CRP(mg/L)	84	189	0.119	31	-1.852	-0.155	-0.576	0.421	(-1.901, 2.743)	
	182	63	0.550	26	-3.833	0.226	-1.981	2.207	(-0.078, 4.491)	
MMP-9(µg/L)	84	163	-47.8	30	-151.6	-66.6	-146.0	79.5	(-21.9, 180.9)	
	182	188	-38.2	26	-99.9	-53.4	-87.7	34.4	(-99.6, 168.3)	
HDL2(mg/dL)	84	141	-0.5	24	-0.1	-0.5	-0.0	-0.5	(-1.7, 0.7)	
	182	121	0.0	19	0.3	-0.0	0.5	-0.5	(-2.2, 1.2)	
HDL3(mg/dL)	84	141	-1.6	24	1.2	-1.4	1.2	-2.6	(-5.2, 0.0)	
	182	121	-1.5	19	-0.6	-1.4	-1.1	-0.4	(-2.7, 2.0)	
d-Dimer(µg/L)	84	181	-11.4	30	9.8	-7.0	-7.6	0.6	(-91.5, 92.7)	
	182	154	33.2	25	-32.6	25.9	-57.0	82.9	(-82.5, 248.3)	
Fibrinogen (g/L)	84	178	-0.145	30	0.276	-0.129	0.205	-0.334	(-0.694, 0.025)	
	182	170	-0.149	25	-0.0109	-0.141	-0.178	0.036	(-0.335, 0.408)	
VCAM(ng/mL)	84	190	20.7	30	13.6	15.3	37.6	-22.13	(-87.4, 42.7)	
	182	64	153.1	26	91.6	166.3	109.0	57.3	(-58.0, 172.5)	
Waist Hip Ratio	84	182	0.00	27	0.0	-0.00	-0.00	-0.00	(-0.02, 0.02)	
	182	196	-0.01	32	-0.01	-0.01	-0.01	-0.01	(-0.02, 0.02)	
Bone-Specific Alk Phosph(U/L)	84	191	0.28	31	-0.06	0.29	-0.14	0.43	(-104, 1.90)	
	182	163	3.86	27	4.04	3.51	4.14	-0.63	(-2.46, 1.20)	
Type 1 Cross-Linked C Telopeptide (ng/L)	84	180	-0.1086	29	-0.0765	-0.097	-0.0842	-0.0128	(-0.062, 0.036)	
	182	156	-0.0796	25	-0.0796	-0.930	0.0071	-0.1001	(0.168, -0.032)	

Source: Table 16, Clinical Study Report S176.3.104, pages 116-117

Reviewer's Comment: The sample size in the above studies was not selected to provide adequate power for these statistical comparisons. Additionally the p-values for these calculations have not been adjusted for multiple comparisons. All between-group comparisons should be regarded as exploratory for these endpoints.

These secondary efficacy variables were also used (along with other vital signs and laboratory values) to assess whether there were any clinical consequences in those patients with outlier testosterone concentrations(>2500 ng/dL) – see Section 6.1.7.

Sex Hormone Binding Globulin (SHBG): The data shows a significant decrease in mean SHBG levels from baseline on Day 84 but not on Day 182 in testosterone gel 1.62% treated subjects. There was some evidence of a difference between actively treated and placebo groups on Day 84.

Luteinizing Hormone (LH): The LH levels decreased significantly from Baseline on Day 84 and Day 182 with testosterone treatment but not with placebo. A mean decrease of 3.47 IU/L and 3.5 IU/L was observed with testosterone treatment of Day 84 and Day 182.

Follicle Stimulating Hormone (FSH): The FSH levels on Day 84 and Day 182 decreased significantly from Baseline with testosterone treatment but not with placebo. A mean decrease of 4.39 IU/L and 4.09 IU/L was observed on Day 184 and Day 182.

Dihydrotestosterone (DHT): The mean concentrations of DHT in the placebo group were generally within but close to the lower limit of the eugonadal reference range (11.2-95.5 ng/dL) on all study days. For testosterone gel 1.62% treatment, mean DHT levels were mostly within the eugonadal reference range for the 1.25g, 2.5g, and 5.00g doses on Day 14, Day 56, Day 112 and Day 182. For the 3.75g dose group, the mean DHT levels over the concentration profile were 1.3% higher on Day 56, 6.8% to 26.7% higher on Day 112 and 4.7 to 29.8% higher on Day 182 than the upper limit of the eugonadal range. Mean DHT concentration profiles generally paralleled the changes seen in testosterone profiles. The mean (SD) for DHT/T ratios for the testosterone gel 1.62% group was 0.167 (0.0619) with 95% prediction intervals of 0.074-0.0330 and was 0.077 for placebo with 95% prediction intervals of 0.034-0.0151.

Estradiol (E2): The mean concentration profiles for E2 for all treatment groups (placebo and testosterone gel doses) were generally within the normal range of 10-40 pg/mL for Day 14, Day 56, Day 112 and Day 182 except for the placebo and 1.25g group on Day 56 which was slightly above the upper limit of the normal range at a single time point. Similar to DHT, mean estradiol concentrations generally paralleled the changes seen in testosterone.

Tumor Necrosis Factor-Alpha (TNF-Alpha): The levels of TNF-alpha decreased slightly on Day 84 and Day 182 when compared with the Baseline results but this decrease was not significantly different when compared to Baseline Values and when compared with the placebo group.

Interleukin-6 (IL-6): The levels of IL-6 decreased slightly on Day 84 and Day 182 when compared with the Baseline results but this decrease was not significantly different when compared to Baseline Values and when compared with the placebo group.

Interleukin-10 (IL-10): The levels of IL-10 decreased significantly from Baseline on Day 84 and Day 182 with testosterone treatment and there was some evidence of a difference between the actively treated group and the placebo group on Day 84.

High Sensitivity-C-Reactive Protein (HS-CRP): HS-CRP levels increased with testosterone treatment but this change was not statistically significant from Baseline or when compared to the placebo group on both Day 84 and Day 182.

Matrix Metalloprotease-9 (MMP-9): The levels of MMP-9 decreased with testosterone treatment but this change was not significantly different from Baseline or when compared to the placebo group on both Day 84 and Day 182.

High Density Lipoprotein-Subfraction 2 (HDL2): The levels of HDL2 decreased with testosterone treatment and this change was significantly different from Baseline on Day 84 but not on Day 182 or when compared to the placebo group on both Day 84 and 182.

High-Density Lipoprotein-Subfraction 3 (HDL3): The levels of HDL3 decreased with testosterone treatment and this change was significantly different from Baseline but not when compared to the placebo group on Both Day 84 and Day 182.

D-Dimer: The levels of d-Dimer decreased with testosterone treatment but this change was not significantly differ rent from Baseline or when compared to the placebo group on both Day 84 and Day 182.

Fibrinogen: The levels of fibrinogen decreased with testosterone treatment and this change was significantly different form Baseline on Day 84 and Day 182 but not significantly different when compared to the placebo group on both Day 84 and Day 182.

Vascular Cell Adhesion Molecule (VCAM): The levels of VCAM increased with testosterone treatment; this change from Baseline was not significant on Day 84, but was significant on Day 182. The increase was not significant when compared to the placebo group on either Day 84 or Day 182.

Bone-Specific Alkaline Phosphatase: The values for bone-specific alkaline phosphatase increased with testosterone treatment but this change was not significantly different from Baseline on Day 84 but significant on Day 182 and not significant when compared to the placebo group. When considering the presence or absence of bone fractures, the increase in bone-specific alkaline phosphatase levels from baseline for testosterone treatment were not significant regardless of age, presence or absence of bone fractures on Day 84. The increase was significant on Day 182 for all age groups in the presence or absence of bone fractures.

Type 1 Cross-Linked C Telopeptide: The values for Type 1 Cross-linked C Telopeptide decreased with testosterone treatment and this change was significantly different from Baseline on Day 84 and Day 182 and when compared to the placebo group on Day 182.

Quality of Life Assessment SF-36: For the FA and PP samples, there were no clinically significant differences in LS mean change from Baseline at Endpoint between the testosterone gel 1.62% groups and the placebo group for any of the domains of the SF-36 survey.

> *Reviewer's Comment: There were only three secondary efficacy variables that were significantly different compared to placebo at Day 182. They 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*

6.1.7 Subpopulations

For subgroup analysis of pharmacokinetic parameters (including Cavg), the following groups were defined:

- Age: 45years, 45-54 years, 55-64 years and >65 years.
- Race: whites and non-whites
- BMI: quartiles of BMI, and BMI pre-defined ranges (normal and underweight, overweight, obese, clinically obese).

The Sponsor believes that the data from the Phase III efficacy study (S176.3.104) on exploratory analysis suggests that these factors have no effect on the pharmacokinetics of testosterone. The study, however, was not powered to detect differences between subgroups. There are no data available for subjects <18 years of age or for women.

Race: No specific PK was conducted to investigate the effect of race. The number of non-Caucasian patients in the Phase III study was too small to draw meaningful conclusions.

Geriatric: 15% of patients in the Phase III study were ≥65 years old. This number of geriatric subjects (35) may be too small to draw meaningful conclusions about this subgroup.

Pediatric: No pediatric study has been conducted with AndroGel 1.62%.

Renal and Hepatic Impairment: No formal studies of testosterone gel 1.62% have been conducted in patients with renal or hepatic insufficiency.

The Four Subjects with Testosterone Concentrations >2500 ng/dL Selected for Further Analysis: The four subjects with a testosterone concentration >2500 ng/dL for whom it was determined that further scrutiny would be done were compared to the Full Analysis patient group

with respect to serum LH, serum FSH, Type 1 Cross-Linked C Telopeptide, serum DHT and serum estradiol levels at Day 182 in an effort to determine any signal indicating higher than anticipated physiologic effects of testosterone replacement. As shown in Table 21, the average levels of DHT for the 2.5 g dose patients (n=2) was 78 ng/dL at Day 182 and for the 5.00 g patients (n=2) was 78 ng/dL at Day 182. These parallel the results in the FA subject population. With respect to estradiol, the 5.00 g patients had an average estradiol level at Day 182 of 37.5 pg/mL, which is about 1 standard deviation greater than the mean for this group.

Reviewer's Comment: Serum DHT and estradiol usually parallel increases in serum testosterone concentration with a 1 to 4 hour time lag based on my analysis of the submitted data. As such, neither of these efficacy variables are a good indicator of long term increased androgen effect. While serum estradiol in the 5 g subjects was slightly elevated, the value for the 2 subjects in question probably lies within the 95% confidence limits.

The point estimate for C_{av} decline of serum LH in testosterone gel 1.62% treated patients is -3.48 ng/dL[see Tables 20 and 21]. The two 5 g testosterone gel 1.62% treated outlier patients in question had an average decline of -4.25 IU/L, while the two 2.5 g testosterone gel 1.62% treated patients in question had an average decline of -2.8 IU/L.

The point estimate for C_{av} decline of serum FSH in testosterone gel 1.62% treated patients is -4.38 ng/dL [see Tables 20 and 21]. The two 5 g testosterone gel 1.62% treated patients in question had an average decline of -7.2 IU/L, while the two 2.5 g testosterone gel 1.62% treated patients in question had an average decline of -7.65 IU/L.

These observations show comparable decreases from baseline in serum LH in the 4 outlier patients compared to the FA group. There appears to be a modestly greater decrease in serum FSH in the 4 outlier patients compared to the FA group. It is not known whether any differences between groups in this exploratory analysis are statistically significant. Additional analyses of other clinical parameters (e.g., weight, serum PSA) were conducted and are shown below.

Table 20: Secondary Efficacy Variables Response in Patients with Testosterone > 2500 ng/dL: Comparison at Day 182

	T-Gel Dose	DHT(ng/dL) Predose on Day 182	E2(pg/mL) Predose on Day 182	LH(IU/L) Day 182	FSH(IU/L) Day 182
FA Population N=234	2.5 g	81.2 n=34 SD=44.9 Placebo n=24 21.1 SD=10.8	27.9 n=26 SD=14.0 Placebo n=22 28.1 SD=16.8	All T-Gel (n=166) 1.22 [Δbsln=-3.48] Placebo (n=27) 7.81 [Δbsln=-0.25]	All T-Gel (n=166) 2.52 [Δbsln=-4.38] Placebo (n=27) 13.91 [Δbsln= 0.56]
	5.0 g	82.3 n=70 SD=46.2	25.8 n=51 SD=12.7		
	T-Gel Dose	DHT(ng/dL) Predose Day 182	E2(pg/mL) Predose Day 182	LH(IU/L) Day 182	FSH(IU/L) Day 182
007-006	5.00 g	64	53	7.4 *(-3.6)	5.0 *(-7.6)
015-005	2.5 g (3.75 g Day 182)	97	23	0.1 *(-3.0)	0.6 *(-9.1)
049-008	2.5g	59	22	0.5 *(-2.6)	0.3 *(-4.2)
058-006	5.00 g	92	22	0.1 *(-4.9)	0.6 * (-6.8)
Average T >2500 Patient Change		78.0, 78.0 Average for 2.5 & 5.0 respectively	22.5, 37.5 Average for 2.5 & 5.0 respectively	*(-3.5)	*(-7.20)

*( ) =change from baseline, Δbsln =Change from baseline, SD=standard deviation
Sources: Clinical Study Report: S176.3.104: Tables 12.1.12, 12.3.2, 12.1.3, 12.3.3, 13.1.2, 13.3.1, 13.1.6, and Listings 43, 44, 57.

Reviewer's Comment: The serum LH changes from baseline do not showan increased level of testosterone exposure response in the four outlier patients as compared to the overall FA sample receiving testosterone gel 1.62%. The relevance of the numeric difference between groups for serum FSH is unknown. Clinical and laboratory parameters that may imply and androgen effect were further evidence analyzed. These include weight, blood pressure, BMI, Hgb/Hct, serum PSA, and blood lipids. See Table 24.

Table 21: Change in Selected Safety Measures Possibly Related to Testosterone Concentrations in Four Testosterone Outliers (T>2500 ng/dL)

		Reference Mean Change From Baseline to Day 182 (SD)								
	Dose	Weight	BMI	HGB	HCT	PSA	BP Systolic	BP Diastolic	Cholesterol	HDL
		kg	kg/m^2	g/L	v/v	ug/L	mmHg Sitting		Mmol/L	
Safety Sample N=234	2.5 g	-0.14 (3.73) n=34		4.91 (10.87) n=33	0.023 (0.037) n=32	0.08 (0.67) n=29	-2.1 (13.2) n=34	-0.8 (7.3) n=34	-0.2 (0.7) n=34	-0.0 (0.2) n=34
	5.0 g	0.13 (4.39) n=72		7.54 (12.74) n=69	0.031 (0.040) n=66	0.10 (0.56) n=65	-1.1 (13.6) n=72	-0.4 (8.9) n=72	-0.1 (1.0) n=69	-0.0 (0.2) n=69
Subject			Individual Changes From Baseline (Baseline)							
007-006	5.00 g	0.5 (120.2)	0.2 (35.9)	1.9 (12.8)	0.41 (0.39)	0.0 (0.2)	-10 (150)	0 (98)	-16 (188)	-1 (53)
015-005	2.5 g (3.75 g Day 182)	0.1 (79.4)	0.1 (26.2)	0.6 (44.5)	0.01 (0.45)	-0.4 (0.8)	0 (122)	-9 (81)	-7 (186)	-8 (31)
049-008	2.5g	-0.4 (90.7)	-0.9 (90.7)	-0.8 (13.3)	-0.05 (0.40)	0.3 (1.5)	-4 (110)	-2 (62)	-35 (165)	-6 (45)
058-006	5.00 g	1.3 (103.0)	0.4 (30.8)	1.0 (15.6)	0.02 (0.47)	2.6[1] (1.4)	4 (104)	-4 (78)	-43 (220)	-48 (47)

BMI=Body Mass Index, HGB=Hemoglobin, HCT=Hematocrit, BP=Blood Pressure, HDL=High Density Lipoprotein, SD=standard deviation [1=]see the Reviewer's Comment below
Source: Clinical Study Report S176.3.104: Tables 4.3.1, 5.0.0, 4.2.0 and 4.0.0; Listings 22, 20 and 27.

Reviewer's Comment: Increased testosterone exposure response is not manifested, in my opinion, by the clinical parameters of weight, BMI, systolic or diastolic blood pressure or in the laboratory parameters of hemoglobin, hematocrit, cholesterol, or high density lipoprotein in the 5 patients with testosterone concentrations >2500 ng/dL who were selected for further analysis. The PSA did increase >0.75 ug/L in subject 058-006. This did not lead to any action or study termination. PSA increase was noted as an adverse event for this patient although there is no reported outcome. In the overall protocol, a total of 34 subjects 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. 7/203 subjects (3.3%) had a PSA post-Baseline >4.0 ng/mL, while 33/209 subjects (15.8%) had an increase in PSA from Baseline > 0.75 ng/mL, and 6/209 subjects (2.9%) met both criteria for "increased PSA". Therefore, increased PSA was not an infrequent finding in the study, irrespective of the serum T concentration. It cannot be concluded that this patient's increase in serum PSA is demonstrative of an increased androgen effect due to a single serum T level >2500ng/dL.

Reviewer's Comment: In summary, the 4 cases of elevations of testosterone >2500 ng/dL that are not attributable to sample contamination/artifiact or to definitie overdosage are sporadic, non-recurrent and do not appear to be associated with increased morbidity. From a safety standpoint, I see no reason why these events should preclude approval.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The distribution of subjects among dose groups for the 199 subjects receiving testosterone gel 1.62% at Day 42, the last day of titration is shown below:

Table 22: Distribution by Dose of Subjects at Last Titration Day

Total T-Gel Subjects N=199	T-Gel 1.25g N=14 (7%)	T-Gel 2.5g N=38 (19.1%)	T-Gel 3.75g N=61 (30.7%)	T-Gel 5.0g N=86 (43.2%)

Source: Clinical Overview 2.5: Text page 50

Based on the dose distribution it appears that all doses tested were needed in this population.

Specific dosing recommendations were established by the following studies:

Phase I study S176.1.001 established that testosterone gel 1.62% was the most highest dose strength that provided comparable exposure to AndroGel® 1% (5.00 g) in hypogonadal males. Comparable exposure to reference was observed at the 2.50 and 3.75 g dose levels based on the 24-hour concentration profiles, C_{av}, C_{max} and proportion comparisons of subjects with concentrations within or above the eugonadal range.

Phase I study S176.1.1002: Based on the Single and multiple dose pharmacokinetics and concentration-time profiles, all 1.62% T-gel levels (1.25 to 6.25 g) evaluated in this study were considered by Sponsor to be evaluable for further clinical development. At dose levels of 5.00 g and 6.25 g testosterone gel 1.62% in hypogonadal males, there was a greater incidence of individual C_{max} values exceeding the upper eugonadal limit, especially at the 6.25gm dose level.

Phase I study S176.1.005 performed in hypogonadal males suggests that most skin absorption for testosterone gel 1.62% likely occurs during the first 2 hours post dose. Male patients using testosterone gel 1.62% should be advised to wash their hands with soap and water immediately after application of testosterone gel 1.62% and to wait 2 hours before washing the application sites or swimming. This study also supports the advise for male patients to wash the application site with soap and water prior to intimate contact with others.

Phase I study S176.1.006 was performed in hypogonadal males to determine the multiple doses PK of testosterone gel 1.62% with and without moisturizer lotion or sunscreen. The results showed that testosterone gel 1.62% may be used in conjunction with sunscreens or moisturizers with minimal effect on testosterone concentrations.

Phase I study S176.1.007 was an open-label three-way crossover study to determine single and multiple-dose PK and comparative bioavailability of testosterone absorption after administration of testosterone gel 1.62% to the abdomen, upper arms/shoulders, or via a rotation schedule in hypogonadal males. Abdominal application resulted in approximately 30-40% lower bioavailability (AUC_{0-24} and C_{max}) compared to application to the upper arms/shoulders, following both single and multiple dosing. A rotation schedule *(3 days abdomen than 4 days arms/shoulders)* provided levels of exposure based on AUC_{0-24} and C_{max} that were greater than abdominal application but comparable to upper arm/shoulder on Day 7.

> *Reviewer's Comment: Several cases of high testosterone concentrations were observed in Phase I studies, but these studies did not include dose titration. From a safety standpoint, I see no reason why these events should preclude approval.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary and secondary efficacy endpoints were pharmacokinetic and not designed to evaluate tolerance effects. The persistence of efficacy is documented through Day 182 of the double-blind portion of the single Phase 3 protocol, Study S176.3.104. The efficacy of testosterone gel 1.62% is not expected to decline over time beyond six months. No tolerance effects are expected to occur based on the nature of the treatment.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or analyses.

7 Review of Safety

Safety Summary

The studies performed by the Sponsor are adequate to assess the safety of testosterone gel 1.62%. 785 subjects have been exposed to testosterone gel 1.62%. The duration of exposure in 191 subjects was 1 year. No patient deaths were reported in any of the studies. The adverse event profile was similar to other drugs in its class. (See Section 2.4 Important Safety Issues With Consideration to Related Drugs) With respect to SAEs, there appeared to be no repetitive occurrence pattern and aside from a single event of malignant hypertension associated with a rise in hematocrit, there was lack of attribution of any SAE to the study drug. In this patient, there was marginally-controlled, serious hypertension at baseline and a baseline hematocrit of 46-47%. Rises of PSA was the most frequent reason for study withdrawal followed by increased

hematocrit. In the double-blind period, the remaining reasons for premature study termination occurred as single events. No new trends were noted in the open-label period.

Important Drug-Related Adverse Events and Safety Issues identified during and recommended actions are discussed below:

Transfer Issue:
Secondary exposure has been documented to occur after testosterone gel 1.62% skin application in males to females and by direct skin contact. There are postmarketing reports of accidental secondary exposure to testosterone in children from adults using different testosterone gels. Any testosterone transfer to pre-pubertal children is of concern as secondary testosterone exposure in subjects with very low testosterone concentrations could have profound developmental effects. Therefore the issue of transfer was investigated for this product in this application.

It is known that skin washing with soap and water removes 84% of 5 g of testosterone gel 1.62% on the skin at 2 hours post dose with similar results at 6 and 10 hours (87.2% and 81.3% respectively) (Study S173.1.1005). Skin washing (at least 2 minutes of soap and water lathering of the site in a shower) at 2 hours after a 5 g testosterone gel 1.62% abdominal application dose in males appears to largely and acceptably decrease the risk of skin transfer to females (Study S176.1.1008). It appears that there is greater risk of transfer of testosterone with shoulder-upper arm to shoulder-upper arm contact than abdomen to abdomen contact. A T-shirt barrier largely eliminates male to female transfer 2 hours after application of the low dose (2.5 g) of testosterone gel 1.62% application. However, a T-shirt barrier only eliminates 52-60% of transfer of the high dose (5 g) of testosterone gel 1.62% under similar circumstances **(Sections 1.1, 1.3, 1.4**, **5.3, 7, 7.4.5, 8).**

> *Reviewer's Comment: The Clinical and Clinical Pharmacology team both believe that a T- shirt barrier does not acceptably eliminate testosterone gel 1.62% transfer. The Clinical Pharmacology team is amenable to approval of this application if the label were to emphasixe the requirement for pre-contact washing as the principal means for preventing transfer. They also ask that the label state that a T-shirt barrier is not sufficient. The Clinical team does not believe that such labeling is reasonable, nor feasible, to preclude transfer and we find this issue to be a continuing concern that will need resolution prior to NDA approval. The Clinical team believes that additional studies need to be done to document appropriate use of a clothing barrier that will largely eliminate transfer. In the opinion of this reviewer, until such studies are performed, I cannot recommend approval of this NDA submission.*

Sporadic Testosterone Levels >2500 ng/dL:
In Study S176.3.104 an increase in serum testosterone concentration was reported in 10 patients receiving testosterone gel 1.62% in the double-blind period and in no patients in the open-label period. Six of these patients were eliminated from further consideration secondary to: 1) a lower testosterone concentration upon repeat testing of the same serum sample (3 subjects, 631, 1363 and 1150 ng/dL of testosterone respectively), 2) a single isolated testosterone concentration spike

with eugonadal values immediately prior to and after the time of the spike (2 subjects) 3) documented over compliance (1 subject). Of the four patients with testosterone concentrations above 2500 ng/dL in the double-blind period, 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 declined over the next 4 hours. 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. These three subjects would have had their testosterone dose titrated downward by following the product label. For unknown reasons Subject 015-005 (Day 14) did not have the testosterone dose titrated downward. 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. In these subjects, these events were sporadic, well circumscribed and non-recurrent. There were no concentrations of testosterone >2500 ng/dL in the Open-label period.

The four subjects who were not eliminated from further evaluation were studied for evidence of excess testosterone exposure or effect. The values for DHT and estradiol for these subjects appear to be within the 95% CI for the general study patient population. Serum DHT, estradiol and LH did not show changes of an increased testosterone response in these 4 patients. Serum FSH appeared higher in these 4 patients compared to other patients, but the significance of this finding is unknown. "Increased testosterone response" as manifested by changes in weight, BMI, Hgb, hematocrit, PSA, BP systolic, BP diastolic, cholesterol, and HDL were not demonstrated in the double-blind period for these 4 subjects. One of these 4 subjects discontinued treatment secondary to an elevated PSA on Day 204 (058-06).

Based upon a cursory review of the approved product labeling, the overall exposures to testosterone between AndroGel 1% and AndroGel 1.62% appear comparable. In light of 1) the fact that AndroGel 1.62% met all other pharmacokinetic endpoints which documented a eugonadal testosterone concentration except for the sporadic, short-lived occurrence of testosterone concentration > 2500 ng/dL in a few subjects, 2) the achievement of supranormal testosterone concentrations of short duration with injectable androgen administration for many years without ill-effect, and 2) general comparability of exposure between AndroGel 1% and AndroGel 1.62% based upon a cursory review of the product labeling, the four subjects selected for further study evaluation do not provide enough evidence in my opinion to preclude approval of this NDA. **(Sections 6.16, 6.15, 7.3, 7.4.2, 8)**

In summary, the events of elevations of testosterone >2500 ng/dL are sporadic, non-recurrent and do not appear to be associated with increased morbidity. From a safety standpoint, I see no reason why these events should preclude approval

Recommendations for periodic assessment of testosterone concentrations and appropriate dose adjustment are present in the proposed product label.

Increased Hematocrit:
Testosterone is known to increase red blood cell production. In some patients, hematocrit can increase. Androgen labeling advises periodic measurements of hematocrit. In Study S176.3.104,

an increase in mean hematotcrit was observed overall for the testosterone gel 1.62% groups compared with placebo (Endpoint: 0.026 V/V versus -0.003 V/V). All of the incidents of markedly abnormal high hematocrit were reported in subjects who had been receiving study medication for 12 or more weeks at the time when the event occurred, and the majority of the discontinuations due to increased hematocrit occurred in the open-label period of the study. In the double-blind period of S176.3.104, the incidence of the adverse event of hematocrit increased was 2/234 (0.9%) in the testosterone gel 1.62% group, while no subject in the placebo group (0/40) reported the event. In the open-label period, the incidence of hematocrit increased was 4/191 (2.1%). One subject, on the last day of the double-blind period had a single markedly high hematocrit which was not reported. There is insufficient data to show an association of this AE and testosterone gel 1.62% dose level. 5 of 7 subjects with markedly high hematocrit had serum concentrations > 1000 ng/dL during the double-blind portion of the study, but no clinically significant increases of hematocrit were noted in the 10 subjects in Study S176.3.104 with total serum concentrations >2500 ng/dL. There were no thromboembolic events noted in these patients. No new safety signal or change in pattern was detected. This AE is appropriately labeled in the proposed product label **(Sections 7.3.3, 7.4.2).**

Prostate Cancer:
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 digitial rectal examination is shown in androgen product labeling. Prostate cancer occurred in 58 year-old subject 012-08 in this NDA. 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 contralateral prostate side to the nodule. On Day 182, this subject had testosterone concentration of 4430 ng/dL 2 hours post-dose. The Cav at Day 112 and 182 were 1160 and 927 ng/dL respectively. The testosterone concentrations in the Open-Label Period were eugonadal. His PSA at baseline was 1.5 ng/mL and at Day 182 was 1.8 ng/mL. The PSA 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 1% containing Gleason's score 3+3 prostate adenocarcinoma. While this patient may have had higher than average testosterone exposure, no statement can be made about causality to his prostate cancer. Nonetheless, it would be prudent to describe this event in product labeling.

Hypertension:

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. Two of the subjects in the double-blind period were not receiving study drug at the time of the event and were removed from analysis. One of the six subjects in the double-blind period experienced malignant hypertension. This patient had marginally controlled, serious hypertension at baseline. The proportion of hypertensive subjects roughly parallels the proportion of subjects in each dose group and there

appears to be no correlation of these events with testosterone concentrations or other laboratory values. The majority of subjects with hypertension as an AE had pre-existing hypertension (7/11). There did not appear to be an increase of the AE of hypertension related to increasing duration of exposure to testosterone gel 1.62%. There were no discernible study population trends regarding blood pressure. This AE is appropriately described in the proposed product label for AndroGel 1.62%. No further action is recommended**. (Sections 7.3.3, 7.7., 7.4.3, 7.3.4, 7.4.1)**

Increased PSA:

Testosterone replacement can increase serum PSA. Subjects were included in Study S176.3.104 if the PSA was <2.5 ng/dL. They were excluded if the PSA became > 4.0 ng/dL or the PSA increase from Baseline was >0.75 ng/dl (average of 2 determinations). A total of 45 subjects reported PSA values on one occasion or more that met exclusion criteria for PSA velocity in Study S176.3.104. 29/234 in the double-blind period (0/40 placebo) and 12/191 subjects in the open-label period. Of these 45 patients, 27 were discontinued. 9 subjects in Study S176.3.104 reported a PSA value >4.0ng/ml (7 in the double-blind and 2 in the open-label periods). Of these 9 subjects, 5 were discontinued. 81% (38/47) of the subjects for whom elevations met the PSA elevation criteria or were reported as an adverse event reported a decrease in PSA after initial elevated value, and 16 subjects (34%) had final PSA values within 10% of the subject's baseline. Increases in serum PSA that qualified as an AE were not correlated with age, race, testosterone gel 1.62% dose, serum testosterone concentration nor time of exposure. In the study population of S176.3.104, the mean change from Baseline in serum PSA at Endpoint was 0.14 ng/mL in the testosterone gel 1.62% group versus -0.12ng/ML in the placebo group. This AE is appropriately described in the proposed product label for AndroGel 1.62%. No Further action is recommended. (**Sections 7.3.3, 7.3.4, 7.4.1, 7.4.2, 7.7**).

Compliance:
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 4% exhibited compliance > 80%. In response to the Division's concerns, the Sponsor states that they have submitted revised labeling for AndroGel 1% as well as a patient-oriented Medication Guide that emphasize instructions for proper dosing and safe use. In particular, the Medication Guide includes the explicit instructions not to double dose the day following a missed dose and to skip the day's dose entirely if less than 12 hours remain before the next scheduled morning dose. This labeling and Medication Guide will also be implemented for AndroGel 1.62%.

> *Reviewer's Comment: In the Med Guide section "How to use the AndroGel 1.62% Pump" a statement should eventually be added "if the pump was not fully depressed during a single depression, do not add an additional depression".*

Correlation of Adverse Events with Peak Testosterone Concentrations:

The Sponsor performed a thorough analysis of adverse events by peak testosterone levels. While there is a possible trend of increased AEs in subjects with higher peak testosterone concentrations, in the majority of patients the serum testosterone concentrations were in the eugonadal range prior to the AE. It did not appear that subjects with an isolated peak testosterone concentrations above 1500 ng/dL had a greater overall exposure to testosterone throughout the study than patients who did not. The number of subjects in the groups with testosterone > 1500 ng/dL was too small to document a new safety finding or trend.

> *Reviewer's Comment: In this reviewer's opinion, the safety issues with the exception of skin transfer issue should not preclude approval and can be managed with labeling. Should the transfer issue be acceptably resolved, it too could be managed with labeling (a Medguide for example). However, the continuing concern of transfer not adequately blocked by a clothing barrier does not allow my recommendation for approval.*

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data is derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008 (transfer, washing and skin irriation studies), and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104.

The safety data are presented in the following cohorts:

- Study S176.1.104;
- Phase I Studies in Hypogonadal Men Combined (integrated analyses of selected safety data across Studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, and S176.1.007);
- Transfer Studies in Healthy Subjects (S176.1.003 and S176.1.008);
- Study S176.1.004 (Skin Irritation and Sensitization Study in Health Males), without integrated analysis.

7.1.2 Categorization of Adverse Events

The adverse events were analyzed in the following categories:

- Deaths
- Other serious adverse events
- Dropouts
- Adverse events associated with dropouts
- Other significant adverse events
- Testosterone concentrations >2500 ng/dL

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

This NDA is supported by a single Phase 3 study. Additional safety is derived from the non-integrated studies S176.1.003, S176.1.004, S176.1.008, and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007. A pooled data safety analysis was performed for the integrated studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In total, the NDA contains safety data from 785 subjects exposed to AndroGel 1.62%. The safety data is derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008, and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104. By prior agreement, the safety data from the open-label period of Study S176.3.104 was submitted with the 120-Day Safety Update. The data in this Update was received and reviewed and provide no new safety signals compared to the data in the original NDA. 382 hypogonadal males are included in the integrated safety data base, and 307 healthy males and 96 females are included in the non-integrated safety data base.

In the Phase 1 integrated studies a total of 172 hypogonadal men were exposed to any dose of T-Gel 1.62 %. 10 men (6.8%) were exposed for 0-7 days, 54 men (36.7%) for 8-14 days, 42 men (28.6%) for 15-21 days, 8 men (5.4%) for 22-28 days and 33 men (22.4%) for greater than 28 days. When analyzed by individual dose, 24 subjects were exposed to 1.25 g of the study drug for a mean of 9.1 days, 40 subjects were exposed daily to 2.5 g of the study drug for a mean of 14.1 days, 22 subjects were exposed to 3.75 g of the study drug for a mean of 9.5 days, 72 subjects were exposed to 5.0 g of the study drug for a mean of 21.8 days and 11 subjects were exposed to the study drug were exposed to 6.25 g of the study drug for a mean of 13.5 days.

In the single Phase 3 Study, S176.3.104, 234 patients were exposed to T-Gel 1.62 % for a mean of 151.9 days. The cumulative duration of exposure was similar for the testosterone gel 1.62% groups and the placebo group at each 4-week interval. The mean exposure to 2.50 g of testosterone gel 1.62% was lower as it was the starting dose from which subjects were titrated based on pre-determined testosterone concentrations. A total of 191 subjects participated in the 182-Day Open Label Period with a total of 161 subjects completing the study.

A total of 405 hypogonadal men were exposed to the to-be-marketed drug. 172 hypogonadal males were exposed to the to-be-marketed drug in the integrated Phase I trials. Of these men, 36.7% were exposed for a mean of 8-14 day and 22.4% for greater than 28 days.

In the non-integrated studies, 235 healthy men were exposed to testosterone gel 1.62% for a total of 26 days in a sensitization and skin irritation study, 48 healthy males and females were exposed to 5.00 g of testosterone gel 1.62% daily for 7days applied to the male only in a transference study, and 24 healthy males and females were exposed to 2 days of exposure to testosterone gel 1.62% (one dose each of 2.5 g or 5.0 g) applied to the male only to evaluate post dose washing and its effect on transfer of testosterone gel.

Section 6.1.2 contains a discussion of the demographics of population studied in S176.3.104.

7.2.2 Explorations for Dose Response

Sponsor conducted Phase 1 trials that explored dosage strengths (1.22%, 1.42% and 1.62%), as well as doses of the 1.62% strength (1.25 mg to 6.25mg). Based upon conclusions from these investigations, the Phase 3 study proceeded with a dose-titration schema at doses of 1.25 to 5 gm. 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. All observations whether secondary efficacy variables, vital signs, clinical chemistry, special chemistry, BMI, and PSA were analyzed by testosterone gel 1.62% dose group and no indication of a relationship between AEs and dose group or dose response was noted.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or *in vitro* testing was performed.

7.2.4 Routine Clinical Testing

Routine clinical testing is shown in Table 3 of this review for Protocol S176.3.104 and is appropriate. The safety assessments included: AEs, clinical laboratory measurements (hematology, chemistry, urinalysis, lipid parameters, PSA, vital signs, physical examination(including digital rectal exam [DRE]), ECG, International Prostate Symptom Score (IPSS-1), application site evaluation, skin assessments, and investigation for the potential transfer of testosterone through skin contact.

7.2.5 Metabolic, Clearance, and Interaction Workup

The following information is available from the approved AndroGel® 1% label and was submitted in this NDA application in support of testosterone metabolism, clearance and interactions:

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10-100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major metabolites of testosterone are E2 and DHT.

Testosterone is primarily cleared by metabolic processes in the liver, skin, genital, and other tissues. This metabolism includes conversion to the active metabolite DHT by 5α-reductases in the skin and liver and to E2 by aromatase complexes (CYP19) found in the liver, fat, and testes. Transdermal delivery of testosterone bypasses the extensive first-pass metabolism in the liver.

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucoronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

It is not anticipated that there will be any differences in the excretion of testosterone released from testosterone gel 1.62%. Therefore, no additional information in this regard is available from the testosterone gel 1.62% development program. However, data from two Phase I studies have shown that serum testosterone concentrations return to Baseline levels by 48-72 hours after the last topical application of testosterone gel 1.62% (S176.1.005 and S176.1.007).

Drug interactions were not addressed specifically in the testosterone gel 1.62% development program. AndroGel 1% (testosterone gel 1.00 %) is an approved drug (NDA21-015). The following drug interactions are based on testosterone class labeling:

- Insulin: Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic may decrease blood glucose and, therefore, insulin requirements.
- Corticosteroids: The current use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.
- Oral Anticoagulants: Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following table shows a cursory comparison of adverse events reported in the AndroGel 1% label to the adverse events reported in the Phase 3 study for AndroGel 1.62%. No conclusions can be drawn from this exploratory cross application comparison.

Table 23: Selected Adverse Event Comparison AndroGel 1% and Testosterone Gel 1.62%

	Study S176.3.1.104		
	Testosterone gel 1.62% All Doses (N=234)	Placebo (N=40)	AndroGel 1% All Doses (N=244)
Patients discontinuing due to AE	25 (10.7%)	0	30 (12.3%)
Patients with ≥ 1 TEAE	130 (55.6%)	15 (37.5%)	15 (37.5%)
Nasopharyngitis	5 (2.1%)	0	20 (8.2%)
Upper Respiratory Tract Infection	11 (4.7%)	0	18 (7.4%)
Hemoglobin Increased	1 (4%)	0	5 (2.0%)
Blood Triglycerides increased	1 (0.4%)	0	8 (3.3%)
PSA increased*	23 (9.8%)	0	6 (2.5%)
Pain in extremity	1 (0.4%)	1 (2.5%)	21 (8.6%)
Back Pain	7 (3.0%)	0	18 (7.4%)
Shoulder Pain	0	0	10 (4.1%)
Arthritis	0	0	5 (2.0%)
Dry Skin	1 (.4%)	0	11 (4.5%)
Erythema	2 (0.9%)	0	11 (4.5%)
Rash Erythematous	0	0	4 (1.6%)
Fatigue	3 (3%)	1 (2.5%)	10 (4.1%)
Nausea	0	0	9 (3.7%)
Vomiting	1 (0.4)	0	9 (3.7%)
Diarrhea	5 (1%)	0	11 (4.5%)
Headache	7 (3.0%)	2 (5.0%)	2 (5.0%)
Dizziness	3 (3%)	0	5 (2.0%)
Dyspnea	0	0	6 (2.5%)
Hypertension	6 (2.6%)	0	19 (7.8%)
Hyperlipidemia	2 (0.9%)	0	8 (3.3%)
Depression	0	0	11 (4.5%)
Neprolithiasis	1 (0.4%)	0	4(1.6%)
Acne	2 (0.9%)	0	13 (5.3%)
Gynecomastia	1 (0.4%)	1 (2.5%)	10 (4.1%)
Subjects with ≥ 1 Related TEAE	47 (20.1	3 (7.5%)	105 (43.0%)
Subjects with ≥ 1 Related Severe TEAE	11 (4.7%)	0	31 (12.7%)

Source: adapted from Table 15, 2.5 Clinical Overview, page 58. * *Reviewer's Comment*: *There were no specific pre-determined PSA change criteria in the AndroGel 1% studies. This is likely to have increased the reported incidence of "PSA increase" in S176.3.104 compared to the AndroGel 1% studies.*

In addition to the above comparisons, 3 of 291 patients receiving testosterone gel 1.62% reported anger or aggression as an adverse event. 3 of 291 patients receiving testosterone gel 1.62%

reported edema NEC and 3 patients reported liver test abnormalities in the 182 double- blind period. No testosterone gel 1.62% patient reported decreased urinary flow or nocturia as an AE.

> *Reviewer's Comment: While a direct comparison for this drug and events associated with its class cannot be performed secondary to changes in coding dictionaries and terminology updates, with respect to events of interest (e. g. emotional lability, urinary symptoms, prostate exam abnormal, abnormal laboratory testing) aside from PSA elevations, testosterone gel 1.62% AE profile is consistent with similar approved drugs in its class. No new signals or patterns were observed.*

7.3 Major Safety Results

The safety discussion will include the Phase III pivotal and the integrated Phase I studies.

7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

In the integrated Phase I 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. The study drug was discontinued in both cases.

Six treatment-emergent serious adverse events (TESAEs) in the Double-Blind period of Protocol S176.3.104 were reported by five subjects in the testosterone gel 1.62% group and included (PT): 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 investigators considered the malignant hypertension "possibly related" (hematocrit was also increased in this patient) and the myocardial infarction as" unlikely related." A retinal detachment was the only TESAE reported by a subject in the placebo group.

There were four TESAEs in the 182-Day Open-Label Period. Subject 012-08 utilizing testosterone gel 1.62% 5 g experienced the adverse of 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 as study- related digital exam (DRE) a subsequent biopsy diagnosed prostate cancer. This SAE was captured with a start date of Day 314. Subject 013-04 using testosterone gel 1.62% 5 g reported non-cardiac chest pain on Day 260 with resolution on Day 261 and completed the study. Subject 033-01 receiving testosterone gel 1.62% 5 g reported the SAE of atrial fibrillation on Day 197 with recovery on Day 199. He

completed the study. Subject 058-02 using testosterone gel 1.62% 3.75 g experienced an acute gastrointestinal hemorrhage on Day 296 with resolution of Day 299. He completed the study.

Table 24: Total Adverse Reactions, Serious Adverse Reactions, Discontinuations Due to Adverse Reactions and Application Site Reactions in the Double-Blind Phase III Study

Assessment	AndroGel 1.6% N=234 Mean Exposure=151.9 days N (%)	Placebo N=40 Mean Exposure=147.9 days N (%)
Any Adverse Event (AE) Severe AE	130(55.6) 11(4.7)	15(37.5) 0(0.0)
Serious Adverse Event Deaths	5(2.1) 0(0.0)	2(5.0) 0(0.0)
Discontinuations Due to TEA	25(10.7)	0(0.0)
Application Site Reactions Hypersensitivity Pruritus	1(0.4) 1(0.4)	0(0.0) 0(0.0)

Source: Clinical Study Report S176.3.104: Table 3.0.0, page 1691(adapted)

Table 25: Total Adverse Reactions, Serious Adverse Reactions, Discontinuations Due to Adverse Reactions and Application Site Reactions in the Integrated Phase I Studies

Assessment	AndroGel 1.62%					
	1.25 g N=24	2.5 g N=40	3.75 g N=22	5.00 g N=72	6.25 g N=11	Combined N=147
Any AE Severe AE	12(50.0) 0(0.0)	16(40.0) 1(2.5)	13(59.1) 1(4.4)	60(83.3) 2(2.8)	8 (72.0) 0(0.0)	105(71.4) 3(2.4)
Serious AE (No Deaths)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(18.1)	2 (1.4)
Discontinuations Due to TEA	0(0.0)	0(0.0)	0(0.0)	3(4.2)	0(0.0)	3 (2.0)
Application Site Reactions	1(4.2)	3(7.5)	5(22.7)	27(37.5)	3(27.3)	40(27.2)

Source: Module 2.7.4, Summary of Clinical Safety, Table 22 (page 65) and Table 4.0.0

Serious Adverse Events:

Herein are provided brief narratives of the serious adverse events:

Subject 26326: S176.1.005:
This 77-year old white male was receiving testosterone gel 1.62% 5.00 g/day when he experienced severe atrial fibrillation, which was considered unrelated to study medication by the Investigator. The subject's medical history was positive for obesity, hypertension, allergic rhinitis, intermittent acid reflux, insomnia, esophageal ulcer, intermittent constipation and hyperlipidemia. The subject had no history of coronary or heart disease; however, the subject had reported five or six episodes of "heart racing" over the last 3 years that were of short duration and usually at night. He was receiving lisinopril 30 mg daily upon entry into the study. The subject's Screening blood pressure and pulse rate were 143/92 mmHg and 63 bpm respectively, and on Day -1 blood pressure and pulse rate were 168/99 mmHg and 62 bpm, respectively. On Day 20, approximately 9.5 hours following administration of study medication, the subject complained of "heart flutter and fullness of chest" shortly after eating dinner. In the emergency room the blood pressure was 148/83 and pulse was 147 bpm. An ECG performed approximately 23 minutes after symptoms occurred revealed supraventricular tachycardia and acute myocardial infarction. The heart rate was 144 bpm. A second ECG 1.5 hours after symptoms occurred revealed atrial flutter and variable heart block with a heart rate of 103 bpm. The next day, Day 21, an ECG revealed normal sinus rhythm with a heart rate of 69 bpm and serial changes of an evolving septal infarct. The final ECG on Day 21 revealed no significant changes. The subject was hospitalized and received oral acetylsalicylic acid (162 mg) on Day 20, and intravenous diltiazem (5mg/hour and intravenous procainamide (2mg/minute) on Day 21. The atrial fibrillation persisted for 9 hours and resolved. There was no supportive laboratory data indicative of a myocardial infarction. At follow-up, 4 days after discontinuation, the subject experienced an AE of vertigo of moderate intensity which persisted for 4 hours. The event resolved and the subject discontinued the study.

> *Reviewer's Comment: My interpretation is that this subject had atrial fibrillation only. Previous episodes of palpiations would imply a background condition.*

Subject 26827:S176.1.007:
This 55-year old white male was receiving testosterone gel 1.62% 5.00 g/day when on Day 6, 0.5 hours prior to administration of the study medication he noted a 'red skin patch" on his "lower front leg" [right]. On Day 7(16 March 2007), the sub-investigator assessed the subject and found right lateral anterior leg erythema which he characterized as "rough feeling" and of "smooth appearance." A biopsy of the lesion showed right lower leg superficial and deep perivascular dermatitis with eosinophilia consistent with a dermal hypersensitivity reaction and a periodic acid-Schiff (PAS) stain negative for fungi), which was considered unrelated to the study. The subject had a positive medical history for dermatitis of the right lower leg and erythema to the right lower extremity which the subject reported as resolved as of 01 February 2007. The event resolved after the application of hydrocortisone on 25 March 2007 and the subject was discontinued from the study on 11 March 2007.

Reviewer's Comment: This adverse event occurred in a patient with a previous disposition to such an event.

In Study 176.1.005 a 47-year old white male was entered into study on 06 March 2007. On that day, he experienced lightheadedness and was observed to be diaphoretic. Blood pressure at the time of lightheadedness was 83/43 mmHg. An ECG done after the subject first experienced the symptoms revealed atrial fibrillation. QT and QTcB were 340 and 399 msec. respectively. The investigator assessed the atrial fibrillation as life-threatening and the subject was discontinued from the study prior to receiving study medication. A CRF was not completed.

Subject 031-10: S176.3.104: This 59 –year old male started testosterone gel 1.62% 2.5 g on (b) (6). He experienced the SAE of pituitary tumor on (b) (6) (Day 78). The presenting symptom was blurred vision which the subject reported last fall. An MRI disclosed a pituitary tumor. At Screening, the patient's prolactin was 8.4 (normal 2.0 to 20.0 mg/ml). The study medication was discontinued due to the event on (b) (6). The outcome reported per patient is that surgery to remove the tumor was a success and the visual problems have resolved. The medical history included glaucoma and farsightedness as well as hyperkeratosis of both forearms.

Subject 037-06: S176.3.104:
This 65 year-old male started testosterone gel 1.62% 2.5 g on (b) (6). He experienced the SAE of malignant hypertension (b) (6) (Day 166). The subject had an active medical history of hypertension, which was marginally controlled with four agents. His blood pressure at Screening was 158/72 mmHg and 152/80 mmHg at Baseline. He experienced the AE of worsening hypertension between 121 June 2007 and 12 July 2007. His blood pressures on those dates were 160/90 mmHg and 152/80 mmHg. The subject decreased the dose of clonidine from 1.5 mg to 0.3 mg on 12 June 2007. During this period, the subject was also taking doxycycline and the NSAID meloxicam. The stop date of the meloxicam coincided with the stop date of the AE. The blood pressures over the course of the study remained in the range of 148-160/86-90 mmHg. The last blood pressure from the study visit to the SAE was 168/100 mm/Hg. On 20 September 2007, Aliskiren was added to the regimen 5 days before the subject presented with elevated blood pressures. The Hgb rose form 16.3g/dL at Baseline to 17.7 g/dL and 17.2 g/dL at Visit 7 on 12 July 2007 and Visit 10 on 11 October 2007. The respective Hct values were 47.1%, 52.7% and 50.1%. The creatinine was 1.08 mg/dL, 1.22 mg/dL and1.31 mg/dL at Screening, Baseline and Visit 10. The last dose of study medication was taken on 11 October 2007, due to the end of the study.

The patient's relevant medical history includes hypertension (1987), hypercholesterolemia (2007), type II diabetes (2000), neuropathy (2006), (COPD) chronic obstructive pulmonary disease (2003), polycythemia secondary to testosterone (2005), and edema in legs (2005). The medications that the patient was taking not mentioned in the narrative to control blood pressure, edema, diabetes, or cholesterol include potassium, metoprolol, valsartan, furosemide, glibenclamide, metformin, exanitide, fenofibrate, aliskiren, and amlodipine.

On (b) (6), the patient was hospitalized for a complaint of "high blood pressure." He also reported left-sided chest pain with nausea. His blood pressure was 210/126, then 190/110. ECG (described sinus rhythm at a rate of 70 with diffuse ST and T changes) and enzymes were reported as unrevealing. Abnormal labs included triglycerides of 424 and 500, glucose 139 and hemoglobin A1c 6.6. Hemoglobin was 17 with a hematocrit of 49%. Ventilation-perfusion (VQ) scan was without evidence of emboli; chest x-ray demonstrated no acute changes and renal ultrasound showed no evidence of obstruction.

While hospitalized, the patient's blood pressure was controlled with appropriate therapy. Discharge vital signs included a blood pressure of 130/70 mmHg and a pulse of 80. The discharge diagnoses included: malignant hypertension; Chest pain syndrome, atypical with positive D-dimer; Organic heart disease functional class II, degenerative with ejection fraction of 45%; Type II diabetes; COPD; Hyperlipemia; Obesity; Gastroesophageal reflux disease; polycythemia secondary to testosterone; irritable bowel syndrome; obstructive sleep apnea; degenerative disc disease (L5-S12), and allergy to nitrates.

On 17 October 2007, the stress echocardiogram was performed showing the resting EKG with sinus mechanism of about 80 per minute with minimal nonspecific ST abnormalities; and the resting echo showed mild generalized hypokinesis with an ejection fraction of about 40-45%. Post exercise echocardiogram images showed an increase in wall motion with an ejection fraction of 55-60%. The final impression revealed a negative stress echo for ischemia based on both EKG and wall motion criteria, fair exercise tolerance, normotensive blood pressure response, and appropriate heart rate recovery post exercise and appropriate increase in ejection fraction with exercise considering a previous diagnosis of cardiomyopathy. The ongoing non-serious adverse event of cardiomyopathy which was added with an onset of 17 July 2007 was deleted as an event term for this case as stated in a follow-up report received by Sponsor on 01 November 2007 but is still noted in the clinical database on the eCRF Adverse Event page.

The patient did not have a history of malignant hypertension prior to this event. The investigator assessed the causal relationship between study medication and malignant hypertension as possible because "testosterone" can cause an increase in hematocrit levels and cause fluid retention which may cause an increase in blood pressure.

> *Reviewer's Comment: Hypertension and increase of hgb/hct are known adverse effects of testosterone replacement and are reflected in AndroGel labeling and should be in labeling for testosterone gel 1.62%. They both are. The patient had marginally controlled, very significant hypertension at baseline. His hematocrit at baseline was 47% and subsequently increased to approximately 49%. Also, meloxicam has a labeled warning of new onset hypertension or worsening of pre-existing hypertension.*

Subject 044-03: S176.3.104: This 45-year old male was started on testosterone gel 1.62% on (b) (6) (b) (6) The subject experienced the serious adverse events of back pain and radicular pain secondary to a fall on (b) (6) (Day 183) which resulted in hospital admission. There is no mention of any pre-fall symptoms such as dizziness, lightheadedness, etc. The event term

was later changed to "fall in the rain." The last dose of study drug was taken on 21 October 2007, due to an administrative issue. The outcome of the events is reported as recovered/ resolved with sequellae.

Abnormal hematology results included hemoglobin (hgb) of 10.0 on 26 September 2007 (14.0 to 18.0 g/dL) and 9.6 on 28 September 2007 and a hematocrit (hct) of 32.7 on 26 September 2007 (40.0 to 54.0% and 30.8 on 28 September 2007. Abnormal chemistry results included a carbon dioxide (CO_2) of 32 on 26 September 2007 (23 to 29 mmol/L) and 33 on 28 September 2007 and glucose of 130 on 26 September 2007 (70 to 105 mg/dL). Stool was negative for occult blood and urinalysis was normal except for a pH of 8.0 (5.0 to 7.5).

The patient had a pre-existing condition of decreased hemoglobin and hematocrit which was deemed not clinically significant by the investigator. The subject has additional medical history of hypertension, erectile dysfunction and hypokalemia. The patient had started tadalafil 18 July 2007. This was the only medication he was using in addition to testosterone 1.62% 2.5 g pre-event.

No abnormalities were viewed on chest x-ray or lumbar spine except for postoperative changes at the fifth lumbar vertebra and the first sacral segment. An MRI revealed postoperative changes and an intermediate soft tissue density anterior to the thecal sac which was thought most likely to represent granulation tissue.

Following hospitalization during which he also received treatment for hypertension, he continued to complain of back pain which radiated to his right leg and difficulty walking. On 30 September 2007, the patient was transferred to a rehabilitation facility and was to follow-up with a pain management specialist.

This patient had 2 SAEs: back pain and radicular pain.

Subject 059-11: S176.3.104: This 59-year old male started testosterone gel 1.62% on (b) (6) (b) (6) The subject experienced the serious adverse event of tachycardia on (b) (6) (Day 72). No heart rate values were recorded while the event was ongoing. Heart rates from Screening to the last visit before the SAE were 80-94 bpm. The subject was hospitalized. No abnormalities were noted as clinically significant in the ECGs. Cardiac workup was unremarkable. Metoprolol was discontinued 09 June 2007. Heart rates after the episode were 64-80 bpm. Last dose of the study medication was taken on 26 September 2007, due to the end of the study. The outcome of the event was reported as recovered/resolved.

The patient's concurrent medical diagnoses included right shoulder and right upper side muscle soreness occurring one day after a fall (tripping over equipment at work) (b) (6), hyperlipidemia and constipation. His concomitant medications include Anacin and Advicor.

The patient reported feeling "something funny in my chest," some mild, non-radiating chest pain and shortness of breath after working in his yard on (b) (6). The patient's primary physician performed an EKG demonstrating a reported sinus tachycardia with a rate of 127 and

referred the patient to emergency. In the ER the heart rate was 100 to 120 bpm without chest pain or shortness of breath. The blood pressure was 107/75 mmHg, and the respiratory rate 18 with an oxygen saturation of 100% on room air. The EKG revealed sinus tachycardia with a rate in the "120s." The patient's chest x ray and labs, including troponin, were negative with the exception of white blood cell (wbc) of 13.1 (normal 4.2 to 10.8), blood urea nitrogen (BUN) of 28 (9 to 20 mg./dL) and Creatine Kinase-MB (CKMB) of 7.9 (0.0 to 4.9 ng/mL).

On 09 June 2007, the patient had an adequate stress test with an exaggerated heart rate response. Blood pressure response was normal and no cardiac arrhythmias occurred. On 12 June 2007, an echocardiogram demonstrated a normal-size ventricle with a normal wall thickness and low normal ventricular systolic function, ejection fraction of 50 to 55%, a trace of mitral and tricuspid regurgitation with mild aortic regurgitation. A small pericardial effusion was noted. In hospital the patient's treatment included Toprol 25 mg and aspirin 81 mg each day.

> *Reviewer's Comment: I cannot relate this discontinuation SAE to testosterone gel 1.62%.*

Subject 060-20:S176.3.104: This 63-year old male started testosterone gel 1.62% 2.5 g on (b) (6). The subject experienced the serious adverse event of myocardial infarction on (b) (6) (Day 166) and was hospitalized. The subject had a history of hypertension, hyperlipidemia, obesity (Screening BMI 32.8 kg/m^2) and a family history of coronary artery disease. The subject was found to have multiple lesions in the LAD and RCA requiring 4 stents at the time "with a 5th stent planned for a circumflex lesion." The last dose of study medication was taken on 09 October 2007, due to the end of the study. The outcome of the event was reported as recovered/resolved.

Prior to entering the study, the patient was maintained on the following medications: chondroitin with glucosamine, galenic/fexofenadine HCL/pseudoephedrine, cholestyramine, Namebutone, Valsartan, Vicodin, Vardenafil. He had the concomitant medical history of osteoarthritis, back pain, seasonal allergies, hypertension, erectile dysfunction and hyperlipemia.

There was no action taken with regard to the study drug.

Subject 012-08:S176.3.004 180 Open Label Period: This 58 year-old male was one of the ten patients with single peak testosterone concentration of > 2500 ng/dL (4430 ng/dL on PK Day 182). His first dose of testosterone gel 1.62% was 30 March 2007. Upon entering the study, the subject was taking minocycline for acne, amlodipine besylate w/ benazepril hydrochlorthiazide and losartan for hypertension as well as simvastation for hypercholesterolemia. The patient had a known mitral valve prolapse.

This patient had a prior history of BPH and was being treatment with Avodart (beginning on 16 February 2006 and stopping on 26 July 2006 [reason not stated]) and started testosterone gel 1.62% 2.5 g daily on (b) (6). On (b) (6) (Day 279) at Visit 12, the subject was found to have a prostate nodule. The prostate was biopsied and the side contralateral to the nodule was found to contain prostate cancer. The subject's PSA value on (b) (6) (Day

279) met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol) (Baseline: 1.5 ng/mL, Day 96: 2.1 ng/mL, Day 186: 1.8 ng/mL, Day 279: 2.3 ng/mL). At the time of the event (prostate neoplasm), the subject was receiving testosterone gel 1.62% 5 g daily. The subject's screening PSA was 1.6 ng/dL. Study medication was discontinued due to the event of prostate cancer on (b) (6). The subject received radiation therapy beginning on (b) (6). The outcome of both events was reported a recovered/resolved with sequellae on 25 April 2008.

It is of note that the nodular irregularity detected during the prostate exam was small and on the right side of the prostate. The prostatic ultrasound was "normal." Prostate biopsies were positive for cancer in the left medial mid gland and medial apex of the prostate. The Gleason's score was 3+3+6. Both cores were 1% involved for cancer. Staging was T2a, NX MO, Stage II and the Prostate Symptom Score (IPSS) was 5.

> *Reviewer's Comment: The only SAE for which I can attribute a possible causal relationship between the study drug and the SAE is Subject 037-06 who experienced malignant hypertension secondary to increase of hematocrit and edema. These are both known effects testosterone replacement therapy. Even in this subject, the adverse event cessation correlates with the use of meloxicam and stopped with cessation of meloxicam. In addition, this patient had "marginally controlled, serious hypertension at baseline, as well as a baseline hematocrit of 46-47% that increased to 49%, a small change from baseline.*
>
> *With respect to the case of prostate cancer, the patient was on Avodart from 16 February 2006 until 26 July 2006. He began the study over 1 year later. At that time his baseline PSA was 1.5ng/mL, which when corrected for dutasteride effect would reflect 3ng/mL. The patient's subsequent rectal findings were the indication for the prostate biopsy. The rectal findings and the location of positive prostatic biopsy sites for prostate cancer are contralateral. However, the patient in whom the prostatic carcinoma occurred is one of the ten patients in Study S176.3.104, who reported an isolated, peak testosterone concentration >2500 ng/dL (4430ng/dL Day 182) in the double-blind period. On Days 112 and 156, he was noted to have multiple testosterone concentrations in excess 1000 ng/dL after dosing during PK testing. I cannot state there is a causal relationship between this cancer and testosterone gel 1.62% use. I also do not know if men of similar demographic background and not on androgen replacement therapy were subjected to prostate biopsy what proportion of them would have biopsies positive for prostate cancer. Such a study has not yet been done and would be a very large, multicenter effort. At his time, I would therefore categorize this cancer as an incidental finding; however, I recommend this specific event be included in labeling.*

7.3.3 Dropouts and/or Discontinuations

Phase III study (double-blind period): Overall, 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 application.

The only TEAE 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 criterion of change from baseline >0.75ng/mL. Four other subjects had a PSA value>4 ng/mL, these subjects had PSA ≤ 4.0ng/mL upon repeat testing. The incidence of premature discontinuation due to increased PSA across the testosterone 1.62% groups was as follows: 1.25 g: 1/17, 5.9%; 2.50 g: 5/60, 8.3%: 3.75 g: 6/66, 9.1%; 5.00 g: 6/91, 6.6% (Source: Table 3.11.0 pages 1955-1963 of S176.3.104 report).

Table 26: Treatment-related Adverse Events Leading to Premature Discontinuation in the Double-blind Phase III Study

Preferred Term	T-Gel 1.62% (N=234)	Placebo (N=40)
Diarrhea	1 (0.4%)	0 (0.0)
Fatigue	1(0.4%)	0 (0.0)
Prostate Specific Antigen Increased[1]	17 (7.3 %)	0 (0.0)
Hematocrit increased	1(0.4%)	0 (0.0)
Blood pressure increased	1(0.4%)	0 (0.0)
Pituitary tumor	1(0.4%)	0 (0.0)
Disturbances in consciousness NEC	1(0.4%)	0 (0.0)
Syncope Vasovagal	1(0.4%)	0(0.0)
Dizziness	1(0.4%)	0 (0.0)
Pollakiuria	1(0.4%)	0 (0.0)
Skin nodule	1(0.4%)	0 (0.0)

[1] One additional subject (045-026) had an AE of increased PSA but withdrew consent prior to confirmation of abnormal values.
Source: Module 2.7.4: Table 21, pages 63-64.

In the Open-Label Safety Extension (Day 183-Day 364), 9 patients discontinued secondary to an adverse event. One subject (012-08) discontinued secondary to the adverse event of prostate cancer and is discussed in narratives of SAEs. Subjects 039-27, 041-30, 049-02, 049-14, 049-30, and 069-01 discontinued due to PSA changes meeting the pre-specified discontinuation criteria. Subjects 047-05 and 063-09 discontinued for hematocrit meeting the pre-specified discontinuation criteria.

Phase III (S176.1.104) Double-Blind Period Discontinuation Narratives [in brief]

Subject 003-10: This subject is a 61-year old male who started testosterone gel 1.62% 2.5 g on 15 March 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious adverse event of elevation of

PSA over baseline on 05 June 2007 (Day83) with a repeat value on 12 June 2007 (Day 90) (Baseline: 0.8 ng/mL: Day 83: 1.9 ng/mL, Day 90: 1.9 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The PSA remained elevated (2.0 ng/mL) at the time of early termination of 25 June 2007 (Day 103). On 16 August 2007 (Day 155), the repeat PSA had decreased to 0.8 ng/mL. Study medication was discontinued due to the event on 19 June 2007 (Day 97). The rectal examination at baseline is characterized as "abnormal" and at time of early termination, 25 June 2007, as "slight increased consistency R lobe." The outcome of the event was reported as recovered/resolved on 16 August 2007 with no additional rectal exams noted.

Subject 003-45: This subject is a 61-year old male who started testosterone gel 1.62% 2.5 g on 03 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 3.75 g. The subject experienced the non-serious adverse event of elevation of PSA over baseline on 25 June 2007 (Day 84) with a repeat value on 05 July 2007 (Day 94) (Baseline: 1.8 ng/mL, Day 84 3.1 ng/mL, Day 94: 2.5 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The average increase from Baseline was 1.0 ng/mL though the second value was not a 0.75 increase from Baseline. At early termination on 20 July 2007(Day 109), the PSA was 2.4 ng/mL. Study medication was discontinued due to the event on 16 July 2007 (Day 105). The PSA was repeated on 08 October 2007 and was 1.5 ng/mL. There is no rectal exam abnormality noted. The outcome of the event was reported as recovered/resolved on 08 October 2007.

Subject 016-09: This subject is a 65-year old male who started testosterone gel 1.62% 2.5 g on 14 March 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious adverse event of elevation of PSA over baseline on 26 June 2007 (Day 105) with a repeat value on 28 June 2007 (Day 107) (Baseline: 1.6 ng/mL, Day 84: 2.5 ng/mL, Day 107: 3.2 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The subject had PSAs of 2.0 and 2.2 ng/mL at Screening A and B. The average increase from Baseline was 1.25 ng/mL. At early termination on 19 July 2007 (Day 128), the PSA was 2.4 ng/mL. The subject was referred to his primary care provider for follow-up of the adverse event and reported to the site that the repeat local PSA was not considered abnormal and no further workup would be pursued. Study medication was discontinued due to the event on 11 July 2007 (Day 120). There is no rectal examination abnormality noted. The outcome of the event was reported as recovered/resolved on 11 July 2007. The Sponsor has been contacted regarding additional PSA values and states in July 15, 2009 answer to Additional Questions Regarding Study S176.3.104 and states that no additional PSA values were available for this subject after July 19, 2007.

Subject 016-26: This subject is a 60-year old male who started testosterone gel 1.62% 2.5 g on 21 March 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious adverse event of elevation of PSA over baseline on 10 July 2007 (Day 112) with a repeat value on 29 August 2007 (Day 162) (Baseline: 2.3 ng/mL, Day 112: 2.5 ng/mL, Day 162: 1.3 ng/mL). The PSA increase did not meet the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the

protocol) or the criterion of >4.0 ng/mL. On 19 June 2007 (Day 91), the PSA had increased to 3.9 ng/mL. The average increase from Baseline was 0.9 ng/mL, though the second value (Day 112) was not a >0.75 ng/mL increase from Baseline. The last dose of medication was 10 August 2007 (Day 143). At early termination on 29 August 2007 (Day 162), the PSA was 1.3 ng/mL. There were no reported rectal examination abnormalities. The outcome of the event was reported as resolved on 29 August 2007.

Subject 018-05: This subject is a 56-year old male who started testosterone gel 1.62% 2.5 g on 04 April 2007. The subject discontinued because of the adverse event of elevated hematocrit while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious event of elevated hematocrit (55.4%; Baseline: 47.3%) on 28 June 2007 (Day 86). On 11 July 2007 (Day 99), the hematocrit was 55.1%. Hematocrit values on Day 86 and 99 both met the per protocol discontinuation criterion of >54%. The study medication was discontinued due to the event on 12 July 2007 (Day 100). The hematocrit on 19 July 2007 was reported as 0.55 V/V. The outcome of the event was reported as recovered/resolved on 11 July 2007. No additional hematocrit values were available for this subject after 19 July 2007 as disclosed by Sponsor in 15 July 2009 response to Additional Questions Regarding Study S176.3.104.

Subject 018-13: This 58 year-old male started testosterone gel 1.62% 2.5 g on 13 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious adverse event of elevation of PSA on 09 July 2007 (Day 88) with a repeat value on 07 August 2007 (Day 117) (Baseline: 0.2 ng/mL, Day 88: 1.4 ng/mL, Day 117: 0.7 ng/ml [subject was still using testosterone gel 1.62%]). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The average increase from Baseline was 0.85 ng/mL, though the repeat was not >0.75 ng/mL above Baseline. Study medication was discontinued due to the event on 13 August 2007. There were no reported rectal examination abnormalities. The subject was using a topical testosterone preparation pre-study until 28 February 2007. The outcome of the event was reported as recovered/resolved on 07 August 2007.

Subject 022-04: This 48 year-old male started testosterone gel 1.62% 2.5 g on 29 March 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 2.5 g. The subject experienced the nonserious adverse event of elevation of PSA over Baseline of 0.8 ng/mL on 21 June 2007 (Day 85) with a repeat value on 06 July 2007 (Day 100) (Baseline: 2.4 ng/mL, Day 85: 3.3 ng/mL, Day 100: 3.1 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The average increase from Baseline was 0.8 ng/mL, though the second value was not a >0.75 ng/mL increase from Baseline. At early termination on 23 July 2007 (Day 117), the PSA was 2.4 ng/mL. Study medication was discontinued due to the event on 22 July 2007. The outcome of the event was reported as recovered/resolved on 23 July 2007.

Subject 024-04: This 79 year-old male started testosterone gel 1.62% 2.5 g on 13 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 3.75 g. The subject experienced the nonserious adverse event of elevation of PSA on 09 July 2007 (Day 88) with a repeat value on 07 August 2007 (Day 117) (Baseline: 1.7 ng/mL, Day

88: 2.8 ng/mL, Day 117: 2.5 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The average increase from Baseline was 0.95 ng/mL. At early termination on 04 September 2007 (Day 145), the PSA was 2.3 ng/mL. Study medication was discontinued due to the event on 17 August 2007. There were no reported rectal examination abnormalities. The outcome of the event was reported as recovered/resolved on 04 September 2007.

Subject 033-04: This 69 year-old male started testosterone gel 1.62% 2.5 g on 26 March 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious adverse event of elevation of PSA on 18 June 2007 (Day 85) with a repeat value on 29 June 2007 (Day 96) (Baseline: 2.1 ng/mL, Day 85: 3.2 ng/mL, Day 96: 3.6 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The average increase from Baseline was 1.3 ng/mL. At early termination on 30 July 2007 (Day 127), the PSA was lower than Baseline at 1.5 ng/mL. Study medication was discontinued due to the event on 18 July 2007. There were no reported rectal examination abnormalities. The subject had a reported history of "benign prostate hypertrophy." The outcome of the event was reported as recovered/resolved on 16 August 2007. The average increase from Baseline was 0.95 ng/mL, though the second value was not a >0.75 ng/mL increase from Baseline. At early termination on 15 August 2007 (Day 128), the PSA had almost returned to Baseline at 2.4 ng/mL. The outcome was reported as recovered/resolved on 13 September 2007.

Subject 034-18: This 58 year-old male started testosterone gel 1.62% 2.5 g on 10 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 3.75 g. The subject experienced the nonserious adverse event of elevation of PSA over baseline on 18 July 2007 (Day 100) with a repeat value on 01 August 2007 (Day 114) (Baseline: 2.1 ng/mL, Day 100: 3.5 ng/mL, Day 114: 2.6 ng/mL). The average increase from Baseline was 0.95 ng/ml, the second value was not a .0.75 ng/ml increase from baseline. The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The study medication was discontinued due to the event on 08 August 2007. The site referred this subject for biopsy. At early termination on 15 August 2007 (Day 128), the PSA had almost returned to Baseline at 2.4 ng/mL. The outcome is reported as resolved/recovered on 13 September 2007. A biopsy was performed on (b) (6) and was benign as documented in 15 July Response to Additional Questions Regarding Study S176.3.104.

Subject 043-07: This 51 year-old male stared testosterone gel 1.62% 2.5 g on 12 March 2007. The subject experienced the nonserious adverse events of fatigue, frequent urination and loose stool on 07 April 2007 (Day 27) while taking testosterone gel 1.62% 3.75 g . The subject did not have any significant laboratory abnormalities from an unscheduled visit on 18 April 2007. No exam findings were noted on this date, and no diagnosis was provided by the study site. Study medication was discontinued due to the events on 18 April 2007.

Subject 043-18: This 67 year-old male started testosterone gel 1.62% on 30 March 2007. The subject has a history of high blood pressure and has taken hydrochlorthiazide since 31 December 2000. The subject experienced the nonserious adverse event of increased blood pressure

(evenings only) (Baseline: 110/74 mmHg); Day 19: 140/66 mmHg; Day 33: 132/58 mmHg) while taking testosterone gel 1.62% 5 g. The subject had study visits on both 01 May 2007 (Day 33) and 15 May 2007 (Day 47). Blood pressures from those days were 132/58 mmHg and 138/74 mmHg. No changes in the subject's antihypertensive regimen were reported. Study medication was discontinued due to the event on 25 May 2007. The outcome was reported as recovered/resolved on 29 May 2007.

Subject 049-02: This 54 year-old male started testosterone gel 1.62% 2.5 g on 01 March 2007. He discontinued because of the adverse event of PSA elevation. The subject experienced the nonserious adverse event of elevation of PSA on 06 September 2007 (Day 190) (Baseline: 0.8 ng/mL, Day 138: 0.8 ng/mL, Day 188: 4.2 ng/mL). No PSA value was reported in the clinical database on 06 September 2007 (Day 190). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). At early termination (date not in report) the PSA was 1.9 ng/mL. The PSA was repeated at a local laboratory on 17 October 2007 and was 1.7 ng/mL. The last dose of study medication was taken 04 September 2007 (Day 188) due to end of study. There were no reported rectal examination abnormalities. The outcome of the event was reported as resolved on 17 October 2007. The Division asked the Sponsor if additional PSAs had been performed after October 17, 2007; in 15 July Response to Additional Questions Regarding Study S176.3.104, there were no additional PSAs included in this patient's narrative.

Subject 049-11: This 44 year-old male started testosterone gel 1.62% 2.5 g on 09 March 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 3.75 g. The subject experienced the nonserious adverse event of elevation of PSA on 11 June 2007 (Day 95) with a repeat value on 12 June 2007 (Day 96) (Baseline: 1.9 ng/mL, Day 85: 2.8 ng/mL, Day 96 5.4 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). At early termination on 25 June 2007 (Day 109), the PSA was 3.1 ng/mL. The subject was referred to his primary care provider who did not feel any evaluation was required. On 30 October 2007, the PSA had returned to Baseline levels at 1.8 ng/mL. The study medication was discontinued due to the event on 20 June 2007. There were no reported rectal examination abnormalities. The outcome of the event was reported as recovered/resolved with sequellae on 23 October 2007.

Subject 049-15: This 73 year-old male started testosterone gel 1.62% on 27 March 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 1.25 g. The subject experienced the nonserious adverse event of elevation of PSA on 05 July 2007 (Day 101) with a repeat value on 10 July 2007 (Day 106) (Baseline: 0.6 ng/mL, Day 106: 1.4 ng/mL). No PSA value was reported in the clinical database on 05 July 2007 (Day 101). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). At early termination on 24 July 2007 (Day 120), the PSA was 1.2 ng/mL. The subject was referred to the primary care provider for evaluation. Study medication was discontinued due to the event on 19 July 2007. There were no reported rectal examination abnormalities. The outcome of the event was reported as recovered/resolved on 29 August 2007.

Subject 050-06: This 50 year-old male started testosterone gel 1.62% 2.5 g on 19 March 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 2.5 g. The subject experienced the nonserious adverse event of elevation of PSA on 11 June 2007 (Day 85) with a repeat value on 21 June 2007 (Day 95) (Baseline: 1.7 ng/mL, Day 85: 4.4 ng/mL, Day 95: 0.7 ng/mL. The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The average increase from Baseline was 0.85 ng/mL, though the second value was actually lower than the Baseline PSA and the subject was still taking the study drug. At early termination on 19 July 2007 (Day 123) the PSA was 2.4 ng/mL. The study medication was discontinued due to the event on 18 July 2007(Day 122). There were no reported rectal examination abnormalities. The outcome of the event was reported as recovered/resolved on 21 June 2007.

Subject 051-02: This 70 year-old started testosterone gel 1.62% 2.5 g on 12 April 2007. The subject experienced the nonserious event of vasovagal syncope, during the pharmacokinetic sampling period, on 25 April 2007 (Day 14) while taking testosterone gel 1.62% 2.5 g. The subject's medical history includes coronary artery disease, asthma and history of syncope (not currently active). Concomitant medications are Drixoral, acetylsalicylic acid and Propacet. The study medication was discontinued due to the event on 25 April 2007. The outcome was reported as recovered/resolved on 09 May 2007.

Subject 052-01: This 50 year- old male started testosterone gel 1.62% on 14 March 2007. The subject experienced the nonserious adverse event of light headedness on 18 March 2007 (Day 5) while taking testosterone gel 1.62% 2.5 g. The subject had a history of hypertension and was taking ramipril. On 14 March 2007 (Baseline), the subject's blood pressure was 120/70 mmHg. On 02 April 2007 (Day 20), the subject's blood pressure was 120/75 mmHg. No diagnosis was provided by the site. Study medication was discontinued due to the event on 22 March 2007. The outcome of the event was reported as recovered/resolved on 01 April 2007.

Subject 060-15: This 61 year-old male started testosterone gel 1.62% 2.5 g on 11 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious adverse event of elevation of PSA elevation on 13 July 2007 (Day 94) with a repeat value on 19 July 2007 (Day 100) (Baseline: 1.3 ng/mL, Day 84: 7.5 ng/Ml, Day 100 2.2 ng/mL). There is no PSA recorded in the database on 13 July 2007 (Day 74). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). At early termination on 23 July 2007 (Day 104), the PSA was 2.4 ng/mL. The PSA was repeated at a local laboratory on 10 September 2007 and was 1.2 ng/mL. There were no reported rectal examination abnormalities. Study medication was discontinued due to the event on 20 July 2007. The outcome of the event was reported as recovered/resolved on 19 September 2007.

Subject 060-18: This 53 year-old male started testosterone gel 1.62% 2.5 g on 13 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious adverse event of elevation of PSA elevation on 09 July 2007 (Day 88) with a repeat value on 19 July 2007 (Day 98) (Baseline: 1.7 ng/mL, Day 88: 3.8, Day 98: 2.4 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase

from Baseline (referred to as "velocity" in the protocol). The average increase from Baseline was 1.4 ng/mL, though the second was not a > 0.75 ng/mL increase from Baseline. There were no reported rectal examination abnormalities. At early termination of 06 August 2007 (Day 116), the PSA was 3.8 ng/mL. The PSA was repeated at a local laboratory on 11 September 2007 (Day 158) and was 0.5 ng/mL. Study medication was discontinued due to the event on 31 July 2007Day 131). The outcome of the event was reported as recovered/ resolved on 19 September 2007.

Subject 060-19: This 69 year-old male started testosterone gel 1.62% 2.5 g on 13 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 3.75 g. The subject experienced the nonserious adverse event of elevation of PSA on 09 July 2007 (Day 88) with a repeat value on 10 August 2007 (Day 120) (Baseline: 0.1 ng/mL, Day 88: 0.8 ng/mL, Day 120: 1.0 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). The average increase from Baseline was 0.9 ng/mL. At early termination on 18 September 2007 (Day 159), the PSA was 0.7 ng/mL. There were no reported rectal examination abnormalities. Study medication was discontinued due to the event on 10 September 2007. The outcome of the event was reported as recovered/resolved on 23 October 2007.

Subject 065-08: This 52 year-old male started testosterone gel 1.62% 2.5 g on 13 April 2007. The subject experienced the nonserious adverse event of diabetes on 24 April 2007 (Day 12) while taking testosterone gel 1.62% 2.5 g. This subject had elevated fasting glucose at Screening of 228 mg/dL. The subject did not report a history of diabetes and the investigator did not feel a hemoglobin A1C was necessary in this subject at the time of Screening. The investigator randomized the subject. The site was contacted, and because the two elevations of fasting glucose met criteria for a diagnosis of diabetes, the site was instructed to obtain a hemoglobin A1C which returned at 9.6% which would have excluded the subject. The site was instructed to discontinue the subject. Study medication was discontinued due to the event on 18 May 2007. The outcome of the event is reported as unknown.

Subject 067-03: This 52 year-old male started testosterone gel 1.62% 2.5 g on 13 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 5 g. The subject experienced the nonserious adverse event of elevated PSA level on 06 July 2007 (Day 85) with a repeat value on 23 July 2007 (Day 102) (Screening A: 0.7 ng/mL, Baseline 0.1 ng/mL, Day 85: 1.1 ng/mL. Day 102: 1.1 ng/ml). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). At early termination on 10 August 2007 (Day 120), the PSA was 0.6 ng/mL. There were no reported rectal examination abnormalities. The study medication was discontinued due to the event on 03 August 2007. The outcome was reported as resolved/recovered on 10 August 2007.

Subject 069-11: This 52 year-old male started testosterone gel 1.62% 2.5 g on 02 April 2007. The subject experienced the nonserious adverse events of erythema in lower legs and nodules on lower legs on 15 April 2007 (Day 14) while taking testosterone gel 1.62% 2.5 g. No diagnosis was provided by the site. Study medication was discontinued due to the events on 16 April 2007. Medical history includes chronic back ache, a prostate disorder (not currently active) and

snoring (not currently active). The patient was receiving protriptylene for his snoring disorder. The outcome of the events was recorded as recovered/resolved on 30 April 2007.

Subject 069-19: This 56 year-old male started testosterone gel 1.62% 2.5 g on 13 April 2007. He discontinued because of the adverse event of PSA elevation while taking testosterone gel 1.62% 3.75 g. The subject experienced the nonserious adverse event of elevation of PSA on 10 July 2007 (Day 89) with a repeat value on 20 July 2007 (Day 99) (Screening B: 1.5 ng/mL, Baseline: 2.9 ng/mL, Day 89: 4.8 ng/mL, Day 99: 2.9 ng/mL). The PSA increase met the criterion of >0.75 ng/mL increase from Baseline (referred to as "velocity" in the protocol). It was noted that the patient's baseline serum PSA was 2.9ng/mL, roughly 2-fold higher than Screening, but the subject had received a waiver to enroll in the study. At early termination on 06 August 2007 (Day 116), the PSA decreased further to 1.7 ng/mL. Study medication was discontinued due to the event on 05 August 2007. There were no reported rectal examination abnormalities. The outcome of the event was reported as recovered/ resolved on 20 July 2007.

Subject 016-07: This 68 year-old male did not receive study medication. The subject experienced the nonserious adverse event of atrial fibrillation on 28 February 2007. The outcome of the event is reported as ongoing.

Of the subjects who discontinued due to AE of increased PSA in the double-blind period, seven subjects met withdrawal criteria on the basis of a single elevated value. In these cases, the second value did not exceed the 0.75 ng/ml criteria, but the initial value was sufficiently high to bring the average change from Baseline above the pre-defined per protocol withdrawal criteria (Subjects 003-45, 016-26, 018-013, 022-004, 034-018, 050-006, 060-018). Four subjects who discontinued due to elevated PSA had maximum PSA levels between 1 and 1.4 ng/mL (Subjects 018-013, 049-015, 060-019, 067-003); two subjects had maximum PSA levels between 2 and 2.8 ng/mL (Subjects 003-010, 024-004). Although four subjects discontinued with PSAs >4 ng/mL, these subjects had PSA ≤4.0 ng/mL upon repeat testing (Subjects 049-011, 050-006, 069-019).

Table 27: Discontinuations Secondary to PSA Elevations Study S176.3.104 Double-Blind Period – Individual Patients

Subject	T-Gel Dose (gms) Day of AE	Baseline PSA (ng/mL)	PSA (Elevation (Study Day)	Follow-up PSA on T-Gel (Day)	Follow-up PSA off T-Gel (Day)	Day T-Gel Discontinued	Rectal Findings
003-10	5.0	0.8	1.9 (83)	1.9 (90)	2.0(103) 0.8(155)	97	Increased Consistency Right Lobe
003-45	3.75	1.8	3.1 (84)	2.5(94)	2.4(109) 1.5(189)	105	None
016-09	5.0	1.6	2.5 (105)	3.2 (107)	2.4 (128)	120	None
016-26	5.0	2.5	3.9 (91)	2.5(112)	1.3 (162)	143	None
018-13	2.5	0.2	1.4 (88)	0.7 (117)		117	None
022-04	2.5	2.4	3.3 (85)	3.1 (100)	2.4 (117)	116	None
024-04	3.75	1.7	2.8 (88)	2.5 (117)	2.3 (145)	127	None
033-04	5.0	2.1	3.2 (85)	3.6 (96)	1.5 (127)	115	None/Refer Biopsy
034-18	3.75	2.1	3.5 (100)	3.6 (114)	2.4 (128)	121	None
049-02	2.5	0.8	0.8 (138)	4.2((188)	1.7 (231)	188	None
049-11	3.75	1.9	2.8 (85)	5.4 (96)	3.1 (109) 1.8 (236)	104	None
049-15	1.25	0.6	1.4 (106)		1.2 (120)	115	None
050-06	2.5	1.7	4.4 (85)	0.7 (96)	2.4 (123)	122	None
060-15	2.5	1.3	7.5 (84)	2.2 (98)	2.4 (104) 1.2 (153)	101	None
060-18	5.0	1.7	3.8 (88)	2.4 (98)	3.8 (131) 0.5 (158)	131	None
060-19	3.75	0.1	0.8 (88)	1.0 (120)	0.7 (159)	151	None
067-03	5.0	0.1	1.1 (85)	1.1 (102)	0.6 (120)	113	None
069-19	3.75	2.9	4.8 (89)	2.9 (99)	1.7 (116)	115	None

Source: Patient narratives Study S176.3.104 and Table 3.11.0 (S176.3.104) pages 1955-1963.

Reviewer's Comment on Discontinuations: One patient had a history of syncope and fainted on a PK sampling day. Two patients had mild elevations of blood pressure.

18 patients discontinued secondary to increases of PSA, based on strict criteria. The incidence of premature discontinuation due to increased PSA across the testosterone 1.62% groups was as follows: 1.25 g: 1/17, 5.9%; 2.50 g: 5/60, 8.3%: 3.75 g: 6/66, 9.1%; 5.00 g: 6/91, 6.6% (Source: Table 3.11.0 pages 1955-1963 of S176.3.104 report).

In 9 of 18 patients with "increased PSA" by the pre-determined criteria, a repeat or second PSA determination while the patient was still on testosterone gel 1.62% decreased. On average, the elevations of PSA leading to discontinuation occurred on Day 87. 9 of 18 subjects returned to at or below baseline levels of PSA with discontinuation of testosterone gel 1.62%. Follow-up was also of adequate length to document return of PSA concentrations to <0.75 ng/mL above the baseline level in 15 of 18 subjects. One subject was referred for a prostate biopsy with negative results. It appears that testosterone gel 1.62%, like testosterone gel 1%, can cause elevations of the PSA which return to baseline levels with cessation of drug administration in most cases. This should be reported in labeling.

Integrated Phase I studies: 4 of 147 subjects receiving testosterone gel 1.62% discontinued due to an adverse event (1 each of atrial fibrillation, dermatitis [and eczema], and hypertension [2]). Subjects 25817 (Days 1-3) and 25802 (Days 1-2) both received T-Gel 5.00 g on the days noted in study 176.1.002. Both had a relevant history of hypertension and were discontinued for the AE of hypertension.

Phase I Discontinuation Narratives:

Subject 25802 (Study S176.1.002):
This 67 year-old white male received testosterone gel 1.62% (5.00 g) on Days 1 and 2, but was prematurely discontinued from the study due to an AE of hypertension. The patient was receiving no concomitant medications and laboratory findings were unremarkable. The event of hypertension was reported on Day 3 (14 May 2006) and was assessed as mild in intensity (186/91 mmHg) and not related to study medication by the opinion of the Investigator. At the scheduled Day 3 vital sign assessment, a blood pressure of 186/91 mmHg was noted. It was further noted that Subject 25802 reported a relevant medical history of hypertension beginning on 08 May 2006 and ongoing at study entry (blood pressure at Screening 163/93 mmHg). Study medication was discontinued prior to Day 3 dosing and the event resolved. The subject was discontinued from the study on Day 4. At termination (Day 4) the blood pressure determinations were 179/86, 138/81, and 179/86 mmHg.

Subject 25817 (Study S176.1.002):
This 67 year-old white male received testosterone gel 1.62% (5.00 g) on Days 1 through 3, but was prematurely discontinued from the study due to an AE of hypertension. The subject was receiving no concomitant medications and there were no relevant laboratory abnormalities noted. The event of hypertension was reported on Day 3 (14 May 2006) with a blood pressure of 175/76 mmHg. and was assessed as mild in intensity and not related to study medication by the investigator. At the scheduled Day 3 vital sign assessment, a blood pressure of 175/76 was noted. It was further noted that the Subject 25817 reported a medical history of hypertension beginning on 03 May 2006 and ongoing at study entry blood pressure at Screening and Day -1

was 162/74 and 171/80 mmHg respectively). Study medication was discontinued prior to the morning dose on Day 4 with a blood pressures of 158/81, 165/79, 148/77, 149/77 and 149/81 mmHg.

> *Reviewer's Comment: In these discontinuations for hypertension, there is a history of the condition pre-existing.*

Subject 1005-26326:
This 77-year old white male was receiving testosterone gel 1.62% 5.00 g/day when he experienced severe atrial fibrillation, which was considered unrelated to study medication by the Investigator. The subject's medical history was positive for obesity, hypertension, allergic rhinitis, intermittent acid reflux, insomnia, esophageal ulcer, intermittent constipation and hyperlipidemia. The subject had no history of coronary or heart disease; however, the subject had reported five or six episodes of "heart racing" over the last 3 years that were of short duration and usually at night. He was receiving lisinopril 30 mg daily upon entry into the study. At study entry, the subject's Screening blood pressure and pulse rate were 143/92 mmHg and 63 bpm respectively, and on Day -1 blood pressure and pulse rate were 168/99 mmHg and 62 bpm, respectively. On Day 20, approximately 9.5 hours following administration of study medication, the subject complained of "heart flutter and fullness of chest" shortly after eating dinner. In the emergency room the blood pressure was 148/83 and pulse was 147 bpm. An ECG performed approximately 23 minutes after symptoms occurred revealed supraventricular tachycardia and acute myocardial infarction. The heart rate was 144 bpm. A second ECG 1.5 hours after symptoms occurred revealed atrial flutter and variable heart block with a heart rate of 103 bpm. The next day, Day 21, an ECG revealed normal sinus rhythm with a heart rate of 69 bpm and serial changes of an evolving septal infarct. The final ECG on Day 21 revealed no significant changes. The subject was hospitalized and received oral acetylsalicylic acid (162 mg) on Day 20, and intravenous diltiazem (5mg/hour and intravenous procainamide (2mg/minute) on Day 21. The atrial fibrillation persisted for 9 hours and resolved. At follow-up, 4 days after discontinuation, the subject experienced an AE of vertigo of moderate intensity which persisted for 4 hours. The event resolved and the subject discontinued the study.

Subject 1007-26827:
This 55-year old white male was receiving testosterone gel 1.62% 5.00 g/day when on Day 6, 0.5 hours prior to administration of the study medication he noted a 'red skin patch" on his "lower front leg" [right]. On Day 7(16 March 2007), the sub-investigator assessed the subject and found right lateral anterior leg erythema which he characterized as "rough feeling" and of "smooth appearance." A biopsy of the lesion showed right lower leg superficial and deep perivascular dermatitis with eosinophilia consistent with a dermal hypersensitivity reaction and a periodic acid-Schiff (PAS) stain negative for fungi), which was considered unrelated to the study. The subject had a positive medical history for dermatitis of the right lower leg and erythema to the right lower extremity which the subject reported as resolved as of 01 February 2007. The event resolved after the application of hydrocortisone on 25 March 2007 and the subject was discontinued from the study on 11 March 2007.

Reviewer's Comment: Subject 1007 has a past history of dermatitis occurring at the same site prior to entry into the study.

Non-integrated studies: 2 of 307 (0.65%) discontinued prematurely due to an adverse event. Both subjects were in study S176.1.004 to evaluate sensitization and skin irritation of T-gel 1.62%. Both subjects (1004-26625 and 1004-26626) developed rashes judged as probably related to the study drug.

Reviewer's comment: "Rash" should be noted in the product labeling.

7.3.4 Significant Adverse Events

In the opinion of this reviewer, significant adverse events observed in these trials are: 1) the worsening of existing hypertension in patients receiving testosterone gel 1.62% and 2) increases in the PSA secondary to testosterone gel 1.62% use. The incidence of PSA elevations was 1.25 g: 1/17, 5.9%; 2.50 g: 5/60, 8.3%: 3.75 g: 6/66, 9.1%; 5.00 g: 6/91, 6.6% (Source: Table 3.11.0 pages 1955-1963 of S176.3.104 report). PSA elevations in most cases with cessation of testosterone gel 1.62% therapy returned to either Baseline or below established levels of concern.

7.3.5 Submission Specific Primary Safety Concerns

The previous sections have described many of the adverse events observed in the investigations for AndroGel 1.62% and known to be potential risks for androgen replacement therapy/ At the current time there is no direct evidence that testosterone replacement therapy leads to prostate cancer.

Reviewer's Comment: Periodic assessments of serum PSA in hypogonadal men on testosterone replacement therapy is warranted. Rises of PSA in this setting require evaluation if they persist after withdrawal of testosterone gel 1.62% and are still of sufficient concern to be evaluated further. In my opinion, it is prudent to discontinue testosterone therapy in the face of increases of the PSA that are considered clinically important. In this trial, the Sponsor selected the following criteria for discontinuation: absolute PSA in excess of 4.0 ng/mL, or increase in PSA >0.75 ng/mL from baseline.

Hypertension is a labeled adverse event for AndroGel and is included in the submitted label for testosterone gel 1.62%.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase III Study**:** Data from the Phase III double-blind study and the integrated Phase I 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.

Table 28: Common Treatment-emergent Adverse Events (>2% for T-gel 1.62% and greater than placebo) for the Double-blind Phase III 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.

The most common TEAEs by category (SOC) for the testosterone gel 1.62% groups compared with placebo were Infections and Infestations (37/234, 15.8% versus 5.40, 12.5%) and Investigations 34.234, 14.5% versus no subject). The most common (≥2% in the testosterone gel 1.62% groups) TEAEs by preferred term (PT) 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.

There were pre-specified criteria for abnormal PSA values 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.

The incidence of hypertension across the testosterone gel 1.62% groups was 1.25 g: 1/17, 5.9%; 2.5 g: 0/60; 3.75 g: 1/66, 1.5%; 5.0 g 4/91, 4.4%.

No other clinically relevant differences in incidences of TEAEs were noted across dose groups of testosterone gel 1.62%

> *Reviewer's Comment: It is notable that diarrhea and upper respiratory conditions are also reported more commonly in the active treatment group compared to placebo in the AndroGel® 1% label and thus, may be treatment related.* (b) (4) (b) (4) *PSA elevations and hypertension are most likely treatment related and are also presented in labeling. There was no indication that application site pruritis and dermatitis increased with increased testosterone concentrations. No patient discontinued because of an application site TEAE.*

The proportion of subjects with at least one TEAE ranged from 52.5% to 80.0% across serum testosterone concentration categories (≤ 1500 ng/dL: 96/183, 52.5%; 1501 to 1800 ng/dL: 9/16, 56.3%; 1800 to ≤ 25000 ng/dL: 17/25, 68.0%; >2500 ng/dL: 8/10, 80.0%). There was no pattern of increasing incidence of single preferred terms with higher serum testosterone concentration category.

Table 29: Incidence of TEAEs by Highest Measured Testosterone Concentration Category for Events that Occurred in at Least One Subject in the >2500 ng/dL Category (Safety Sample Testosterone gel 1.62% Group)

Preferred Term	T≤2500 N=224	T>2500 N=10
Subjects with at least one AE	n (%) 122(54.5)	n (%) 9(90.0)
Toothache	0	1(10.0)
PSA Increased	22(9.8)	1(10.0)
Weight Increased	1(0.4)	1(10.0)
Mood Swings	0	1(10.0)
Libido Increased	0	1(10.0)
Nephrolithiasis	0	1(10.0)
Nipple Disorder	0	1(10.0)
Erectile Dysfunction	1	1(10.0)
Erection Increased	0	1(10.0)
Testicular Pain	1(0.4)	1(10.0)
Acne	1(0.4)	1(10.0)
Hypotension	1(0.4)	1(10.0)

Source: Clinical Study Report S176.3.104, Table 23, Page 148

Table 30: TEAEs by Testosterone (ng/dL) C_{max} and Body System (Safety Sample)

Primary SOC (Disorder)	≤1500 T level N=183	1501-<1800 N=16	1800-≤2500 N=25	>2500 N=10
Pt with at least one AE	N (%) 96(52.5)	N (%) 9(56.3)	N (%) 17(68.0)	N (%) 8(80.0)
Cardiac	3(1.6)	0	2(8.0)	0
Endocrine	1(0.5)	0	0	0
Eye	0	0	1(4.0)	0
Gastrointestinal	8(4.4)	0	0	1(10.0)
General and Site Conditions	15(8.2)	0	0	0
Immune System	4(2.2)	0	0	0
Infections Infestations	31(16.9)	1(6.3)	4(16.0)	1(10.0)
Injury, Poisoning, Procedural Complications	12(6.6)	1(6.3)	3(12.0)	0
Investigations	27(14.8)	1(6.3)	4(16.0)	2(20.0)
Metabolism Nutrition	1(0.5)	3(18.8)	3(12.0)	0
Musculoskeletal Connective Tissue	11(6.0)	3(18.8)	6(24.0)	0
Nervous System	8(4.4)	2(12.5)	3(12.0)	0
Psychiatric	8(4.4)	2(12.5)	2(8.0)	2(20.0)
Renal, Urinary	1(0.5)	0	0	1(10.0)
Reproductive, Breast	5(2.7)	1(6.3)	0	1(10.0)
Respiratory, Thoracic, Mediastinal	7(3.8)	2(12.5)	1(4.0)	0
Skin, SubQ	13(7.1)	2(12.5)	0	1(10.0)
Vascular	0	1(6.3)	0	0

Source: Clinical Study Report S176.3.104; Table 3.17.0, page 1830

Reviewer's Comment: The number of reports in the higher exposure groups are too small to make meaningful comparisons to the other groups, other than to state that the TEAE rate in subjects with testosterone levels >1500 ng/dL(n=34) is 66.7% versus 52.5% for men with testosterone levels <1500 ng/dL.

In the Open-Label Safety Extension the TEAEs occurring in ≥5% of subjects are displayed in the table below:

Table 31: Open-Label Safety Extension TEAEs occurring in 5% or more of Subjects

Term (HLT) Statistic n (%)	Formerly Placebo N=28	T-Gel 1.62% Total N=191	T-Gel 1.62% 1.25 g N=15	T-Gel 1.62% 2.5 g N=41	T-Gel 1.62% 3.75 g N=43	T-Gel 1.62% 5.0 g N=92
Diarrhea	1(3.6)	2(1.0)	2(13.3)	0	0	0
Asthenia	0	3(1.6)	1(6.7)	0	1(2.3)	1(1.1)
Viral infection	2(7.1)	3(1.6)	0	0	1(2.3)	2(2.2)
Lower Respiratory Infection	1(3.6)	5(2.6)	1(6.7)	1(2.4)	1(2.3)	2(2.2)
Upper Respiratory Infection	2(7.1)	18 (9.4)	0	2(4.9)	4 (9.3)	12(13.0)
PSA increase	3(10.7)	10(5.2)	2(13.3)	3(7.3)	1(2.3)	4(4.3)
Triglyceride increase	0	2 (1.0)	1 (6.7)	0	0	1 (1.1)
Sexual Desire Disorders	0	2 (1.0)	1 (6.7)	0	0	1(1.1)
Skin Rashes, Eruptions	0	1 (0.5)	1 (6.7)	0	0	0

Source: 120 Day Safety Update: Tables 3.2.0 and 3.1.0

Reviewer's Comment: The incidence and categories of AEs in the Open-Label Period appear comparable to those noted in the double blind period. The distribution of C_{max} values of testosterone for the subjects in the safety extension is as follows: ≤ 2500 N=179, ≤ 1500 N=158, 1501≤ 1800 N=9, 1800 ≤ 2500 N=12, and > 2500 N=0. Upon review of Table 3.17.3, it is my opinion that there was not a disproportionate number of AEs associated with higher C_{max} testosterone concentrations.

Adverse Events Reported in the Combined Phase I Studies in Hypogonadal Men (Studies S176.1.001, S176.1.002, S176.1.005, S176.1.006 and S176.1.007).

Table 32: Summary of Adverse Events in Phase I Studies (Combined Safety Sample) Testosterone Gel 1.62

	Testosterone Gel 1.62%					
Statistic n(%)	1.25g N=24	2.5g N=40	3.75g N=22	5.0g N=72	6.25 N=11	Combined N=147
≥ 1 TEAE	12(5.0)	16(40.0)	13(59.1)	16(83.3)	8(72.7)	105(72.4)
Skin Site TEAE	1(4.2)	3(7.5)	5(22.7)	27(37.5)	4(36.4)	40(27.2)

Source: Table 22, 2.7.4 Summary of Clinical Safety: page 65

Overall, of the 147 subjects enrolled, 105 subjects (71.4%) experienced at least one TEAE. The 5.00 g dose group had a higher proportion of subject who experienced at least one TEAE (60/72, 83.3%) compared with the other dose groups (1.25 g: 12/24, 50.0%; 2.5 g: 16/40, 40.0%; 3.75 g: 13/22, 59.1%; 6.25g: 8/11, 72.7%).

In the Phase 1 studies, the most frequently reported SOCs are listed below:

- General disorders and Administration site conditions were the most frequently reported TEAEs (49/147, 33%). The most frequently reported PTs were: application site papules (16/147, 10.9%), application site excoriation (8/147, 5.4%), application site dermatitis (7/147, 4.8%) and application site erythema 1/147, 4.8%).
- Skin and subcutaneous tissue disorders (47/147, 32.0%) included the preferred terms (PTs) dry skin (9/147, 6.1%) and acne (7/147, 4.8%). The most frequently reported skin application site events included application site papules (16/147, 10.9%), application site excoriation (8/147, 4.8%), application site dermatitis (7/147, 4.8%), and application site erythema (7/147, 4.8%). All skin application site TEAEs were mild and did not lead to discontinuation.
- Nervous system disorders (23/147, 15.6 %) included PT headache (19/147, 12.9%).
- Musculoskeletal and connective disorders (12/147, 8.2%) included the PTs of arthralgia (4/147, 2.7%), muscle spasms (3/147, 2.0%), and back pain (3/147, 2.0%).

Reviewer's comment: It might be reasonable to describe the skin-related AEs in the Phase 1 studies in product labeling.

8 of 147 subjects reported hypertension (5.4%). Two of these subjects had a previous history of hypertension.

A total of 4/147 subjects had PSA change from Baseline >0.75 ng/mL at their Early Termination Visit; all of these four subjects had PSA <2.5 ng/mL. No subject had PSA >4.0 ng/mL. One subject had a PSA>2.5 ng/mL at Early Termination Visit (2.81 ng/mL) and one subject met this criterion at the Screening Visit (2.93 ng/mL; repeat value prior to study entry was 2.20 ng/mL). Based on the criteria used in Study S176.3.104, these PSA values would

not have required any further laboratory evaluation or subject follow-up (confirmation of PSA change) since the magnitude of change was not>0.75 ng/mL and the value was not >4.0 ng/mL.

None of the 147 subjects had an HCT value>54%.

Reviewer's Comment: A safety review of the Phase I studies (integrated review) has not revealed any additional safety concerns.

7.4.2 Laboratory Findings

The incidence of clinically significant abnormalities for the Phase I studies in hypogonadal men (S176.1.001, S176.1.002, S176.1.005, S176.1.006, and S176.1.007) is presented in the table below. There were no clinically significant hemoglobin or hematocrit abnormalities.

Table 33: Clinically Significant Chemistry Abnormalities Phase I Integrated Studies

	Statistic	T-Gel 1.62%					
	n (%)	1.25 g	2.5 g	3.75 g	5.0 g	6.25 g	Combined
		N=24	N=40	N=22	N=72	N=11	N=147
ALT		0	1(2.5)	0	0	0	1(0.7)
Cholesterol		0	0	0	0	1(9.1)	1(0.7)
Glucose		0	1(2.5)	0	1(1.4)	1(9.1)	3(2.0)
LDL		0	0	0	0	1(9.1)	1(0.7)
Triglycerides		0	0	0	0	1(9.1)	1(0.7)
VLDL		0	0	0	0	1(9.1)	1(0.7)

Source: Table 5.0.1 2.7.4 Clinical Summary of Safety

In the integrated Phase I studies, no subject met the criteria of Hct >54%, ALT >3x ULN, or AST >3x ULN.

Clinically significant abnormal results included clinically significant abnormal glucose result observed for 3/147 subjects (2.0%) (Subjects 1002-25800, 1002-25825, 1002-25827); for two of these subjects this was reported as an AE of hyperglycemia (Subjects 1002-25825, 1002-25827). One subject had clinically significant abnormal cholesterol (1/147, 0.7%), LDL (1/87, 1.1%), and very low density lipoprotein (VLDL) (1/147, 0.7%), and the AE of hyperlipidemia was reported for this subject (Subject 1002-25808). In addition, one subject had an elevated PSA value at Screening (Subject 1007-26821: 2.93 ng/mL). Micro-urinalysis showed clinically significant abnormal results for one subject, Subject 1002-25800 who had +4 bacteria result. This subject was noted to have urinary tract infection. In addition, this subject had a clinically significant nitrate finding at the early termination visit.

Table 34: Listing of Clinically Significant Laboratory Parameters Integrated Phase I Studies – Individual Subjects

Subject Number	T-Gel Dose Group	Age/Race /Ethnicity	Visit	Treatment Day	Parameter	Unit	Baseline Value	Visit Value
S176.1.1002-25875	2.5 g	45/white/ Non Hispanic	Early Termination	15	ALT (SGPT)	U/L	61	52
S176.1.1002-25808	6.25 g	67/white/ Hispanic	Early Termination	15	Cholesterol LDL Triglycerides VLDL	MMOL/L MMOL/L MMOL/L MMOL/L	8.4175 5.7498 2.599 1.1914	6.9153 4.0404 3.7064 1.7094
S176.1.1002-25825	2.5 g	66/white/ Non Hispanic	Early Termination	15	Glucose	MMOL/L	6.771	17.205
S176.1.1002-25827	5.00 g	52/white/ Hispanic	Early Termination	15	Glucose	MMOL/L	6.9375	12.4875

Source: Listing 5.0, 2.7.4 Clinical Summary of Safety

Reviewer's Comment: There appear to be no discernable safety concerns noted in the laboratory findings of the Phase I integrated studies.

Discussion in this next section is limited to Study S176.3.104 Double-blind period. Clinical laboratory (hematology, serum chemistry, and urinalysis) tests were performed at screening, at Baseline (Day 1) and at Visit 10 (Day 182). Safety testosterone levels were performed at baseline and at all Visits (1-10). Safety labs (PSA, Hct, Hgb, SGOT, SGPT, lipids) and sex steroid labs (testosterone, DHT, E2) and SHBG were performed at baseline and at all Visits (1-10). PK samples were done at Visits 3 (Day 14), 6 (Day 56), 9 (Day 140) and 10 (Day 182). PD samples were obtained at Visits 1, 8(Day 112), and 10.

An increase in Hgb was observed for the testosterone gel 1.62% group compared with the placebo group(changes in from baseline for hemoglobin were -1.74 for placebo and 6.50 for testosterone gel 1.62% at 182 day endpoint). 4.8% of the Testosterone Gel 1.62% group had a shift in Hgb from normal at Baseline to High at endpoint versus none for placebo. There was a similar shift for hematocrit. 5 subjects had hematocrits >54%. One of these subjects (018-005) discontinued per protocol on Day 86 (See discontinuation narrative). Four subjects had elevations of hematocrit >54% in the open-label extension and were discontinued. See table below:

Table 35: Open-Label Period Subjects with Hct of 54% or Higher – Individual Patients

Subject Number	T-Gel 1.62% Dose	Visit	HCT/HGB
016-02	1.25 g	Baseline	46.9/16
		Day 204	39.3/13.4
		Day 254	55.2/18.5
036-02	5 g	Baseline	44.2/15.3
		Day 270	52.1/18.2
		Day 277	50.6/17.6
		Day 361	55.6/19
		Day 374	51.3/18
047-05	3.75 g	Baseline	46.1/15.7
		Day 265	57/19.1
		Day 274	54.1/18.5
		Day 288	54.8/19
016-05	1.25 g	Baseline	45.4/15.4
		Day 196	54/17.6
		Day 272	44.7/15.5
		Day 310	51/16.2

Source: Listings 20 and 24 of 120 Day Safety Update

> *Reviewer's Comment: There is appropriate labeling in the proposed product label relating to increase of the hematocrit and testosterone gel 1.62% use. This is a known phenenomen with testosterone replacement and hemoglobin/hematocrit monitoring is recommended in product labeling. The discontinuation rate for elevations of the Hct> 54% did not differ from what was expected for this class of drugs and consideration of the protocol's discontinuation thresholds.*

In the 182-Day Open-Label Safety Extension, clinical chemistry, CBC, and urinalysis were performed on Visit 10 (Day 182) and Visit 14 (Day 364). Safety labs consisting of PSA, HCT, HGB, SGOT, SGPT, and lipids were performed on Visit 10, Visit 12 (Day 266), and Visit 14. Two subjects were noted to have an elevation of the BUN >=10.7 mmol/L (Testosterone gel 1.62% 3.75 g and 5 g), two subjects had a serum calcium <= 2.1 mmol/L (2.5 g and 5 g), and one subject had a fasting glucose >=13.9 mmol/L (5.0 g). There were no subjects with AST>3x ULN and ALT>3x ULN.

A total of 34 subjects in the double-blind phase of S176.3.104 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. 7/203 subjects (3.3%) had a PSA post-Baseline >4.0 ng/mL, while 33/209 subjects (15.8%) had an increase in PSA from Baseline > 0.75 ng/mL, and 6/209 subjects (2.9%) met both criteria for "increased PSA".

A total of 17 subjects discontinued from the study during the double-blind portion of this study due to an AE of "increased PSA". Four of the subjects who discontinued had maximum PSA levels between 1 and 1.4 ng/mL (Subjects 018-013, 049-015, 060-019,067-003) while two

subjects had maximum PSA levels between 2 and 2.8 ng/mL (Subjects 003-010, 024-004). 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 (subject 049-011, 050-006, 060-015, 069-019). The remaining subjects either withdrew consent (subject 045-026), had a repeat PSA value bringing the average PSA results with normal limits (Subjects 013-015, 042-009, 058-005, 060-004, 061-003, 064-009), or discontinued after the database lock of the double-blind portion of the study (Subjects 015-001, 016-003, 018-006, 028-021, 039-009, 043-016, 049-002, 049-030, 058-006, 069-003).

In the 182-Day Open-Label Safety Extension, 12 subjects had either a PSA increase from Baseline >0.75 ng/mL or a PSA Post-Baseline value > 4.0 ng/dL. Six of these subjects met the predetermined discontinuation criteria.

Table 36: Average Serum PSA Changes in the 182-Day Pivotal Double-Blind Period (Mean from Baseline)

PSA(ug/L)	Placebo	Testosterone Gel 1.62				
(n, %) statistic	N=40	1.25 g N=17	2.5g N=60	3.75g N=66	5.0g N=91	All T-Gel N=234
Baseline(mean)	0.85	0.74	0.86	0.98	0.87	0.89
Day 84 (Δ)	0.01	0.05	0.07	0.19	0.15	0.14
Day 182 (Δ)	-0.15	0.04	0.08	0.07	0.12	0.09
Endpoint (Δ)	-0.12	0.10	0.08	0.12	0.20	0.14

Source: Clinical Study Report S176.3.104, Table 4.3.0 pages 2114-2115.

Table 37: Average Serum PSA Changes in the 182-Day Pivotal Double-Blind Period (Mean from Baseline)-In Men over 65 years of age

PSA(ug/L)	Placebo	Testosterone Gel 1.62				
(n, %) statistic	N=8	1.25 g N=4	2.5g N=11	3.75g N=11	5.0g N=9	All T-Gel N=35
Baseline(mean)	1.25	0.38	1.16	0.77	1.13	0.94
Day 84 (Δ)	0.16	0.40	0.34	0.31	0.52	0.38
Day 182 (Δ)	-0.18	0.00	0.08	0.19	0.36	0.19
Endpoint (Δ)	-0.13	0.37	0.03	0.35	0.70	0.35

Source: Clinical Study Report S176.3.104, Table 4.3.1, pages 2124-2125.

> *Reviewer's Comment: The mean PSA, as expected, rose modestly and of note had declined by Day 182. There were greater baseline means and greater average rises in men over 65 years of age. Day 112 (Endpoint Day) had the highest PSA levels and testosterone levels.*

There were no clinically meaningful treatment group differences in mean changes from Baseline to Day 182 for hematology, chemistry, lipids (panel, enzyme profiles), special laboratory

parameters, or urinalysis within the treatment groups. The changes in hemoglobin in the T-Gel patients (Baseline 148.4 g/L to 154.9 g/L at Endpoint) were expected.

Clinical laboratory evaluations by sex, race, and age: Due to the small number of subjects in the placebo group in the different age groups and race categories and the low incidence of markedly abnormal values, no conclusions were drawn by the Sponsor from these subgroup analyses.

There were 10 subjects with 11 testosterone elevations >2500 ng/dL. See Table 6. In each case other testosterone levels on the same day (when done) were not elevated.

> *Reviewer's comments: Each patient with a T >2500 ng/dL has been analyzed in depth in the efficacy section.*

Data from the 120-Day Safety Update with respect to the 10 subjects with testosterone concentrations above 2500 ng/dL have been analyzed previously. The four subjects in this category selected for further analysis are presented in the table below:

Table 38: Open-label Safety Results on 4 patients with T>2500 ng/dL Selected for Further Analysis

Subject Number	T-Gel Treatment Group	Age	Investigator term/ PT	TEAE Day Start/ Stop	Action Taken/ Study Med Last Dose	Outcome
007-06	5 g	51	Chest Cold/Lower Respiratory Infection	259/256	None/362	Recovered
			Sore Throat/ Pharyngolaryngeal Pain	363/371	None/362	
			Flu like symptoms/ influenza-like illness	364/371	None/362	
015-05	5 g	57	Bilateral lower abdominal hair growth/Hair growth abnormal	64/ongoing	None/368	Recovered
			Darkened color chest hair/hair color changes	64/ongoing	None/368	Recovered
			Bilateral lower back hair growth/hair growth abnormal		None/368	Recovered
			Sinus infection/sinusitis	161/ongoing		
			Pneumonia/pneumonia		None/368	Recovered
			Contact dermatitis not application site	218/234	None/368	Recovered
			Bilateral Shoulder petechiae/application site rash	222/234 228/ongoing	None/368	Recovered
			Viral syndrome/viral infection			
			Asthma/asthma	266/269		
			Viral syndrome/viral infection		None/368	Recovered
					None/368	Recovered
				277/299	None/368	Recovered
				302/ongoing 302/312		
049-08	1.25 g	54	Pneumonia/Pneumonia	219/221	None/367	Recovered
			Elevated Triglycerides/ blood triglycerides increased	265/369	None/367	Recovered
			Diarrhea/diarrhea	361/367	None/367	Recovered
058-06	3.75 g	60	Elevated PSA/Prostate Specific Antigen Increased	177/204	Drug/199 Discontinued	Study/204 Termination

Source: Listing 16, 120 Day Safety Update

With respect to the other 6 subjects with testosterone concentrations >2500 ng/dL, Subject 003-08 had no TEAEs, Subject 005-28 had acne on back (not application site), Subject 039-09 had an elevated PSA and study drug was discontinued Day 233, Subject 044-05 noted erectile dysfunction but continued in the study, and Subject 067-001 is not listed as participating in safety extension.

Subject 012-08 who developed prostate cancer in the 182-Day Open-Label Safety Extension also had experienced a single peak testosterone concentration >2500 ng/dL in the double-blind period. The Sponsor forwarded to the Division a detailed narrative for this case which has been discussed in detail in the SAE discontinuation narratives.

Reviewer's Comment: The 10 subjects with testosterone concentrations >2500 g/dL did not appear to have any unique proclivity for TEAEs.

7.4.3 Vital Signs

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], respiratory rate [RR], temperature [T]), EKGs, and IPSS score.

In the double-blind period, 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 vital signs and no important differences across dose groups were noted in the mean change from baseline. Using a change from baseline of 7% as "clinically meaningful", there were more patients on T-Gel compared to placebo for both a decrease from Baseline ≥7% in weight (12/222, 5.4% T-Gel versus 1/38, 2.6% for placebo) and an increase from baseline ≥7% in weight (16/222, 7.2% T-Gel versus 1/38, 2.6%).

Because of the small numbers in each treatment group, no discernable trends were noted based on age or race.

Table 39: Marked Abnormalities of Vital Signs in the 182 Day Pivotal Study

Statistic n(%)	Placebo N=40	T gel 1.25g N=17	T gel 2.5g N=60	T gel 3.75g N=66	T gel 5.0 N=91
Weight					
>7%↓	1(2.6)	1(5.9)	3(6.3)	5(7.6)	3(3.3)
>7%↑	1(2.6)	2(11.8)	2(4.2)	5(7.6)	7(7.7)
Systolic BP					
bsl≤90&↓≥20	1(2.6)	1(5.9)	1(2.1)	1(1.5)	1(1.1)
bsl≥180&↑≥20	0	0	0	1(1.5)	0
Diastolic BP					
bsl<50&↓≥15	0	0	0	1(1.5)	1(1.1)
bsl≥105&↑≥15	0	0	1(2.1)	1(1.5)	0
Pulse (bpm)					
bsl≤50&↓≥15	1(2.6)	1(5.9)	2(4.2)	1(1.5)	2(2.2)
bsl≥120&↑≥15	1(2.6)	0	0	0	0

*bsl=baseline
Source: Clinical Study Report S176.3.104, Table 5.1.0, and page 2281

> *Reviewer's comment: In this reviewer's opinion, there are no discernable trends of concern in this vital sign data.*

In the 182 Day Open Label Safety Extension, the average weight gain per subject was -0.22 kg (Baseline [Day 182] to endpoint [Day 364]). The sitting systolic blood pressure increased on average 0.1 mmHG per subject. The sitting diastolic blood pressure changed from Baseline at endpoint -1.3 mmHg. Sitting pulse changed from Baseline at endpoint -0.3 bpm.

Table 40: Marked Abnormalities of Vital Signs in the 182 Open-Label Safety Extension

Statistic n(%)	Formerly Placebo N=28	T gel 1.25g N=15	T gel 2.5g N=41	T gel 3.75g N=43	T gel 5.0 N=92
Weight					
>7%↓	2 (7.1)	0	6 (15.0)	2 (4.9)	9 (10.1)
>7%↑	2 (7.1)	1 (7.1)	1 (2.5)	3 (7.3)	7 (7.9)
Systolic BP					
bsl≤90&↓≥20	0	2 (1.1)	0	1 (2.5)	1 (1.1)
bsl≥180&↑≥20	0	2 (1.1)	0	1 (2.5)	1 (1.1)
Diastolic BP					
bsl<50&↓≥15	0	0	0	0	1 (1.1)
bsl≥105&↑≥15	0	0	1 (2.5)	0	1 (1.1)
Pulse (bpm)					
bsl≤50&↓≥15	0	0	1 (2.5)	0	1 (1.1)
bsl≥120&↑≥15	0	0	0	0	0

*bsl=Baseline
Source: Table 5.1.0 120 Day Safety Update, Page 2364

Reviewer's Comment: There are no discernable trends of concern in this data. The small numbers in each treatment group may preclude noting any differences with respect to age or race.

7.4.4 Electrocardiograms (ECGs)

ECGs were obtained at screening and at Visit 10 (Day 182). The percentage of subjects who shifted from normal at Baseline to abnormal not clinically significant at Endpoint for global ECG evaluations was similar for the testosterone gel 1.62% groups and the placebo group (19/181, 10.5% versus 3/29, 10.3%). No subject in either treatment group shifted from normal to abnormal clinically significant at Endpoint for global ECG evaluations. One subject (058-07) using testosterone gel 1.62% 2.5 g shifted from abnormal not clinically significant to abnormal clinically significant at Week 26. The subject was allocated to treatment for the 182-Day Open Label Period. At Week 52 his ECG was reported as abnormal, clinically insignificant. This subject is not included in Listing 16, Listing of AEs: General.

In the 182-Day Open-Label Safety Extension 12-Lead ECGs were obtained at Day 182 and Visit 14 (Day 364). The percentage of subjects who shifted from normal at baseline (the last non-missing value collected before the first double-blind study drug administration) to abnormal, not clinically significant, was 10.0%. One subject (017-23) using testosterone gel 1.62% 2.5 g shifted from abnormal not clinically significant to abnormal clinically significant at Week 52 as

determined by 2 ECGs 1 day apart. The ECG abnormality was described as a T wave abnormality in the Listing of Adverse Events.

Reviewer's Comment: There appear to be no significant trends or adverse findings with respect to ECGs throughout Study S173.3.104.

7.4.5 Special Safety Studies/Clinical Trials

The Sponsor conducted a dedicated skin irriation study and two studies dedicated to the issue of transfer. The skin transfer studies were S176.003 and S.176.008 and these will be reviewed first.

Skin Transfer Studies

S176.1.003 was a single center, open label, randomized, single and multiple exposures, parallel group study in healthy male and female couples. Each male-female couple was randomized to one of three treatment groups. Each group consisted of 16 couples. The pharmacokinetic objectives of the study were 1) to determine the pharmacokinetics of total testosterone concentrations in female subjects after single and multiple episodes of skin contact with a male partner dosed with testosterone gel 1.62%, and to 2) to evaluate skin-to-skin testosterone transfer from males dosed with testosterone gel 1.62% to non-dosed female subjects when direct contact occurred 2 hours or 12 hours post-dose and when contact occurred with a t-shirt at 2 hours post dose (the three treatment groups). The testosterone gel was applied to the abdomen and each couple engaged in abdomen to abdomen contact in the vertical position for 15 minutes daily. The drug dose used in the study was 5 g of testosterone gel 1.62% applied once a day.

There were three treatment groups:

- Treatment A: Direct skin contact occurred two hours post dose (no t-shirt)
- Treatment B: Skin contact occurred two hours post dose with the male wearing a t-shirt
- Treatment C: Direct skin contact occurred 12 hours post dose (no t-shirt)

Blood samples for measurement of serum testosterone, DHT, and estradiol concentrations were collected from female subjects only at the following times: serially over a 24-hour period on Day-1 (baseline), serially over the 24-hour period following the end of contact on Days 1 and 7, and at 48 hours after end of contact on Day 7.

Results: PK was performed only on the female subjects. The baseline testosterone concentrations were similar across all treatment groups (20.1-29.3 ng/dL [normal range 8-75 ng/dL]). Based on the concentration- time profiles, mean observed testosterone concentrations increased from baseline yet remained within the normal range (for females) on Days 1 and 7 for all treatments except for direct skin contact 2 hours post-dose, where the the normal range was exceeded. In treatment A at 16 hours post skin contact on Day 1, the testosterone average level was 81.5 ng/dL ng/L with an SD of 31.2 ng/dL. On Day 7 in Treatment A at 16 hours post skin contact, the average testosterone level was 65.2 ng/dL with an SD of 25.1 ng/dL. The Time 0 average testosterone concentration was 47.0 ng/dL on Day 7. The mean Cavg for observed

testosterone was within the normal female range after single and multiple episodes of skin contact except for Day 1 of treatment A at 16 hours (81.5 ng/dL). This demonstrates clear evidence of transfer in Treatment Group A - which used no barrier.

There was variation amongst the subjects as is reflected in the standard deviations of 31.2 ng/dL at 16 hours on Day 1 and 25.1 ng/dL on Day 7 at 16 hours in Treatment A subjects. In Treatment B, the standard deviations ranged from 11.6 to 19.0.

Covering the site of application on the male partner prior to post dose contact reduced the amount of exposure by 40-48% according to the Sponsor, as seen in Treatment Group B. The mean Cmax remained within the normal range for adult women. Accumulation of testosterone was minimal in females after daily skin contact for 7 days. Mean testosterone concentrations in females returned to baseline levels 48 hours after last skin contact with a dose male partner.

Table 41: Study S176.1.003 Average Testosterone (ng/dL) Concentrations by Treatment for Female Subjects

Treat-ment	Study Day	Nominal Time (h)									
		0	2	4	6	8	10	12	16	24	48
A	-1	20.1	22.6	23.6	24.9	25.8	23.1	24.0	28.9	24.6	NA
	1	24.6	36.4	45.2	56.6	47.4	60.2	57.8	81.5	46.2	NA
	7	47.0	52.9	68.0	68.5	60.4	61.0	64.2	65.2	53.3	34.0
B	-1	23.1	23.0	23.1	24.1	24.1	22.8	24.2	26.3	23.8	NA
	1	23.8	31.6	39.8	38.9	36.0	37.6	36.0	46.2	35.3	NA
	7	39.5	36.8	38.1	38.0	37.1	34.6	35.0	47.3	33.1	26.3
C	-1	22.3	23.0	26.9	29.3	27.5	29.0	28.4	27.7	21.3	NA
	1	21.3	43.8	44.1	66.3	74.7	69.6	68.6	55.2	57.4	NA
	7	32.3	51.6	47.0	48.5	55.5	55.4	52.2	48.6	41.5	30.4

NA=not applicable Source: Clinical Study Report S176.1.003 Table 10.2.1

Reviewer's Comment: In this study, covering the site of application reduced the exposure in women compared to not covering the site. However, a T-shirt barrier still permitted a significant amount of testosterone exposure in females. By my calculation the amount of transfer could be reduced by as much as 60% by a T-shirt. This is still unacceptably high.

Study S176.1.008 was a randomized, open-label, parallel group study to evaluate the effects of a 2.5 gm dose (with/without a T-shirt), post-application washing, and application site on the transfer potential of testosterone gel 1.62% from dosed males to a non-dosed partner. Contact time was 15 minutes. 24 healthy male-female couples participated. The study objectives were:

- To evaluate skin-to-skin testosterone transfer potential from males dosed with gel to non-dosed female subjects using a dose of 2.5 g gel, when contact occurred 2 hours post dose with and without a t-shirt.

- To evaluate skin-to-skin testosterone transfer potential from males dosed with 5.0 g gel to non-dosed female subjects when direct contact occurred 2 hours post dose with and without post dose washing.
- To evaluate skin-to-skin testosterone transfer potential from males dosed with 5.0 g gel to non-dosed female subjects when direct contact occurred 2 hours post dose after application to upper arms/shoulders or abdomen of males with the corresponding site in females.

Each treatment group was composed of eight couples, for a total of 24 couples. Within each treatment group, subjects received two single dose/exposure treatments in randomized order. Within 1 hour prior to the targeted time of dose application, male subjects showered and washed the application site with soap and water. Subjects were not allowed to remain in the shower for longer than 10 minutes. The designated area for gel application was to be thoroughly dried. Each dosing day included 15 minutes of supervised skin contact between the dosed male and his non-dosed female partner. Dose application and subsequent skin contact occurred on Days 1 and 8 of the study (7 day washout period). The three treatment groups were the following:

- **Treatment Group I: Treatment A**: Male subject-2.5 gm testosterone gel 1.62% (40.5 mg testosterone) applied to the abdomen. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt). **Treatment B**: Male subject-2.5 gm testosterone gel 1.62% (40.5 mg testosterone) applied to the abdomen. Contact with female-contact occurred 2 hours post dose with the male wearing a t-shirt.
- **Treatment Group II: Treatment C**: Male subject-5.00 g testosterone gel 1.62% (81 mg testosterone) applied to the abdomen. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt). **Treatment D:** Treatment Male subject-5.00 testosterone gel 1.62% (81 mg testosterone) applied to the abdomen. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt) after washing of the male application site. Washing of the application prior to contact is described on page 22 of Clinical Study Report S176.1.1008 as "*male subjects showered and thoroughly washed the application site with soap and water 15 minutes prior to the scheduled contact time. The abdomen was thoroughly dried.*" No further detail is provided about washing duration or technique.
- **Treatment Group III: Treatment E**: Male subject-5.0 g testosterone gel 1.62% (81 mg testosterone) applied to the upper arms/shoulders. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt). **Treatment F**: Male subject-5.0 g testosterone gel 1.62% (81 mg testosterone) applied to the abdomen. Contact with female-direct skin contact occurred 2 hours post dose (no t-shirt).

Results: Mean baseline testosterone concentrations (females only) were within the normal range for all groups (16.2-30.3 ng/dL). Mean observed testosterone concentrations increased above baseline for all treatments except for abdomen-abdomen contact 2 hours post dose (2.5g) with the male wearing a t-shirt. Observed testosterone concentrations returned to approximate baseline levels at or before 48 hours following the last contact for all treatments.

A T-shirt barrier largely eliminated population mean transfer in this study for the 2.5 g testosterone gel 1.62% dose. However, two subjects, 27403 and 27419, had baseline-adjusted testosterone increases of 17.4 and 13.8 ng/dL at the maximum, as well as a few other testosterone increases over baseline in excess of 10 ng/dL but less than maximum. In addition, Subject 27398 had negative values (lower than baseline) throughout the entire collection period.

Reviewer's Comment: There is a wide amount of variability in female testosterone levels. One cause of variability is cyclic variation of testosterone. If the sample size is adequate, this variation (both up and down) would be expected to even out. In future protocols, females should be studied at the same time in their menstrual cycle or be postmenopausal to decrease this type of variability. Despite two subjects (#27403 and #27419) with small increases above baseline, I concur that a T-shirt barrier largely eliminated population mean transfer in this study for the 2.5 g testosterone gel 1.62% dose.

Table 42: Protocol S176.1.1008: Baseline Adjusted Testosterone (ng/dL) Treatment B (T-Shirt Barrier)

	Nominal Time (h)									
Subject	0	2	4	6	8	10	12	16	24	48
27398	-21.2	-21.0	-18.1	-22.6	-14.8	-18.7	-14.3	-17.2	-2.20	-4.60
27400	0.40	-2.50	-2.30	-0.70	-10.1	2.50	-4.30	2.30	-40.3	-43.3
27403	14.8	0.80	12.3	**17.4**	16.9	4.70	14.2	11.0	-19.6	-18.8
27407	-0.10	-0.20	0.80	0.00	-0.10	1.80	6.40	8.70	3.80	2.80
27410	-1.80	-2.10	-0.60	6.40	2.60	0.20	4.20	-3.70	3.60	1.30
27412	-5.00	-1.40	3.30	0.70	1.90	-1.50	-4.90	6.80	2.50	5.10
27415	1.80	0.50	4.20	1.10	3.70	2.40	7.70	1.40	1.90	1.40
27419	9.60	1.60	**13.8**	11.2	8.60	7.70	4.40	2.00	-29.7	-35.7

Source: Adapted from Table 10.2.7: Clinical Study Report S176.1.1008, page 118

Washing the transfer site prior to direct skin contact (Group D) substantially limited the transfer of testosterone - AUC_{0-24} and Cavg were comparable to baseline and Cmax was only slightly increased. However, there were two subjects, 27405 and 27411 with notable increases from baseline (perhaps showing evidence for skin transfer of testosterone) and 4 subjects, 27399, 27402, 27404, 27417 with lesser and modest increases from baseline in serum testosterone.

Table 43: Protocol S176.1.008: Baseline Adjusted Testosterone (ng/dL) Treatment D (Site Washing)

	Nominal Time (h)									
Subject	0	2	4	6	8	10	12	16	24	48
27399	0.400	8.40	4.00	2.90	1.30	4.90	3.50	3.70	2.60	3.50
27402	0.00	6.00	5.00	4.80	7.40	7.30	0.60	-4.30	1.80	-1.30
27404	4.60	3.90	3.80	-1.00	3.80	2.60	6.10	-0.80	-5.50	-4.20
27405	12.3	8.70	12.3	11.0	**13.4**	6.90	1.30	10.2	-6.80	-10.8
27411	21.3	**16.9**	2.90	7.60	-1.50	1.30	-4.00	1.60	0.70	-4.90
27413	-3.30	0.80	0.10	2.00	1.50	0.10	-0.90	0.10	1.20	3.30
27416	1.10	-1.00	-0.90	-1.50	-1.10	0.50	0.30	2.30	-6.00	-4.90
27417	11.3	5.30	0.10	-1.40	2.40	2.00	0.60	3.30	-12.2	3.30

Source: Adapted from Table 10.2.7: Clinical Study Report S176.1.1008, page 120

Reviewer's Comment: The current data appears to support the conclusion that skin washing prior to physical contact largely eliminates risk of transfer of testosterone gel 1.62% to the female partner, but within the study there were two individuals with increases in testosterone from baseline, perhaps signaling testosterone transfer. Significant variability of female testosterone levels and cyclic variation to testosterone concentrations provide possible explanations for the two individuals with very modest testosterone increases. If the sample size is large enough, patients with increases and decreases of testosterone secondary to female cyclic variation would cancel each other out.

It is notable that the technique of washing the application site used in Protocol S176.1.008 included a shower and soap and water lathering of the application site for at least 2 minutes. If this precaution were to be used in future labeling, the specif details for washing will need to be stated.

The Clinical Pharmacology team finds that washing the site prior to contact precludes transfer and this method can be used as the principal precaution for transfer. However, the Clinical team does not agree, as we find the requirement to wash prior to any contact, including clothed contact, to be burdensome and not feasible.

After direct application to upper/shoulders (Group E) or abdomen (Group F) and shin-to-skin contact of a female with the corresponding application site on a male partner dosed within 5.0 g of testosterone gel 1.62 %, an increase in testosterone was observed with the normal range for both contact sites however, mean Cmax increased above the upper limit of normal following upper/shoulder contact. Testosterone transfer was higher for the upper arms/shoulders contact compared to the abdomen.

The table below illustrates the standard deviations per treatment at highest testosterone concentration:

Table 44: Study S176.1.008 Highest Baseline Adjusted Testosterone Level per Treatment

Treatment	Highest Testosterone Level (NG/Dl) and Nominal Time	Standard Deviation (ng/dL
A	15.4 at 12 hours	26.6
B	1.67 at 12 hours	8.97
C	12.8 at 12 hours	13.3
D	6.12 at 2 hours	5.52
E	66.8 at 2 hours	28.3
F	29.6 at 16 hours	32.2

Sources: Clinical Study Report S176.1.008 Tables 10.2.1 and 10.2.2

Table 45: Study S176.1.008 Average Serum Concentrations (ng/dL) of Testosterone by Treatment for Female Subjects

Treat-ment	Nominal Time (h)									
	0	2	4	6	8	10	12	16	24	48
A	32.1	24.3	32.3	36.9	24.8	31.5	43.1	24.3	23.7	39.6
B	20.6	17.0	21.2	20.9	21.6	19.2	20.3	21.5	21.5	20.0
Baseline	20.8	20.0	19.5	19.2	20.5	19.3	18.7	20.0	31.5	
C	23.1	31.1	26.3	28.1	26.2	26.3	29.1	22.7	21.8	21.6
D	20.8	21.4	18.7	19.0	19.0	18.6	16.4	17.3	17.4	18.4
Baseline	14.9	15.2	15.9	15.4	15.8	15.0	16.4	15.5	20.4	
E	52.2	80.4	60.8	50.1	67.0	57.3	54.5	61.0	42.1	54.0
F	32.6	36.1	42.1	37.8	31.8	43.7	41.2	44.0	36.5	32.7
Baseline	13.3	13.7	15.0	14.0	16.0	15.2	14.6	14.4	39.1	

Source: Clinical Study S176.1.008, Table 10.2.4, Table 10.2.1 Baseline is Day -1 for the two groups above each baseline row.

Reviewer's Comment: It appears that the female exposure to testosterone due to secondary exposure, as documented in S176.1.003 and S176.1.008, can be mitigated by coverage of the application site for the 2.5gm dose, but the current data does not appear to support the conclusion that a T-shirt barrier is fully effective as a barrier to skin transfer of testosterone gel 1.62%, under the conditions the transfer studies, for the 5gm dose. Washing prior to physical contact with the 5 g dose appears to adequately decrease testosterone transfer at 2 to 10 hours post-dose.

Skin Sensitization and Skin Irritation Study

Study S176.1.004 was a double-blind, randomized, placebo controlled study to evaluate the sensitization and irritation potential of repeat applications of testosterone gel 1.62 % in healthy male subjects. This was a double-blinded study using a randomized design where each subject received all test articles. The study was performed in the US. The subjects in the study during

the induction phase applied a skin patch (3.14 cm^2) to separate sites on the upper outer arm which contained Testosterone Gel 1.62 % 100mg. This amount of testosterone is 5 fold higher than the highest clinical dose in Study S176.3.004. The patch was applied every 48-72 hours for a total of 9 applications. Skin reactions to the patch were recorded. A rest phase of 12-17 days occurred during which no patches were applied. In the following challenge phase, the skin patches were applied to sites on the upper back for 48 hours. These sites were then evaluated 30 minutes and 48 hours after patch removal. If a rechallenge was necessary, it was conducted 3-4 weeks following the final evaluation of the challenge phase.

235 men were enrolled and 214 men completed the protocol. Four subjects were lost to follow-up. Six subjects were dropped due to non-compliance, and 2 subjects were discontinued due to a nonserious AE of rash. There were 4 test articles used:

a. Testosterone gel 1.62%
b. Placebo gel
c. Positive irritant control
d. Low irritant control

The irritation potential for each patch was determined by the scores obtained during the induction phase. Irritation was graded as follows: 0-no evidence of irritation, 1-minimal erythema, 2-definite erythema, 3-erythema and papules, 4- definite edema, 5-erythema edema and papules, 6-vesicular eruption, and 7-strong reaction extending beyond test site

Sensitization reaction was evaluated as follows: inflammatory responses were graded: 0-no visible reaction or erythema, 0.5-slight confluent or patchy erythema, 1 mild reaction-macular erythema, 2-moderate reaction-macular erythema, 3-strong to severe reaction-macular erythema.

Results: No serious adverse events or deaths occurred during the study. Fifty-one subjects (51/235, 21.7%) reported 97 nonserious events over the course of the study. The most common AE was headache (20 events in 13 subjects, 5.5%).

The following (2) subjects discontinued from study participation due to the nonserious AEs of rash:

- Subject 26625, a 20 year-old Caucasian male assigned to random sequence A, C, D, B experienced a nonserious AE of rash of moderate intensity considered probable in relationship to treatments. The rash occurred one day after last exposure to test articles and resolved with topical and oral therapy. The subject was exposed a total of 18 days at the time concomitant topical hydrocortisone acetate was administered.
- Subject 26626, a 38 year-old White male randomly assigned to sequence C, B, A, D experienced a non serious AE of rash on the right arm and chest that was considered unlikely related to treatments. He received topical clobetasol ointment. He was exposed to the test articles for a total of 16 days at the time the concomitant medication was administered.

Three subjects experienced application site pruritis comprising 4 non-serious AEs that were attributed to the treatments by the investigator on a probable basis. The Sponsor concluded that

there we no findings of patch irritation of clinical relevance. There was no evidence that Testosterone gel 1.62% produced sensitization as results during the challenge phase were similar to placebo gel. The Sponsor also concluded that Testosterone Gel 1.62% produced very mild irritation (all irritation scores<2, and 98% of scores were either 0 or 0.5 [similar to placebo]).

No trends or clinically significant changes were noted in clinical laboratory data, vital sign data, or physical examinations.

Reviewer's Comment: Testosterone Gel 1.62% appears to have no sensitization potential and minimal irritation potential as compared to placebo. However, rash was reported in 2 patients and "rash" should be included in labeling.

Table 15: TEAEs in Study S176.1.104

System Organ Class	Preferred Term	Total (N=235)
Total Number TEAEs		141
Patients with ≥ TEAE		68(29%)
		n (%)
Ear and Labyrinth	Ear discomfort	1(0.4)
	Ear pain	3(1.3)
Eye Disorders	Ocular hyperemia	2(0.9)
Gastrointestinal Disorders	Abdominal pain	1(0.4)
	Abdominal Pain upper	5(2.1)
	Constipation	1(0.4)
	Dyspepsia	1(0.4)
	Nausea	3(1.3)
	Retching	1(0.4)
	Toothache	3(1.3)
	Vomiting	1(0.4)
Gen Disorders, Administration site	Applic site pruritis	3(1.3)
	Fatigue	1(0.4)
	Irritability	2(0.9)
	Pyrexia	2(0.9)
Infections, Infestations	Conjunctivitis	1(0.4)
	Herpes Simplex	1(0.4)
	Influenza	1(0.4)
	Lower respiratory	1(0.4)
	Nasopharyngitis	7(3.0)
Injury, Poisoning, Procedural Complications	Arthropod bite	1(0.4)
	Hand fracture	1(0.4)
	Joint dislocation	1(0.4)
	Sunburn	3(1.3)

Metabolism, Nutrition	Anorexia	1(0.4)
	Dehydration	1(0.4)
Musculoskeletal Connective	Arthralgia	1(0.4)
	Back pain	2(0.9)
	Myalgia	3(1.3)
	Musculoskeletal pain	1(0.4)
	Neck pain	1(0.4)
	Pain extremity	1(0.4)
Nervous System Disorders	Headache	19(8.1)
	Lethargy	1(0.4)
	Syncope	3(1.3)
Psychiatric Disorders	Insomnia	2(0.9)
Respiratory, Thoracic, Mediastinal Disorders	Cough	9(3.8)
	Dysphonia	1(0.4)
	Epistaxis	1(0.4)
	Secretions increased (upper airway)	1(0.4)
	Nasal congestion	2(0.9)
	Nasal discomfort	1(0.4)
	Pharyngolaryngeal pain	6(2.9)
	Rhinitis allergic	1(0.4)
	Rhinorhea	11(4.7)
Skin, Subcutaneous	Pruritis	1(0.4)
	Rash	3(1.3)
Vascular Disorders	Dizziness	1(0.4)
	Flushing	1(0.4)
	Hot flush	1(0.4)

Source: S176.1.004 [PRACS Study M/ R06-1122, Table 10.3.1, page 645

Reviewer's Comment: These subjects received five times the testosterone dose of patients using 5 g of Testosterone 1.62%. Aside from the 3 patients in whom syncope was reported, the TEAEs are quite benign. The incidence of syncope was evaluated further in the pivotal study results. Subject 051-02 (receiving testosterone gel 1.62% 2.5g) in Protocol S176.3.104 experienced syncope during the pharmacokinetic sampling period on Day 14 and was discontinued. A total of 3 subjects receiving testosterone gel 1.62% (1-2.5g, 2-5.0 g) experienced syncope during the double blind period versus none for placebo. Dizziness occurred in 3 subjects receiving testosterone gel 1.62 %(1-2.5 g and 2-5.0 g) and in no placebo subjects. Syncope is not known to be an adverse reaction to testosterone. Additional discussion of syncope appears in Section 7.7.1.

7.4.6 Immunogenicity

For the assessment of immunogenicity potential, the Sponsor conducted a contact sensitization study, showing no evidence of sensitization. The review also used Table 3.1.1, Incidence of TEAE's Safety Sample, on page 1698 of the Clinical Study Report S176.3.104 for this issue.

Under the Primary MedDRA SOC General Disorders and Administrative Site Conditions, 1 testosterone gel 1.62% 1.25 g (N=17, 5.9%) subject reported application site hypersensitivity and 1 testosterone gel 1.62% 5.0 g (N=91, 1.1%) subject reported application site pruritis.

Under the Primary MedDRA SOC Immune System Disorders, 1 subject receiving testosterone gel 1.62% 3.75 g (N=66, 1.5%) reported allergy to an arthropod bite, and 3 subjects receiving testosterone gel 1.62% 5.0 g (N=91, 3.3%) reported seasonal allergy.

Under the Primary MedDRA SOC Respiratory, Thoracic, and Mediastinal Disorders, 1 subject receiving testosterone gel 1.62% 5 g (N=91, 1.1%) reported breathing abnormalities and 1 subject reported wheezing (N=91. 1.1). In addition, one subject each in the placebo group (N=40, 2.5%), testosterone gel 1.62% 1.25 g (n=17, 2.5%), and testosterone gel 1.62% 5 g (N=91, 1.1%) reported pharyngolaryngeal pain. One subject receiving testosterone gel 1.62% 2.5 g (N=60, 1.7%) reported throat irritation.

Under the Primary MedDRA SOC Skin and Subcutaneous Tissue Disorders, skin-related AEs reported in Study 104 are listed in the table below:

Table 46: Skin Adverse Events S173.3.104

Preferred Term	Placebo	Testosterone gel 1.62%			
Statistic n (%)	N=40	1.25 g N=40	2.5 g N=1.25g	3.75 g N=66	5.0 g N=91
Acne	0	1(5.9)	0	0	1 (1.1)
Heat Rash	0	0	0	0	1 (1.1)
Dermatitis	0	0	1 (1.7)	0	0
Dermatitis Contact	0	1 (5.9)	0	4 (6.1)	0
Skin Irritation	0	0	0	0	1 (1.1)
Drug Eruption	0	0	0	0	1 (1.1)
Erythema	0	0	1 (1.7)	0	1 (1.1)
Pruritis	0	0	0	0	1 (1.1)
Rash Papular	0	0	0	1 (1.5)	1 (1.1)

Source: Table 3.1.0, Clinical Study Report S176.3.104, Page 1693.

No subject discontinued from Study S176.3.104 for site reactions or dermatologic AEs.

The entire clinical study report was searched for the terms angioedema, anaphylaxis, urticaria, hives, generalized skin rash, pharyngeal edema and laryngeal edema with no reports found.

Reviewer's Comment: While there were application site reactions and dermatitis, there were no clinically or statistically significant differences in mean scores at any timepoint between testosterone gel 1.62% and placebo groups for the skin irritation assessment. There appears to be no evidence of major systemic immunologic or allergic phenomena secondary to testosterone gel 1.62% in Protocol S176.3.104.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No clinically significant trend attributing the frequency of adverse events to the testosterone gel 1.62% dose was found.

7.5.2 Time Dependency for Adverse Events

Table 47: Time Dependency Adverse Events S176.3.104

Assessment Statistic n (%)	Testosterone gel 1.62% Double-Blind Period N=234	Testosterone gel 1.62% Open-Label Period N=191
	Mean Exposure=151.9 Days	Mean Exposure 319.7 Days
Deaths	0	0
Serious Adverse Events	5 (2.1)	4 (2.1)
Discontinuations Due to TEAE	25 (10.7)	9 (4.7)
TEAEs	130 (55.6)	79 (41.4)
Application Site Hypersensitivity	1 (0.4)	1 (0.5)
PSA either > 4.0 and/or increase of >0.75 ng/	34 (14.9)	12 (6.3)
PSA Discontinuation	17 (7.3)	6 (3.1)
Hematocrit > 54%	5 (2.1)	4 (2.6)
Hematocrit Discontinuation	1 (0.4)	4 (2.1)

Sources: Clinical Study Report S176.3.104: Table 3.0.0 page 1691: Listing 18, Pages 2961-2994: S176.3.104 120 Day Safety Update Table 3.1.0 Pages 2293-2303: Table 29 of this NDA review.

Reviewer's Comment: There does not appear to be a time dependency noted for adverse events.

7.5.3 Drug-Demographic Interactions

Based on the low incidences of markedly abnormal clinical laboratory and vital signs values and the small number of subjects in the placebo group, no between-treatment comparisons can be made based on subgroup analysis for age (<45 years N=40; 45-54 years N=90; 55-64 years N=69; ≥ 65 years N=8) and race (white, non-white).

Safety analyses by extrinsic factors show that there were no clear patterns across the number of hours after dose application subjects washed their skin (two, six, or 10 hours Post dose), the presence or absence of moisturizer lotion or sunscreen, or across three difference administration site schedules. Secondary to the small sample sizes for some categories and the low incidence of markedly abnormal clinical laboratory and vital signs, Sponsor states no definitive conclusions can be drawn.

7.5.4 Drug-Disease Interactions

There were no clinically or statistically differences in least- squares (LS) mean change from Baseline at each timepoint between the testosterone gel 1.62% and placebo groups in the IPSS Total Score. The LS mean change from Baseline at Endpoint was 0.8 in the testosterone gel 1.62% and 0.3 in the placebo group.

Reviewer's Comment: Testosterone is known to increase the PSA in males. A concern is that this rise of PSA may indicate increase of prostate volume and lead to increasing voiding symptoms and urinary retention. Only a modest increase of the IPSS was noted in patients receiving testosterone gel 1.62%, and there was no reported urinary retention events in Study S176.3.104.

7.5.5 Drug-Drug Interactions

In Study S176.1.006, Testosterone gel (2.5 g dose: 40.5 mg testosterone) was applied once daily to the upper arms/shoulders for 7 days, either alone or 1 hour before application of 6.0 g of moisturizer lotion or 6.0 g of sunscreen. Testosterone pharmacokinetic parameters $AUC_{0-24,}$ Cav and C_{max} were calculated on Day 7 and compared between treatments. It was found that application of moisturizer lotion 1 hour after application of 2.5 g testosterone gel 1.62% once daily to the same skin site increased bioavailability of testosterone by 14% and 17% increase in AUC_{0-24} and C_{max}, respectively, compared to testosterone gel 1.62% alone. Application of sunscreen under similar circumstances had no effect on overall exposure (AUC_{0-24}) of testosterone, but increased C_{max} by 13% compared to testosterone gel 1.62% administered alone. Individual and mean concentrations of C_{av} and C_{max} values were within the eugonadal range (300-1000 ng/dL) for all three treatments.

No drug-drug interaction studies have been conducted for testosterone gel 1.62%. The following information is available from the approved AndroGel 1% label:

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

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

Oral Anticoagulants: Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

The Sponsor adds in their submission the following additional interactions that have been reported in the literature:

Bupropion: Use of systemic steroids concomitantly with bupropion has been reported to lower the seizure threshold. The prescribing information for Wellbutrin® and Zyban® recommends minimizing the potential for occurrence by not exceeding the prescribed dose of buproprion, increasing the dose gradually, and/or using divided doses when applicable.

Cyclosporine: Concomitant administration of cyclosporine and anabolic steroids may result in increased cyclosporine blood levels and toxicity. It is recommended that such combinations be avoided, or if concomitant administration is necessary, that circulating cyclosporine levels be monitored and cyclosporine dosage be adjusted as appropriate, and the patients be monitored for signs of increased cyclosporine toxicity (such as renal dysfunction or neurotoxicity).

Dehydroepiandrosterone (DHEA): Concomitant use of DHEA with testosterone is reported to result in an increased risk for androgenic and hepatic side-effects. The effect appears to be dose-dependent, and at doses commonly used by body builders (e.g. 1000 mg), androgenic effects are likely. It is recommended that concomitant use of DHEA be avoided.

Paclitaxel: Testosterone has been reported to inhibit the metabolism of paclitaxel (via inhibition of CYP2C8) to its primary metabolite 6α-hydroxypaclitaxel *in vitro*, and may also alter the pharmacokinetics of placlitaxel *in vivo.* The prescribing information for TAXOL® recommends that caution be exercised with the concomitant use of paclitaxel and CYP2C8 inhibitors such as testosterone. Patients should be monitored for increased adverse effects due to paclitaxel toxicity including bone marrow suppression, myalgia/arthralgia, nausea/vomiting, and mucositis. Dose adjustment of either medication may be required.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

At the current time, I am not aware of any evidence of the carcinogenicity of AndroGel® or testosterone gel 1.62%. There is also is no definitive evidence that testosterone replacement in general is causative of prostate cancer, although large studies in geriatric males at risk of prostate cancer have not been conducted .

As of 8 August 2007, a total of 22 cases of nonprostatic malignancies involving patients taking AndroGel® were identified in the Sponsor's database. There were 18 different types of malignancies and no one malignancy was reported more than twice. From 2004 to 2007, there was an increase in the number of malignancies in Solvay's database from zero cases in 2004 to three in 2005, five in 2006 and seven in 2007. All seven cases reported in 2007 were from different cancer sites and the patient either had a duration of testosterone therapy of less than one year, and previous history of cancer and tumors, and /reported risks factors for cancer. No specific trend of a specific cancer site was detected.

Of the 22 cases of nonprostatic malignancies, two were pituitary tumors, one was a meningioma in a formerly resected pituitary tumor site, two were breast cancer at 5 and 6 weeks of AndroGel® therapy and may represent the same case, two were recurrent testicular cancer and one was testicular seminoma.

7.6.2 Human Reproduction and Pregnancy Data

Testosterone gel 1.62% is not intended for use by, and should not be used by pregnant or lactating women. The clinical safety data is related only to the treatment of males with testosterone gel 1.62% and therefore, safety information is not available, nor applicable, for use in pregnancy and lactation. It is not known how much testosterone transfers into human milk. Exposure of the fetus to androgens may result in varying degrees of virilization.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of AndroGel 1.62% in males <18 years old has not been established. Improper use may result in premature closure of the epiphyses.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Sponsor in their submission references one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels up to 11,400 ng/dL and had a cerebrovascular accident (Investigator Brochure Testosterone gel 1.62%. Edition No. IB-17600, 30 October 2006). Treatment of overdosage would consist of discontinuation of testosterone gel 1.62% together with appropriate symptomatic and supportive

care. Date from two Phase I studies have shown that serum testosterone concentrations return to approximately Baseline levels by 48-72 hours after the last topical application of testosterone gel 1.62%.

Testosterone gel 1.62% contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act. Oral ingestion of testosterone gel 1.62% should not result in clinically significant serum testosterone concentrations due to excessive first-pass metabolism. Pump weight verification data in Study S176.3.104 did not appear to contain evidence of consistent drug overuse.

No information on testosterone withdrawal or rebound is available from the testosterone gel 1.62% development program or in the approved AndroGel 15 label.

7.7 Additional Submissions

7.7.1 Response to 74-Day Filing Letter Requests.

In the 74-Day Filing Letter for NDA 22-309, the Division asked for additional summary and analysis for six Clinical and Clinical Pharmacology review issues. The Sponsor responded to these requests in 15 July 2009 Response to Additional Questions Regarding Study S176.3.104. Each of the 6 requests (italics) and the Sponsor's response is discussed below:

1) Hypertension was reported as a clinical adverse event in 6 drug treated patients and no placebo patients in the double-blind period of Study S176.3.104. In one of these patients, worsening of hypertension may have been coincident with a rise in hematocrit. Provide an executive summary and analysis of hypertension as an adverse event (AE) and the relation of this AE to drug dose, systemic exposure, and duration of treatment. Include a discussion of potential worsening of pre-existing hypertension, and narratives for patients involved. Your analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

Discussion of Sponsor's Response: A total of 13 subjects experienced the adverse event of hypertension while enrolled in Study S176.3.104: 6 subjects in the double-blind period only (012-09, 033-01, 037-06, 044-03, 060-10, 060-19), 5 subjects in the open-label period only (007-21, 024-05, 059-03, 060-04, 060-16), and 2 subjects experienced events of hypertension which began in the double-blind period and continued into the open-label period (013-13, 017-30). Of the subjects who experienced the event of hypertension during the double-blind period, 2 subjects were not receiving the study drug at the time of the event (013-13, 060-19). These subjects were not analyzed further by the Sponsor.

Table 48: Hypertension S176.3.104 Double-Blind Period

Patient	Baseline Blood pressure medication	Baseline BP (mmHg)	T-Gel Dose	BP elevation (mmHg)/ [Day]	Resolution/ [Day and BP]	Actions Re Study Medication
012-09	Yes	140/84	2.5 g	160/100 [137]	182-140/96	None
033-01	No	150/87	2.5	150/87 [1]	42-150/74	None
037-06	Yes	152/80	5 g	160/90 [61]		
				210/126 [166]	140/86 [182]	Study Discontinuation
044-03	Yes	116/70	3.75 g	* [184]	122/78 [210]	None
060-10	No	116/78	3.75 g	* [22]	116/74 [42]	None
016-19	Yes	146/82	3.75	161/83 [159]	Not available [194]	None
013-13	Yes	142/90	2.5 g	158/98 [-3]	146/93 [368]	None
017-30	Yes	127/86	1.25 g	171/101 [117]	134/91 [270]	None

*Blood Pressure elevation occurred between study visits – data not available. Source: Subject narratives

Reviewer's Comment: In the double-blind period of S176.3.104, the incidence of hypertension was 6/234 or 2.6% versus 0/40 in the placebo group. In the open- label period, the incidence of hypertension was 5/191 or 2.6%. The proportion of hypertensive subjects roughly parallels the proportion of subjects in each dose group. There appears to be no correlation of these events with testosterone concentrations or other laboratory values. The majority of subjects with hypertension as an AE had pre-existing hypertension (7/11).

(b) (4)

2) Syncope was reported as a clinical adverse event in 3 drug treated patients and no placebo patients in the double-blind period of Study s176.3.104. Provide an executive summary and analysis of syncope as an adverse event. Discuss related adverse events, such as presyncope, and their relation to drug dose, systemic exposure, and the duration of treatment. Provide narratives for patients involved. Your analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

Discussion of Sponsor's Response: A total of 7 subjects experienced syncope and /or related events while enrolled in Study S176.3.104: 5 subjects (012-28, 043-18, 051-02, 052-01, 060-25) in the double-blind period and 2 subjects (033-01, 059-02) in the open-label period. In the double-blind period, these events included dizziness (3 subjects), syncope vasovagal (1 subject), presyncope (1 subject); while the open-label period included syncope (1 subject) and dizziness (1 subject).

Subject 021-28 experienced dizziness on 2 occasions during the double-blind period while taking testosterone gel 1.62% 2.5 g (Day 3) and 5 g (Day 177) of mild and moderate intensity respectively. The blood pressure on both occasions was not available.

Subject 043-18 has a history of hypertension and diabetic neuropathy. He experienced dizziness on 2 occasions while taking testosterone gel 1.62% 3.75 g (Day 3 and Day 45) of the double-blind period. On both occasions, the blood pressure for the event was not available. The study medication was discontinued on Day 57 as result of increased blood pressure.

> *Reviewer's Comment: This subject is not listed as having the AE of hypertension in Sponsor's response.*

Subject 043-02 had the adverse event of vasovagal syncope while taking testosterone gel 1.62% 2.5 g on Day 14 of the double-blind. The blood pressure at the time of the event was 115/76 mmHg. He had a 2 year medical history of syncope. The subject was discontinued due to the adverse event on Day 14.

Subject 052-01 experienced dizziness (light headedness) on Day 5 of the double-blind period while taking testosterone gel 1.62% 2.5g. The subject's blood pressure was unavailable at the time of the event. Study medication was discontinued on Day 9 due to the event.

Subject 060-25 experienced the adverse event of presyncope on Day 59 while taking placebo. He had a history of coronary artery disease and hypertension.

In the open-label period, subject 033-01 experienced the AE of syncope while having the AE of atrial fibrillation and subject 058-02 experienced dizziness while having the AE of lower GI bleeding.

Reviewer's Comment: The events of syncope/dizziness do not correlate with dose. 3/5 (60%) of the events within the first 7 days of testosterone gel 1.62% use. Only 2 of the episodes had serum testosterone concentrations available prior to the diagnosis of dizziness in the double-blind period and both were in the eugonadal range. There we no markedly abnormal laboratory values reported for any of the subjects coincident with syncope or related events.

This analysis has generated no new safety signal and dizziness and syncope are listed in AndroGel 1.62% proposed label in ***6.1 Clinical Trial Experience*** *as adverse events that led to discontinuation. I believe this labeling is appropriate.*

3) Hematocrit: Five patients in the double-blind portion of Study S 176.3.104 were reported to have an increase of hematocrit to greater than 54%. Provide an executive summary and analysis of these events in the double-blind and open-label periods of Study S176.3.104, and their relation to drug dose, systemic exposure, and duration of treatment. Provide narratives for the patients involved. Your analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

Discussion of Sponsor's Response: A total of 7 (13 incidents) subjects had an increase in hematocrit to greater than 54% (defined as markedly abnormal) while enrolled in study S176.3.104: 2 subjects (018-05, 057-45) in the double-blind period only, 2 subjects (036-02, 047-05) in the open-label period only, and 3 subjects (016-02, 016-03, 018-06) were reported to have markedly abnormal increases in hematocrit during both the double-blind and open-label periods of the study.

Two subjects (003-45, 044-07) had hematocrit levels of 54% during the double-blind period which were not noted as adverse events. Both subjects were receiving testosterone gel 1.62% 3.75 g daily at the time of the events. An additional subject experienced an adverse event of polycythemia during the open-label period of the study; however the subject's hematocrit value was not above the normal range at the time of the event or at any time during the study. These three subjects were not considered in further analysis by the Sponsor.

In the double-blind period of Study 176.3.104, the incidence of the adverse event of hematocrit increased was 2/234 (0.9%) in the testosterone gel 1.62% group, while no subject in the placebo group (0/40) reported this event. In the open-label period, the incidence of hematocrit increased was 4/191 (2.1%). All subjects who had markedly abnormal high hematocrit values were discontinued from the study. Of the subjects for whom hematocrit was reported as an adverse event 4/6 (67%) had a markedly abnormal high hematocrit on another day that was not reported as an adverse event and 1 subject had 2 additional markedly high hematocrit values that were not reported as adverse events. In addition, there was 1 subject who had a single markedly abnormal high hematocrit value which was not reported as an adverse event, likely due to the fact that the value was reported on the last day of the double-blind period.

None of the events of hematocrit increased met the regulatory criteria for SAEs.

Reviewer's Comment: Considering the proportion of subjects on each dose of testosterone gel 1.62% after titration in the double-blind period and the overall frequency of increased hematocrit in the open-label period, there is insufficient data to show an association of this AE and testosterone gel 1.62% dose level.

In Study S176.3.104, all incidents of markedly abnormal high hematocrit were reported in subjects who had been receiving study medication for 12 or more weeks at the time when the event occurred, and the majority of study discontinuations due to increased hematocrit occurred in the open-label period of the study.

Sponsor has observed that a moderate rise in hematocrit (3-5%) is expected with the attainment of physiologic testosterone concentrations. In Study S176.3.104, an increase in mean hematocrit was observed overall for the testosterone gel 1.62% groups compared with placebo (Endpoint: 0.026 V/V versus -0.003 v/v). Five of the 7 subjects who had markedly abnormal high hematocrit values had C_{max} serum testosterone concentrations noted during the double-blind portion of the study that were greater than 1000 ng/dL; however, no clinically significant hematocrit increases were observed for any of the 10 subjects in Study S176.3.104 with total serum concentrations >2500 ng/dL. Not all subjects with a C_{max} >1000 ng/dL experienced an increase in hematocrit.

There were no thromboembolic events noted in this group of patients

Table 49: Summary for Subjects with Markedly Abnormal High Hematocrit Values (>54%) During Study S176.3.104 (Safety Sample)

Subject Number	Study Day	Hemoglobin (g/L)	Hematocrit (V/V)	Testosterone Cmax (ng/dL)
016-02	183	176	0.55	1810
	254	185	0.55	
016-03	178	175	0.55	1060
	206	181	0.55	
018-05	86	181	0.55	883
	99	178	0.55	
	107	183	0.58	
018-06	182	189*	0.56	1670
	194	185	0.55	
057-45+	198	182	0.55	1340
036-02	361	190*	0.55	790
047-05+	265	191	0.57	1140
	288	190	0.55	

Source: Table 6, Page 80, Executive Summaries in Response to 74-Day Letter for AndroGel 1.62% Submission + = Reside at altitude >4900 feet *=hemoglobin values reported as AE

Reviewer's Comment: No new safety signal or change in pattern was detected by the analysis of increased hematocrit coincident with testosterone gel therapy.

(b) (4)

*In **6.1 Clinical Trial Experience**, hematocrit increased is included as an event that led to discontinuation in clinical trials. The proposed labeling is appropriate.*

4) PSA: Twenty patients (9.8%0 were observed to have "increased PSA"' defined as PSA >4 ng/dL or an increase from baseline in serum PSA of > 0.75 ng/dL during the double-blind period of Study S176.3.104. Provide an executive summary and analysis of these "increased PSA's in the double-blind and open-label periods of Study S 176.3.104. Provide a discussion of this event in relation to drug dose, systemic exposure, and duration of treatment. Provide narratives for patients involved. Include information related to performance of prostate biopsies, biopsy results, and any changes in lower urinary tract symptoms in these patients. Your analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

Discussion of Sponsor's Response: In Study S176.3.104, there were pre-specified criteria for discontinuation of subjects reporting abnormal changes in PSA values and/or PSA values: change form Baseline>0.75 ng/mL (velocity) and/or >4.0 ng/mL. For any subject during the study with an increase in PSA >0.75 ng/mL from Baseline, a repeat test was performed. If the average of the two measurements confirmed a change from Baseline <0.75 ng/mL, the subject was allowed to continue in the study. If the change was confirmed to be >0.75 ng/mL, the subject was discontinued and early termination assessments were completed. Men treated with 5 α reductase inhibitors had PSA change form Baseline thresholds half the above values. If a subject had an absolute PSA value >4.0 ng/mL, the subject was allowed to continue in the study if the average of the two measurements was >4.0 ng/mL, the subject had to be discontinued.

Table 7 on page 111 of Executive Summaries in Response to 74-Day Letter for AndroGel 1.62% Submission list 48 patients who experienced the adverse event of PSA increased.

A total of 9 subjects reported PSA value >4.0 ng/mL while enrolled in Study S176.3.104: 7 subjects were in the double-blind period and 2 were in the open label period. Of the 9 subjects with PSA values >4.0 ng/mL reported, 5 subjects were discontinued as result of the incident: 2 subjects because they met the > 4.0 ng/mL criteria for discontinuation and the remaining 3 subjects because they met the velocity criteria for discontinuation or because the value was reported as an adverse event. Of the remaining 4 subjects, 2 subjects were discontinued on the basis of velocity criteria, 1 subject completed the study before a repeat PSA value was available and 1 subject withdrew consent and terminated the study before a repeat PSA test could be completed.

All 7 subjects who reported PSA values >4.0 ng/mL during the double-blind period had been receiving study medication for 12 weeks or more the time the value was reported. Both subjects who reported PSA values >4.0 ng/mL during the open-label period had been receiving the study medication for more than 43 weeks. The testosterone gel 1.62% doses at the time of the event were: 1.25 g: 0/9; 2.5 g: 3/9 (33%); 3.75 g: 3/9 (33%); 5 g: 3/9 933%). 3/9 had C_{max} concentrations that were greater than 1000ng/dL and one had a Cmax serum concentration of >1500 ng/dL. No age or race related disposition was noted.

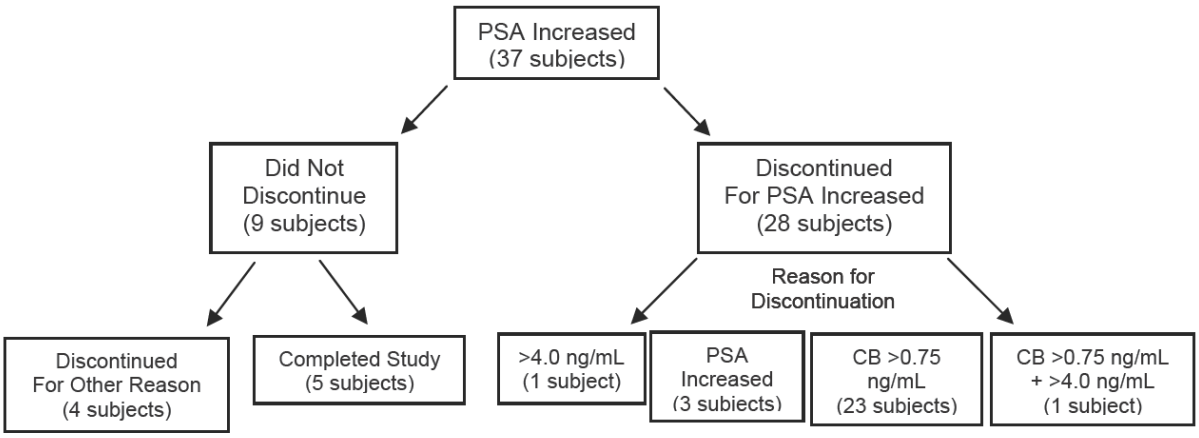
A total of 45 subjects reported PSA values with a change from Baseline >0.75 ng/mL while enrolled in Study S176.3.104: 29 subjects in the double-blind period (29/234, 12.4 %; 0/40 placebo subjects) only, 12 subjects in the open-label period (13/191, 6.8%) only and 4 subjects who had increased PSA velocity in both study phases. Of these 45 subjects, there was a total of

73 incidents of PSA change from Baseline >0.75 ng/mL. Of the 45 subject who reported PSA values with a change from Baseline >0.75 ng/mL, 27 subjects were discontinued as a result to an incident of change from Baseline >0.75 ng/mL; 23 subjects because they met the >4.0 ng/mL criteria for discontinuation or because the value was reported as an adverse event. Two subjects completed the study before they could be discontinued for meeting the change from Baseline >0.75 ng/mL, 2 subjects completed the study before a repeat PSA could be drawn, and 6 subjects discontinued for another reason. In 18 subjects, a repeat PSA brought the average PSA results within normal limits.

One subject (012-08: see discontinuation narrative) reported a PSA value with a change from Baseline >0.75 ng/mL that was not reported as an adverse event. He was found to have a prostate nodule that, after referral for biopsy, resulted in the diagnosis of prostate neoplasm. Prostate cancer was found in areas of the prostate contra-lateral to the nodule. This subject on Day 182 had a serum testosterone concentration of 4430 ng/dL 2 hours after a 5.0 g dose of testosterone gel 1.62%. His PSA at Baseline was 1.5 ng/mL and at Day 182 was 1.8 ng/ml. On Day 279, the day the nodule was palpated, the PSA was 2.3 ng/mL.

Subjects who reported PSA values with a change from Baseline >0.75 ng/mL during either period of the study were receiving the following doses of testosterone gel 1.62% at the time of the event: 1.2 g: 3/73 incidents (4%); 2.5 g: 14/73 (19%); 3.75 g: 23/73 (31%); 5 g: 31/73 (42%); 2 incidents were reported while subjects were not receiving study medication. In the double-blind period, subjects had been receiving the study drug for 11 weeks when the abnormal value was reported as opposed to 36 weeks in the open-label period. 40% of these subjects (18/45) in the double-blind period had Cmax serum testosterone concentrations that exceeded 1000 ng/dL. 8 subjects reported C_{max} serum testosterone concentrations >1500 ng/dL and <2500 ng/dL. 3 subjects reported C_{max} concentrations > than 2500 ng/dL. Subject 012-08 has been discussed. Subject 039-09 was categorized as a blood sample contamination or artifact result. Subject 058-06 was one of 5 subjects evaluated further with respect to testosterone concentration > 2500 ng/dL. None of these subjects showed testosterone levels consistently elevated in the supraphysiologic range.

Figure 1: S176.3.104 Double-Blind Disposition of Subjects Who Experienced Adverse Events of PSA Increased



Source: Copy Figure 1, Executive Summaries in Response to 74-Day Letter for AndroGel 1.62% Submission

There appeared to be no predilection to the adverse event of increased PSA velocity from the standpoint of age or race. Overall, there were 7 subjects who experienced the adverse event of PSA increased or increased PSA velocity that had either mild or moderate symptoms of BPH as assessed by the IPSS prior to study entry. 5 of these subjects increased to moderate and 2 increased to severe with regard to prostate symptoms. Two regressed to their original IPPS score with continued follow-up (1 severe to moderate and 1 moderate to mild). The Sponsor could not discern any clear trend in prostate symptoms in patients who experienced events of PSA increased or reported PSA values with a change from Baseline >0.75 ng/mL during the study.

In study S176.3.104, the mean change from Baseline at Endpoint was 0.14 ng/mL in the testosterone gel 1.62% group and the placebo group was -0.12 ng/mL.

> *Reviewer's Comment: The Sponsor states that the selection of a change in threshold of 0.75 ng/mL from Baseline for dropping subjects appears, in retrospect, to be an overly conservative limit given that all men started with PSAs <2.5ng/mL, and there is a normal variation in PSA laboratory values. I agree that the velocity threshold was conservative in an attempt to assure subject safety. The value of change in PSA evaluations for a time period < year is not clear. 81 % (38/47) of the subjects for whom elevations met the criteria of >4.0 ng/mL, change from Baseline >0.75 ng/mL, or were reported as an adverse event reported a decrease in PSA after the initial elevated value, and 16 subjects (34%) had final PSA values within 10% of the subject's baseline value.*
>
> *The Sponsor has also surveyed the literature in an attempt to put these PSA findings into context. They note that the incidence of prostate cancer in the 750 patients studied in the articles footnoted on page 109 of Executive Summaries in Response to 74-Day Letter for*

AndroGel 1.62% was 7/750. The one prostate cancer diagnosed in this protocol was incidentally discovered in my opinion. The palpated nodule within the prostate was at site contralateral from the cancer location. The rectal finding was the indication for the biopsy performance. Only 1% of the positive cores (2) was positive for prostate carcinoma. While I cannot make any statement about causality, the occurrence of this cancer should be mentioned in the product label.

(b) (4)

The occurrence of prostate cancer in a study patient should be mentioned in labeling. The changes in serum PSA should be mentioned in labeling.

5) In two patients with serum testosterone level >2500 ng/dL, we note that the product was being used at more than the recommended dose, and in one patient with testosterone > 2500 ng/dL, the product was being used more frequently than advised. Provide an executive summary and analysis of all situations in the clinical studies where the recommended dose or frequency of dosing was exceeded. Consider proposing a strategy to limit these occurrences, which might include specific new instructions to patients.

Discussion of Sponsor's Response: Three of the ten patients with reported testosterone concentrations in excess of 2500 ng/dL, in the Sponsor's analysis, used either more than the recommended dose (067-001, 015-005) or shorter dosing interval (049-008) which were contributory factors for the elevated testosterone concentration. The Sponsor also believes that abnormal hydration/permeability of the skin due to swimming (049-008) may have been contributory.

The Sponsor has collected compliance data throughout S176.3.104. In the active treatment group 84% of subjects were compliant (80-120%). 4% exhibited compliance > 120%. 12% exhibited compliance <80%. The Sponsor also performed statistical analysis by compliance category (under <80%, compliant 80-120%, over >1205) and C_{max} and C_{av}. Using the Cochran-Mantel-Haenszel Test there was no statistically significant correlation between compliance category and testosterone concentrations.

Reviewer's Comment: Chemistry has not voiced concerns regarding the accuracy of pump volume delivery.

The Sponsor further states that they have submitted revised labeling and a new Medication Guide, for their approved product, AndroGel 1% , that emphasize instructions for proper dosing and safe use. In particular, the Medication Guide includes the explicit instructions not to double dose the day following a missed dose and to skip the day's dose entirely if less than 12 hours remain before the next scheduled morning dose. This labeling and Medication Guide will also be implemented for AndroGel 1.62%.

*Reviewer's Comment: In the Med Guide section "**How to use the AndroGel 1.62% Pump**" a statement should be added "if the pump was not fully depressed during a single depression, do not add an additional depression."*

6) *It is not clear whether clinical adverse events correlate with peak testosterone levels in Study S176.3.104. Provide an executive summary and analysis comparing clinical adverse events and systemic exposure. Include all adverse events, but pay special attention to hypertension, increased serum PSA and hemoglobin/hematocrit values.*

Discussion of Sponsor's Response: The Sponsor performed a thorough analysis of adverse events by peak testosterone levels. The Table below summarizes the results. While there is a possible trend of increased AEs in subjects with higher peak testosterone concentrations, in the majority of patients the serum testosterone concentrations were in the eugonadal range prior to the AE. It was not determined if subjects with peak testosterone concentrations above 1500 ng/dL had a greater overall exposure to testosterone throughout the study than patients who did not.

Reviewer's Comment: I agree with the Sponsor's conclusion that there was no pattern of increasing incidence of single preferred item with higher testosterone concentration category in either the double-blind or open-label period of Study S176.3.104.

Table 50: TEAEs by Highest Measured Testosterone Concentration Category for Events of Special Interest and Events Occurring in >1 Concentration in > 3 Subjects or >5% of Subjects in Any Category in Either Period of S176.3.104

	Double- Blind Period				Open-Label Period*		
Testosterone Range	≤1500	1501-<1800	1800--<2500	>2500	≤1500	1501-<1800	1800--<2500
At least 1 AE	96/183 52%	9/16 56.3%	17/25 68.0%	8/10 80%	69/158 43.7%	2/9 22.2%	6/12 50%
Hypertension	5 (2.7%)	1 (6.3%)			3 (1.9%)	1 (11.9%)	1 (8.3%)
PSA Increased	19 (10.4%)		3 (12.8%)	1 (10.0%)	9 (5.7%)		
Hematocrit Increased	1 (0.5%)	1 (6.3%)			2 (1.3%)		
Hemoglobin Increased		1 (6.3%)			1 (0.6%)		
Double-Blind							
Myalgia	3 (1.6%)		2 (8.0%)				
Insomnia	3 (1.6%)	2 (12.5%)	2 (8.0%)				
Back Pain	4 (2.2%)	2 (12.5%)	1 (4.0%)				
Headache	5 (2.7%)		2 (8.0%)				
Open-Label							
Influenza					2 (1.3%)		1 (8.3%)
Pneumonia					1 (0.6%)		1 (8.3%)
Nasopharyngitis	4 (2.2%)		1 (4.0%)		4 (2.5%)	1 (11.1%)	
Hypertriglyceridemia		1(6.3%)			1 (0.6%)	1 (11.1%)	

* No subject had a testosterone concentration > 2500 ng/dL in the Open-Label period.
Sources: Table 9, page 245 and Table 10 page 248 and pages 244-251 of Executive Summaries in Response to 74-Day Letter for AndroGel 1.62% Submission

7.7.2 Submission to Facilitate Review of Testosterone Transfer

On September 2, 2009, Solvay Pharmaceuticals Submitted Amendment 0009 to this NDA. This was based on a concern of secondary exposure of children due to drug transfer for their approved product AndroGel 1%. In recent discussions with the Agency, the risk of transfer has been deemed the most significant review issue for this NDA according to the Sponsor. This submission includes:

- Executive Summary
- A Cross Study Comparison of Transfer of Testosterone from Three Testosterone Gel Formulations
- Tracked and accepted changes of AndroGel 1.62% Revised Full Prescribing Information
    - Integrated Summary Tables to support revisions to Adverse Table 2
- AndroGel 1.62% Revised Full Prescribing Information in Structured Product Label (SPL) format.
- Proposed Medication Guide
- Proposed Rems and REMS supporting document
- Carton and pump label artwork.

In the Cross Study Comparison of Transfer of Testosterone from Three Testosterone Gel Formulations, the Sponsor acknowledges that there may be limitations to cross study comparisons due to differences in study design, bioanalytical assay methodology, and methods of data analysis.

In this comparison, AndroGel 1%, AndroGel 1.62% and Testim 1% are compared. Only publicly available data for Testim1% is provided. This comparison provides no new data. Five studies are compared.

Table 55: List of Studies Referred to in Summary Document

Study	Product	Reference
S176.1.003	Testosterone gel 1.62%	CSR S176.1.003; NDA 22-309
S176.1.008	Testosterone gel 1.62%	CSR S 176.1.008; NDA 22-309
UMD-98-37	AndroGel 1%	UMD-99-037R; NDA 21-454
AUX-TG-206	Testim 1%	SBA-Testim 1% (21-454)
AUX-TG-209	Testim 1%	SBA-Testim 1% (21-454)

SBA = Summary Basis of Approval Source: Table 1 page 4 of Sponsor's submission

In the Sponsor's analysis the impact of bioanalytical differences is felt to be low. The Sponsor believes that skin contact techniques used in the transfer studies were similar. The time points for PK determinations were different.

In brief, the Sponsor believes that the results of cross-study, cross-application comparisons between these 3 products with respect to mean and percent change from baseline after a single, direct exposure of female partners to the male site at 1-2 hours after dose administration favors AndroGel 1.62% and AndroGel 1% over Testim.

The Sponsor further compared the mean and percent change from baseline after once-daily, direct exposure of female partners to the male application site for seven consecutive days at contact times between two and 12 hours after application for AndroGel 1.62% and AndroGel 1% only. The Sponsor believes that AndroGel 1.62% had less transfer than AndroGel 1%.

> *Reviewers Comment: Cross-application and cross-study comparison between these three products is exploratory and fraught with potential bias that can lead to erroneous conclusions. Further, the Sponsor has access to the AndroGel 1% information (as they are the Sponsor), but only to the publicly available information for Testim. These exploratory comparisons of limited information do not provide the information needed to maximize the safe use of testosterone gel 1.62% which is my main concern.*

The Sponsor provided analyses of transfer studies using AndroGel 1% and Testim, two products that are already approved. The Testim data they used come from the the Testim label. The Sponsor has no access to data or analyses submitted to the Testim NDA and according to the reviews posted on the Drugs at FDA website and the Testim label, these additional analyses showed that *"When males wore a long-sleeved T-shirt and rubbing was started at 1 and 4 hours after application, the transfer of testosterone from male to female partners was prevented"* (as taken from Dr. Chatterjee's Clinical Pharmacology review which is posted on the Drugs at FDA website).

Herein, the Sponsor's exploratory analyses are summarized for completeness sake, but the reporting of these analyses should not be taken by the reader as agreement with the Sponsor's conclusions. In fact, the comparisons should be viewed with great caution, as the studies were conducted with different procedures, different patients, etc, and the Sponsor could not take into account all available Testim data, due to the proprietary nature of that data. There are no head-to-head studies.

The Sponsor analyzed studies utilizing a clothing barrier with female contact times between one and 12 hours after male testosterone gel application. In these analyses, the Sponsor believes that testosterone gel 1.62% showed less transfer potential than either AndroGel 1% or Testim 1%. In these studies Testim 1% was applied to the upper arms and shoulders while testosterone gel 1.62% was applied to the abdomen and AndroGel 1% was applied to both the abdomen and upper arms and shoulder sites.

The reviewer makes the observation, however, that the mean percent change from baseline after once-daily direct exposure of female partners to the male application site at two hours after application for seven consecutive days using a clothing barrier appears higher for testosterone gel 1.62% than for AndroGel 1% (5 g of the 1.62% strength compared to 10 g for the 1% strength). For this exploratory comparison, the mean changes from baseline for C_{max} were 25

and 7 ng/dL, for AndroGel 1.62% and AndroGel 1%, respectively, and for AUC_{0-24} [ng*h/dL] were 247 and 102, respectively.

> *Reviewer's Comment: In the section Potential for Testosterone Transfer in the publicly available* **Clinical Pharmacology** review of Testim**,** *in commenting upon Trial AUX-TG-209, page 11, there is the statement "When males wore a long-sleeved T-shirt and rubbing was started at 1 and 4 hours after application, the transfer of testosterone from male to female partners was prevented." At issue is not this comparison but rather how to minimize transfer of testosterone gel 1.62% either with a change in application sites of the 5 g dose or different type of clothing barriers. Based on the difference between the 2.5 and 5 g T-shirt studies with testosterone gel 1.62% , I am unable to propose adequate labeling that would allow feasible precautions and acceptable safety with a T-shirt barrier. Additional studies, in my opinion, need to be done. These could include the application of the 3.75 and 5gm dose of testosterone gel 1.62% to multiple sites (e.g. both the abdomen and arm/shoulder sites), different types of clothing, or different types of clothing materials.*

The Sponsor next analyzes the effect of application site skin washing on male to female testosterone transfer for AndroGel 1.62%. This discussion also includes an exploratory comparison between products.

The Sponsor notes that skin washing appears to prevent the risk of transfer in all studies for all products in which this was studies, but they point out that male-female skin contact occurred in Protocol S176.1.008 (testosterone gel 1.62% 5 g) at 2 hours after skin application and in Protocol AUX-TG-209 (for Testim 1% 10 g) at 4 hours post drug skin application. The Sponsor notes that in the AndroGel 1.62% washing study, male subjects washed the application site before drug application and female subjects washed the sites of contact with the male application site after contact had occurred. The Sponsor states that similar physical contact techniques were used in all studies. The Sponsor's comparisons showed that the percent increase in mean testosterone AUC_{0-24} from baseline following application and washing of testosterone gel 1.62% prior to direct skin-to-skin contact resulted in 9% increase in AUC_{0-24} from baseline, indicating that transfer of testosterone gel 1.62% is largely prevented by washing of the site of application prior to direct contact. C_{max} percent change from baseline was 14%. The mean change from baseline AUC_{0-24} percent change was 9%. The reviewer points out that there were 6 female subjects in this study in whom testosterone concentration increased from baseline, with two of those subjects (27405 and 27411) showing slightly greater increase from baseline compared to the other 4 subjects (27399, 27402, 27404, 27417). The minor increase in these 6 subjects may indicate that the protective effect of washing was not uniform throughout the patient population, or may be related to variability of serum T in normal women, including cyclic variation in pre-menopausal women. This variability is reflected in the table below, which shows slightly differing results for two of the six treatment arms of Protocol S178.1.008 (C and F), in which 5 g of testosterone gel 1.62% was applied to the male's abdomen followed by skin-to-skin contact 2 hours later in both arms (C and F).

Table 51: S176.1.008 Direct Contact Male to Female Skin Transfer Treatments C and F

Treat-ment	Nominal Time (h)									
	0	2	4	6	8	10	12	16	24	48
C	23.1	31.1	26.3	28.1	26.2	26.3	29.1	22.7	21.8	21.6
Baseline	14.9	15.2	15.9	15.4	15.8	15.0	16.4	15.5	20.4	
F	32.6	36.1	42.1	37.8	31.8	43.7	41.2	44.0	36.5	32.7
Baseline	13.3	13.7	15.0	14.0	16.0	15.2	14.6	14.4	39.1	

Source: Excerpted from Table 49 of this review.

Reviewer's Comment: Despite the variability in normal serum T concentrations in women, and the apparent variability in the amount of skin transfer of testosterone using testosterone gel 1.62%, skin washing prior to skin-to-skin contact largely and acceptably reduces the risk of skin transfer of testosterone using testosterone gel 1.62%.

In comparison, the Sponsor believes that serum T increased substantially in women studied in the Testim program, wherein male to female direct skin contact occurred at 4 hours after male application of Testim 1%

Reviewer's Comment: From this exploratory cross-study comparison, the Sponsor believes that there is less transfer after skin washing with testosterone gel 1.62% than there is with Testim 1%. The reviewer cannot draw this conclusion from the Sponsor's exploratory assessment. There appears to be some variability in efficacy of skin washing regarding skin transfer even within couples in the AndroGel 1.62% study. There also appears to be group to group variability with regard to skin transfer. It is possible that differences in washing technique, or in contact technique, or in some latent variable, could account for cross-study differences.

Finally, the Sponsor does acknowledge the Division's concern about the difference in transfer with a T-shirt barrier between the 2.5 and 5 g testosterone gel 1.62% doses. The Sponsor states that it is unclear why transfer of testosterone occurred after the administration of 5 g dose of testosterone gel 1.62%, but states this may be due in part to the increased amount of testosterone applied to a single location.

Reviewer's Overall Comments: Submission to Facilitate Review of Testosterone Transfer

The Sponsor's believes that the risk of transfer for testosterone gel 1.62% is less than for Testim 1%. However, the comparisons are based on only publicly available data, and compare results across studies and across applications. The studies themselves varied in techniques both known and unknown. The Sponsor's contentions about superiority in this regard are of interest, but do not affect the Clinical decision re: transfer prevention for

AndroGel 1.62%. The information submitted does not allow labeling that will permit the maximum safe use to testosterone gel 1.62% with respect the issue of issue of transfer of testosterone by direct skin contact from male to female and by inference from a male testosterone gel 1.62% user to children.

Of most importance:

- *With respect to T-shirt barrier, the dose discrepancy between the 2.5 mg and 5 mg studies poses significant barriers to adequate labeling. Additional studies with site application site variation and other clothing barriers are necessary.*
- *In the absence of a T-shirt barrier providing adequate mitigation of the transfer risk, relying heavily on skin washing prior to physical contact with others (even clothed skin contact) is impractical and not feasible..*

Also, in designing future transfer studies, investigators should consider the following:

- *The previous studies do not control for cyclical female testosterone variation.*
- *There appears to be variability of male to female testosterone transfer even within the same study, with numbers of patients too small in the previous protocols to adequately define or control for this variability.*

In the absence of adequate information to permit appropriate labeling to maximize the safety of testosterone gel 1.62% with respect to skin transfer, it is premature to comment upon:

- *Tracked and accepted changes of AndroGel 1.62% Revised Full Prescribing Information*
  - *Integrated Summary Tables to support revisions to Adverse Table 2*
- *AndroGel 1.62% Revised Full Prescribing Information in Structured Product Label (SPL) format.*
- *Proposed Medication Guide*
- *Proposed REMS and REMS supporting document*

7.7.3 Submission in Response to August 28, 2009, NDA Information Request/Advice

A request for information was sent to Sponsor August 28, 2009. In this request the Division's concerns regarding the risk of transfer and the utility of a T-shirt barrier and application site washing to prevent such transfer for AndroGel 1.62% were conveyed to the Sponsor, with several questions, and requests for additional information.

In an attempt to better understand and review the transfer studies, information was requested and the Sponsor provided responses. These requests and reponses are discussed individually herein:
:

- The female subjects' baseline testosterone concentrations were established seven days prior to testosterone gel 1.62% dosing in male partners. Can the baseline values vary over time by subject?

Discussion of Sponsor's Response: The Sponsor observed that endogenous testosterone production in women is produced by both adrenal and ovarian sources and can vary widely due to both circadian and menstrual cycles. The Sponsor noted that blood samples were obtained in the AndroGel 1.62% transfer studies at the same timepoints at baseline (Day-1) as they were on days of evaluation (Day 1 and Day 7) to minimize the effects of diurnal variation.

- In Study S176.1.1008, Group I, Treatments A and B, which utilized 2.5 g of testosterone gel 1.62% (abdominal application) with abdomen to abdomen skin contact occurring on Day 1 at 2 hours post dose, it appears that a T-shirt largely prevented female exposure. However, the Division had concerns about two Group B (testosterone gel 1.62%, 2.5 g and T-shirt barrier) female subjects in that study (#27403 and #27419); there were still baseline-adjusted testosterone increases of 16.9 and 13.3 ng/dL at the maximum, respectively.

Discussion of Sponsor's Response: The Sponsor pointed out that female subjects in this study had wide variation of testosterone concentrations including negative values at 24 and 48 hours.

> *Reviewer's comment: In both of the subjects, the baseline testosterone concentrations were obtained 8 days prior to the performance of the T-shirt barrier study. In patient 27403, the last menstrual period was 29 November 2007 and the protocol exposure to testosterone/T -shirt barrier occurred 12 December 2007 which assuming a 28 day menstrual cycle would place her in the highest cyclical testosterone concentration. In patient 27419, the last menstrual period was 4 December 2007, the same day as her last menses which is the lowest cyclical level of testosterone in the female. Eight days later, she underwent protocol exposure to testosterone/T -shirt barrier. The testosterone increases of C_{av} and the AUC-24 over baseline in the 8 subjects in Group B of Study S176.1.1008 were 1.0 ng/dL and -23 ng·h/dL respectively. Some of the variation in the two subjects could be attributed to cyclic variation. The reviewer inteprets the results of this investigation to show that a T-shirt largely blocks the transfer of 2.5 testosterone gel 1.62%.*

- The Division expressed concern that in Study 003, the T-shirt did not appear to fully block testosterone transfer.

Discussion of Sponsor's response: With respect to S176.1.003 (Treatment B; 5 g dose) the Sponsor states "*It is unclear why transfer of testosterone occurred after administration of a 5.0 g (81 mg testosterone) dose of testosterone gel 1.62% with a t-shirt barrier. This may be due, in part, to the increased amount of testosterone applied to a single location (i.e. 40.5 and 81 mg of testosterone applied to the abdomen with the 2.5 g and 5.0g doses of the testosterone gel 1.62% respectively).*" The Sponsor points out that in the development of AndroGel 1% that spreading a large 10 g (100 mg) dose of testosterone on both right and left arm/shoulders and abdomen lowered the amount of transfer. "*Therefore, it is possible that application of gel over four sites and covered with a t-shirt may minimize the risk of transfer.*"

Reviewer's Comment: How to mitigate or lower the transfer potential of the 5 g dose of testosterone gel 1.62% 5 g to acceptable levels remains an unresolved issue. The concept of spreading the dose out onto 4 sites may prove effective, but requires formal testing. If that were to be effective, then it would be necessary to show comparable T exposure in men who apply T to all 4 application sites, compared to men using the rotating regimen used in Phase 3.

- Comment on the differences between Studies 003 and 008 that may have lead to differences in the transfer study results. Is transfer risk greater at the higher dose?

Discussion of Sponsor's Response: Reader is referred to the above discussion

- Do you consider the transfer studies as a reasonable test of transfer risk under real-life conditions, or do you consider the conditions of the transfer study unrealistic?

Discussion of Sponsor's response: The Sponsor states that the conditions in Studies S176.1.003 and S176.1.008 "*represent the most extreme contact conditions*." They point out "*The potential for testosterone transfer after application in the morning hours followed by contact with the use of a T-shirt barrier at any time after 2 hours of application has not been evaluated. It is possible that transfer through a T-shirt barrier lessens with increased time since application*."

The Sponsor further states, "*A common theme from post-marketing cases of secondary exposure is that improper handling of the product and failure to adhere to labeled precautions intended to minimize contact between dosed and non-dosed individuals increased the risk of transfer (FDA PAC Briefing Book)*."

Reviewer's Comment: Transfer potential at different times after application and application of larger doses of testosterone gel 1.62% (3.75gm and 5gm) to multiple application sites are mentioned in the Sponsor's response and could be evaluated in additional transfer studies. The idea of spreading the large dose out onto more application sites appears promising.

- Comment upon the potential clinical significance of the transfer study results to a child. In responding, consider average and worst case scenarios based upon the transfer study results.

Discussion of Sponsor's response: The Sponsor calculated the projected pediatric exposure to testosterone based on the worst case of female exposure in Study S176.1.003. Subjects 26401 and 26404 were used. Skin permeability and pediatric size and weights were used to project a 4.5 times increase of comparable pediatric exposure. This translates into the following projected (roughly estimated) exposures:

Table 52:S176.1.003 (5 g daily dose; T-shirt arm) Projected Pediatric Testosterone Exposure (Worst Case Scenario)

Day 1	Observed Values From Study	Hour	Estimated Exposure
Subject	Baseline-adjusted increase (Cmax/Cav)		Adjusted value (Cmax/Cav)
26401	54.8ng/dL/31.3ng/dL	10	247ng/dL/140mg/dL
26404	30.4ng/dL/ND	6	137ng/dL/ND
Day 7			
Subject			
26401	116ng/dL/65.3ng/dL	6	522ng/dL/293.9ng/dL
26404	54.3ng/dL/ND	4	244 ng/dL/ND

Source Page 8 of submission ND=not done

Sponsor states "*The theoretical increases from subjects 26401 and 26404 raised testosterone levels above the normal range for adult and Tanner Stages III and IV women (>75 ng/dL). It is important to note that subjects 26401 and 26404 represent maximum baseline-adjusted increases in testosterone values that are 2 to 5 times greater than their treatment peers from treatment arm B of Study S176.1.003.*" As Sponsor points out these are crude approximations.

- With respect to the concern of the efficacy of skin application site washing in mitigating the risk of transfer, the Division asked

  What were the application site washing instructions/procedures? Were the procedures consistently followed and their performance documented? Were other application site washing procedures considered?

Discussion of Sponsor's response: In their response Sponsor states that in Study 176.1.008 male subjects were instructed to shower and thoroughly wash the application site with soap and water 15 minutes prior to the scheduled contact time, the abdomen was to be thoroughly dried. These procedures were completed under the direct supervision of the clinic staff and start time and duration of showering was recorded in the source documentation. Other washing instructions are mentioned in the Sponsor's response, but it is not mentioned if they were considered in the study design. Sponsor points out that the mean change from baseline in the washing group study was 1.72 ng/dL. They believe that this change is negligible and within the variability of the data according to the Sponsor.

Reviewer's Comment: We concur that application site washing as described in Study 176.1.008 largely eliminates testosterone skin transfer. We have concerns, however, that the need for washing (especially a total body shower)prior to any physical contact (even clothed contact)to prevent transfer will not be a feasible precaution because it simply cannot be complied with on all occasions by all patients. This makes it all the more important that

additional studies be done with clothing barriers to demonstrate a feasible, simpler method to mitigate the risk of transfer.

- Do you consider the transfer studies as a reasonable test of transfer risk under real-life conditions, or do you consider the conditions of the transfer study unrealistic?

Discussion of Sponsor's response: The Sponsor states that the conditions in Studies S176.1.003 and S176.1.008 "*represent the most extreme contact conditions.*"

The Sponsor states, "*a common theme from post-marketing cases of secondary exposure is that improper handling of the product and failure to adhere to labeled precautions intended to minimize contact between dosed and non-dosed individuals increased the risk of transfer (FDA PAC Briefing Book).*"

- Baseline T concentrations in the female subjects were obtained 1 week prior to the active treatment phase of the protocol. Is baseline shifting of testosterone concentration a concern and how is this controlled for?

Discussion of Sponsor's response: Sponsor in response observed that endogenous testosterone production in women is produced by both adrenal and ovarian sources and can vary widely due to both circadian and menstrual cycles. Blood samples were obtained at the same time-points at baseline (Day-1) as they were on days of evaluation (Day 1 and Day 7) to minimize the effects of diurnal variation. In their response, Solvay assumed where endogenous serum testosterone levels changed due to diurnal/circadian rhythms or menstrual cycles over one week periods, that these changes were evenly distributed within the study populations

- Comment upon the potential clinical significance of the transfer study results to a child. In responding, consider average and worst case scenarios based upon the transfer study results.

Discussion of Sponsor's response: Sponsor used similar methodology to roughly estimate the comparable pediatric exposure based on the worst case scenario. They are presented in the table below:

Table 53:S176.1.008 (5 g daily dose; washing arm) Projected Pediatric Testosterone Exposure

Day 1	Observed Values From Study	Hour	Estimated Exposure
Subject	Baseline-adjusted increase (Cmax/Cav)		Adjusted value (Cmax/Cav)
27405	13.4ng/dL/6.33 ng/dL	8	60.3ng/dL/28.5ng/dL
27411	21.3ng/dL/2.98ng/dL	0	95.9ng/dL/13.4ng/dL

Source: page 16 of submission

Sponsor points out that these results and projections are from a single episode of testosterone exposure. The Sponsor believes that the clinical consequences of secondary exposure are unlikely to be seen following isolated instances of secondary exposure.

Reviewer's Overall Comment: Application site washing largely mitigates transfer of testosterone; but patient compliance with this technique prior to any physical contact (clothed or unclothed) is doubtful. Like Clinical Pharmacology as well as the Sponsor, I still have concerns about the efficacy of T-shirt barrier in adequately mitigating transfer of testosterone in testosterone gel 1.62%. Additional studies should be done to determine a simple clothing barrier. The modifications to dose technique mentioned in this response by the Sponsor seem like a reasonable approach for a future study(ies).

8 Postmarket Experience

Testosterone gel 1.62% is not currently marketed. However, extensive post-marketing safety information is available for AndroGel® (testosterone gel) 1% formulation which is approved and marketed internationally and will be discussed herein. AndroGel® was approved in the United States in 2000 to treat men with low testosterone. The cumulative experience with testosterone gel 1% is derived from serial PSURs and a Safety Update Report since the International Birth Date [IBD 928 February 2000)] and the Summary of Clinical Safety listed in the testosterone gel 1.62% Investigational Brochure [IB]. The safety findings noted in testosterone gel 1.62% Phase I-III clinical studies appear similar and consistent with testosterone gel 1 % and this class of drug.

A crude estimate of the number of patients exposed to AndroGel® was calculated by the Sponsor which resulted in an estimate of approximately (b) (4) patients or roughly 1.13 million patient years of treatment with AndroGel® for the 28 February 2000-27 September 2008 cumulative post-marketing review period.

The Sponsor has completed 3 post-marketing clinical studies for AndroGel® 1%. UMD-01-080 studied the steady-state serum testosterone levels, pharmacokinetics and the safety and tolerability of testosterone gel 1% in prepubertal boys with insufficient testosterone production. UMD-01-090 was an observational study of adolescent boys with hypogonadism. S176.2.101 evaluated the efficacy and safety of AndroGel® as an adjunct to hypoglycemic therapy in the treatment of hypogonadal and low testosterone men with type 2 diabetes. None of these studies yielded new safety signals.

Previously identified potential risks and their current status:

- Prostate Cancer: The available data are inadequate to draw conclusions about the association of prostate cancer and testoterone replacement in hypogonadal men. The data is not adequate to conclude that that testosterone actually causes the development of new prostate cancer nor that it stimulates the growth of pre-existing occult prostate cancer in such patients. Nonetheless, this issue is discussed in the product labeling with recommendations to monitor serum PSA and prostate examination via DRE. The

Sponsor has a standard follow-up procedure for all postmarketing reports of prostate cancer and there is appropriate labeling to exclude use in patients with pre-existing prostatic and breast cancer prior to beginning treatment.

- Thromboembolic Events: A thorough review of pre-clinical and clinical data did not reveal evidence for testosterone gel 1% causing thromboembolic events. Monitoring for these events will continue.
- Malignancies (excluding prostate): There have been 22 reports of non-prostatic malignancies in patients using AndroGel 1%. The Sponsor conducted a thorough investigation, no causal link between testosterone gel 1% and malignancies was demonstrated in the scientific literature or from the pre-clinical/animal data. Sponsor will continue to monitor reports and literature associating malignancy and testosterone gel 1%.

Experience with Drug-Drug Interactions: During the more than 8-year post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, 30 postmarketing reports mentioned a possible drug interaction: all were nonserious. The Periodic Safety Update Reports, Drug Interactions, 2000-2008 were reviewed. No new safety signals were detected or and no new safety actions were undertaken by Sponsor re: drug interactions.

Experience with Overdose: There is one report of suspected overdose in a 46-year-old man. While using the indicated therapeutic dose of testosterone gel, 50 mg of testosterone in 5 g of gel daily, the patient experienced testosterone levels of 8,700 ng/dL and 10, 875 ng/dL. Androgen abuse could not be ruled out due to the patient's history of illicit androgen abuse associated with bodybuilding. One week after AndroGel 1% discontinuation, total testosterone level remained elevated (9,350 ng/dL).

Drug Abuse of Misuse: During the more than 8-year post-marketing review period of AndroGel 1% from 28 February 2000 through 27 September 2008, there were eight postmarketing reports of advers events in users who may have been abusing or misusing AndroGel 1%. Five of the reports are from health care providers (HCP) and three are from consumers. Three literature reports concern men who are bodybuilders. These cases are shown individually in the next table.

Table 54: AndroGel® Abuse or Misuse

Case ID	Sex/Age	Concomitant Medications	Adverse Event	Resolution
TEST00208000191/ HCP	M/26	Amino acids, AAS and systemic steroids over 5 years	Acneiform lesions, seborrhea, striae	With all drug cessation, striae persisted but all other lesions resolved
TEST00208000190/ HCP	M/31	Not stated	Hemilateral tubular gynecomastia	Recovered
TEST00307035079/ HCP	M/43	25 years of AAS use (many forms)	Hepatic adenoma and hepatic rupture	Completely recovered
TEST00204001006/ HCP	M/49	Self injection of t-gel into penis and testicles	Injection site ulcer and penile edema	Hospitalized and treated. Outpatient psychiatric follow-up
TEST00205001289/ HCP	M/49	Used 200 mg T-gel instead of 100 mg qd, Testim® 100 mg and vardenafil	12 h post Testim Headache, rash, hypertension and anxiety	Treated in ER with symptoms abating
TEST00208000809/ Consumer	F/26	During rape had T-gel applied topically, vaginally and injected	Vulvovaginal discomfort, aggression, extremity pain with peripheral edema	Attempts at follow-up unsuccessful
TEST00208000809/ Consumer	M/27	Not stated	Non serious ADR not stated	Self-titrate dose and frequency of T-gel
TEST002080004311/ Consumer	M/58	Not stated	Non serious ADR not stated	Self-titrate dose and frequency of T-gel

*AAS= anabolic systemic steroids, HCP=health care provider
Source: Pages 19, 20 Section 5.3.6, Section Reports of Post-Marketing Experience

Reviewer's Comment: *The labeled warnings and precautions for use are clear, but cannot totally prevent misuse or abuse of the drug. The number of reports of adverse events in association with abuse or misuse is low.*

Pregnancy or Lactation: During the post-marketing review period from 28 February 2000 through 27 September 2008, there were 18 postmarketing reports of possible AndroGel exposure during pregnancy. One report (TEST0020732758) involved a one-day secondary exposure during the first trimester and placenta previa 10 days prior to due date. The neonate was born with a normal APGAR score and a lung infection. A second report (TEST00207032758) involved a one-day secondary exposure during the gestation week 19. The neonate experienced jaundice and recovered completely after three days of phototherapy. There were no AEs in the remaining 16 cases. In the Sponsor's opinion, no new safety action is indicated.

Children: During the post-marketing review period from 28 February 2000 through 27 September 2008, a total of 11 adverse events were reported in children who were being treated with AndroGel 1% and another 26 postmarketing adverse event reports were received for Androgel 1% with possible inadvertent AndroGel exposure in children (≤17 years old).

The cases presented in the tables below (Tables 56 and 57) were obtained from the Sponsor's Periodic Safety Update Reports 28 February 2000 through 27 September 2008, as submitted in the AndroGel 1.62% NDA. The cases in the PSURs are from line listings and some have scant detail or a short narrative. Duplications may exist. Some of the cases in the table were not in the line listings but were obtained from text from the PSURs 2002 to 2008.

Reviewer's Comment: The reader should be aware that many, and perhaps all, of the cases of inadvertent exposure have been previously reviewed in great detail by the review teams in DRUP, DMEP, PMHS and OSE. This multi-Divisional review led to extensive labeling changes and a Medication Guide.

Table 55: Adverse Events for Children Being Actively Treated with Androgel

Case ID/ PSUR	Age	Gender	Dosage	Time to Onset*	Reaction/event
TEST00204002492/ 2000-2005	16	M	15 mg	17 weeks	Slipped capital femoral epiphysis
TEST00204003968/ 2000-2005	17	M	12.5 mg	9 months	Benign intracranial hypertension
TEST00204000122/ 2000-2005	13	M	5 mg	7 weeks 6 days	Suicidal ideation, major depression, obsessive compulsive disorder, blood alkaline phosphatase increased
TEST00205001971/ 2005-2006 Delayed puberty	12	M	500 mg	24 weeks	Hospitalized depression, adjustment reaction, continued on testosterone and recovered
Case ID not provided/ 2005-2006	Teenage not otherwise specified	M	Not specified/ hypogonadal	Not specified	Drug ineffective, therapeutic response delayed, blood testosterone decreased
Case ID not provided 2007-2008 Low testosterone	11-15 years	M	Unknown	Not specified	Abnormal behavior (one day) Application site reaction Drug ineffective Change in testicular size Gynecomastia Specific AE is not specified to a specific patient
Case ID not provided 2007-2008 Delayed puberty			Unknown	Not specified	
Case ID not provided 2007-2008 Chromosome XXYY Syndrome			Unknown	Not specified	
Case ID not provided 2007-2008			Unknown	Not specified	
Solvay00208002151/ 28FEB2008-27SEP2008	17 years	M	2.5 mg AndroGel/ hypogonadal	Not specified	Breath fish odor secondary to carnitine
Solvay0028002930/	14 years	M	1.25 mg	8 m	fatigue

28FEB2008-27SEP2008			AndroGel/ delayed puberty		

Sources: PSURs for AndroGel® as specified in table
*Time to Onset: This reviewer is unsure in all cases what Time to Onset or TTO means.

Table 56: Pediatric Adverse Events Associated with Possible Inadvertant AndroGel Exposure (Postmarketing)

Case ID/ PSUR	Age	Gender	Dosage	Time to Onset*	Reaction/event
TEST00204000509/ 2000-2005	0	M	100 mg Tertiary Exposure 1st Trimester	unknown	Neonatal lung infection, neonatal ICU for 7 day, antibiotic Rx
TEST00204000122/ 2000-2005	9 m	F	Unknown, Secondary exposure	unknown	Enlarged clitoris
TEST00205000005/ 2000-2005	5	unknown	Unknown, Secondary exposure	unknown	Blood testosterone increased
TEST00202000992/ 2000-2005	10	M	Not reported Secondary exposure	1 week 3 days	Aggressive behavior, rash
TEST00205000342/ 2000-2005	unknown	F	Unknown Secondary exposure	unknown	Hair growth abnormal, blood testosterone increased
TEST00205000478/ 2000-2005	4 m	F	Unknown Secondary exposure	unknown	Skin discoloration
TEST00204000046/ 2000-2005	unknown	M	Unknown Secondary exposure	unknown	Precocious puberty
TEST00204000047/ 2000-2005	unknown	M	Unknown Secondary exposure	unknown	Precocious puberty
Case ID not provided/ 2005-2006	3	F	Unknown Secondary exposure	Not in report	Virilism, enlarged clitoris
Case ID not provided/ 2005-2006	13	F	Unknown Secondary exposure	Not in report	Virilism, enlarged clitoris, acne, alopecia
Case ID not provided/ 2006-2007	11 months	F	Unknown Secondary Exposure	Not specified	Facial hair growth, increased blood testosterone
Case ID not provided/ 2006-2007	7 years	F	Unknown Secondary exposure	Not specified	Facial hair growth increased

Case ID not provided/ 2006-2007	Infant not otherwise specified	M	Unknown Secondary exposure	Not specified	Increased blood testosterone
Case ID not provided/ 2006-2007	4 years	M	Unknown Secondary exposure	Not specified	Increased blood testosterone
Case ID not provided 2007-2008 Low testosterone	11-15 years	M	Unknown	Not specified	Abnormal behavior (one day) Application site reaction Drug ineffective Change in testicular size gynecomastia
Case ID not provided 2007-2008 Delayed puberty			Unknown	Not specified	
Case ID not provided 2007-2008 Chromosome XXYY Syndrome			Unknown	Not specified	
Case ID not provided 2007-2008			Unknown	Not specified	
Solvay00207033614 2007-2008	6 M	M	Unknown, Secondary exposure	Not specified	Precocious puberty
Solvay00207001172 2007-2008	Unknown	F	Unknown, Secondary exposure	Not specified	Virilism
Sovay00307034470 2007-2008	Unknown	F	Unknown, Secondary exposure	Not specified	Virilism
Case ID not provided 2007-2008	Unknown	Unknown	Unknown, Secondary exposure	Not specified	Precocious puberty
Solvay002070327858	1 day	M	Maternal 1 day exposure 19th week	Not specified	Jaundice
Solvay00308003152/ 28FEB2008-27SEP2008	2 years	M	Unknown Secondary exposure	Not Specified	Precocious puberty, penis disorder, above normal height, elevated testosterone (events abated and resumed with stop/restart of father's T)

Solvay00208002091/ 28FEB2008-27SEP2008	5 years	M	Unknown Secondary exposure	16 m	Premature epiphyses fusion, precocious puberty, aggression, bone disorder, sexual dysfunction
Solvay0028002930/ 28FEB2008-27SEP2008	7 months	Not specified	Unknown Secondary exposure	Not specified	Acne on chin

Sources: PSURs for AndroGel® as specified in table
* TTO or Time to Onset is not defined in the PSURS and I am not sure exactly what it means.

Reviewer's Comment: Each of these cases has been previously reviewed in great detail by a number of review teams including Urology, Endocrinology, Pediatrics, and Safety. The reader did not conduct additional detailed reviews of these same cases. Suffice to say that the cases of pediatric inadvertent exposure document a risk to the pediatric population occurring from secondary exposure to testosterone gel. The adverse events of advanced bone age and clitoral hypertrophy may not regress with drug withdrawal.

Solvay 002002091 is also described in ISR#5323992-5-00-01. In this ISR and with additional information received from the patient's mother and pediatrician, it was noted that the child had a slightly greater degree of skeletal maturation compared to chronological age but did not have premature epiphyses fusion as noted by Sponsor (Medical Officer's Memorandum: Post-Marketing Safety Issue, NDA 21-015, Placed in DARRTS January 29, 2009).

DRUP reviewed a total of 26 reports of inadvertent exposure to testosterone in children of AndroGel users, as derived from AERS and from Solvay (Medical Officer's Memorandum: Post-Marketing Safety Issue, NDA 21-015, and Placed in DARRTS January 29, 2009*)*. The report reached the following conclusions:

"*From a Clinical perspective, it does appear that the transfer of AndroGel from an adult male to a child over prolonged periods can result in virilization of the child, including enlargement of the penis or clitoris, development of pubic hair, aggressive behavior, erections and libido, and advanced bone age. In most cases, the symptoms and the signs regress with removal of the offending exposure. However, that is not always the case; for example, enlarged genitalia may not fully return to normal size and two girls in this series underwent clitoral reduction surgery. In general, it appears that bone age will "catch-down" to the chronological age over time*."

Some of these cases are quite well documented and serve to elucidate drug handling behaviors that may have increased the risk of testosterone transfer from adult male to child. For example, of the 11 cases derived from AERS (the best documented cases), the following drug handling issues were detected:

- *In 5 cases, AndroGel was applied to the chest – a non-approved body site*
- *In 7 cases, skin-to-skin contact between adult and child was documented, and in 4 of*

those cases, such contact was extensive.

- *In 4 cases, the adult male acknowledged not wearing a T-shirt after applying AndroGel.*
- *In 6 cases, the adult slept in the same bed with the child.*
- *In 2 cases, children were found to be handling the used AndroGel packet from the trash.*
- *In 1 case each, the dose was either higher than maximum recommended, or more frequently applied than recommended.*
- *In 1 case, there was evidence of androgen abuse.*

Taken together, this information suggests that improper handling of the product and failure to adhere to labeled precautions that are intended to minimize skin-to-skin contact between user and child can increase the risk of transfer."

The report suggests to mitigate this problem, that specific information be directed to the patient via a MedGuide that would reinforce the labeled precautions re: preventing secondary exposure."

Reviewer's Comment: The analysis in the above seems reasonable and I concur with the recommendations.

There is an additional review submitted in DARRTS under NDA 21-015 February 11, 2009 from the Division of Pharmacovigilance I, Office of Surveillance and Epidemiology (OSE) which summarizes pediatric adverse event reports in AERS (Adverse Event Report System) associated with testosterone gel (AndroGel). In this review, five direct exposure cases (four of the five cases were ages 13-16 and drug use was off-label) and nine cases of indirect exposure (one new born and eight children less than six years of age (exposed to testosterone used by their father) were analyzed.

The new born's pulmonary infection, in the reviewer's opinion, was not likely to be causally related to the testosterone used by the father for an unknown time during the first trimester. The report observed "*It is possible individuals using AndroGel are not aware or do not adhere to the labeled recommendations to reduce testosterone transfer to others (including children). This review suggests some fathers are applying the testosterone gel after showering in the morning, wearing a t-shirt or shirt as recommended in the labeling but may not wear a t-shirt to bed or when they have close contact with their children.*" The review also raises the possibility of transfer from inanimate objects. A study is cited in the report that theorized that "natural shedding" (desquamation of stratum corneum provides the mechanism for testosterone transfer to the t-shirts, but recommended further studies to consider the possibilities of transfer (J Sex Med 2005; 2:227-234, available a http://www3.interscience.wiley.com/cgi-bin/fulltext/118719228/PDFSTART).

Reviewer's Comment: In my opinion, the possibility of transfer from inanimate objects to people needs to be further studied before evidence-based recommendations can be made.

The review recommends a Medication Guide for approved testosterone gel products, a boxed warning to further alert users to the risk of testosterone transfer and to highlight the serious consequences of testosterone transfer, a FDA healthcare alert, and that the Sponsor(s) perform studies investigating other possibilities of testosterone transfer and the amount of residual testosterone left on the skin at fixed time intervals post-application.

> *Reviewer's Comment: The labeling changes, medication guide, and healthcare guide are reasonable suggestions and have been carried out. Further studies (e.g, transfer from inanimate objects)could be done in the post marketing period.*

From 2001 to 2007 there has been an overall increase in US testosterone prescriptions (all formulations) to (b) (4) prescriptions for all testosterone products in 2007. Between 2002 and November 2008, (b) (4) of the testosterone prescriptions were for a gel testosterone formulation. This represents a (b) (4) increase in gel formulation use between 2002 and November 2008. AndroGel is the most commonly prescribed gel product (b) (4) prescriptions dispensed in 2007). 2 The breakdown of AndroGel® prescriptions by age is as follows:

- (b) (4)

2 SDI Vector One®; National (VONA). Extracted 1/7/2009
3 Ibid.

In terms of secondary exposure, the table below illustrates the secondary testosterone exposure cases by year for AndroGel:

Table 57: Reports of Possible AndroGel Secondary Exposure - Cases by Year

Year	Number Prescriptions	Secondary Exposure	
		Pediatric*	Adult*
2000	(b) (4)	0	1
2001		0	8
2002		1	15
2003		0	15
2004		4	14
2005		5	12
2006		5	16
2007		5	21
2008		4	20
2009(through April)		1	15
Total		25	137

* Solvay's pharmacovigilance activities
Source: Slide 6: Pediatric Advisory Committee Presentation, 23 June 2009: Elizabeth M Mustisya MD, Vice President and Chief Medical Officer, Solvay Pharmaceuticals, Inc.

> *Reviewer's Comment: There is a known risk of secondary exposure to testosterone from gel formulations. Testosterone gel 1.62% is not significantly different that other testosterone gel formulations to qualify as out of the drug class. The Sponsor was asked to submit a REMS as well as a Medguide dealing with the problem of secondary exposure, and they have done so. When the fundamental issue of transfer has been resolved (e.g. a simple clothing barrier), then the MedGuide and REMS will undergo a comprehensive review.*

Women: During the post-marketing review period (28 February 2000 through 27 September 2008), a total of 190 post-marketing reports involving females were received by the Sponsor. Of these, 57 females reported using AndroGel outside the labeled indications. The remaining 137 reports involved possible inadvertent secondary exposure. The indication for primary off-label exposure included:

- Decreased sexual arousal and libido
- Androgen/testosterone replacement
- Hypogonadism in a transgender female
- Vaginal dryness/irritation
- Menopausal symptoms
- Sexual dysfunction
- Clitoral enlargement

- Pituitary disorder
- Lichen sclerosis
- Depression
- Fatigue
- Decreased muscle strength

The majority of reported ADRs were mild in nature and some may reflect known adverse effects of testosterone gel which include hair growth, acne, skin rash, nipple pain, increased cholesterol and increased irritability. However, a previous detailed review of these adult cases by DRUP and OSE failed to demonstrate a clear association of these commonly reported AEs to inadvertent exposure, a situation different from the pediatric inadvertent exposure cases.

Elderly: During the post-marketing review period (28 February 2000 through 27 September 2008), there were 658 reports received by the Sponsor involving patients with known ages of 65 years or older, of which 61 (9.3%) met the serious criteria. A review of the post-marketing ADRs revealed to new specific risk to elderly patients. The most common ADRs reported by this population, in the Sponsor's opinion, are consistent with those reported overall and the serious ADRs are not uncommon in an elderly population with underlying medical conditions.

Reviewer's Comment: I concur with Sponsor's opinion.

Long-Term Treatment: Overall the longest duration of AndroGel treatment was eight years. During the post-marketing review period (28 February 2000 through 27 September 2008), 400 reports were received by the Sponsor with known durations of treatment longer than one year with 61 of these reports categorized as serious. The Sponsor analyzed the data and concluded that no new safety issue was detected. An increased risk for the patient treated with testosterone gel 1 % exceeding one year could not be established.

Prescription/ Medication Errors: During the post-marketing review period (28 February 2000 through 27 September 2008), There were 32 non-serious reports of medication errors. The majority (n=15) of reports involved men who intentionally applied AndroGel to not recommended areas (e. g. genitals); one man as instructed by his physician. There were three reports of oral administration. There were 12 reports of incorrect dose. All ADRs were nonserious and most were listed events.

Reviewer's Comment: Aside from secondary exposure in children, the PSURs and Sponsor's submission adequately addresses the post-marketing adverse events noted for this application. When the transfer issue is resolved, the MedGuide and REMS recently submitted by Sponsor will be reviewed.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

The Medical Officer defers to provide labeling revisions pending resolution of the unresolved transfer issue. The reviewer believes that additional studies are needed in this regard. The results of additional studies will guide important parts of the label. However, Clinical Pharmacology has submitted draft labeling changes.

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comment: (b) (4)

(b) (4)

Reviewer's Comment: (b) (4)

(b) (4)

(b) (4)

(b) (4)

At the current time, I am not aware of data establishing and characterizing the risk of testosterone transfer from inanimate objects to individuals. "Close contact" is difficult to define. It is not made clear that close contact also means close contact with a man wearing a T-shirt, not just skin-to-skin contact.

(b) (4)

Reviewer's Comment: While a T-shirt barrier completely prevented transfer to females at the 2.5 g dose of AndroGel 1.62%, it did not at the 5 g dose. We have no data about the 3.75 dose. From a labeling standpoint, a single method of clothing barrier that largely mitigates testosterone transfer at all to be marketed doses is needed and indeed, is possible (applying the gel at 4 different sites may lessen transfer potential through a T-shirt) and should be studied prior to approval.

(b) (4)


(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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

/s/

A R WIEDERHORN
11/02/2009

MARK S HIRSCH
11/02/2009
I concur.

NDA 22-309

Medical Officer's Memorandum: Filing New NDA

Date Submitted: February 11, 2009
Date Received: February 11, 2009

45-Day Filing Review Date: March 31, 2009
60- Day Filing Date: April 13, 2009
74-Day Letter Date: April 27, 2009
PDUFA Goal Date: December 12, 2009

Date Memo Completed: April 15, 2009

Related Submissions: NDA 21-015 (Androgel 1%)
IND 50,377 (Androgel 1.62%)

Product: AndroGel (testosterone gel) 1.62%

Dose and Route: 1.25 gm – 5 gm, once daily, by topical application

Indication: For replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone (Primary hypogonadism [congenital or acquired] or hypogonadotrophic hypogonadism [congenital or acquired])

I. Summary

Objective:
This review assesses whether NDA 22-309 is suitable for filing from the Clinical perspective under 21 CFR 314.50, Content and Format of an Application, and 21 CFR 314.71, Procedures for Submission of a new NDA. This document also serves as the basis for communication to Sponsor potential Clinical review issues identified during the initial review period.

Conclusion:
Following a preliminary review of the major components of this NDA (including one Phase III study of efficacy and safety [S176.3.104], eight Phase I clinical pharmacology studies. the draft label, and financial disclosure information for these studies), NDA 22-309 is fileable from a Clinical perspective.

II. Background

Brief Regulatory History:
AndroGel 1.62% is a topical gel testosterone product which is to be used for once a day dosing for the treatment of conditions associated with a deficiency or absence of endogenous testosterone. The Sponsor, Solvay Pharmaceuticals, Inc., also markets

AndroGel 1% under NDA 21-015. The new product, AndroGel® (testosterone gel) 1.62%, has (b) (4), reduced volume of application, (b) (4) (b) (4) compared to AndroGel 1%. The proposed starting dose of AndroGel® 1.62% is 2.5 gm (2 pump actuations) once daily. Dose adjustments are made in increments of 1.25 gm based upon trough serum testosterone determinations, in order to achieve and maintain serum testosterone levels in the normal range.

All studies for AndroGel 1.62% were conducted under IND #50,377 which was the original AndroGel 1% IND. The opening study for AndroGel 1.62% was a Phase 1 protocol, 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*" (Protocol S1761001) and was submitted by the Sponsor on August 25, 2005.

The Sponsor supports approval with one Phase 3 study (S176.3.104) and supportive evidence from five Phase 1 safety studies in hypogonadal males (S176.1.001, S176.1.002, S176.1.005, S176.1.006 and S176.1.007) and individual safety results from three Phase 1 safety studies in eugonadal males (S176.1.003, S176.1.004, and S176.1.008). The Division agreed at the EOP2 Meeting on 18 October 2006 that a single Phase 3 study evaluating the efficacy and safety testosterone gel 1.62% would be sufficient to file the application for review.

At the 18 October 2006 EOP2 meeting, the Division agreed that at least 6 months data from the Phase 3 study should be submitted in the original NDA, and that the Division would accept the completed study report for S176.3.104, including the full 1 year of data, with the 4 month Safety Update. The Division also stated that it would not be necessary to integrate the safety data from the Phase 1 studies with the Phase 3 data.

(b) (4)

(b) (4)

(b) (4) served as a laboratory for most of the Phase 1 studies and the Phase 3 (S176.3.104) study evaluating the safety and efficacy of AndroGel 1.62% in hypogonadal

men. These studies were conducted under IND # 50,377 for submission to NDA 22-309. Analytes specifically affected include testosterone, dihydrotestosterone, estradiol, and sex hormone-binding globulin.

A meeting between the Division and Solvay was held on August 13, 2008 in order to discuss the (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. 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 1.6% 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 (b) (4) These data from (b) (4) are included in the bioanalytical reports contained within Module 5 of the NDA, Section 5.3.1.4.

At the Pre-NDA meeting on 21 January 2008, the Sponsor agreed not to submit the initial NDA until Study 176.1.008 (the second "transfer study") was completed and the study report would be included in the NDA submission. This would allow the Division to have adequate data for review regarding the potential for transfer to others. In addition, the Division voiced concerns regarding several patients with maximum serum T concentrations above 2500 ng/dL. The Sponsor has provided in their submission detailed analyses for each case of Cmax greater than 2500 ng/dL.

III NDA Filling Review

Filing Review: The review is based on three criteria proposed in FDA guidance for the filing review, based on the Agency's interpretation of 21 CFR 314.101 (d) (3) and 21 CFR 314.50:

1. Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner.
2. Failure to include evidence of effectiveness compatible with the statute and regulations.
3. Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Submitted materials:
The Sponsor submitted the safety and efficacy from 8 clinical pharmacology studies (including 1 dermotoxicity trial) and 1 Phase 3 safety and efficacy trial (see Table 1).

Table 1: Summary of Clinical Studies with Androgel 1.62%

Type of Study	Objective	Design	Test Product	Duration of Treatment	Enrolled Completed Age Range
Phase I Clinical Pharmacology				(total days of exposure)	Hypogonadal Males
S176.1.001	Bioavailability (BA) and Multiple Dose Pharmacokinetics (PK)	Randomized, Open label, parallel	Testosterone (T)gel: to abdomen for each dose level of 1.25, 2.50 and 3.75	Daily, 5 days at each dose level (20 days)	38 36 26-72 yrs
S176.1.002	Single and Multiple Dose PK	Randomized, Open label, parallel	T gel 1.62%; 1.25 g, 2.50 g, 5.00 g or 6.25 g. Abdomen, upper arm/shoulders (rotation)	Daily for 14 Days	56 51 27-69 yrs
S176.1.005	Multiple dose PK/BA with/without Postdose skin washing	Randomized, Open-label, three-way crossover	T gel 1.62%; 5.00 g upper arm/shoulders	Daily, 7 days at each dose level (21 days)	24 17 34-77 yrs
S176.1.006	Multiple dose PK/BA with/without moisturizer or sunscreen	Randomized, Open-label, three-way crossover	T gel 1.62%; 2.50 g upper arm/shoulders	Daily, 7 days at each dose level (21 days)	18 15 31-60 yrs
S176.1.007	Singe and Multiple Dose PK/BA	Randomized, open-label, three-way crossover	T gel 1.62% 5.00 g, Abdomen, upper arms/shoulders+ both sites in rotation	Daily, 5 day washout between Treatments (31 days)	36 32 29-73 yrs
Healthy Subjects					Healthy Subjects
S176.1.003	PK of female subjects after contact with partner dosed with T gel	Randomized, open-label	Males: T gel 1.62% 5.00 g Females: 15 minutes of contact time; no direct dose	(7 days)	96 (48 couples) 47 M, 48 F; 18-65 yrs

S176.1.004	Skin sensitization Skin irritation of 1.62% T gel in males	Randomized, double-blind, placebo controlled	T gel 1.62%; 100 mg gel/3.14 cm^2 patch	(6 weeks): three phases: 21d induction, 12-17 day rest, and 5d rechallenge	235 214 18-79 yrs
S176.1.008	PK eval of dose, postdose washing, and application site transfer - dosed male to non-dosed female	Randomized, open-label, parallel group	Males: T gel 1.62%; 2.5 or 5.00 g, 2 single daily doses to abdomen or shoulders/arms: Females: 15 minute contact time: no direct dose	(2 days), separated by 1-week washout period	48 (24 couples) 48 (24 couples) 18-59 yrs

Review Results

1. Does this amendment omit a section required under CFR 314.50, or was a particular section presented in such a manner as to render it incomplete for the clinical Review?

Response: No

This NDA contains the critical sections in sufficient detail (see Table 2 and Appendix A).

Table 2: Checklist for Critical Sections

Comprehensive Table of Contents	Yes
Summary of the application	Yes
Technical Sections (CMC, pharmacology/toxicology, clinical pharmacology, clinical)	Yes
Case tabulations	Yes

2. Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:

- ***a. Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant endpoints***
- ***b. Presentation of what appears to be only a single adequate and well controlled trial without adequate explanation***
- ***c. Use of a study design clearly inappropriate***

Response: No.

The following section of the filing review summarizes the efficacy findings from the single Phase 3 study (S176.3.104) with open-label extension. All clinical efficacy data were obtained from the double-blind phase of Study S176.3.104.

> *Reviewer's Comment: The Sponsor is seeking approval of a new concentration of testosterone gel. Study S176.3.104 is a multicenter study that appears to have internal consistency of study findings and strength of statistical results. This single confirmatory study provides sufficient evidence to support filing of this NDA.*

2.1 Study Design of S176.3.104

This was a multi-center, 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. Patients, 18-80 years of age, with average serum testosterone concentration of <300 ng/dL and who had no significant medical conditions that would be adversely impacted by testosterone replacement were eligible for study inclusion. Patients with low testosterone concentrations secondary to causes other than primary or secondary hypogonadism (congenital or acquired) were excluded.

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. 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 3 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).

At 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.

The Safety Sample consisted of all subjects who were allocated to the Treatment Sample and had at least one dose of study medication administered. Three patient populations were used in the analysis of efficacy: 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, the Efficacy Sample consisted of all subjects included in the FA Sample and had any efficacy data for Day 112 (the primary timepoint), and 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. Only available parameters were used for all analytes. LOCF was used only for secondary endpoints.

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 NDA presents data collected in the study up to and including Day 182. By prior agreement, a Final Integrated Clinical Study Report will be produced including data from Baseline through the end of the Study (Day 364) and will be included in the 120 day Safety Update.

Table 3: Pre-specified Testosterone Gel 1.62% Dose Titration Criteria

Total Testosterone Concentrations	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 %

Table 4: Doses Administered of Testosterone

Gel Strength	Gel Dose (g)	T Dose (mg)	Number Pump Actuations
1.62%	1.25	20.3	1
1.62%	2.50	40.5	2
1.62%	3.75	60.8	3
1.62%	5.00	81.0	4

Source: adapted from Table 2, Clinical Study Report S1763104, 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. Success in the study was defined as ≥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 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:

- Cmax ≤1500 ng/dL in ≥85% of the subjects
- Cmax between 1800-2500 ng/dL in ≤5% of the subjects
- Cmax >2500 ng/dL in none of the subjects

Reviewer's Comment: According to Pre-NDA discussions with the Sponsor, failure to achieve Cmax >2500 ng/dl in none of the subjects does not preclude a review nor categorically preclude approval of the NDA. The Sponsor was

advised at the Pre-NDA meeting, on 21 January 2008, that it has their burden to explain the findings and convince the Division that such elevated values are not an important safety issue. The Sponsor was asked to provide as much detail as possible to provide evidence of a non-product cause for each case of Cmax greater than 2500 ng/dL.

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.

Reviewer's Comment: The overall protocol is acceptable.

2.2 Patient Disposition and Baseline Characteristics of S176.3.104

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 (168 T-Gel [71.8%] and 28 [70.0%] placebo). The most common last titrated dose was 5.00 g testosterone gel 1.62%. Similar percentages of placebo and T-Gel patients discontinued from the study groups. The most common AE leading to discontinuation was increased PSA which was prespecified as a discontinuation criteria and will be discussed in the Safety section.

Table 4: Subject Disposition S176.3.104-180 Day Pivotal Period

Subjects	Placebo N=40	T-Gel 1.25g N=17	T-Gel 2.5g N=60	T-Gel 3.75g N=66	T-Gel 5.0g N=91	Total T-Gel N=234
Completed	28(70.0)	129(70.6)	35(58.3)	50(75.8)	71(78)	168(71.8)
Premature Terminate	12(30.0)	5(29.4)	25(41.7)	16(24.2)	20(22.0)	66(28.2)
Reasons	n (%)					
Adv event	0	1(5.9)	6(10.0)	8(12.1)	10(11.0)	25(9.1)
Lack Efficacy	0	1(5.9)	0	1(1.5)	0	2(0.7)
Lost Follow-up	2(5.0)	0	3(5.0)	0	2(2.2)	7(2.6)
Withdrew Consent	8(20.0)	1(5.9)	10(16.7)	4(6.1)	4(4.4)	27(9.9)
Admin	1(2.5)	0	1(1.7)	1(1.5)	3(3.3)	6(2.2)
Protocol Violation	1(2.2)	1(11.8)	5(8.3)	2(3.0)	1(1.1)	11(4.0)

Note: Treatment groups are based on subject's last titrated dose.
Source: Clinical Study Report S176.3.104 adapted from Table 1.0.0

The average age in the placebo treatment group was 55.5 years and in the T-Gel group was 53.6 years. The arithmetic and geometric means for baseline serum testosterone in the placebo treatment group was 282 and 228 ng/dL respectively, and 294 and 266 for the T-Gel group respectively. Other baseline characteristics, including race, height, weight, waist-to-hip ratio, BMI, blood pressure, and percent free PSA were balanced evenly between the two groups. There was a slightly higher incidence of eye disorder in the placebo group and the T-Gel patients had a slightly higher incidence of ear and labyrinth disorders, and gastrointestinal-hepatobiliary disorders. The placebo group had a slightly higher incidence of use of drugs for peptic ulcer disease. The overall compliance for the Full Analysis Data set was 97.70 % for placebo and 94.29% for the T-Gel group.

2.3 Efficacy Findings of S176.3.104

2.3.1 Primary Endpoint:

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.

Based on Day 112 results, ≥75% of subjects on active treatment were to be 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%. 81.6% (95% CI of 75.1% to 87.0%) of subjects in the FA sample on testosterone treatment had Cavg values within the normal concentration range on Day 112.

Table 5a: Percentage of Patients Achieving Target Testosterone Concentration (FA)

		T-Gel	T-Gel	Placebo	
Study Day	Total T(Cav) ng/DL	n/N (%)	95% CI	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

Table 5b: Number and Percentage of Subjects Achieving Cmax Ranges by Day (Full Analysis Set)

	n/N(%) for Subjects Achieving Testosterone Cmax Range			
Day	≤1500 ng/dL	1501-1799 ng/dL	1800-2500 ng/dL	>2500 ng/dL
14	203/210(96.7)	1/210(0.5)	5/210(2.4)	1/210(0.5)
56	178/183/(97.3)	2/183(1.1)	1/183(0.5)	2/183(1.1)
112	159/179(88.8)	9/179(5.0)	10/179(5.6)	1/179(1.1)
182	156/169(92.3)	6/169(3.6)	6/169(3.6)	1/169(0.6)

N=number of subjects with evaluable PK parameter for the given day
Source: Clinical Study Report: S176.3.104, Adapted from Table 13 (column 1501-1799 ng/dL added by calculation), page 69.

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.

> *Reviewer's Comment: In this study, Day 112 appears to be the day most likely for a patient to have an elevated serum testosterone level as well as their maximal PSA level (see Safety discussion). This observation may be relevant for labeling. Additional review is necessary.*

2.3.2 Secondary Endpoints:

During the double-blind phase of the study, individual Cmax values were to be ≤1500 ng/dL in ≥85% of the subjects, between 1800-2500 ng/dL in ≤5% of the subjects, and >2500 ng/dL in none of the subjects.

> *Reviewer's Comment: The Sponsor was asked to provide evidence that the serum testosterone levels >2500 ng/dL were due to factors other than the product itself (e.g., technical error, overdosage, etc).*

In the FA Sample, 93.9% (696/741) of Cmax observations were ≤1500 ng/dL when considering all four PK days combined. The percentage of subjects on testosterone treatment with Cmax values ≤1500 ng/dL was 96.7% (203/210) on Day 14; 97.3% (178/183) on Day 56; 88.8% (159/179) on Day 112; and 92.3% (156/169) on Day 182. Overall, 3.0% (22/741) of Cmax observations were in the range of 1800-2500 ng/dL when considering all four PK days combined in the FA sample.

A total of 10 subjects had a total of 11 observations of total testosterone concentrations >2500 ng/dL during the double-blind phase of the study (See Table 6). Testosterone concentrations that exceeded the 2500 ng/dL threshold were rare, sporadic, and inconsistent. In 9 of 10 subjects, they occurred on just one occasion on just 1 PK day and resolved despite continued treatment. The Sponsor has put forward several types of factors in explaining these abnormal testosterone values. First, there are laboratory and site specific factors such as blood sample collection (individual needle sticks versus

indwelling venous catheters, re-use of torniquets, keeping subjects in clinic during PK days versus allowing the subject to leave clinic between blood draws), and secondly, there are subject-specific factors such as exercise prior to blood draws, cutaneous vasodilation, overdosage, and third, environmental factors such as heat, and humidity at the time of blood collection.

Reviewer's Comment: These abnormalities will be reviewed in detail during the NDA review process. At the current time this issue is not judged to preclude filing of the NDA.

Table 6: Serum Total Testosterone Concentrations >2500ng/dL in Study S176.3.104

Subject Number	Dose (g/day)	Day	Timepoint After Dosing	Total Testosterone (ng/dL)	DHT (ng/dL)	DHT/T Ratio (95% interval)	E2 (pg/mL)	Comments Narrative Analysis
Normal Range						(0.074-0. 330)	<20 pg//mL	
Cases of Suspected Blood Sample Contamination Artifact Influencing PK Profiles								
003-008	N/A Before drug	1	Baseline Day 1 (No active treatment yet)	3270	18	0.006	48	Handling error-repeat 631
039-009	5.00	56	1 hour	3750	43	0.011	14	Blood Sample contamination
012-008	5.00	182	2 hour	4430	77	0.017	22	Blood Sample contamination
005-028	3.75	28	Pre-dose	3867	100	0.026	No value	Blood Sample contamination
044-005	2.50	14	Pre-dose	2850	193	0.068	No value	Handling error-repeat 1030ng/dL
								0 5h post – dose 1150ng/dL
Case of Acute Increases in Systemic Absorption Primarily Influencing PK Profiles								
007-006	5.00	112	8 hour	2550	137	0.054	16	Increased absorption from dermal compartment/ heat stress & Blood Sample contamination
058-006	5.00	112	2 hour	2510	237	0.094	43	Rare acute increase in systemic absorption – ? etiol
067-001	3.75	112	Pre-dose	2730	267	0.098	64	Higher than prescribed dosing
015-005	2.5	14	Pre-dose	3290	341	0.104	31	Suspected double dosing Day 14
049-008	2.50	56	0.5 hour	2810	354	0.126	35	Applied every 17h,skin hydration
049-008	2.50	14	0.5 hour	3200	414	0.129	17	Applied every 17h

Source: 2.5 Clinical Overview of NDA submissions adapted from Table 8, page 39

2.4 Preliminary Efficacy Conclusions

The Sponsor has achieved their primary efficacy endpoint. With regard to the secondary endpoints, they have achieved the endpoints of serum testosterone levels ≤1500 ng/dL in ≥85% of the subjects, between 1800-2500 ng/dL in ≤5% of the subjects; however, there

were 10 subjects and 11 instances of serum testosterone levels > 2500 ng/dL. The endpoint was none. These cases will be reviewed in detail.

With respect to baseline characteristics, slightly more whites than non-whites achieved the primary efficacy endpoint, but both groups achieved the primary efficacy goal. There were no major differences noted in BMI, age, and percent free PSA.

A significant decrease was observed in LH, FSH, HDL-3, Type 1 cross-linked C-telopeptide (certain age groups) and bone-specific telopeptide in the patients receiving testosterone. There were no significant changes noted in bone-specific alkaline phosphatase, vascular adhesion molecule, waist-to-hip ratio, tumor necrosis factor, IL-6, IL-10, C-reactive protein, matrix metalloprotease 9, HDL-2, D-Dimer, and fibrinogen.

Serum DHT and estradiol levels generally paralleled changes seen in serum total testosterone. The mean concentrations were generally within the normal range for all treatment groups (10-40 pg/ml estradiol). In the testosterone gel 1.62% treatment groups the mean DHT levels were mostly in the eugonadal range (11.2-95.5 ng/dL) with the exception of the 3.75 mg dose group on Day 56 (+1.3%), Day 112 (+6.8 - 26.7%), and Day 182 (+4.7 - 29.8%).

Reviewer's Comment: Day 112 appears to be the time in this population that serum testosterone levels, metabolites, and PSA levels peak.

3.1 Safety Exposure

In total, the NDA contains safety data from 785 subjects exposed to Androgel 1.62%. The safety data is derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008, and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104. By prior agreement, the safety data from the open-label period of Study S176.3.104 will be submitted with the 120-Day Safety Update. 382 hypogonadal males are included in the integrated safety base, and 307 healthy males and 96 females are included in the non-integrated safety data base.

In the Phase 1 integrated studies a total of 172 hypogonadal men were exposed to any dose of T-Gel 1.62 %. 10 men (6.8%) were exposed for 0-7 days, 54 men (36.7%) for 8-14 days, 42 men (28.6%) for 15-21 days, 8 men (5.4%) for 22-28 days and 33 men (22.4%) for greater than 28 days. When analyzed by individual dose, 24 subjects were exposed to 1.25 g of the study drug for a mean of 9.1 days, 40 subjects were exposed daily to 2.5 g of the study drug for a mean of 14.1 days, 22 subjects were exposed to 3.75 g of the study drug for a mean of 9.5 days, 72 subjects were exposed to 5.0 g of the study drug for a mean of 21.8 days and 11 subjects were exposed to the study drug were exposed to 6.25 g of the study drug for a mean of 13.5 days.

In the single Phase 3 Study, S176.3.104, 234 patients were exposed to T-Gel 1.62 % for a mean of 151.9 days. The cumulative duration of exposure was similar for the

testosterone gel 1.62% groups and the placebo group at each 4-week interval. The mean exposure to 2.50 g of testosterone gel 1.62% was lower as it was the starting dose from which subjects were titrated.

In the non-integrated studies, 235 healthy men were exposed to testosterone gel 1.62% for a total of 26 days in a sensitization and skin irritation study, 48 healthy males and females were exposed to 5.00 g of testosterone gel 1.62% daily for 7days applied to the male only in a transference study, and 24 healthy males and females were exposed to 2 days of exposure to testosterone gel 1.62% (one dose each of 2.5 g or 5.0 g) applied to the male only to evaluate post dose washing and its effect on transfer of testosterone gel.

Reviewer's Comments:

1) *A total of 405 hypogonadal men were exposed to the to-be-marketed drug. 234 patients in the Phase III protocol were exposed to the to-be-marketed drug for an average of 15l.9 days. The results of a one year safety study are to be submitted with the 120-Day Safety Update. 172 hypogonadal males were exposed to the to-be-marketed drug in the integrated Phase I trials. Of these men, 36.7% were exposed for a mean of 8-14 day and 22.4% for greater than 28 days. Although these exposure numbers are less than ICH guidelines for a chronically administered drug, the safety profile of Androgel 1% is well known and this reviewer believes that the extent of exposure is adequate to evaluate safety of AndroGel 1.62%.*
2) *Safety data from 5 Phase I integrated studies are presented separately form the 1 Phase III study. This approach is acceptable because the design, dose, and exposure duration differed significantly between the Phase I and III studies.*
3) *Three studies (S176.1.003, S176.1.008, and S176.1.004) were not integrated for the following appropriate reasons:*
    - *They involved healthy male subjects.*
    - *Two assessed drug transference and effects of washing on transference*
    - *One study evaluated skin sensitization and utilized a skin patch.*

3.2 Patient Demographics

The demographics of the hypogonadal patients in Study S176.3.104 are shown in Table 7.

Table 7: Demographics of Hypogonadal Patients in the Phase III Study

Characteristics	T-Gel 1.62% N=234 N(%)	Placebo N=40 N(%)
Age		
Mean	53.5	40
< 65 years	199 (85%)	32 80)
≥ 65 years	35 (15.0)	8 (20)
Race		
Asian	7 (3.0)	0
American Indian	4 (1.7)	0
Black	29 (12.4)	2 (5.0)
White	196 (83.3)	38 (95%)
Multi-races	1 (0.4)	0
BMI (kg/m^2) (mean[SD])	31.3 (4.2)	30.6 (4.1)
Percent Free PSA (%)	24.5 (11.6)	24.7 (11.4)

Source: Clinical Study Report: S176.3.104: Tables 2.0.1, 2.1.0: pages 227, 231.

Subject 045-06 is diagnosed as Klinefelter's syndrome. There are no patients with the diagnosis of Kalman's Syndrome in the protocol.

Reviewer's Comment: The Phase III study population was similar to those of other approved testosterone replacement products.

3.3 Dose Rationale

The Sponsor used data from an *in vitro* human cadaver skin experiment (PD 0299685.176.7.08.CRO study report), and a multiple-dose Phase I study in 38 hypogonadal men (S176.1.001) to select the dose for Phase 3. The Sponsor believes that these studies showed that testosterone gel at a formulation strength of 1.6-1.62% provides testosterone absorption/release characteristics that are comparable to the 1% gel strength but at a lower gel application volume. In the cadaver skin study, testosterone gel strengths of 1.2%, 1.4% and 1.6% had (b) (4) compared to testosterone gel 1% and the cumulative amount of released testosterone was highest for the 1.6% gel. The 1.62% gel strength was most comparable to AndroGel 1% based on the 24-hour concentration profiles, Cav, Cmax and on comparisons of subject proportions within concentrations within and above the eugonadal range in the Phase 1 multiple-dose study. Linear increase in testosterone Cmax and AUC_{0-24} with increasing dose was observed over the dose range of 1.25-5.00 g following single dosing and over the entire dose range of 1.25-6.25 g following multiple dosing. Because of high variability, dose proportionality could not be statistically demonstrated.

> *Reviewer's Comment: It was decided to initiate treatment in the Phase 3 study at 2.5 g per day and then titrate up or down at 1.25 g increments based on serum testosterone determinations in order to maintain testosterone concentrations in the eugonadal range. In my opinion, this is reasonable.*

3.4 Specific Populations

No formal analysis of the effects of **age, and body weight** on the pharmacokinetics of testosterone gel 1.62% have been conducted. For pharmacokinetic parameters (including Cavg) by age, race, and BMI subgroups, the following groups were defined:

- Age: 45years, 45-54 years, 55-64 years and >65 years.
- Race: whites and non-whites
- BMI: quartiles of BMI, and BMI pre-defined ranges (normal and underweight, overweight, obese, clinically obese).

The Sponsor believes that the data from the Phase III efficacy study (S176.3.104) on exploratory analysis suggests that these factors have no effect on the pharmacokinetics of testosterone. The study, however, was not powered to detect differences between subgroups. There are no data available for subjects <18 years of age or women.

Race: No specific PK was conducted to investigate the effect of race. The number of non-Caucasian patients in the Phase III study was too small to draw meaningful conclusions.

Geriatric: 15% of patients in the Phase III study were ≥65 years old. This number of geriatric subjects (35) may be too small to draw meaningful conclusions about this subgroup.

Pediatric: No pediatric study has been conducted with Androgel 1.62%.

Renal and Hepatic Impairment: No formal studies of testosterone gel 1.62% have been conducted in patients with renal or hepatic insufficiency.

3.5 Safety Results

3.5.1 Adverse Events

The summaries of safety findings are presented in Tables 8 and 9. For the remainder of this review, the treatment group in the Phase III protocol refers to patients randomized to receive Androgel 1.62% in the double blind 182 day period. The open- label results are not reviewed in this filing memorandum.

Table 8: Total Adverse Rections, Serious Adverse Reactions, Discontinuations Due to Adverse Reactions and Application Site Reactions in the Double-Blind Phase III Study

Assessment	Androgel 1.6% N=234 Mean Exposure=151.9 days N(%)	Placebo N=40 Mean Exposure=147.9 days N(%)
Any Adverse Event (AE) Severe AE	130(55.6) 11(4.7)	15(37.5) 0(0.0)
Serious Adverse Event Deaths	5(2.1) 0(0.0)	2(5.0) 0(0.0)
Discontinuations Due to TEA (DC/AE)	25(10.7)	0(0.0)
Application Site Reactions Hypersensitivity Pruritis	1(0.4) 1(0.4)	0(0.0) 0(0.0)

Source: Clinical Study Report S176.3.104: Table 3.0.0, page 1691(adapted)

Table 9: Total Adverse Rections, Serious Adverse Reactions, Discontinuations Due to Adverse Reactions and Application Site Reactions in the Integrated Phase I Studies

Assessment	Androgel 1.62%					
	1.25 g N=24	2.5 g N=40	3.75 g N=22	5.00 g N=72	6.25 g N=11	Combined N=147
Any AE Severe AE	12(50.0) 0(0.0)	16(40.0) 1(2.5)	13(59.1) 1(4.4)	60(83.3) 2(2.8)	8 (72.0) 0(0.0)	105(71.4) 3(2.4)
Serious AE (No Deaths)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(18.1)	2 (1.4)
DC/AE	0(0.0)	0(0.0)	0(0.0)	3(4.2)	0(0.0)	3 (2.0)
Applic site Rxn	1(4.2)	3(7.5)	5(22.7)	27(37.5)	3(27.3)	40(27.2)

Source: Module 2.7.4, Summary of Clinical Safety, Table 22 (page 65) and Table 4.0.0

Serious Adverse Events

Deaths: No deaths occurred in the Phase I integrated studies or in the Phase III double-blind protocol.

Non-fatal SAE's: In the integrated Phase I 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. The study drug was discontinued in both cases.

Six treatment-emergent serious adverse events (TESAEs) in Protocol S176.3.104 were reported by five subjects in the testosterone gel 1.62% group and included (PT):

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 investigators considered the malignant hypertension "possibly related" (hematocrit was also increased in this patient) and the myocardial infarction as" unlikely related." A retinal detachment was the only TESAE reported by a subject in the placebo group.

> *Reviewer's Comment: A preliminary review of all SAE case narratives was performed. In this reviewer's opinion, Subject 06 in Protocol S176.3.104, Testosterone Gel 2.5 g, had malignant hypertension the occurrence of which was associated with a rise of hematocrit from 47.1% (baseline) to 52.7% (Visit 7) and to 50.1% (Visit 10). Such an increase in hematocrit can lead to fluid retention and an increase in the blood pressure. This case will be assessed in further detail as the review progresses. The other SAEs are not considered treatment related, in this reviewer's opinion.*

Adverse Events Leading to Discontinuation

Phase III study (double-blind period): Overall, 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 application.

The only TEAE that occurred in more than one subject in the testosterone gel 1.62% group (17/234, 7.3% 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 criterion of change from baseline >0.75ng/mL. Four other subjects had a PSA value>4 ng/mL, these subjects had PSA ≤ 4.0ng/mL upon repeat testing. The incidence of premature discontinuation due to increased PSA across the testosterone 1.62% groups was as follows: 1.25 g: 1/17, 5.9%; 2.50 g: 2/60, 3.3%: 3.75 g: 7/66, 10.6%; 5.00 g: 7/91, 7.7%.

> *Reviewer's Comment: Case narratives were provided for all subjects discontinuing due to an adverse event. There does not appear to be a dose or exposure- related increase in the incidence of premature withdrawal secondary to increased PSA or increased PSA velocity. Only one of ten patients (10.0%) with testosterone >2500 ng/dL had increased PSA or increased PSA velocity, 3 of 25 patients (12%) with testosterone in the 1800 to ≤2500 ng/dL range had increased PSA or increased PSA velocity, 0 of 16 patients (0.0%) with testosterones in the 1501- <1800 ng/dL range had PSA abnormalities, and 19 of 183 patients (0.4%) with testosterones ≤ 1500 ng/dL had increased PSA or PSA increased velocity. There were no PSA abnormalities in placebo subjects.*

Table 10: Treatment-related adverse events leading to premature discontinuation in the double-blind Phase III study

Preferred Term	T-Gel 1.62% (N=234)	Placebo (N=40)
Diarrhea	1 (0.4%)	0 (0.0)
Fatigue	1(0.4%)	0 (0.0)
Prostate Specific Antigen Increased[1]	17(8.1%)	0 (0.0)
Hematocrit increased	1(0.4%)	0 (0.0)
Blood pressure increased	1(0.4%)	0 (0.0)
Pituitary tumor	1(0.4%)	0 (0.0)
Disturbances in consciousness NEC	1(0.4%)	0 (0.0)
Syncope Vasovagal	1(0.4%)	0(0.0)
Dizziness	1(0.4%)	0 (0.0)
Pollakiuria	1(0.4%)	0 (0.0)
Skin nodule	1(0.4%)	0 (0.0)

[1] One additional subject (045-026) had an AE of increased PSA but withdrew consent prior to confirmation of abnormal values.

Source: Module 2.7.4: Table 21, pages 63-64.

Integrated Phase I studies: 4 of 147 subjects receiving testosterone gel 1.62% discontinued due to an adverse event (1 each of atrial fibrillation, dermatitis [and eczema], and hypertension). Subjects 25817 (Days 1-3) and 25802 (Days 1-2) both received T-Gel 5.00 g on the days noted in study 176.1.002. Both had a relevant history of hypertension and were discontinued for the AE of hypertension.

Non-integrated studies: 2 of 307 (0.65%) discontinued prematurely due to an adverse event. Both subjects were in study S176.1.004 to evaluate sensitization and skin irritation of T-gel 1.62%. Both subjects (1004-26625 and 1004-26626) developed rashes judged as probably related to the study drug.

Treatment Emergent Adverse Events

Phase III Study**:** Data from the Phase III double-blind study and the integrated Phase I studies are presented in the tables that follow. The most common adverse events were related to PSA elevations, upper respiratory infections, hypertension and contact dermatitis.

Table 11: Common treatment-emergent adverse events (>2% for T-gel 1.62% and greater than placebo) for the double-blind Phase III 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.

> *Reviewer's Comment: The diarrhea and upper respiratory conditions in the active treatment group are unlikely to be treatment related. PSA elevations and hypertension are most likely treatment related and should be presented in labeling. There was no indication that application site pruritis and dermatitis increased with increased testosterone concentrations. No patient discontinued because of an application site TEAE.*

The proportion of subject with at least one TEAE ranged from 52.5% to 80.0% across serum testosterone concentration categories (≤ 1500 ng/dL: 96/183, 52.5%; 1501 to 1800 ng/dL: 9/16, 56.3%; 1800 to ≤ 25000 ng/dL: 17/25, 68.0%; >2500 ng/dL: 8/10, 80.0%). There was no pattern of increasing incidence of single preferred terms with higher serum testosterone concentration category.

Table 12: TEAEs by Testosterone <2500 ng/dL versus Testosterone > 2500 ng/dL

Preferred Term	T≤2500 N=224	T>2500 N=10
Subjects with at least one AE	n (%) 122(54.5)	n (%) 9(90.0)
Toothache	0	1(10.0)
PSA Increased	22(9.8)	1(10.0)
Weight Increased	1(0.4)	1(10.0)
Mood Swings	0	1(10.0)
Libido Increased	0	1(10.0)
Nephrolithiasis	0	1(10.0)
Nipple Disorder	0	1(10.0)
Erectile Dysfunction	1	1(10.0)
Erection Increased	0	1(10.0)
Testicular Pain	1(0.4)	1(10.0)
Acne	1(0.4)	1(10.0)
Hypotension	1(0.4)	1(10.0)

Source: Clinical Study Report S176.3.104, Table 23, Page 2390

Table 13: TEAEs by Testosterone Level and Body System

Primary SOC (Disorder)	≤1500 T level N=183	1501-<1800 N=16	1800-≤2500 N=25	>2500 N=10
Pt with at least one AE	N (%) 96(52.5)	N (%) 9(56.3)	N (%) 17(68.0)	N (%) 8(80.0)
Cardiac	3(1.6)	0	2(8.0)	0
Endocrine	1(0.5)	0	0	0
Eye	0	0	1(4.0)	0
Gastrointestinal	8(4.4)	0	0	1(10.0)
General and Site Conditions	15(8.2)	0	0	0
Immune System	4(2.2)	0	0	0
Infections Infestations	31(16.9)	1(6.3)	4(16.0)	1(10.0)
Injury, Poisoning, Procedural Complications	12(6.6)	1(6.3)	3(12.0)	0
Investigations	27(14.8)	1(6.3)	4(16.0)	2(20.0)
Metabolism Nutrition	1(0.5)	3(18.8)	3(12.0)	0
Musculoskeletal Connective Tissue	11(6.0)	3(18.8)	6(24.0)	0
Nervous System	8(4.4)	2(12.5)	3(12.0)	0
Psychiatric	8(4.4)	2(12.5)	2(8.0)	2(20.0)
Renal, Urinary	1(0.5)	0	0	1(10.0)
Reproductive, Breast	5(2.7)	1(6.3)	0	1(10.0)
Respiratory, Thoracic, Mediastinal	7(3.8)	2(12.5)	1(4.0)	0
Skin, SubQ	13(7.1)	2(12.5)	0	1(10.0)
Vascular	0	1(6.3)	0	0

Source: Clinical Study Report S176.3.104; Table 3.17.0, page 1830

Reviewer's Comment: The numbers in the outlier groups are too small to make meaningful comparisons, other than to state that the TEAE rate in subjects with testosterone levels >1500 ng/dL(n=34) is 66.7% versus 52.5% for men with testosterone levels <1500 ng/dL.

Adverse Events Reported in the Combined Phase I Studies in Hypogonadal Men (Studies S176.1.001, S176.1.002, S176.1.005, S176.1.006 and S176.1.007).

Table 14: Summary of Adverse Events in Phase I Studies (Combined Safety Sample)

	Testosterone Gel 1.62%					
Statistic n(%)	1.25g N=24	2.5g N=40	3.75g N=22	5.0g N=72	6.25 N=11	Combined N=147
≥ 1 TEAE	12(5.0)	16(40.0)	13(59.1)	16(83.3)	8(72.7)	105(72.4)
Skin Site TEAE	1(4.2)	3(7.5)	5(22.7)	27(37.5)	4(36.4)	40(27.2)

Source: Table 22, 2.7.4 Summary of Clinical Safety: page 65

In the Phase 1 studies, the most frequently reported SOCs are listed below:

- General disorders and Administration site conditions were the most frequently reported TEAEs (49/147, 33%). The most frequently reported PTs were: application site papules (16/147, 10.9%), application site excoriation (8/147, 5.4%), application site dermatitis (7/147, 4.8%) and application site erythema 1/147, 4.8%).
- Skin and subcutaneous tissue disorders (47/147, 32.0%) included the preferred terms (PTs) dry skin (9/147, 6.1%) and acne (7/147, 4.8%).
- Nervous system disorders (23/147, 15.6 %) included PT headache (19/147, 12.9%).
- Musculoskeletal and connective disorders (12/147, 8.2%) included the PTs of arthralgia (4/147, 2.7%), muscle spasms (3/147, 2.0%), and back pain (3/147, 2.0%).

8 of 147 subjects reported hypertension (5.4%). Two of these subjects had a previous history of hypertension.

3.5.2 Skin Transfer Studies

S176.1.003 was a single center, open label, randomized, single and multiple exposure, parallel group study in healthy male and female couples. Each male-female couple was randomized to one of three treatment groups. Each group consisted of 16 couples. The pharmacokinetic objectives of the study were to determine the pharmacokinetics of testosterone concentrations in female subjects after single and multiple doses of testosterone gel 1.62% (5.0 g) and to evaluate skin-to-skin testosterone transfer potential from males dosed with gel to non-dosed female subjects when direct contact occurred 2 hours or 12 hours post-dose or when contact occurred with a t-shirt at 2 hours post dose (the three treatment groups). The testosterone gel was applied to the abdomen and each couple engaged in abdomen to abdomen contact in the vertical position for 15 minutes daily.

Blood samples for measurement of serum testosterone, DHT, and estradiol concentrations were collected from female subjects only at the following times: serially over a 24-hour

period on Day-1 (baseline), serially over the 24-hour period following the end of contact on Days 1 and 7, and at 48 hours after end of contact on Day 7.

Results: The baseline testosterone concentrations were similar across all treatment groups (20.1-29.3 ng/dL [normal range 8-75 ng/dL]). Based on the concentration- time profiles, mean observed testosterone concentrations increased from baseline yet remained within the normal range on Days 1 and 7 for all treatments except for direct skin contact 2 hours post-dose. At 16 hours post skin contact, the testosterone Cmax level was 81ng/dL ng/L on Day 7. On Day 1 the Cmax was 70ng/dL. The mean Cavg for observed testosterone was within the normal female range after single and multiple episodes of skin contact.

Covering the site of application on the male partner prior to post dose contact reduced the amount of exposure by 40-48%. With site coverage the mean Cmax remained within the normal range. Accumulation of testosterone was minimal after daily skin contact for 7 days. Mean testosterone concentrations in females returned to baseline levels 48 hours after last skin contact with a dose male partner.

Study S176.1.008 was a randomized, open-label, parallel group study to evaluate the Effects of Dose, Postdose Washing, and Application Site on the transfer potential of testosterone gel 1.62% from dosed males to a non-dosed partner. Contact time was 15 minutes. 24 healthy male-female couples participated. The study objectives were:

- To evaluate skin-to-skin testosterone transfer potential from males dosed with gel to non-dosed female subjects using a dose of 2.5 g gel, when contact occurred 2 hours post dose with and without a t-shirt.
- To evaluate skin-to-skin testosterone transfer potential from males dosed with 5.0 g gel to non-dosed female subjects when direct contact occurred 2 hours postdose with and without postdose washing.
- To evaluate skin-to-skin testosterone transfer potential from males dosed with 5.0 g gel to non-dosed female subjects when direct contact occurred 2 hours postdose after application to upper arms/shoulders or abdomen of males with the corresponding site in females.

Results: Mean baseline testosterone concentrations were within the normal range for all groups (16.2-30.3 ng/dL). Mean observed testosterone concentrations increased above baseline for all treatments except for abdomen-abdomen contact 2 hours post dose (2.5g) with the male wearing a t-shirt and for direct skin-to-skin abdomen to abdomen contact 2 hours post 5.0 g dose after washing of the male application site. Observed testosterone concentrations returned to approximate baseline levels at or before 48 hours following the last contact for all treatments. No abnormal testosterone levels were recorded.

A t-shirt barrier eliminated transfer in this study. Washing the transfer site prior to direct skin contact substantially limited the transfer of testosterone - AUC_{0-24} and Cavg were comparable to baseline and Cmax was only slightly increased. After direct abdominal or upper/shoulders skin contact of a female with the corresponding application site on a male partner dosed with 5.0 g of testosterone gel 1.62 %, an increase in testosterone was

observed with the normal range for both contact sites however, mean Cmax increased above the upper limit of normal following upper/shoulder contact. Testosterone transfer was higher for the upper arms/shoulders contact compared to the abdomen.

> *Reviewer's Comment: It appears that the female exposure to testosterone due to secondary exposure, as documented in S176.1.003 and S176.1.008, can be mitigated by coverage of the application site with clothing and by washing of the application site 2 hours post dose. It further appears that this potential risk can be managed by appropriate labeling and may be further evaluated in a post marketing study.*

3.5.3 Skin Sensitization and Skin Irritation Study

Study S176.1.004 was a double-blind, placebo controlled study to evaluate the sensitization and irritation potential of repeat applications of Testosterone Gel 1.62 % in healthy male subjects. The study was performed in the US. The subjects in the study during the induction phase applied a skin patch (3.14 cm^2) to separate sites on the upper outer arm contained Testosterone Gel 1.62 % 100mg. This is 6 fold higher than the highest clinical dose. The patch was applied every 48-72 hours for a total of 9 applications. Skin reactions to the patch were recorded. A rest phase of 12-17 days occurred during which no patches were applied. In the following challenge phase, the skin patches were applied to sites on the upper back for 48 hours. These sites were then evaluated 30 minutes and 48 hours after patch removal. If a rechallenge was necessary, it was conducted 3-4 weeks following the final evaluation of the challenge phase.

235 men were enrolled and 214 men completed the protocol. 21 subjects were exposed to at least one application. Four subjects were lost to follow-up. Six subjects were dropped due to non-compliance, and 2 subjects were discontinued due to a nonserious AE of rash. There were 4 test articles used:

a. Testosterone gel 1.62%
b. Placebo gel
c. Positive irritant control
d. Low irritant control

The irritation potential for each patch was determined by the scores obtained during the induction phase. Irritation was graded as follows: 0-no evidence of irritation, 1-minimal erythema, 2-definite erythema, 3-erythema and papules, 4- definite edema, 5-erythema edema and papules, 6-vesicular eruption, and 7-strong reaction extending beyond test site

Sensitization reaction was evaluated as follows: inflammatory responses were graded: 0-no visible reaction or erythema, 0.5-slight confluent or patchy erythema, 1 mild reaction-macular erythema, 2-moderate reaction-macular erythema, 3-strong to severe reaction-macular erythema.

Results: No serious adverse events or deaths occurred during the study. Fifty-one subjects (51/235, 21.7%) reported 97 nonserious events over the course of the study. The most common AE was headache (20 events in 13 subjects, 5.5%).

The following (2) subjects discontinued from study participation due to the nonserious AEs of rash:

- Subject 26625, a 20 year-old Caucasian male assigned to random sequence A, C, D, B experienced a nonserious AE of moderate intensity considered probable in relationship to treatments. The rash occurred one day after last exposure to test articles and resolved with topical and oral therapy. The subject was exposed a total of 18 days at the time concomitant topical hydrocortisone acetate was administered.
- Subject 26626, a 38 year-old White male randomly assigned to sequence C, B, A, D experienced a non serious AE rash on the right arm and chest that was considered unlikely related to treatments. He received topical clobetasol ointment. He was exposed to the test articles for a total of 16 days at the time the concomitant medication was administered.

Three subjects experienced application site pruritis comprising 4 non-serious AEs that were attributed to the treatments by the investigator on a probable basis. The Sponsor concluded that there we no findings of patch irritation of clinical relevance. There was no evidence that Testosterone gel 1.62% produced sensitization as results during the challenge phase was similar to placebo gel. The Sponsor also concluded that Testosterone Gel 1.62% produced very mild irritation (all irritation scores<2, and 98% of scores were either 0 or 0.5 [similar to placebo]).

No trends or clinically significant changes were noted in clinical laboratory data, vital sign data, or physical examinations.

Reviewer's Comment: Testosterone Gel 1.62% appears to have minimal sensitization and irritation potential as compared to placebo.

Table 15: TEAEs in Study S176.1.104

System Organ Class	Preferred Term	Total (N=235)
Total Number TEAEs		141
Patients with ≥ TEAE		68(29%)
		n (%)
Ear and Labyrinth	Ear discomfort	1(0.4)
	Ear pain	3(1.3)
Eye Disorders	Ocular hyperemia	2(0.9)
Gastrointestinal Disorders	Abdominal pain	1(0.4)
	Abdominal Pain upper	5(2.1)
	Constipation	1(0.4)
	Dyspepsia	1(0.4)
	Nausea	3(1.3)
	Retching	1(0.4)
	Toothache	3(1.3)
	Vomiting	1(0.4)

Gen Disord, Adm site	Applic site pruritis	3(1.3)
	Fatigue	1(0.4)
	Irritability	2(0.9)
	Pyrexia	2(0.9)
Infections, Infestations	Conjunctivitis	1(0.4)
	Herpes Simplex	1(0.4)
	Influenza	1(0.4)
	Lower respiratory	1(0.4)
	Nasopharyngitis	7(3.0)
Injury, Poisoning, Procedural Complications	Arthropod bite	1(0.4)
	Hand fracture	1(0.4)
	Joint dislocation	1(0.4)
	Sunburn	3(1.3)
Metabolism, Nutrition	Anorexia	1(0.4)
	Dehydration	1(0.4)
Musculoskeletal Connective	Arthralgia	1(0.4)
	Back pain	2(0.9)
	Myalgia	3(1.3)
	Musculoskeletal pain	1(0.4)
	Neck pain	1(0.4)
	Pain extremity	1(0.4)
Nervous System Disorders	Headache	19(8.1)
	Lethargy	1(0.4)
	Syncope	3(1.3)
Psychiatric Disorders	Insomnia	2(0.9)
Respiratory, Thoracic, Mediastinal Disorders	Cough	9(3.8)
	Dysphonia	1(0.4)
	Epistaxis	1(0.4)
	Secretions increased (upper airway)	1(0.4)
	Nasal congestion	2(0.9)
	Nasal discomfort	1(0.4)
	Pharyngolaryngeal pain	6(2.9)
	Rhinitis allergic	1(0.4)
	Rhinorrhea	11(4.7)
Skin, Subcutaneous	Pruritis	1(0.4)
	Rash	3(1.3)
Vascular Disorders	Dizziness	1(0.4)
	Flushing	1(0.4)
	Hot flush	1(0.4)

Source: S176.1.004 (b) (4) Study M/ R06-1122, Table 10.3.1, page 645

Reviewer's Comment: These subjects received five times the testosterone dose of patients received using 5 g of Testosterone 1.62%. Aside from the 3 patients in whom syncope was reported, the TEAEs are quite benign. The incidence of syncope was evaluated further in the pivotal study results. Subject 051-02 (receiving testosterone gel 1.62% 2.5g) in Protocol S176.3.104 experienced syncope during the pharmacokinetic sampling period on Day 14 and was discontinued. A total of 3 subjects receiving testosterone gel 1.62% (1-2.5g, 2-5.0 g) experienced syncope during the double blind period versus none for placebo. Dizziness occurred in 3 subjects receiving testosterone gel 1.62 %(1-2.5 g and 2-5.0 g) and in no placebo subjects. This is an area for continued review.

3.5.4 Laboratory Findings

Discussion in this section is limited to Study S176.3.104 Double-blind period. Clinical laboratory (hematology, serum chemistry, and urinalysis) tests were performed at screening, at Baseline (Day 1) and at Visit 10 (Day 182). Safety testosterone levels were performed at baseline and at all Visits (1-10). Safety labs (PSA, Hct, Hgb, SGOT, SGPT, lipids) and sex steroid labs (testosterone, DHT, E2) and SHBG were performed at baseline and at all Visits (1-10). PK samples were done at Visits 3 (Day 14), 6 (Day 56), 9 (Day 140) and 10 (Day 182). PD samples were obtained at Visits 1, 8(Day 112), and 10.

An increase in Hgb was observed for the testosterone gel 1.62% compared with the placebo group (at endpoint 6.50g/L versus 1.74g/L). 4.8% of the Testosterone Gel 1.62% group had a shift in Hgb from normal at Baseline to High at endpoint versus none for placebo. There was a similar shift in hematocrit. 5 subjects had hematocrits >54%. One of these subjects (018-005) discontinued per protocol on Day 86. Three of the remaining four subjects discontinued during the open-label portion of the study (including Subjects 016-002, 016-003, and 018-006 [discontinued due to increased PSA]) and one subject (057-045) who was lost to follow-up.

Reviewer's Comment: Individual increases in serum hemoglobin and hematocrit will be subject to additional review.

A total of 34 subjects 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. 7/203 subjects (3.3%) had a PSA post-Baseline >4.0 ng/mL, while 33/209 subjects (15.8%) had an increase in PSA from Baseline > 0.75 ng/mL, and 6/209 subjects (2.9%) met both criteria for "increased PSA".

A total of 17 subjects discontinued from the study during the double-blind portion of this study due to an AE of "increased PSA". Four of the subjects who discontinued had maximum PSA levels between 1 and 1.4 ng/mL(Subjects 018-013, 049-015, 060-019,067-003) while two subjects had maximum PSA levels between 2 and 2.8 ng/mL (Subjects 003-010, 024-004). 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 (subject 049-011, 050-006, 060-015, 069-019). The remaining subjects either withdrew consent (subject 045-026), had a repeat PSA value bringing the average

PSA results with normal limits (Subjects 013-015, 042-009, 058-005, 060-004, 061-003, 064-009), or discontinued after the database lock of the double-blind portion of the study (Subjects 015-001, 016-003, 018-006, 028-021, 039-009, 043-016, 049-002, 049-030, 058-006, 069-003).

Table 16: Average Serum PSA Changes in the 182-Day Pivotal Double-Blind Period (Mean from Baseline)

PSA(ug/L)	Placebo	Testosterone Gel 1.62				
(n, %) statistic	N=40	1.25 g N=17	2.5g N=60	3.75g N=66	5.0g N=91	All T-Gel N=234
Baseline(mean)	0.85	0.74	0.86	0.98	0.87	0.89
Day 84 (Δ)	0.01	0.05	0.07	0.19	0.15	0.14
Day 182 (Δ)	-0.15	0.04	0.08	0.07	0.12	0.09
Endpoint (Δ)	-0.12	0.10	0.08	0.12	0.20	0.14

Source: Clinical Study Report S176.3.104, Table 4.3.0 pages 2114-2115.

Table 16a: Average Serum PSA Changes in the 182-Day Pivotal Double-Blind Period (Mean from Baseline) – In men over 65 years of age

PSA(ug/L)	Placebo	Testosterone Gel 1.62				
(n, %) statistic	N=8	1.25 g N=4	2.5g N=11	3.75g N=11	5.0g N=9	All T-Gel N=35
Baseline(mean)	1.25	0.38	1.16	0.77	1.13	0.94
Day 84 (Δ)	0.16	0.40	0.34	0.31	0.52	0.38
Day 182 (Δ)	-0.18	0.00	0.08	0.19	0.36	0.19
Endpoint (Δ)	-0.13	0.37	0.03	0.35	0.70	0.35

Source: Clinical Study Report S176.3.104, Table 4.3.1, pages 2124-2125.

> *Reviewer's Comment: The mean PSA, as expected, rose modestly and of note had declined by Day 182. See **Table 5b** and reviewer's comment below. Day 112 (Endpoint Day) had the highest PSA levels and testosterone levels.*

There were no clinically meaningful treatment group differences in mean changes form Baseline to Day 182 for hematology, chemistry, lipids (panel, enzyme profiles), special laboratory parameters, or urinalysis within the treatment groups. The changes in hemoglobin in the T-Gel patients (Baseline 148.4 g/L to 154.9 g/L at Endpoint were expected.

Clinical laboratory evaluations by sex, race, age: Due to the small number of subjects in the placebo group in the different age groups and race categories and the low incidence of markedly abnormal values, no conclusions were drawn by the Sponsor from these subgroup analyses.

There were 10 subjects with 11 testosterone elevations >2500 ng/dL. See Table 6. In each case other testosterone levels on the same day (when done) were not elevated.

Reviewer's comments: Each patient with a T >2500 ng/dL will be analyzed in depth. In addition, clinical pharmacology will provide an assessment of the T assay used and the methods of sample collection.

3.5.5 Other Safety Evaluations

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], respiratory rate [RR], temperature [T]), EKGs, and IPSS score.

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 vital signs and no important differences across dose groups were noted in the mean change from baseline. Using a change from baseline of 7% as "clinically meaningful", there were more patients on T-Gel compared to placebo for both a decrease from Baseline ≥7% in weight (12/222, 5.4% T-Gel versus 1/38, 2.6% for placebo) and an increase from baseline ≥7% in weight (16/222, 7.2% T-Gel versus 1/38, 2.6%).

Because of the small numbers in each treatment group, no discernable trends were noted based on age or race.

Table 17: Marked Abnormalities of Vital Signs in the 182 Day Pivotal Study

Statistic n(%)	Placebo N=40	T gel 1.25g N=17	T gel 2.5g N=60	T gel 3.75g N=66	T gel 5.0 N=91
Weight					
>7%↓	1(2.6)	1(5.9)	3(6.3)	5(7.6)	3(3.3)
>7%↑	1(2.6)	2(11.8)	2(4.2)	5(7.6)	7(7.7)
Systolic BP					
bsl≤90&↓≥20	1(2.6)	1(5.9)	1(2.1)	1(1.5)	1(1.1)
bsl≥180&↑≥20	0	0	0	1(1.5)	0
Diastolic BP					
bsl<50&↓≥15	0	0	0	1(1.5)	1(1.1)
bsl≥105&↑≥15	0	0	1(2.1)	1(1.5)	0
Pulse (bpm)					
bsl≤50&↓≥15	1(2.6)	1(5.9)	2(4.2)	1(1.5)	2(2.2)
bsl≥120&↑≥15	1(2.6)	0	0	0	0

*bsl=baseline
Source: Clinical Study Report S176.3.104, Table 5.1.0, and page 2281

Reviewer's comment: In this reviewer's opinion no discernable trends of concern in this data.

Electrocardiograms (ECGs): ECGs were obtained at screening and at Visit 10 (Day 182). The percentage of subjects who shifted from normal at Baseline to abnormal at Endpoint for global ECG evaluations was similar for the testosterone gel 1.62% groups and the placebo group (19/181, 10.5% versus 3/29, 10.3%). No subject in either treatment group

shifted from normal to abnormal clinically significant at Endpoint for global ECG evaluations.

IPSS Total Score: There were no clinically or statistically significant differences in the in the LS mean change from Baseline at each timepoint between the testosterone gel 1.62% and placebo groups in the IPSS Total Score.

3.5.6 Preliminary Safety and Tolerability Conclusions

1. The total patient exposure and skin tolerability to AndroGel 1.62% are acceptable.
2. The safety profile of Testosterone Gel 1.62% is on its face acceptable and is similar to other products approved for testosterone replacement therapy.
3. In light of increased testosterone levels and PSAs of patients at Day 112, an in depth review of adverse events at that time point is advisable in the NDA review
4. The adverse events of hypertension (occurring in 6 drug-treated patients) and possible worsening of hypertension coincident with a rise in hematocrit will be further reviewed.
5. The adverse event of syncope occurring in 3 drug treated patients versus 0 for placebo in the Phase III double blind treatment period will be further evaluated.
6. Subjects who experienced increased PSAs (PSA > 4ng/dL or increase of >0.75ng/dL) will be further reviewed.
7. Increase in hematocrit in drug-treated patients will be further studied.
8. A detailed review of patients with serum testosterone level >2500ng/dL will be conducted.
9. In patients with testosterone>2500 ngd, two patients appeared to be using more than the recommended dose, and 1 patient was using the product more frequently than advised.
10. Secondary exposure via skin transference will be further reviewed. Specific information to patients (e.g. via a MedGuide) appears to be necessary with regard to avoidance of secondary exposure to children and women. If a MedGuide is deemed necessary, then the Agency would need to make a formal request to Sponsor for a Risk Mitigation and Evaluation Strategy (REMS) – which would likely consist of a MedGuide only.

4 Other Considerations of Filing Review

4.1 Review of Financial Disclosure Documents

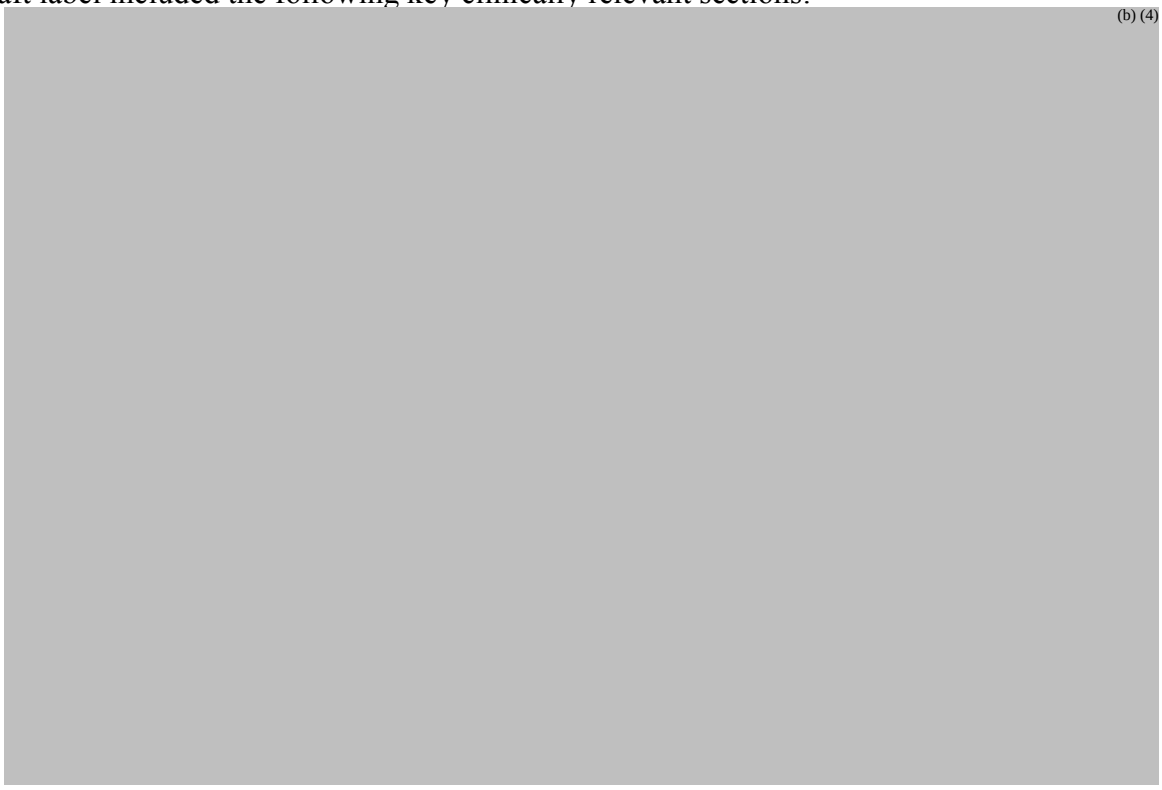
Form FDA 3454 signed 26 June 2008 was provided in the submission. Financial disclosures were submitted for the principal investigators in Protocols S176.1.001, S176.1.002, S176.1.003, S176.1.004, S176.1.005, S176.1.006, S176.1.007, S176.1.008, and the pivotal Phase 3 study S176.3.104.

A total of 77 investigators (all from all protocols and study sites) had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54, 2(a)], proprietary interest in the covered product or significant equity interest in the Sponsor of the covered product [21 CFR 54.2(b)], significant payments of other sorts from the Sponsor of the covered study [12 CFR 54.2(f)]. There was no missing financial disclosure information for investigators in the above listed studies.

4.2 Labeling

The proposed label complies with the basic requirements of the Physician Labeling Rule (PLR). The content of the label is based on the findings of the clinical development of testosterone gel 1.62% and previously approved testosterone gel products. The proposed draft label included the following key clinically relevant sections:

(b) (4)



<u>Reviewer's Comment</u>: It may be necessary to increase the prominence of the secondary exposure issue in labeling. We might even consider a bolded or Boxed Warning specific to this issue.

5. Clinical Comments to Sponsor

The following Clinical comments and requests should be conveyed to the Sponsor in the 74-Day Letter:

1. Potential for secondary exposure of testosterone to women and children will be further reviewed. Additional labeling may be requested, including information directed to patients to assure safe use.

2. A detailed review of patients with serum testosterone level >2500ng/dL will be conducted. In addition to the analysis already provided in your NDA, we request a comparison of the frequency of this occurrence to the pivotal study for AndroGel 1%.

3. Hypertension was reported as an adverse event in 6 drug treated patients and 0 placebo subjects. In one of these cases, worsening of hypertension may have been coincident with a rise in hematocrit. Provide an executive summary and analysis of hypertension as an adverse event ,and the relation of this AE to drug dose, exposure, and duration of treatment. Please include a discussion of potential worsening of pre-existing hypertension, narratives for the patients involved, and a comparison of these events and their frequency to similar events occurring in controlled studies for AndroGel 1%. The analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

4. Syncope was reported as an adverse event in 3 drug treated patients and in 0 placebo patients in the double-blind period of S176.3.104. Provide an executive summary and analysis of syncope as an adverse event. Please discuss related events or terms (such as presyncope) and their relation to drug dose, exposure , and the duration of treatment. Please provide narratives for the patients involved and a comparison of these events and their frequency to similar events occurring in controlled studies (pivotal) for AndroGel 1%. The analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

5. Five patients in the double-blind portion of S176.3.104 were reported have increase of hematocrit to greater than 54%. Provide an executive summary and analysis to include these events (in Study 176.3.104 double-blind and open label periods) and their relation to drug dose, exposure, and duration of treatment. Please provide narratives for the patients involved and a comparison of these events and their frequency to similar events occurring in controlled studies (pivotal) for AndroGel 1%. Also, compare per cent increase of hemoglobin and hematocrit in the double-blind portion of S176.3.104 and the comparable periods in the pivotal studies for Androgel 1%. The analysis is to consider demographics, concurrent medications and concomitant medical diagnoses.

6. Twenty patients (9.8%) were observed to have “increased PSA”, defined as serum PSA > 4ng/dL or an increase from baseline in serum PSA of >0.75ng/dL during the double- blind period of S176.3.1004. Provide an executive summary and analysis of these “increased PSAs” in Study 176.3.104 double-blind and its open label period. Provide a discussion of the relation to drug dose, exposure, and duration of treatment. Provide narratives for the patients involved and a comparison of these events and their frequency to similar events occurring in controlled studies (pivotal) for AndroGel 1%. Also, please include information related to performance of prostate biopsies, their results, and any changes in the

IPSS in the open- label period in these patients. The analysis should consider demographics, concurrent medications and concomitant medical diagnoses.

7. In patients with testosterone>2500 ng/dL, two patients appeared to be using the product at more than the recommended dose, and 1 patient was using the product more frequently than advised. Provide an executive summary and analysis of all situations in the clinical studies where the recommended dose or frequency of dosing was exceeded. You may wish to propose a strategy to limit these occurrences and this might include instruction to patients or future pump modifications.

8. We note that testosterone and PSA levels appear to peak at Day 112. It is not clear, however, that clinical adverse events correlate with peak terstsoterone levels. Provide an executive summary and analysis relating to adverse events and exposure, with discussion of adverse events at Day 112. Please include all adverse events, but pay special attention to hypertension, increased serum PSA, and hemoglobin/hematocrit values.

Appendix A: GRMP Clinical Reviewer Filing Checklist

NDA Number: 22-309 **Applicant: Solvay Pharmaceuticals** **Stamp Date: February 12.**

Drug Name: Androgel 1.62% **NDA Type: standard, original application**

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: S176.1.002 Study Title: 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 6.25 g in Hypogonadal Males Sample Size: 56 Arms: 5	X			

	Content Parameter	Yes	No	NA	Comment
	Location in submission: Module 5 – 5.3.3.2.1 Study Number: S176.1.001 Study Title: The Multiple Dose Pharmacokinetics and Comparative Bioavailability of Testosterone After Administration of 1.25, 2.5, and 3.75 g Dose Levels of Investigational Testosterone Hydro-Alcoholic Gel Formulations in Hypogonadal Male Volunteers Sample Size: 38 Arms: 3 Location in submission: Module 5 – 5.3.3.2.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study#1: S176.3.104 Indication: Testosterone replacement therapy in hypogonadal males.	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	All studies, including the Phase III study, were conducted in the U.S.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Thorough QT study was not necessary
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	There has been no marketing experience with Androgel 1.62% in any country. The worldwide experience with Androgel 1% is discussed.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			The exposure is less than the ICH guidelines but is sufficient to assess safety and efficacy of

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
					Androgel 1.62% based on the developmental and marketing experience with Androgel 1%.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			The sponsor has only provided narratives for SAE's and deaths. Case narratives for some dropouts due to non-SAEs will be requested in the 74-Day letter.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Pertinent Narratives have been provided
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?

Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74 Day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

Roger Wiederhorn
4/13/2009 02:28:24 PM
MEDICAL OFFICER

Mark S. Hirsch
4/13/2009 04:11:08 PM
MEDICAL OFFICER
I concur.