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RESEARCH**

APPLICATION NUMBER:
203098Orig1s000

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

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA Number: 203098

Submission Dates: 07/05/2011, 07/28/2011, 11/08/2011, 02/01/2012, 04/13/2012, 08/01/2012, 09/13/2012 and 01/25/2013

Brand Name: No proposed name

Generic Name: Testosterone (T) gel

OCP Reviewer: Hyunjin Kim, Pharm.D., M.S.

OCP Team Leader: Myong Jin Kim, Pharm. D.

OCP Division: Division of Clinical Pharmacology III

OND Division: Division of Reproductive and Urologic Products

Sponsor: Perrigo Israel Pharmaceuticals Ltd.

Submission Type: Resubmission

Formulation, Strengths, and Dosing regimen: Topical gel, (b) (4) 25 mg and 50 mg T in packets, and 12.5 mg T per actuation in a metered dose pump, 50 mg, 75 mg, or 100 mg T once daily

Indication: Treatment of hypogonadism

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1 Executive Summary

The Clinical Pharmacology review of NDA 203098 (DARRTS, 12/20/2012) stated that NDA 203098 was acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert labeling. The final agreement was reached on January 25, 2013 and there are no pending issues from the Office of Clinical Pharmacology. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this addendum.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the labeling of NDA 202398 acceptable.

2 Final Agreed Upon Package Insert Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TESTOSTERONE gel safely and effectively. See full prescribing information for TESTOSTERONE gel.

TESTOSTERONE gel, for topical use, CIII
Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

See full prescribing information for complete boxed warning

- Virilization has been reported in children who were secondarily exposed to testosterone gel (5.2, 6.2).
- Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel (2.2, 5.2).
- Healthcare providers should advise patients to strictly adhere to recommended instructions for use (2.2, 5.2, 17).

INDICATIONS AND USAGE

Testosterone is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary Hypogonadism (Congenital or Acquired) (1)
- Hypogonadotropic Hypogonadism (Congenital or Acquired) (1)

Important limitations of use:

- Safety and efficacy of testosterone gel in males less than 18 years old have not been established. (8.4)
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure. (1, 12.3)

DOSAGE AND ADMINISTRATION

- Starting dose of testosterone gel is 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet), applied once daily in the morning. (2.1)
- Apply to clean, dry, intact skin of shoulders and upper arms and/or abdomen. Do NOT apply testosterone gel to any other parts of the body including the genitals, chest or back. (2.2)
- Dose adjustment: Testosterone gel can be dose adjusted using 50 mg, 75 mg, or 100 mg of testosterone on the basis of total serum testosterone concentration. Additionally, serum testosterone concentration should be assessed periodically. (2.1)
- Patients should wash hands immediately with soap and water after applying testosterone gel and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)

DOSAGE FORMS AND STRENGTHS

Testosterone gel for topical use is available as follows:

- Metered-dose pump that delivers 12.5 mg of testosterone per actuation. (3)

- Packets containing 25 mg of testosterone. (3)
- Packets containing 50 mg of testosterone. (3)

CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected prostate cancer (4, 5.1).
- Pregnant or breast feeding women. Testosterone may cause fetal/neonatal harm (4, 8.1, 8.3).

WARNINGS AND PRECAUTIONS

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.1).
- Avoid unintentional exposure of women or children to testosterone gel. Secondary exposure to testosterone can produce signs of virilization. Testosterone gel should be discontinued until the cause of virilization is identified. (5.2)
- Exogenous administration of androgens may lead to azoospermia (5.5).
- Edema, with or without congestive heart failure (CHF), may be a complication in patients with preexisting cardiac, renal, or hepatic diseases (5.7, 6.2).
- Sleep apnea may occur in those with risk factors (5.9).
- Monitor serum testosterone, prostatic specific antigen (PSA), hemoglobin, hematocrit, liver function tests and lipid concentrations periodically (5.1, 5.3, 5.6, 5.10).
- Testosterone gel is flammable until dry (5.13).

ADVERSE REACTIONS

Most common adverse reactions (incidence \geq 5%) are acne, application site reactions, abnormal lab tests, and prostatic disorders (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Androgens may decrease blood glucose and therefore may decrease insulin requirements in diabetic patients (7.1).
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio ("INR") and prothrombin time is recommended (7.2).
- Use of testosterone with adrenocorticotropic hormone ("ACTH") or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3).

USE IN SPECIFIC POPULATIONS

- There are insufficient long-term safety data in geriatric patients using testosterone gel to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

FULL PRESCRIBING INFORMATION

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel** [see *Warnings and Precautions (5.2) and Adverse Reactions (6.2)*].
- **Children should avoid contact with any unwashed or unclothed application sites in men using testosterone gel** [see *Dosage and Administration (2.2), Warnings and Precautions (5.2)*].
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use** [see *Dosage and Administration (2.2), Warnings and Precautions (5.2) and Patient Counseling Information (17)*].

1 INDICATIONS AND USAGE

Testosterone is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary Hypogonadism (congenital or acquired) - testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle stimulating hormone (FSH), luteinizing hormone (LH)) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired) - idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Important limitations of use:

- Safety and efficacy of testosterone gel in males less than 18 years old have not been established [see *Use in Specific Populations (8.4)*].
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure. (1, 12.3)

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Dose Adjustment

The recommended starting dose of testosterone gel is 50 mg of testosterone (4 pump actuations, two 25 mg packets, or one 50 mg packet), applied topically once daily in the morning to the shoulders and upper arms and/or abdomen area (preferably at the same time every day).

Dose Adjustment

To ensure proper dosing, serum testosterone levels should be measured at intervals. If the serum testosterone concentration is below the normal range, the daily testosterone gel dose may be increased from 50 mg to 75 mg and from 75 mg to 100 mg for adult males as instructed by the physician (see Table 1, Dosing Information for testosterone gel). If the serum testosterone concentration exceeds the normal range, the daily testosterone gel dose may be decreased. If the serum testosterone concentration consistently exceeds the normal range at a daily dose of 50 mg, testosterone gel therapy should be discontinued. In addition, serum testosterone concentration should be assessed periodically.

2.2 Administration Instructions

Testosterone gel should be applied to clean, dry, healthy, intact skin of the right and left upper arms/ shoulders and/or right and left abdomen. Area of application should be limited to the area that will be covered by the patient's short sleeve T- shirt. Do not apply testosterone gel to any other part of the body including the genitals, chest or back. Testosterone gel should be evenly distributed between the right and left upper arms/shoulders or both sides of the abdomen.

The prescribed daily dose of testosterone gel should be applied to the right and left upper arms/shoulders and/or right/left abdomen as shown in the shaded areas in the figure below.

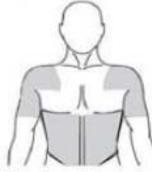


Figure 1: Application Sites for Testosterone gel

After applying the gel, the application site should be allowed to dry prior to dressing. Hands should be washed with soap and water after testosterone gel has been applied. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including testosterone gel, are flammable.

The patient should be advised to avoid swimming or showering for at least 5 hours after the application of testosterone gel.

Multi-Dose Pump

To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose. After the priming procedure, patients should completely depress the pump one time (actuation) for every 12.5 mg of testosterone required to achieve the daily prescribed dosage. The product should be delivered directly into the palm of the hand and then applied to the desired application sites. Alternatively, testosterone gel can be applied directly to the application sites. Table 1 provides dosing information for adult males.

Table 1: Dosing Guidelines for Using the Multi-Dose Pump

Prescribed Daily Dose	Number of Pump Actuations
50 mg	4 (once daily)
75 mg	6 (once daily)
100 mg	8 (once daily)

Packets

The entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. Alternately, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from testosterone gel-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using testosterone gel.
- Patients should wash their hands immediately with soap and water after applying testosterone gel.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the gel has dried.
- Prior to any situation in which skin-to-skin contact with the application site is anticipated, patients should wash the application site(s) thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which testosterone gel has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

7 DRUG INTERACTIONS

7.1 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, may decrease insulin requirements.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens, therefore 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.

7.3 Corticosteroids

The concurrent use of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4)]:

Testosterone gel is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens, such as testosterone, may result in varying degrees of virilization. If this

drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, testosterone gel is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation. [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and efficacy of testosterone gel in pediatric males less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing testosterone gel to determine whether efficacy in those over 65 years of age 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.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH.

8.6 Renal Impairment

No studies were conducted involving patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

12 CLINICAL PHARMACOLOGY

12.1 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 maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism can present as primary hypogonadism caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, while secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using testosterone gel.

12.3 Pharmacokinetics

Absorption

In a single-dose, crossover clinical study conducted in 24 hypogonadal males under fasting conditions, the serum testosterone exposure (AUC_{0-72}) and maximum testosterone concentration (C_{max}) following a topical administration of 100 mg testosterone administered as 2 x 5 g testosterone gel packets (2 packets applied to the shoulder/upper arm) were bioequivalent to those following a topical administration of an approved testosterone gel product.

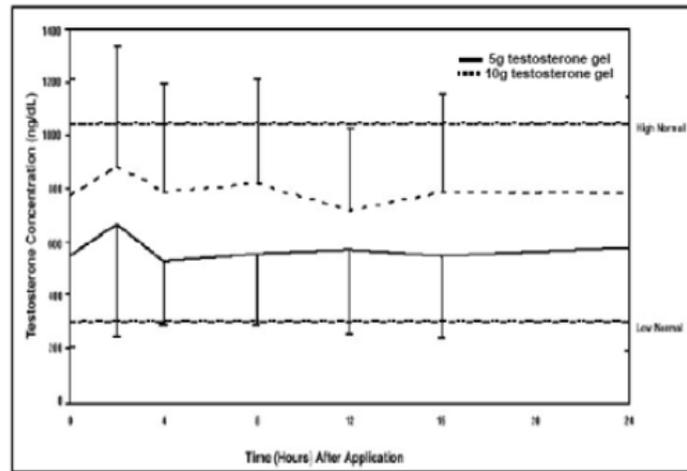
Testosterone gel delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal concentrations (298 to 1043 ng/dL) seen in healthy men.

Testosterone gel provides continuous transdermal delivery of testosterone for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

Testosterone gel is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone dose applied on the skin surface from testosterone gel is absorbed into systemic circulation. In a study with testosterone gel 100 mg, all patients showed an increase in serum testosterone within 30 minutes, and eight of nine patients had a serum testosterone concentration within normal range by 4 hours after the initial application. Absorption of testosterone into the blood continues for the entire 24 hour dosing interval. Serum concentrations approximate the steady-state concentration by the end of the first 24 hours and are at steady state by the second or third day of dosing.

With single daily applications of testosterone gel, follow-up measurements 30, 90, and 180 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the eugonadal range. **Figure 2** summarizes the 24-hour pharmacokinetic profiles of testosterone for hypogonadal men (< 300 ng/dL) maintained on testosterone gel 50 mg or 100 mg of for 30 days. The average (\pm SD) daily testosterone concentration produced by 100 mg on Day 30 was 792 (\pm 294) ng/dL and by testosterone gel 50 mg was 566 (\pm 262) ng/dL.

Figure 2: Mean (\pm SD) Steady-State Serum Testosterone Concentrations on Day 30 in Patients Applying Testosterone Gel Once Daily



Distribution

Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (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.

Metabolism

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT.

DHT concentrations increased in parallel with testosterone concentrations during testosterone gel treatment. The mean steady-state DHT/T ratio during 180 days of testosterone gel treatment remained within normal limits and ranged from 0.23 to 0.29 (5 g/day) and from 0.27 to 0.33 (10 g/day).

Excretion

There is considerable variation in the half-life of testosterone concentration as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic 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.

When testosterone gel treatment is discontinued after achieving steady state, serum testosterone concentrations remain in the normal range for 24 to 48 hours but return to their pretreatment concentrations by the fifth day after the last application.

Testosterone Transfer from Male Patients to Female Partners

The potential for dermal testosterone transfer following testosterone gel use was evaluated in a clinical study between males dosed with testosterone gel and their untreated female partners. Two (2) hours after application of 100 mg of testosterone from 10 g (2 x 5 g packets) of testosterone gel to upper arm and shoulder of one side by the male subjects, the couples (N = 20 couples) engaged in a 15 minute session of vigorous skin-to-skin contact so that the female partners gained maximum exposure to the testosterone gel application sites. Serum concentrations of testosterone were monitored in the female subjects for 24 hours after the transfer procedure. Under these study conditions, unprotected female partners had a mean testosterone AUC₀₋₂₄ and C_{max} that were more than 2 times greater than their mean baseline values. When a shirt covered the application site, study results showed a 16% and 48% increase in testosterone AUC₀₋₂₄ and C_{max}, respectively, compared to baseline in these females. The potential for dermal testosterone transfer following testosterone gel application on the abdomen has not been evaluated.

Effect of Hand Washing and Showering

In a separate clinical study conducted to evaluate the effect of hand washing on the residual amount of testosterone, 33 healthy male subjects received 100 mg of testosterone from 10 g (2 x 5 g packets) of testosterone gel on a hand and applied testosterone gel to the upper arm and shoulder of one side. Subjects washed their hands with liquid soap and warm tap water immediately after drug application. Then the hand was wiped with 3 ethanol dampened gauzes which were then combined together and analyzed for

testosterone content. A mean (SD) of 0.40 (0.20) mg of residual testosterone (i.e., approximately 0.4% of the theoretical dose of 100 mg testosterone administered) was recovered after washing hands with liquid soap and warm tap water.

The same study also evaluated the effect of showering on the residual amount of testosterone on the application site. Subjects washed the application site by showering two hours after drug application. The application site was then wiped with 3 ethanol dampened gauzes which were then combined together and analyzed for testosterone content. A mean (SD) of 5.80 (2.77) mg of residual testosterone (i.e., approximately 5.8% of the theoretical dose of 100 mg testosterone administered) was recovered after showering.

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/s/

HYUNJIN KIM
01/25/2013

MYONG JIN KIM
01/25/2013

Clinical Pharmacology Review

NDA Number:	203098
Submission Dates:	07/05/2011, 07/28/2011, 11/08/2011, 02/01/2014, 04/13/2012, 08/01/2012 and 09/13/2012
Brand Name:	No proposed name
Generic Name:	Testosterone (T) gel
OCP Reviewer:	Hyunjin Kim, Pharm.D., M.S.
OCP Team Leader:	Myong Jin Kim, Pharm. D.
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Reproductive and Urologic Products
Sponsor:	Perrigo Israel Pharmaceuticals Ltd.
Submission Type:	Resubmission
Formulation, Strengths, and Dosing regimen:	Topical gel, (b) (4) 25 mg and 50 mg T in packets, and 12.5 mg T per actuation in a metered dose pump, 50 mg, 75 mg, or 100 mg T once daily
Indication:	Treatment of hypogonadism

An Intra-Divisional Level Clinical Pharmacology Briefing was held on December 3rd, 2012 in room 3134 of White Oak Bldg 51. Attendees included Drs' E. Dennis Bashaw, Hae Young Ahn, Myong-Jin Kim, and Hyunjin Kim

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1 EXECUTIVE SUMMARY

This resubmission contains the Sponsor's complete response (CR) to the Agency's CR letter dated May 3, 2012 for original New Drug Application (NDA) 203098.

On July 5, 2011, the Sponsor submitted a 505(b)2 NDA for testosterone (T) gel (b) (4) to seek an approval for the treatment of male hypogonadism. The Sponsor used AndroGel (1%, w/w) (NDA 021015, approved on February 20, 2000) marketed by Unimed Pharmaceuticals Inc. as the reference listed drug (RLD).

In support of the original NDA, the Sponsor conducted 3 Clinical Pharmacology studies including a pivotal bioequivalence (BE) study bridging the safety and efficacy findings of the RLD to the proposed product, an inter-personal transfer study evaluating the transfer potential of T from user to non-user, and a hands/application sites washing study determining the residual amount of T present on these sites following washing procedures.

On May 3, 2012, the Agency issued a CR letter based on the inspection findings of clinical and bioanalytical sites of the pivotal BE study. Two other Clinical Pharmacology studies, an inter-personal transfer study and a hands/application sites washing study, were acceptable in support of the NDA during the original review cycle.

In this resubmission, the sponsor submitted the supporting data to address the deficiencies listed in the CR letter dated May 3, 2012.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 203098 acceptable provided that an agreement is reached between the sponsor and the Division regarding the labeling language in the package insert.

1.2 Phase IV Commitments/Requirements

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

BE Assessment

During the original review cycle, the Office of Scientific Investigations (OSI) conducted an inspection of clinical and bioanalytical sites of the pivotal BE study (Study 03-0415-0010). Two major deficiencies identified by the OSI are as follows:

- 1) Clinical site: drug administration records for Period 3 did not indicate the date and time at which the drug was administered. The proper dosing of subjects during Period 3 can not be assured. Therefore, OSI recommended that the data from Period 3 should be excluded from statistical evaluation.
- 2) Bioanalytical site: the measured concentrations of plasma T were not adjusted for the endogenous T in blank plasma used to prepare calibrators and quality control (QC) samples.

Details of these OSI inspection findings can be found in Dr. Gopa Biswas's OSI consult review and addendum dated April 2, 2012 and April 20, 2012, respectively, in DARRTS.

Based on the findings of OSI inspection, data from study period 3 of the pivotal BE study were excluded from the BE assessment during the first review cycle. As a result, the number of study subjects eligible for BE analysis was reduced from 24 to 8. The small sample size (N=8) of the BE study made it unfeasible to do any meaningful statistical analysis for BE evaluation (*refer to the Clinical Pharmacology*

review of the original NDA 203098 by Dr. Li Li dated on May 1, 2012 in DARRTS).

In the current resubmission, the Sponsor submitted the missing drug administration records for the study period 3 of the pivotal BE study. In addition, the Sponsor submitted a new full data set for concentration of plasma T adjusted for the endogenous T.

Based on the review of the new data set and the drug administration records from study period 3 of the pivotal BE study, the Sponsor's T product and the RLD is bioequivalent.

Transfer Potential Assessment

The results of the study indicated that covering the application site with clothing barrier such as a t-shirt may significantly reduce the T transfer to others (*refer to the Clinical Pharmacology review of the original NDA 203098 by Dr. Li Li dated on May 1, 2012 in DARRTS*).

Hand and Application Site Washing Study

The study showed that hand washing removed 95.3% of recoverable T and showering procedure (2 hours after dose application) removed 79.5% of recoverable T from the arm/shoulder dosing area, indicating that washing hands with soap and water and a shower can sufficiently remove T gel (b) (4) from the hands and application sites (*refer to the Clinical Pharmacology review of the original NDA 203098 by Dr. Li Li dated on May 1, 2012 in DARRTS*).

Drug Product Formulation

T gel Clinical versus To-Be-Marketed (TBM) formulations

Clinical formulation (T06P033, used in all clinical studies) was manufactured with Carbomer 940, NF. For commercial formulation, the sponsor plans to use Carbopol 980 instead of Carbomer 940 to be consistent with the RLD formulation. According to the Chemistry, Manufacturing and Controls (CMC) review by Dr. Rajiv Agarwal dated March 6, 2012, this change is classified as a Level 2 excipient change, requiring updated stability data and comparative *in vitro* release data, and not a BE study. The results of the above *in vitro* studies demonstrated no significant differences in the release of T gel (CMC review on April 11, 2012 in DARRTS).

T gel versus the RLD

The two formulations are almost the same, except that isostearic acid is used (b) (4) in the proposed T product whereas isopropyl myristate is used in the RLD.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Specific studies describing the ADME of T were not conducted. The Sponsor proposed to use the publically available information of the RLD (i.e., AndroGel[®], 1 %) for their product.

Drug-Drug Interactions (DDI):

No new DDI studies were conducted with T gel. The Sponsor proposed to use the publically available information for the RLD for their product.

Specific Populations:

- Pediatric use: No pediatric studies were conducted.
- Geriatric use: No geriatric studies were conducted.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments.
- Contraindicated for pregnant or breast feeding women.
- Warnings and Precaution for children and women for secondary exposure.

Bioanalytical Method:

Study samples were analyzed for total T concentrations using the following methods:

- BE study: Gas Chromatography/Mass Spectrometry (GC/MS)
- Inter-personal transfer study: Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)
- Hand and application sites washing study: High performance liquid chromatography with ultraviolet detector (HPLC-UV).

Overall, the bioanalytical method is acceptable satisfying the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, 2001).

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What is the pertinent regulatory background or history contributing to the current submission?

Upon review of the data submitted during the original review cycle, the Agency issued a CR letter dated on May 3, 2012. The following is from the CR letter:

Clinical Pharmacology

Your BE study between the proposed product (T gel) and the RLD cannot be adequately evaluated. As outlined in Form 483s (dated March 1 and 30, 2012), there are unresolved clinical and bioanalytical site inspection deficiencies. Specifically, a major deficiency of missing dosing records for study period 3 was reported in FDA Form 483. As a result, data from study period 3 were excluded from statistical evaluation. The resultant small sample size makes it unfeasible to do any meaningful statistical analysis for the BE evaluation. In addition, as reported in Form 483 from the bioanalytical site inspection, the measured concentrations of plasma T are not adjusted for the endogenous T in blank plasma used to prepare calibrators and QC samples. To date, you have not adequately addressed these deficiencies.

Information Needed to Address the Clinical Pharmacology Deficiency

A study demonstrating the safety and efficacy of the proposed product (T gel) needs to be conducted. This can be done by conducting a pivotal BE study using an approved T product as a RLD or a new clinical trial to assess the efficacy and safety of the proposed product. This should be submitted as a part of the NDA resubmission. We recommend that you submit the study protocol to the Agency before initiation of the study. Alternatively, you may provide an adequate response to the outstanding deficiencies listed in Form 483s. If you choose to submit a response to these deficiencies, you should also submit a letter to your NDA notifying the Division that you have done so.

2.1.2 How did the Sponsor address the Clinical Pharmacology deficiencies listed in the CR letter dated on May 3, 2012?

Missing dosing records for study period 3 reported in clinical site inspection:

The sponsor contacted a former employee of the Contract Research Organization (CRO) where the BE study was performed in 2003 in an effort to understand the study documentation. It was learned that electronic data entry was not used at CRO during the time period of the BE study. The sponsor conducted a further review of the BE study documentation and found the Period 3 drug administration record in one of the study document binders. This document was not initially located by either the Agency or the Sponsor because it was improperly filed in Section 6, which contained the records for laboratory

certification. The Period 3 drug administration record contained hand written entries by the study staff. The records all bore the date and time of drug administration, and the initials of the CRO staff member.

Non-adjustment for endogenous T reported in bioanalytical site inspection:

The data set for T concentration submitted during the original review cycle was not adjusted for endogenous T concentration in blank plasma samples used to prepare calibrators and QC samples. The endogenous T concentration in blank plasma was calculated to be 0.128 ng/mL. Therefore, Dr. Gopa Biswas, OSI reviewer, recommended adding the same 0.128 ng/mL to all the study sample concentrations (refer to Dr. Gopa Biswas’s review dated on May 2, 2012 in DARRTS).

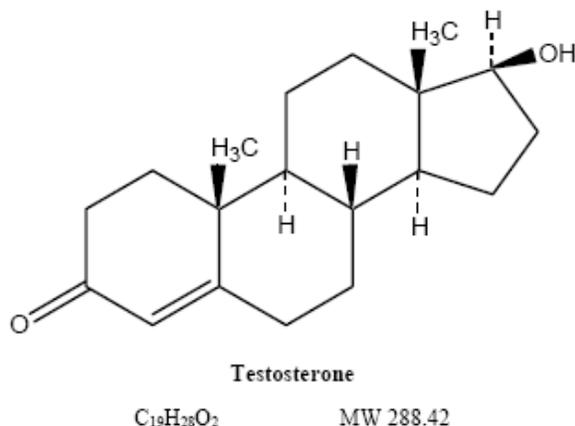
In the current review cycle, the Sponsor submitted a new data set for T concentration as recommended by Dr. Gopa Biswas.

2.1.3 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Active substance:

The active pharmacologic ingredient in T gel is T. T USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:

Figure 1 T chemical structure



Formulation:

T gel is a clear colorless hydroalcoholic gel containing (b) (4) T for topical administration to clean, dry, intact skin of shoulders, upper arms and/or abdomen. Inactive ingredients in T gel are sodium hydroxide, dehydrated alcohol, Carbopol 980, isostearic acid and purified water (**Table 1**).

Table 1 Composition of T gel

INGREDIENTS	GRADE	FUNCTION	QUANTITY (% w/w)
T, USP	USP	Active Ingredient	(b) (4)
Sodium Hydroxide NF	NF		(b) (4)
Dehydrated Alcohol,	USP		

USP			
Carbopol 980, NF	NF	(b) (4)	
Isostearic Acid	-		
Purified Water, USP	USP		
Total			100.000

2.1.4 What are the proposed mechanism of action and therapeutic indication?

Indication:

Replacement therapy in males for conditions associated with a deficiency or absence of endogenous T:

- Primary Hypogonadism (Congenital or Acquired)
- Hypogonadotropic Hypogonadism (Congenital or Acquired)

Mechanism of Action:

Endogenous androgens, including T and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include: the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement; vocal chord thickening; and alterations in body musculature and fat distribution. T and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of T and is characterized by low serum T concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter’s Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (follicle stimulation hormone, luteinizing hormone).

2.1.5 What are the proposed dosage(s) and dose titration scheme?

The recommended starting dose of T gel, (b) (4) is 50 mg T once daily (preferably in the morning), applied on clean, dry, intact skin of shoulders, upper arms and/or abdomen. To ensure proper dosing, serum T concentrations should be measured at intervals and replaced to serum T concentrations in the range (298 - 1043 ng/dL). If the serum T concentration is below the specified range, the daily T gel dose may be increased from 50 mg to 75 mg and from 75 mg to 100 mg for adult males as instructed by the physician. If the serum T concentration exceeds the “normal” range, the daily dose may be decreased. If the serum T concentration consistently exceeds the “normal” range at a daily dose of 50 mg T gel therapy should be discontinued.

2.1.6 What clinical and clinical pharmacology data is submitted to support the approval of T gel?

In support of this NDA, the Sponsor conducted 3 clinical pharmacology studies and 2 clinical studies.

Clinical Pharmacology Studies:

- BE study: A Randomized, Single-Dose, Three-Way Crossover Relative Bioavailability Study of T gel Formulations in Hypogonadal Men (Study 03-0415-001)
- Inter-personal transfer study: A Study to Determine the transfer of T from a Male to his Female Partner for Perrigo Pharmaceuticals’ T gel (Study M11U09001)

- Hand and application sites washing study: A Pivotal Study to Evaluate the Residual Amount of Topically Delivered T gel Present on Normal Skin of the Hand, Arm, and Shoulder in Healthy Adult Male Subjects Following Washing Procedures (Study PRG-806)

Clinical Studies:

- Irritation study: A 21-Day, Randomized, Controlled Study to Evaluate the Irritation Potential of T gel on Healthy Volunteers, Using a Cumulative Irritation Patch Test Design (Study DS310208)
- Sensitization study: A Randomized, Controlled Study to Evaluate the Sensitizing Potential of T gel on Healthy Volunteers, Using a Repeat Insult Patch Test Design (Study DS102308)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 Is test T gel BE to the RLD (AndroGel® 1%) regarding to total T exposure?

Study Design:

This was a randomized, single-dose, three-way crossover study in 24 hypogonadal men. In each treatment period, each study subject received a 100 mg application of either one of the test formulations (T gel: Formulation T06P030 and Formulation T06P033) or the RLD (AndroGel® 1%) applied to his shoulders and upper arms. The difference between two test formulations is that Formulation T06P030 contains (b) (4), whereas Formulation T06P033 contains (b) (4). A series of blood samples were collected pre-dose (-12 & 0 hrs) for endogenous T concentrations and sixteen times over 72 hours following each dose for determination of plasma T concentrations. Each treatment was separated by 7-day washout period.

During the drug development period, Formulation T06P030 was dropped from the clinical development due to the high C_{max} (90% confidence interval: 0.885 – 1.273) compared to the RLD. Formulation T06P033 was used as the clinical formulation throughout the clinical development program.

Study Results:

- BE analysis conducted by the Sponsor (new data set adjusted for endogenous T, 24 subjects) Baseline corrected BE analysis showed that the Formulation T06P033 was BE to the RLD (AndroGel® 1%) with respect to both mean T C_{max} and AUC_{0-72hr}.

Table 2 Baseline corrected BE analysis for T gel (Formulation T06P033; N=24)

Parameter	Ratio (90% Confidence Interval)
AUC _{0-t} (ng · hr/mL)	0.958 (0.832 – 1.103)
C _{max} (ng/mL)	0.965 (0.805 – 1.157)

- BE analysis conducted by this reviewer (new data set adjusted for endogenous T, 22 subjects)

During the original review cycle, Dr Li Li, a Clinical Pharmacology reviewer, stated that the two study subjects should be excluded from the BE analysis. Specifically, subject 18 had average T baseline concentrations > 3 ng/mL (violation of the inclusion criterion) and subject 20 (received insulin lispro 16 minutes after the beginning and 11 minutes before the end of the 10-hour period during the first period, and received insulin lispro, ramipril, aspirin and carvediolol 11, 6, 6, and 6 minutes, respectively, before the end of the 10-hour period during the second period.) had concomitant medications that may affect the T systemic exposure during the study period. As shown in **Table 3**, the clinical Formulation T06P033 was BE to the RLD when data from subject 18 and subject 20 were excluded from the BE analysis.

Table 3 Baseline corrected BE analysis for T gel (Formulation T06P033) (N=22)

Parameter	Ratio (90% Confidence Interval)
AUC _{0-t} (ng · hr/mL)	0.938 (0.811 – 1.085)
C _{max} (ng/mL)	0.971 (0.807 – 1.168)

Based on the new data set for T concentration adjusted for endogenous T, test T gel is BE to RLD (AndroGel® 1%).

2.2.2 What is the interpersonal transfer potential of T from T gel?

Study M11U09001 determined the transfer potential of T from a male to his female partner for T gel. The results of the study indicated that covering the application site with clothing barrier such as a t-shirt may significantly reduce the T transfer to others.

For detailed review, see the Clinical Pharmacology review of original NDA 203098 by Dr. Li Li dated on May 1, 2012 in DARRTS.

2.2.3 What are the finding from hands and application sites washing study after T gel application?

Study PRG-806 evaluated the residual amount of topically delivered T gel present on hand, arm and shoulder following washing procedure. The results of the study suggested that washing hands with soap and water and a shower (2 hour after dose application) can sufficiently remove residual T from the hands and application sites for T ^(b)₍₄₎ gel.

For detailed review, see the Clinical Pharmacology review of original NDA 203098 by Dr. Li Li dated on May 1, 2012 in DARRTS.

2.2.4 What are the characteristics of drug distribution?

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

2.2.5 What are the characteristics of drug metabolism?

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

2.2.6 What are the characteristics of drug excretion?

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

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Renal or Hepatic Impairment

No formal studies were conducted involving patients with renal or hepatic insufficiencies. No additional information is available in the labeling of topical drugs in the same drug class (i.e., Testim®, Axiron®, or

AndroGel®, 1%) regarding this aspect.

Pediatric subjects

The Sponsor has submitted pediatric waiver request. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of these criteria apply to this application, the Pediatric Review Committee (PeRC) has determined that the Sponsor is exempt from this requirement.

2.4 EXTRINSIC FACTORS

There was no drug-drug interaction conducted for T gel. The Sponsor is proposing to use the following publicly available information of the RLD for T gel:

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 T 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.

2.5 GENERAL BIOPHARMACEUTICS

2.5.2 Is the clinical formulation same as the TBM formulation?

No. Clinical formulation (T06P033, used in all clinical studies) was manufactured with Carbomer 940, NF. For commercial formulation, the sponsor plans to use Carbopol 980 instead of Carbomer 940 to be consistent with the RLD formulation. The compositions of the clinical and the commercial formulations in comparison to the RLD formulation are summarized in the **Table 4**. According to the CMC review by Dr. Rajiv Agarwal dated March 6, 2012, this change would qualify as a Level 2 excipient change, requiring updated stability data and comparative *in vitro* release data, not a BE study. The sponsor submitted required data and Dr. Rajiv found it acceptable (CMC review on April 11, 2012 in DARRTS).

Table 4 The composition of Sponsor's clinical and commercial formulations in comparison with RLD (AndroGel® 1%) formulation

Ingredient	Clinical Formulation	Commercial Formulation	RLD Formulation
	Concentrations (%w/w)	Concentrations (%w/w)	Concentrations (%w/w)
T, USP	(b) (4)		
Dehydrated Alcohol			
Carbomer 980, NF			

Carbomer 940, NF
Isopropyl Myristate
Isostearic Acid
Sodium Hydroxide
Purified Water

(b) (4)

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess concentrations and are they acceptable?

Study samples were analyzed for total T concentrations using the following methods:

- BE study: Gas Chromatography/Mass Spectrometry (GC/MS)
- Inter-personal transfer study: Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)
- Hand and application sites washing study: High performance liquid chromatography with ultraviolet detector (HPLC-UV)

Table 5 Summary of Bioanalytical Methods for total T

	BE study	Transfer study	Washing study
Biological Matrix	plasma	serum	50/50 Ethanol/Water dampened gauze used to wipe T
Method	GC-MS	LC/MS/MS	HPLC/UV
Range of Standard Curve	0.250 - 10.0 ng/mL	0.05 - 50.0 ng/mL	0.03 to 2.5 µg/mL
QC inter-assay accuracy	-5.9 – 5.0 %	-3.0 – 0.1%	2.3 – 15.8 %
QC inter-assay precision	5.5 – 6.8 %	2.3 – 2.8%	1.35 – 3.96 %
Stability at -20 °C	at least 19 days	79 days	45 days

Overall, the bioanalytical method is acceptable satisfying the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, 2001).

3 DETAILED LABELING RECOMMENDATIONS

The labeling recommendation will be added in the addendum.

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

/s/

HYUNJIN KIM
12/20/2012

MYONG JIN KIM
12/20/2012

Clinical Pharmacology Review

NDA Number:	203098
Submission Dates:	07/05/11, 07/28/11, 11/08/11, 02/01/12, 04/13/12
Brand Name:	pending
Generic Name:	Testosterone gel
OCP Reviewer:	Li Li, Ph.D
OCP Team Leader:	Myong Jin Kim, Pharm. D
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Reproductive and Urologic Products
Sponsor:	Perrigo Israel Pharmaceuticals
Submission Type:	Original
Formulation and Dosing regimen:	Topical gel; (b) (4) 50 mg, 75 mg, or 100 mg T once daily
Indication:	Treatment of hypogonadism

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Executive Summary

The Sponsor submitted a New Drug Application (NDA) under 505 (b)(2) for testosterone (T) gel, (b) (4) on July 5, 2011 to seek approval for the treatment of male hypogonadism. The Sponsor used AndroGel® (1%, w/w) (NDA 021015, approved on February 20, 2000) marketed by Unimed Pharmaceuticals Inc. as the reference listed drug (RLD).

T gel (b) (4) is a clear colorless hydroalcoholic gel with two packaging configurations: 2.5 g (or 25 mg T)

and 5 g (or 50 mg T). The proposed starting dose is 50 mg T once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen. Dose can be adjusted between 50 to 100 mg T/day to maintain serum T concentration within the range of 298-1043 ng/dL.

In support of this NDA, the Sponsor conducted 3 Clinical Pharmacology studies including a pivotal bioequivalence (BE) study bridging the safety and efficacy findings of the RLD to the proposed product, an inter-personal transfer study evaluating the transfer potential of T from user to nonuser, and a hand and application sites washing study determining the residual amount of T present on these sites following washing procedures. The Sponsor also conducted an irritation study and a sensitization study which will be reviewed by the clinical reviewer.

Based on the inspection findings of clinical and bioanalytical sites of the pivotal BE study, the results of the BE study can not be used to support the approval of the proposed product (T gel (b) (4)).

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 203098 not acceptable. The pivotal BE study results cannot be used to support the approval of proposed product (T gel (b) (4)) based on the findings of the Office of Scientific Investigations (OSI) following an audit of the study.

A study demonstrating the safety and efficacy of the proposed product needs to be conducted. This can be done by conducting a pivotal BE study using an approved T product as a RLD or a new clinical trial to assess the efficacy and safety of the proposed product. This should be submitted as a part of the NDA re-submission.

1.2 Phase IV Requirement

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

BE Assessment

An inspection of clinical and bioanalytical sites of the pivotal BE study (Study 03-0415-0010) has been conducted by OSI. Two major deficiencies were identified by the OSI: 1) Clinical site: drug administration records for Period 3 did not indicate the date and time at which the drug was administered. The proper dosing of subjects during Period 3 can not be assured. Therefore, OSI recommended that the data from Period 3 should be excluded from statistical evaluation. 2) Bioanalytical site: the measured concentrations of plasma T were not adjusted for the endogenous T in blank plasma used to prepare calibrators and quality control (QC) samples. Details of these OSI inspection findings can be found in Dr. Gopa Biswas's OSI consult review and addendum dated April 2, 2012 and April 20, 2012, respectively, in DARRTS.

Based on the findings of OSI inspection, data from study period 3 of the pivotal BE study were excluded from the BE assessment. As a result, the number of study subjects eligible for BE analysis was reduced from 24 to 8. The small sample size (N=8) of the BE study makes it unfeasible to do any meaningful statistical analysis for BE evaluation.

A written response to address the deficiency in the bioanalytical portion was received on April 27, 2012. OSI has not commented on the response as of this writing.

Transfer Potential Assessment

A single-dose, open-label, four way-crossover study was conducted in 20 healthy male/female couples to assess the inter-personal transfer potential of T gel (b) (4). The female subjects enrolled in this study were postmenopausal or surgically sterile. A single-dose (10 g) of either T gel (b) (4) was applied to one side of the male subject's upper arm/shoulder. Female subjects had one arm/shoulder designated as the "contact site". Starting at 2 hours after dosing, each couple was instructed to engage in a total of 15 minutes of contact with male subject wearing or not wearing a long-sleeved t-shirt.

The results showed that unprotected female partners had a 136% and 250% increase from baseline for mean T AUC_{0-24hr} and C_{max}, respectively, after direct skin contact. In contrast, when a shirt covered the application site, female subjects had a 16% and 48% increase in AUC₀₋₂₄ and C_{max}, respectively, compared to baseline values. The results of the study indicated that covering the application site with clothing barrier such as a t-shirt may significantly reduce the T transfer to others.

Hand and Application Site Washing Study

A single-dose, open label, four way-crossover study was conducted in 33 healthy adult men to quantify the amount of T remaining on hands and arm/shoulder following washing procedure in T gel (b) (4). On Day 1 of each treatment period, 10 g of either T gel (b) (4) was applied to one side of the subject's arm/shoulder. Depending upon the treatment groups (no wash or wash), subjects had their hand wiped with ethanol dampened gauze pads before or after hand washing to obtain a residual hand sample for T measurement. Approximately 2 hours after the dose was applied, subjects had their arm/shoulder wiped with ethanol dampened gauze pads before or after a shower to obtain a residual application site sample for T measurement.

The study showed that hand washing removed 95.3% of recoverable T and showering procedure (2 hours after dose application) removed 79.5% of recoverable T from the arm/shoulder dosing area, indicating that washing hands with soap and water and a shower can sufficiently remove T gel (b) (4) from the hands and application sites.

Drug Product Formulation

T gel (b) (4): Clinical versus To-Be-Marketed (TBM) formulation

Clinical formulation (T06P033, used in all clinical studies) was manufactured with Carbomer 940, NF. The commercial formulation will switch from Carbomer 940 to Carbopol 980 to be consistent with the RLD formulation. According to the CMC review by Dr. Rajiv Agarwal dated March 6, 2012, this change would qualify as a Level 2 excipient change, requiring updated stability data and comparative *in vitro* release data, not a BE study. The results of the above studies demonstrated no significant differences in the release of T gel, (b) (4).

T gel (b) (4) versus the RLD

The two formulations are almost the same, except that the test T gel (b) (4) uses isostearic acid (b) (4) rather than isopropyl myristate in the RLD.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Specific studies describing the ADME of T were not conducted. The Sponsor is proposing to use the publically available information of the RLD (i.e., AndroGel[®], 1 %) for their product.

Drug-Drug Interactions:

No new DDI studies were conducted with T gel (b) (4). The Sponsor is proposing to use the publically available information for the RLD for their product.

Specific Populations:

- Pediatric use: No pediatric studies were conducted. Exemption for the pediatric study was granted.
- Geriatric use: No geriatric studies were conducted
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant or breast feeding women
- Warnings and Precaution for children and women for secondary exposure

Bioanalytical Method:

Study samples were analyzed for total T concentrations:

- BE study: Gas Chromatography/Mass Spectrometry (GC/MS)
- Inter-personal transfer study: Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)
- Hand and application sites washing study: High performance liquid chromatography with ultraviolet detector (HPLC-UV).

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the Clinical Pharmacology and Biopharmaceutics of this drug?

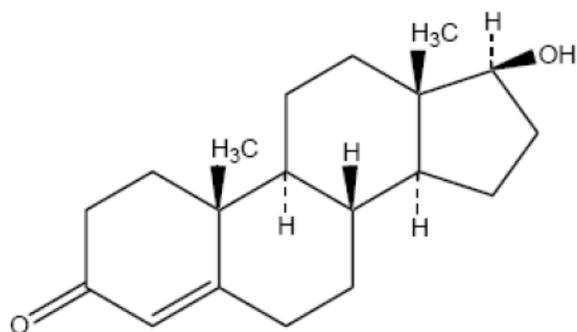
T gel (b) (4) was originally submitted for approval to the Office of Generic Drugs (OGD) (b) (4) for the multi-dose pump and unit dose packets (2.5 and 5 g) on June 15, 2007 and December 16, 2008, respectively. The formulations of T gel (b) (4) and the RLD (AndroGel 1%) are almost the same, except that T gel (b) (4) used isostearic acid (b) (4) rather than isopropyl myristate in the RLD. Subsequent to these submissions, a Citizens Petition was filed on February 27, 2009 by Auxilium Pharmaceuticals. As a response, the Agency determined that any application for a T gel product that has different (b) (4) than the RLD will have to be submitted as an NDA under section 505(b) of the Act (Docket No. FDA-2009-P-0123 dated August 26, 2009). After receiving the written communication from OGD on August 28, 2009, the Sponsor submitted an Investigational New Drug Application (IND 107130) to the Office of New Drugs (OND). A type C guidance meeting was held with the Division of Reproductive and Urologic Product (DRUP) on May 19, 2010 to discuss the clinical study plan and the approval requirement for a 505 (b)(2) NDA for T gel (b) (4) Multi-dose Pump and a Unit dose Packet.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Active substance:

The active pharmacologic ingredient in T gel (b) (4) is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:

Figure 1 T chemical structure



Testosterone

C₁₉H₂₈O₂

MW 288.42

Formulation:

T gel, (b) (4) is a clear colorless hydroalcoholic gel containing (b) (4) T for topical administration to clean, dry, intact skin of shoulders, upper arms and/or abdomen. Inactive ingredients in T gel (b) (4) are sodium hydroxide, dehydrated alcohol, Carbopol 980, isostearic acid and purified water (**Table 1**).

Table 1 Composition of T gel (b) (4)

INGREDIENTS	GRADE	FUNCTION	QUANTITY (% w/w)
Testosterone, USP	USP	Active Ingredient	(b) (4)
Sodium Hydroxide NF	NF		(w) (4)
Dehydrated Alcohol, USP	USP		
Carbopol 980, NF	NF		
Isostearic Acid	-		
Purified Water, USP	USP		
Total			100.000

2.1.3 What are the proposed mechanism of action and therapeutic indication?

Indication:

Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary Hypogonadism (Congenital or Acquired)
- Hypogonadotropic Hypogonadism (Congenital or Acquired)

Mechanism of Action:

Endogenous androgens, including T and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include: the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement; vocal chord thickening; and alterations in body musculature and fat distribution. T and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of T and is characterized by low serum T concentrations. Signs/symptoms

associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

2.1.4 What are the proposed dosage(s) and dose titration scheme?

The recommended starting dose of T gel, (b) (4) is 5 g (equivalent to 50 mg T) once daily (preferably in the morning), applied on clean, dry, intact skin of shoulders, upper arms and/or abdomen. To ensure proper dosing, serum T concentrations should be measured at intervals and replaced to serum T concentrations in the range (298 -1043 ng/dL). If the serum T concentration is below the specified range, the daily T gel, (b) (4) dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g for adult males as instructed by the physician. If the serum T concentration exceeds the "normal" range, the daily dose may be decreased. If the serum T concentration consistently exceeds the "normal" range at a daily dose of 5 g T gel (b) (4) therapy should be discontinued.

2.1.5 What clinical and clinical pharmacology data is submitted to support the approval of T gel, (b) (4)?

In support of this NDA, the Sponsor conducted 3 clinical pharmacology studies and 2 clinical studies.

Clinical Pharmacology Studies:

- BE study: A Randomized, Single-Dose, Three-Way Crossover Relative Bioavailability Study of T gel Formulations in Hypogonadal Men (Study 03-0415-001)
- Inter-personal transfer study: A Study to Determine the transfer of T from a Male to his Female Partner for Perrigo Pharmaceuticals (b) (4) T gel (Study M1IU09001)
- Hand and application sites washing study: A Pivotal Study to Evaluate the Residual Amount of Topically Delivered T gel (b) (4) Present on Normal Skin of the Hand, Arm, and Shoulder in Healthy Adult Male Subjects Following Washing Procedures (Study PRG-806)

Clinical Studies:

- Irritation study: A 21-Day, Randomized, Controlled Study to Evaluate the Irritation Potential of T gel (b) (4) on Healthy Volunteers, Using a Cumulative Irritation Patch Test Design (Study DS310208)
- Sensitization study: A Randomized, Controlled Study to Evaluate the Sensitizing Potential of T gel (b) (4) on Healthy Volunteers, Using a Repeat Insult Patch Test Design (Study DS102308)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 Is test T gel (b) (4) BE to the RLD (AndroGel® 1%) regarding to total T exposure?

BE between test T gel (b) (4) and the RLD (AndroGel® 1%) can not be adequately evaluated. Specifically, based on the findings from OSI inspection, the data from study period 3 were excluded from the BE analysis. As a result, the number of study subjects eligible for BE analysis was reduced from 24 to 8. The resulting small sample size (N=8) of the BE study makes it unfeasible to do any meaningful statistical analysis for BE evaluation.

The following review on BE study was written before the OSI inspection results became available. Therefore, it should be noted that these findings are no longer applicable to support the approval of T gel (b) (4):

Study Design:

This was a randomized, single-dose, three-way crossover study in 24 hypogonadal men. In each treatment period, each study subject received a 10-g application of either one of the test formulations (T gel (b) (4) Formulation T06P030 and Formulation T06P033) or the RLD (AndroGel® 1%) applied to his shoulders and upper arms. The difference between two test formulations is that Formulation T06P030 contains (b) (4) whereas Formulation T06P033 contains (b) (4). A series of blood samples were collected pre-dose (-12 & 0 hrs) for endogenous T concentrations and sixteen times over 72 hours following each dose for determination of plasma T concentrations. Each treatment was separated by 7-day washout period.

It should be noted that the application site of the RLD in the current BE study (i.e. upper arms/shoulders) is different from that in the pivotal phase 3 study (UMD-96-017), where 10 g of the RLD was administered to both abdomen and upper arms/shoulders (reference is made to Dr. Dhruba, J. Chatterjee's Clinical pharmacology review dated on February 25, 2000). As a clinical study with RLD (UMD-98-012) showed T PK parameters following 1-site (left upper arm/shoulder) or 4-sites (left and right upper arm/shoulder, left and right abdomen) application were not statistically significant different, the change in application site in current study may not affect the T bioavailability of the RLD and the outcome of the BE evaluation.

Study Results (FULL DATASET):

As the study objective is to compare the exposure of T contributed by the drug product, it is necessary to measure the endogenous T concentrations and subtract these concentrations from the total concentrations measured from each subject after the drug product is administered. Given the diurnal variation of baseline T concentrations, a 24-hour baseline measurement will be ideal as it allows for a time-specific baseline correction. However, it should be noted that only two time points (-12hr and 0 hr before dosing) were measured for baseline characterization.

- BE analysis conducted by the Sponsor

Baseline corrected BE analysis showed that the Formulation T06P033 was BE to the RLD (AndroGel® 1%) with respect to both mean T C_{max} and AUC_{0-72hr} . However, Formulation T06P030 was not BE to the RLD due to higher C_{max} (**Table 3**). Given the results of the BE study, Formulation T06P030 was dropped from the clinical development and Formulation T06P033 was used as the clinical formulation throughout the clinical development program.

Table 3 Baseline corrected BE analysis for T gel (b) (4) (Formulation T06P030 and T06P033) (N=24)

Parameter	Ratio (90% Confidence Interval)	
	Formulation T06P030	Formulation T06P033
AUC_{0-t} (ng·hr/mL)	1.015 (0.882-1.169)	0.959 (0.833-1.104)
C_{max} (ng/mL)	1.061 (0.885-1.273)	0.965 (0.805-1.158)

- ORIGINAL BE analysis conducted by this reviewer prior to OSI findings

This reviewer believes that two study subjects should be excluded from the BE analysis. Specifically, subject 18 had average T baseline concentrations > 3 ng/mL and subject 20 had concomitant medications that may affect the T systemic exposure during the study period. As shown in **Table 4**, the clinical Formulation T06P033 was BE to the RLD when data from subject 18 and subject 20 were excluded from the BE analysis.

Table 4 Baseline corrected BE analysis for T gel (b) (4) (Formulation T06P030 and T06P033) (N=22)

Parameter	Ratio (90% Confidence Interval)	
	Formulation T06P030	Formulation T06P033
AUC _{0-t} (ng·hr/mL)	0.971 (0.839-1.124)	0.940 (0.812-1.087)
C _{max} (ng/mL)	1.015 (0.843-1.222)	0.972 (0.808-1.169)

It should be noted that given about 30% intra-subject variability (rough estimation) and small subject numbers (N=22), statistic power of the BE Analysis was only about 57%. Nonetheless, as the 90% CI for the geometric mean ratio (GMR) of C_{max} and AUC_{0-72hr} was contained within the BE limit of 80% to 125%, Formulation T06P033 was considered BE to the RLD. This conclusion (BE) was subsequently rejected due to the results of the OSI inspection findings that resulted in the removal of all but 8 subjects from the dataset available for evaluation.

2.2.2 What is the interpersonal transfer potential of T from T gel (b) (4)?

Study M1IU09001 determined the transfer potential of T from a male to his female partner for T gel (b) (4). The results of the study indicated that covering the application site with clothing barrier such as a t-shirt may significantly reduce the T transfer to others.

Study Design:

A single-dose, open-label, four way-crossover study was conducted in 20 healthy male/female couples to assess the inter-personal transfer potential of T gel (b) (4) and the RLD. The female subjects enrolled in this study were postmenopausal or surgically sterile. A single dose (10 g) of either T gel (b) (4) or the RLD was applied to one side of the male subject's arm/shoulder. Female subjects had one arm/shoulder designated as the "contact site". Starting at 2 hours after dosing, each couple was instructed to engage in a total of 15 minutes of contact with male subject wearing or not wearing a long-sleeved t-shirt. A series of blood samples were collected in female subjects at pre-dose (9 times over 24 hours) for endogenous T concentrations and eight times over 24 hours following each dose transfer for determination of serum T concentrations.

It should be noted that the Sponsor initially proposed (b) (4). However, in the current study, all of the 10 g gel was applied to one side of arm/shoulder, which leads to a 50% reduction in the surface area for transfer as compared to the original proposal.

Study Results:

As shown in **Table 5** and **Table 6**, female subjects had a 136% and 250% increase from baseline for AUC_{0-24hr} and C_{max}, respectively, when males not were wearing a T-shirt during the transfer procedure. In contrast, female subjects had a 16% and 48% increase from baseline for mean T AUC_{0-24hr} and C_{max}, respectively, when males were wearing a T-shirt. Therefore, the results of the study indicate covering the application site with clothing barrier such as a t-shirt may significantly reduce the T transfer to others.

Table 5 Summary of Baseline-Unadjusted PK Parameters for T gel (b) (4) and the RLD without a T-shirt

N=20	Parameters	Before transfer (baseline)	After transfer	% increase from baseline
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T gel (b) (4)	AUC _{0-24hr} (ng·hr /mL)	2.883	6.800	136
	C _{max} (ng/mL)	0.146	0.510	250
RLD	AUC _{0-24hr} (ng·hr /mL)	2.937	8.210	180
	C _{max} (ng/mL)	0.141	0.602	325

Table 6 Summary of Baseline-Unadjusted PK Parameters for T gel (b)
(4) and the RLD with a T-shirt

N=20	Parameters	Before transfer (baseline)	After transfer	% increase from baseline
T gel (b) (4)	AUC _{0-24hr} (ng·hr /mL)	2.798	3.254	16
	C _{max} (ng/mL)	0.132	0.195	48
RLD	AUC _{0-24hr} (ng·hr /mL)	2.970	3.184	7
	C _{max} (ng/mL)	0.141	0.159	13

2.2.3 What are the finding from hands and application sites washing study after T gel application?

Study PRG-806 evaluated the residual amount of topically delivered T gel (b)
(4) present on hand, arm and shoulder following washing procedure. The results of the study suggested that washing hands with soap and water and a shower (2 hour after dose application) can sufficiently remove residual T from the hands and application sites for T (b)
(4) gel.

Study Design:

This was an open-label, four way-crossover study in 33 healthy adult male subjects. The total duration of the study, screening through study exit, was approximately 8 weeks with 14 days between periods. On Day 1 of each treatment period, 10 g of either the T gel (b)
(4) or the RLD was applied to one side of the subject's arm/shoulder. Depending upon the treatment groups (no wash or wash), subjects had their hand wiped with ethanol dampened gauze pads before or after hand washing to obtain a residual hand sample for T measurement. Approximately 2 hours after the dose was applied, subjects had their arm/shoulder wiped with ethanol dampened gauze pads before or after a shower to obtain a residual application site sample for T measurement.

Study Results:

The results from T gel (b)
(4) showed that hand washing removed 95.3% of recoverable T and showering procedure (2 hours after dose application) removed 79.5% of recoverable T from the arm/shoulder dosing area, indicating that washing hands with soap and water and a shower can sufficiently remove T gel (b)
(4) from the hands and application sites (**Table 7**).

Table 7 Residual T amount recovered as % of applied dose for hand and for application site (the arm/shoulder)

	T gel, (b) (4)			RLD (AndroGel® 1%)		
	Treatment A (No Wash)	Treatment C (Wash)	Change (%)	Treatment B (No Wash)	Treatment D (Wash)	Change (%)
Hand	8.48 ± 3.55	0.40 ± 0.20	95.3	8.32 ± 3.06	0.39 ± 0.20	95.3
Application Site	28.33 ± 7.63	5.80 ± 2.77	79.5	27.75 ± 7.29	6.69 ± 4.68	75.9

2.2.4 What is the instruction regarding to timing of shower after gel application?

To wait 5 hours before showering or swimming to ensure that the greatest amount of T gel (b)
(4) is

absorbed over the course of the day.

Based on the Citizen's Petition (Docket No. FDA-2009-P-0123 dated August 26, 2009), showering study may not be needed if the product is BE to the RLD and hand-washing study demonstrates that the test product behaves similar to the RLD with respect to the amount of T remaining on the skin after washing. Given that T gel (b) (4) appears to meet both criteria, showering study may not be necessary. On the other hand, as no showering data available for this product, the Sponsor will have to use the same criteria for showering as the RLD, i.e., patient shouldn't shower for 5 hours after application.

2.2.5 What are the characteristics of drug distribution?

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

2.2.6 What are the characteristics of drug metabolism?

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

2.2.7 What are the characteristics of drug excretion?

About 90% of a dose of T given intramuscularly is excreted in the urine as glucuronic 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.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Renal or Hepatic Impairment

No formal studies were conducted involving patients with renal or hepatic insufficiencies. No additional information is available in the labeling of topical drugs in the same drug class (i.e., Testim®, Axiron®, or AndroGel®, 1%) regarding this aspect.

Pediatric subjects

The Sponsor has submitted pediatric waiver request. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of these criteria apply to this application, the Division has determined that the Sponsor is exempt from this requirement.

2.4 EXTRINSIC FACTORS

There was no drug-drug interaction conducted for T gel (b) (4). The Sponsor is proposing to use the following publicly available information of the RLD for T gel (b) (4):

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 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.

2.5 GENERAL BIOPHARMACEUTICS

2.5.2 Is the clinical formulation same to the TBM formulation?

No. Clinical formulation (T06P033) was manufactured with Carbomer 940, NF. The TBM formulation will be using Carbopol 980 (using Carbomer homopolymer type C, NF) to be consistent with the RLD formulation. The compositions of the clinical and the commercial formulations in comparison to the RLD formulation are summarized in the **Table 8**. According to the CMC review by Dr. Rajiv Agarwal dated March 6, 2012, this change would qualify as a Level 2 excipient change, requiring updated stability data and comparative *in vitro* release data, not a BE study. In addition, the results of the above studies demonstrated no significant differences in the release of T gel, (b) (4).

Table 8 The composition of Sponsor's clinical and commercial formulations in comparison with RLD (AndroGel® 1%) formulation

Ingredient	Clinical Formulation	Commercial Formulation	RLD Formulation
	Concentrations (%w/w)	Concentrations (%w/w)	Concentrations (%w/w)
Testosterone, USP	(b) (4)		
Dehydrated Alcohol			
Carbomer 980, NF			
Carbomer 940, NF			
Isopropyl Myristate			
Isostearic Acid			
Sodium Hydroxide			
Purified Water	q.s. 100	q.s. 100	q.s. 100

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>)

Study samples were analyzed for total T concentration:

- BE study: Gas Chromatography/Mass Spectrometry (GC/MS)
- Hand and application sites washing study: High performance liquid chromatography with ultraviolet detector (HPLC-UV).
- Inter-personal transfer study: Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)

Table 9 Summary of Bioanalytical Methods for total T

	BE study	Transfer study	Washing study
Biological Matrix	plasma	serum	50/50 Ethanol/Water
Method	GC-MS	LC/MS/MS	HPLC/UV
Range of Standard Curve	0.250 - 10.0 ng/mL	0.05 - 50.0 ng/mL	0.03 to 2.5 µg/mL
QC inter-assay accuracy	-5.9 – 5.0 %	-3.0 – 0.1%	2.3 – 15.8 %
QC inter-assay precision	5.5 – 6.8 %	2.3 – 2.8%	1.35 – 3.96 %
Stability at -20 °C	at least 19 days	79 days	45 days

An OSI inspection of the bioanalytical site of the BE study has been conducted. One major deficiency was identified: the measured concentrations of plasma T were not adjusted for the endogenous T in blank plasma used to prepare calibrators and quality control (QC) samples. As a result, the accuracy of T determination can not be assured. Details of these OSI inspection findings can be found in Dr. Gopa Biswas's OSI consult review dated April 2, 2012. A written response to address deficiencies in the bioanalytical portion was received on April 27, 2012. OSI has not commented on the response as of this writing.

3 DETAILED LABELING RECOMMENDATIONS

The label will be revised at the time of approval.

APPEARS THIS WAY ON ORIGINAL



4 APPENDICES

4.1 INDIVIDUAL STUD REVIEW

4.4.1 BE study: Study 03-0415-001

A randomized, Single-Dose, Three-Way Crossover Relative Bioavailability Study of Testosterone Gel Formulations in Hypogonadal Men

Protocol No: 03-0415-001

Phase: 1

Principal Investigator: Dr. Antonio Pizarro

Clinical Study Center:

(b) (4)

Clinical Study Dates:

Analytical Study Facility:

OBJECTIVE

To investigate the bioequivalence (BE) of test testosterone (T) (b) (4) gel (Formulation T06P030 and Formulation T06P033) and the reference list drug (RLD, AndroGel® 1%) in hypogonadal men

STUDY ENDPOINTS

The PK parameters used for BE evaluation were AUC_{0-last} and C_{max} of total T (baseline corrected and uncorrected)

STUDY DESIGN

This was a randomized, single-dose, three-way crossover BE study in 24 hypogonadal men. In each treatment period, each study subject received a 10-g application of either one of the test formulations (T (b) (4) Formulation T06P030, Formulation T06P033) or the reference formulation (AndroGel® 1%) applied to the shoulders and upper arms. A series of blood samples were collected pre-dose (-12 and 0hr) for endogenous levels and sixteen times over 72 hours following each dose for determination of plasma T concentrations. Each treatment was separated by 7-day washout period.

Disposition of Study Subjects

Twenty four study subjects enrolled and completed the study. The age of study subjects ranged between 31-69 years old with average body mass index (BMI) of 29.6 kg/m² (range: 21.8-35.5 kg/m²). Of the 24 subjects, there were 21 Caucasians and 3 Hispanics.

Inclusion Criteria

- individual a hypogonadal adult man who volunteers to participate?
- Is his serum testosterone ≤ 300 ng/dL?
- Is he 18-70 years of age, inclusive?
- Is his body mass index ≥ 15 and ≤ 35 ?
- Is he considered reliable and capable of understanding his responsibility and role in the study?
- Has he provided written informed consent?

A no answer to any of the above questions indicated that the individuals was ineligible for enrollment.

Exclusion Criteria

- Does the individual have a history of allergy or hypersensitivity to exogenous testosterone, soybean, soy, or soya lecithin?
- Does he have clinically significant abnormal findings on the physical examination (including ECG), medical history, or clinical laboratory results (other than low testosterone) during screening that would interfere with the conduct or interpretation of the study or jeopardize his safety?
- Does he have significant history or clinical evidence of auto-immune, cardiovascular, gastrointestinal, hematological, hematopoietic, hepatic, neurological, ongoing infection, pancreatic, or renal disease which is unstable and/or not controlled by concomitant medication or would interfere with the conduct or interpretation of the study?
- Does he have any skin condition (sores, rash, eczema, etc.) or excessive hair in the intended dosing area that may affect absorption?
- Has he used any oral or any topical exogenous testosterone during the two week period preceding study initiation, any injectable exogenous testosterone during the four week period preceding study initiation, or any implantable exogenous testosterone during the six month period preceding study initiation?
- Is he currently using any medication that in the opinion of the investigator would interfere with the conduct or interpretation of the study or jeopardize his safety?

A yes answer to any of the above questions indicated that the individual was ineligible for enrollment.

Formulations

RLD Formulation

AndroGel[®] 1%: manufactured by Unimed Pharmaceuticals with an expiration date of December, 2004 (Lot No. 20325).

Test Formulations

- Formulation 1 (T06P030) was manufactured (b) (4) with a manufacture date of July 29th, 2003.
- Formulation 2 (T06P033) was manufactured (b) (4) with a manufacture date of July 30th, 2003.

The difference between two test formulations is that Formulation T06P030 contains (b) (4), whereas Formulation T06P033 contains (b) (4). Per CMC reviewer Dr. Rajiv Agarwal. (b) (4)

The compositions of the two tested formulations are presented in **Table 1**.

Table 1 Composition of Formulation T06P030 and Formulation T06P033

RAW MATERIAL	FORMULATION 1 T06P030	FORMULATION 2 T06P033
	COMPOSITION % (w/w)	
TESTOSTERONE, USP		(b) (4)
DEHYDRATED ALCOHOL, USP (ETHANOL ABSOLUTE)		
CARBOMER 940, NF (CARBOPOL 940, NF)		
SODIUM HYDROXIDE, NF	(b) (4)	(b) (4)
PURIFIED WATER, USP		
TOTAL		

Study Drug Administration

- An adhesive, transparent dressing (Tegaderm®) was placed above the antecubital space of each arm prior to study drug application to prevent contamination of the analytical samples.
- Packets containing the drug to be applied to each subject was placed in individual plastic bags and the bags was closed and weighed. At dosing, the individual packets were removed from the bag and the gel was squeezed away from the end of the packet to be opened. The ends of the packets were removed and returned to the bag, and the gel was squeezed from the packets onto the shoulders and upper arms (taking care to avoid contamination of the antecubital area with study drug). The emptied packets were returned to the plastic bag and the bag was reweighed. The individual applying the drug was then donned a pre-weighed rubber glove. The drug was distributed evenly throughout the area by hand and the glove was then be removed and reweighed.
- Approximately 10 g (two packets) of study drug was applied to the area on each subject at approximately 7:00 AM on study days 1, 8 and 15 in cross-over fashion. As soon as the gel dried (approximately 30 minutes) the plastic drape was removed carefully and the subjects wore a short sleeve scrub top.
- Immediately following collection of the 24 hour blood sample the subjects showered so as to remove any residual, unabsorbed study drug, and wore a clean shirt.
- Study drugs were administered sequentially to the subjects at four Minute intervals to insure that subsequent blood samples could be collected precisely as scheduled.
- Subjects were instructed not to engage in any strenuous physical activity (e.g., that which would lead to increased heart and/or respiratory rates) at any time while sequestered if required by an adverse event, a subject may lie on his stomach for a brief period.

Concomitant Food, Drinks and Therapy

On the first day of each treatment period after the drug application at 7 am, a standardized, low-fat meals intended to provide about 2500 Kcal/day were served at 8 am, 11 am and 5 pm and, a snack was provided at 9 pm. Drinking water was permitted ad libitum. No alcohol, caffeine or other xanthine-containing foods or beverages were permitted during the periods beginning 48 hours prior to test material administration and ending when the last blood sample was taken.

No concomitant medications were to be used during the period from 10 hours prior to study drug administration through collection of the 10 hour blood samples in each study period.

Protocol Deviation

Two subjects received concomitant medication during the 10-hour periods proceeding and following study drug administration. Subject 10 received gemfibrozil three minutes before the end of the 10-hour period during the first period. Subject 20 received Humalog 16 minutes after the beginning and 11 minutes before the end of the 10-hour period during the first period, and received Humalog, Altace, aspirin and Coreg 11, 6, 6, and 6 minutes, respectively, before the end of the 10-hour period during the

second period.

Reviewer’s Comments:

Application site of the RLD

The application site of the RLD in the current BE study (i.e. upper arms/shoulders) is different from that in the pivotal phase 3 study (study # UMD-96-017), where 10 g of RLD was administered to both abdomen and upper arms/shoulders (reference is made to Dr. Dhruba, J. Chatterjee’s Clinical pharmacology review dated on February 25, 2000). As a clinical study with RLD (study # UMD-98-012) showed T PK parameters following 1-site (left upper arm/shoulder) or 4-sites (left and right upper arm/shoulder, left and right abdomen) application were not statistically significant different, the change in application site in current study may not affect the T bioavailability of the RLD and thus the outcome of the BE evaluation.

Concomitant mediations:

- Prohibiting concomitant medication for only 10 hours postdose may not be adequate. The plasma concentration of T peaked at about 19 hours and lasted over the 72 hour after gel application. Therefore, the concomitant drugs taken after 10 hours postdose may still affect the PK of the T and thus confound the BE evaluation.
- Gemfibrozil is an inhibitor of CYP2C8 and OATP1B1(Parkinson, Kazmi et al. 2010). To the current knowledge, none of these enzymes involve in T metabolism. Therefore, it is unlikely that coadministration of gemfibrozil will affect T systemic exposure.
- The interaction between T and Humalog (insulin) is also not expected.
- Altace (Ramipril) is not metabolized by cytochrome P450 enzymes, and thus not likely to affect the T exposure.
- Per Coreg (carvedilol) label, the primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes were CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1. Although no concrete data on the inhibitory potential of carvedilol on CYP 3A4 enzyme activity, we can not exclude the possibility of altered T metabolism/systemic exposure due to the coadministration of carvedilol.

PHARMACOKINETIC EVALUATION

Blood Sampling

Blood samples (10mL) were collected 12(± 2) hours before, just prior to, and 1, 2, 3, 4, 6, 8, 10, 12, 14, 17, 20, 24, 30, 36, 48 and 72 hours after study drug application.

Bioanalytical method

Plasma concentrations of T and its main metabolite 5a- Dihydrotestosterone were determined by Negative Ion Chemical Ionization Gas Chromatography/Mass Spectrometry (GC/MS). T and the internal standard (D₃-T) were extracted from human plasma by liquid/liquid-extraction followed by a derivatization step. Extracts were analyzed by a validated GC/MS with the lower limit of quantification (LLOQ) of 0.250 ng/mL and upper limit of quantification (ULOQ) of 10.0 ng/mL. For each quality control (QC) concentration level (0.400, 2.00 and 8.00 ng/mL), the precision and accuracy were within 10%. The detailed analytical conditions are presented in **Table 2**.

Table 2 GC-MS analysis for plasma T concentration

Calibration range	0.250 – 10.0 ng/mL
LLOQ	0.250 ng/mL
Inter-assay Standard Precision (% CV)	1.7 ~ 4.4 %

Inter-assay Standard Accuracy (% Bias)	-8.0 ~ 5.9 %
Inter-assay QC precision (% CV)	5.5 ~ 6.8 %
Inter-assay QC Accuracy (% Bias)	-5.9 ~ 5.0 %
Extraction Recovery (%)	81.4% ~ 90.6 %
Stability in plasma at room temperature	at least 24 hour
Stability in plasma at - 20°C	at least 19 days
Stability of plasma samples at 3 thawing/freezing cycles	no problems observed

An inspection of the bioanalytical site of the BE study has been conducted by OSI. The following deficiencies were identified and reported in FDA Form 483:

1. Failure to adjust calibrator and QC samples concentrations for endogenous testosterone in blank plasma matrix used for preparing them.

2. Failure to document the following aspects of method validation and study conduct:

a) For freeze-thaw stability demonstration (b) (4) movements of QC samples during freeze-thaw cycles were not documented in sample processing sheet or freezer log book.

b) A freezer log for (b) (4) freezer was not maintained to record sample movement from and to the freezer during validation and study sample analysis.

c) Failure to document anticoagulant used for all the plasma lots used as blanks or for preparing calibrators and, QC samples, during method validation and study sample analysis.

d) Documents were not available to ensure that all plasma lots used during method validation and study were stripped with charcoal in order to eliminate endogenous testosterone.

3. Failure to reject analytical runs with blank samples showing 20% or more of LLOOC response. Blank samples in the majority of analytical runs showed 20% to 30% of LLOQ response but all the runs were accepted based on SOP BAS-RMT-02.

4a) Failure to demonstrate selectivity in charcoal stripped plasma.

4b) Failure to reject selectivity experiment in nonstripped plasma although the selectivity samples failed acceptance criteria (b) (4).

Of the findings listed above, item #1 was identified as the major deficiency. Details of these inspection findings can be found in Dr. Gopa Biswas's OSI consult review dated April 2, 2012. A written response to address the deficiency in the bioanalytical portion was received on April 27, 2012. OSI has not commented on the response as of this writing.

SAFETY ASSESSMENTS

- Screen examination: Vital signs, electrocardiogram (ECGs), clinical laboratory tests (blood chemistry, hematology, and urinalysis parameters) and physical examinations

- Pre- and Post-treatment examination: vital signs were determined just prior to and 2, 4, and 6 hours after study drug administration. A description of adverse events (AE) reported by subjects or observed by clinical trial staff was recorded and the adverse events were monitored until they resolved.

DATA ANALYSIS

BE will be established if the 90% confidence intervals (CI) for the geometric mean ratios (GMR) of test versus reference formulation based on AUC_{0-last} and C_{max} for T were contained within the regulatory acceptance range of 80.00 to 125.00%.

PHARMACOKINETIC RESULTS

An OSI inspection of clinical site of the BE study has been conducted. The following deficiencies were identified and reported in FDA Form 483:

1. An investigation was not conducted in accordance with the investigational plan.

- Subject 12 experienced an adverse event of hypertension that was not reported to the sponsor.
- Period 1 pre-dose erythema and edema scores were not recorded for any of the 24 subjects.
- 48-hour erythema and edema scores were not recorded for subjects 01 (Period 1), 12 (Period 3), and 19 (Period 3).
- Four blood samples were taken outside of the protocol specified window.
- Subject 02 did not receive a hepatitis C test at screening.
- Subject 05 did not receive a CBC test at screening.
- Subject 20 took medication during the 10 hour post dose restriction period. The subject was dosed at 0816 on 09/06/03, 09/13/03, and 09/20/03. The 10 hour restriction period expired at 1816.

2. The general requirements for informed consent were not met in that the information given was not in language understandable to the subject or the subject's representative. Specifically, Subject 22 was originally consented into the study on 08/18/03 using a Spanish language consent form. He was reconsented with an English version of the updated ICF on 09/05/03.

3. Investigational drug disposition records are not adequate with respect to dates. Specifically, the drug administration records for Period 3 do not indicate the date and time at which the drug was administered.

Of the inspection findings listed above, the item #1 was identified as the major deficiency, i.e., no dosing record for study period 3. Therefore, OSI recommended that the data from Period 3 should be excluded from statistical evaluation. Details of these OSI inspection findings can be found in Dr. Gopa Biswas's OSI consult review and addendum dated April 2, 2012 and April 20, 2012, respectively, in DARRTS.

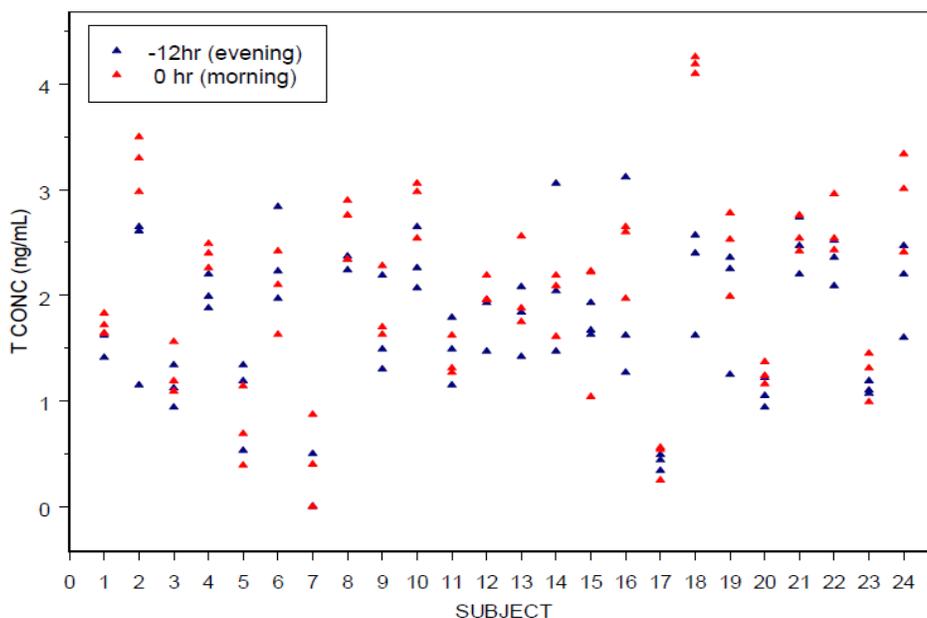
Based on the findings of OSI inspection, data from study period 3 of the pivotal BE study were excluded from the BE assessment. As a result, the number of study subjects eligible for BE analysis was reduced from 24 to 8. The small sample size (N=8) of the BE study makes it unfeasible to do any meaningful statistical analysis for BE evaluation.

The following review on BE study was written before the OSI inspection results became available. Therefore, it should be noted that these findings are no longer applicable to support the approval of T gel (b) (4)

Baseline Characterization

Given the endogenous T secretion, it is necessary to measure and approximate the endogenous T levels in plasma and subtract these levels from the total concentrations measured from each subject after the drug product is administered. In the current study, T baseline concentrations were characterized by two time points measurement prior to drug administration, i.e., 12 hrs before and immediate before dosing in each study period. The exogenous T concentrations were calculated by subtracting the mean of the two pre-dose values (-12 and 0 hr) from total T concentration for each study period. **Figure 1** shows the T baseline concentrations from three study periods at 12hr before and just prior to dosing. The mean values of baseline T concentration for the 24 hypogonadal men in the current study is 1.72 ± 0.62 ng/mL in the evening time and 2.03 ± 0.89 ng/mL in the morning time.

Figure 1 Baseline T concentrations at 12hr before and immediate before dosing for each study subject in three study periods (N = 24).



Reviewer's Comments:

- The BE study protocol stated that hypogonadism status of each subject would be confirmed by the mean of the two pre-dose values for each study period (-12 and 0 hr). Subject 18 had average baseline T concentrations over 3 ng/mL for two study periods (**Table 3**). Considering the inclusion criteria of hypogonadal men with baseline T values less than 3 ng/mL, this reviewer believes that subject 18 should be excluded from the BE analysis.
- Circulating T concentration have a diurnal variation in healthy young men, usually reaching a mean maximum level of 7.1 ng/mL at approximately 8 A.M. and declining to a mean minimum concentration of 4.26 ng/mL at approximately 10 P.M. (Winters 1999). The circadian variation in T concentrations is also expected in hypogonadal men. In the current study, the mean T concentrations in the morning were generally higher than that in the evening time.

Table 3 Baseline concentrations (ng/mL) for subject 18 in each study period

Treatment	-12hr	0hr	Average baseline
TEST (T06P030)	2.40	4.26	3.3300
TEST (T06P033)	1.62	4.10	2.8600
RLD (AndroGel [®] 1%)	2.57	4.19	3.3800

Original BE analysis prior to OSI findings: Baseline Corrected PK Parameters

Baseline corrected mean T concentration-time profiles following a single dose of either test formulations or the RLD are presented in **Figure 2** with PK parameters summarized in **Table 4**.

Both test formulations displayed similar PK profiles as compared to the RLD. The plasma concentration of total T peaked at about 20 hours postdose with average values about 5 ng/mL. BE analysis using the baseline corrected PK parameters indicated that test Formulation T06P033, but not Formulation T06P030, was BE to the RLD with respect to mean T C_{max} and AUC_{0-72hr} (**Table 5**). Individual PK profiles of T for the RLD and test formulation T06P033 are presented in **Figure 3**.

Figure 2: Baseline corrected Arithmetic Mean T Concentration-Time Profile following a single dose of either T gel (b) (4) (Formulation T06P030 or T06P033) or the RLD (N=24)

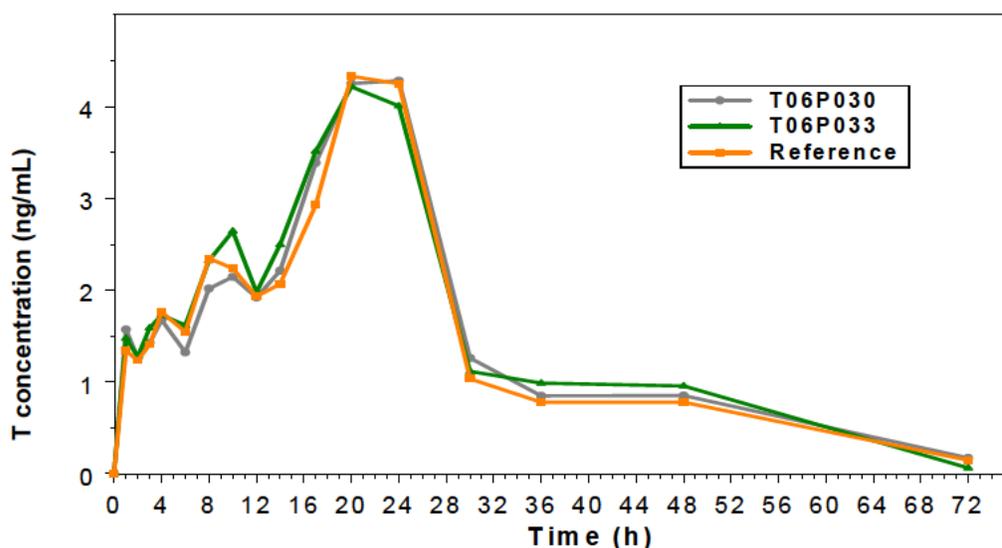


Table 4: Baseline corrected PK parameters (arithmetic mean \pm SD) for T gel (b) (4) (Formulation T06P030 and T06P033) and the RLD (AndroGel® 1%)(N=24)

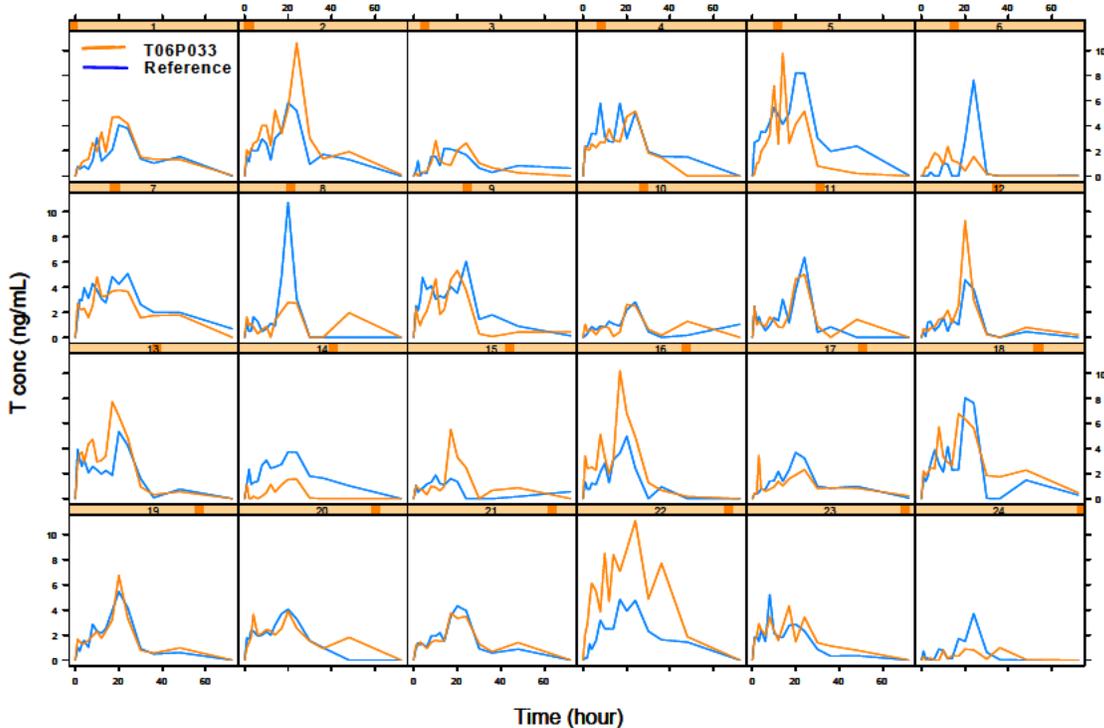
Parameter	Formulation T06P030	Formulation T06P033	RLD
AUC_{0t} (ng·hr/mL)	101.2 \pm 53.2	101.1 \pm 62.6	96.9 \pm 44.9
C_{max} (ng/mL)	5.72 \pm 2.82	5.46 \pm 2.96	5.18 \pm 2.01
T_{max} (hr)	20.2 \pm 4.2	18.6 \pm 6.4	19.2 \pm 4.7

Table 5 Baseline corrected BE analysis for T gel (b) (4) (Formulation T06P030 and T06P033) (N=24)

Parameter ¹	Ratio ² (90% Confidence Interval)	
	Formulation T06P030	Formulation T06P033
AUC_{0t} (ng·hr/mL)	1.015 (0.882-1.169)	0.959 (0.833-1.104)
C_{max} (ng/mL)	1.061 (0.885-1.273)	0.965 (0.805-1.158)

1. Least-square geometric means for Ln-transformed data
2. Ratio calculated as Test least-square mean divided by Reference least-square mean

Figure 3 Individual T Concentration-Time profile for Test Formulation (T06P033) and the RLD (AndroGel® 1%)



Reviewer’s Comments

- The Sponsor’s BE analysis using data from 24 subjects was confirmed to be valid based on the reviewer’s own BE analysis.
- For subject 6, 10 out of 17 time points had T concentrations equal to zero for the RLD. However, considering that zero concentrations were mainly from the beginning or the end of PK profile, which may not greatly affect C_{max} and AUC values, data for subject 6 can be included for the BE analysis.
- This reviewer believes that two study subjects should be excluded from the BE analysis. Specifically, subject 18 had average T baseline concentrations > 3 ng/mL and subject 20 had concomitant medications that may affect the T systemic exposure during the study period. As shown in **Table 6** and **Table 7**, Formulation T06P033 was BE to the RLD when subject 18 or both subject 18 and 20 were excluded from analysis.

Table 6 Reviewer’s Baseline corrected BE analysis (N=23 when exclude subject 18)

Parameter	Ratio (90% Confidence Interval)	
	Formulation T06P030	Formulation T06P033
AUC _{0-t} (ng·hr/mL)	1.011 (0.873-1.171)	0.950 (0.820-1.100)
C _{max} (ng/mL)	1.073 (0.888-1.280)	0.976 (0.808-1.180)

Table 7 Reviewer’s Baseline corrected BE analysis (N=22 when exclude subject 18 and 20)

Parameter	Ratio (90% Confidence Interval)	
	Formulation T06P030	Formulation T06P033
AUC _{0-t} (ng·hr/mL)	0.971 (0.839 -1.124)	0.940 (0.812 -1.087)
C _{max} (ng/mL)	1.015 (0.843 -1.222)	0.972 (0.808 -1.169)

- *Statistic Power Analysis*
 - *Power of the BE analysis is 63.5% given*
 - *intra-subject variability (rough estimation) = 30%*
 - *sample size= 24*
 - *expected test/reference ratio=100%*
 - *Power of the BE analysis is 57.0% given same condition with sample size of 22*
- The lower statistic power leads to a wider confidence interval. Nonetheless, as Formulation T06P033 met BE criteria of 80% to 125%, we consider Formulation T06P033 BE to the RLD.*

Original BE analysis prior to OSI findings: Baseline Uncorrected PK parameters

Baseline uncorrected mean T concentration-time profiles following a single dose of either test or reference formulations are presented in **Figure 4** with PK parameters summarized in **Table 8**. Both test formulations displayed similar PK profiles as compared to the RLD. Plasma T concentrations rose rapidly to 1.5 times the baseline concentration and into the desired range (298-1043 ng/mL) within 1 hour. T concentrations continued to slowly rise through the day to 3-fold of C_{baseline} at 24 hr postdose. BE analysis using the baseline uncorrected PK parameters indicated that both Formulation T06P033 and T06P030 were BE to the RLD (AndroGel® 1%) with respect to mean T C_{max} and AUC_{72hr} (**Table 9**).

Figure 4 Baseline unadjusted Arithmetic Mean T Concentration-Time Profile following a single-dose of either T gel (b) (4) (Formulation T06P030 and T06P033) and the RLD (AndroGel® 1%) (N=24)

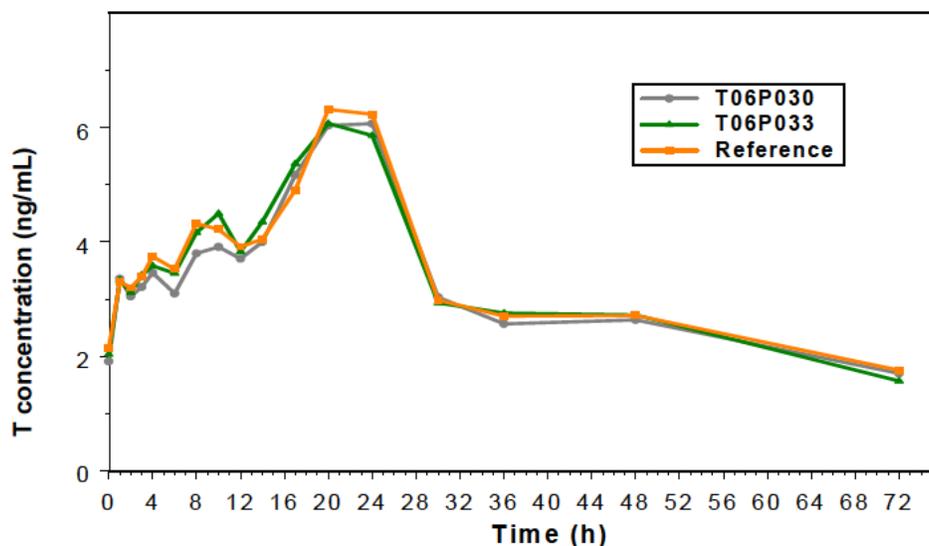


Table 8 Baseline uncorrected PK parameters (arithmetic mean ± SD) for T gel (b) (4) (Formulation T06P030 and T06P033) and RLD (AndroGel® 1%) (N=24)

Parameter	Formulation T06P030	Formulation T06P033	RLD
AUC _{0-t} (ng·hr/mL)	231.0 ± 74.4	236.3 ± 85.4	238.9 ± 62.9
C _{max} (ng/mL)	7.51 ± 2.96	7.32 ± 3.02	7.17 ± 2.28
T _{max} (hr)	20.1 ± 4.2	18.6 ± 6.4	19.2 ± 4.7

Table 9 Baseline uncorrected BE analysis for T gel (b) (4) (Formulation T06P030 and T06P033) (N=24)

Parameter	Ratio (90% Confidence Interval)	
	Formulation T06P030	Formulation T06P033
AUC _{0-t} (ng·hr/mL)	0.953 (0.903-1.006)	0.967 (0.916 - 1.020)
C _{max} (ng/mL)	1.024 (0.901-1.163)	0.990 (0.872 - 1.125)

SAFETY RESULTS

A total of 23 adverse events were observed in or reported by 12 subjects; six of the 23 adverse events were judged as possibility or probably related to study drug administration.

CONCLUSIONS

Based on the original BE analysis, T gel (b) (4) from Formulation T06P033 was BE to Reference Formulation (AndroGel[®] 1%). However, this conclusion (BE) was subsequently rejected due to the results of the OSI inspection findings that resulted in the removal of all but 8 subjects from the dataset available for evaluation.

REFEREMCE

- Parkinson, A., F. Kazmi, et al. (2010). "System-dependent outcomes during the evaluation of drug candidates as inhibitors of cytochrome P450 (CYP) and uridine diphosphate glucuronosyltransferase (UGT) enzymes: human hepatocytes versus liver microsomes versus recombinant enzymes." *Drug Metab Pharmacokinet* **25**(1): 16-27.
- Winters, S. J. (1999). "Current status of testosterone replacement therapy in men." *Arch Fam Med* **8**(3): 257-263.

4.4.2 Transfer Potential Study: Study M1IU9001

A study to determine the transfer of testosterone from a male to his female partner for Perrigo Pharmaceuticals (b) (4) testosterone gel

Protocol No: M1IU9001
Phase: 1
Principal Investigator: Lawrence Galitz, MD
Clinical Study Center: (b) (4)
Clinical Study Dates:
Analytical Study Facility:
Clinical Study Period: October, 2010 to November, 2010

OBJECTIVE

- To evaluate testosterone (T) transfer from male to female partner when the male was wearing a T-shirt and when the male was not wearing a T-shirt for Perrigo Pharmaceuticals (b) (4) T gel following a single topical dose (10g of gel for a total of 100 mg testosterone).
- To evaluate T transfer from males to females for reference listed drug (RLD, AndroGel® 1%) with each treatment condition (with a T-shirt and without a T-shirt)

STUDY ENDPOINTS

The percentage transferred to the non-dosed female when the male user is without a T-shirt and when the same male user wears a T-shirt for the Test product (T gel (b) (4))

STUDY DESIGN, TREATMENTS, AND SUBJECTS

This was an open-label, single-dose, four way-crossover study to assess the inter-personal transfer potential of the test T gel (b) (4) and the RLD AndroGel® 1%. The female subjects enrolled in this study were postmenopausal or surgically sterile. A single topical dose of either test T gel (b) (4) or the AndroGel® 1% (10 g, applied to one side of upper arm and shoulder) with or without males wearing a T-shirt was applied to the male subjects (Table 1). Female subjects had one arm/shoulder designated as the “contact site”. Starting at 2 hours after dosing, each couple was instructed to engage in a total of 15 minutes of contact. The total duration of the study, screening to the end of the study, was approximately 12 weeks with at least a 7-day washout period between doses.

The male subjects received 1 topical application on Day 1 of each study period of test or reference drug over 8-weeks with a 7-day washout period between dosing periods. Total study participation, exclusive of screening, was 8 weeks.

Table 1 Treatment groups in inter-personal transfer study

T gel (b) (4) (TEST)		AndroGel® 1% (RLD)	
Treatment A (not wearing T shirt)	Treatment B (wearing T shirt)	Treatment C (not wearing T shirt)	Treatment D (wearing shirt)

Disposition of Study Subjects

A total of 24 couples were enrolled in the study and 20 couples completed the study. Specifically, subject 03, 08, 14 and 16 were withdrawn from the study. The reasons for discontinuation

are listed below:

- Subject 03: Female partner 03-A that tested positive for Benzodiazepine at Period 1
- Subject 08: Male partner 08-B that tested positive for THC (Marijuana) at Period 1
- Subject 14: Female partner 14-A that tested positive for cotinine at Period 4 admission
- Subject 16: Noncompliance of Female partner 16-A at Period 1.

Of the 20 female who completed the study, the mean age of study subjects is 53.9 years (range: 44-62 years) with mean body mass index (BMI) of 28.1 kg/m² (range: 24.7 -31.0). Eighteen subjects are Caucasians and two subjects are African Americans.

Inclusion Criteria

- Healthy male or female volunteer 18 – 65 years of age at the time of dosing.
- Body mass index (BMI) between 18 – 32 kg/m².
- Judged by an investigator to be in good health as documented by medical history, physical examination, vital sign assessments, 12-lead ECG, clinical laboratory assessments, and by general observations.
- Females were postmenopausal or surgically sterile. Females were of post-menopausal status (no menses) for at least 1 year and if <55 years of age, had a documented FSH level of ≥ 40 mIU/mL. Surgically sterile included bilateral oophorectomy, hysterectomy, or Essure® procedure.
- Both males and females had T levels in the normal range (220-1000 ng/dL for males and 0-90 ng/dL for females) at screening and at each period check-in.
- Completed the screening process within four weeks prior to Period I dosing.

Exclusion Criteria

Volunteers or subjects who met any of the following criteria were excluded from the study:

- Anyone who received any investigational drug within 30 days prior to Period I dosing.
- Anyone who had a presence of any clinically significant results from laboratory tests, vital signs assessments, and ECG, as judged by the investigator.
- Anyone who demonstrated a reactive screen for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody and was confirmed upon additional testing.
- For males, baseline prostate specific antigen (PSA) > 2.5 ng/mL. If the volunteer had documentation of a negative prostate biopsy within the past 6 months, a PSA of 2.6 – 3.74 ng/mL was allowed.
- For males, who had untreated prolactinoma.
- For females, who had a previous history of, or current or suspected, hirsutism.
- Anyone who used any over the counter (OTC) medications within seven days prior to the first dose of study medication or used any prescription medications or herbal and dietary supplements within 14 days prior to the first dose of study medication. The exclusion was extended to 28 days for any drugs known to induce CYP3A enzymes and 14 days for any drugs known to inhibit CYP3A enzymes or 5 α -reductase, such as finasteride and dutasteride.
- Anyone who reported a history of an allergic response(s) to testosterone or related drugs (e.g. topical androgens) or alcohol-based topical products, or clinically significant allergies to foods or medications.
- Anyone who displayed the presence of a skin condition, sun-burn, scar tissue, tattoo, open sore, body piercing or branding, or coloration that would have interfered with placement of test sites, their assessments, and their reaction to drug or could have compromised the safety of the subject.

Concomitant Therapy, Food, and Drinks

- No prescription medications or herbal/dietary supplements were allowed for a period of 14 days prior to dosing and no OTC medications were allowed for a period of 7 days to dosing with the exception of CYP3A enzyme inducers which were restricted for 28 days, and 14 days for any drug known to inhibit CYP3A or 5 α -reductase (e.g. finasteride and dutasteride).
- Standard daily dose multivitamins (non-therapeutic doses) were consumed until initial check-in and were restricted until the end of the study.
- Use of any monoamine oxidase inhibitor (MAOI), excluding St. John's Wort, was avoided for a period of 14 days before the first dose through 14 days after the final dose of the study.
- Use of St. John's wort was avoided for a period of 28 days before the first dose through 14 days after the final dose of the study.
- No subject was allowed to apply any cream, ointment, lotion, moisturizer, etc. to the dosing areas 48 hours prior to study conduct and throughout the study period.
- Hormone Replacement Therapy (e.g., oral, vaginal insert, patch, injectable, or topical) was not to have been used by female subjects for at least three consecutive months prior to Period I dosing and throughout the study.
- Caffeine/xanthine such as coffee, tea, chocolate, and all caffeine-containing soft drinks or energy drinks and alcoholic beverages and/or other alcohol containing products were not consumed 48 hours prior to each period dosing and throughout the study until the last scheduled blood sample collection.
- Grapefruit, Seville oranges, and grapefruit and/or pomelo containing products were not to be consumed for 14 days prior to Period I dosing and throughout the study until the last scheduled blood sample collection

Study Drug

- Test Formulation (T gel (b) (4) Perrigo Pharmaceuticals, Inc., Lot/Batch No: 028508, Manufacture date: 12/22/2009
- RLD (AndroGel[®] 1%): Solvay Pharmaceuticals, Inc., Lot/Batch No: 31791, Expiration date: 11/2011

Dose Application

Dose application for each male subject occurred at the same time for each treatment period under the supervision of the clinical research staff. One hour prior to the targeted time of dose application, male subjects showered and washed the application site with soap and water. Subjects did not remain in the shower for longer than 10 minutes. The designated area for gel application was thoroughly dried.

The total dose applied to each male subject per period was 10 g (provided in 2 applications of 5 g). Clinic staff applied one 5 gram packet of the designated testosterone gel formulation to the central palm area of the subject's dominant hand (the dominant hand was recorded in the source documents). The subject applied the dose to their opposing arm and shoulder (front, side, and back) with monitoring by clinic staff to ensure even distribution. A second application of one (1) 5 gram packet was dosed to the subject's dominant central palm area as mentioned above, with application to the same opposing arm and shoulder in the identical manner as the first application. Following the last incremental gel application, for those subjects assigned to wear a T-shirt, the T-shirt was worn as soon as the gel dried on the designated application area.

Transfer process

Female subjects had one upper arm/shoulder designated as the "contact site" and were instructed to rub their upper arm and shoulder up and down the upper arm and shoulder of their male partner during the 15 minute contact period as follows:

- Each couple engaged in a total of 15 minutes of contact.

- Female subjects were instructed to gently rub (for approximately 15 seconds per stroke) their upper arms and shoulders up and down the upper arms and shoulders of their male partner during the contact period for a total of one minute.
- One minute periods of alternating active rubbing and resting of the female's arms on the male's shoulders occurred until the 15 minute time period was completed.

Each couple was monitored and coached by one staff member throughout the contact period.

Female subjects thoroughly washed their hands with soap and water immediately after skin contact was completed. After the completion of the contact period, female subjects re-clothed with their T-shirt. Female subjects did not shower or bathe until at least 24 hours after the contact period. For those periods where the male wore a T-shirt, the T-shirt was worn throughout the contact rubbing session.

Protocol Deviation

- Blood sampling deviations: No impact on the study results as PK parameters were computed from the plasma concentration data using the actual sample collection times.
- Concomitant medications: Three subjects took the medications that are restricted from the study protocol and were excluded from the study analysis

PHARMACOKINETIC EVALUATION

Blood Sampling

- Pre-dose: blood samples (6mL) were collected on Day -1 from female subjects at 0, 2, 4, 6, 8, 10, 12, 16 and 24 hours.
- Post-dose: blood samples (6mL) were collected on Day 1 from females subjects within 10 minutes prior to dose transfer (0 hour) and after dose transfer at 2, 4, 6, 8, 10, 12, 16 and 24 hours.

(One single blood sample was collected to represent both the Day -1, 24 hour sample and the Day 1, 0 hour sample)

Bioanalytical method

Measurement of total serum T concentrations was performed at [REDACTED] (b) (4) [REDACTED] from November 22, 2010 to December 09, 2010. The detailed method description is presented in **Table 2**.

Table 2 Analysis of total T serum concentration using High Performance Liquid Chromatograph with Tandem Mass Spectrometry

Method Description	
AP Number	AP LC/MS/MS 114.102
Analyte	Testosterone
Internal Standard	Testosterone-d3
Matrix	Human serum
Extraction Method	Liquid-liquid procedures
Method of Detection	LC/MS/MS
Sample Aliquot Volume	200 µL
Regression and Weighting	Linear, 1/x ²
Calibration Range	0.05000 to 50.00 ng/mL
Quality Control Concentrations	LQC-1 0.1500 ng/mL LQC-1 0.3000 ng/mL MQC-1 1.500 ng/mL MQC-2 15.00 ng/mL HQC 37.50 ng/mL
Assay Performance	
Inter-Assay Standard Precision (%CV)	1.1 to 4.0%
Inter-Assay Standard Accuracy (%Bias)	-1.7 to 1.4%
Inter-Assay QC Precision (%CV)	2.3 to 2.8%
Inter-Assay QC Accuracy (%Bias)	-3.0 to 0.1%
Batch Performance	21 acceptable runs
Sample Storage	
Samples Received	1450 samples received
Samples Analyzed	1360 samples analyzed
Storage Stability	79 days @ -20°C ±10°C

SAFETY ASSESSMENTS

- Physical examination, vital sign, electrocardiogram (ECG), blood and urine clinical laboratory tests at screening and at the end of study
- Record AEs and concomitant medication during treatment phase

PHARMACOKINETIC RESULTS

With Baseline Correction

As shown in **Table 3**, wearing a T-shirt substantially blocked the inter-person T transfer for both test and reference products. Specifically, for test T gel ^{(b) (4)} C_{max} and AUC_{0-24hr} of total T transferred from males wearing a T-shirt as measured in the females was 81.88% and 90.22% lower than that of T transferred from males without a T-shirt, respectively.

Table 3 Summary of Baseline-Adjusted PK Parameters for test and reference products

N=20	Parameters	with T-shirt	w/o T-shirt	% Ratio	% of transfer blocked by a T-shirt
T gel ^{(b) (4)} (TEST)	AUC _{0-24hr} (ng·hr /mL)	0.3216	3.2889	9.78	90.22
	C _{max} (ng/mL)	0.0472	0.2605	18.12	81.88
AndroGel® 1% (RLD)	AUC _{0-24hr} (ng·hr /mL)	0.2722	3.8806	7.01	92.99
	C _{max} (ng/mL)	0.0355	0.3007	11.82	88.18

Without Baseline Correction

As shown in **Table 4** and **Table 5**, female subjects had a 16% and 48% increase from baseline in AUC_{0-24hr} and C_{max} of total T, respectively, after direct skin contact with males wearing a T-shirt. In contrast,

female subjects had a 136% and 250% increase from baseline in AUC_{0-24hr} and C_{max} of total T, respectively, when males were not wearing a T-shirt. The results indicated that covering the application site with a clothing barrier reduced the magnitude of transfer.

Table 4 Summary of Baseline-Unadjusted PK Parameters for test and reference products when male subject were wearing a t-shirt

N=20	Parameters	Before transfer (baseline)	After transfer	% increase from baseline
T gel (TEST) (b) (4)	AUC _{0-24hr} (ng·hr /mL)	2.798	3.254	16
	C _{max} (ng/mL)	0.132	0.195	48
AndroGel® 1% (RLD)	AUC _{0-24hr} (ng·hr /mL)	2.970	3.184	7
	C _{max} (ng/mL)	0.141	0.159	13

Table 5 Summary of Baseline-Unadjusted PK Parameters for test and reference products when male subjects were not wearing a t-shirt

N=20	Parameters	Before transfer (baseline)	After transfer	% increase from baseline
T gel (TEST) (b) (4)	AUC _{0-24hr} (ng·hr /mL)	2.883	6.800	136
	C _{max} (ng/mL)	0.146	0.510	250
AndroGel® 1% (RLD)	AUC _{0-24hr} (ng·hr /mL)	2.937	8.210	180
	C _{max} (ng/mL)	0.141	0.602	325

Reviewers' comments

- The potential for T transfer following T gel (b) (4) application on the abdomen has not been evaluated.
- In a type C guidance meeting dated on May 19, 2010, the Sponsor proposed to apply 5 g gel to each side of the subject's upper arm/shoulder. However, in the current study, 10 g gel was all applied to one side of arm/shoulder, which leads to a 50% reduction in the surface area for transfer as compared to the original proposal.
- For T gel (b) (4) C_{max} of T increased by 48% from baseline in female partners even when males were wearing a T-shirt.

SAFETY RESULTS

No serious adverse events (AEs) were reported over the course of this study.

Overall, there were two AEs reported during the study. Hypertension occurred on one occasion in a subject (2.08%) following administration of Treatment C, and was considered by the investigator to be unrelated to the treatment. Irritability occurred on one occasion in a subject (2.08%) following administration of Treatment C, and was considered by the investigator to be unlikely related to the treatment. Both adverse events were mild in intensity.

No subject was discontinued due to an AE.

CONCLUSION

Covering the application site with clothing barrier such as a t-shirt may significantly reduce the T transfer to others.

4.4.3 Hand and Application Site Washing Study: Study PRG-806

A Pivotal Study to Evaluate the Residual Amount of Topically Delivered Testosterone Gel (b) (4) Present on Normal Skin of the Hand, Arm, and Shoulder in Healthy Adult Male Subjects following Washing Procedures

Protocol No: PRG-806
Phase: 1
Principal Investigator: Alan K. Copa, Pharm.D.
Clinical Study Center: (b) (4)
Analytical Study Facility: (b) (4)
Clinical Study Period: December, 2010 to January, 2011

OBJECTIVE

To quantify the amount of testosterone (T) remaining on the hands and arm/shoulder before and after washing in test T (b) (4) gel manufactured by Perrigo Israel Pharmaceuticals and the reference listed drug (RLD, AndroGel® 1%) following a single topical dose (10 g of gel for a total of 100 mg T)

STUDY DESIGN, TREATMENTS, AND SUBJECTS

This was an open-label, four-period crossover study on 36 healthy adult male subjects (Table 1). The total duration of the study, screening through study exit, was approximately 8 weeks with 14 days between periods.

On Day 1 of each treatment period, 10 g (2 x 5 g packets) of either the T gel (b) (4) or AndroGel® 1% was applied to one side of the subject's arm/shoulder. Depending upon the treatment groups (no wash or wash), subjects had their hand wiped with ethanol dampened gauze pads before or after hand washing to obtain a residual hand sample for T measurement. Approximately 2 hours after the dose was applied, subjects had their arm/shoulder wiped with ethanol dampened gauze pads before or after a shower to obtain a residual application site sample for T measurement.

Table 1 Treatment groups in hand and application sites washing study

T gel (b) (4) (TEST)		AndroGel® 1% (RLD)	
Treatment A (No wash)*	Treatment C (Wash)	Treatment B (No wash)*	Treatment D (Wash)
* wipe the dosed hand immediately following dosing and the arm/shoulder application site two hours after dose application			

Disposition of Study Subjects

Thirty six (36) healthy male subjects were enrolled in the study and 33 completed. Of the subjects who did not complete the study, Subject 06 elected to withdraw prior to Period II check-in due to schedule conflict. Subject 20 was discontinued by the Investigator prior to Period II check-in due to an AE (viral infection). Subject 32 elected to withdraw prior to Period III check-in due to schedule conflict.

Of the 33 subject who completed the study, the mean age of study subjects is 29.2 years (range: 19-63 years) with mean body mass index (BMI) of 26.6 kg/m² (range: 21.1 -33.6). Thirty one (31) subjects are Caucasians, three subjects are Asians, one subject is African American and one subject is American Indian or Alaskan Native.

Inclusion Criteria

- Male, non-smoking (minimum of 14 days), 18 to 65 years of age
- BMI between 19 to 34 kg/m²
- Volunteer's hands, upper arms, and shoulders were free from scars, cuts, excessively thick calluses, or skin diseases that could have affected absorption or interfered with evaluation of the test site.
- Willing to follow study restrictions and shower using the same soap/cleansers between the Screening Visit and until completion of study related activities.

Exclusion Criteria

Volunteers or subjects who met any of the following criteria were excluded from the study:

- Reported participating in another investigational drug, medical device, or biologics study within 30 days prior to dosing.
- Reported a past or current medical condition that might have significantly affected percutaneous absorption to topical testosterone.
- Reported a history of sensitivity/allergy to the ingredients found in the test formulations or had a history of adverse reactions to topical or systemic corticosteroids.
- Reported a significant history of allergy to soaps, lotions, emollients, ointments, creams, cosmetics, adhesives, or latex.
- Reported a history of significant skin conditions or disorders, for example, psoriasis, atopic dermatitis, etc.
- Reported a history of significant dermatologic cancers, for example, melanoma or squamous cell carcinoma. Basal cell carcinomas that were superficial and did not involve the investigative site were acceptable.
- Reported a known or suspected case of prostate cancer.
- Reported using a tobacco product within 14 days of study conduct. Anyone who received any investigational drug within 30 days prior to Period I dosing.

Concomitant Therapy, Food, and Drinks

Concomitant medication was not allowed during the study. Any concomitant medication, other than the test product was recorded.

Study Drug

- Test Formulation (T gel (b) (4) Perrigo Pharmaceuticals, Inc., Lot/Batch No: 028508, Manufacture date: 12/22/2009
- RLD (AndroGel 1%): Solvay Pharmaceuticals, Inc., Lot/Batch No: 31791, Expiration date: 11/2011

Dose Application

One 5g packet of T gel was applied to the central palm area of the subject's dominant hand by (b) (4) staff. The subject's dominant hand was recorded in the source documents. The subject distributed the dose to the 400 cm² demarcated area of the upper arm and posterior and anterior shoulder with monitoring by clinic staff to ensure even distribution.

The applied dose was evenly spread throughout the arm/shoulder area by the subject and gently rubbed into the test site. A second application of one 5g packet of T gel was applied to the same central palm area and the subject distributed the dose to the same area of the upper arm and posterior and anterior shoulder. The applied dose was evenly spread throughout the arm/shoulder area by the subject and gently rubbed into the test site. The packets of T gel were weighed before being opened and within 5 minutes after application for all periods and all packets.

Washing Methods

- Hand-Washing

Subjects were required to wash their hands at the designated timed intervals. At the defined time, subjects wet their hands with warm tap water (96.0°F – 104.0°F) and had 2 mL of liquid soap (Dial® liquid hand soap) dispensed to the hands (wash steps 0 and 1) within 5 seconds. The subject then performed wash steps 2 – 7 at 5 seconds per step (total time 30 seconds) followed by a 15 second rinse with warm tap water, then dried their hands with a dry cotton towel for 10 seconds.

- Arm/Shoulder Washing

Subjects were required to wash their arm/shoulder at the designated timed intervals. At the defined time, subjects performed a full body shower in which they wet their bodies with warm tap water (96.0°F – 104.0°F) and had 2 mL of liquid soap (Dial® liquid hand soap) dispensed to the hands within 5 seconds, washed their arm/shoulder with a controlled hand scrubbing for 30 seconds, followed by a 15 second body rinse, then dried their bodies with a dry cotton towel for 15 seconds.

Sample Collection

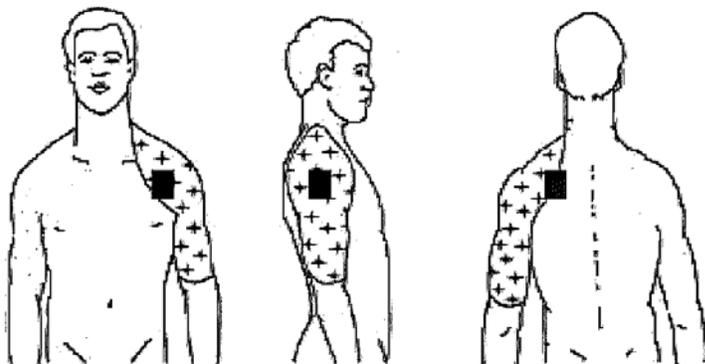
- Hand Swabbing

At the designated times, the palm, fingers, and back of the dosing hand (“no wash visits”) or from both hands (“wash visits”) were wiped with gauze pads (e.g. 2” × 2”) dampened with approximately 2 mL of ethanol (1 gauze to palm, 1 gauze to fingers, and 1 gauze to back of hand) to collect any residual T remaining on the skin surface. The three gauze pads per hand were combined into one vial, with a second vial for the three gauze pads from the other hand. The vials were appropriately labeled as to subject identification, hand, collection sequence number, and collection time.

- Arm/Shoulder Swabbing

As shown in **Figure 1**, the arm/shoulder was demarcated with three collection areas (anterior shoulder, posterior shoulder and lateral arm) within the central area of the dose application area. Each area was 50 cm² (e.g. 5 cm × 10 cm or equivalent). Each area was wiped with three gauze pads (e.g. 2” × 2”) dampened with approximately 2 mL of ethanol to collect any residual T left on the skin surface. The three gauze pads per each area were combined into separate vials (total of three vials with three gauze pads in each vial). The vials were appropriately labeled as to subject identification, body site, collection sequence number, and collection time.

Figure 1 Demonstration of sample collection areas (black boxes)



Protocol Deviation

No protocol deviations occurred over the course of this study.

Bioanalytical Method

Bioanalyses for T present in the gauze was performed (b) (4) from January 14th, 2011 to March 1st, 2011. The detailed method description is presented in **Table 2**.

Table 2 Analysis of T in gauze wipe using High Performance Liquid Chromatography with Diode Array Detector (HPLC/UV)

<p>Method Description</p> <p>Name of Compound(s): Stock Solution Matrix: Sample Matrix (Diluent): Internal Standard: Instrument: Mobile Phase A: Mobile Phase B: Gradient or Isocratic: Column Description: Flow-rate (mL/min): Run Time (min): Column temperature (°C): Injection Volume (µL) Wavelength1: Wavelength2: Limit of Detection: Calibration Range</p>	<p>Testosterone Ethanol 50/50 Ethanol/Water N/A HPLC/UV Water (25%) Methanol (75%) Isocratic Phenomenex Luna C18, 3µ, 4.6mm x 100mm 0.75 mL/min 5.00 min (May be adjusted.) 40°C 30 µL Sample + 5 µL Water 245 nm (5 nm) – 450 nm (50 nm) N/A 0.003 µg/mL 0.03 to 2.5 µg/mL (0.03, 0.09, 0.180, 0.360, 0.720, 1.2, 1.8, 2.5)</p>
<p>Assay Performance</p> <p>Inter-Assay Standard Precision (%CV) Inter-Assay Standard Accuracy (% Bias) Inter-Assay QC Precision (%CV) Inter-Assay QC (% Bias) long term stability at -20°C</p>	<p>0.20 % - 2.69 % 99.7 % - 101.4 % 1.35 % - 3.96 % 102.3 % - 115.8 % 45 day</p>

SAFETY ASSESSMENTS

Safety measurements were obtained at the discretion of the Investigator in addition to Adverse Event queries.

RESIDUAL T ANALYSIS RESULTS

Residual T amount recovered for hand and for application site are presented as mass recovered (**Table 3**) and percent of dose (**Table 4**). Application sites results are normalized to the 400 cm² total application area.

The data from test T gel (b) (4) indicated that hand washing removed 95.3% of recoverable T and showering procedure (2 hours after dose application) removed 79.5% of recoverable T from the arm/shoulder dosing area. For AndroGel[®] 1%, hand washing removed 95.3% of recoverable T and showering procedure removed 75.9 % of recoverable T from the arm/shoulder dosing area.

Table 3 Residual T amount (µg) recovered for hand and for application site (the arm/shoulder)

	AndroGel [®] 1% (RLD)	T gel, (b) (4) (TEST)
--	--------------------------------	-----------------------

	Treatment B (No Wash)	Treatment D (Wash)	Change (%)	Treatment A (No Wash)	Treatment C (Wash)	Change (%)
Hand	8323 ± 3060	395 ± 197	95.3	8478 ± 3552	399 ± 199	95.3
Application Site	27754 ± 7285	6693 ± 4675	75.9	28326 ± 7627	5802 ± 2770	79.5

Table 4 Residual T amount recovered as % of applied dose for hand and for application site (the arm/shoulder)

	AndroGel® 1% (RLD)			T gel, (b) (4) (TEST)		
	Treatment B (No Wash)	Treatment D (Wash)	Change (%)	Treatment A (No Wash)	Treatment C (Wash)	Change (%)
Hand	8.32 ± 3.06	0.39 ± 0.20	95.3	8.48 ± 3.55	0.40 ± 0.20	95.3
Application Site	27.75 ± 7.29	6.69 ± 4.68	75.9	28.33 ± 7.63	5.80 ± 2.77	79.5

Reviewers' Comment

Washing procedure can effectively remove the T gel (b) (4) from hands and application site and thus may effectively reduce the transfer potential to non-dosed subject due to the skin contact.

SAFETY RESULTS

No serious adverse events (SAEs) were reported over the course of this study.

Four (4) subjects experienced a total of 6 adverse events (AEs) over the course of the study. The AEs were mild in intensity. No SAEs were reported. Cough, oropharyngeal pain, scratch, and viral infection each occurred on one occasion in 1 subject (2.78%) and were considered by the investigator to be unlikely or not related to the treatment. Non-application site skin laceration occurred on one occasion in 2 subjects (5.56%) and was also considered by the investigator to be unlikely or not related to the treatment. Overall, the most common AE reported was skin laceration. During the test drug treatment arms, skin laceration was reported by one subject (3.03%) following no hand and application site wash (Treatment A), and by one subject (2.94%) following a hand and application site wash (Treatment C).

CONCLUSION

The results of the study indicated that washing hands with soap and water and a shower (2 hour after dose application) can sufficiently remove T gel (b) (4) from the hands and application sites.

4.2 NDA FILING AND REVIEW FORM

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence (BE) data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			A single dose BE study using upper arm and shoulder as the site of application
2	Has the applicant provided metabolism and drug-drug interaction information?			x	Refers to information publically available (i.e., AndroGel [®] label)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			BE approach to a reference product AndroGel [®]
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	BE approach to a reference product AndroGel [®]
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	BE approach to a reference product AndroGel [®]
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	BE approach to a reference product AndroGel [®]
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	BE approach to a reference product AndroGel [®]
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	BE approach to a reference product AndroGel [®]
17	Is there adequate information on the pharmacokinetics and	x			

7	exposure-response in the clinical pharmacology section of the label?				
General					
1 8	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
1 9	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

Filing Memo
Clinical Pharmacology Review

NDA: **203098**
 Compound: **Testosterone (T) gel,** (b)(4)
 Sponsor: **Perrigo Israel Pharmaceuticals**
 Date: **8/21/2011**
 Reviewer: **Li Li, Ph.D.**

Introduction:

Perrigo Israel Pharmaceuticals submitted a New Drug Application (NDA) under 505 (b)(2) for testosterone (T) gel, (b)(4) on July 5, 2011 to seek an approval for the treatment of hypogonadism. Sponsor used AndroGel® (1%, w/w) marketed by Unimed Pharmaceuticals Inc. as the reference listed drug (RLD).

AndroGel® (T gel 1%) was approved by FDA on February 28, 2000 for Unimed Pharmaceuticals, Inc. Abbott Laboratories is the current NDA holder for AndroGel®. The recommended starting dose of AndroGel®, 1% is 5 g once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen (area of application should be limited to the area that will be covered by the patient’s short sleeve t-shirt). To ensure proper dosing, serum T concentrations should be measured at intervals and replaced to serum T concentrations in the normal range. If the serum T concentration is below the normal range, the daily AndroGel®, 1% dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g for adult males as instructed by the physician. If the serum T concentration exceeds the normal range, the daily AndroGel®, 1% dose may be decreased. If the serum T concentration consistently exceeds the normal range at a daily dose of 5 g, AndroGel®, 1% therapy should be discontinued.

The active ingredient, route of administration, dosage form, and strength for the proposed drug product are the same as those of the RLD (AndroGel®, 1%), except that Perrigo formulation used isostearic acid rather than isopropyl myristate used in the RLD.

Regulatory History

Perrigo has had multiple regulatory interactions with FDA relating to this drug product. On June 15, 2007, and December 16, 2008, Perrigo submitted two separate ANDAs (b)(4) for the multi-dose pump and unit dose packets (2.5 and 5 g to the Office of Generic Drugs (OGD). Subsequent to these submissions, a Citizens Petition was filed on February 27, 2009 by Auxilium Pharmaceuticals. As a response, the Agency determined that any application for a T gel product that has different (b)(4) than the RLD cannot be submitted as an ANDA and, instead, will have to be submitted as an NDA under section 505(b) of the Act (Docket No. FDA-2009-P-0123 dated August 26, 2009). After receiving the written communication from OGD on August 28, 2009 in this regard, Perrigo submitted an Investigational New Drug Application (IND 107130) to the Office of New Drugs (OND). A type C guidance meeting was held with the DRUP on May 19, 2010 to discuss the clinical study plan and the approval requirement for a 505 (b)(2) NDA for T Gel (b)(4) Multi-dose Pump and a Unit dose Packet.

Clinical Development of T gel

This application contains a full report of:

- BE study: A Randomized, Single-Dose, Three-Way Crossover Relative Bioavailability Study of T Gel Formulations in Hypogonadal Men (Study 03-0415-001)
- Hand and application sites washing study: A Pivotal Study to Evaluate the Residual Amount of Topically Delivered T Gel (b) (4) Present on Normal Skin of the Hand, Arm, and Shoulder in Healthy Adult Male Subjects Following Washing Procedures (Study PRG-806)
- Inter-personal transfer study: A Study to Determine the transfer of T from a Male to his Female Partner for Perrigo Pharmaceuticals (b) (4) T Gel (Study M1IU9001)
- Irritation study: A 21-Day, Randomized, Controlled Study to Evaluate the Irritation Potential of T Gel (b) (4) on Healthy Volunteers, Using a Cumulative Irritation Patch Test Design (Study DS310208)
- Sensitization study: A Randomized, Controlled Study to Evaluate the Sensitizing Potential of T Gel (b) (4) on Healthy Volunteers, Using a Repeat Insult Patch Test Design (Study DS102308)

Drug Product Formulation:

Two formulations are used to support this NDA:

- T Gel, (b) (4) manufactured with Carbomer 940, NF (clinical trial formulation T06P033);
- T Gel, (b) (4) manufactured with Carbopol 980 (using Carbomer homopolymer type C, NF), which will be used for commercial distribution. The use of Carbopol 980 was to be consistent with the RLD formulation.

The compositions of the clinical trial and the commercial formulations in comparison to the RLD formulation are summarized in the **Table 1** below.

Table 1 The composition of Perrigo’s clinical trial and commercial formulations in comparison with AndroGel® formulation

Ingredient	Perrigo Clinical Formulation	Perrigo Commercial Formulation	AndroGel® Formulation
	Concentrations (%w/w)	Concentrations(%w/w)	Concentrations (%w/w)
Testosterone, USP	(b) (4)		
Dehydrated Alcohol			
Carbomer 980, NF			
Carbomer 940, NF			
Isopropyl Myristate			
Isostearic Acid			
Sodium Hydroxide			
Purified Water			

BE Assessment

A single-dose, three way-crossover BE study was conducted in 24 hypogonadal men to compare the test T (b) (4) gel (Formulation T06P030 and Formulation T06P033) and the RLD (AndroGel®). In each study period, each subject received a 10-g application of either one of the test formulations or the reference formulation applied to the shoulders and upper arms. A series of blood samples were collected pre-dose (-12 & 0 hrs) for endogenous T concentrations and sixteen times over 72 hours following each dose for determination of serum T concentrations (**Table 2**). Statistical analysis on PK parameters (i.e., C_{max} and AUC) from baseline corrected T concentrations indicated that the RLD is bioequivalent to Formulation T06P033, but not to Formulation T06P030. Following the BE assessment, the non-bioequivalent Formulation T06P030 was dropped from clinical development and Formulation T06P033 was used in all clinical studies submitted in the current application.

Table 2 Treatment groups in the BE study

T Gel ^(b) ₍₄₎ (Test)	T Gel ^(b) ₍₄₎ (Test)	AndroGel [®] 1% (Reference)
Formulation T06P030	Formulation T06P033*	
* T06P033 is the basis for clinical service formulation		

Transfer Potential Assessment

An open-label, single-dose, four way-crossover study was conducted to assess the inter-personal transfer potential of the test T ^(b)₍₄₎ gel and the RLD. A total of 24 couples were enrolled in the study and 20 couples completed the study. The female subjects enrolled in this study were postmenopausal or surgically sterile. A single dose (10 g, with 5g applied to each side of upper arm and shoulder) of either test T ^(b)₍₄₎ gel or the RLD with or without males wearing a T-shirt was applied to the male subjects (**Table 3**). Female subjects had one arm/shoulder designated as the “contact site”. Starting at 2 hours after dosing, each couple was instructed to engage in a total of 15 minutes of contact. A series of blood samples were collected pre-dose (9 times over 24 hours) for endogenous T concentrations and eight times over 24 hours following each dose transfer for determination of serum T concentrations. Per sponsor, the results of the study showed that wearing a T-shirt can substantially block the inter-personal T transfer for both test and reference products. For test T ^(b)₍₄₎ gel, baseline adjusted C_{max} and AUC of T in the females from males wearing a T-shirt group is 81.88% and 90.22% lower than that from males without a T-shirt group, respectively.

Table 3 Treatment groups in inter-personal transfer study

T Gel ^(b) ₍₄₎ (Perrigo)		AndroGel [®] 1%	
Treatment A (not wearing T shirt)	Treatment B (wearing T shirt)	Treatment C (not wearing T shirt)	Treatment D (wearing T shirt)

Hand and application sites Washing Study

A single-dose, open label, four way-crossover study in healthy adult men was conducted to quantify and compare the amount of residual drug remaining on the hands and arm/shoulder before and after washing in test T ^(b)₍₄₎ gel and the RLD (**Table 4**). Thirty six subjects were enrolled in the study and 32 completed. On Day 1 of each treatment period, the hand and arm/shoulder designated for drug application were wiped with three ethanol dampened gauze (blank control sample). Subsequently, 10 g (2 x 5 g packets) of either the T gel or the RLD was applied to the subject’s palm of their dominate hand by the clinical staff. The subject then applied the dose to their opposite arm/shoulder. Depending upon the treatment groups (no wash or wash), subjects had their hand wiped with three ethanol dampened gauze pads before or after hand washing to obtain a residual hand sample for T measurement. Finally, approximately 2 hours after the dose was applied, subjects had their arm/shoulder wiped with three ethanol dampened gauze pads before or after a shower to obtain a residual application site sample for T measurement. The data from test T ^(b)₍₄₎ gel indicated that hand washing removed 95.3% of recoverable T and showering procedure removed 79.5% of recoverable T from the arm/shoulder dosing area.

Table 4 Treatment groups in hand and application sites washing study

T Gel ^(b) ₍₄₎ (Perrigo)		AndroGel [®] 1%	
Treatment A (No wash)*	Treatment C (Wash)	Treatment B (No wash)*	Treatment D (Wash)
* wipe the dosed hand immediately following dosing and the arm/shoulder application site two hours after dose application			

Absorption, Distribution, Metabolism, and Excretion (ADME)

Specific studies describing the ADME of T were not conducted. The Sponsor is proposing to use the publically available information of the RLD (i.e., AndroGel[®], 1 % w/w) for their product.

Drug-Drug Interactions:

No DDI studies were conducted with T gel.

Specific Populations:

- Pediatric use: No pediatric studies were conducted
- Geriatric use: No geriatric studies were conducted
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant or breast feeding women
- Warnings and Precaution for children and women for secondary exposure

Bioanalytical Method Validation:

Serum samples were analyzed for total T by validated bioanalytical assays.

- BE study: Gas Chromatography/Mass Spectrometry (GC/MS)
- Hand and application sites washing study: High performance liquid chromatography with ultraviolet detector (HPLC-UV).
- Inter-personal transfer study: Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 203098 is fileable.

Office of Scientific Investigation (OSI) Inspection Request

An OSI inspection of the clinical and bioanalytical sites of the pivotal BE study has been requested.

Reviewer's Comments:

The BE was evaluated between the clinical trial formulation containing carbomer 940 and AndroGel® (RLD) formulation containing Carbopol 980. Perrigo's commercial formulation of T (b)(4) gel will switch from Carbomer 940 to Carbopol 980 to be consistent with the formulation of the RLD. Per CMC reviewer, Dr. Rajiv Agarwal, the PK performance of the test T (b)(4) gel is unlikely to be affected by the change in this expedient. Therefore, a new BE study of the commercial formulation and the RLD was not necessary.

Perrigo has confirmed with DRUP that none of the studies were conducted or analyzed at Cetero (Houston, TX). Reference is made to the amendment to NDA submission (sequence 0002) dated Aug 4th 2011.

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

/s/

LI LI
04/30/2012

MYONG JIN KIM
05/01/2012

EDWARD D BASHAW
05/01/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	N o	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence (BE) data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			A single dose BE study using upper arm and shoulder as the site of application
2	Has the applicant provided metabolism and drug-drug interaction information?			x	Refers to information publically available (i.e., Androgel [®] label)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			BE approach to a reference product Androgel [®]
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	BE approach to a reference product Androgel [®]
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	BE approach to a reference product Androgel [®]
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	BE approach to a reference product Androgel [®]
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	BE approach to a reference product Androgel [®]
1	Did the applicant submit all the pediatric exclusivity data, as described			x	BE approach to a reference

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

6	in the WR?				product Androgel®
1 7	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
General					
1 8	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
1 9	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY 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.

- *In the BE study (Study 03-0415-001), the use of two time points for testosterone baseline measurement (-12hr & 0hr) will be a review issue.*

We request the Sponsor to submit the following information:

- *In the BE study, both baseline corrected and baseline uncorrected testosterone pharmacokinetic (PK) parameters will be assessed for the bioequivalence (Refer to the meeting minutes on May 19, 2010). Provide the PK parameters (i.e., C_{max} and AUC) and the corresponding BE evaluation based on total testosterone concentrations without baseline subtraction.*
- *In the inter-personal transfer study, please provide the comparison between the baseline and post-transfer PK parameters (i.e., C_{max} and AUC) of testosterone in female partners for both test and reference products. This information should include the % calculation of difference between the baseline vs. post-transfer PK parameters (i.e., C_{max} and AUC) for each individual.*

If the requested information has been provided in the application, please provide the location of the information.

Li Li	8/24/2011
Reviewing Clinical Pharmacologist	Date
Myong Jin Kim	8/24/2011
Team Leader/Supervisor	Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo

Clinical Pharmacology Review

NDA: 203098
Compound: Testosterone (T) gel, (b) (4)
Sponsor: Perrigo Israel Pharmaceuticals

Date: 8/21/2011
Reviewer: Li Li, Ph.D.

Introduction:

Perrigo Israel Pharmaceuticals submitted a New Drug Application (NDA) under 505 (b)(2) for testosterone (T) gel, (b) (4) on July 5, 2011 to seek an approval for the treatment of hypogonadism. Sponsor used AndroGel® (1%, w/w) marketed by Unimed Pharmaceuticals Inc. as the reference listed drug (RLD).

AndroGel® (T gel 1%) was approved by FDA on February 28, 2000 for Unimed Pharmaceuticals, Inc. Abbott Laboratories is the current NDA holder for AndroGel®. The recommended starting dose of AndroGel®, 1% is 5 g once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt). To ensure proper dosing, serum T concentrations should be measured at intervals and replaced to serum T concentrations in the normal range. If the serum T concentration is below the normal range, the daily AndroGel®, 1% dose may be increased from 5 g to 7.5 g and from 7.5 g to 10 g for adult males as instructed by the physician. If the serum T concentration exceeds the normal range, the daily AndroGel®, 1% dose may be decreased. If the serum T concentration consistently exceeds the normal range at a daily dose of 5 g, AndroGel®, 1% therapy should be discontinued.

The active ingredient, route of administration, dosage form, and strength for the proposed drug product are the same as those of the RLD (AndroGel®, 1%), except that Perrigo formulation used isostearic acid rather than isopropyl myristate used in the RLD.

Regulatory History

Perrigo has had multiple regulatory interactions with FDA relating to this drug product. On June 15, 2007, and December 16, 2008, Perrigo submitted two separate ANDAs (b) (4) for the multi-dose pump and unit dose packets (2.5 and 5 g to the Office of Generic Drugs (OGD). Subsequent to these submissions, a Citizens Petition was filed on February 27, 2009 by Auxilium Pharmaceuticals. As a response, the Agency determined that any application for a T gel product that has different (b) (4) than the RLD cannot be submitted as an ANDA and, instead, will have to be submitted as an NDA under section 505(b) of the Act (Docket No. FDA-2009-P-0123 dated August 26, 2009). After receiving the written communication from OGD on August 28, 2009 in this regard, Perrigo submitted an Investigational New Drug Application (IND 107130) to the Office of New Drugs (OND). A type C guidance meeting was held with the DRUP on May 19, 2010 to discuss the clinical study plan and the approval requirement for a 505 (b)(2) NDA for T Gel (b) (4) Multi-dose Pump and a Unit dose Packet.

Clinical Development of T gel

This application contains a full report of:

- BE study: A Randomized, Single-Dose, Three-Way Crossover Relative Bioavailability Study of T Gel Formulations in Hypogonadal Men (Study 03-0415-001)
- Hand and application sites washing study: A Pivotal Study to Evaluate the Residual Amount of Topically Delivered T Gel (b) (4) Present on Normal Skin of the Hand, Arm, and Shoulder in Healthy Adult Male Subjects Following Washing Procedures (Study PRG-806)
- Inter-personal transfer study: A Study to Determine the transfer of T from a Male to his Female Partner for Perrigo Pharmaceuticals (b) (4) T Gel (Study M1IU09001)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

- **Irritation study:** A 21-Day, Randomized, Controlled Study to Evaluate the Irritation Potential of T Gel (b) (4) on Healthy Volunteers, Using a Cumulative Irritation Patch Test Design (Study DS310208)
- **Sensitization study:** A Randomized, Controlled Study to Evaluate the Sensitizing Potential of T Gel (b) (4) on Healthy Volunteers, Using a Repeat Insult Patch Test Design (Study DS102308)

Drug Product Formulation:

Two formulations are used to support this NDA:

- T Gel, (b) (4) manufactured with Carbomer 940, NF (clinical trial formulation T06P033);
- T Gel, (b) (4) manufactured with Carbopol 980 (using Carbomer homopolymer type C, NF), which will be used for commercial distribution. The use of Carbopol 980 was to be consistent with the RLD formulation.

The compositions of the clinical trial and the commercial formulations in comparison to the RLD formulation are summarized in the **Table 1** below.

Table 1 The composition of Perrigo’s clinical trial and commercial formulations in comparison with Androgel® formulation

Ingredient	Perrigo Clinical Formulation	Perrigo Commercial Formulation	Androgel® Formulation
	Concentrations (%w/w)	Concentrations(%w/w)	Concentrations (%w/w)
Testosterone, USP	(b) (4)		
Dehydrated Alcohol			
Carbomer 980, NF			
Carbomer 940, NF			
Isopropyl Myristate			
Isostearic Acid			
Sodium Hydroxide			
Purified Water			

BE Assessment

A single-dose, three way-crossover BE study was conducted in 24 hypogonadal men to compare the test T (b) (4) gel (Formulation T06P030 and Formulation T06P033) and the RLD (AndroGel®). In each study period, each subject received a 10-g application of either one of the test formulations or the reference formulation applied to the shoulders and upper arms. A series of blood samples were collected pre-dose (-12 & 0 hrs) for endogenous T concentrations and sixteen times over 72 hours following each dose for determination of serum T concentrations (**Table 2**). Statistical analysis on PK parameters (i.e., C_{max} and AUC) from baseline corrected T concentrations indicated that the RLD is bioequivalent to Formulation T06P033, but not to Formulation T06P030. Following the BE assessment, the non-bioequivalent Formulation T06P030 was dropped from clinical development and Formulation T06P033 was used in all clinical studies submitted in the current application.

Table 2 Treatment groups in the BE study

T Gel (b) (4) (Test)	T Gel (b) (4) (Test)	AndroGel® 1% (Reference)
Formulation T06P030	Formulation T06P033*	
* T06P033 is the basis for clinical service formulation		

Transfer Potential Assessment

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

An open-label, single-dose, four way-crossover study was conducted to assess the inter-personal transfer potential of the test T ^(b)₍₄₎ gel and the RLD. A total of 24 couples were enrolled in the study and 20 couples completed the study. The female subjects enrolled in this study were postmenopausal or surgically sterile. A single dose (10 g, with 5g applied to each side of upper arm and shoulder) of either test T ^(b)₍₄₎ gel or the RLD with or without males wearing a T-shirt was applied to the male subjects (Table 3). Female subjects had one arm/shoulder designated as the “contact site”. Starting at 2 hours after dosing, each couple was instructed to engage in a total of 15 minutes of contact. A series of blood samples were collected pre-dose (9 times over 24 hours) for endogenous T concentrations and eight times over 24 hours following each dose transfer for determination of serum T concentrations. Per sponsor, the results of the study showed that wearing a T-shirt can substantially block the inter-personal T transfer for both test and reference products. For test T ^(b)₍₄₎ gel, baseline adjusted C_{max} and AUC of T in the females from males wearing a T-shirt group is 81.88% and 90.22% lower than that from males without a T-shirt group, respectively.

Table 3 Treatment groups in inter-personal transfer study

T Gel ^(b) ₍₄₎ (Perrigo)		AndroGel [®] 1%	
Treatment A (not wearing T shirt)	Treatment B (wearing T shirt)	Treatment C (not wearing T shirt)	Treatment D (wearing T shirt)

Hand and application sites Washing Study

A single-dose, open label, four way-crossover study in healthy adult men was conducted to quantify and compare the amount of residual drug remaining on the hands and arm/shoulder before and after washing in test T ^(b)₍₄₎ gel and the RLD (Table 4). Thirty six subjects were enrolled in the study and 32 completed. On Day 1 of each treatment period, the hand and arm/shoulder designated for drug application were wiped with three ethanol dampened gauze (blank control sample). Subsequently, 10 g (2 x 5 g packets) of either the T gel or the RLD was applied to the subject’s palm of their dominate hand by the clinical staff. The subject then applied the dose to their opposite arm/shoulder. Depending upon the treatment groups (no wash or wash), subjects had their hand wiped with three ethanol dampened gauze pads before or after hand washing to obtain a residual hand sample for T measurement. Finally, approximately 2 hours after the dose was applied, subjects had their arm/shoulder wiped with three ethanol dampened gauze pads before or after a shower to obtain a residual application site sample for T measurement. The data from test T ^(b)₍₄₎ gel indicated that hand washing removed 95.3% of recoverable T and showering procedure removed 79.5% of recoverable T from the arm/shoulder dosing area.

Table 4 Treatment groups in hand and application sites washing study

T Gel ^(b) ₍₄₎ (Perrigo)		AndroGel [®] 1%	
Treatment A (No wash)*	Treatment C (Wash)	Treatment B (No wash)*	Treatment D (Wash)
* wipe the dosed hand immediately following dosing and the arm/shoulder application site two hours after dose application			

Absorption, Distribution, Metabolism, and Excretion (ADME)

Specific studies describing the ADME of T were not conducted. The Sponsor is proposing to use the publically available information of the RLD (i.e., AndroGel[®], 1 % w/w) for their product.

Drug-Drug Interactions:

No DDI studies were conducted with T gel.

Specific Populations:

- Pediatric use: No pediatric studies were conducted
- Geriatric use: No geriatric studies were conducted
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant or breast feeding women
- Warnings and Precaution for children and women for secondary exposure

Bioanalytical Method Validation:

Serum samples were analyzed for total T by validated bioanalytical assays.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

- BE study: Gas Chromatography/Mass Spectrometry (GC/MS)
- Hand and application sites washing study: High performance liquid chromatography with ultraviolet detector (HPLC-UV).
- Inter-personal transfer study: Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 203098 is fileable.

Office of Scientific Investigation (OSI) Inspection Request

An OSI inspection of the clinical and bioanalytical sites of the pivotal BE study has been requested.

Reviewer's Comments:

The BE was evaluated between the clinical trial formulation containing carbomer 940 and Androgel® (RLD) formulation containing Carbopol 980. Perrigo's commercial formulation of T (b) (4) gel will switch from Carbomer 940 to Carbopol 980 to be consistent with the formulation of the RLD. Per CMC reviewer, Dr. Rajiv Agarwal, the PK performance of the test T (b) (4) gel is unlikely to be affected by the change in this expedient. Therefore, a new BE study of the commercial formulation and the RLD was not necessary.

Perrigo has confirmed with DRUP that none of the studies were conducted or analyzed at Cetero (Houston, TX). Reference is made to the amendment to NDA submission (sequence 0002) dated Aug 4th 2011.

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

/s/

LI LI
09/14/2011

MYONG JIN KIM
09/14/2011