CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204399Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA 204399	
Brand Name	Vogelxo®
Generic Name	Testosterone 1% Gel
Reviewer	Li Li, PhD
Acting Team Leader	Myong Jin Kim, PharmD
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Bone Reproductive and Urologic Products
Sponsor	Upsher-Smith Laboratories, Inc.
Submission Type	505(b)(2)/ Original
Formulation; Strengths; Regimen	Topical gel; 1%; 50 mg, 100 mg T, once daily
Proposed Indication	Treatment of male hypogonadism

1 Executive Summary

NDA 204399 was submitted as a 505(b)(2) NDA application with Testim® (NDA 21454) as the reference list drug on October 18, 2012. The original clinical pharmacology review was performed by Dr. Lanyan (Lucy) Fang. Tentative Approval was granted on August 16, 2013, pending patent expiration for the referenced listed drug. The Sponsor resubmitted the NDA on December 5, 2013.

1.1 Recommendation

The Division of Clinical Pharmacology-3, Office of Clinical Pharmacology finds the NDA 204399 acceptable.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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
06/02/2014

MYONG JIN KIM
06/02/2014

ONDQA- Biopharmaceutics Review

Original NDA	204-399
Stamp Dates:	Original - October 17, 2012, Amendments - April 5, 2013, June 29, 2013, and July 3, 2013
Applicant:	Upsher-Smith Laboratories, Inc
Accepted Tradename:	Vogelxo
Established Name:	Testosterone Gel 1%
Dosage Form:	Gel
Route of Administration:	Topical
Indication:	Testosterone replacement therapy in adult males for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).
Reviewer	Tapash Ghosh, Ph.D.

Submission: The proposed product, Testosterone Gel 1% (Vogelxo) is a topical gel intended for Testosterone replacement therapy in adult males for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired). The drug product is a clear, translucent, alcohol-based testosterone gel at 1% strength. The bulk gel is packaged into unit dose tubes of 50 mg of testosterone per 5 g of gel, sachets of 50 mg of testosterone per 5 g of gel, and metered dose pumps of 12.5 mg testosterone per pump actuation delivering 1.25 g of gel. Each metered dose pump contains 75 g of gel and can dispense 60 doses.

Review: The Biopharmaceutics review is focused in the evaluation of the proposed *in-vitro* drug release method and the acceptance criteria for the drug release rate limits

Recommendation: Based on the review of the provided information/data, the following *in-vitro* drug release method and acceptance criteria are acceptable for product release and on stability.

In vitro Drug Release Method for Testosterone Gel 1%

Test parameters: diffusion cell system	Stirring speed: 600 RPM Temperature: 33 °C Temperature Tolerance: ± 5 °C Rinse volume: 1.5 mL Collect volume: 1.0 mL Rack type: 12 x 32 vials	Test length: 4 hours Number of sampling times: 6 Sampling times: 30, 60, 90, 120, 180, 240 minutes Pre-start time: 45 sec.

Acceptance Criteria (In Vitro Drug Release Rate) for Testosterone Gel 1%

In-Vitro Release [HPLC] (R,S)	(b) (4) 1811-LC	(b) (4) µg/cm^2/minutes$^{1/2}$

From the Biopharmaceutics perspective, the original NDA submission 204-399 for Testosterone Gel 1% is recommended for approval.

Tapash K. Ghosh, Ph.D.
Primary Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Reference ID: 3341440

BIOPHARMACEUTICS ASSESSMENT

Drug Product

The drug product is a clear, translucent, alcohol-based testosterone gel at 1% strength. The bulk gel is packaged into unit dose tubes of 50 mg of testosterone per 5 g of gel, sachets of 50 mg of testosterone per 5 g of gel, and metered dose pumps of 12.5 mg testosterone per pump actuation delivering 1.25 g of gel. Each metered dose pump contains 75 g of gel and can dispense 60 doses.

The formulation is as follows:

Table 2: Qualitative/Quantitative Composition of USL's Testosterone Gel 1%

Component (Proprietary Name)	Grade	Function	1% Bulk Gel Formulation		Unit Dose Tube or Unit Dose Packet	Multiple Dose Metered Pump	
			% (w/w)	mg/g	Amount per 50 mg Dose (5 g gel) (mg)	Amount per 1.25 g Actuation (mg)	Amount per 75 g Pump (mg)
Testosterone	USP	Drug substance (API)	1.00	10.00	50.00	12.50	750.00
Alcohol (Ethyl Alcohol, (b) (4)	USP	(b) (4)					(b) (4)
Glycerin (b) (4)	USP						
Diisopropyl Adipate (b) (4)	House Standard						
Methyl Laurate (b) (4)	House Standard						
Oleyl Alcohol (b) (4)	NF						
Carbomer Homopolymer Type C (b) (4) (b) (4)	NF						
Carbomer Copolymer Type B (b) (4)	NF						
Propylene Glycol	USP						
Polyethylene Glycol (b) (4) (b) (4)	NF						
Purified Water	USP						
Tromethamine (b) (4)	USP						
TOTAL							
				Nominal fill	(b) (4)	not applicable	(b) (4)
				Overfill		not applicable	
				Total fill	5.2 g	not applicable	88.0 g

14 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

TAPASH K GHOSH
07/15/2013

ANGELICA DORANTES
07/16/2013

CLINICAL PHARMACOLOGY REVIEW

NDA:	204399
Type/Category:	505(b)(2)/Original
Brand Name:	Vogelxo
Generic Name:	Testosterone (T) gel
Indication:	Treatment of male hypogonadism
Dosage Form:	Clear translucent, alcohol-based gel containing 1% testosterone
Route of Administration:	Topical gel
Dosing Regimen and Strength:	Starting dose at 50 mg testosterone (one tube/packet or 4 pump actuations) applied topically once daily
Sponsor:	Upsher-Smith Lab
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Submission Dates:	October 18, 2012
Primary Reviewer:	Lanyan Fang, Ph.D.
Secondary Reviewer:	Hae-Young Ahn, Ph.D.

TABLE OF CONTENTS

1 Executive Summary 2
- 1.1 Recommendations 2
- 1.2 Post-marketing Requirements / Commitments 2
- 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings 2

2 Question Based Review 5
- 2.1 General Attributes 5
- 2.2 Clinical Pharmacology and Biopharmaceutics Related Questions 6
- 2.3 Intrinsic Factors 10
- 2.4 Extrinsic Factors 11
- 2.5 General Biopharmaceutics 11
- 2.6 Analytical Section 12

3 Labeling 15

4 Appendix 16

Reference ID: 3340391

1 EXECUTIVE SUMMARY

Upsher-Smith Laboratories (USL) is seeking approval of Testosterone gel (T gel or USL240, used interchangeably in this review) under 505(b)(2) for the treatments of primary and hypogonadotropic hypogonadism in adult men. T gel is clear translucent, alcohol-based gel containing 1% testosterone. The proposed dosing instructions for USL's Testosterone gel state that a single application of 5 gm of gel (one tube/packet) or 4 metered-dose pump actuations (12.5 mg per pump) containing 50 mg testosterone be applied once daily (preferably in the morning) to clean, dry intact skin of the shoulders and/or upper arms. Dose adjustment is recommended if the serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved, the daily T gel dose may be increased to 100 mg of testosterone as instructed by the physician (two tubes/packets or 8 pump actuations).

To support the approval of this 505(b)(2) New Drug Application (NDA 204399), the sponsor submitted five Biopharmaceutics/Clinical Pharmacology and Clinical studies including a pilot bioavailability (P06-001), a pivotal bioequivalence (BE) study (P06-011) bridging the safety and efficacy findings of the Reference Listed Drug (RLD) to the proposed product, a hand and application sites washing study (P10-002) determining the residual amount of T present on these sites following washing procedures, an inter-personal transfer study (P10-003) evaluating the transfer potential of T from user to nonuser , and an irritation and sensitization studies (P08-001). The bioavailability, bioequivalence, and irritation and sensitization studies included Testim® (NDA 021454; Auxilum Pharmaceuticals) as the reference product.

A formal consult to the Office of Scientific Investigations (OSI) was made for clinical and bioanalytical study sites inspections of the pivotal BE study (P06-011). OSI's memorandum reveals that there are no unresolved issues that would affect the approvability of Testosterone gel (refer to DSI's memorandum in DARRTS dated May 21, 2013).

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 204399 submitted on October 18, 2012. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language.

1.2 POST-MARKETING REQUIREMENTS / COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Formulation:

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

The proposed product is clear translucent, alcohol-based gel containing 1% testosterone intended for topical administration. During the development process, the Sponsor developed three formulations - A (USL240), B (pilot formulation), and C (pilot formulation). The Sponsor conducted a pilot bioavailability study (Study P06-001) comparing the bioavailability of their formulations (formulations A, B and C) to Testim®. Formulation A was further pursued based on the pilot bioavailability study and is the formulation the sponsor is seeking approval. The pivotal bioequivalence study was further conducted to bridge the safety and efficacy findings of Testim® to formulation A (USL240).

T gel versus the RLD

The Sponsor's gel formulation is similar to Testim® with some differences in [redacted] (b) (4). The Sponsor's application includes three dosage forms –5 gram tubes, 5 gram foil packages and a metered-dose pump. Testim® is available in a single dosage form – 5 gram tubes.

Reference ID: 3340391

Bioequivalence Assessment:
The Sponsor conducted an open-label, randomized, 2-treatment, 4-way replicate crossover bioequivalence study (Study P06-011) under fasting conditions comparing equal doses of USL240 (test article) and Testim® (reference product). Each treatment consisted of a single application of 2 x 5 gram (100 mg testosterone) topical gel using USL240 or Testim® applied over a 500 cm^2 area on the upper arms/shoulder/back. The treatment phases were separated by washout periods of 7 days. The 90% confidence intervals about the ratio of the geometric means of USL240 to Testim® were within the 80.00% and 125.00% limits for PK parameters C_{max}, $AUC_{0\text{-}24hr}$ and $AUC_{0\text{-}72hr}$ of the ln-transformed baseline-corrected data (**Table 1**). The results of this study suggest that USL240 and the reference product, Testim®, are bioequivalent under fasting conditions.

Table 1 Baseline Corrected BE analysis for T Gel (Study P06-011: PK Eligible Subjects, N=58)

Parameter	USL240 (Test) Mean	Testim® (RLD) Mean	Ratio[1]	90% Geometric CI[2]
C_{max} (pg/mL)	5084.02	4898.21	103.79%	96.90%, 111.18%
$AUC_{0\text{-}24hr}$ (pg*h/mL)	58778.32	53233.56	110.42%	104.55%, 116.61%
$AUC_{0\text{-}72hr}$ (pg*h/mL)	94370.14	85296.16	110.64%	104.19%, 117.49%

CI=confidence interval.
1. Calculated using least-squares means of USL240/Testim®.
2. 90% Geometric Confidence Interval using ln-transformed data.

Interpersonal Transfer Potential
A person-to-person transfer study (Study P10-003) was conducted to assess the transferability of USL240 during skin-to-skin contact with and without clothing or after washing an application site. This was a randomized, open-label, 3-way crossover study in ninety-six healthy subjects (48 pairs of dosed male and non-dosed female subjects). Male subjects received a single dose of 5 gram of gel USL240 applied on the upper arm/shoulder/back in each treatment period. Female subjects rubbed the anterior portion of her forearm over the application site of male subjects. Blood samples were taken from the non-dosed female subjects for determination of serum testosterone concentrations.

The results showed that unprotected female partners' mean T serum exposures were approximately 3-4 folds of the baseline values after direct skin contact with dosed males. In contrast, when a shirt covered the application site or the application site is washed before the contact, female subjects had comparable testosterone levels compared to baseline values. The results of the study indicated the wearing of clothing or the washing of the application site are two effective methods to prevent the transferability of testosterone between dosed and non-dosed individuals.

Effects of Hand Washing
An open-label, randomized, 3-way crossover study was conducted in 36 healthy male subjects to quantify the amount of T remaining on hands following washing procedure. Subjects self-applied the entire contents of one tube (5 gram of gel) over the upper shoulder/arm opposite to the subject's dominant hand. Depending upon the treatment groups, subjects had their hand washed and rinsed immediately or air dry for 3 minutes followed by wash and rinse. Skin swab samples of the application hand were collected for testosterone within 15 min prior to dosing, after testosterone application, and after washing.

The results from this study indicated that independent of the testosterone removal method used, washing hands with or without drying period allowed nearly complete (~99%) removal of USL240 from the surface of the skin, thereby greatly reducing the risk of potential cross contamination between individuals.

Drug-Drug Interactions

Reference ID: 3340391

No drug-drug interaction (DDI) studies were conducted with Testosterone gel. The Sponsor is proposing to use the publically available information of the RLD (i.e., Testim®) for their product.

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 for the RLD for their product.

Use in Specific Populations

- Pediatric use: No pediatric studies were conducted. Exemption for the pediatric study was granted.
- Geriatric use: No geriatric studies were conducted. No information is available in the labeling of Testim® regarding this aspect.
- Contraindicated for pregnant or breast feeding women
- Warnings and Precaution for children and women for secondary exposure

Bioanalytical Methods
Serum and skin swab samples were analyzed for total T concentrations using validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) bioanalytical assays. The OSI has conducted an inspection at the clinical and bioanalytical study site of the pivotal BE study and concluded that although inconsistent integration in chromatogram processing is identified, the inspection did not identify any incidents in which integrity or accuracy of data was compromised. Therefore, there are no unresolved issues that would affect the approvability of Testosterone gel (refer to OSI's memorandum in DARRTS dated May 21, 2013).

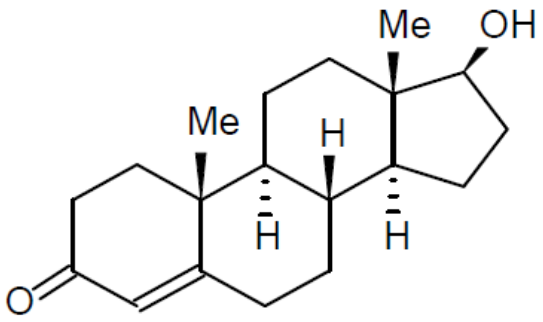
2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is Testosterone Gel and its active pharmacological ingredient?

Testosterone gel is a clear translucent hydroalcoholic topical gel containing 1% testosterone. Testosterone is an androgen. The active pharmacological ingredient in Testosterone gel is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-β hydroxyandrost-4-en-3-one.

The structural formula is:



Testosterone ($C_{19}H_{28}O_2$) MW: 288.42

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

Testosterone gel is available in unit-dose tubes and packets. Each tube or packet provides 50 mg testosterone in 5 g of gel. Testosterone gel is also available in a metered-dose pump. Each pump actuation provides 12.5 mg of testosterone and each container is capable of dispensing 60 pump actuations. One pump actuation dispenses 1.25 g of gel.

Inactive ingredients in Testosterone gel are carbomer copolymer Type B, carbomer homopolymer Type C, diisopropyl adipate, ethyl alcohol, glycerin, methyl laurate, oleyl alcohol, polyethylene glycol, propylene glycol, purified water, and tromethamine.

2.1.2 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:
뻐 Primary Hypogonadism (Congenital or Acquired)
뻐 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

Reference ID: 3340391

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).

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

The proposed starting dose of T gel is 5 g (equivalent to 50 mg T) once daily (preferably in the morning), applied on clean, dry, intact skin of shoulders and/or upper arms. One tube or packet provides 50 mg testosterone in 5 g of gel. One pump actuation delivers 12.5 mg testosterone in 1.25 g of gel (4 actuations = 50 mg T). To ensure proper dosing, serum T concentrations should be measured at intervals and replaced to serum T concentrations in the range (300 -1000 ng/dL). If the serum T concentration is below the normal range or if the desired clinical response is not achieved, the daily T gel dose may be increased from 5 g to 10 g (two tubes/packets or 8 pump actuations) for adult males as instructed by the physician.

2.1.4 What clinical data and related information is submitted to support the approval of Testosterone gel?

USL has conducted 5 clinical studies (P06-001, P06-011, P08-001, P10-002, and P10-003) to evaluate USL240 as a new drug for testosterone replacement therapy in the treatment of males with low or no testosterone. Two studies were bioequivalence/bioavailability studies that compared USL240 to the reference drug, Testim® . One study was designed to evaluate irritation and sensitization of USL240 compared with Testim®. Two studies assessed the potential for transferability of USL240: one evaluating the effect of hand washing in removing residual testosterone and one to measure transfer through skin-to-skin contact of the application site.

- Study P06-001, the pilot bioequivalence study, was conducted in 32 hypogonadal male subjects to evaluate the bioavailability of three pilot formulations of USL240 versus Testim®. This study is not reviewed in depth in this review.
- Study P06-011, the pivotal bioequivalence study, was conducted in 84 hypogonadal male subjects to evaluate the bioequivalence of USL240 versus Testim®. This study is reviewed in details in this review.
- Study P10-002 was conducted in 36 healthy male volunteers to determine if washing the hands following application of USL240 removed testosterone from the surface of the skin. This study is reviewed in details in this review.
- Study P10-003 was conducted in 48 healthy male and 48 healthy female (matched pairs) volunteers to determine the extent of skin-to-skin testosterone transfer from male subjects dosed with USL240 to non-dosed female subjects in the presence of clothing, in the absence of clothing, and after the application site had been washed. This study is reviewed in details in this review.
- Study P08-001 was conducted in 255 healthy male volunteers to evaluate the irritation and sensitization produced by repeat applications of USL240 compared to the irritation and sensitization produced by repeat applications of the reference drug (Testim®). This study is reviewed in depth in the clinical review.

2.2 General Clinical Pharmacology and Biopharmaceutics

2.2.1 Is the test T gel comparable to the RLD (Testim®) regarding to total T exposure?

Based on the review of the data of the pivotal BE study and acceptable status from inspection results (please refer to the review by Dr. Seongeun (Julia) Cho, Office of Scientific Investigation, in DARRTS dated May 21, 2013), the Sponsor's T product and the RLD are bioequivalent.

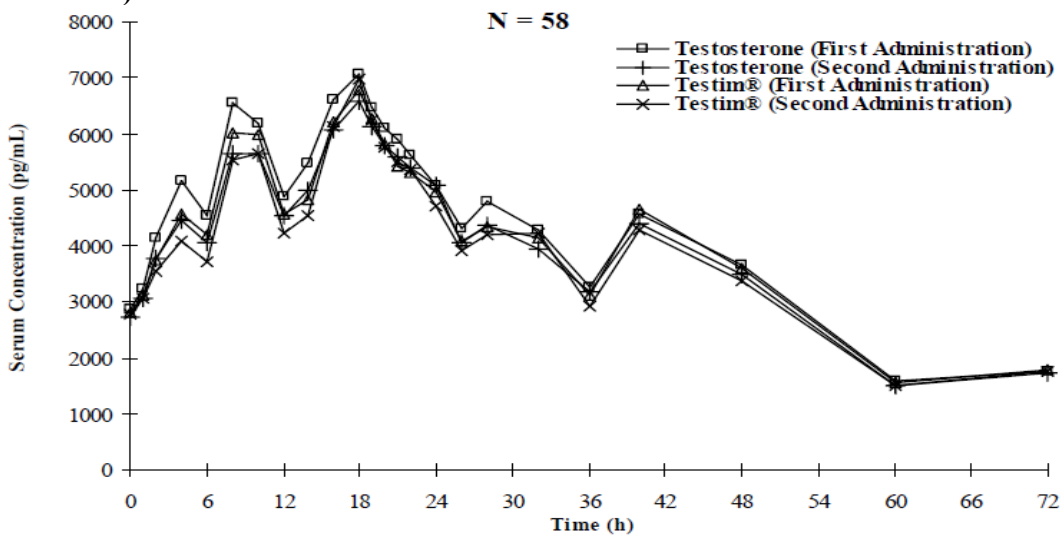
Study Design:
Study P06-011 was an open-label, randomized, 2-treatment, 4-way replicate crossover bioequivalence study conducted under fasting conditions comparing equal doses of USL240 (test article) and Testim® (reference product). The study enrolled and dosed 84 hypogonadal male subjects; 58 subjects with a mean baseline testosterone less than or equal to 350 ng/dL were included in the PK analysis. Subjects were randomly assigned to a treatment order consisting of 2 treatment periods with USL240 and 2 treatment periods with Testim®. Subjects fasted at least 10 hours prior to each treatment application and 4 hours following each treatment application. Each treatment consisted of a single application of 2 x 5 gram (100 mg testosterone) topical gel using USL240 or Testim® applied over a 500 cm^2 area on the upper arms/shoulder/back. The treatment phases were separated by washout periods of 7 days. In each treatment period, a total of 27 blood samples were collected at -12, -8, and -4 hour, immediately before the gel application (for baseline correction), and at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 19, 20, 21, 22, 24, 26, 28, 32, 36, 40, 48, 60, and 72-hour post-gel application.

Study Results:
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. The baseline correction method used in this study is acceptable, i.e., four time points (-12, -8, -4 hr and 0 hr before dosing) for baseline characterization. Mean baseline T concentrations were calculated for each subject by averaging the 4 pre-dose values (-12, -8, -4 hours and pre-dose (0 hour) for each period. All concentrations, including the pre-dose concentration for each subject and period, were subtracted by the mean of the 4 pre-dose concentrations. Every negative concentration obtained after correction was set equal to zero.

The subjects behaved similarly in regards to the treatment effect; therefore, the sponsor pooled the data from the two administrations to compare the two treatments (USL240 vs. Testim®) for PK parameters, i.e., C_{max}, $AUC_{0\text{-}24hr}$ and $AUC_{0\text{-}72hr}$. Uncorrected testosterone mean concentration-time profiles of the two treatments after two administrations were presented in **Figure 1**. It should be noted that baseline-corrected $AUC_{0\text{-}24hr}$ is about 50% of baseline uncorrected $AUC_{0\text{-}24hr}$, baseline-corrected $AUC_{0\text{-}72hr}$ is about 40% of baseline uncorrected $AUC_{0\text{-}72hr}$.

Reference ID: 3340391

Figure 1 Uncorrected Mean Testosterone Concentration-Time Profiles of USL240 (labeled as Testosterone) vs. Testim® Treatments



The 90% confidence intervals about the ratio of the geometric means of USL240 to Testim® were within the 80.00% and 125.00% limits for the PK parameters C_{max}, $AUC_{0\text{-}24hr}$ and $AUC_{0\text{-}72hr}$ of the ln-transformed baseline-corrected data (**Table 1**).

Table 1 Baseline Corrected BE analysis for T Gel (Study P06-011: PK Eligible Subjects, N=58)

Parameter	USL240 (Test) Mean	Testim® (RLD) Mean	Ratio[1]	90% Geometric CI[2]
C_{max} (pg/mL)	5084.02	4898.21	103.79%	96.90%, 111.18%
$AUC_{0\text{-}24hr}$ (pg*h/mL)	58778.32	53233.56	110.42%	104.55%, 116.61%
$AUC_{0\text{-}72hr}$ (pg*h/mL)	94370.14	85296.16	110.64%	104.19%, 117.49%

CI=confidence interval.
1. Calculated using least-squares means of USL240/Testim®.
2. 90% Geometric Confidence Interval using ln-transformed data.

The baseline corrected BE analysis showed that the Formulation USL240 was BE to the RLD (Testim®) under fasting condition.

Reviewer's comment
Although the proposed starting dose is 50 mg testosterone, the sponsor conducted the study with the 100 mg testosterone. This reviewer finds the 100 mg testosterone reasonable because the 100 mg could minimize the impact of endogenous testosterone level on assessing the bioequivalence between the two products.

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

Study P10-003 determined the transfer potential of T from a male to his female partner for T gel . The results of the study indicated that washing the application site or the wearing of clothing significantly reduced testosterone transfer from dosed males to non-dosed females when compared to skin-to-skin contact without clothes.

Study Design:

Reference ID: 3340391

Study P10-003 was a single-center, randomized, open-label, 3-way crossover study to assess the transferability of Testosterone Gel (USL240) during skin to skin contact with and without clothing or after application site washing. In each treatment period a total of 22 blood samples were collected non-dosed female subjects at -24, -20, -16-12, -8, -4-hour, 0 hours before initiating contact, and at 1, 2, 4, 6, 8, 10, 11, 12, 13, 14, 16, 18, 20, 22, and 24 hours post-contact. Plasma testosterone concentrations were evaluated in non-dosed female subjects for each treatment period; no blood samples were drawn from the dosed male subjects for PK analysis.

The treatment periods were separated by a washout of at least 14 days. In each period, one 5.0 g tube of USL240 (testosterone gel [50 mg]) was applied topically over a 500 cm^2 area of the shoulder/upper arm of a single side of the male subject's body by the study staff. The subjects were required to follow the transfer procedures i.e., skin-to-skin contact after application site washing (Treatment C), and with clothing (Treatment A) covering the application site and without clothing (Treatment B). The study enrolled 96 subjects (48 males and 48 females in pairs), of which 47 paired subjects received Treatment A, 47 paired subjects received Treatment B, and 42 paired subjects received Treatment C.

Study Results:

As shown in **Table 2**, unprotected female partners' mean Testosterone $AUC_{0\text{-}24hr}$ and C_{max} values were approximately 3- and 4-fold of the baseline values, respectively, after direct skin contact with dosed males (Treatment B). In contrast, when a shirt covered the application site (Treatment A) or the application site is washed before the contact (Treatment C), female subjects had comparable testosterone levels compared to baseline values. The results of the study indicated the wearing of clothing or the washing of the application site are two effective methods to prevent the transferability of testosterone between dosed and non-dosed individuals.

Table 2 Summary of Baseline-Unadjusted PK Parameters for T gel in Non-dosed Females Before and After Skin to Skin Contact

Treatment	N	Parameters	Before transfer (baseline)	After transfer
A (with clothing)	47	C_{max} (pg/mL)	198.18	203.76
		$AUC_{0\text{-}24hr}$ (pg*h/mL)	3659.99	3762.06
B (without clothing)	47	C_{max} (pg/mL)	186.74	793.81
		$AUC_{0\text{-}24hr}$ (pg*h/mL)	3441.78	11272.90
C (application site wash)	42	C_{max} (pg/mL)	191.35	194.83
		$AUC_{0\text{-}24hr}$ (pg*h/mL)	3420.96	3597.64

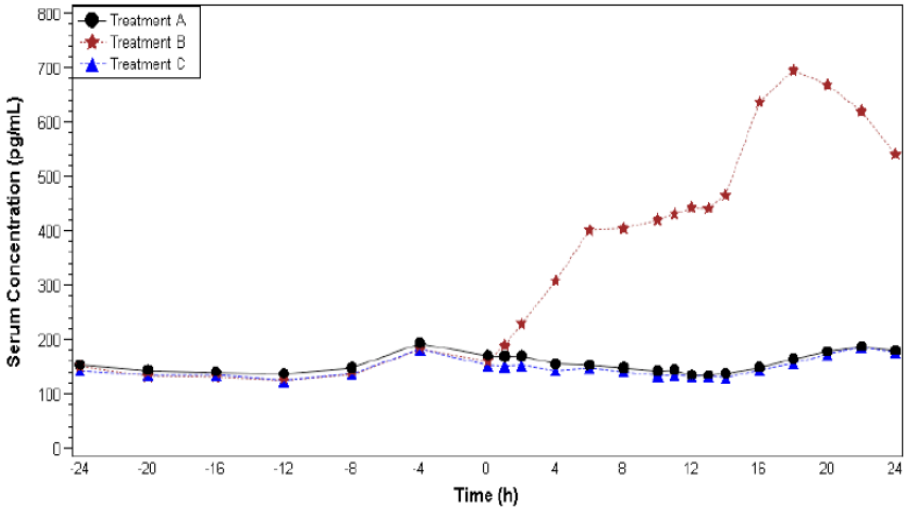
The baseline-corrected $AUC_{0\text{-}24hr}$ following exposure was also reported as a percentage of the prior-to-exposure $AUC_{0\text{-}24hr}$, that is the relative difference for $AUC_{0\text{-}24hr}$ defined as:

$$RD_{AUC} = 100 * \frac{AUC_{0-24hr,observed} - AUC_{0-24hr,baseline}}{AUC_{0-24hr,baseline}}$$

The mean percentage increase from baseline for $AUC_{0\text{-}24hr}$ (RD_{AUC}) was approximately 277% for Treatment B (without clothing); however, clothing (Treatment A) and washing of the application site (Treatment C) markedly reduced the potential for transfer as evidenced by RD_{AUC} <10% for both treatment groups (4% and 9% for Treatment A and C, respectively). The change from baseline in testosterone serum concentration was insignificant for Treatment A (with clothing) and Treatment C (application site washed; **Figure 2**); while markedly increased for Treatment B (without clothing).

Reference ID: 3340391

Figure 2 Mean Serum Concentration (pg/mL) – Time Profiles (Study P10-003)
(Pre-transfer: -24 to 0 hour; Post-transfer: 0 to 24 hour)



In conclusion, the wearing of clothing or the washing of the application site are two effective methods to prevent the transferability of testosterone between dosed and non-dosed individuals with a change from baseline below 10% for both treatments. In the absence of clothing or application site washing, a 3-fold increase in testosterone exposures is observed in non-dosed females following skin-to-skin contact with dosed males.

2.2.3 What are the findings from hands washing study after T gel application?

Study P10-002 evaluated the removal of T gel from the hands after being washing with soap and water. The study indicated that independent of the testosterone removal method used, washing hands with or without drying period allowed nearly complete (~99%) removal of USL240 from the surface of the skin, thereby greatly reducing the risk of potential cross contamination between individuals.

Study Design:
Study P10-002 was an open-label, randomized, 3-way crossover study to assess the removal of USL240 from the hands following washing procedure. On Day 1 of each treatment period, subjects self-applied the entire contents of one tube (5 gram of testosterone gel [50 mg]) over a 500 cm^2 area of the upper shoulder/arm opposite to the subject's dominant hand. Depending upon the treatment groups, subjects had their hand swab samples collected right after drug administration, washed and rinsed immediately (Treatment C) or air dry for 3 minutes followed by hand swab sample collection, then wash and rinse (Treatment A) or air dry for 3 minutes followed by hand swab sample collection, then wash/rinse and air dry (Treatment B). Skin swab samples of the application hand were collected for testosterone within 15 min prior to dosing, after testosterone application, and after washing. The study enrolled 36 subjects, of which 36 subjects received Treatment A and 35 subjects received Treatments B and C. The treatment phases were separated by washout periods of 7 days.

Study Results:
Testosterone concentrations on the skin surface of the hand, including percentage of testosterone removed from the skin surface after washing were evaluated. No PK parameters were evaluated in this study. The testosterone levels obtained from skin swab samples before washing were slightly higher for Treatment C (no drying period) compared to Treatments A and B (drying period of 3 minutes for each) as shown by the mean testosterone levels of 58.6, 60.5, and 70.3 µg for Treatments A, B, and C, respectively (**Table 3**). Following hand washing, the mean testosterone levels were comparable between Treatments A and B (0.64 and 0.52 µg, respectively) and slightly lower for Treatment C (0.16 µg) in comparison. The removal of testosterone levels following hand washing was similar for all treatments (98.7%, 99.0%, and 99.8% for Treatments A, B, and C, respectively; **Table 3**).

Reference ID: 3340391

Table 3 Testosterone Level (µg) in Skin Swab Samples Before and After Washing Procedures (Study P10-002)

Treatment	N	Before wash (µg, mean ± SD)	After wash (µg, mean ± SD)	% Removal by washing (mean)
A (air-dry followed by wash/rinse)	36	58.59 ± 38.74	0.64 ± 1.03	98.7%
B (air-dry followed by wash/rinse and air-dry)	35	60.54 ± 41.67	0.52 ± 1.24	99.0%
C (wash/rinse immediately)	35	70.29 ± 43.58	0.16 ± 0.46	99.8%

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 information is available in the labeling of topical drugs in the same drug class (i.e., Testim®, Axiron®, or AndroGel®) 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 Sponsor is exempt from this requirement.

2.4 Extrinsic Factors

2.4.1 Did the Sponsor conduct any DDI studies?

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

2.5.1 What is the quantitative composition of the drug products used in the clinical trials of this application?

Testosterone Gel is a clear translucent, alcohol-based gel containing 1% testosterone in dissolved form. The drug product is topically applied and provides transdermal delivery of testosterone following application to the skin. The Sponsor's gel formulation is similar to Testim® with some differences (b) (4) as shown in **Table 4**. The Sponsor's application includes three dosage forms –5 gram tubes, 5 gram foil packages and a metered-dose pump. Testim® is available in a single dosage form – 5 gram tubes.

Table 4. Composition of USL and Testim Testosterone Gel

Component	Function	Gel Formulation % (w/w)	
		USL	**Testim**
Testosterone	Drug substance	1.00	1.00
Ethyl Alcohol, (b) (4)	(b) (4)		
Glycerin			
Diisopropyl Adipate			
Methyl Laurate			
Oleyl Alcohol			
(b) (4)			

Propylene Glycol	(b) (4)		
Polyethylene Glycol (b) (4)			
Purified Water			
Tromethamine			
TOTAL		100.0	100.0

2.5.2 Is the clinical formulation same as the TBM formulation?
Yes.

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 satisfying the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, 2001) . Therefore, it is concluded that assays and their validations are acceptable.

- BE and Inter-personal transfer studies (Study P06-001, P06-011 and P10-003): Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)

All serum samples for Studies P06-001, P06-011, and P10-003 were analyzed for testosterone concentrations using a liquid chromatography with tandem mass spectrometry (LC/MS/MS) bioanalytical assay. (b) (4) The validated calibration range for this assay had a range of 39.96 to 7992.00 pg/mL. In Study P06-001, the inter-assay accuracy ranged from -7.98% to 1.84% and the precision (expressed as % confidence variables [CV]) ranged from 2.22% to 10.91%. In Study P06-011, the inter-assay accuracy ranged from -0.82% to 0.56% and the precision (expressed as % CV) ranged from 2.08% to 3.89%. In Study P10-003, the inter-assay accuracy ranged from -2.56% to -1.64% and the precision (expressed as % CV) ranged from 3.18% to 4.61%. The general properties of the method are outlined in **Table 5**.

Table 5 Bioanalytical Method Description: Testosterone Serum Sample

Analytes	Testosterone
Matrix	human serum
Sample Volume	0.2 mL
Testosterone Validated Range	39.96 to 7992.00 pg/mL
Internal Standard	Testosterone
Sample Storage Conditions	-20°C

Assay Validation Performance				
Analyte	Intra-Assay Quality Control Samples		Inter-Assay Quality Control Samples	
	Precision (%CV)	Accuracy (% of Bias)	Precision (%CV)	Accuracy (% of Bias)
Study P06-001	2.48 – 9.04	-1..28 – 1.15	2.22 – 10.91	-7.98 – 1.84
Study P06-011[a]	2.08 – 3.89	-0.82 – 0.56	0.48 – 4.47	-15.93 – 2.36
Study P10-003	2.04 – 6.33	-0.88 – 0.74	3.18 – 4.61	-2.56 - -1.64

CV=confidence variable.

a. Results are provided for charcoal stripped samples.

An OSI inspection of the bioanalytical sites of the pivotal BE study (P06-011) has been conducted. No major deficiencies were identified. In a number of runs for the study P06-011, integration parameters used for peak identification and quantification were not consistent for all samples in a run. Calibrators, quality control samples, and subject samples were individually reintegrated without proper documentations. The firm re-processed all runs according to the new integration procedure implemented in 2009, which requires application of consistent integration parameters to all samples in a run. Following re-integration, the acceptance of all runs in the study remained unchanged except for one (Run 96). For Run 96, the acceptance status changed from fail to pass, which was attributed to a minute change in the peak area value for a matrix blank sample. This discrepancy was verified by examining the chromatograms and determined not to be deliberate. The results of Run 96 from the original analysis, repeated analysis, and re-integration were compared and differences were found not to be significant (<5%) in the majority of the samples. Overall, although inconsistent integration in chromatogram processing is objectionable, the inspection did not identify any incidents in which integrity or accuracy of data was compromised.

- Hand washing study (Study P10-002): Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS).

Skin swab samples for Study P10-002 were analyzed for testosterone concentrations using a validated LC/MS/MS bioanalytical assay. (b) (4) The method has a range of quantification of 1.00 to 200.44 µg/swab. The inter-assay accuracy ranged from 0 to 2.59% and the precision (expressed as % CV) ranged from 3.99% to 6.30%. General properties of the method are outlined in **Table 6**.

Table 6 Bioanalytical Method Description: Testosterone Skin Swab Sample

Analytes	Testosterone
Matrix	Swab Sample
Sample Volume	One swab sample
Testosterone Validated Range	1.00 to 200.44 µg/swab
Internal Standard	Testosterone
Sample Storage Conditions	-20°C

Assay Validation Performance				
Analyte	Intra-Assay Quality Control Samples		Inter-Assay Quality Control Samples	
	Precision (%CV)	Accuracy (% of Bias)	Precision (%CV)	Accuracy (% of Bias)
Testosterone	1.96 – 5.12	-1.88 - 2.00	3.99 – 6.30	0.00 - 2.59

CV=confidence variable.

LABELING

The following Clinical Pharmacology related parts of the Sponsor's proposed label were submitted together with this NDA. Strikes are used for deletion and double underline is used for addition in OCP and DRUP's draft changes to the Sponsor's proposal.

Reference ID: 3340391

Appendix

Individual Study Review

Study P06-011

STUDY TITLE: Randomized, Open-Label, 2-Treatment, 4-Way Replicate Crossover, Bioequivalence Study of Testosterone Topical Gel Formulation by Upsher-Smith Laboratories Versus Testim® (Testosterone) (Reference) in Hypogonadal Male Volunteers.

STUDY DURATION: The time from the first subject dosed to when the last subject completed the study (i.e., the date the last pharmacokinetic sample was taken) was 95 days.

OBJECTIVE: The objective of this study was to compare the rate and extent of absorption of testosterone gel (test) by Upsher-Smith Laboratories, Inc., U.S.A., versus Testim® (reference) testosterone by Auxilium Pharmaceuticals, Inc., U.S.A., applied as a single dose (2 x 50 mg) in hypogonadal male subjects.

METHODOLOGY: This single dose, randomized, four-period, two-treatment, two-sequence, replicate crossover study was conducted to compare the relative bioequivalence of two formulations of testosterone gel under fasting conditions. The study was conducted with 84 (73 completing) hypogonadal male subjects. In each study period, a single dose of 2 x 50 mg (for a total dose of 100 mg) was administered to all subjects following an overnight fast of at least 10 hours. The test formulation was Upsher-Smith's Laboratories, Inc., testosterone 50 mg gel and the reference formulation was Testim® (testosterone) 50 mg gel (Auxilium Pharmaceuticals, Inc.). The subjects received the test product in one study period and the reference product in the other study period. This procedure was repeated in two other study periods. Drug administration occurred according to the dosing randomization schedule. There was a 7-day washout interval between treatments. Blood samples were collected prior to dosing and at intervals over 72 hours after each dose. In each treatment period a total of 27 blood samples were collected at -12, -8, -4-hour, immediately before the gel application, and at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 19, 20, 21, 22, 24, 26, 28, 32, 36, 40, 48, 60, and 72-hour post-gel application. For determination of testosterone concentrations, the plasma samples for all subjects completing all periods of the study were sent to (b) (4)

NUMBER OF SUBJECTS: A total of 84 hypogonadal male subjects participated in this study.

MAIN DIAGNOSIS FOR ENTRY: All subjects were male, asymptomatic, hypogonadal, adult subjects who met the inclusion/exclusion criteria for this study. Subject had to have an average of two morning total serum testosterone levels (measured on two separate days) ≤ 300 ng/dL, the lower limit of the normal range for healthy young males (with the two morning individual values no higher than 350 ng/dL).

TEST PRODUCT: testosterone gel 5 g tube (corresponding to 50 mg of testosterone); Upsher-Smith laboratories, Inc., U.S.A. (Batch/Lot No.: 46322).

REFERENCE PRODUCT: Testim® (testosterone) testosterone gel 5 g tube (corresponding to 50 mg of testosterone); Auxilium Pharmaceuticals, Inc., U.S.A. (Lot No.: XFAL; Exp. Date: 6/2008)

ROUTE OF ADMINISTRATION: Topical

STATISTICAL METHODS:
Pharmacokinetics:
The analytical data were used to calculate the pharmacokinetic parameters:
- for baseline-corrected and uncorrected: AUC_{0-24}, AUC_{0-t}, C_{max}, and T_{max};
- for baseline-corrected: AUC_{0-inf}, $AUC_{t/inf}$, K_{el}, and $T_{1/2\ el}$.

Reference ID: 3340391

Statistical analysis:
For baseline-corrected data of testosterone, ln-transformed AUC_{0-24}, AUC_{0-t} and C_{max} and untransformed Tmax were analyzed using PROC MIXED in SAS. The study was dosed in more than one group. The covariates in the linear mixed effect model included group, sequence, sequence*group, period (group), treatment and treatment*group as fixed factors. Subject was entered in the model as random effect. Intra-subject coefficient of variation (ISCV%) was estimated for each formulation. Subject by formulation variance was also estimated. For baseline-corrected data of testosterone, the ratio of means (A/B) and 90% geometric confidence interval for the ratio of means were calculated for AUC_{0-24}, AUC_{0-t} and C_{max} using the Estimate statement. Bioequivalence was evaluated using baseline-corrected, non-dose-normalized ln-transformed AUC_{0-24}, AUC_{0-t} and C_{max}.

SUMMARY OF RESULTS:
Eighty-four (84) subjects began the study and 73 subjects completed the clinical portion of the study in its entirety. Fifteen (15) subjects had a mean baseline testosterone serum concentration higher than 350 ng/dL during at least one dosing period. Therefore, these subjects were excluded from the pharmacokinetic analysis. The serum samples from 58 subjects with a mean baseline testosterone concentration < 350 ng/dL (3500 pg/mL) during all four dosing periods were included in the determination of bioequivalence.

A summary of the PK results for baseline-corrected, dose non-normalized ln-transformed data is provided in **Table 7**. Due to physiological fluctuation of endogenous levels of testosterone, the AUC_{0-inf} was not properly characterized for most of the subjects. Therefore, no statistical analysis was performed on ln-transformed AUC_{0-inf} and untransformed K_{el} and $T_{1/2, el}$. The mean $AUC_{t/inf}$ was greater than 80% for both treatments, indicating that the duration of sampling was sufficient (**Table 7**).

Table 7 Summary of Results of Pharmacokinetic Parameters for Testosterone Baseline-Corrected Data (Study P06-011)

Parameter	Statistic	USL240 (1st administration) N=58	USL240 (2nd administration) N=58	Testim® (1st administration) N=58	Testim® (2nd administration) N=58
AUC_{0-t} (pg·h/mL)	Mean ± SD	109837.05 ± 56558.79	98662.44 ± 59667.63	98433.89 ± 57319.81	94420.43 ± 55470.65
	CV (%)	51.49	60.48	58.23	58.75
AUC_{0-24} (pg·h/mL)*	Mean ± SD	70372.16 ± 38302.63	62134.81 ± 38445.52	62030.69 ± 36115.62	59315.86 ± 36355.87
	CV (%)	54.43	61.87	58.22	61.29
AUC_{0-inf} (pg·h/mL)*	Mean ± SD	151815.60 ± 62905.76	115017.87 ± 64272.31	117469.92 ± 68191.79	112971.59 ± 49555.69
	CV (%)	41.44	55.88	58.05	43.87
$AUC_{t/inf}$ (%)*	Mean ± SD	95.02 ± 5.95	88.67 ± 10.43	88.71 ± 9.09	88.40 ± 9.18
	CV (%)	6.26	11.76	10.25	10.38
C_{max} (pg/mL)	Mean ± SD	6132.94 ± 3090.09	5336.00 ± 3110.85	5554.11 ± 3354.01	5822.06 ± 3869.23
	CV (%)	50.39	58.30	60.39	66.46
T_{max} (h)	Mean ± SD	17.4 ± 8.9	17.9 ± 6.8	17.0 ± 8.0	16.9 ± 6.4
	CV (%)	50.93	37.97	47.11	38.13
T_{max} (h) **	Median ± SD	18.0 ± 9.0	18.0 ± 5.0	18.0 ± 9.0	18.0 ± 9.0
	CV (%)	-	-	-	-
K_{el} (h^{-1}) *	Mean ± SD	0.0989 ± 0.0535	0.0828 ± 0.0635	0.0854 ± 0.0635	0.0847 ± 0.0772
	CV (%)	54.12	76.69	74.33	91.07
$T_{1/2\ el}$ (h) *	Mean ± SD	8.63 ± 3.92	11.76 ± 5.98	11.31 ± 5.36	11.80 ± 5.69
	CV (%)	45.41	50.88	47.40	48.23

CV=confidence variables; SD=standard deviation; PK=pharmacokinetic.
* For these parameters, N = 14 and 19 for USL240 and N = 17 and 16 for first and second administrations, respectively.
** Median and interquartile range are presented.

Reference ID: 3340391

Table 1 Baseline Corrected BE analysis for T Gel (Study P06-011: PK Eligible Subjects, N=58)

Parameter	USL240 (Test) Mean	Testim® (RLD) Mean	Ratio[1]	90% Geometric CI[2]
C_{max} (pg/mL)	5084.02	4898.21	103.79%	96.90%, 111.18%
AUC_{0-24hr} (pg*h/mL)	58778.32	53233.56	110.42%	104.55%, 116.61%
AUC_{0-72hr} (pg*h/mL)	94370.14	85296.16	110.64%	104.19%, 117.49%

CI=confidence interval.
1. Calculated using least-squares means of USL240/Testim®.
2. 90% Geometric Confidence Interval using ln-transformed data.

For the ln-transformed testosterone baseline-corrected data, the 90% confidence intervals about the ratio of the test (A) geometric mean to the reference (B) geometric mean were within the 80.00% to 125.00% limits for AUC_{0-t}, AUC_{0-24hr} and C_{max} (**Table 1**).

CONCLUSIONS:
Based on these results, the testosterone gel 1% (by Upsher-Smith Laboratories, Inc., USA) and the Testim® (testosterone gel) (by Auxilium Pharmaceuticals, Inc., USA) are bioequivalent under fasting condition.

No serious adverse events were reported over the course of the study. Overall, testosterone was well tolerated as a single dose of 2 x 5 g tubes (2 x 50 mg of testosterone) administered under fasting conditions.

Reviewer's comment:

- *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. The baseline correction method used in this study is acceptable, i.e., four time points (-12, -8, -4 hr and 0 hr before dosing) for baseline characterization. Mean baseline T concentrations were calculated for each subject by averaging the 4 pre-dose values (-12, -8, -4 hours and pre-dose (0 hour) for each period. All concentrations, including the pre-dose concentration for each subject and period, were subtracted by the mean of the 4 pre-dose concentrations. Every negative concentration obtained after correction was set equal to zero.*

- *The subjects of all subgroups behaved similarly in regards to the treatment effect; therefore, the Sponsor pooled the data from the two administrations to compare the two treatments (USL240 vs. Testim®) for PK parameters, i.e., C_{max}, AUC_{0-24hr} and AUC_{0-72hr}. This is considered acceptable. The 90% confidence intervals about the ratio of the geometric means of USL240 to Testim® were within the 80.00% and 125.00% limits for the PK parameters C_{max}, AUC_{0-24hr} and AUC_{0-72hr} of the ln-transformed baseline-corrected data.*

-

Reference ID: 3340391

Study P10-002

STUDY TITLE: A Randomized, Single-Center, Open-Label, Three-Way Crossover Study of the Removal of Upsher-Smith Laboratories, Inc. Testosterone Gel by Hand Washing

OBJECTIVE: The primary objective was to determine if washing the hands following application of USL240 removed testosterone from the surface of the skin.

DURATION: The duration of the study was approximately 6 weeks: 4 weeks for screening, 3 treatment periods with approximately 7 days between treatments.

METHODOLOGY: This was a single-center, randomized, open-label, 3-way crossover study to assess the removal of Upsher-Smith Laboratories, Inc. Testosterone Gel (USL240) from the hands, after being washed with soap and water. Prior to entering the trial, subjects underwent screening assessments to establish eligibility within 28 days before study drug application. Upon arrival for confinement, subjects were randomized to receive a single dose of testosterone in each study treatment period in accordance with the randomization scheme generated by (b) (4). Subjects reported to the study center on Day-1 and were confined up to 24 hours post-dose. The treatment phases were separated by washout periods of 7 days.

In each period, one 5.0 g tube of USL240 (testosterone gel [50 mg]) was applied topically over a 500 cm2 area of the shoulder/upper arm of a single side of the subject's body by the subject. Skin swab samples were collected within 15 minutes prior to dosing (0 hour), after testosterone gel application, and after washing (according to the randomization scheme and the procedures defined below). The procedure for each treatment group was as follows:

- Treatment A: After application of USL240, the hand used to apply the gel was allowed to dry for a period of 3 minutes, after which time a swab collection from a 10 cm2 area of the palm was taken. The hand was then washed with mild hypoallergenic soap for 1 minute and rinsed with warm water for 1 minute. The hand was patted dry with a cloth towel for 1 minute, and a swab sample was collected from a different 10 cm2 area of the palm 3 minutes after the start of drying.

- Treatment B: After application of USL240, the hand used to apply the gel was allowed to dry for a period of 3 minutes, after which time a swab collection from a 10 cm2 area of the palm was collected. The hand was then washed with mild hypoallergenic soap for 1 minute and rinsed with warm water for 1 minute. After the subject's hand had been allowed to air dry for 9 minutes, a swab sample was collected from a different 10 cm2 area of the palm.

- Treatment C: After application of USL240, the hand used to apply the gel was not allowed to dry and a swab collection was taken from a 10 cm2 area of the palm immediately after application. The hand was then washed with mild hypoallergenic soap for 1 minute and rinsed with warm water for 1 minute. The hand was patted dry with a cloth towel for 1 minute, and a swab sample was collected from a different 10 cm2 area of the palm 3 minutes after the start of drying.

Testosterone concentrations on the skin surface of the hand, including percentage of testosterone removed from the skin surface after washing and percentage of testosterone dose remaining on the skin surface of the hand before and after washing were evaluated for each time point. No PK parameters were evaluated in this study.

NUMBER OF SUBJECTS:
Number of subjects who completed the study: 35
Number of subjects included in the data set for safety analysis: 36
Number of subjects included in the data set for skin swab data analysis: 36

INCLUSION CRITERIA:

Reference ID: 3340391

A subject was eligible for enrollment in the study if all of the following criteria applied:
1. Healthy male subjects 18-65 years of age, inclusive, at the time of consent;
2. Had a body mass index (BMI) between 18 and 35 kg/m2, inclusive, and weight of at least 110 lbs (49.9 kg);
3. Generally healthy, as documented by the medical history, physical examination (PE, including, but not limited to, an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems), vital sign assessments, clinical laboratory assessments, including a prostatespecific antigen (PSA) analysis, and by general observations. Any abnormalities/deviations from the acceptable range that might have been considered clinically relevant by the study physician was evaluated as individual cases, documented in study files, and agreed upon by the QI (or Sub-Investigator) and Sponsor prior to enrolling the subject in this study;
4. Had a screening prostate specific antigen (PSA) between 0-2.5 ng/mL for subjects ≤50 years of age and between 0-4 ng/mL >50 years of age;
5. Had not used tobacco products within 90 days prior to screening and willing to abstain from use of tobacco products through final study visit;
6. Was willing to participate in each study period;
7. Was able to communicate effectively with study personnel and was considered reliable, able, willing and cooperative with regard to complying with protocol-defined requirements as assessed by the study investigator;
8. Could voluntarily give written informed consent to participate in the study prior to the completion of any study-related procedures.

TEST PRODUCT: USL240, Testosterone Gel (50 mg testosterone per 5 g tube) applied topically as a single dose, batch number 64540A.

ROUTE OF ADMINISTRATION: Topical

STATISTICAL METHODS:
Skin Swab Data Assessments:
For each treatment, baseline was defined as the results obtained prior to dosing in each period. Baseline corrected testosterone levels were calculated for each subject and treatment at both post-dose time points, before and after washing. Negative baseline-corrected values were considered as 0 for the purpose of the statistical analysis. Summary statistics (sample size [N], mean, median, standard deviation [SD], coefficient of variation [CV], minimum [Min], and maximum [Max]) were presented by treatment for uncorrected and baseline-corrected testosterone for each skin swab sample collection time.

To evaluate testosterone levels on the skin surface of the hand, two types of percentages were computed and summarized with descriptive statistics. For each subject in each period, the percentage of testosterone removed from the skin surface by washing was calculated as follows:

$$100 \times \frac{\text{(Baseline-corrected level before washing — Baseline-corrected level after washing)}}{\text{Baseline-corrected level before washing}}$$

For each treatment and for both post-dose time points (before and after washing), the percentage of testosterone dose remaining on the skin surface of the hand was calculated by dividing the testosterone level found on the palm of the dominant hand by the testosterone total dose applied (the result was then multiplied by 100). The testosterone total dose applied for each subject in each period was fixed, i.e., 50 mg (equivalent to 5000 µg). The dominant hand for each subject was divided into four equal areas of 10 cm^2, using a template; for each time point, a single skin swab sample was collected from randomly selected area, in accordance with the randomization scheme. The testosterone level (baseline-corrected) obtained from this sample was then multiplied by four to obtain the total testosterone level remaining on the entire hand (in µg). For each subject in each period, the percentage of testosterone dose remaining on the hand before and after washing was calculated as follows:

$$100 \times \frac{\text{(Baseline-corrected level before or after washing x 4)}}{5000}$$

Reference ID: 3340391

Individual uncorrected and baseline-corrected testosterone levels, as well as calculated percentages were also presented.

SUMMARY OF RESULTS:
No testosterone concentration was detected at baseline for any treatment and for any subject. Therefore, no baseline correction was performed on testosterone concentrations. The testosterone levels obtained from skin swab samples before washing were slightly higher for Treatment C (no drying period) compared to Treatments A and B (drying period of 3 minutes for each) as shown by the mean testosterone levels of 58.6, 60.5, and 70.3 µg for Treatments A, B, and C, respectively (**Table 8**). Following hand washing, the mean testosterone levels were comparable between Treatments A and B (0.647, 0.523 µg) and slightly lower for Treatment C (0.163 µg) in comparison. The diminution of testosterone levels following hand washing was similar for all treatments (98.7%, 99.0%, and 99.8% for Treatments A, B, and C, respectively; **Table 9**).

Table 8 Testosterone Levels (µg) Obtained From Skin Swab Samples (Study P10-002)

Timepoint	Value	Statistic	Treatment A	Treatment B	Treatment C
Baseline	Actual	N	36	35	35
		Mean	0.000	0.000	0.000
		SD	0.0000	0.0000	0.0000
		CV	0.0	0.0	0.0
		Median	0.000	0.000	0.000
		Min., Max.	0.00, 0.00	0.00, 0.00	0.00, 0.00
Before washing	Change from Baseline	N	36	35	35
		Mean	58.588	60.542	70.291
		SD	38.7416	41.6717	43.5757
		CV	66.1	68.8	62.0
		Median	50.425	50.960	67.520
		Min., Max.	11.23, 141.86	7.57, 185.74	10.75, 174.98
After washing	Change from Baseline	N	36	35	35
		Mean	0.647	0.523	0.163
		SD	1.0310	1.2421	0.4628
		CV	159.4	237.7	284.2
		Median	0.000	0.000	0.000
		Min., Max.	0.00, 3.95	0.00, 6.61	0.00, 1.64

CV=confidence variable; SD=standard deviation.

Table 9 Percentage (%) of Testosterone Level on the Hand (Study P10-002)

Parameter	Statistic	Treatment A	Treatment B	Treatment C
Testosterone Removed From the Skin Surface After Washing[1]	N	36	35	35
	Mean	98.65	99.02	99.77
	SD	2.32	2.58	0.70
	CV	2.35	2.60	0.70
	Median	100.00	100.00	100.00
	Min., Max.	92.25, 100.00	85.70, 100.00	96.96, 100.00
Testosterone Dose Remaining on the Hand Before Washing[2]	N	36	35	35
	Mean	0.47	0.48	0.56
	SD	0.31	0.33	0.35
	CV	66.13	68.83	61.99
	Median	0.40	0.41	0.54
	Min., Max.	0.09, 1.13	0.06, 1.49	0.09, 1.40
Testosterone Dose Remaining on the Hand After Washing[2]	N	36	35	35
	Mean	0.01	0.00	0.00
	SD	0.01	0.01	0.00
	CV	159.37	237.69	284.16
	Median	0.00	0.00	0.00
	Min., Max.	0.00, 0.03	0.00, 0.05	0.00, 0.01

CV=confidence variable; SD=standard deviation.

1. Calculated as 100 x (Baseline-corrected level before washing minus Baseline-corrected level after washing) divided by Baseline-corrected level before washing.
2. Calculated as 100 x (Baseline-corrected level before or after washing x 4 / 1000) divided by 50.

The results from this study indicated that independent of the testosterone removal method used, washing hands with or without drying period allowed nearly complete (~99%) removal of USL240 from the surface of the skin, thereby greatly reducing the risk of potential cross contamination between individuals.

CONCLUSIONS:

Overall, independent of the washing method used, hand washing removed almost all (~99%) USL240 from the surface of the skin, reducing the risk of transfer between individuals. AEs were reported in low frequencies among subjects, with a majority of the reported AEs being mild in intensity, with no severe or serious AEs reported, indicating that the study formulation was well tolerated. No safety issues were observed over the course of the study with respect to vital sign measurements, PEs, and clinical laboratory measurements.

Study P10-003

STUDY TITLE: A Randomized, Single-Center, Open-Label, Three-Way, Crossover Study of the Transferability of Upsher-Smith Laboratories, Inc. Testosterone Gel During Skin-to-Skin Contact With Clothing, Without Clothing, and After Washing.

OBJECTIVE: The primary objective was to determine the extent of skin-to-skin testosterone transfer from male subjects dosed with USL240 (Testosterone Gel) to non-dosed female subjects under the following conditions: in the presence of clothing, in the absence of clothing, and after the application site had been washed.

DURATION: The duration of the study was approximately 8 weeks: 4 weeks for screening, 3 treatment periods with approximately 14 days between treatments.

METHODOLOGY: This was a randomized, single-center, open-label, three-way, crossover study to assess the transferability of Upsher-Smith Laboratories, Inc. Testosterone Gel (USL240) during skin-to-skin contact after application site washing, and with and without clothing in 48 healthy male and 48 healthy female subjects who met all enrollment criteria. Prior to entering the study, subjects underwent screening assessments to establish eligibility within 28 days before the first study drug application. Upon arrival for confinement in Period 1, subjects were randomized in pairs (a dosed male and a non-dosed female) to apply a single dose of testosterone in each study period in accordance with the randomization scheme generated by (b) (4). The subjects were matched in pairs for the duration of the study. The subjects reported to the study center on Day-1 of each study period and were confined from at least 24 hours prior to drug administration and up to 30 hours post-dose. The treatment periods were separated by a washout of at least 14 days.

In each treatment period a total of 22 blood samples were collected non-dosed female subjects at -24, -20, -16-12, -8, -4-hour, 0 hours before initiating contact, and at 1, 2, 4, 6, 8, 10, 11, 12, 13, 14, 16, 18, 20, 22, and 24 hours post-contact. Plasma testosterone concentrations were evaluated in non-dosed female subjects for each treatment period; no blood samples were drawn from the dosed male subjects for PK analysis.

The treatment periods were separated by a washout of at least 14 days. In each period, one 5.0 g tube of USL240 (testosterone gel [50 mg]) was applied topically over a 500 cm2 area of the shoulder/upper arm of a single side of the male subject's body by the study staff. The subjects were required to follow the transfer procedures (skin-to-skin contact after application site washing, and with and without clothing), which correspond to Treatments A, B, and C defined below:

Treatment A: At 30 minutes after application of USL240, the male dosed subject put on a long-sleeved 100% cotton shirt. At 2 hours after initiation of dosing, the non-dosed female subject rubbed the anterior portion of her dominant forearm over the dosed male subject's clothed application site for 5 minutes (10-15 rubs per minute) and then maintained contact with the same forearm at the application site for another 10 minutes without the rubbing motion.

Treatment B: At 2 hours after application of USL240, the non-dosed female subject rubbed the anterior portion of her dominant forearm over the dosed male subject's unclothed application site for 5 minutes (10-15 rubs per minute) and then maintained contact with the same forearm at the application site for another 10 minutes without the rubbing motion.

Treatment C: At 1 hour and 30 minutes after application of USL240, the dosed male subject showered for approximately 7 minutes. At approximately 3 minutes after initiation of showering, the application site was washed with mild hypoallergenic soap and a washcloth for 30 seconds. The application site was then rinsed with fresh water for the remainder of the showering time. At completion of the shower, the dosed male subject dried his body with a clean towel. Drying included a 1 minute pat dry of the application site. At 2 hours after initiation of dosing, the non-dosed female subject rubbed the anterior portion of her dominant forearm over the dosed

Reference ID: 3340391

male subject's unclothed application site for 5 minutes (10-15 rubs per minute) and then maintained contact with the same forearm at the application site for another 10 minutes without the rubbing motion.

Data from all randomized non-dosed female subjects who had serum concentration data that allowed calculation of PK parameters in at least 1 study period were included in the PK population and, therefore, used for analyses (N=48). The following PK parameters were calculated in this study: $AUC_{0\text{-}24}$, average serum concentration during 24 hours (C_{avg}), C_{max}, relative difference between the $AUC_{0\text{-}24}$ post and prior exposure to USL240 (RD_{AUC}), T_{max}, terminal elimination rate constant (λ_z; calculated for baseline-corrected testosterone only), and $T_{1/2\ el}$ (calculated for baseline-corrected testosterone only).

NUMBER OF SUBJECTS:
Number of subjects enrolled, randomized and dosed (via direct and indirect exposure): 96 (48 non-dosed females and 48 dosed males)

TEST PRODUCT:
USL240, Testosterone Gel (50 mg testosterone per 5.0 g tube) applied topically as a single dose on dosed subjects, batch number 64540A.

ROUTE OF ADMINISTRATION: Topical

STATISTICAL METHODS:
Transferability Assessments:
Testosterone baseline serum concentration for a subject at a particular treatment (period) was defined as the arithmetic mean of the pre-dose levels (blood samples collected at -24.0, -20.0, -16.0, -12.0, -8.00, -4.00, and 0.000 hours prior to initiation of skin contact). Baseline serum concentrations were set at missing only if all seven pre-dose concentrations were reported as missing. Concentration value at time 0.000 hour and all subsequent values were corrected for the baseline concentrations (observed value - baseline value calculated from the corresponding period). Any negative concentration results (after baseline correction) were set equal to zero.

Listings and descriptive statistics (number of observation [n], arithmetic mean, standard deviation [SD], standard error of the mean [SEM], coefficient of variation [CV], median, minimum value [Min], maximum value (Max), and number of BLQ [nBLQ]) of the serum concentrations versus time were provided for each treatment for uncorrected and baseline corrected data. Moreover, the relative difference in serum concentration (100 x [observed value-baseline value]/baseline value) was also reported for each time point, after the initiation of skin contact, with descriptive statistics.

Uncorrected, baseline-corrected and pre-dose testosterone serum concentrations were used to calculate the following parameters for all evaluable non-dose female subjects by standard non-compartmental methods: Primary ($AUC_{0\text{-}24}$) and secondary (C_{avg}, C_{max}, T_{max}, λ_z and $T_{½\ el}$).

Additionally, the baseline-corrected $AUC_{0\text{-}24}$ following exposure was also reported as a percentage of the prior-to-exposure $AUC_{0\text{-}24}$, that is the relative difference for $AUC_{0\text{-}24}$ defined as:

$$RD_{AUC} = 100 * \frac{AUC_{0-24h,observed} - AUC_{0-24h,baseline}}{AUC_{0-24h,baseline}}$$

SUMMARY OF RESULTS:
The baseline testosterone levels were similar in non-dosed females, independent of the treatment group with mean $AUC_{0\text{-}24hr}$, C_{max}, and C_{avg}, respectively, ranging from 3421 to 3660 hr*pg/mL, 187 to 198 pg/mL, and 143 to 152 pg/mL. The post-exposure mean PK parameters calculated on uncorrected data for Treatment A (with

Reference ID: 3340391

clothing), C (application site washed) and B (without clothing) were respectively 3762, 3598, and 11273 hr*pg/mL for AUC_{0-24}, 204, 195, and 794 pg/mL for C_{max} and 157, 150, and 470 pg/mL for C_{avg} (**Table 10**). The mean RD_{AUC} was approximately 277% for Treatment B (without clothing); however, clothing (Treatment A) and washing of the application site (Treatment C) markedly reduced the potential for transfer as evidenced by RD_{AUC} <10% for both treatment groups (**Table 10**). In treatment group B (without clothing), the C_{max} (794 pg/mL) for non-dosed females was increased 4-fold from baseline (C_{max} = 187 pg/mL). In treatment groups A (with clothing) and C (washing of the application site), the C_{max} observed post-exposure was very close to maximum concentration observed at baseline, indicating no noticeable transfer from dosed males to nondosed females in these treatment groups. The mean T_{max} was comparable between treatment groups with values ranging from 16 to 19 hours (**Table 10**). The mean $T_{½\ el}$ was comparable between treatment groups with values respectively ranging from 4 to 8 hours. The elimination rate constant could not be properly estimated for several subjects, either due to a low correlation coefficients of the ln-linear portion of the terminal elimination phase or an insufficient number of detectable concentrations in the terminal elimination phase. These subjects were therefore excluded from all analyses involving λ_z and $T_{½\ el}$ (total number of subjects for these parameters was 8 for Treatments A and C and 22 for Treatment B).

Table 10 Descriptive Statistics for Pharmakinetic Parmaters of Treatments A, B and C for Uncorrected Testosterone (Study P10-003)

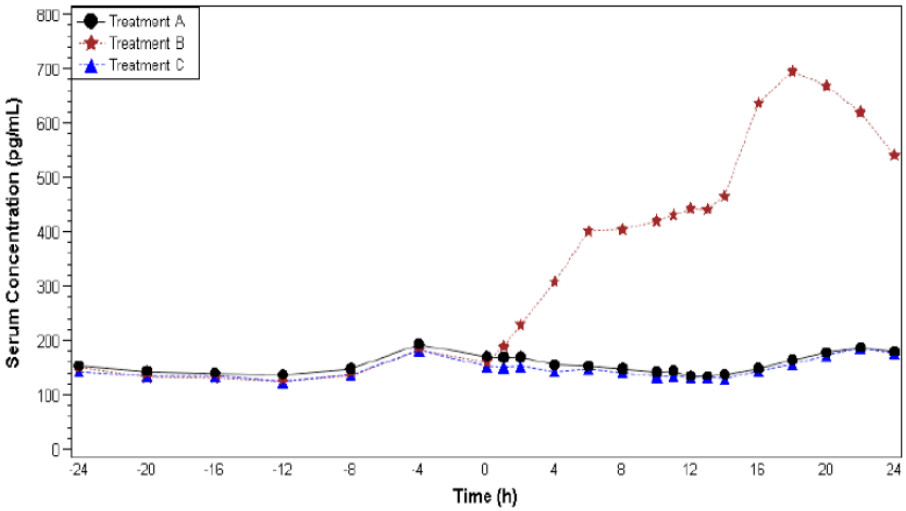
Statistic	AUC_{0-24} (hr*pg/mL)	RD_{AUC} (%)	C_{max} (pg/mL)	T_{max} (hour)	C_{avg} (pg/mL)
Treatment A					
N	47	47	47	47	47
Mean	3762.065	4.012	203.757	15.582	156.753
SD	2115.2678	11.6945	103.3358	9.5303	88.1357
CV (%)	56.2	291.5	50.7	61.2	56.2
SEM	308.5435	1.7058	15.0731	1.3901	12.8559
Median	3256.404	2.944	178.620	20.000	135.680
Min	676.45	-33.59	76.07	0	28.19
Max	11230.11	30.32	530.62	24	467.92
Treatment B					
N	47	47	47	47	47
Mean	11272.90	276.967	793.811	19.087	469.703
SD	5866.7931	217.4409	655.1025	3.2365	244.4495
CV (%)	52.0	78.5	82.5	17.0	52.0
Median	855.7597	31.7170	95.5565	0.4721	35.6566
Min	9618.646	212.534	664.050	20.000	400.780
Max	3692.38	28.24	229.17	6	153.85
Treatment C					
N	42	42	42	42	42
Mean	3597.636	8.721	194.828	18.235	149.902
SD	1697.6765	21.7192	83.1385	7.4127	70.7375
CV (%)	47.2	249.0	42.7	40.7	47.2
Median	261.9572	3.3514	12.8285	1.1438	10.9150
Min	3269.450	6.856	171.745	22.000	136.225
Max	1116.30	-38.67	94.82	0	46.51

CV=confidence variable; Max=maximum; Min=minimum; SD=standard deviation; SEM=standard error of the mean.

Reference ID: 3340391

The mean percent relative difference in testosterone serum concentration ranged from -18% to 28% for Treatment A (with clothing), from 15% to 452% for Treatment B (without clothing) and from -11% to 32% for Treatment C (application site washed; **Figure 2**). Therefore, washing the application site or the wearing of clothing reduced testosterone transfer from dosed males to non-dosed females when compared to skin-to-skin contact without clothes.

Figure 2 Mean Serum Concentration (pg/mL) – Time Profiles (Study P10-003)
(Pre-transfer: -24 to 0 hour; Post-transfer: 0 to 24 hour)



CONCLUSIONS:

In conclusion, the wearing of clothing or the washing of the application site are two effective methods to prevent the transferability of testosterone between dosed and non-dosed individuals with a change from baseline below 10% for both treatments. In the absence of clothing or application site washing, a 3-fold increase in testosterone levels is observed in non-dosed females following skin-to-skin contact with dosed males.

AEs were reported in low frequencies among subjects, with a majority of the reported AEs being mild in severity, with no severe AEs or SAEs, indicating that the study formulation was well tolerated. There was no notable difference observed in the distribution of TEAEs with respect to severity and causality among treatments and between genders (direct dosing and indirect dosing). No safety issues were observed over the course of the study with respect to vital sign measurements, PEs, and clinical laboratory measurements.

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

/s/

LANYAN FANG
07/12/2013

HAE YOUNG AHN
07/12/2013

NDA Number: 204399 **Applicant: Upsher-Smith Lab** **Stamp Date: October 18, 2012**

Drug Name: Testosterone Gel 1% **NDA Type: Original**

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
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			
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	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
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	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Seeking full pediatric

Reference ID: 3230458

					waiver
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	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_____

The following are reviews issues to be conveyed to the sponsor:

- The bioequivalence of Upsher-Smith's Testosterone Gel 1% and Testim® will be a review issue.
- The washing of testosterone from hands and application sites will be a review issue.
- The transfer of testosterone from a user to a non-user will be a review issue

LaiMing Lee	November 29, 2012
Reviewing Clinical Pharmacologist	Date
Myong-Jin Kim	December 3, 2012
Team Leader/Supervisor	Date

Reference ID: 3230458

Office of Clinical Pharmacology Filing Memo

NDA: 204399
Compound: Testosterone Gel 1%
Sponsor: Upsher-Smith Laboratories

Submission Date: October 18, 2012
Filing Review Date: November 29, 2012
Reviewer: LaiMing Lee, PhD

Upsher-Smith Laboratories (USL) is seeking approval of Testosterone Gel 1% (USL240) for the treatment of primary and hypogonadotropic hypogonadism in adult men. To support the approval of this 505(b)(2) NDA, the sponsor submitted five clinical studies including one bioavailability, one bioequivalence, two safety (hand washing and person-to-person transfer), and one irritation and sensitization studies. The bioavailability (P06-001), bioequivalence (P06-011), and irritation and sensitization (P08-001) studies included Testim® (NDA 021454; Auxilum Pharmaceuticals) as the reference product.

The proposed dosing instructions for USL's Testosterone Gel 1% state that a single application of 5 gm of gel (one tube or 4 pump actuations) containing 50 mg testosterone be applied once daily (preferably in the morning) to clean, dry intact skin of the shoulders and/or upper arms. If the serum testosterone concentration is below the normal range, or if the desired clinical response is not achieved, the daily dose may be increased from 5 gm to 10 gm of gel (two tubes or 8 pump actuations) containing 100 mg testosterone as instructed by the physician.

The proposed dosage forms are unit-dose tubes (5 gm of gel containing 50 mg testosterone; supplied in cartons of 30) and a metered-dose pump (1.25 gm of gel containing 12.5 mg testosterone per pump actuation; supplied in cartons of 2). Each metered-dose pump can dispense 60 metered pump actuations.

During the development process, the sponsor developed three formulations - A (USL240), B (pilot formulation), and C (pilot formulation) - and conducted a pilot bioavailability study (Study P06-001) comparing the bioavailability of their formulations to Testim. Formulation A was further pursued based on the pilot bioavailability study and is the formulation the sponsor is seeking approval. A total of five clinical studies were conducted to evaluate the safety of Testosterone Gel 1% and the bioequivalence of Testosterone Gel 1% against Testim

PROPOSED FORMULATION

The proposed product is clear translucent, alcohol-based gel containing 1% testosterone. Testosterone gel is applied topically to the skin. The following table lists the components and composition of USL's Testosterone Gel 1%.

Reference ID: 3230458

Component (Proprietary Name)	Grade	Function	1% Bulk Gel Formulation		Unit Dose Tube or Unit Dose Packet	Multiple Dose Metered Pump	
			% (w/w)	mg/g	Amount per 50 mg Dose (5 g gel) (mg)	Amount per 1.25 g Actuation (mg)	Amount per 75 g Pump (mg)
Testosterone	USP	Drug substance (API)	1.00	10.00	50.00	12.50	750.00
Alcohol (Ethyl Alcohol (b) (4)	USP						(b) (4)
Glycerin (b) (4)	USP						
Diisopropyl Adipate (b) (4)	House Standard						
Methyl Laurate (b) (4)	House Standard						
Oleyl Alcohol (b) (4)	NF						
Carbomer Homopolymer Type C (b) (4) (b) (4)	NF						
Carbomer Copolymer Type B (b) (4)	NF						
Propylene Glycol	USP						
Polyethylene Glycol (b) (4) (b) (4)	NF						
Purified Water	USP						
Tromethamine (b) (4)	USP						
TOTAL							
				Nominal fill	(b) (4)	not applicable	(b) (4)
				Overfill		not applicable	
				Total fill	5.2 g	not applicable	88.0 g

PHASE II AND III CLINICAL TRIALS

No Phase II or III clinical studies were conducted to support this NDA.

PHASE I STUDIES

Study P06-001

Study P06-001 is a relative bioavailability study comparing the exposure of three different USL testosterone gel formulations (test products) and Testim (reference product). Each treatment consisted of a single application of 5 gm (50 mg testosterone) topical gel 1% applied over a 500 cm^2 area on the upper arm/shoulder/back.

Study P06-011

Study P06-011 is a pivotal bioequivalence study evaluating the bioequivalence of USL240 and Testim in 84 hypogonadal male subjects (58 subjects were used for treatment comparison) under fasted condition. Each treatment consisted of a single application of 2 x 5 gm (100 mg testosterone) topical gel 1% using USL240 or Testim applied over a 500 cm^2 area on the upper arms/shoulder/back.

Treatment Comparisons[4]: Testosterone (A) vs Testim® (B)

	Ratio[1]	90% Geometric C.I.[2]		Intra-Subject CV		σ_D[3]
		Lower	Upper	Testosterone (A)	Testim® (B)	
AUC_{0-t}	110.64%	104.19%	117.49%	25.51%	27.68%	6.6092
AUC_{0-24}	110.42%	104.55%	116.61%	23.73%	25.55%	3.5477
C_{max}	103.79%	96.90%	111.18%	29.19%	33.22%	4.7274

Note: AUC_{0-t} refers to area under the curve for testosterone concentration from t= 0 to 72 hrs.

Study P08-001

Study P08-001 is an irritation and sensitization study to evaluate the cumulative irritation and sensitization produced by USL240 compared with Testim. The study was conducted in 255 healthy male subjects with four 3.14 cm 2 sites demarcated on the upper outer region of both arms. The four treatments include (1) 80 µL containing 0.3 mg USL240; (2) 80 µL containing 0.3 mg Testim; (3) 0.2 mL of a positive irritant control (sodium lauryl sulfate); and (4) 0.2 mL of a low irritant control (0.9% sodium chloride).

Study P10-002

Study P10-002 is a hand washing study conducted in 32 healthy male subjects. This was a randomized, open-label, 3-way crossover study. Subjects self-applied the entire contents of one tube (5 gm of gel) over a 500 cm^2 area of the upper shoulder/arm opposite to the subject's dominant hand. Skin swab samples of the application hand were collected for testosterone within 15 min prior to dosing, after testosterone application, and after washing.

Treatment A: After application of USL240, hands were allowed to dry for 3 minutes, then washed and rinsed, and dried with a cloth towel.

Treatment B: After application of USL240, hands were allowed to dry for 3 minutes, then washed and rinsed, and air dried for 9 minutes.

Treatment C: After application of USL240, hands were not allowed to dry, but were washed and rinsed immediately, and dried with a cloth towel.

Study P10-003

Study P10-003 is a person-to-person transfer study to assess the transferability of USL240 during skin-to-skin contact with and without clothing. This was a randomized, open-label, 3-way crossover study. Ninety-six healthy subjects (48 pairs of dosed male and non-dosed female subjects) were included in the study. Male subjects received a single dose of 5 gm of gel USL240 applied on the upper arm/shoulder/back in each treatment period. Female subjects rubbed the anterior portion of her forearm over the application site of male subjects for 5 minutes and then maintained contact with the same forearm at the application site for another 10 min without rubbing; total contact time was 15 min. Blood samples were taken from the non-dosed female subjects for determination of serum testosterone concentrations.

Treatment A: After application of USL240, the dosed subject clothed the site application with a long-sleeve 100% cotton shirt (with clothing barrier).

Treatment B: After application of USL240, the dosed subject maintained site application unclothed (without clothing barrier).

Treatment C: After application of USL240, the dosed subject washed the site of application (with a washcloth).

Reference ID: 3230458

Bioanalytical Sites for Pivotal Bioequivalence Study P06-011

The sponsor is relying on the safety and efficacy findings from Testim (the reference product in bioequivalence Study P06-011). Study P06-011 was conducted by (b) (4) . The bioanalytical laboratory was (b) (4) . Per communication with Michael Skelly, PhD, a pharmacologist in the Division of Bioequivalence and GLP Compliance, Office of Scientific Investigation (OSI), the clinical and bioanalytical sites were inspected multiple times over the recent years with no major issues reported.

The Clinical Pharmacology Review Team requested an OSI inspection of the bioanalytical site for bioequivalence Study P06-011. (b) (4)

(b) (4)

Based upon the pivotal BE study for the current NDA, the test/reference ratios for AUC_{0-t}, AUC_{0-24}, and Cmax are shifted to the higher end suggesting a higher exposure from the proposed product compared to the reference Testim product. The test/reference ratio (90%CI) for AUC_{0-t}, AUC_{0-24}, and Cmax are 110.6% (104.2, 117.5%), 110.4% (104.5, 116.6%), and 103.8% (96.9, 111.2%), respectively as currently reported by the sponsor.

Considering the totality of available information (OSI report, timeframe for two similar BE studies, and current data), the Clinical Pharmacology Review Team recommended an inspection of the bioanalytical site for NDA 204399. The OCP DCP3 Division Director Dennis Bashaw signed off on the inspection request December 12, 2012.

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

/s/

LAI M LEE
12/13/2012

MYONG JIN KIM
12/13/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-399 (Original)
Product name, generic name of the active, and dosage form and strength	Testosterone Topical Gel 1%
Submission Date	October 17, 2012
PDUFA Date	August 17, 2013
Applicant	Upsher-Smith Laboratories, Inc
Medical Division	DRUP
Type of Submission	Original NDA Submission
Biopharmaceutics Reviewer	Tapash K. Ghosh, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution/release data?	X		The following in vitro drug release method is proposed for routine testing: ▪ [redacted] (b) (4)
2.	Is the dissolution/release test part of the DP specifications?	X		[redacted] (b) (4) µg/(cm^2/minutes$^{1/2}$)
3.	Does the application contain the dissolution method development report?	X		Yes
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application include a biowaiver request?		X	
6.	Does the application include an IVIVC model?		X	
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	Not required
8.	Is there any in *vivo* BA or BE information in the submission?	X		

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
9.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		➢ The NDA is filable from the Biopharmaceutics Perspective ➢ The acceptability of the proposed in vitro drug release method and acceptance criteria will be a review issue.
10.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
12.	Are there any potential review issues identified?			No
13.	**Reviewer's Comments:** None at this point.			

{See appended electronic signature page}

Tapash K. Ghosh, Ph.D. — 12/11/12
Biopharmaceutics Reviewer — Date
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D. — 12/11/12
Biopharmaceutics Team Leader — Date
Office of New Drug Quality Assessment

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

/s/

TAPASH K GHOSH
12/11/2012

ANGELICA DORANTES
12/11/2012