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APPLICATION NUMBER:

22309Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 022309	Submission Dates: 02/11/2009, 05/14/2009, 09/02/2009, 09/17/2009, 11/06/2009, 11/24/2009, 12/03/2009, 12/11/2009, 12/23/2009, 01/25/2010, 10/29/2010, and 04/26/2011
Brand Name	Androgel
Generic Name	Testosterone (T) gel
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Abbott Products, Inc.
Relevant IND, NDA	IND 050377, NDA 021015
Submission Type	Resubmission
Formulation and Strength	Androgel 1.62% in a multi-dose pump (20.25 mg of T per actuation), 20.25 mg – 81 mg T
Indication	T replacement therapy in male hypogonadism o Primary hypogonadism (congenital or acquired) o Hypogonadotrophic hypogonadism (congenital or acquired)

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Reference ID: 2938751

1 Executive Summary

The Clinical Pharmacology review of NDA 022309 (DARRTS, 04/25/2011) stated that NDA 022309 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 04/26/2011 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 NDA 022309 acceptable.

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Reference ID: 2938751

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
04/28/2011

MYONG JIN KIM
04/28/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 022309	Submission Dates: 02/11/2009, 05/14/2009, 09/02/2009, 09/17/2009, 11/06/2009, 11/24/2009, 12/03/2009, 12/11/2009, 12/23/2009, 01/25/2010, and 10/29/2010
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Indication	T replacement therapy in male hypogonadism o Primary hypogonadism (congenital or acquired) o Hypogonadotrophic hypogonadism (congenital or acquired)

An Optional Inter-Division Level Clinical Pharmacology Briefing was held in conference room 3200 of White Oak Bldg 51 on March 31, 2011. Attendees included Drs'. Ruben Ayala, George Benson, Roger Wiederhorn, Sayed Al Habet, Li Li, Doanh Tran, Chongwoo Yu, Mark Hirsch, Myong-Jin Kim, Hae Young Ahn and Hyunjin Kim AND Kai Yeung (OCP intern)

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1 Executive Summary

The subject of NDA 022309 is Androgel (testosterone (T) gel) 1.62% with the proposed indication of replacement therapy in males for conditions associated with a deficiency or absence of endogenous T. Androgel 1.62% is supplied in a multi-dose pump which dispenses 1.25 g gel (20.25 mg T) per actuation. The proposed starting dose for Androgel 1.62% is 2.5 g (40.5 mg T) applied once daily to clean, dry, intact skin of upper arms/shoulders. The dose can be subsequently increased or decreased in 1.25 g (20.25 mg T) increments within the range of 1.25 to 5.0 g (20.25 to 81 mg T).

Original NDA Submission

- The original NDA for Androgel 1.62 % was submitted to Agency on February 11, 2009. During the original review cycle, it was concluded that the interpersonal transfer potential for Androgel 1.62% was mitigated in presence of a clothing barrier, when the Androgel 1.62% 2.5 g was applied to abdomen (S176.1.008). However, it was evident that interpersonal transfer potential was significant for Androgel 1.62% even in presence of a clothing barrier when the Androgel 1.62% 5.0 g was applied to abdomen (S176.1.003). In an attempt to assuage the Division's concern in this regard, the sponsor conducted a new transfer study (S176.1.009) employing revised dosing instructions to mitigate transfer potential. A 5.0 g dose of the gel was applied to both upper arms/shoulders and abdomen of the male subjects in this study as opposed to the completed clinical program (S176.3.104) for Androgel 1.62 % gel where the gel was applied to either upper arms/shoulders or abdomen (on a rotation basis) but not to both sites at once.
- The results from the new transfer study S176.1.009 suggested that the T transfer to non-dosed females was largely mitigated when contact occurred with a T-shirt barrier on male who applied a Androgel 1.62 % 5.0 g to both upper arms/shoulders and abdomen.
- While dosing over multiple sites (both upper arms/shoulders and abdomen) appeared to mitigate transfer potential, no efficacy or skin irritation data was available from this continuous once daily application method of the 1.62 % gel to multiple application sites to support the approval of the NDA.
- Therefore, the Division issued a Complete Response letter on March 12, 2010. In the Complete Response letter, the followings were listed under the section entitled with "Information needed to address the clinical and clinical pharmacology deficiency":

  Conduct and provide a complete report for a steady-state, 2-way crossover, comparative bioavailability study of Androgel 1.62% in hypogonadal males, evaluating the following two regimens:

  1. Application of a 5.0 g dose to 2 anatomic sites utilizing the upper arms/shoulders or abdomen on a rotating basis, as per the instructions for use in the Phase 3 Study S176.3.104, versus

  2. Application of a 5.0 g dose to 4 anatomic sites utilizing both upper arms/shoulders and both sides of the abdomen, as per the instructions for use in Study S176.1.009.

  In addition to assessing serum T concentrations, this study should capture data for application site skin irritation.

Complete Response

- In the current submission, the sponsor submitted the following two new clinical studies to address deficiencies identified in the Complete Response letter.
  - S176.1.010 entitled "A Multiple Dose PK and Comparative Bioavailability Study of T Absorption after Administration of 5.0 g Androgel 1.62% to the Upper Arms/Shoulders and Abdomen using an Application Site Rotation or a Combination of Application Sites in Hypogonadal Males" and;

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- S176.1.011 entitled "An Open-Label Study of Serum T Levels in Non-dosed Females after Secondary Exposure to Androgel 1.62% Applied to the Upper Arms and Shoulders and Use of a T-shirt Barrier"

- [redacted] (b) (4)

From a Clinical Pharmacology perspective, sponsor's [redacted] (b) (4) application method should demonstrate the followings:

- **Transferability**: No significant or minimum transferability to non-dosed individuals when contact occurs while covering the application sites with a clothing barrier,
- **Exposure comparison**: Comparable exposure to application method (either upper arms/shoulders or abdomen) used in the pivotal phase 3 study (S176.3.104), and
- **Skin irritation comparison**: Comparable skin irritation to application method (either upper arms/shoulders or abdomen) used in the pivotal phase 3 study (S176.3.104).

1.1 Recommendation

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

1.2 Post Marketing Requirement

A clinical trial entitled "An Evaluation of the Effect of Hand Washing on the Amount of Residual T on the Hands after Application of Androgel 1.62%" to assess the amount of residual T before and after washing primary user's hands will be conducted with a following timeline which was agreed upon between the Division and the sponsor (DARRTS, January 26, 2011):

- Final Protocol Submission: July 2011
- Trial Completion: October 2011
- Final Report Submission: July 2012

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

For "application of Androgel 1.62% to both upper arms/shoulders and abdomen"

- **Transferability**: Study S176.1.009 (submitted during the original review cycle) demonstrated that the transferability by application of Androgel 1.62% 5.0 g to both upper arms/shoulders and abdomen while covering the application sites with T-shirts was not significant (increases of C_{max} and AUC by 6 and 7%, respectively, Table 1). *See Clinical Pharmacology review by Dr. Apparaju Sandhya (NDA 022309, DARRTS, March 4, 2010).*
- **Exposure comparison**: Study S176.1.010 was the comparative bioavailability study (Androgel 1.62% 5.0 g) which was requested by the Division in the Complete Response letter. This new application method (treatment B; both upper arms/shoulders and abdomen for 7 days) was associated with 16 to 27% lower total T exposure compared to the application method (treatment A; abdomen for 3 days and upper arms/shoulders for 4 days) representing the dosing instruction (either upper arms/shoulders or abdomen but not to both at the same time) used in the pivotal phase 3 study (Table 2).
- [redacted] (b) (4)

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(b) (4)

Table 1 Statistical Comparison of PK Parameters of Total T – Transferability to Female Partners when Androgel 1.62% 5.0 g was Applied to Both Upper Arms/Shoulders and Abdomen of Male Subjects with T-shirts; S176.1.009 (original review cycle)

	Day	N	Geometric mean	Geometric mean ratio (Day1/Day-1)	90% CI
C_{max} (ng/dL)	Day -1	12	19.5	1.06	0.92 – 1.23
	Day 1	12	20.7		
AUC_{0-24} (ng·hr/dL)	Day -1	12	395.1	1.07	0.98 – 1.16
	Day 1	12	421.3		
C_{avg} (ng/dL)	Day -1	12	16.5	1.07	0.98 – 1.16
	Day 1	12	17.6		

Day -1: before contact; Day 1: after contact

Table 2 Statistical Comparison of PK Parameters of Total T on Day 7 – Exposure Comparison with Androgel 1.62% 5.0 g – Abdomen Once Daily for 3 Days and Upper Arms/Shoulders Once Daily for 4 Days vs. Both Upper Arms/Shoulders and Abdomen Once Daily for 7 Days; S176.1.010

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

A: Once daily application of Androgel 1.62% 5.0 g to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% 5.0 g to both upper arms/shoulders and abdomen for 7 days

For "application of Androgel 1.62% to upper arms/shoulders"

- **Transferability**: Study S176.1.011 (submitted in the current resubmission) demonstrated that the transferability by application of Androgel 1.62% 5.0 g to upper arms/shoulders while covering the application sites with T-shirts was not significant (increases of C_{max} and AUC by 11 and 6%, respectively, Table 3).
- **Exposure comparison**: Study S176.1.007 (submitted during the original review cycle) demonstrated that the total T exposure from the new application method (treatment B: upper arms/shoulder for 7 days) was bioequivalent to the total T exposure from the application method (treatment A; abdomen for 3 days and upper arms/shoulders for 4 days) representing the application method (either upper arms/shoulders or abdomen but not to both at the same time) used in the pivotal phase 3 study (Table 4).
- **Skin irritation comparison**: Skin irritation potential from the two application methods (treatment A; abdomen for 3 days and upper arms/shoulders for 4 days; treatment B: upper arms/shoulders for 7 days, Study S176.1.007) was found to be comparable. See Clinical review by Dr. Roger Wiederhorn (NDA 022309).

- Therefore, the [redacted] (b) (4) application method of applying Androgel 1.62% to the upper arms/shoulders is acceptable.

Table 3 Statistical Comparison of PK Parameters of Total T – Transferability to Female Partners when Androgel 1.62% 5.0 g was Applied to Upper Arms/Shoulders of Male Subjects with T-shirts; S176.1.011

	Day	N	Geometric mean	Geometric mean ratio (Day1/Day-1)	90% CI
C_{max} (ng/dL)	Day -1	12	21.5	1.11	0.99 – 1.25
	Day 1	12	23.9		
AUC_{0-24} (ng·hr/dL)	Day -1	12	443.1	1.06	0.98 – 1.15
	Day 1	12	470.0		
C_{avg} (ng/dL)	Day -1	12	18.5	1.06	0.98 – 1.15
	Day 1	12	19.6		

Day -1: before contact; Day 1: after contact

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

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

B: Once daily application of Androgel 1.62% 5.0 g to upper arms/shoulders for 7 days; C: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days
*Results for treatment A (once daily application of Androgel 1.62% 5.0 g to abdomen for 7 days) are not shown here. See Table 13 for results including the treatment A.

The sponsor has provided adequate evidence to link the existing safety and efficacy data to the new mode of administration (application of Androgel 1.62% to upper arms/shoulders).

- *This new application method*
  - *mitigated transfer of T to non-dosed females.*
  - *demonstrated the comparable exposure of total T by the application method used in the phase 3 study.*
  - *demonstrated the comparable skin irritation potential by the application method used in the phase 3 study. See Clinical review by Dr. Roger Wiederhorn (NDA 022309).*

1 year Efficacy Data

- The efficacy of Androgel 1.62% was established in the original review cycle of the NDA based on the pivotal phase 3 clinical study, S176.3.104, of which the study duration was 182 days (Clinical Pharmacology review of NDA 022309 by Dr. Apparaju Sandhya, DARRTS, October 26, 2009). Sponsor's resubmission included additional efficacy data from the open-label period (from Days 183 to 364) of S176.3.104.

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- On Days 266 and 364, the proportion of responders for the Continuing Active Androgel 1.62% group was 78.4 and 77.9%, respectively, suggesting the long term efficacy of Androgel 1.62% up to 1 year (Table 5).

Table 5 Number and Percentage of Subjects Achieving Target Range for T C_{avg} by Day and Treatment in the Full Analysis* Sample; Open-Label; S176.3.104

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

*Full Analysis Sample: See section 4.1 Individual Clinical Study Review for definition.

2 Question Based Review

2.1 General Attributes

2.1.1 What is the relevant regulatory background information leading to the Complete Response in the original review cycle?

- The original NDA for Androgel 1.62 % was submitted on February 11, 2009. The dosing instructions provided to patients during the phase 3 clinical trial S176.3.104 were that over any 7-day period, the application site could be rotated between the upper arms/shoulders or the abdomen (e.g., 4 days upper arms/shoulders; 3 days abdomen). On PK sampling and titration days, dosing was to occur on shoulders/upper arms alone. Patients applied gel once daily (preferably at the same time every day) to clean, dry, intact skin. During the original review cycle, it was evident that interpersonal transfer potential was significant. Furthermore, covering the application site with a clothing barrier (T-shirt) did not completely eliminate transfer with 5.0 g dose when the 5.0 g dose was applied to abdomen.
- While washing the application site prior to physical contact was shown to prevent transfer, the clinical review team preferred a simpler method for preventing transfer (e.g. use of a T-shirt).
- These concerns were communicated to the sponsor in a teleconference held on October 01, 2009. In the meeting, sponsor expressed their interest in conducting a new transfer study to evaluate whether spreading out the gel on multiple sites (i.e. both upper arms/shoulders and abdomen, instead of either site alone) would minimize transfer potential.
- Division acknowledged the sponsor's proposal but also noted that even if the new application instructions proved effective in preventing transfer, further information may be needed to link the existing safety and efficacy data to the new mode of administration.
- On November 9 and December 8, 2009, the Division received the major amendments to this application. These contained additional clinical and clinical pharmacology safety information pertaining to a new transfer study, S176.1.009 and rationale associated with the applicability of completed clinical trial data to the new dosing instructions.
- The results from the new phase 1 transfer study S176.1.009, in addition to a supporting document justifying the absence of a formal bridging study linking the revised dosing

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instructions to those employed in the phase 3 program, constituted the primary components of the major NDA amendment.

- The study results (S176.1.009) indicated that when contact occurred in presence of a clothing barrier with males who applied the 5.0 g dose over both upper arms/shoulders and abdomen, mean (range) fold-change in C_{avg} of T in females was 1.07 (range, 0.78 - 1.21 fold) i.e. 7 % over baseline. For the females who experienced the increase in C_{avg} of T, the range of absolute increases in C_{avg} of T in these females was 0.23 – 3.9 ng/dL. Mean increase in C_{max} of T was 1.06 (range, 0.67-1.74) i.e. 6 % over baseline. Therefore, T transfer to non-dosed females was largely mitigated when contact occurred with males with T-shirts when a 5.0 g dose of the 1.62 % gel was applied to both upper arms/shoulders and abdomen. While dosing over the both upper arms/shoulders and abdomen appeared to mitigate transfer, no PK (exposure comparison) or skin irritation data was available from continuous once daily application of the 1.62 % gel to these application sites without rotation. Therefore, the Division issued a Complete Response letter on March 12, 2010. In the Complete Response letter, the followings were listed under the section entitled with "Information needed to address the clinical and clinical pharmacology deficiency":

  Conduct and provide a complete report for a steady-state, 2-way crossover, comparative bioavailability study of Androgel 1.62% in hypogonadal males, evaluating the following two regimens:

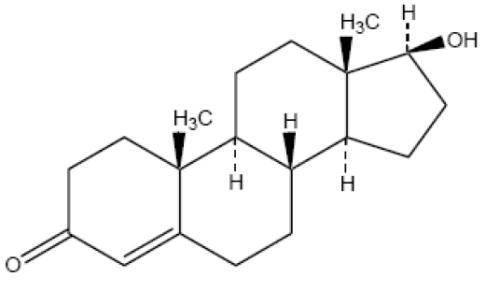
  1. Application of a 5.0 g dose to 2 anatomic sites utilizing the upper arms/shoulders or abdomen on a rotating basis, as per the instructions for use in the Phase 3 Study S176.3.104, versus

  2. Application of a 5.0 g dose to 4 anatomic sites utilizing both upper arms/shoulders and both sides of the abdomen, as per the instructions for use in Study S176.1.009.

  In addition to assessing serum T concentrations, this study should capture data for application site skin irritation.

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?

Androgel 1.62% is a clear, colorless hydroalcoholic gel containing 1.62% T. The Androgel 1.62% doses, 1.25 g, 2.5 g, 3.75 g, and 5.0 g, contain 20.25 mg, 40.5 mg, 60.75 mg, and 81 mg of T, respectively. The active pharmacologic ingredient in Androgel 1.62% 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:



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

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Pharmacologically inactive ingredients in Androgel 1.62% are carbopol 980, ethyl alcohol (b) (4), isopropyl myristate, purified water, and sodium hydroxide.

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

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.

Androgel 1.62% is indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous T:

- Primary Hypogonadism (Congenital or Acquired) – e.g., testicular failure due to 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 T levels and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadropic Hypogonadism (Congenital or Acquired) – e.g., idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low T serum levels, but have gonadotropins in the normal or low range.

2.1.4. What are the proposed dosage(s) and route(s) of administration?

Androgel 1.62% is supplied in a multi-dose pump which dispenses 1.25 g gel (20.25 mg T) per actuation. The recommended starting dose of Androgel 1.62% is 2.5 g once daily (equivalent to 40.5 mg T) in the morning to clean, dry, intact skin of the shoulders/upper arms. To ensure proper dosing, serum T concentrations should be measured and the dose should be adjusted to achieve and maintain serum T concentrations in the normal range (300 -1000 ng/dl). If serum T concentrations are above or below the normal range, adjust dose in 1.25 g increments to a daily dose between 1.25 g and 5.0 g (i.e. 20.25 mg – 81 mg T doses).

2.2 General Clinical Pharmacology

2.2.1 Which methods of applying Androgel 1.62% were proposed in the current review cycle?

In the current review cycle, the sponsor proposed the following two new dosing instructions for the two higher doses (3.75 and 5.0 g):

- Application of Androgel 1.62% to both upper arms/shoulders and abdomen
- Application of Androgel 1.62% to upper arms

2.2.2 Which studies were conducted to support the sponsor's proposed application site of both upper arms/shoulders and abdomen and what were the results and implications from those

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studies?

- Study S176.1.009 (submitted during the original review cycle; Dr. Sandhya Apparaju's review - DARRTS on March 3, 2010) was conducted in order to assess the transferability of Androgel 1.62% 5.0 g while covering the application sites (both upper arms/shoulders and abdomen) with T-shirts.
    - The study demonstrated that transferability of Androgel 1.62% 5.0 g was mitigated by covering the application sites with T-shirts.
- Study S176.1.010 (submitted in the current resubmission) was conducted in order to compare the total T exposure by applying Androgel 1.62% 5.0 g to both upper arms/shoulders and abdomen vs. abdomen for 3 days and upper arms/shoulders for 4 days (representing the phase 3 application method).
    - The study demonstrated that the total T exposure on Day 7 following the application of Androgel 1.62% 5.0 g daily to both upper arms/shoulders for 7 days was approximately 16 to 27% lower compared to applying Androgel 1.62% to abdomen for 3 days and upper arms/shoulders for 4 days.
- (b) (4)

Study S176.1.009: An Open-Label, Parallel Group Study of Serum T Levels in Non-dosed Females after Secondary Exposure to Androgel 1.62%

The followings are from Clinical Pharmacology review by Dr. Sandhya Apparaju (DARRTS, March 4, 2010).

- Study objective
    - To determine the PK of total T concentrations in female subjects after a single episode of skin contact with a male partner dosed with Androgel 1.62% (5.0 g).
    - To evaluate skin-to-skin T transfer from males dosed with Androgel 1.62% (5.0 g) to non-dosed female subjects when contact with the application site, upper arms/shoulders and abdomen, occurs at 2 hours post-dose with a T-shirt barrier.
- Study design
    - The study was a single center, single-dose (males only), open-label PK and transfer evaluation (to females only) study in healthy male and female volunteers.
    - N = 12 male-female couples were enrolled and completed. The test product was Androgel 1.62%, 5.0 g of gel containing 81 mg T.
    - On Day 1 all male subjects received 5.0 g Androgel 1.62% to four sites as follows: 1.25 g applied to the left upper arm/shoulder, 1.25 g applied to the right upper arm/shoulder, 1.25 g applied to the left abdomen and 1.25 g applied to the right abdomen.
    - Female partners did not receive the test dose, but underwent transfer with their male partners at 2 h post-dose on Day 1 with the male wearing a full-sleeved 100 % cotton T-shirt to cover the application sites. Female subjects were given a tube top to wear to expose the shoulders/arms and abdomen.
    - For skin contact with the upper arms/shoulders and abdomen combination application site, a waistband was placed around the couple to ensure maximum contact. During the contact session, the couples swayed their abdomens in opposing directions (left/right) for duration of 1 minute starting at the beginning of minute 2, 5, 8, 11, and 14. In addition, the female continuously kept her arms resting on the male's shoulders and for duration of 1 minute starting at the beginning of minute 3, 6, 9, 12, and 15, female subjects were instructed to rub

their hands, wrists, arms, and shoulders up and down the upper arms and shoulders of their male partner.

- PK measurements and blood samples
  - Whole blood samples for serum analyses of T, DHT and estradiol were collected from female participants at the following time points during this study:
    - Day -1 (baseline) at 0, 2, 4, 6, 8, 10, 12, 16, and 24 (pre-dose on Day1) hours with respect to the planned end time of skin contact on subsequent days.
    - Day 1 at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 16, 24, and 48 hours after the end of skin contact that occurred over 15 minutes starting at 2 hours following gel application in males.
    - Serum concentrations of T, DHT and estradiol were determined and PK data analyses were performed using non-compartmental methods.
- Results
  - Average (SD) PK parameters of total T in N = 12 female subjects are shown at baseline (Day -1) and on Day 1 when contact occurred at 2 hour post-dose to males who received 5.0 g of the new 1.62 % gel formulation (Figure 1 and Table 6). Males used long-sleeve T-shirt to cover the application sites during contact session.

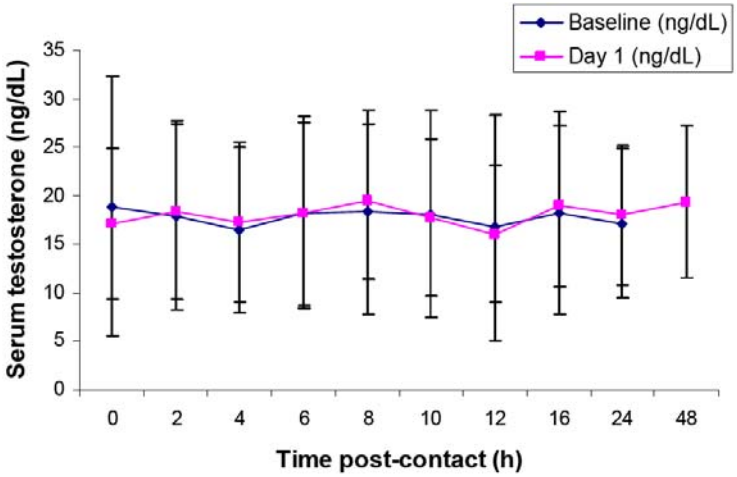

Figure 1 Mean (SD) Total T Concentrations of Females Before (Day-1) and After (Day 1) Contact with Males on T-Shirts; S176.1.009; N = 12

Table 6 Arithmetic Mean (SD) PK Parameters of Total T; S176.1.009 (original review cycle)

	Day	N	Arithmetic mean (SD)
C_{max} (ng/dL)	Day -1	12	21.6 (13.1)
	Day 1	12	22.2 (10.4)
AUC_{0-24} (ng·hr/dL)	Day -1	12	424.5 (236.1)
	Day 1	12	432.3 (180.3)
C_{avg} (ng/dL)	Day -1	12	17.7 (9.8)
	Day 1	12	18.0 (7.5)
*T_{max} (hr)	Day -1	12	17.7 (9.8)
	Day 1	12	18.0 (7.5)

*shown as median (range)
Day -1: before contact; Day 1: after contact

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- On Day 1, after coming into contact with the T application sites in males that were covered by clothing, T concentrations in females were generally comparable to those seen at baseline. T concentrations on Day 1 ranged between 6.31-43.5 ng/dL. No consistent increase or decrease was noted on Day 1 in the change from baseline at various time points post-contact.
- Fold-increase in C_{avg} on Day 1 was 1.07 i.e. 7 % over baseline (Table 7). On Day 1, 8 out of 12 females demonstrated small increase in C_{avg} over baseline ranging from 1.13 fold to 1.21 fold. The absolute values of increase in C_{avg} in these females were in the range of 0.23 – 3.9 ng/dL. It is difficult to conclude whether these small changes are due to transfer or due to day-to-day variability in baseline T concentrations in these females.
- Mean increases in C_{max} were 1.06 on average i.e. 6 % over baseline (Table 7). The individual fold increases ranged from 1.04 to 1.74 fold in 7 out of 12 individuals.

Table 7 Statistical Comparison of PK Parameters of Total T; S176.1.009 (original review cycle)

	Day	N	Geometric mean	Geometric mean ratio (Day1/Day-1)	90% CI
C_{max} (ng/dL)	Day -1	12	19.5	1.06	0.92 – 1.23
	Day 1	12	20.7		
AUC_{0-24} (ng·hr/dL)	Day -1	12	395.1	1.07	0.98 – 1.16
	Day 1	12	421.3		
C_{avg} (ng/dL)	Day -1	12	16.5	1.07	0.98 – 1.16
	Day 1	12	17.6		

Day -1: before contact; Day 1: after contact

- Conclusion
  - The results from the new transfer study S176.1.009 suggested that the T transfer to non-dosed females was largely mitigated when contact occurred 2-hours post-dose with a T-shirt barrier on male who applied a 5.0 g dose of the 1.62 % gel formulation to both upper arms/shoulders and abdomen.

S176.1.010: A Multiple Dose PK and Comparative Bioavailability Study of T Absorption after Administration of 5.0 g Androgel 1.62% to the Upper Arms/Shoulders and Abdomen using an Application Site Rotation or a Combination of Application Sites in Hypogonadal Males

- Study objective
  - To determine the multiple dose PK of T after administration of 5.0 g Androgel 1.62% in hypogonadal males.
  - To determine the relative bioavailability of T after administration of 5.0 g Androgel 1.62% using an application site rotation between the upper arms/shoulders and abdomen or both upper arms/shoulders and abdomen.
- Study design
  - This was a phase I, open-label, randomized, two-treatment, two-period, crossover study in 62 hypogonadal males (18 - 80 years old). The total duration of the study was approximately 24 days, not including the screening period. The overall study design is presented in Figure 2.

Reference ID: 2937578

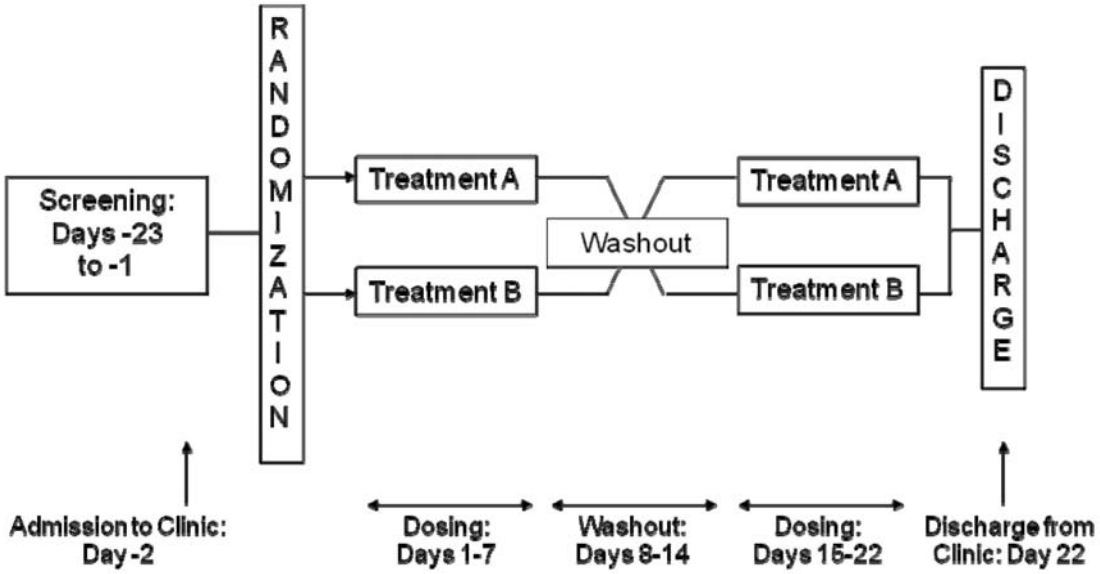

Figure 2 Study design; S176.1.010

- Two treatments
  - Treatment A: Once daily application of Androgel 1.62% to the abdomen for 3 days (2.5 g to each the right and left side of the abdomen) followed by application to the upper arms/shoulders (2.5 g to each the right and left upper arm/shoulder) for 4 days. The total daily gel dose was 5.0 g. *Application method of Androgel 1.62% in treatment A is same as in the pivotal phase 3 study (S176.3.104).*
  - Treatment B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days. The total daily gel dose was 5.0 g consisting of 1.25 g applied to the left upper arm/shoulder, 1.25 g applied to the right upper arm/shoulder, 1.25 g applied to the left abdomen and 1.25 g applied to the right abdomen.

- PK measurements and blood samples
  - Whole blood samples (6 mL) were collected in anticoagulant-free tubes for determination of total T, DHT, and estradiol at the following times:
    - Day -1 and Day 14 (baseline): 0, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours with respect to the projected time of T administration
    - Days 7 and 21: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose
- Results
  - Following treatment with 5.0 g Androgel 1.62%, the mean concentration-time profile for Treatment B was lower in magnitude than Treatment A (Figure 3 and Table 9).

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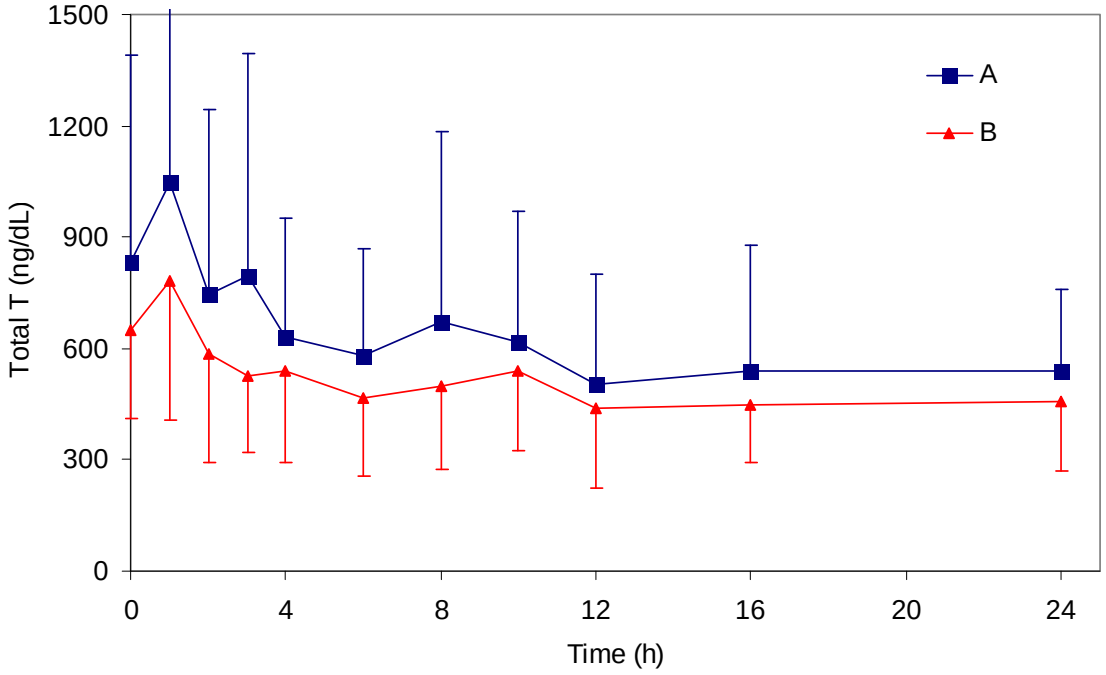

Figure 3 Arithmetic Mean (SD) Serum Concentrations of Total T in Two Treatment Groups after 7 Days of Once Daily Application of Androgel 1.62% 5.0 g; S176.1.010; N (A) = 62, N (B) = 62

A: Once daily application of Androgel 1.62% 5.0 g to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% 5.0 g to both upper arms/shoulders and abdomen for 7 days

Table 8 Arithmetic Mean (SD) PK Parameters of Total T; S176.1.010

	Treatment	N	Arithmetic mean (SD)
C_{max} (ng/dL)	A	62	1283 (817)
	B	62	866 (369)
AUC_{0-24} (ng·hr/dL)	A	62	14433 (5880)
	B	62	11817 (3981)
C_{avg} (ng/dL)	A	62	601 (245)
	B	62	492 (166)
*T_{max} (hr)	A	62	1 (0-24)
	B	62	1 (0-24)

*shown as median (range)

A: Once daily application of Androgel 1.62% 5.0 g to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% 5.0 g to both upper arms/shoulders and abdomen for 7 days

The geometric mean ratios for AUC and C_{max} of T demonstrated that AUC and C_{max} from treatment B were approximately 16% and 27% lower than those from treatment A, respectively (Table 9). These mean differences were even greater with the geometric mean ratios for AUC and C_{max} of baseline-adjusted T, 33% and 37%, respectively (Table 10).

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Table 9 Statistical Comparison of PK Parameters of Total T; S176.1.010

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

A: Once daily application of Androgel 1.62% 5.0 g to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% 5.0 g to both upper arms/shoulders and abdomen for 7 days

Table 10 Statistical Comparison of PK Parameters of Baseline-Adjusted Total T; S176.1.010

	Treatment	N	Geometric mean	Geometric mean ratio (B/A)	90% CI
C_{max} (ng/dL)	A	62	752	0.63	0.53 – 0.74
	B	62	471		
AUC_{0-24} (ng·hr/dL)	A	62	6092	0.67	0.57 – 0.80
	B	62	4094		
C_{avg} (ng/dL)	A	62	254	0.67	0.57 – 0.80
	B	62	171		

A: Once daily application of Androgel 1.62% 5.0 g to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% 5.0 g to both upper arms/shoulders and abdomen for 7 days

- Conclusion
  - The new application method, (treatment B, both upper arms/shoulders AND both sides of the abdomen) can potentially reduce the exposure of 5.0 g dose leading to reduced efficacy; hence, the use of new application method, (treatment B, both upper arms/shoulders AND both sides of the abdomen) is not supported by study S176.1.010.

2.2.3 Which studies were conducted to support the sponsor's proposed application site of upper arms/shoulders and what were the results and implications from those studies?

- Study S176.1.011 (submitted in the current resubmission) was conducted in order to assess the transferability of Androgel 1.62% 5.0 g while covering the application sites (upper arms/shoulders) with T-shirts.
  - The study demonstrated transferability of Androgel 1.62% 5.0 g was mitigated by covering the application sites with T-shirts.
- Study S176.1.007 (submitted during the original review cycle; Dr. Sandhya Apparaju's review - DARRTS on October 26, 2009) was conducted in order to compare the total T exposure by applying Androgel 1.62% to upper arms/shoulders for 7 days vs. abdomen for 3 days and upper arms/shoulders for 4 days (representing the phase 3 application method).
  - The study demonstrated that the total T exposure from the application method of applying Androgel 1.62% to upper arms/shoulders for 7 days was bioequivalent

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to the total T exposure from the application method of applying Androgel 1.625 to abdomen for 3 days and upper arms/shoulders for 4 days.
    - The study demonstrated that the skin irritation by applying Androgel 1.62% to upper arms/shoulders for 7 days was comparable to the skin irritation by applying Androgel 1.62% to abdomen for 3 days and upper arms/shoulders for 4 days (Medical review by Dr. Roger Wiederhorn).
- The new proposed method of applying Androgel 1.62% to upper arms/shoulders is acceptable.

S176.1.011: An Open-Label Study of Serum T Levels in Non-dosed Females after Secondary Exposure to Androgel 1.62% Applied to the Upper Arms and Shoulders and Use of a T-shirt Barrier

- Study objective
    - To determine the PK of total T concentrations in female subjects after a single episode of skin contact with a male partner dosed with Androgel 1.62% (5.0 g).
    - To evaluate T transfer from males dosed with Androgel 1.62% (5.0 g) to non-dosed female subjects when contact with the upper arms/shoulders application site occurred at 2 hours post-dose with a T-shirt barrier.
- Study design
    - This study was a single center, single dose, open-label study in 12 healthy male and female volunteers. On Day 1, all male subjects applied Androgel 1.62% 5.0 g. Two hours following gel application to the male subjects, 15 minutes of supervised skin contact of the application site occurred between the dosed male and his non-dosed female partner as described below.
    - Males: Application of Androgel 1.62% to the upper arms/shoulders (2.5 g of gel applied to each the left and right upper arm/shoulder for a total dose of 5.0 g). The total time for measuring all incremental doses and application to the subject was less than 5 minutes. Following the last incremental gel application, subjects waited at least 5 minutes for the gel to dry before putting clothes over the gel application area.
    - Females: Skin contact with application site at 2 hours post-dose while males wore T-shirts.
    - Female subjects were given a tube top to wear to expose the shoulders and arms. Male subjects were given a long-sleeved 100% cotton T-shirt to cover the application site. Each couple engaged in a total of 15 minutes of contact. Female subjects were instructed to rub their hands, wrists, arms, and shoulders up and down the upper arms and shoulders of their male partner during the contact period. One minute periods of alternating active rubbing and resting of the female's arms on the male's shoulders occurred until the 15 minute time period was complete. After contact, female subjects waited at least 5 minutes prior to putting clothes over the exposed area. Female subjects were not allowed to take a shower or bathe until 24 hours after the contact period.
- PK measurements and blood samples
    - Whole blood samples (6 mL) were collected in red-top anticoagulant-free tubes from female subjects only for determination of total T, estradiol, and DHT at the following times:
        - Day -1 (baseline) at 0, 2, 4, 6, 8, 10, 12, 16, and 24 (pre-dose on Day1) hours with respect to the planned end time of skin contact on Day 1
        - Day 1 at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 16, 24, and 48 hours after the end of skin contact
- Results

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- The total T time-matched baseline (Day -1) concentrations across all females ranged from 5.9 to 63.6 ng/dL over the 24-hour measurement period. The total T concentrations across all females after contact with males on T-shirts (Day 1) ranged from 6.8 to 74.5 ng/dL over a 24 hour period.
- Based on the concentration-time profiles, mean T concentrations were similar on Day -1 and Day 1 (Figure 4 and Table 11). In addition, the total T concentration of females at 48 hours after the contact with males did not show any trend of decreasing total T compared to T profiles during the 24-hour following contact.
- Statistical comparison of total T exposure demonstrated that there were approximately 6 – 11 % increases of total T exposure in females following the contact with males (Table 12).

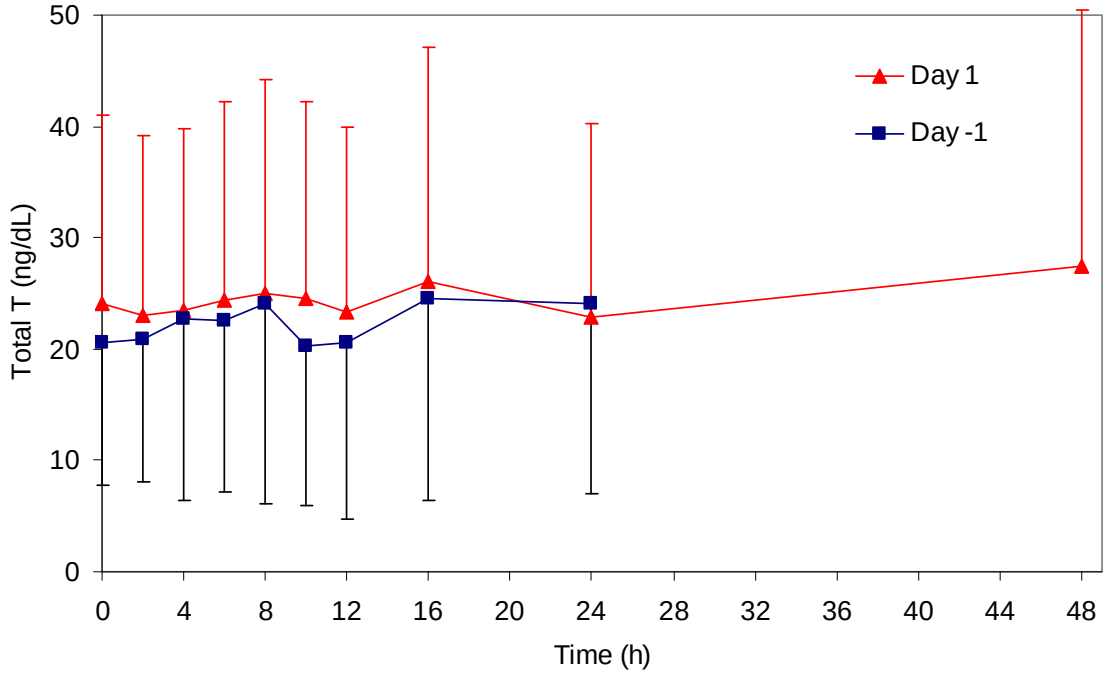

Figure 4 Mean (SD) Total T Concentrations of Females Before (Day-1) and After (Day 1) Contact with Males on T-Shirts; S176.1.011; N = 12

Table 11 Mean (SD) PK Parameters of Total T; S176.1.011

	Day	N	Arithmetic mean (SD)
C_{max} (ng/dL)	Day -1	12	26.4 (18.1)
	Day 1	12	29.5 (20.3)
AUC_{0-24} (ng·hr/dL)	Day -1	12	546.4 (387.2)
	Day 1	12	581.4 (430.8)
C_{avg} (ng/dL)	Day -1	12	22.8 (16.1)
	Day 1	12	24.2 (18.0)
*T_{max} (hr)	Day -1	12	16 (0-24)
	Day 1	12	90 (0-24)

*shown as median (range)

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Table 12 Statistical Comparison of PK Parameters of Total T; S176.1.011

	Day	N	Geometric mean	Geometric mean ratio (Day1/Day-1)	90% CI
C_{max} (ng/dL)	Day -1	12	21.5	1.11	0.99 – 1.25
	Day 1	12	23.9		
AUC_{0-24} (ng·hr/dL)	Day -1	12	443.1	1.06	0.98 – 1.15
	Day 1	12	470.0		
C_{avg} (ng/dL)	Day -1	12	18.5	1.06	0.98 – 1.15
	Day 1	12	19.6		

- Conclusion
  - C_{avg}, AUC and C_{max} of total T were similar between Day 1 and Day -1. The 90% CI of the Day 1/Day -1 ratio were within 80 to 125% for these PK parameters. Therefore, transfer of T to female subjects was prevented with a T-shirt barrier when males applied the 5.0 g Androgel 1.62% to the upper arms and shoulders.

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

The followings are from Clinical Pharmacology review by Dr. Sandhya Apparaju (DARRTS, October 26, 2009).

- Design
  - This study was a single center, open-label, randomized, three-way crossover study in 36 hypogonadal male volunteers. Subjects received 5.0 g of Androgel 1.62% once daily for each of three 7-day treatment regimens. There was a 5-day washout period between treatments. Dosing occurred once daily in the morning on Days 1-7, Days 12-18, and Days 23-29 as indicated by treatment randomization.
  - Treatment A: Once daily application of 5.0 g Androgel 1.62% to the abdomen, for 7 days. Treatment B: Once daily application of 5.0g Androgel 1.62% to the upper arms/shoulders for 7 days. Treatment C (reference): Once daily application of 5.0 g Androgel 1.62% to the abdomen for 3 days, followed by application to the upper arms/shoulders for 4 days.
- PK measurement and blood samples
  - Whole blood samples for measurement of T, DHT, and estradiol concentrations were collected at Baseline (Day -1), Days 1, 12, and 23, and Days 7, 18, and 29 for PK assessments; and Days 3-6, 14-17, and 25-28 for pre-dose assessments.
- Results
  - Achievement of steady-state: Graphical and statistical assessment of pre-dose concentrations demonstrate that steady-state was achieved by Day 2 post-dose in groups A (application to shoulders/upper arms only) and B (application to abdomen only). In case of treatment C (abdomen for 3 days, followed by shoulders/upper arms for 4 days), two different plateaus of trough concentrations are noted, one around Day 3 (abdominal application) and another around Day 6 (during shoulders/upper arms application). The trough levels during the first three days were lower compared to those seen during the last four days when

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drug was applied to shoulders/upper arms. Statistical analyses show steady-state achievement by Day 5.

- On Day 1 of treatment, serum total T concentrations rose from hypogonadal baseline concentrations to 'normal' (eugonadal; > 300 ng/dL) range within 2 hours of dosing with Androgel 1.62 % gel dose. Highest concentrations were observed with treatment B (shoulders/upper arms alone), while treatment groups A and C that employed the abdomen as drug application site on Day 1 demonstrated comparable systemic exposure on Day 1. Baseline-adjusted data demonstrated similar trends.
- On Day 7, systemic exposure was the lowest for the treatment group A (abdominal application), while it was comparable for the groups B and C, both of which utilized shoulders/upper arms (during the last 4 days for treatment C). Day 7 data suggested that steady systemic concentrations of T were relatively within the eugonadal range (300-1000 ng/dL).

Table 13 Mean PK Parameters of Total T on Day 7; S176.1.007

	Treatment	N	Geometric mean	Geometric mean ratio		90% CI
C_{max} (ng/dL)	A	31	610	A/B	0.61	0.54 – 0.69
	B	33	1000	B/C	1.06	0.94 – 1.20
	C	32	942	A/C	0.65	0.57 – 0.74
AUC_{0-24} (ng·hr/dL)	A	31	10500	A/B	0.66	0.60 – 0.72
	B	33	16000	B/C	1.04	0.95 – 1.14
	C	32	15400	A/C	0.68	0.62 – 0.75
C_{avg} (ng/dL)	A	31	437	A/B	0.66	0.60 – 0.72
	B	33	666	B/C	1.04	0.95 – 1.14
	C	32	642	A/C	0.68	0.62 – 0.75

A: Once daily application of Androgel 1.62% to abdomen for 7 days; B: Once daily application of Androgel 1.62% to upper arms/shoulders for 7 days; C: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days

- Conclusion
  - Study S176.1.007 (submitted during original review cycle) demonstrated that the total T exposure from the new application method (treatment B: upper arms/shoulder for 7 days) was bioequivalent to the total T exposure from the application method (treatment A; abdomen for 3 days and upper arms/shoulders for 4 days, Table 13).

2.2.4 How was the efficacy of Androgel 1.62% up to 1 year of treatment supported?

Sponsor submitted the data supporting the efficacy of Androgel 1.62% up to 1 year of treatment from the open-label period of the pivotal phase 3 clinical study, S176.3.104.

- Study design; open-label period:

Subjects who completed the initial 182-day portion of the study were eligible to enter the open-label extension period of the study for up to one year of total participation. On Day 182, subjects initially randomized to active therapy continued on the T dose from their Day 42 visit unless they required a titration. Titration scheme in open-label period was same as double-blind period based on C_{trough}. Subjects transitioning from active therapy had opportunities to titrate based on Days

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182, 196, 210, and 266 total T assessments where necessary. If a subject transitioning from active therapy did not require a titration on Day 182, then they were seen next on Days 224 and 266 without visits on Days 196 and 210.

Subjects transitioning from placebo were started on the 2.5 g dose and had three titration visits on Days 196, 210, and 266 which were required visits for subjects transitioning from placebo. Therefore, subjects transitioned from placebo had three visits (Days 196, 210, and 266) where titration could have occurred, while subjects transitioned from active could have three or four visits (Days 182, 224, and 266 OR Days 182, 196, 210, and 266) where titration could have occurred during the entire open-label period.

During open-label period, 24 hour PK assessments occurred on Days 266 and 364. Dose titration schemes during the open-label period and double-blind period were same.

- Results:

Primary endpoint: The % of subjects on active treatment within the normal serum T concentration range of 300-1000 ng/dL. In addition, the lower bound of the 95% CI was to be not less than 65% based on the Day 112 PK results for the pivotal phase of the trial.

In the Fully Analysis (FA; see 4.1 Individual Clinical Study Review for definition) samples on Days 266 and 364, the proportions of responders for the Continuing Active Androgel 1.62% group were 78.4 and 77.9%, respectively, suggesting the long term efficacy of Androgel 1.62% up to 1 year (Table 14). Although the proportion of responders for Formerly Placebo group was 69.2% on Day 266 (84 days after active treatment), it increased to 87% by Day 364 (182 days after active treatment).

Table 14 Number and Percentage of Subjects Achieving Target Range for T C_{avg} by Day 266 and Day 364 and Treatment in the FA Sample; Open-Label; S176.3.104

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

n: number of subjects achieving target T range; N: number of subjects with evaluable PK parameter for the given study day

Secondary endpoints: The individual total T C_{max} values were to be in the following ranges:
- $C_{max} \leq 1500$ ng/dL in $\leq 85\%$ of the subjects
- C_{max} between 1800-2500 ng/dL in $\leq 5\%$ of the subjects
- $C_{max} > 2500$ ng/dL in none of the subjects

The individual C_{max} results from the FA samples for Days 266 and 364 in Continuing Active Androgel 1.62% and Formerly Placebo arms were within the acceptable criteria during the open-label period of the study (Table 15).

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Table 15 Number and Percentage of Subjects Achieving C_{max} Range on Days 266, 364 and Overall; Open-Label; S176.3.104

	n/N (%) for Subjects Achieving T C_{max} range								
	Continuing Active Androgel 1.62%			Formerly Placebo			Total		
Day	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL
Overall	258/275 (93.8)	9/275 (3.3)	0 /275 (0.0)	45/49 (91.8)	2/49 (4.08)	0/49 (0.0)	303/324 (93.5)	11/324 (3.4)	0/324 (0.0)
266	131/139 (94.2)	5/139 (3.6)	0/139 (0.0)	24/26 (92.3)	2/26 (7.7)	0/26 (0.0)	155/165 (93.9)	7/165 (4.2)	0/165 (0.0)
364	127/136 (93.4)	4/136 (2.9)	0/136 (0.0)	21/23 (91.3)	0/23 (0.0)	0/23 (0.0)	148/159 (93.1)	4/159 (2.5)	0/159 (0.0)

For the overall results, n: number of observations and N: number of evaluable observations across all study days.
n: number of subjects achieving T C_{max} range; N: number of subjects with evaluable PK parameter for the given study day

2.3 Analytical Section

Serum T and DHT were determined using a ultra performance liquid chromatography (UPLC) with MS/MS method. Serum estradiol was determined using high performance liquid chromatography (HPLC) with MS/MS method. The method validation reports, LCMSC 260.6 v2 for T and DHT AND LCMSC 350.1 for estradiol, satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, May 2001).

	T	DHT	Estradiol
Type of Biological Fluid	Human serum	Human serum	Human serum
Range of Standard Curve	5.0 - 1000 ng/dL, R^2 = 0.9980	5.0 - 1000 ng/dL, R^2 = 0.9975	1.0 – 100 pg/mL
QC Sample Accuracy	< 5.4 %	< 6.08 %	< 7.54%
QC Sample Precision	< 8.0 %	< 9.33	< 6.7%
Recovery	> 95.8%	> 85%	> 88.8%
Stability	2045 days at -20°C	516 days at -20°C	1952 days at -20°C

Sensitivity: The accuracy and precision of the lowest calibration standards were lower than 20%. Therefore, the use of the level of the lowest calibration standard (5.0 ng/dL for T and DHT) as lowest limit of quantification was justified.

Selectivity: Blank surrogate matrix (0.5% albumin in phosphate buffered saline) samples showed adequate specificity. There were no other peaks shown at the retention times of the analytes or internal standards.

All human serum samples of studies S176.1.010 and S176.1.011 analyzed for the content of T and DHT according to the validated method validation report, LCMSC 260.6 v2. In addition, all human serum samples of studies S176.1.010 and S176.1.011 analyzed for the content of estradiol according to the validated method validation report, LCMSC 350.1.

3 Detailed Labeling Recommendations

This section will be added later.

4 Appendix

4.1 Individual Clinical Study Review

S176.1.010: A Multiple Dose PK and Comparative Bioavailability Study of T Absorption after Administration of 5.0 g Androgel 1.62% to the Upper Arms/Shoulders and Abdomen using an Application Site Rotation or a Combination of Application Sites in Hypogonadal Males

- Study objective
  - To determine the multiple dose PK of T after administration of 5.0 g Androgel 1.62% in hypogonadal males.
  - To determine the relative bioavailability of T after administration of 5.0 g Androgel 1.62% using an application site rotation between the upper arms/shoulders and abdomen or both upper arms/shoulders and abdomen.
- Study design
  - This was a phase I, open-label, randomized, two-treatment, two-period, crossover study in 62 hypogonadal males (18 - 80 years old). The total duration of the study was approximately 24 days, not including the screening period. Subjects who consented to participate in this study and met the inclusion/exclusion criteria underwent two sequential treatment periods in a randomized order. Each treatment period included baseline PK sample collections. There was a one week washout between treatments. The overall study design is presented in Figure 5.

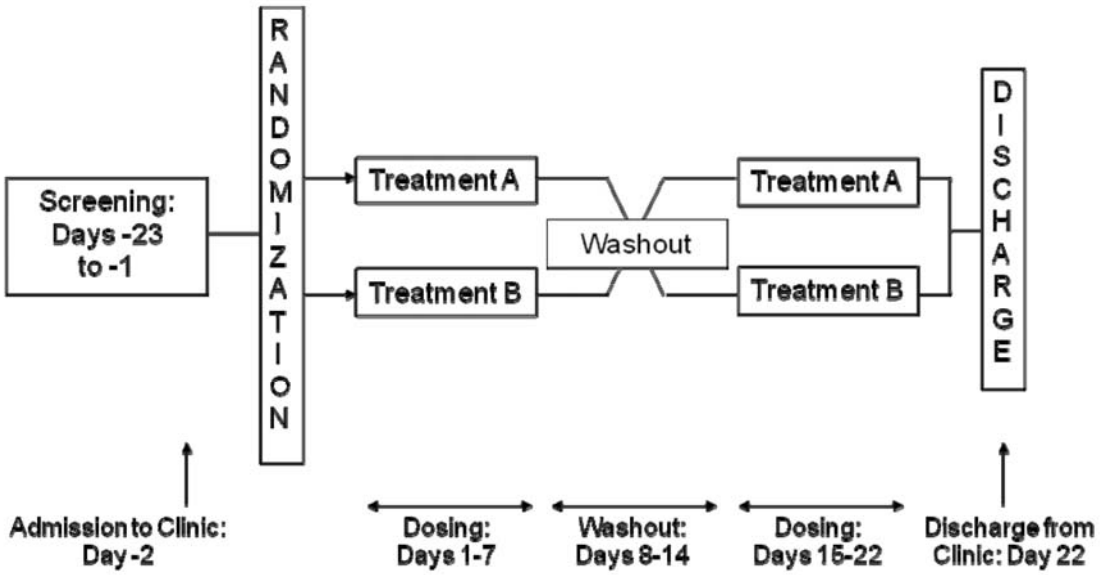

Figure 5 Study design; S176.1.010

  - Two treatments
    - Treatment A: Once daily application of Androgel 1.62% to the abdomen for 3 days (2.5 g to each the right and left side of the abdomen) followed by application to the upper arms/shoulders (2.5 g to each the right and left upper arm/shoulder) for 4 days. The total daily gel dose was 5.0 g.

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Application method of Androgel 1.62% in treatment A is same as in pivotal phase 3 study (S176.3.104).

- Treatment B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days. The total daily gel dose was 5.0 g consisting of 1.25 g applied to the left upper arm/shoulder, 1.25 g applied to the right upper arm/shoulder, 1.25 g applied to the left abdomen and 1.25 g applied to the right abdomen.

- Study drug formulation
  - The investigational product is a Androgel 1.62% manufactured by Abbott Products, Inc. (formerly Solvay Pharmaceuticals, Inc.). Androgel 1.62% is dispensed via a multi-dose pump capable of dispensing 75.0 g (or 60 metered 1.25 g doses).
- Disposition of subjects
  - N = 62, subject consented and allocated to treatment A or B
    - *Most (60/62) subjects completed the study without protocol deviations related to dosing.*
    - *There were 2/62 subjects with protocol deviations related to dosing.*
      - *ID 27523: On Day 1 with treatment B, Androgel 1.62% was applied to right upper arm in error instead of right side of abdomen.*
        - *Observed AUC ratio for treatment B/A was 0.90 (21224 ng·h/dL / 23661 ng·h/dL) which was higher than ratio of least squares mean AUC for treatment B/A, 0.84 (Table 18).*
        - *Baseline adjusted AUC ratio for treatment B/A was 0.85 (13214 ng·h/dL / 15484 ng·h/dL) which was higher than ratio of least squares mean AUC for treatment B/A, 0.67 (Table 20).*
      - *ID 27544: On Day 1 with treatment B, subject rubbed Androgel 1.62% for right side of abdomen across both sides of abdomen.*
        - *Observed AUC ratio for treatment B/A was 1.24 (10025 ng·h/dL / 8066 ng·h/dL) which was higher than ratio of least squares mean AUC for treatment B/A, 0.84 (Table 18).*
        - *Baseline adjusted AUC ratio for treatment B/A was 1.92 (3515 ng·h/dL / 1829 ng·h/dL) which was higher than ratio of least squares mean AUC for treatment B/A, 0.67 (Table 20).*
      - *Although there were protocol violations by these two subjects (ID 27523 & ID 27544), there is no need for recalculation of AUC ratio for treatment B/A, since recalculation excluding these two subjects would reduce the ratio of least square mean AUC even further, which again supports the reviewer's conclusion that the new application method (treatment B) exhibits lower exposure than phase 3 method (treatment A).*
    - *There were 17 subjects with protocol deviations not related to dosing. This reviewer considers these protocol violations not to affect the PK results. These protocol violations are as following: late (3-8 minutes) blood sampling, missing vital signs, and missing time of application site evaluation.*
- Inclusion criteria
  - Documentation of written informed consent was received. The subjects had adequate written and oral fluency to understand the informed consent and converse with the investigator in the language in which the informed consent was written.

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- Male subjects with 18 - 80 years of age
- Serum total T < 300 ng/dL. Documented lab result was obtained during screening visit, within 6 weeks of Day -2 for subjects not currently on androgen replacement therapy, or following washout of androgen replacement therapy.
- Subjects were naive to androgen replacement or washout of 16 weeks following intramuscular androgen injections; 4 weeks following topical or buccal androgens; and 3 weeks following oral androgens.
- Subjects had a BMI of 20 - 35 kg/m^2, inclusive.
- In the opinion of the investigator the subject was determined otherwise healthy by vital signs, medical history, physical exam, electrocardiogram (ECG), and laboratory examination (hematology, clinical chemistry, and urinalysis).

- Exclusion criteria
  - Participants in any investigational drug trial within the previous 30 days.
  - Receipt of any prescription medication within 21 days prior to Day -2 of the study or receipt of non-prescription medication within 7 days of Day -2 without Sponsor approval. Volunteers on a stable medication regimen (> 3 months) for hypertension, hyperlipidemia, blood glucose control, or other conditions were evaluated on a case by case basis.
  - Blood or plasma donation within the 60 days previous to Day -2.
  - Volunteers with any clinical/biochemical impairment of liver function or receipt of known hepatic enzyme inducing or inhibitory agents within 60 days prior to Day -2.
  - Use of any drug with a half-life greater than 24 hours in the past 6 months prior to Day -2 without Sponsor approval.
  - Volunteers who were smokers or ex-smokers who had quit smoking for a period of less than 12 months prior to Day -2.
  - Consumption of caffeine containing products or beverages in excess of 5 cups/cans of coffee, tea or cola per day, or any consumption of caffeine containing products or beverages within 24 hours of Day -2 (caffeine containing products was not allowed during each study period).
  - Findings of any kind of lesions (e.g. ulcer, erosion, lichenification, crust, inflammation) on the skin surface of the application site during physical examination (small tattoos were acceptable).
  - Previous history of, or current or suspected, prostate or breast cancer.
  - Untreated prolactinoma.
  - Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
  - Previous history of, or current or suspected, eczema or psoriasis.
  - Abnormal digital rectal examination (DRE) defined as presence of nodule or induration.
  - International Prostate Symptom Score (IPSS) > 15.
  - Baseline prostate specific antigen (PSA) > 2.5 ng/mL.
  - Positive screen for alcohol or drugs of abuse.
  - Positive human immunodeficiency virus (HIV) or Hepatitis B/C.
  - Hematocrit > 48% or hemoglobin > 16 g/dL.
  - Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.
- Dosing conditions
  - Dose application for each subject occurred at the same time each treatment day in the morning (ranging from 7:00 a.m. to 9:13 a.m.) under supervision of the

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clinical research staff. The study drug was applied in 1.25 g increments until the total 5.0 g dose had been reached as described in detail below.

- On each dosing day (Days 1-7 and Days 15-21), within 30 minutes prior to the targeted time of dose application, subjects showered and washed the application site with soap and water. Subjects were not allowed to remain in the shower for longer than 10 minutes. The designated area for gel application was thoroughly dried. Subjects did not shower again until the next morning.
- Site personnel directly involved with the dosing procedures wore gloves when handling the study gel. A fresh pair of gloves was used for each male subject. Each incremental gel dose of 1.25 g +/- 0.02 g was weighed on a sheet of weighing paper on a balance. The exact weight was recorded in the source documentation. Immediately after measuring the appropriate amount of gel, the weighing paper with the measured gel dose was wiped directly onto the subject's designated site of application by the study personnel. The subject then rubbed the product into the skin of the designated application site using his hand. The gel should not have been rubbed or massaged excessively. This process was repeated until the total 5.0 g dose had been reached.

- PK measurements and blood samples
  - Whole blood samples (6 mL) were collected in anticoagulant-free tubes for determination of total T, DHT, and estradiol at the following times:
    - Day -1 and Day 14 (baseline): 0, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours with respect to the projected time of T administration
    - Days 7 and 21: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose
    - Days 5, 6, 19, 20: pre-dose
- Demographics

	Treatment A/B	Treatment B/A	All
Age (years)			
Mean (SD)	46.9 (10.7)	47.8 (8.9)	47.4 (9.8)
Range	29 - 72	33-74	29-74
Race, n (%)			
White	29 (93.5)	28 (90.3)	57 (91.9)
Black	2 (6.5)	3 (9.7)	5 (8.1)
American Indian or Alaska native	0 (0)	1 (3.2)	1 (1.6)
Ethnicity, n (%)			
Hispanic or Latino	28 (90.3)	28 (90.3)	56 (90.3)
Not Hispanic or Latino	3 (9.7)	3 (9.7)	6 (9.7)
Body weight (kg)			
Mean (SD)	87.0 (13.5)	81.2 (10.5)	84.1 (12.4)
Range	61.1 – 117.3	63.0 – 101.8	61.1 – 117.3
Height (cm)			
Mean (SD)	171.3 (8.9)	170.7 (5.6)	171.0 (7.4)
Range	157 - 191	159 - 181	157 – 191
BMI (kg/cm^2)			
Mean (SD)	29.5 (3.1)	27.8 (3.1)	28.7 (3.2)
Range	23.0 – 34.9	21.2 – 34.6	21.2 – 34.9

- Results

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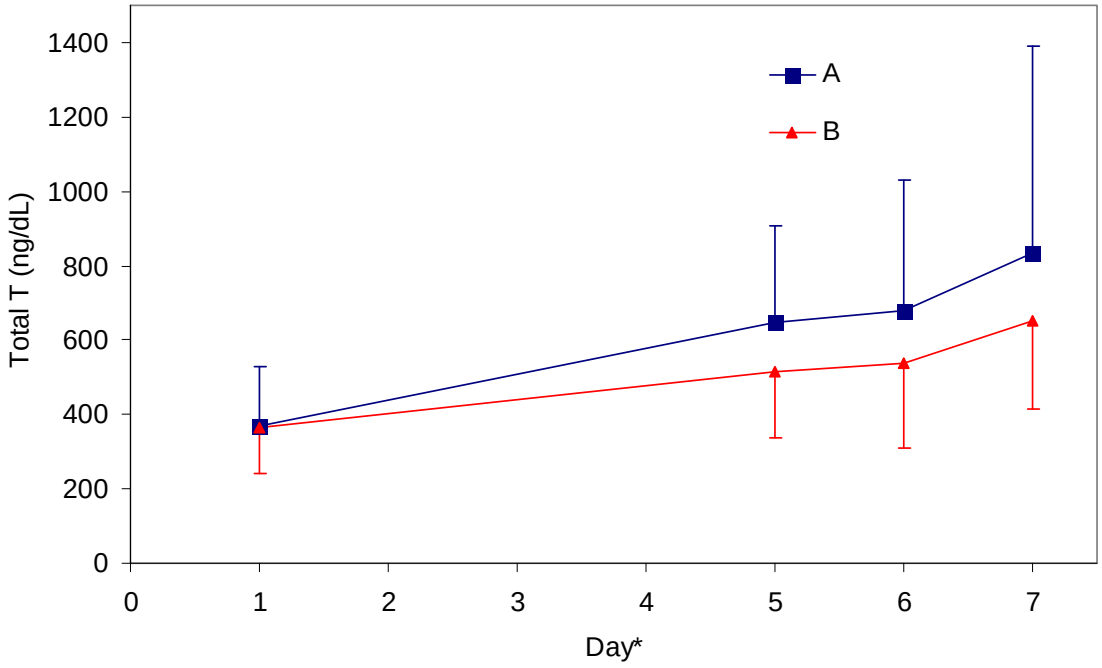

Figure 6 Arithmetic Mean (SD) Serum Trough Concentrations of Total T in Two Treatment Groups; S176.1.010; N (A) = 62, N (B) = 62
*Day: Day represents time since treatment A or B began.
A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

Table 16 Arithmetic Mean (SD) Serum Trough Concentrations of Total T in Two Treatment Groups; S176.1.010; N (A) = 62, N (B) = 62

		Day, Arithmetic mean (SD)			
		1	5	6	7
Treatment	A	371 (158)	646 (264)	681 (350)	834 (555)
	B	366 (125)	517 (180)	537 (227)	651 (238)

*Day: Day represents time since treatment A or B began.
A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

Mean T trough concentrations on Days 1, 5, 6, 7 were 371, 646, 681, and 834 ng/dL for treatment A AND 366, 517, 537, and 651 ng/dL for treatment B (Figure 6 and Table 16). Visual assessment suggested that the mean T trough concentrations were stable between Days 5 and 6. The mean T trough concentrations increased 22% (153/681 ng/dL) and 18% (114/537) from Days 6 to 7 in treatments A and B respectively, these increases were within the SD of each treatment on Days 6 and 7 (treatment A: 350 ng/dL (Day 6) and 555 ng/dL (Day 7) AND treatment B: 227 ng/dL (Day 6) and 238 ng/dL (Day 7)). It appeared that the steady state reached within 5-7 days after starting daily application of Androgel 1.62%.

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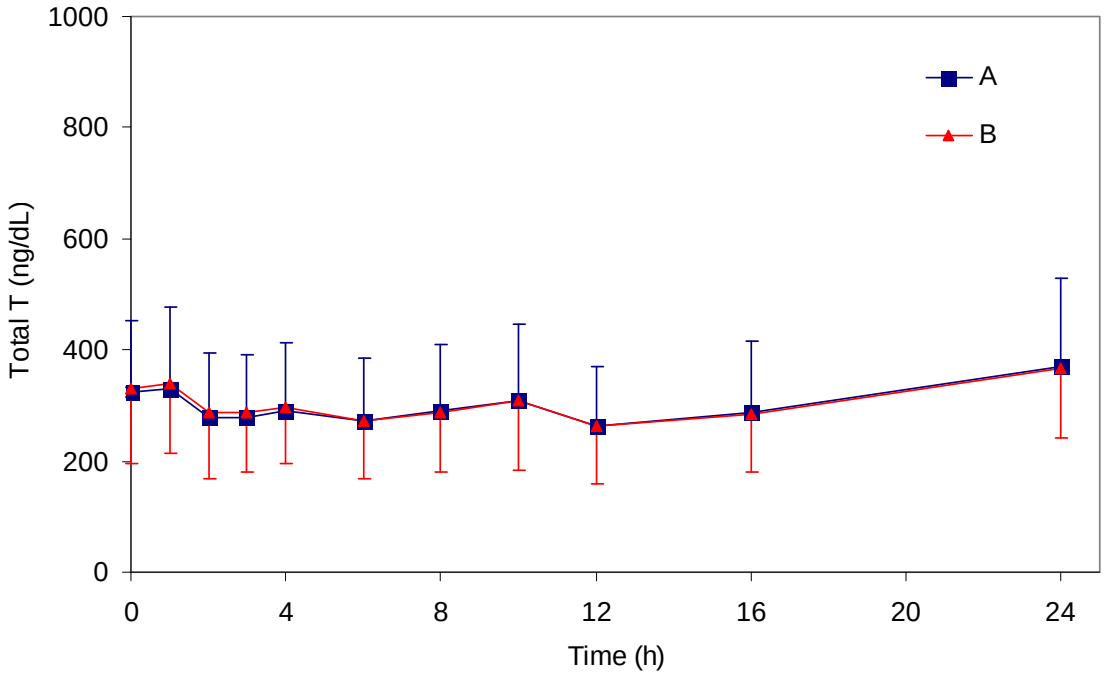

Figure 7 Arithmetic Mean (SD) Serum Concentrations of Baseline Total T in Two Treatment Groups; S176.1.010; N (A) = 62, N (B) = 62
A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

Mean baseline (Days -1 and 14) concentrations of T ranged from 263- 371 ng/dL for treatment A and 262 - 338 ng/dL for treatment B (Figure 7), representing values close to the lower end of the eugonadal range (e.g. 300-1000 ng/dL).

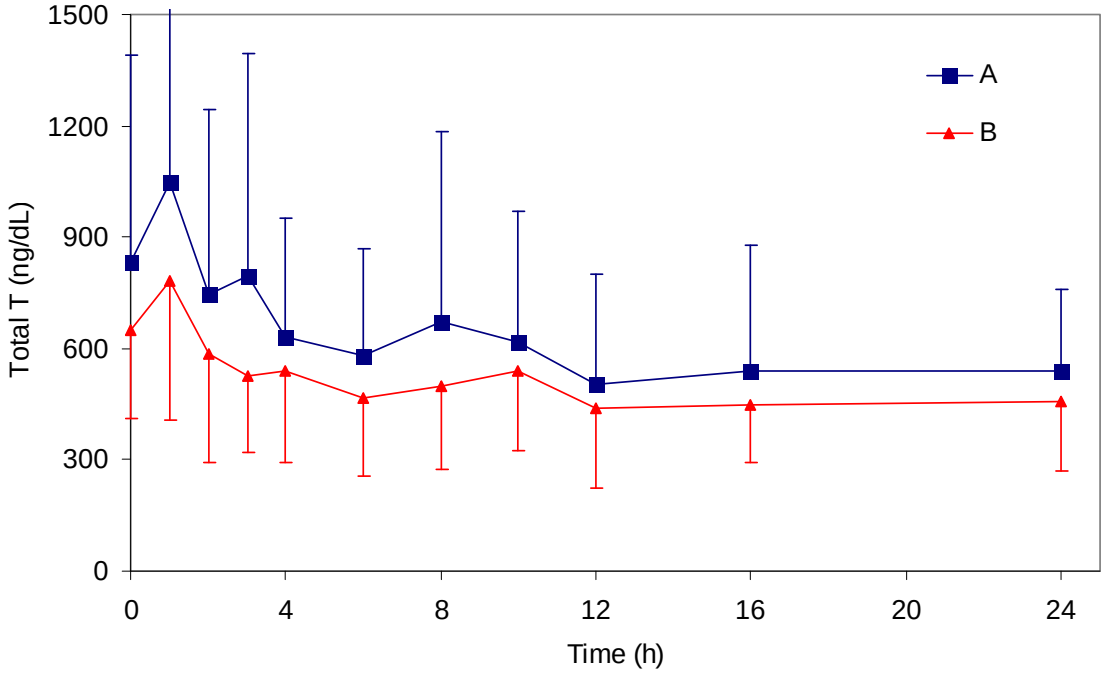

Figure 8 Arithmetic Mean (SD) Serum Concentrations of Total T in Two Treatment Groups after 7 Days of Once Daily Application of Androgel 1.62%; S176.1.010; N (A) = 62, N (B) = 62

A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

The mean concentration-time profile for treatment B was lower than treatment A (Figure **8**).

Table 17 Arithmetic Mean (SD) PK Parameters of Total T; S176.1.010

	Treatment	N	Arithmetic mean (SD)
C_{max} (ng/dL)	A	62	1283 (817)
	B	62	866 (369)
AUC_{0-24} (ng·hr/dL)	A	62	14433 (5880)
	B	62	11817 (3981)
C_{avg} (ng/dL)	A	62	601 (245)
	B	62	492 (166)
*T_{max} (hr)	A	62	1 (0-24)
	B	62	1 (0-24)

*shown as median (range)

A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

Table 18 Statistical Comparison of PK Parameters of Total T; S176.1.010

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

A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

Table 19 Arithmetic Mean (SD) PK Parameters of Baseline-Adjusted Total T; S176.1.010

	Treatment	N	Arithmetic mean (SD)
C_{max} (ng/dL)	A	62	1000 (833)
	B	62	578 (380)
AUC_{0-24} (ng·hr/dL)	A	62	7891 (5578)
	B	62	5270 (3647)
C_{avg} (ng/dL)	A	62	329 (232)
	B	62	220 (152)
*T_{max} (hr)	A	62	1 (0-24)
	B	62	1 (0-24)

*shown as median (range)

A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

Table 20 Statistical Comparison of PK Parameters of Baseline-Adjusted Total T; S176.1.010

	Treatment	N	Geometric mean	Geometric mean ratio (B/A)	90% CI
C_{max} (ng/dL)	A	62	752	0.63	0.53 – 0.74
	B	62	471		
AUC_{0-24} (ng·hr/dL)	A	62	6092	0.67	0.57 – 0.80
	B	62	4094		
C_{avg} (ng/dL)	A	62	254	0.67	0.57 – 0.80
	B	62	171		

A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

The geometric mean ratio for AUC and C_{max} of T demonstrated that AUC and C_{max} for treatment B was approximately 16% and 27% lower than treatment A, respectively (Table 9). These mean

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differences are even greater with the geometric mean ratio for AUC and C_{max} of baseline-adjusted T, 33% and 37% respectively. (Table 20).

- Since the primary endpoint used to assess the efficacy of Androgel 1.62% product is based on T concentrations, following estimation of dose based on exposure comparison is made based on the results from the T concentration (Table 18).
- The estimated dose to exhibit 16% (AUC comparison of total T, Table 18) lower exposure than exposure from 5.0 g dose equals to 4.2 g.
    - Dose linearity is supported by study S176.1.002 (original review cycle).

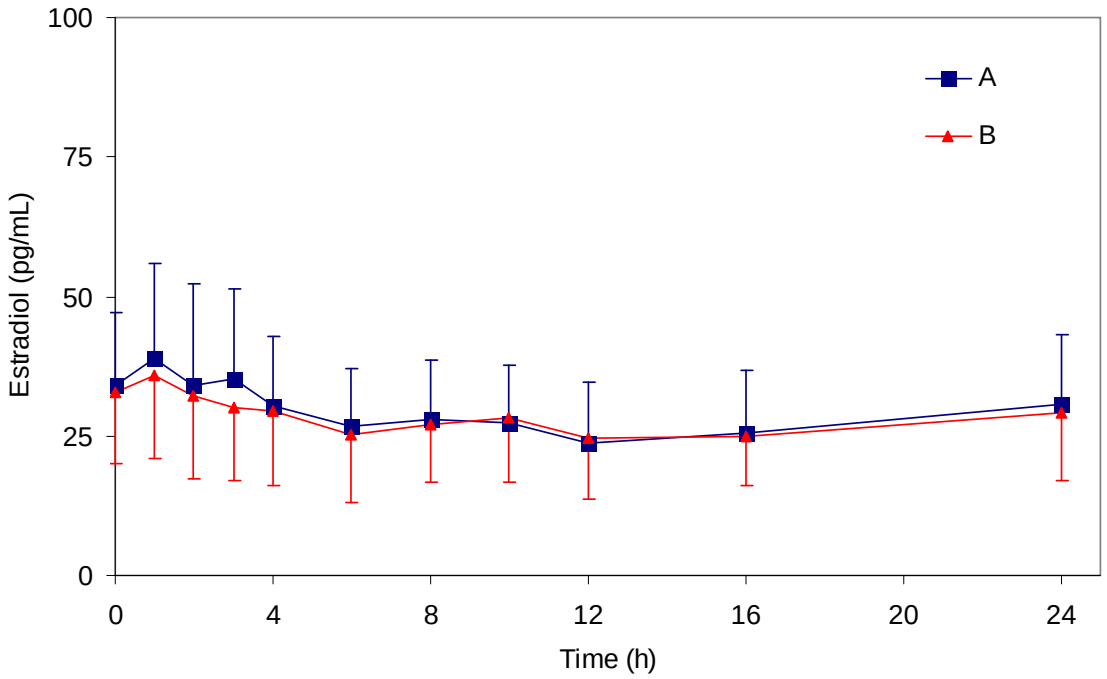

Figure 9 Arithmetic Mean (SD) Serum Concentrations of Estradiol in Two Treatment Groups after 7 Days of Once Daily Application of Androgel 1.62%; S176.1.010; N (A) = 62, N (B) = 62

A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

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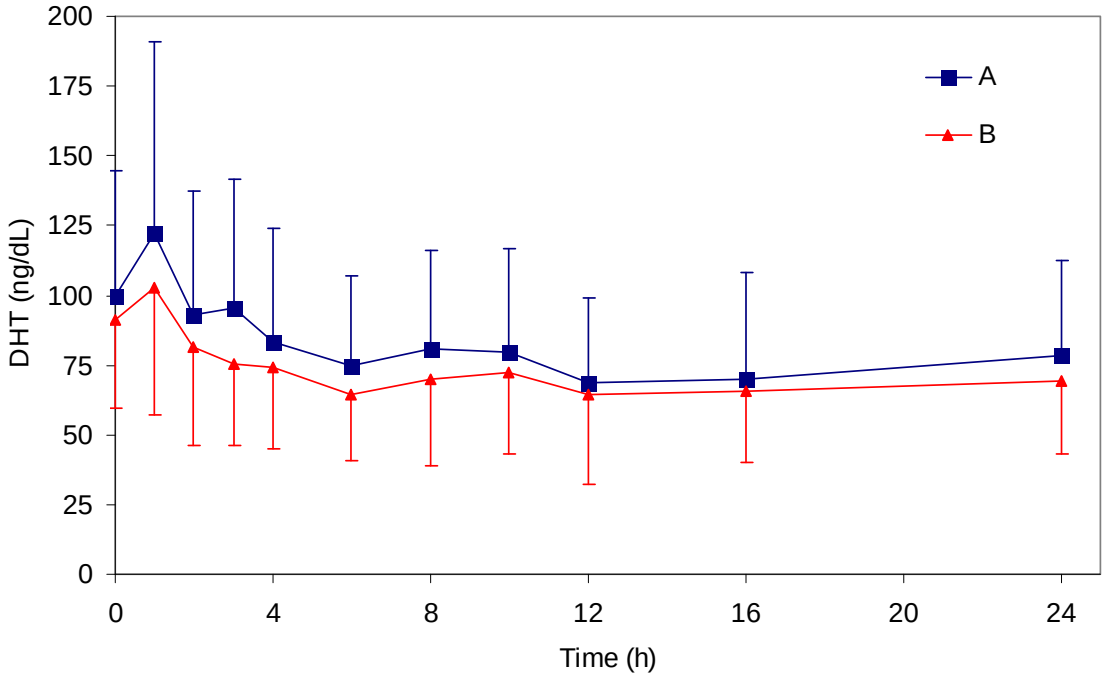

Figure 10 Arithmetic Mean (SD) Serum Concentrations of DHT in Two Treatment Groups after 7 Days of Once Daily Application of Androgel 1.62%; S176.1.010; N (A) = 62, N (B) = 62

A: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days; B: Once daily application of Androgel 1.62% to both upper arms/shoulders and abdomen for 7 days

Concentrations of estradiol ranged from 23.6 to 38.8 pg/mL and 24.7 to 35.9 pg/mL after 7 days of once daily application in treatments A and B, respectively (Figure 9). Concentrations of DHT ranged from 68.5 to 122.0 ng/dL and 64.2 to 103.0 ng/dL after 7 days of once daily application in treatments A and B, respectively (Figure 10). Mean estradiol (Figure 9) and DHT (Figure 10) concentration-time profiles followed the same general pattern as the total T concentration data (Figure 3) and were comparable between treatments.

- Conclusion
  - The new application method, treatment B (both upper arms/shoulders AND both sides of the abdomen) can potentially reduce the exposure of 5g dose to the estimated exposure of 4.2 g dose (by phase 3 application method) leading to reduced efficacy; hence the use of new application method, treatment B (both upper arms/shoulders AND both sides of the abdomen) is not supported by study S176.1.010.

<u>S176.1.011: An Open-Label Study of Serum T Levels in Non-dosed Females after Secondary Exposure to Androgel 1.62% Applied to the Upper Arms and Shoulders and Use of a T-shirt Barrier</u>

- Study objective
  - To determine the PK of total T concentrations in female subjects after a single episode of skin contact with a male partner dosed with Androgel 1.62% (5.0 g).

- To evaluate T transfer from males dosed with Androgel 1.62% (5.0 g) to non-dosed female subjects when contact with the upper arms/shoulders application site occurred at 2 hours post-dose with a T-shirt barrier.

- Study design
  - This study was a single center, single dose, open-label study in healthy male and female volunteers. Twelve male-female couples who consented to participate in this study and met the inclusion/exclusion criteria were enrolled into the study. All male-female couples enrolled underwent the same dose and skin contact procedures. On Day 1, all male subjects applied Androgel 1.62%. Two hours following gel application to the male subjects, 15 minutes of supervised skin contact of the application site occurred between the dosed male and his non-dosed female partner as described below.
  - Males: Application of Androgel 1.62% to the upper arms/shoulders (2.5 g of gel applied to each the left and right upper arm/shoulder for a total dose of 5.0 g). The total time for measuring all incremental doses and application to the subject was less than 5 minutes. Following the last incremental gel application, subjects waited at least 5 minutes for the gel to dry before putting clothes over the gel application area.
  - Females: Skin contact with application site at 2 hours post-dose while males wear T-shirts.
  - Female subjects were given a tube top to wear to expose the shoulders and arms. Male subjects were given a long-sleeved 100% cotton T-shirt to cover the application site. Each couple engaged in a total of 15 minutes of contact. Female subjects were instructed to rub their hands, wrists, arms, and shoulders up and down the upper arms and shoulders of their male partner during the contact period. One minute periods of alternating active rubbing and resting of the female's arms on the male's shoulders occurred until the 15 minute time period was complete. After contact, female subjects waited at least 5 minutes prior to putting clothes over the exposed area. Female subjects were not allowed to take a shower or bathe until 24 hours after the contact period.
- Study drug formulation
  - The investigational product is a Androgel 1.62% manufactured by Abbott Products, Inc. (formerly Solvay Pharmaceuticals, Inc.). Androgel 1.62% is dispensed via a multi-dose pump capable of dispensing 75.0 g (or 60 metered 1.25 g doses).
- Disposition of subjects
  - 12 couples (12 males and 12 females) were enrolled and finished the study.

  No protocol deviations pertained to study conduct including inclusion/exclusion criteria and PK sample collection occurred.
- Inclusion criteria
  - Males
    - Documentation of written informed consent. The subject must have had adequate written and oral fluency to understand the informed consent and converse with the investigator in the language in which the informed consent is written.
    - Male subjects 18 - 80 years of age, inclusive.
    - Subjects with a Body Mass Index of 20-35 kg/m2, inclusive.
    - In the opinion of the investigator, the subject was determined to be in good health as determined by vital signs, medical history, physical exam, electrocardiogram (ECG), and laboratory examination (hematology, clinical chemistry, and urinalysis).

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        - Negative hepatitis B/C and HIV.
    - Females
        - Documentation of written informed consent. The subject must have had adequate written and oral fluency to understand the informed consent and converse with the investigator in the language in which the informed consent is written.
        - Female subjects 18 - 80 years of age, inclusive.
        - In the opinion of the investigator, the subject was determined to be in good health as determined by vital signs, medical history, physical exam, ECG, and laboratory examination (hematology, clinical chemistry, and urinalysis).
        - Subjects with a Body Mass Index of 20-30 kg/m2, inclusive.
        - Subjects with a screening T in the normal range, as specified by the normal range at the testing facility.
        - Negative hepatitis B/C and HIV.
- Exclusion criteria
    - Males
        - Positive screen for alcohol or drugs of abuse.
        - Subject with a hematocrit > 48%.
        - Previous history of, or current or suspected, prostate or breast cancer.
        - Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
        - Findings of any kind of lesions (e.g. ulcer, erosion, lichenification, crust, inflammation) on the skin surface of the upper arms/shoulders during physical examination (small tattoos are acceptable).
        - Participants in any investigational drug trial within the previous 30 days.
        - Receipt of any prescription medication within 21 days prior to Day -2 of the study or receipt of non-prescription (over-the-counter (OTC)) medication within 7 days of Day -2 without sponsor approval.
        - Subjects who smoked or used other nicotine products within the past 12 months.
        - Consumption of caffeine-containing products or beverages in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day -2 (caffeine-containing products were not to be allowed during each study period).
        - Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.
        - Baseline Prostate Specific Antigen (PSA) > 2.5 ng/mL. If the subject had documentation of a negative prostate biopsy within the past six months, a PSA of 2.6 - 3.74 ng/mL was to be allowed.
        - Abnormal digital rectal examination (DRE) defined as presence of nodule or induration.
        - Untreated prolactinoma.
        - Previous history of, or current or suspected, eczema or psoriasis.
    - Females
        - Subjects who were pregnant or lactating.
        - Subjects of child-bearing potential who were not using an acceptable method of birth control. Barrier methods of birth control (i.e., diaphragm/condom with spermicide) were to be acceptable for study participation. Oral or implanted contraceptives were to be unacceptable

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methods of birth control for study participation. Female subjects who were surgically sterile may have been enrolled.
        - Previous history of, or current or suspected, hirsutism.
        - Participants in any investigational drug trial within the previous 30 days.
        - Positive screen for alcohol or drugs of abuse.
        - Receipt of any prescription medication within 21 days prior to entry into the study, or receipt of non-prescription medication or herbal products within 7 days of study commencement without sponsor approval.
        - Blood or plasma donation within the 60 days prior to study entry.
        - Subjects with any clinical/biochemical impairment of liver function or receipt of known hepatic enzyme inducing or inhibitory agents within 90 days prior to entry into study.
        - Use of any drug with a half-life greater than 24 hours in the past 6 months without Sponsor approval.
        - Subjects who smoked or used other nicotine products within the past 12 months.
        - Consumption of caffeine-containing products or beverages in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day -2 (caffeine-containing products were not to be allowed during each study period).
        - Findings of any kind of lesions (e.g. ulcer, erosion, lichenification, crust, inflammation) on the skin surface of the upper arms/shoulders during physical examination (small tattoos were to be acceptable).
        - Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments, and ECG.
        - Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
        - Previous history of, or current or suspected, eczema or psoriasis.
- Dosing conditions
    - Application of Androgel 1.62% to males' upper arms/shoulders (2.5 g of gel applied to each the left and right upper arm/shoulder for a total dose of 5.0 g) between 9:45 a.m. and 10:35 a.m.
        - The first 1.25 g was applied to one shoulder and spread across the maximum surface area.
        - The second 1.25 g was applied to the opposite shoulder and spread across the maximum surface area without re-applying gel to the previously dosed area.
        - The third 1.25 g was applied to one of the upper arms, from the edge of the shoulder region to just above the elbow and including the back of the arm, spread over the maximum surface area without re-applying gel to the previously dosed areas.
        - The fourth 1.25 g was applied to the opposite upper arm area as described above without re-applying gel to the previously dosed areas.
- PK measurements and blood samples
    - Whole blood samples (6 mL) were collected in red-top anticoagulant-free tubes from female subjects only for determination of total T, estradiol, and DHT at the following times:
    - Day -1 (baseline) at 0, 2, 4, 6, 8, 10, 12, 16, and 24 (pre-dose on Day1) hours with respect to the planned end time of skin contact on Day 1
    - Day 1 at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 16, 24, and 48 hours after the end of skin contact

- Demographics

	Female	Male
Age (years) Mean (SD) Range	 40.3 (13.3) 21 - 59	 41.9 (6.4) 29 -52
Race, n (%) White Black American Indian or Alaska native	 12 (100) 0 (0) 0 (0)	 10 (83.3) 2 (16.7) 0 (0)
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino	 12 (100) 0 (0)	 12 (100) 0 (0)
Body weight (kg) Mean (SD) Range	 67.4 (5.7) 59.7 – 76.0	 83.2 (8.9) 69.4 – 105.2
Height (cm) Mean (SD) Range	 160.3 (4.6) 150 - 168	 171.3 (6.6) 163 – 184
BMI (kg/cm^2) Mean (SD) Range	 26.3 (2.5) 22.5 – 30.0	 28.4 (2.2) 22.7 – 31.1

- Results

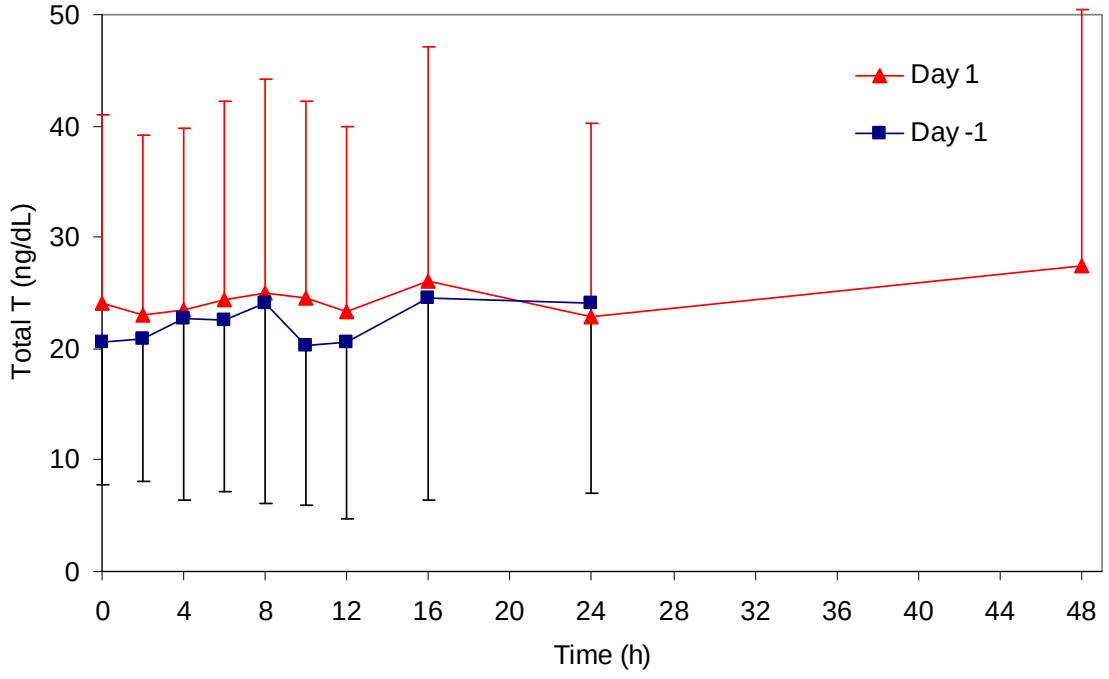

Figure 11 Mean (SD) Total T Concentrations of Females Before (Day-1) and After (Day 1) Contact with Males on T-Shirts; S176.1.011; N = 12

The total T baseline (Day -1) concentrations across all females ranged from 5.9 to 63.6 ng/dL over the 24-hour measurement period. The total T concentrations across all females after contact with males on T-shirts (Day 1) ranged from 6.8 to 74.5 ng/dL over a 24 hour period of 0 to 90 ng/dL. Based on the concentration-time profiles, mean T concentrations were similar on Day -1

and Day 1. In addition, the total T concentration of females at 24 and 48 hours following contact with males were similar (22.9 and 27.4 ng/dL). Therefore, covering T application site of males with T-shirts seemed to prevent the transfer of T to females following contact with males.

Table 21 Mean (SD) PK Parameters of Total T; S176.1.011

	Day	N	Arithmetic mean (SD)
C_{max} (ng/dL)	Day -1	12	26.4 (18.1)
	Day 1	12	29.5 (20.3)
AUC_{0-24} (ng·hr/dL)	Day -1	12	546.4 (387.2)
	Day 1	12	581.4 (430.8)
C_{avg} (ng/dL)	Day -1	12	22.8 (16.1)
	Day 1	12	24.2 (18.0)
*T_{max} (hr)	Day -1	12	16 (0-24)
	Day 1	12	90 (0-24)

*shown as median (range)

Table 22 Statistical Comparison of PK Parameters of Total T; S176.1.011

	Day	N	Geometric mean	Geometric mean ratio (Day1/Day-1)	90% CI
C_{max} (ng/dL)	Day -1	12	21.5	1.11	0.99 – 1.25
	Day 1	12	23.9		
AUC_{0-24} (ng·hr/dL)	Day -1	12	443.1	1.06	0.98 – 1.15
	Day 1	12	470.0		
C_{avg} (ng/dL)	Day -1	12	18.5	1.06	0.98 – 1.15
	Day 1	12	19.6		

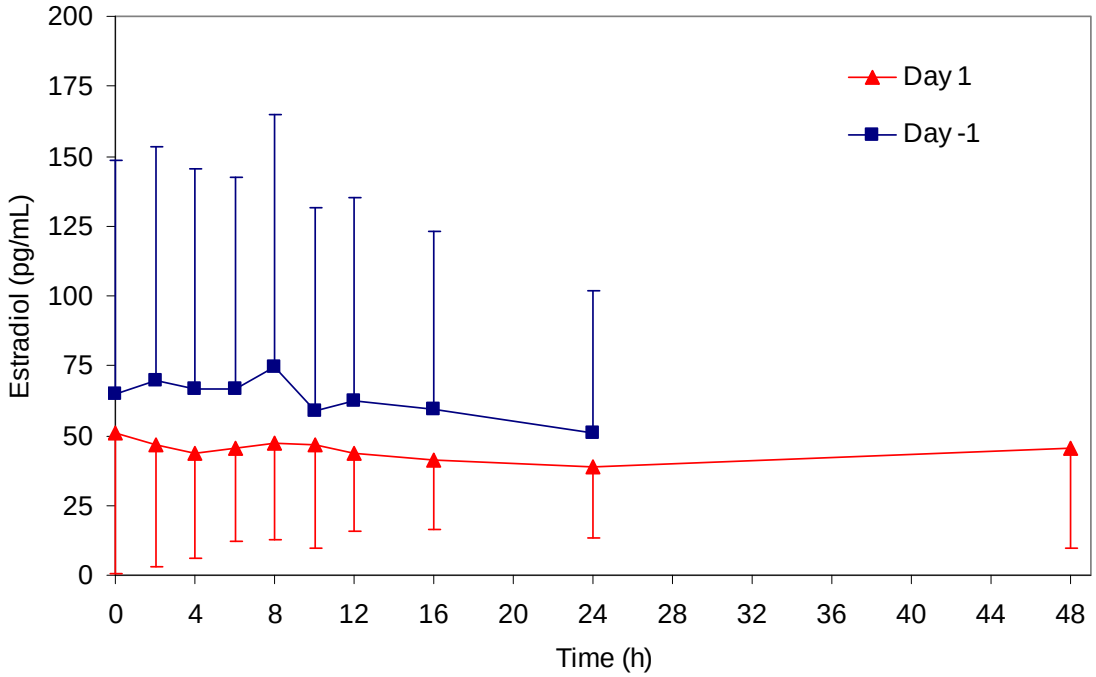

Figure 12 Mean (SD) Estradiol Concentrations of Females Before (Day-1) and After (Day 1) Contact with Males on T-Shirts; S176.1.011; N = 12

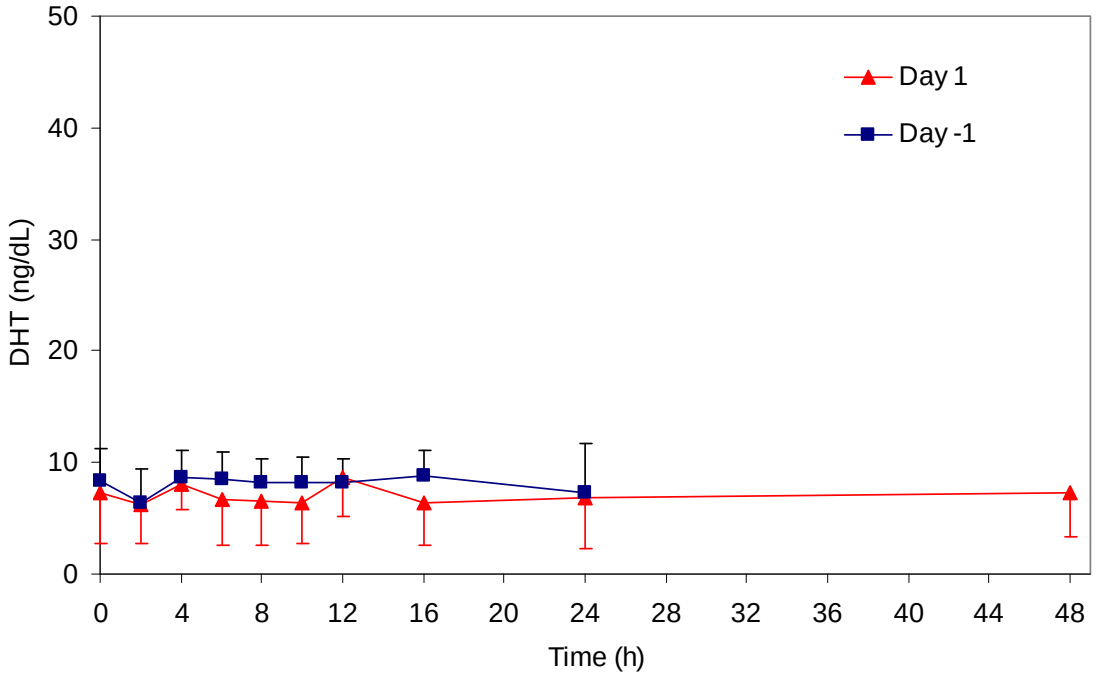

Figure 13 Mean (SD) DHT Concentrations of Females Before (Day-1) and After (Day 1) Contact with Males on T-Shirts; S176.1.011; N = 12

Reference ID: 2937578

The difference of mean estradiol concentrations in each time point was within the range of SD of each corresponding time point. Therefore, there were no notable changes in estradiol concentrations of females before and after contact with males covering the application sites with T-shirts (Figure 12). Mean DHT concentrations of females before and after contact with males covering the application sites with T-shirts were similar (Figure 13).

- Conclusion
  - C_{avg}, AUC and C_{max} of total T were similar between Day 1 and Day -1, and the 90% CI of the Day 1/Day -1 ratio were within 80 to 125% for all parameters. Therefore, transfer of T to female subjects was prevented with a T-shirt barrier when males applied the highest dose of 5.0 g Androgel 1.62% to the upper arms and shoulders.

S176.1.011: An Open-Label Study of Serum T Levels in Non-dosed Females after Secondary Exposure to Androgel 1.62% Applied to the Upper Arms and Shoulders and Use of a T-shirt Barrier

- Study objective
  - To determine the PK of total T concentrations in female subjects after a single episode of skin contact with a male partner dosed with Androgel 1.62% (5.0 g).
  - To evaluate T transfer from males dosed with Androgel 1.62% (5.0 g) to non-dosed female subjects when contact with the upper arms/shoulders application site occurred at 2 hours post-dose with a T-shirt barrier.
- Study design
  - This study was a single center, single dose, open-label study in healthy male and female volunteers. Twelve male-female couples who consented to participate in this study and met the inclusion/exclusion criteria were enrolled into the study. All male-female couples enrolled underwent the same dose and skin contact procedures. On Day 1, all male subjects applied Androgel 1.62%. Two hours following gel application to the male subjects, 15 minutes of supervised skin contact of the application site occurred between the dosed male and his non-dosed female partner as described below.
  - Males: Application of Androgel 1.62% to the upper arms/shoulders (2.5 g of gel applied to each the left and right upper arm/shoulder for a total dose of 5.0 g). The total time for measuring all incremental doses and application to the subject was less than 5 minutes. Following the last incremental gel application, subjects waited at least 5 minutes for the gel to dry before putting clothes over the gel application area.
  - Females: Skin contact with application site at 2 hours post-dose while males wear T-shirts.
  - Female subjects were given a tube top to wear to expose the shoulders and arms. Male subjects were given a long-sleeved 100% cotton T-shirt to cover the application site. Each couple engaged in a total of 15 minutes of contact. Female subjects were instructed to rub their hands, wrists, arms, and shoulders up and down the upper arms and shoulders of their male partner during the contact period. One minute periods of alternating active rubbing and resting of the female's arms on the male's shoulders occurred until the 15 minute time period was complete. After contact, female subjects waited at least 5 minutes prior to putting clothes over the exposed area. Female subjects were not allowed to take a shower or bathe until 24 hours after the contact period.
- Study drug formulation

Reference ID: 2937578

- The investigational product is a Androgel 1.62% manufactured by Abbott Products, Inc. (formerly Solvay Pharmaceuticals, Inc.). Androgel 1.62% is dispensed via a multi-dose pump capable of dispensing 75.0 g (or 60 metered 1.25 g doses).

- Disposition of subjects
  - 12 couples (12 males and 12 females) were enrolled and finished the study.

  No protocol deviations pertained to study conduct including inclusion/exclusion criteria and PK sample collection occurred.
- Inclusion criteria
  - Males
    - Documentation of written informed consent. The subject must have had adequate written and oral fluency to understand the informed consent and converse with the investigator in the language in which the informed consent is written.
    - Male subjects 18 - 80 years of age, inclusive.
    - Subjects with a Body Mass Index of 20-35 kg/m2, inclusive.
    - In the opinion of the investigator, the subject was determined to be in good health as determined by vital signs, medical history, physical exam, electrocardiogram (ECG), and laboratory examination (hematology, clinical chemistry, and urinalysis).
    - Negative hepatitis B/C and HIV.
  - Females
    - Documentation of written informed consent. The subject must have had adequate written and oral fluency to understand the informed consent and converse with the investigator in the language in which the informed consent is written.
    - Female subjects 18 - 80 years of age, inclusive.
    - In the opinion of the investigator, the subject was determined to be in good health as determined by vital signs, medical history, physical exam, ECG, and laboratory examination (hematology, clinical chemistry, and urinalysis).
    - Subjects with a Body Mass Index of 20-30 kg/m2, inclusive.
    - Subjects with a screening T in the normal range, as specified by the normal range at the testing facility.
    - Negative hepatitis B/C and HIV.
- Exclusion criteria
  - Males
    - Positive screen for alcohol or drugs of abuse.
    - Subject with a hematocrit > 48%.
    - Previous history of, or current or suspected, prostate or breast cancer.
    - Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
    - Findings of any kind of lesions (e.g. ulcer, erosion, lichenification, crust, inflammation) on the skin surface of the upper arms/shoulders during physical examination (small tattoos are acceptable).
    - Participants in any investigational drug trial within the previous 30 days.
    - Receipt of any prescription medication within 21 days prior to Day -2 of the study or receipt of non-prescription (over-the-counter (OTC)) medication within 7 days of Day -2 without sponsor approval.
    - Subjects who smoked or used other nicotine products within the past 12 months.

Reference ID: 2937578

        - Consumption of caffeine-containing products or beverages in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day -2 (caffeine-containing products were not to be allowed during each study period).
        - Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments and ECG.
        - Baseline Prostate Specific Antigen (PSA) > 2.5 ng/mL. If the subject had documentation of a negative prostate biopsy within the past six months, a PSA of 2.6 - 3.74 ng/mL was to be allowed.
        - Abnormal digital rectal examination (DRE) defined as presence of nodule or induration.
        - Untreated prolactinoma.
        - Previous history of, or current or suspected, eczema or psoriasis.
    - Females
        - Subjects who were pregnant or lactating.
        - Subjects of child-bearing potential who were not using an acceptable method of birth control. Barrier methods of birth control (i.e., diaphragm/condom with spermicide) were to be acceptable for study participation. Oral or implanted contraceptives were to be unacceptable methods of birth control for study participation. Female subjects who were surgically sterile may have been enrolled.
        - Previous history of, or current or suspected, hirsutism.
        - Participants in any investigational drug trial within the previous 30 days.
        - Positive screen for alcohol or drugs of abuse.
        - Receipt of any prescription medication within 21 days prior to entry into the study, or receipt of non-prescription medication or herbal products within 7 days of study commencement without sponsor approval.
        - Blood or plasma donation within the 60 days prior to study entry.
        - Subjects with any clinical/biochemical impairment of liver function or receipt of known hepatic enzyme inducing or inhibitory agents within 90 days prior to entry into study.
        - Use of any drug with a half-life greater than 24 hours in the past 6 months without Sponsor approval.
        - Subjects who smoked or used other nicotine products within the past 12 months.
        - Consumption of caffeine-containing products or beverages in excess of 5 cups/cans of coffee, tea, or cola per day or any consumption of caffeine-containing products or beverages within 24 hours of Day -2 (caffeine-containing products were not to be allowed during each study period).
        - Findings of any kind of lesions (e.g. ulcer, erosion, lichenification, crust, inflammation) on the skin surface of the upper arms/shoulders during physical examination (small tattoos were to be acceptable).
        - Any clinically significant abnormality in physical exam, vital signs, clinical laboratory assessments, and ECG.
        - Known sensitivity or contraindications to topical androgens or alcohol-based topical products.
        - Previous history of, or current or suspected, eczema or psoriasis.
- Dosing conditions
    - Application of Androgel 1.62% to males' upper arms/shoulders (2.5 g of gel applied to each the left and right upper arm/shoulder for a total dose of 5.0 g) between 9:45 a.m. and 10:35 a.m.

        - The first 1.25 g was applied to one shoulder and spread across the maximum surface area.
        - The second 1.25 g was applied to the opposite shoulder and spread across the maximum surface area without re-applying gel to the previously dosed area.
        - The third 1.25 g was applied to one of the upper arms, from the edge of the shoulder region to just above the elbow and including the back of the arm, spread over the maximum surface area without re-applying gel to the previously dosed areas.
        - The fourth 1.25 g was applied to the opposite upper arm area as described above without re-applying gel to the previously dosed areas.
- PK measurements and blood samples
    - Whole blood samples (6 mL) were collected in red-top anticoagulant-free tubes from female subjects only for determination of total T, estradiol, and DHT at the following times:
    - Day -1 (baseline) at 0, 2, 4, 6, 8, 10, 12, 16, and 24 (pre-dose on Day1) hours with respect to the planned end time of skin contact on Day 1
    - Day 1 at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 16, 24, and 48 hours after the end of skin contact
- Demographics

	Female	Male
Age (years)		
Mean (SD)	40.3 (13.3)	41.9 (6.4)
Range	21 - 59	29 -52
Race, n (%)		
White	12 (100)	10 (83.3)
Black	0 (0)	2 (16.7)
American Indian or Alaska native	0 (0)	0 (0)
Ethnicity, n (%)		
Hispanic or Latino	12 (100)	12 (100)
Not Hispanic or Latino	0 (0)	0 (0)
Body weight (kg)		
Mean (SD)	67.4 (5.7)	83.2 (8.9)
Range	59.7 – 76.0	69.4 – 105.2
Height (cm)		
Mean (SD)	160.3 (4.6)	171.3 (6.6)
Range	150 - 168	163 – 184
BMI (kg/cm^2)		
Mean (SD)	26.3 (2.5)	28.4 (2.2)
Range	22.5 – 30.0	22.7 – 31.1

- Results

Reference ID: 2937578

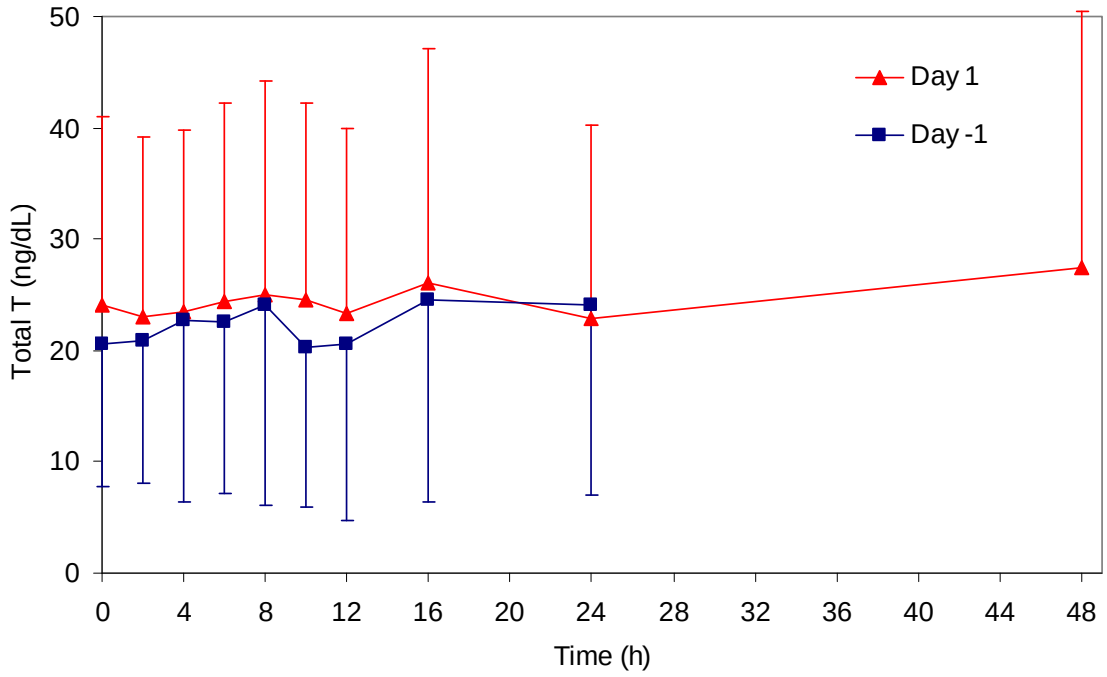

Figure 14 Mean (SD) Total T Concentrations of Females Before (Day-1) and After (Day 1) Contact with Males on T-Shirts; S176.1.011; N = 12

The total T baseline (Day -1) concentrations across all females ranged from 5.9 to 63.6 ng/dL over the 24-hour measurement period. The total T concentrations across all females after contact with males on T-shirts (Day 1) ranged from 6.8 to 74.5 ng/dL over a 24 hour period of 0 to 90 ng/dL. Based on the concentration-time profiles, mean T concentrations were similar on Day -1 and Day 1. In addition, the total T concentration of females at 24 and 48 hours following contact with males were similar (22.9 and 27.4 ng/dL). Therefore, covering T application site of males with T-shirts seemed to prevent the transfer of T to females following contact with males.

Table 23 Mean (SD) PK Parameters of Total T; S176.1.011

	Day	N	Arithmetic mean (SD)
C_{max} (ng/dL)	Day -1	12	26.4 (18.1)
	Day 1	12	29.5 (20.3)
AUC_{0-24} (ng·hr/dL)	Day -1	12	546.4 (387.2)
	Day 1	12	581.4 (430.8)
C_{avg} (ng/dL)	Day -1	12	22.8 (16.1)
	Day 1	12	24.2 (18.0)
*T_{max} (hr)	Day -1	12	16 (0-24)
	Day 1	12	90 (0-24)

*shown as median (range)

Table 24 Statistical Comparison of PK Parameters of Total T; S176.1.011

	Day	N	Geometric mean	Geometric mean ratio (Day1/Day-1)	90% CI
C_{max} (ng/dL)	Day -1	12	21.5	1.11	0.99 – 1.25
	Day 1	12	23.9		
AUC_{0-24} (ng·hr/dL)	Day -1	12	443.1	1.06	0.98 – 1.15
	Day 1	12	470.0		
C_{avg} (ng/dL)	Day -1	12	18.5	1.06	0.98 – 1.15
	Day 1	12	19.6		

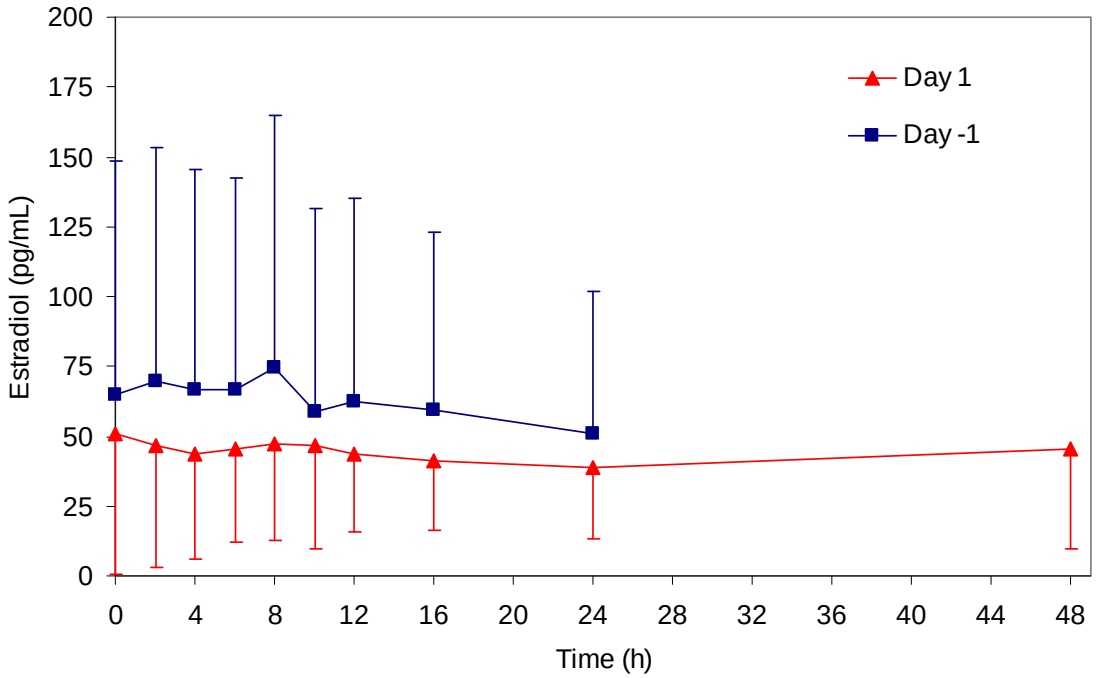

Figure 15 Mean (SD) Estradiol Concentrations of Females Before (Day-1) and After (Day 1) Contact with Males on T-Shirts; S176.1.011; N = 12

Reference ID: 2937578

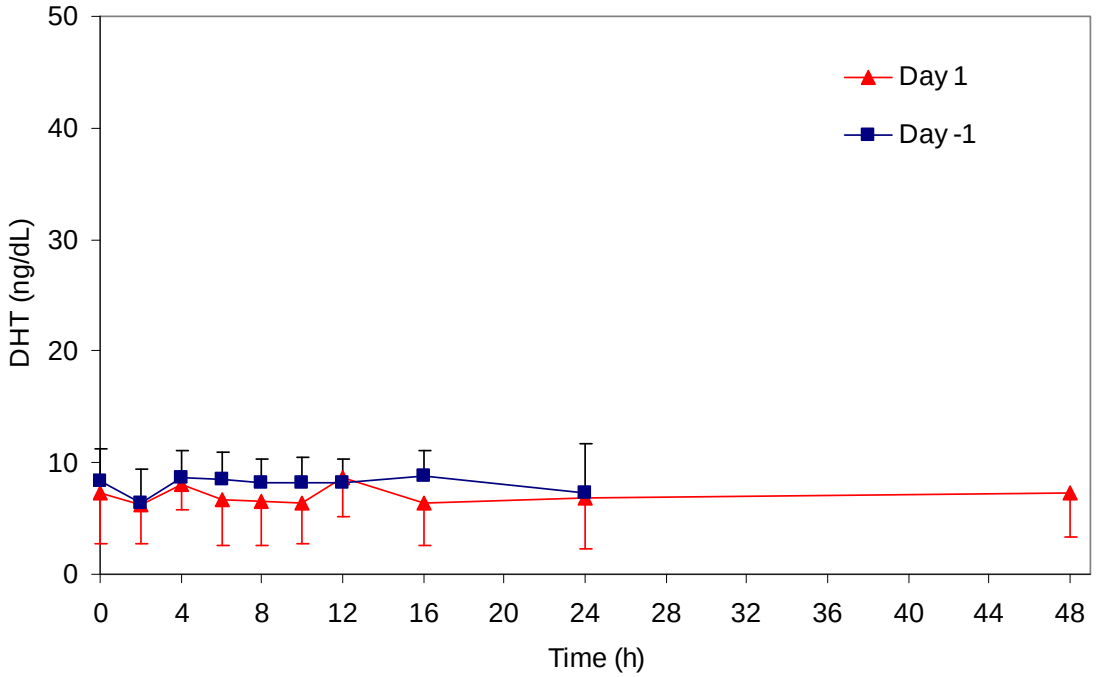

Figure 16 Mean (SD) DHT Concentrations of Females Before (Day-1) and After (Day 1) Contact with Males on T-Shirts; S176.1.011; N = 12

The difference of mean estradiol concentrations in each time point was within the range of SD of each corresponding time point. Therefore, there were no notable changes in estradiol concentrations of females before and after contact with males covering the application sites with T-shirts (Figure 15). Mean DHT concentrations of females before and after contact with males covering the application sites with T-shirts were similar (Figure 16).

- Conclusion
  - C_{avg}, AUC and C_{max} of total T were similar between Day 1 and Day -1, and the 90% CI of the Day 1/Day -1 ratio were within 80 to 125% for all parameters. Therefore, transfer of T to female subjects was prevented with a T-shirt barrier when males applied the highest dose of 5.0 g Androgel 1.62% to the upper arms and shoulders.

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

The efficacy of Androgel 1.62% was established in the original review cycle of the NDA based on the pivotal phase 3 clinical study, S176.3.104 of which the duration was 182 days (Clinical Pharmacology review of NDA 022309 by Dr. Apparaju Sandhya, DARRTS, October 26, 2009). Sponsor's resubmission included additional efficacy data from the open-label period (from Days 183 to 364) of S176.3.104.
The first double-blind period of S176.3.104 submitted during the original review cycle and the second open-label period of S176.3.1.104 submitted in the current resubmission are referred as "double-blind period" and "open-label period", hereafter.

Information (e.g., study design, results) relevant to double-blind period is from Clinical Pharmacology review of NDA 022309 by Dr. Apparaju Sandhya (DARRTS, October 26, 2009).

- Study design; double-blind period:

This was a phase 3, multi-center, randomized, double-blind, placebo-controlled study of four different doses of Androgel 1.62% (1.25 g, 2.5g, 3.75 g, and 5.0 g equivalent to 20.25, 40.5, 60.75 and 81 mg T, respectively) in hypogonadal males (18-80 years; baseline morning serum T level < 300 ng/dL based on the average of two morning blood draws). The efficacy and safety of Androgel 1.62% were evaluated following administration of active treatment or placebo to hypogonadal men for a period of 182 days. Study medication was applied to intact dry skin once-daily in the morning to shoulders/upper arms or abdomen after showering. Over a 7-day period, study gel could be rotated between the upper arms/shoulders or abdomen (e.g., 4 days upper arms/shoulders; 3 days abdomen) as long as drug was applied to shoulders/upper arms during PK visits.

All subjects started at 2.5 g of Androgel 1.62% or matching placebo on Day 1 of the study. Subjects returned to the clinic on Days 14, 28, and 42 for pre-dose serum total T assessments for potential dose-titrations in 1.25 g increments within the 1.25 g – 5.0 g range. Dose titration was based on total T concentrations at pre-dose (C_{trough}). Within 2 days of each visit (Days 14, 28, and 42), subjects were up-titrated if C_{trough} was < 350 ng/dL, down-titrated if C_{trough} was > 750 ng/dL or remained on the same dose if C_{trough} was within 350- 750 ng/dL range. Subjects were maintained at their respective Day 42 dose until Day 182. PK sampling was conducted over 24 hours on Days 14, 56, 112 (end point), and 182 during the double-blind phase for assessment of T, DHT and estradiol. Non-compartmental methods were used for the computation of PK parameters.

- Study design; open-label period:

Subjects who completed the initial 182-day portion of the study were eligible to enter the open-label extension period of the study for up to one year of total participation. On Day 182, subjects initially randomized to active therapy continued on the T dose from their Day 42 visit unless they required a titration. Titration scheme in open-label period was same as double-blind period based on C_{trough}. Subjects transitioning from active therapy had opportunities to titrate based on Days 182, 196, 210, and 266 total T assessments where necessary. If a subject transitioning from active therapy did not require a titration on Day 182, then they were seen next on Days 224 and 266 without visits on Days 196 and 210.

Subjects transitioning from placebo were started on the 2.5 g dose and had three titration visits on Days 196, 210, and 266 which were required visits for subjects transitioning from placebo. Therefore, subjects transitioned from placebo had three visits (Days 196, 210, and 266) where titration could have occurred, while subjects transitioned from active could have three or four visits (Days 182, 224, and 266 OR Days 182, 196, 210, and 266) where titration could have occurred during the entire open-label period.

During open-label period, 24 hour PK assessments occurred on Days 266 and 364. Dose titration schemes during the open-label period and double-blind period were same.

- Subject disposition:

  - Double-blind period

Reference ID: 2937578

- 274 subjects (Androgel 1.62%: 234 subjects, placebo: 40 subjects) were randomized and analyzed for safety.
- 206 subjects (Androgel 1.62%: 179 subjects, placebo: 27 subjects) were analyzed for efficacy.

- Open-label period (Table 25)
  - 191 subjects (163 subjects had formerly received active treatment during the double-blind period and 28 subjects had formerly received placebo during the double-blind period) received active treatment, Androgel 1.62%, and analyzed for safety
  - 170 subjects were included in full analysis (FA) sample
    - FA sample consisted of subjects who were in the safety sample and had data for at least one post-baseline assessment of any efficacy measurement up to and including Day 364.
  - 87 subjects were included in per protocol (PP) sample
    - PP sample consisted of subjects who were included in the FA sample and did not present any protocol violation.

Table 25 Subject Disposition for Open-Label Period; S176.3.104

	Formerly Placebo (N=28)	Continuing Active Androgel 1.62% (N=163)	Total (N=191)
Safety sample Total	28 (100%)	163 (100%)	191 (100%)
FA sample Total Excluded from FA sample No Days 266 or 364 efficacy data	26 (93%) 2 (7%) 2 (7%)	144 (88%) 19 (12%) 19 (12%)	170 (89%) 21 (11%) 21 (11%)
PP sample Total Excluded from PP sample No Days 266 or 364 efficacy data Protocol violations*	12 (43%) 16 (57%) 2 (7%) 15 (54%)	75 (46%) 88 (54%) 19 (12%) 82 (50%)	87 (46%) 104 (54%) 21 (11%) 97 (51%)

*Protocol violations were defined as overall < 80% or > 120% compliance measured by the use of the gel (i.e. gel use = pre use weight – post use weight) OR PK samplings for Day 364 for conducted outside the visit window (± 4 days).

- Results:

Primary endpoint: The primary efficacy parameter was the percentage of subjects (i.e. responders) with serum total T C_{avg} within the normal range of 300- 1000 ng/dL on Day 112.

Success in the study was defined as ≥ 75% of subjects on active treatment within the normal serum T concentration range of 300-1000 ng/dL. In addition, the lower bound of the 95% CI was to be not less than 65% based on the Day 112 PK results for the pivotal phase of the trial.

On Day 112, the proportion of responders for the active treatment groups was 81.6 % [146/179; 95 % CI: 75.1 – 87.0], thus fulfilling the pre-defined primary endpoint success criteria. This was significantly different compared to 37 % responder rate observed in the placebo group ($p < 0.0001$, Table 26).

Reference ID: 2937578

Table 26 Percentage of Subjects Achieving Target Range for T C_{avg} by Day and Treatment in the FA Sample; Double-Blind; S176.3.104

Population	Study Day	Testosterone gel 1.62%		Placebo		p-value
		n/N (%)	95% CI	n/N (%)	95% CI	
FA	14	138/210 (65.7)	(58.9, 72.1)	11/37 (29.7)	(15.9, 47.0)	<0.0001
	56	151/183 (82.5)	(76.2, 87.7)	11/32 (34.4)	(18.6, 53.2)	<0.0001
	112	146/179 (81.6)	(75.1, 87.0)	10/27 (37.0)	(19.4, 57.6)	<0.0001
	182	139/169 (82.2)	(75.6, 87.7)	8/28 (28.6)	(13.2, 48.7)	<0.0001

n: number of subjects achieving target T range; N: number of subjects with evaluable PK parameter for the given study day

In the FA sample on Days 266 and 364, the proportion of responders for the Continuing Active Androgel 1.62% group was 78.4 and 77.9%, suggesting the long term efficacy of Androgel 1.62% up to 1 year (Table 27). Although the proportion of responders for Formerly Placebo group was 69.2% on Day 266 (84 days after active treatment), it increased to 87% by Day 364 (182 days after active treatment). PP sample analysis also demonstrated long term efficacy of Androgel 1.62% up to 1 year as shown in Table 28.

Table 27 Number and Percentage of Subjects Achieving Target Range for T C_{avg} by Day 266 and Day 364 and Treatment in the FA Sample; Open-Label; S176.3.104

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

n: number of subjects achieving target T range; N: number of subjects with evaluable PK parameter for the given study day

Table 28 Number and Percentage of Subjects Achieving Target Range for T C_{avg} by Day 266 and 364 and Treatment in the PP Sample; Open-Label; S176.3.104

Study Day	Continuing Active Androgel 1.62%		Formerly Placebo		Total	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
266	61/74 (82.4)	(71.8, 90.3)	6/12 (50.0)	(21.1, 78.9)	67/86 (77.9)	(67.7, 86.1)
364	54/71 (76.1)	(64.5, 85.4)	8/9 (88.9)	(51.8, 99.7)	62/80 (77.5)	(66.8, 86.1)

n: number of subjects achieving target T range; N: number of subjects with evaluable PK parameter for the given study day

Secondary endpoints:

A critical secondary endpoint was to evaluate C_{max} of total T during the first 182 days of the study. The individual total T C_{max} values were to be in the following ranges:
- $C_{max} \leq 1500$ ng/dL in $\leq 85\%$ of the subjects
- C_{max} between 1800-2500 ng/dL in $\leq 5\%$ of the subjects
- $C_{max} > 2500$ ng/dL in none of the subjects

Across all 24-hour PK days (14, 56, 112 and 182 days) in the FA sample, 93.9 % (696/741) had C_{max} values ≤ 1500 ng/mL; 3 % had C_{max} values between 1800-2500 ng/dL and 0.8 % had C_{max} values > 2500 ng/dL (Table 29). Although there were 6 instances (0.8%) where subjects experienced C_{max} values > 2500 ng/dL, Dr. Sandhya Apparaju found that the instances of T outliers were infrequent, random and usually attributable to either sample contamination or potential compliance issues with the dose and/or regimen (Clinical Pharmacology review of NDA 022309, DARRTS, October 26, 2009).

Table 29 Number and Percentage of Subjects Achieving C_{max} Range on Days 14, 56, 112, 182 and Overall; Double-Blind; S176.3.104

		n / N (%) for Subjects Achieving Testosterone C_{max} Range					
		Testosterone gel 1.62%			Placebo		
Study Pop	Day	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL
FA	Overall[1]	696/741 (93.9)	22/741 (3.0)	6/741 (0.8)	123/124 (99.2)	0/124	0/124
	14	203/210 (96.7)	5/210 (2.4)	1/210 (0.5)	37/37 (100.0)	0/37	0/37
	56	178/183 (97.3)	1/183 (0.5)	2/183 (1.1)	32/32 (100.0)	0/32	0/32
	112	159/179 (88.8)	10/179 (5.6)	2/179 (1.1)	26/27 (96.3)	0/27	0/27
	182	156/169 (92.3)	6/169 (3.6)	1/169 (0.6)	28/28 (100.0)	0/28	0/28

[1]For the overall results, n: number of observations and N: number of evaluable observations across all study days.
n: number of subjects achieving T C_{max} range; N: number of subjects with evaluable PK parameter for the given study day

The individual C_{max} results from the FA sample for Days 266 and 364 in Continuing Active Androgel 1.62% and Formerly Placebo arms were within the acceptable criteria during the open-label period of the study (Table 30).

Table 30 Number and Percentage of Subjects Achieving C_{max} Range on Days 266, 364 and Overall; Open-Label; S176.3.104

	n/N (%) for Subjects Achieving T C_{max} range								
	Continuing Active Androgel 1.62%			Formerly Placebo			Total		
Day	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL
Overall	258/275 (93.8)	9/275 (3.3)	0 /275 (0.0)	45/49 (91.8)	2/49 (4.08)	0/49 (0.0)	303/324 (93.5)	11/324 (3.4)	0/324 (0.0)
266	131/139 (94.2)	5/139 (3.6)	0/139 (0.0)	24/26 (92.3)	2/26 (7.7)	0/26 (0.0)	155/165 (93.9)	7/165 (4.2)	0/165 (0.0)
364	127/136 (93.4)	4/136 (2.9)	0/136 (0.0)	21/23 (91.3)	0/23 (0.0)	0/23 (0.0)	148/159 (93.1)	4/159 (2.5)	0/159 (0.0)

For the overall results, n: number of observations and N: number of evaluable observations across all study days.
n: number of subjects achieving T C_{max} range; N: number of subjects with evaluable PK parameter for the given study day

- Effectiveness of dose titration regimen in study arms with Androgel 1.62%:

During the double-blind period, the % responders (C_{avg} within the normal range) increased from 65.7 % (Day 14) to 81.6 – 82.5 % (Days 56 - 182; Table 26). This suggested that a pre-dose

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(C_{trough}) based titration (conducted on Days 14, 28 and 42) in this study was effective in identifying non-responders or supra-responders and titrating these subjects to their efficacious doses.

During the open-label period, the % responders in Continuing Active Androgel 1.62% arm were 78.4% and 77.9% on Days 266 and 364, respectively (Table 27), which were smaller than the % responders on Days 56 – 182 (81.6 – 82.5%; Table 26) during the double-blind period.

During the double-blind period, mean C_{avg} in Androgel 1.62% arms ranged from 457 to 643 ng/dL in four different dose groups (1.25 to 5.0 g) on Day 112 (Table 31). On Day 182 without further titration since Day 112, mean C_{avg} in Androgel 1.62% arms ranged from 431 to 586 ng/dL. Within each dose group, there were less than 10% difference between mean C_{avg} on Days 112 and 182.

Table 31 PK Parameters for T by Day and Dose; Double-Blind; S176.3.104

	Arithmetic mean (SD)					
	Placebo	**1.25 g**	**2.5 g**	**3.75 g**	**5.0 g**	**All active**
Day 14						
C_{avg} (ng/dL)	257 (93.1)	-	397 (205)	-	-	-
C_{max} (ng/dL)	334 (125)	-	597 (385)	-	-	-
t_{max} (h)*	3.98 (0.45, 24.0)	-	8.0 (0.42, 24.13)	-	-	-
C_{min} (ng/dL)	209 (84.1)	-	269 (150)	-	-	-
AUC_{0-24} (ng*h/dL)	6160 (2230)	-	9560 (4950)	-	-	-
C_{trough} (ng/dL)	286 (131)	-	437 (403)	-	-	-
Day 56						
C_{avg} (ng/dL)	316 (213)	409 (151)	438 (144)	529 (164)	436 (181)	461 (171)
C_{max} (ng/dL)	442 (307)	673 (325)	687 (416)	768 (290)	687 (480)	709 (407)
t_{max} (h)*	3.99 (0.48, 24.33)	4.99 (0.5, 24.08)	8.0 (0.48, 24.05)	8.0 (0.5, 24.08)	4.05 (0.45, 24.08)	7.97 (0.45, 24.08)
C_{min} (ng/dL)	251 (173)	277 (122)	299 (104)	342 (121)	275 (108)	300 (115)
AUC_{0-24} (ng*h/dL)	7590 (5100)	9850 (3660)	10500 (3450)	12700 (3930)	10500 (4360)	11100 (4110)
C_{trough} (ng/dL)	334 (261)	463 (271)	523 (336)	483 (222)	415 (251)	462 (267)
Day 112	n = 27	n = 12	n = 34	n = 54	n = 79	n = 179
C_{avg} (ng/dL)	303 (135)	457 (275)	524 (228)	643 (285)	537 (240)	561 (259)
C_{max} (ng/dL)	450 (349)	663 (473)	798 (439)	958 (497)	815 (479)	845 (480)
t_{max} (h)*	4.0 (0.5-25.50)	8.0 (0.45-24.0)	8.0 (0.5-24.0)	8.01 (0.25-24.02)	8.0 (0.42-24.08)	8.0 (0.25-24.08)
C_{min} (ng/dL)	215 (102)	242 (58.4)	312 (141)	371 (179)	333 (148)	334 (155)
AUC_{0-24} (ng*h/dL)	7280 (3230)	10900 (6460)	12600 (5470)	15400 (6830)	12900 (5790)	13500 (6210)
C_{trough} (ng/dL)	283 (133)	332 (86.4)	497 (256)	494 (390)	495 (307)	484 (317)
Day 182	n = 28	n = 12	n = 35	n = 50	n = 72	n = 169
C_{avg} (ng/dL)	270 (152)	431 (162)	494 (231)	586 (241)	539 (240)	536 (236)
C_{max} (ng/dL)	345 (190)	562 (231)	742 (418)	888 (461)	830 (573)	810 (497)
t_{max} (h)*	1.50 (0.42-24.0)	12.0 (0.45-24.40)	4.03 (0.48-24.05)	8.0 (0.48-24.50)	8.0 (0.42-24.0)	8.0 (0.42- 24.5)
C_{min} (ng/dL)	210 (122)	289 (106)	313 (136)	353 (149)	329 (158)	330 (147)
AUC_{0-24} (ng*h/dL)	6480 (3630)	10400 (3900)	11900 (5550)	14100 (5780)	13000 (5800)	12900 (5660)

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C_{trough} (ng/dL)	291 (157)	377 (160)	480 (224)	553 (322)	512 (350)	507 (310)

*shown as median (range)

During the open-label period, mean C_{avg} in Androgel 1.62% arms ranged from 441 to 482 ng/dL in four different dose groups (1.25 to 5.0 g) on Day 266 (Table 32). On Day 364, mean C_{avg} in Androgel 1.62% arms ranged from 386 to 513 ng/dL. Within each dose group, there were less than 20% difference between mean C_{avg} on Days 226 and 364.

Table 32 PK Parameters for T by Day and Dose; Open-Label; S176.3.104

	Arithmetic mean (SD)									
	Formerly Placebo					**Continuing Active Androgel 1.62%**				
	1.25 g	2.5 g	3.75 g	5.0 g	Overall	1.25 g	2.5 g	3.75 g	5.0 g	Overall
Day 266	n = 4	n = 10	n = 7	n = 5	n = 26	n = 7	n = 30	n = 31	n = 71	n = 139
C_{avg} (ng/dL)	721.3 (554.6)	461.4 (210.2)	392.6 (167.4)	315.4 (91.1)	454.8 (277.9)	469.7 (329.6)	477.8 (206.9)	482.3 (226.2)	441.3 (187.0)	459.7 (206.6)
C_{max} (ng/dL)	1034 (780)	750.5 (595.9)	540.1 (243.2)	456.0 (147.4)	680.8 (506.0)	681.7 (565.8)	734.1 (444.4)	696.0 (414.4)	671.2 (354.7)	690.8 (396.5)
t_{max} (h)*	2.00 (2.00-24.00)	12.02 (0.92-24.02)	2.18 (1.00-11.83)	2.0 (0.50-24.05)	3.88 (0.50-24.05)	8.00 (0.50-23.92)	8.05 (0.48-24.02)	8.00 (0.42-24.08	4.02 (0.13-24.17)	8.00 (0.13-24.17)
C_{min} (ng/dL)	408.0 (205.9)	298.8 (88.3)	271.1 (105.0)	214.4 (83.4)	291.9 (123.1)	276.1 (68.2)	294.5 (110.0)	332.5 (150.3)	305.5 (114.6)	307.6 (120.6)
AUC (ng*h/dL)	17320 (13330)	11060 (10340)	9413 (4042)	7564 (7302)	10910 (6679)	11240 (7627)	11470 (4977)	11580 (5441)	10600 (4497)	11040 (4963)
C_{trough} (ng/dL)	931.0 (742.0)	435.1 (175.7)	487.4 (326.4)	404.6 (226.4)	519.6 (379.2)	516.9 (221.2)	443.8 (266.3)	522.4 (299.3)	467.2 (271.7)	477.3 (273.5)
Day 364	n = 3	n = 7	n = 7	n = 6	n = 23	n = 7	n = 26	n = 29	n = 74	n = 136
C_{avg} (ng/dL)	491.3 (122.0)	488.0 (239.0)	444.6 (268.3)	380.3 (105.2)	447.2 (202.7)	386.3 (129.5)	473.8 (176.4)	512.9 (221.9)	431.7 (185.5)	454.7 (191.5)
C_{max} (ng/dL)	900.7 (236.5)	814.9 (415.6)	606.0 (422.5)	569.8 (158.8)	698.6 (346.9)	562.3 (187.3)	715.0 (305.5)	839.1 (568.3)	648.5 (329.4)	697.4 (388.8)
t_{max} (h)*	1.08 (0.50-24.08)	7.98 (0.50-24.05)	8.00 (0.42-24.00)	2.5 (0.50-12.00)	4.00 (0.42-24.08)	4.00 (0.50-24.00)	6.03 (0.45-24.00)	8.13 (0.43-24.00)	8.00 (0.43-24.58)	8.00 (0.43-24.58)
C_{min} (ng/dL)	340.0 (133.1)	309.3 (116.4)	274.0 (131.9)	264.0 (52.7)	290.7 (106.8)	277.6 (94.4)	315.9 (112.9)	330.6 (155.4)	291.9 (126.3)	304.0 (129.2)
AUC (ng*h/dL)	11810 (2960)	11730 (5742)	10680 (6472)	9128 (2520)	10740 (4881)	9263 (3100)	11370 (4222)	12290 (5314)	10360 (4444)	10910 (4584)
C_{trough} (ng/dL)	784.0 (441.1)	430.1 (93.5)	352.4 (219.9)	423.2 (88.8)	452.1 (236.1)	467.1 (181.5)	522.1 (250.9)	526.4 (352.1)	439.1 (296.2)	474.3 (296.4)

*shown as median (range)

Table 33 describes the number of subjects at each dose following titration days in Formerly Placebo group in open-label period. % subjects needed dose titration on each titration day was 39% (11/28), 54% (15/28), and 23 % (6/26) on Days 196 (14 days after Androgel 1.62% treatment), 210 (28 days after Androgel 1.62% treatment), and 266 (84 days after Androgel 1.62% treatment), respectively.

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Table 34 describes the number of subjects at each dose following titration days in Continuing Active Androgel group in both double-blind and open-label periods. % subjects needed dose titration on each titration day was 63% (136/216), 51% (106/208), 33% (71/216), 35% (57/163), 27% (13/49), 29% (5/17), 0% (0/148), and 22% (31/144).

Approximately half the subjects (39%: Day 182-Formerly Placebo, 54%: Day 196-Formerly Placebo, 63%: Day 14-Continuing Active Androgel, 51%: Day 28-Continuing Active Androgel) needed dose titration within 28 days of active Androgel 1.62% treatment in Formerly Placebo and Testosterone gel 1.62% arm during the double-blind period AND Continuing Active Androgel arm during the open-label period.

Table 33 Number of subjects at each dose following titration days - Formerly Placebo; S176.3.104

Dose adjustment at the following titration days	Dose			
	20.25 mg	40.5 mg	60.75 mg	81 mg
	Formerly Placebo			
Day 182	Total: 0 Stayed on 20.25 mg: 0 Decreased from 40.5: 0	Total: 27 Stayed on 40.5 mg: 27 Increased from 20.25 mg: 0 Decreased from 60.75 mg: 0	Total: 1 Stayed on 60.75 mg:0 Increased from 40.5 mg: 1 Decreased from 81 mg: 0	Total: 0 Stayed on 81 mg: 0 Increased from 60.75 mg: 0
Day 196	Total: 1 Stayed on 20.25 mg: 0 Decreased from 40.5: 1	Total: 16 Stayed on 40.5 mg: 16 Increased from 20.25 mg: 0 Decreased from 60.75 mg: 0	Total: 11 Stayed on 60.75 mg: 1 Increased from 40.5 mg: 10 Decreased from 81 mg: 0	Total: 0 Stayed on 81 mg: 0 Increased from 60.75 mg: 0
Day 210	Total: 4 Stayed on 20.25 mg: 1 Decreased from 40.5: 3	Total: 10 Stayed on 40.5 mg: 9 Increased from 20.25 mg: 0 Decreased from 60.75 mg: 1	Total: 7 Stayed on 60.75 mg: 3 Increased from 40.5 mg: 4 Decreased from 81 mg: 0	Total: 7 Stayed on 81 mg: 0 Increased from 60.75 mg: 7
Day 266	Total: 3 Stayed on 20.25 mg: 3 Decreased from 40.5: 0	Total: 8 Stayed on 40.5 mg: 7 Increased from 20.25 mg: 1 Decreased from 60.75 mg: 0	Total: 7 Stayed on 60.75 mg: 4 Increased from 40.5 mg: 3 Decreased from 81 mg: 0	Total: 8 Stayed on 81 mg: 6 Increased from 60.75 mg: 2

Table 34 Number of subjects at each dose following titration days; S176.3.104

Dose adjustment at the following titration days	Dose			
	20.25 mg	40.5 mg	60.75 mg	81 mg
	Continuing Active Androgel			
Day 14	Total: 20 Stayed on 20.25 mg: 0 Decreased from 40.5: 20	Total: 80 Stayed on 40.5 mg: 80 Increased from 20.25 mg: 0 Decreased from 60.75 mg: 0	Total: 116 Stayed on 60.75 mg: 0 Increased from 40.5 mg: 116 Decreased from 81 mg: 0	Total: 0 Stayed on 81 mg: 0 Increased from 60.75 mg: 0
Day 28	Total: 17 Stayed on 20.25 mg: 11 Decreased from 40.5: 6	Total: 49 Stayed on 40.5 mg: 38 Increased from 20.25 mg: 7 Decreased from 60.75 mg: 4	Total: 85 Stayed on 60.75 mg: 53 Increased from 40.5 mg: 32 Decreased from 81 mg: 0	Total: 57 Stayed on 81 mg: 0 Increased from 60.75 mg: 57
Day 42	Total: 15 Stayed on 20.25 mg: 12 Decreased from 40.5: 3	Total: 39 Stayed on 40.5 mg: 27 Increased from 20.25 mg: 5 Decreased from 60.75 mg: 7	Total: 61 Stayed on 60.75 mg: 41 Increased from 40.5 mg: 18 Decreased from 81 mg: 2	Total: 89 Stayed on 81 mg: 53 Increased from 60.75 mg: 36
Day 182	Total: 11 Stayed on 20.25 mg: 5 Decreased from 40.5: 6	Total: 38 Stayed on 40.5 mg: 19 Increased from 20.25 mg: 7 Decreased from 60.75 mg: 12	Total: 41 Stayed on 60.75 mg: 22 Increased from 40.5 mg: 9 Decreased from 81 mg: 10	Total: 73 Stayed on 81 mg: 60 Increased from 60.75 mg: 13
Day 196	Total: 2 Stayed on 20.25 mg: 2 Decreased from 40.5: 0	Total: 19 Stayed on 40.5 mg: 13 Increased from 20.25 mg: 3 Decreased from 60.75 mg: 3	Total: 12 Stayed on 60.75 mg: 10 Increased from 40.5 mg: 2 Decreased from 81 mg: 0	Total: 16 Stayed on 81 mg: 11 Increased from 60.75 mg: 5
Day 210	Total: 4 Stayed on 20.25 mg: 1 Decreased from 40.5: 3	Total: 5 Stayed on 40.5 mg: 4 Increased from 20.25 mg: 0 Decreased from 60.75 mg: 1	Total: 2 Stayed on 60.75 mg: 1 Increased from 40.5 mg: 1 Decreased from 81 mg: 0	Total: 6 Stayed on 81 mg: 6 Increased from 60.75 mg: 0
Day 224	Total: 9 Stayed on 20.25 mg: 9 Decreased from 40.5: 0	Total: 33 Stayed on 40.5 mg: 33 Increased from 20.25 mg: 0 Decreased from 60.75 mg: 0	Total: 33 Stayed on 60.75 mg: 33 Increased from 40.5 mg: 0 Decreased from 81 mg: 0	Total: 73 Stayed on 81 mg: 73 Increased from 60.75 mg: 0
Day 266	Total: 8 Stayed on 20.25 mg: 6 Decreased from 40.5: 2	Total: 27 Stayed on 40.5 mg: 22 Increased from 20.25 mg: 1 Decreased from 60.75 mg: 4	Total: 32 Stayed on 60.75 mg: 18 Increased from 40.5 mg: 9 Decreased from 81 mg: 5	Total: 77 Stayed on 81 mg: 67 Increased from 60.75 mg: 10

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/s/

HYUNJIN KIM
04/22/2011

MYONG JIN KIM
04/25/2011

EDWARD D BASHAW
04/25/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-309	Submission Date(s): 02/11/2009, 05/14/2009, 09/02/2009, 09/17/2009 (original NDA related submissions) 11/06/09, 11/24/09, 12/03/09, 12/11/09, 12/23/09, 01/15/2010 (major amendment related submissions)
Brand Name	AndroGel®
Generic Name	Testosterone
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology III
OND Division	Division of Reproductive and Urologic Products
Sponsor	Solvay Pharmaceuticals
Relevant IND and NDA	IND 50377, NDA 21-015
Submission Type	Major amendment to the original NDA
Formulation; Strength(s)	Transdermal gel; 1.62 %
Indication	Testosterone replacement in hypogonadal males

Table of Contents

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the original NDA submitted on 02/11/2009, as well as major amendment related submissions for NDA 22-309 [AndroGel® (Testosterone gel) 1.62 %]. The information contained within NDA 22-309 is **not acceptable** for approval from a Clinical Pharmacology perspective. Based on the review of the major amendments submitted on 11/06/2009, 11/24/2009, 12/03/2009, 12/11/2009, 12/23/2009, and 01/15/2010, the sponsor has not provided adequate evidence to justify that the safety and efficacy of the drug would remain unchanged under the proposed new conditions of use.

- The proposed revisions to the application instructions for AndroGel 1.62 % gel require the use of both shoulders/upper arms as well as the abdominal sites for the two higher doses (i.e. three sites and four sites, respectively for the 3.75 g and 5.0 g doses). While this regimen has been demonstrated to mitigate transfer to non-dosed individuals, this is different from the phase 3 clinical trial (S176.3.104), in which dose was applied to either shoulders/upper arms or abdomen but not to both at the same time (i.e. two sites). The potential impact of this increased surface area of gel application with the use of additional application sites (relative to phase 3 usage) on the pharmacokinetics (PK) is unknown for the new 1.62 % formulation.

- The proposal to use limited PK information from a subgroup of phase 3 patients who'd deviated from the protocol and have documented sporadic use of the gel onto multiple application sites is considered as inadequate evidence in this regard and sets a low standard for approval.

- Additionally, skin safety (irritation) data following continuous once daily application to multiple sites is not available from the completed clinical trials for Androgel 1.62 % formulation. The proposed new application instructions require use of all four sites (at the 5.0 g dose) on a daily basis and therefore wouldn't allow rotation of sites to minimize irritation potential. The impact of these changes to the overall patient convenience and compliance is not known. Furthermore, increased skin irritation can also impact the dermal absorption of testosterone which the current data cannot support.

Action items to resolve deficiency:

In order to bridge the phase 3 clinical trial findings to the revised dose application instructions, the sponsor should conduct the following study:

- A steady-state, 2-way crossover, comparative bioavailability study of AndroGel 1.62 % gel (5.0 g dose) in hypogonadal male patients, evaluating the following two regimens:

- Dose application over 2 sites to upper arms/shoulders or abdomen via rotation (per phase 3 clinical trial usage)

vs.

- Dose application over 4 sites to both upper arm/shoulders and both sides of abdomen (per revised application instructions).

Dr. Edward D. Bashaw, Division Director for Division of Clinical Pharmacology 3, Office of Clinical Pharmacology has concurred with the final recommendation as well as the action items recommended to resolve the deficiencies.

1.2 Phase IV Commitments

Not applicable

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

- The original NDA for AndroGel 1.62 % testosterone gel formulation was submitted on February 11, 2009. During the review cycle it was evident that interpersonal transfer potential was significant for the gel even in presence of a clothing barrier. In an attempt to assuage the Division's concern in this regard, the sponsor conducted a new transfer study (S176.1.009) employing revised dosing instructions aimed at minimizing drug amount at any one skin site so as to mitigate transfer. A 5.0 g dose of the gel was distributed over multiple skin sites of the male subjects (both upper arms/shoulders and both sides of the abdomen, "four sites") in this study as opposed to the completed clinical program for AndroGel 1.62 % gel where drug was applied to either upper arms/shoulders or abdomen but not to both sites at once.
- The results from this new phase 1 transfer study S176.1.009 as well as a supporting document justifying the absence of a formal bridging study linking the revised dosing instructions to those employed in the phase 3 program for AndroGel 1.62 % gel, constituted the primary components of this major NDA amendment.
- Results of the new transfer study (S176.1.009) indicate that when contact occurred in presence of a clothing barrier with males who applied the 5.0 g dose over all four skin sites, mean (range) fold-increase in average testosterone concentration over 24 hour period (Cavg) in females on day 1 was 1.06 (range, 0.78-1.21 fold) i.e. 6 % over baseline. The range of absolute increases in Cavg in these females was 0.23 – 3.9 ng/dL. Mean increase in Cmax was 1.08 (range, 0.67-1.74) i.e. 8 % over baseline. The individual with the highest Cmax change over baseline was # 27445 who showed a net increase in Cmax over baseline of 16 ng/dL. This was a one-time occurrence in this individual in whom the remaining concentrations were identical to those in her baseline.
- The results from the new transfer study S176.1.009 suggest that the testosterone transfer to non-dosed females was largely mitigated when contact occurred with a

T-shirt barrier on male who applied a 5.0 g dose of the 1.62 % gel formulation to 4 different application sites (both upper arms/shoulders and both sides of abdomen).

- (b) (4)

(b) (4)

- While dosing over multiple sites appears to mitigate transfer, no PK (efficacy) or safety data is currently available from continuous once daily application of the 1.62 % gel to multiple application sites (both sides of upper arms/shoulders and abdomen, without rotation).
- No formal 'bridging' study was conducted to justify the applicability of the phase 3 clinical trial data (where only 2 sites were used for spreading out the 3.75 g or 5.0 g doses), to the newly proposed regimen involving use of multiple application sites despite the doubling of the application surface area with use of two additional sites. The potential impact of this increased surface area of gel application with the use of two additional application sites (relative to phase 3 usage) on PK is unknown for the new 1.62 % formulation.
- Skin safety (irritation) data following continuous once daily application to all four sites is also not available from the completed clinical trials. The proposed new application instructions require use of all four sites (at the 5.0 g dose) on a daily basis and therefore wouldn't allow rotation of sites to minimize irritation potential.
- Data was presented by the sponsor for a small group of phase 3 patients (n=41) who were identified by the case report forms to have applied the drug to multiple application sites (three or four sites) on few occasions during the study period. This data was found to be inadequate evidence due to several reasons:
    - data originates from a group of phase 3 patients who'd deviated from the protocol (i.e. in using four sites instead of the protocol stipulated two site usage) and therefore use of such data for revising dosing instructions for clinical use is questionable and sets a low standard for drug approval.

    - multiple site usage was sporadic in these patients over the 180 day study period, with only 6 patients reporting more than one occasion of documented multiple site usage on PK days (i.e. on days 56, 112 or 182).
    - during the review it was identified that several of the patients did not apply the gel per the revised dosing table shown above (17 out of 41 patients). Additionally, the degree of supervision by the clinic staff for those in clinic doses couldn't be confirmed by the sponsor.
- Owing to the absence of a formal study to bridge the revised dosing instructions to the existing phase 3 clinical trial data and due to the deficiencies identified with the data presented in lieu of such a study, the Office of Clinical Pharmacology finds the clinical pharmacology information submitted in the major amendment for NDA 22-309 **not acceptable** for approval. The sponsor has not provided adequate evidence to show that the safety of the formulation remains unaffected under the proposed new conditions of use.

2 Question-Based Review

2.1 What is the relevant regulatory background leading up to this major amendment to NDA 22-309?

- The original NDA for AndroGel 1.62 % testosterone gel formulation was submitted on February 11, 2009. The dosing instructions provided to patients during the phase 3 clinical trial S176.3.104 were that over any seven-day period, study gel could be rotated between the upper arms/shoulders or the abdomen (e.g., four days upper arms/shoulders; three days abdomen). On PK sampling and titration days, dosing was to occur on shoulders/upper arms alone. The originally proposed dosing instructions for clinical use (per draft labeling submitted with the original NDA) were also that patients should apply gel once daily (preferably at the same time e (b) (4) . During the review cycle it was evident that interpersonal transfer potential was significant for the gel, and covering the application site with a clothing barrier (T-shirt) did not completely eliminate transfer.
- While washing the application site prior to physical contact was shown to prevent transfer, the clinical review team preferred a simpler method for preventing transfer (e.g. use of a T-shirt).
- These concerns were communicated to the sponsor in a teleconference held with the Division on October 01, 2009. In the meeting, sponsor expressed their interest in conducting a new transfer study to evaluate whether spreading out the gel on multiple sites (i.e. both upper arms/shoulders and both sides of abdomen, instead of either site alone) would minimize transfer potential.
- Division acknowledged the sponsor's proposal but also noted that even if the new application instructions proved successful in preventing transfer further information may be needed to link the existing safety and efficacy data to the new mode of administration.
- On November 9 and December 8, 2009, the Division received the November 6 and 24, 2009 major amendments to this application, containing additional clinical and clinical pharmacology safety information pertaining to a new transfer study and rationale associated with the applicability of completed clinical trial data to the new dosing instructions.
- Since the receipt date was within three months of the user fee goal date, the goal date was extended by three months to provide time for a full review of the submission. The extended user fee goal date is March 12, 2009.

2.2 What are the Clinical Pharmacology components of this amendment?

There are two components to the Clinical Pharmacology review of this major amendment:

1. Results from a new phase 1 study S176.1.009 evaluating the transfer potential to non-dosed females when contact occurred in presence of a T-shirt with

males who applied 5.0 g dose of the drug to multiple sites (both upper arms/shoulders and both sides of abdomen; i.e. 4 sites).

2. Bridging rationale including PK data from a sub-group of Phase 3 patients (S176.3.104) who'd applied the drug to multiple-sites (three or four sites) instead of the protocol-stipulated application to upper arms/shoulders (i.e. 2 sites) only on PK days.

2.3 What were the objectives and design of the new phase 1 clinical trial S176.1.009 and what are the major findings from this study?

- Study S176.1.009 was titled 'An Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62%'.

- The objectives of this study were as follows:

    - To determine the pharmacokinetics of total testosterone concentrations in female subjects after a single episode of skin contact with a male partner dosed with Testosterone Gel 1.62% (5 g).
    - To evaluate skin-to-skin testosterone transfer from males dosed with Testosterone Gel 1.62% (5 g) to non-dosed female subjects when contact with the application site, upper arms/shoulders and abdomen, occurs at 2 hours post-dose with a t-shirt barrier.

- The study design was that of a single center, single-dose (males only), open-label pharmacokinetic and transfer evaluation (to females only) study in healthy male and female volunteers.

- N = 12 male-female couples were enrolled and completed. The test product was Testosterone Gel 1.62%, 5 g of gel containing 81 mg testosterone.

- On Study Day 1 all male subjects received 5 g testosterone gel to four sites as follows: 1.25 g applied to the left upper arm/shoulder, 1.25 g applied to the right upper arm/shoulder, 1.25 g applied to the left abdomen and 1.25 g applied to the right abdomen.

- Female partners did not receive the test dose, but underwent transfer with their male partners at 2 h post-dose on day 1 with the male wearing a full-sleeved 100 % cotton T-shirt to cover the application sites. Female subjects were given a tube top to wear to expose the shoulders/arms and abdomen.

- For skin contact with the upper arms/shoulders and abdomen combination application site, a waistband was placed around the couple to ensure maximum contact. During the contact session, the couples swayed their abdomens in opposing directions (left/right) for duration of 1 minute starting at the beginning

of minute 2, 5, 8, 11, and 14. In addition, the female continuously kept her arms resting on the male's shoulders and for duration of 1 minute starting at the beginning of minute 3, 6, 9, 12, and 15, female subjects were instructed to rub their hands, wrists, arms, and shoulders up and down the upper arms and shoulders of their male partner.

- Whole blood samples for serum analyses of testosterone, dihydrotestosterone (DHT) and estradiol (E2) were collected from female participants only at the following time points during this study:

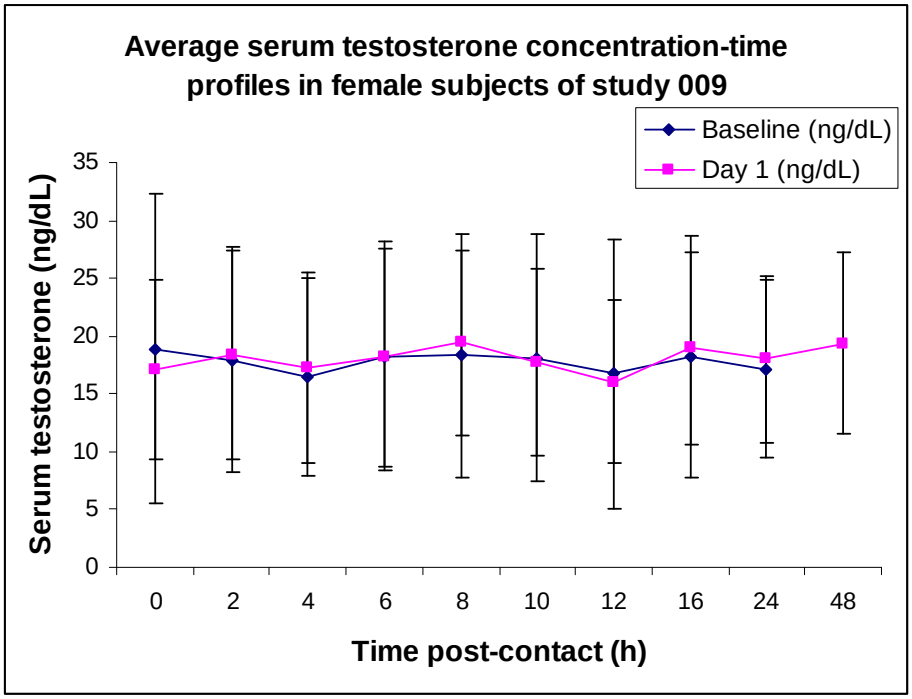
    - Day -1 (baseline) at 0, 2, 4, 6, 8, 10, 12, 16 hours with respect to the planned end time of skin contact on subsequent days.
    - Day 1 at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 16, 24, and 48 hours after the end of skin contact that occurred over 15 minutes starting at 2 hours following gel application in males.

- Serum concentrations of testosterone, DHT and E2 were determined using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methodology and pharmacokinetic data analyses were performed using non-compartmental methods.

Results:

- Average (SD) serum testosterone concentration-time profiles in N = 12 female subjects are shown at baseline (day -1) and on day 1 when contact occurred at 2 h post-dose to males who received 5 g of the new 1.62 % gel formulation. Males used long-sleeve t-shirt to cover the application sites during contact session.

Time (h)	Testosterone Day -1 (ng/dL)	SD	Testosterone Day 1 (ng/dL)	SD
0	18.88	13.36	17.15	7.73
2	17.97	9.77	18.4	9.02
4	16.42	8.57	17.26	8.2
6	18.24	9.91	18.19	9.42
8	18.3	10.59	19.42	8.05
10	18.1	10.72	17.73	8.11
12	16.75	11.66	16.06	6.99
16	18.2	10.44	18.94	8.26
24	17.16	7.73	18	7.17
48			19.39	7.9



- Baseline serum testosterone values in females were in the range of 6.31-57.3 ng/dL, with concentrations at most time points in most individuals typically at < 30 ng/dL (exception was subject 27446 who had baseline values ranging from 36-57.3 ng/dL).

- On day 1, after coming into contact with the testosterone application sites in males that were covered by clothing, testosterone concentrations in females were in general comparable to those seen at baseline. Testosterone concentrations on day 1 ranged between 6.31-43.5 ng/dL. No consistent increase or decrease was noted on day 1 in the change from baseline at various time points post-contact.

- Fold-changes from baseline in serum testosterone pharmacokinetics in female subjects are shown:

Subject	Cmax (ng/dL)	Cavg (ng/dL)
27445	1.74	1.13
27446	0.76	0.78
27448	1.16	1.16
27449	1.00	1.11
27450	1.23	1.21
27451	1.01	1.12
27452	1.10	1.02
27453	0.67	0.92
27454	1.24	1.16
27455	0.92	0.86
27456	1.04	1.13

27457	1.12	1.18
Average	**1.08**	**1.06**
Std Dev	**0.27**	**0.14**

- Fold-increase in Cavg on day 1 was 1.06 i.e. 6 % over baseline. On day 1, 8 out of 12 females demonstrated small increase in Cavg over baseline ranging from 1.13 fold to 1.21 fold. The absolute values of increase in Cavg in these females were in the range of 0.23 – 3.9 ng/dL. It is difficult to conclude whether these small changes are due to transfer or due to day-to-day variability in baseline testosterone concentrations in these females.
- Mean increases in Cmax were 1.08 on average i.e. 8 % over baseline. The individual fold increases ranged from 1.04 to 1.74 fold in 7 out of 12 individuals. The individual with the highest Cmax change over baseline was # 27445 who showed a net increase in Cmax over baseline of 16 ng/dL.
- This was a one-time occurrence in this individual in whom the remaining concentrations were identical to those in her baseline. Sponsor suspects that this individual's samples may have been switched with those of subject # 27446 whose PK was unexpectedly and markedly lower on day 1 compared to baseline. While no evidence was found in this regard, based on an inspection of the serum concentration-time profiles of these individuals it seems to be a likely explanation.

- In the original NDA for AndroGel 1.62 % gel formulation, two transfer evaluation studies were conducted. Study S176.1.003 assessed transfer to females when dosing and transfer occurred from the abdominal site with or without T-shirt on males. Study S176.1.008 evaluated among others, transfer of a low dose (2.5 g) from the abdomen with or without T-shirt in males. A side-by-side tabulation of absolute testosterone increases over baseline and fold-changes over baseline in females in these various studies is shown (T-shirt groups only):

	S176.1.003	**S176.1.008**	**S176.1.009**
Dose/Site(s)	**5.0g/Abdomen**	**2.5g/Abdomen**	**5.0g/upper arms/Shoulders & Abdomen**
Cavg			
Baseline adjusted Cavg; mean (s.d.)	8.61 (9.9) ng/dL	-1.14 (6.97) ng/dL	0.24 (3.75) ng/dL
Range of absolute increases in Cavg over baseline	0.3 – 31.5 ng/dL	1.5 -3.8 ng/dL	0.23 - 3.9 ng/dL
Cavg fold-changes over baseline Mean (Range)	1.58 [0.83-3.18]	1.00 [0.51-1.27]	1.06 [0.78-1.21]
Cmax			

Baseline adjusted Cmax; mean (s.d.)	17.1 (15.2) ng/dL	7.64 (6.09) ng/dL	5.66 (5.83) ng/dL
Range of absolute increases in Cmax over baseline	4.2 – 51.9 ng/dL	2.4- 5.6 ng/dL	0.20- 16.0 ng/dL
Cmax fold-changes over baseline Mean (Range)	1.53 [0.9-3.63]	0.80 [0.37-1.36]	1.08 [0.67-1.74]

Conclusions: The results from the new transfer study S176.1.009 suggest that the testosterone transfer to non-dosed females was largely mitigated when contact occurred with a T-shirt barrier on male who applied a 5.0 g dose of the 1.62 % gel formulation to 4 different application sites (both upper arms/shoulders and both sides of abdomen).

2.4 Subsequent to the findings of the new phase 1 transfer study S176.1.009, (b) (4) changes to the dosage and administration of AndroGel 1.62 % (testosterone gel) formulation, relative to that which was employed in the completed Phase 3 clinical program?

- (b) (4) revisions to the application instructions of AndroGel 1.62 % gel are being (b) (4) compared to those employed in the phase 3 clinical trial S176.3.104. In the Phase 3 clinical trial for AndroGel 1.62 % gel, the following instructions were provided to the patients with regard to application of the gel:
    - "The subject was instructed by the investigator (or designee) to apply the study medication gel topically once daily to intact, clean, dry skin of the upper arms/shoulders or abdomen for the duration of the study.
    - Application occurred after showering or bathing and when the skin was completely dry. Over any seven-day period, study gel could be rotated between the upper arms/shoulders or abdomen (e.g., four days upper arms/shoulders; three days abdomen). Gel was applied to shoulders/upper arms only during PK visits.
    - All patients started the study at a dose of 2.5 g of the 1.62 % gel. During the study, patients could be down-titrated to 1.25 g or up-titrated to 3.75 g or 5.0 g doses of the gel. Each pump actuation delivered 1.25 g of the gel. During visit days, the below application scheme was followed for application to the shoulder/upper arm region; application(s) occurred until subject's respective dose was reached:
        - The first 1.25 g was applied to one shoulder and spread across the maximum surface area.
        - The second 1.25 g was applied to the opposite shoulder and spread across the maximum surface area without re-applying gel to the previously dosed area.
        - The third 1.25 g was applied to one of the upper arms, from the edge of the shoulder region to just above the elbow and including the back of the arm. The gel was spread over the maximum surface area without re-applying gel to the previously dosed areas.

- The fourth 1.25 g was applied to the opposite upper arm area as described above without re-applying gel to the previously dosed areas.

- The proposed revisions recommend the use of both shoulders/upper arms as well as the abdomen for the two higher doses (3.75 g and 5.0 g), which is different from that used in the phase 3 clinical trial where dose was applied to either shoulders/upper arms or abdomen but not to both at the same time.
- While each of these sites have independently been assessed in earlier phase 1 and phase 3 trials, the surface area of application would approximately double when all 4 sites are used concurrently. At present, the effects of these increases in surface area on the PK (safety and efficacy) are not known for the AndroGel 1.62 % formulation.

2.5 Was there a bridging/comparative PK study to support the proposed changes to dose application (relative to that employed in the phase 3 clinical trial)? If there was no bridging study, what was the rationale provided in support of these modifications?

- No formal 'bridging' study was conducted to justify the applicability of the phase 3 clinical trial data to the newly proposed regimen involving use of multiple application sites.
- (b) (4). In addition, sponsor presents PK data from a small group of phase 3 patients who had deviated from the protocol by applying drug to multiple sites. Sponsor also notes that a relative bioavailability study conducted for AndroGel 1 % (approved formulation) did not show significant increases in

systemic testosterone concentrations when 4 sites of application instead of one site were used for dosing.

- Favorable aspects of this information that warrant further mention are as follows:

    - Evidence of bioavailability with new multi-site mode of application: PK profiles from patients who had applied gel to 3 or 4 sites (for 3.75 g or 5.0 g doses) on one or more PK days in the phase 3 trial suggests that the drug is bioavailable with characteristic peaks and troughs over a 24 hour period [see Appendix 2].
    - Comparison of this data from multiple site usage to PK profiles or PK parameters where only arms/shoulders or abdomen alone were used do not suggest marked differences (note that sample sizes are markedly different across these groups).
    - Titratable drug: The clinical use of AndroGel 1.62 % will involve titration to individual efficacious doses (i.e. maintenance of eugonadal testosterone concentrations).

2.6 *Are the*re *any unresolved issues with the new transfer study S176.1.009 and with the level of evidence presented in support of the revised dosing and administration changes?*

There are no unresolved issues with the new transfer study S176.1.009. However, there are several issues with the data and rationale presented in support of the revised application instructions:

- While dosing over multiple sites appears to mitigate transfer, no PK (efficacy) or safety data is currently available from continuous once daily application of the 1.62 % gel to multiple application sites (both sides of upper arms/shoulders and abdomen, without rotation).
- Neither the phase 3 clinical trial nor the phase 1 relative bioavailability studies to date for the 1.62 % formulation evaluated a combination of application sites, but rather employed each site independently or via rotation. Thus the available efficacy, safety and titratability information for the proposed formulation in the intended dose range (1.25 g to 5.0 g) is derived entirely from drug application to a reduced surface area (b) (4)
- The potential impact of increased (potentially doubled) surface area of gel application with the use of two additional application sites (relative to phase 3 usage) on PK is therefore not known for the 1.62 % formulation.
- Skin safety (irritation) data following continuous once daily application to all four sites is not available from the completed clinical trials. (b) (4)
- Available PK data from multiple site usage is from a subgroup of phase 3 patients who deviated from the study protocol with respect to site(s) of application. The

use of multiple sites in these individuals was not prospectively planned and was not adequately controlled.

- In addition, per CRF documentation several of these patients (17 out of 41) did not use multiple sites as intended in the proposed revised dosing instructions. Some patients either employed multiple sites where it was not required (e.g. for a 1.25 g or 2.5 g dose) or used it incorrectly (i.e. 3 sites for a 5.0 g dose or 4 sites for a 3.75 g doses of gel). The relevance of such data is therefore questionable.
- The degree of supervision during dose application on multiple sites in this subgroup couldn't be confirmed by the sponsor even for in-house dosing on visit days. Hence adherence to the proposed new dosing instructions (e.g. consistent application of 1.25 g of gel per each site) can't be confirmed.
- Use of multiple application sites was also sporadic in this subgroup with no evidence of consistent use over time; most patients had documented use of multiple sites only once during the 180 day study period. Since consistent daily use is not documented, the impact of earlier daily doses (possibly using different sites of application) on PK profiles resulting from the day of multiple-site usage is not known.
- From a regulatory perspective, use of this subgroup data requires post-hoc analyses of phase 3 information from a subgroup; Use of such data for revising dose application instructions for the entire patient population is questionable.
- While the 1 % and 1.62 % formulations are qualitatively similar, there are quantitative differences, the effect of which on drug absorption and PK is not known. For e.g. clinical trial formulations for the 1 % AndroGel product had (b) (4) % isopropyl myristate (IPM; (b) (4) while the new 1.62 % formulation contains (b) (4) IPM.
- The approved 1 % formulation also requires a larger volume of gel compared to the 1.62 % formulation. The impact of distributing a smaller volume of gel containing a (b) (4) and active ingredients on the absorption and therefore PK (safety and efficacy) is not known.
- While, the statistical analyses of the phase 1 study that evaluated PK differences with surface area of application for the AndroGel 1 % gel (UMD-96-012; small sample size of n= 9) concluded absence of significant differences, nevertheless there was ~25 % increase in Cavg for 4-sites vs. 1-site.
- It should also be noted that the earlier program for the 1 % formulation did not rely on the PK study alone to allow multiple-site application during clinical use. Instead the phase 3 program for that product included use of multiple application sites for the two higher doses (7.5 g and 10 g) and thus safety/efficacy as well titration success using this regimen was well established. In contrast, the current clinical program for the 1.62 % gel formulation did not allow simultaneous use of multiple sites in any of its clinical studies.
- Finally, the expectation that the phase 3 clinical trial reflects the conditions of clinical usage is not met due to the proposed revisions to the application regimen. The level of evidence provided in support of the change is not acceptable and further information is needed to bridge the gap.

2.7 Analytical

Were the Bioanalytical methods used in the analysis of samples from study S176.1.009 adequately validated and were the results of the study sample assay acceptable? Are there any unresolved analytical issues from the original NDA submission?

- The bioanalytical method validation and study sample assay findings for testosterone, DHT and estradiol were acceptable. There are no unresolved analytical issues with this submission. The determination of total testosterone and DHT in human serum samples from study S176.1.009 was done by UPLC with MS/MS detection. The same validated bioanalytical methods were used in the analysis of testosterone and DHT in the original NDA. The methods were adequately validated and findings were captured in the review of the original NDA. The results from the study sample assay were also acceptable and are briefly summarized:

- All three analysis batches in study 009 were accepted for assay of testosterone and DHT. The incurred sample reproducibility (ISR) results were also acceptable for both analytes. No sample was reassayed.

Validation:

- Response function: The average correlation coefficient for the 3 runs during the assay was 0.9984. The average correlation coefficient for the 3 runs during DHT assay was 0.9985. The intercepts were close to zero, the slopes were reproducible. The model used is a suitable calibration model.

- Testosterone and DHT in calibration standards (over the range of 5-1000 ng/dL) were back-calculated using the derived calibration curve parameters. Acceptable accuracy (% difference from theoretical) and precision (% CV) were demonstrated for standards justifying the use of the calibration model.

- Accuracy and Precision: Summary of accuracy and precision for individual QC samples in each of the 3 runs are shown below for testosterone and DHT:

- Testosterone QC results: The reported bias at the testosterone QC levels of 10, 25, 70, 220 and 760 ng/dL were 1.12, 2.07, 2.79, 0.542, and 0.735%, respectively.
- The inter-day C.V. was 6.29, 4.58, 3.24, 2.39, and 4.57% at these QCs, respectively.

- DHT QC results: The reported bias at DHT QC levels of 10, 25, 63, 220 and 753 ng/dL were 0.768, 1.95, 6.31, -0.520, and 7.23%, respectively.
- The inter-day C.V. was 6.37, 8.65, 8.15, 4.68, and 3.26% at these QC levels, respectively.

- Accuracy and Precision at the lowest calibration standard (5 ng/dL) were within 20 % thereby justifying the use of this standard as LLOQ.

Study samples:

- None of the testosterone values in study S176.1.009 samples were below the LLOQ. For DHT, several samples had concentrations below LLOQ of 5 ng/dL.

- 24 samples were re-assayed during the test for ISR. ISR samples met the pre-determined acceptance criteria (relative % difference vs. original analyses within 20 %).

Conclusion:

- Overall, the performance of the UPLC methods with MS/MS detection employed for testosterone and DHT assay during study 009 are acceptable. The analytical results are of sufficient integrity to be used in study conclusions.

Division of Scientific Investigations (DSI) audit findings and conclusions for Study S176.3.104:

> During the original NDA review cycle, at the request of Division of Clinical Pharmacology III, the DSI audited the analytical portion of the Phase 3 study S176.3.104. The analytical portion of the study was conducted at (b) (4), (b) (4). Following the inspection of (b) (4)), a Form FDA-483 was issued. Based on their assessment of the deficiencies noted and their potential impact, DSI provided the following recommendation to the Division:

"Following the above inspection, DSI recommends that the analytical portion of study S17 6.3.104 is acceptable for review".

There are no unresolved concerns related to analytical methodologies.

3 Detailed Labeling Recommendations

A detailed review of the labeling will not be conducted at this time.

4 Appendix

4.1 Individual Study Reviews

Appendix 1: Clinical Pharmacology review of study S176.1.009

Appendix 2: Pharmacokinetic data from a subgroup of Phase 3 patients

4.2 Consult Review (DSI)

Appendix 3: Division of Scientific Investigations (DSI) inspection review

APPENDIX 1: Clinical Pharmacology review of Study S176.1.009

S176.1.009: *An Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62%*

Investigator(s) and Study Center(s):
Lawrence Galitz, MD, Cetero Research, 1405 NW 167th Street, Miami Gardens, FL 33169

Study Period: 20 October 2009 (first subject enrolled) to 25 October 2009 (last subject completed)

Objectives:

- To determine the pharmacokinetics of total testosterone concentrations in female subjects after a single episode of skin contact with a male partner dosed with Testosterone Gel 1.62% (5 g).
- To evaluate skin-to-skin testosterone transfer from males dosed with Testosterone Gel 1.62% (5 g) to non-dosed female subjects when contact with the application site, upper arms/shoulders and abdomen, occurs at 2 hours postdose with a t-shirt barrier.

In addition, the safety of subjects was monitored and evaluated throughout the study.

Design: Single center, single-dose (in males), open-label pharmacokinetic and transfer evaluation (in females) study in healthy male and female volunteers.

N = 12 male-female couples were enrolled and completed.

Test product and dose: The test product was Testosterone Gel 1.62%, 5 g of gel containing 81 mg testosterone (Batch Number EA1214).

On Study Day 1 all male subjects received 5 g testosterone gel as follows:

1.25 g applied to the left upper arm/shoulder, 1.25 g applied to the right upper arm/shoulder, 1.25 g applied to the left abdomen and 1.25 g applied to the right abdomen

Details of dose application procedure (from the protocol) are as follows:

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

Site personnel directly involved with the dosing procedures wore gloves when handling the study gel. A fresh pair of gloves was used for each male subject. Each incremental gel dose of 1.25 g +/- 0.02 g was weighed on a sheet of weighing paper on a balance. The exact weight was recorded in the source documentation. Immediately after measuring the appropriate amount of gel, the weighing paper with the measured gel dose was wiped directly onto the subject's designated site of application by the study personnel. The subject rubbed the product into the skin of the designated application site using his hand. The gel should not be rubbed or massaged excessively. This process was repeated until the total target dose has been reached. After each 1.25 g dose increment is wiped onto the subject, the weighing paper was re-weighed to determine residual weight. This data was recorded in the source documentation.

Following the last incremental gel application, subjects waited at least 5 minutes for the gel to dry before putting clothes over the gel application area. Subjects thoroughly washed their hands with soap and water immediately after gel application is complete.

Details of skin contact:

Females did not receive the test dose, but underwent transfer with her male partner at 2 h post-dose on day 1 with male wearing a T-shirt to fully cover the application sites. Details are as follows:

At 2 hours post-dose, each couple engaged in 15 minutes of supervised contact of the dosed site. Female subjects showered within 30 minutes prior to the contact time and the abdomen and shoulders/arms were thoroughly dried. Female subjects were given a tube top to wear to expose the shoulders/arms and abdomen.

For skin contact with the upper arms/shoulders and abdomen combination application site, a waistband was placed around the couple to ensure maximum contact. During the contact session, the couples swayed their abdomens in opposing directions (left/right) for duration of 1 minute starting at the beginning of minute 2, 5, 8, 11, and 14. In addition, the female continuously kept her arms resting on the male's shoulders and for duration of 1 minute starting at the beginning of minute 3, 6, 9, 12, and 15, female subjects were instructed to rub their hands, wrists, arms, and shoulders up and down the upper arms and shoulders of their male partner.

After contact, female subjects were to wait at least 5 minutes prior to putting clothes over the exposed area. Female subjects thoroughly wash their hands with soap and water immediately after skin contact is complete. Female subjects were instructed not to shower or bathe until 24 hours after the contact period. The anticubital region of the females' arms was covered during the contact period to prevent potential blood sample contamination.

Clothing: A long-sleeved Gildan 100% cotton 6.1 oz. t-shirt was used to cover the site of gel application on males during the contact period. Females were given a tank-top during the transfer procedure to allow skin contact on abdomen and shoulders/upper arms with clothing on corresponding male application sites.

Pharmacokinetic blood-draws: Whole blood samples (6 mL) for serum analyses of testosterone (T), dihydrotestosterone (DHT) and estradiol (E2) were collected from female participants only at the following time points during this study:

- Day -1 (baseline) at 0, 2, 4, 6, 8, 10, 12, 16 hours with respect to the planned end time of skin contact on subsequent days.
- Day 1 at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 16, 24, and 48 hours after the end of skin contact that occurred over 15 minutes starting at 2 hours following gel application in males.

Bioanalytical assay: Serum concentrations of T, DHT and E2 were determined using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methodology by (b) (4)).

Pharmacokinetic analyses: Data analysis was done using noncompartmental methods with WinNonlin (Pharsight). PK parameters calculated include observed maximum and minimum serum concentrations (Cmax and Cmin), area under the serum concentration-time curve from zero to 24 hours (AUC0-24 or AUC0-τ), the lowest serum concentration observed over 24-hours (Cmin), average concentration over the dosing interval over a 24-hour period (Cavg), time to reach maximum observed serum concentration (Tmax), time of minimum observed serum concentration (Tmin), and peak to trough fluctuation (PTF).

Statistical methods: Comparison of PK parameters AUC0-24, Cmax and Cavg on day 1 to baseline (day -1) in females was the primary objective. Statistical comparisons were to be made to compare the difference between baseline (Day -1) and postdose (Day 1) for Cavg, AUC 0-24, and Cmax using a paired t-test on non-transformed data. If the data are normally distributed, 95% confidence intervals were to be constructed for the differences. In case of violations of normality, the Wilcoxon Signed Ranked test was to be used, and 95% confidence intervals around the median were to be constructed using the Hodges-Lehmann method. Ratio of means was to be expressed as a percentage relative to the mean of Day 1 for Cavg, AUC0-24, and Cmax. The 95% and 90% confidence intervals for the ratio of means were to be calculated for the non-transformed data.

The time to reach maximal observed concentration, Tmax, was not to be statistically tested. Sponsor notes that the data were not normally distributed for AUC and Cavg, thus a nonparametric signed rank test was used to assess change from baseline comparison. Cmax data was normally distributed, thus a paired t-test was used to assess change from baseline. Statistical analysis was performed using SAS version 8.2.

Safety: Per protocol, screening assessments included medical history, vital signs, 12-lead ECG, physical examination (including weight and height), DRE prostate examination for males, clinical laboratory determinations, testosterone measurement, serum β-HCG for females, and PSA measurement for males.

Final assessments included vital signs, 12-lead ECG, physical examination including weight, clinical laboratory determinations, PSA measurement and application site evaluation for males, and serum β-HCG and contact site evaluation for females.

Throughout the study vital signs, application site evaluation (males), contact site evaluation (females), adverse events and concomitant medications were monitored. Tests for blood alcohol and urinary drugs of abuse were performed at Screening and prior to the confinement period.

Results:

Subject disposition:

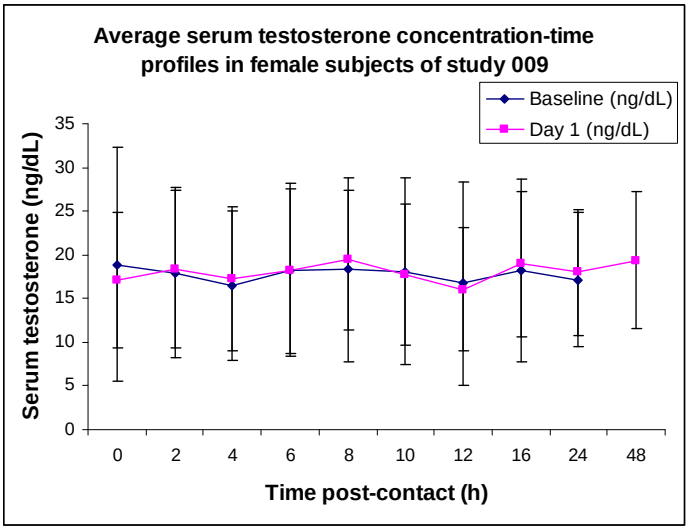
Subject Demographics (Mean (Range))

Gender	N	Age (years)	BMI (kg/m^2)
Males	12	46 (23-59)	27 (21-31)
Females	12	41 (24-50)	25 (21-30)

Concentration-time data:

Average serum testosterone concentration-time profiles in N = 12 female subjects are shown when contact occurred at 2 h post-dose to males who received 5 g of the new 1.62 % gel formulation; males used long-sleeve t-shirt to cover the application sites during contact session.

Time (h)	Testosterone Day -1 (ng/dL)	Std Dev	Testosterone Day 1 (ng/dL)	Std dev
0	18.88	13.36	17.15	7.73
2	17.97	9.77	18.4	9.02
4	16.42	8.57	17.26	8.2
6	18.24	9.91	18.19	9.42
8	18.3	10.59	19.42	8.05
10	18.1	10.72	17.73	8.11
12	16.75	11.66	16.06	6.99
16	18.2	10.44	18.94	8.26
24	17.16	7.73	18	7.17
48	-	-	19.39	7.9



Individual serum testosterone concentration data and C-T profiles are shown below. Baseline serum testosterone values in females were in the range of 6.31-57.3 ng/dL, with concentrations at most time points in most individuals typically at < 30 ng/dL (exception was subject 27446 who had baseline values ranging from 36-57.3 ng/dL).

On day 1, after coming into contact with the testosterone application sites in males that were covered by clothing, testosterone concentrations were in general comparable to those seen at baseline. T concentrations in females on day 1 ranged between 6.31-43.5 ng/dL. No consistent trend (increase or decrease) was noted on day 1 in the change from baseline at various time points post-contact.

Testosterone concentration data in individuals

(b) (6)

Individual concentrations at various time points after baseline-adjustment are shown:

Baseline adjusted serum testosterone concentrations in females on day 1:

Subj									
27445	(b) (4)								
27446									
27448									
27449									
27450									
27									
27452									
27453									
27454									
27455									
27456									
27457									
N	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
MEAN	**-1.73**	**0.42**	**0.85**	**-0.05**	**1.1**	**-0.37**	**-0.69**	**0.74**	**0.85**
STDEV	**6.35**	**2.05**	**2.93**	**4.53**	**11.36**	**4.87**	**5.75**	**4.89**	**2.45**
SEM	**1.83**	**0.59**	**0.85**	**1.31**	**3.28**	**1.41**	**1.66**	**1.41**	**0.71**
MIN	**-20.6**	**-2.5**	**-3.98**	**-7.8**	**-23.3**	**-10.7**	**-17.9**	**-10.4**	**-4.8**
MAX	**2.95**	**3.8**	**5.3**	**10.6**	**20.8**	**5.3**	**4.9**	**9.8**	**3.6**
%CV	**-367.46**	**485.11**	**344.73**	**-9535.79**	**1029.13**	**-1332.03**	**-832.71**	**661.69**	**289.23**
MEDIAN	**-0.25**	**0.33**	**0.54**	**-0.05**	**2.45**	**1.37**	**0.3**	**1.64**	**0.55**

Individual plots comparing baseline to day 1 testosterone concentrations are shown:

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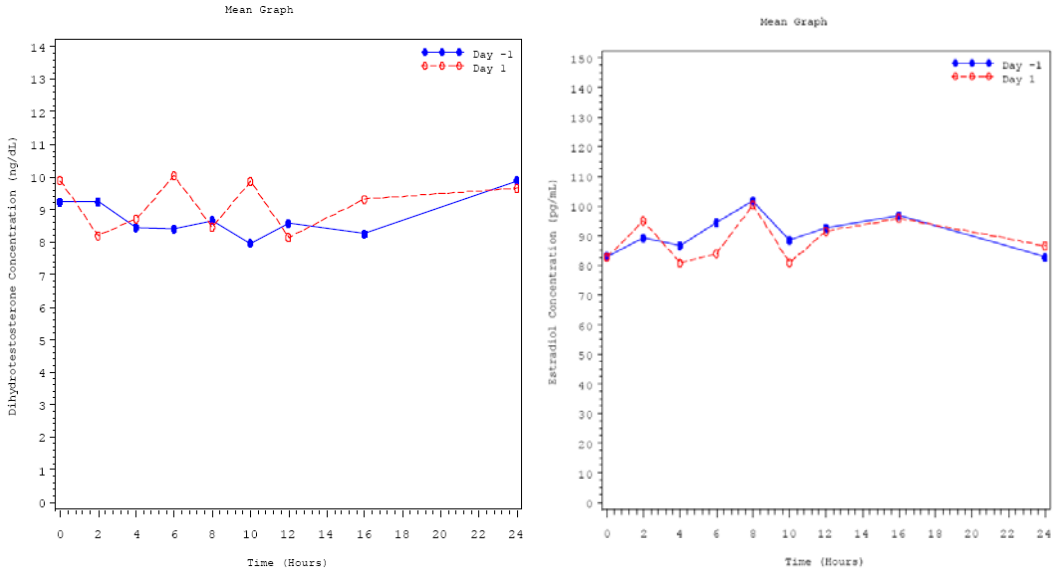
The highest increase over baseline in this study was observed in subject 27445 at 8 h post-dose (20.8 ng/dL). The remaining concentrations in this individual were similar to the baseline T levels. A clear separation (in the upward direction) of the C-T profiles on day 1 relative to baseline was noted in 3 of the individuals (27450, 27454, 27457). The highest concentrations in these subjects were observed around 6-12 h post dose and represented 4.9- 10.8 ng/dL increases over baseline. In the remaining individuals concentration profiles on day 1 either overlapped or were interspersed (without a consistent trend towards increase or decrease) with those on day -1.

Average c-t profiles for dihydrotestosterone and estradiol are shown below:



Pharmacokinetic parameters:

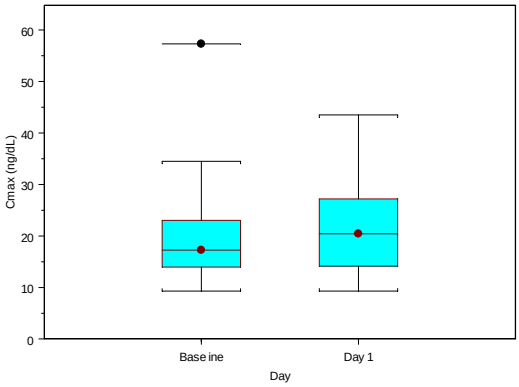
PK parameters generated by reviewer using WinNonlin (version 5.2) are provided below for each patient. Non-compartmental analysis was done (extravascular input; dose = 5 g; steady-state dosing; Tau- 24 h).

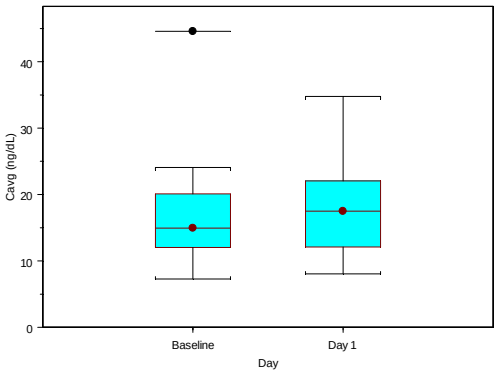
Day -1 (baseline):

Subject	Tmax (h)	Cmax (ng/dL)	AUCall (ng.h/dL)	Clast (ng/dL)	Tmin (h)	Cmin (ng/dL)	Cavg (ng/dL)	Fluc %
27445	2	21.50	430.70	17.40	4.00	15.70	17.95	32.32
27446	0	57.30	1070.10	36.70	24.00	36.70	44.59	46.20
27448	24	24.60	528.00	24.60	16.00	18.70	22.00	26.82
27449	24	9.29	174.78	9.29	8.00	6.31	7.28	40.92
27450	16	21.10	436.00	19.00	6.00	15.30	18.17	31.93
27451	16	16.30	324.05	12.90	0.00	9.95	13.50	47.03
27452	0	14.50	309.87	12.70	12.00	9.79	12.91	36.48
27453	8	34.50	607.80	20.80	24.00	20.80	24.06	56.95
27454	10	17.60	369.10	15.40	4.00	14.40	15.38	20.81
27455	6	13.40	267.92	9.40	12.00	8.74	11.16	41.74
27456	2	11.80	234.82	10.80	12.00	8.14	9.78	37.41
27457	24	16.90	348.10	16.90	4.00	11.40	14.50	37.92
Average		21.57	425.10	17.16	10.50	14.66	17.61	38.04
Std Dev		13.08	236.69	7.73	7.78	8.23	9.78	9.64
Median	9							

Day 1 (post-contact PK)

Subject	Tmax (h)	Cmax (ng/dL)	AUCall (ng.h/dL)	AUC0-24 (ng.h/dL)	Clast (ng/dL)	Tmin (h)	Cmin (ng/dL)	Cavg (ng/dL)	Fluc %
27445	8	37.50	943.90	486.70	21 00	12.00	15.70	20.28	107.50
27446	6	43.50	1662.40	834.40	37.10	8.00	19 80	34.77	68.17
27448	16	28.50	1289.60	611.60	28 30	6.00	19 60	25.48	34.92
27449	24	9.31	428.54	193.22	10 30	12.00	6 31	8.05	37.26
27450	6	25.90	1029.90	529.50	19 90	4.00	18 20	22.06	34.90
27451	8	16.50	810.80	362.00	21 00	0.00	12 90	15.08	23.87
27452	24	16.00	755.90	315.50	20.70	16.00	11.10	13.15	37.27
27453	24	23.20	1030.10	529.70	18 50	8.00	17 60	22.07	25.37
27454	8	21.80	835.60	428.80	17.70	4.00	14 50	17.87	40.86
27455	8	12.30	420.92	230.48	7.42	10.00	7 39	9.60	51.13
27456	6	12.30	537.89	264.29	11.70	10.00	9.49	11.01	25.52
27457	10	19.00	836.50	410.50	19.10	4.00	16 00	17.10	17.54
Average		22.15	881.84	433.06	19 39	7.83	14 05	18.04	42.03
Std Dev		10.38	354.79	181.14	7.91	4.47	4 63	7.55	24.64
Median	8								





Summary of baseline-adjusted total testosterone PK parameters in females:

Subject	Cmin (ng/dL)	Cmax (ng/dL)	Tmax (h)	Tmin (h)	AUC0-24 (ng*h/dL)	Cavg (ng/dL)	PTF (%)
27445	-2.90	20.80	8.00	0.00	50.70	2.11	1123.22
27446	-23.30	-0.60	6.00	8.00	-235.70	-9.82	-231.16
27448	-3.60	9.80	16.00	6.00	79.53	3.31	404.83
27449	-0.72	2.27	16.00	12.00	13.04	0.54	553.70
27450	1.40	10.60	6.00	0.00	92.30	3.85	238.96
27451	-0.40	3.80	2.00	12.00	37.27	1.55	270.97
27452	-3.20	3.30	24.00	16.00	5.22	0.22	2954.55
27453	-16.90	2.40	24.00	8.00	-78.10	-3.25	-593.85
27454	-0.90	6.90	8.00	0.00	54.51	2.27	343.61
27455	-4.29	0.80	8.00	6.00	-37.44	-1.56	-326.28
27456	-1.71	3.00	16.00	10.00	25.45	1.06	444.34
27457	-0.50	4.90	12.00	24.00	61.32	2.55	211.76
N	12.00	12.00	12.00	12.00	12.00	12.00	12.00
MEAN	-4.75	5.66	12.17	8.50	5.68	0.24	449.56
STDEV	7.47	5.83	7.11	7.09	89.97	3.75	906.53
STDERR	2.16	1.68	2.05	2.05	25.97	1.08	261.69
MIN	-23.30	-0.60	2.00	0.00	-235.70	-9.82	-593.85
MAX	1.40	20.80	24.00	24.00	92.30	3.85	2954.55
CV	-157.26	102.93	58.42	83.42	1585.46	1589.21	201.65
MEDIAN	-2.31	3.55	10.00	8.00	31.36	1.31	307.29

Note: Baseline is defined as the Day -1 total testosterone concentration at each time point. For each subject, the Day -1 pre-dose concentration at a specific time-point was subtracted from its corresponding Day 1 post-dose concentration.

After baseline-adjustment of serum testosterone concentrations, the Cmax and Cavg (average) values were 5.66 ng/dL and 0.24 ng/dL, respectively. The highest values of testosterone Cmax and Cavg following baseline-adjustment were 20.8 ng/dL and 3.85 ng/dL, respectively.

Baseline adjusted PK parameters are shown (data analyses was done using individual day 1 and day -1 concentrations and then PK parameters are adjusted for baseline):

Change from baseline in PK parameters (Testosterone in females of study 009):

Subject	Cmax (ng/dL)	AUC24 (ng.h/dL)	Cmin (ng/dL)	Cavg (ng/dL)
27445	16.00	56.00	0.00	2.33
27446	-13.80	-235.70	-16.90	-9.82
27448	3.90	83.60	0.90	3.48
27449	0.02	18.44	0.00	0.77
27450	4.80	93.50	2.90	3.90
27451	0.20	37.95	2.95	1.58
27452	1.50	5.63	1.31	0.23
27453	-11.30	-78.10	-3.20	-1.99
27454	4.20	59.70	0.10	2.49
27455	-1.10	-37.44	-1.35	-1.56
27456	0.50	29.47	1.35	1.23
27457	2.10	62.40	4.60	2.60
Average	0.59	7.95	-0.61	0.44
Std Dev	7.59	91.11	5.53	3.70

Statistical analyses outcomes:

Sponsor's statistical results are presented below:

Testosterone Gel 1.62% Median Difference, Ratio of LSM, 90% and 95% Confidence Intervals (CI) N = 12 females						
Parameter	**Median Difference (Day 1 – Day -1)**	**95% CI for Median Difference**	***p*-value**	**Ratio of LSM[a] (Day -1/ Day 1)**	**90% CI for Ratio of LSM**	**95% CI for Ratio of LSM**
AUC_{0-24} (ng-hr/dL)	33.985	-80.00, 159.99	0.3013	95.24	88.28, 102.75	86.78, 104.53
C_{avg} (ng/dL)	1.42	-3.33, 6.67	0.3013	95.24	88.28, 102.75	86.78, 104.52
C_{max} (ng/dL)	1.6	-4.60, 7.30	0.3013	94.84	83.60, 107.59	81.25, 110.70

Median difference and 95% confidence interval for the median difference were calculated using Hodges-Lehmann method.
#P-value was calculated from Wilcoxon Signed Rank test.
*Ratio, 90% and 95% confidence interval for the LSMeans were calculated based on Ln-transformed data. LSMeans were derived from GLM model using Subject as a random effect and Day as a fixed effect.

A 95% confidence interval around the median difference between baseline (Day -1) and post-dose (Day 1) total testosterone concentrations in female subjects for non-transformed AUC0-24, Cavg and Cmax was constructed. The confidence interval for all parameters contained 0, indicating that there was no significant change in total testosterone concentrations in females from Day -1 to Day 1.

The 90% and 95% confidence intervals for the ratio of least squares means relative to Day 1 for nontransformed AUC0-24, Cavg and Cmax were also calculated. The Day -1/Day 1 ratios were within 6% for all parameters and the 90% and 95% confidence intervals were all within 80 to 125%.

Additional analyses: The sponsor notes the following in the final study report about couple of observations of testosterone that were different from the rest of the profile in these individuals:

Visual inspection of the serum concentration data suggested that some samples may have been switched. Comparison of the 8 h samples from Subject 27453 and Subject 27454 and also the 8 h samples from Subject 27445 and Subject 27446 suggested that the Day 1 total testosterone and estradiol samples within both pairs of subjects may have been switched. An investigation was conducted by the Quality Assurance group of Cetero Research – Miami; the investigation did not find conclusive evidence of samples being switched at the clinical site. The analytical laboratory also investigated the apparent discrepancy, and no conclusive evidence of a switch was found.

An additional pharmacokinetic/statistical analysis was subsequently conducted in which the 8 h samples from the affected subjects were treated as missing. The results of these analyses show that there was little impact on the final results. The 95% confidence interval for the median difference still included zero for all parameters, and the 90% and 95% confidence intervals for the ratio of least squares means were still within 80 to 125%. The results of this secondary analysis are summarized in the table below:

Parameter	Median Difference (Day 1 – Day -1)	95% CI for Median Difference	Ratio of LSM (Day -1/Day 1)	90% CI for Ratio of LSM	95% CI for Ratio of LSM
AUC_{0-24} (ng-hr/dL)	18.99	-80.00, 140.75	95.45	89.07, 102.28	87.69, 103.89
C_{avg} (ng/dL)	0.785	-3.33, 5.86	95.44	89.06, 102.28	87.68, 103.89
C_{max} (ng/dL)	1.35	-4.80, 6.30	99.54	90.77, 109.16	88.90, 111.46

Based on the c-t profiles presented for individual subjects above it appears likely that the samples at 8 h for subjects 27455 and 27456 may have been switched during the study or analyses. However, there is no concrete evidence at this time to support this and data needs to be retained. The fold-change over baseline in the Cmax of subject 27455 was the highest in this study (1.74-fold), although the net effect on the overall AUC and Cavg was small (1.17-fold) since this increase over baseline was noted at only one time point post-dose.

Fold-changes from baseline in serum testosterone pharmacokinetics in females are shown:

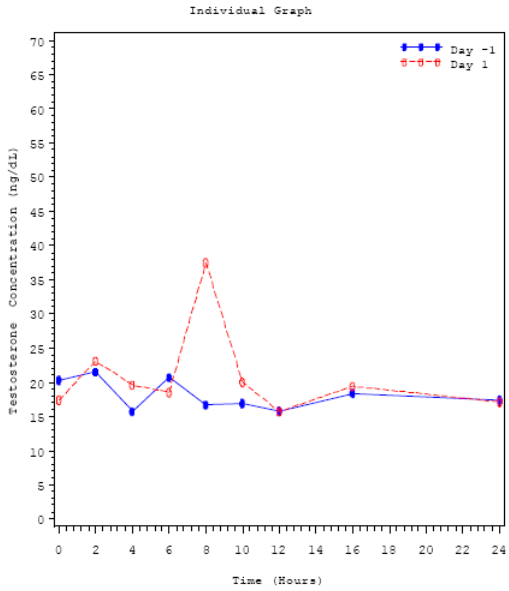
Fold changes (Day 1/Day -1)

Subject	Cmax (ng/dL)	AUC24 (ng.h/dL)	Cmin (ng/dL)	Cavg (ng/dL)
27445	1.74	1.13	1.00	1.13
27446	0.76	0.78	0.54	0.78
27448	1.16	1.16	1.05	1.16
27449	1.00	1.11	1.00	1.11
27450	1.23	1.21	1.19	1.21
27451	1.01	1.12	1.30	1.12
27452	1.10	1.02	1.13	1.02
27453	0.67	0.87	0.85	0.92
27454	1.24	1.16	1.01	1.16
27455	0.92	0.86	0.85	0.86
27456	1.04	1.13	1.17	1.13
27457	1.12	1.18	1.40	1.18
Average	1.08	1.06	1.04	1.06
Std Dev	0.27	0.14	0.23	0.14

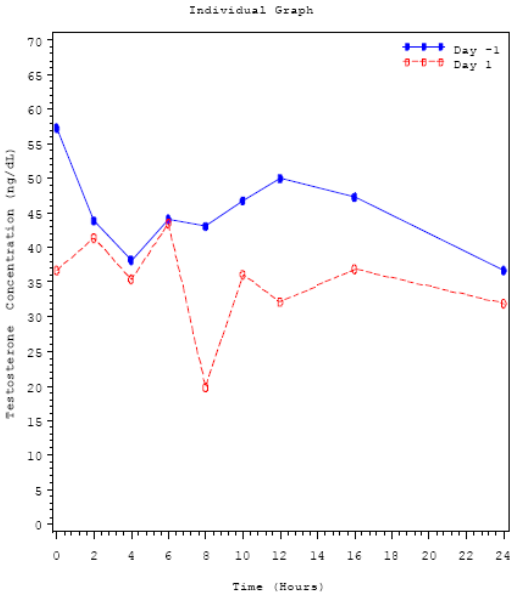
Fold-increase in Cavg on day 1 was 1.06 i.e. 6 % over baseline. On day 1, 8 out of 12 females demonstrated small increase in Cavg over baseline ranging from 1.13 fold to 1.21 fold. The absolute values of increase in Cavg in these females were in the range of 0.23 – 3.9 ng/dL. It is difficult to conclude whether these small changes are due to transfer or due to day-to-day variability in baseline testosterone concentrations in these females. Mean increases in Cmax were 1.08 on average i.e. 8 % over baseline. The individual fold increases ranged from 1.04 to 1.74 fold in 7 out of 12 individuals. The individual with the highest Cmax change over baseline was # 27445 who showed a net increase in Cmax over baseline of 16 ng/dL. This was a one-time occurrence in this individual in whom the remaining T concentrations were identical to that in her baseline. Sponsor has expressed doubts that this individuals samples may have been switched with those of # 27446 whose PK was unexpectedly and markedly lower on day 1 compared to baseline. While no evidence was found in this regard, it seems to be a likely explanation.

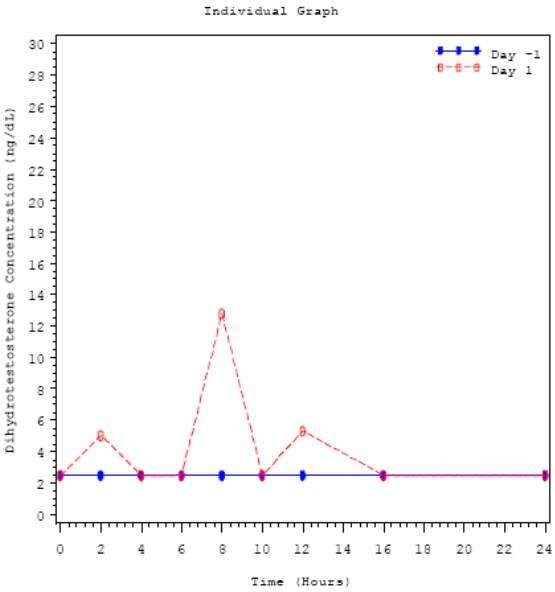
Serum total testosterone and dihydrotestosterone profiles (possible 8 h sample mix-up):

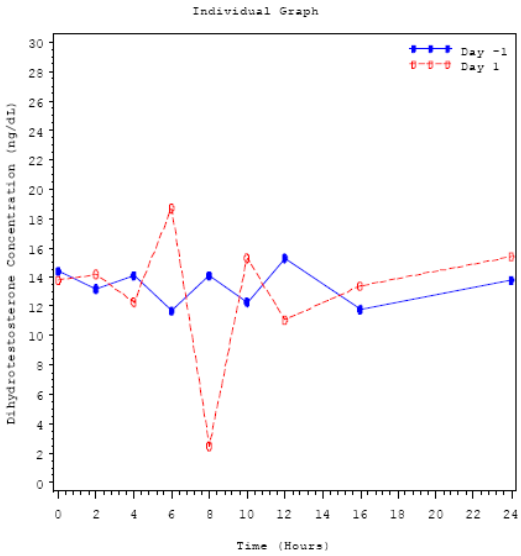
Subject 27445



Subject 27446







Conclusions: Testosterone transfer to non-dosed females was largely mitigated when contact occurred with a T-shirt barrier on male who applied a 5.0 g dose of the 1.62 % gel formulation to 4 different application sites (both upper arms/shoulders and both sides of abdomen).

Comparing results across various transfer studies in NDA 22309 (T-shirt related only):

	S176.1.003	S176.1.008	S176.1.009
Dose/Site(s)	5.0g/Abdomen	2.5g/Abdomen	5.0g/ArmSho & Abdomen
Baseline adjusted Cavg; ng/dL; mean (s.d.)	8.61 (9.9)	-1.14 (6.97)	0.24 (3.75)
Range of absolute increases (if any) in individuals in Cavg over baseline	0.3 – 31.5 ng/dL	1.5 -3.8 ng/dL	0.23 - 3.9 ng/dL
Cavg fold-changes over baseline Mean (Range)	1.58 [0.83-3.18]	1.00 [0.51-1.27]	1.06 [0.78-1.21]
Baseline adjusted Cmax; ng/dL; mean (s.d.)	17.1 (15.2)	7.64 (6.09)	5.66 (5.83)
Absolute increases in individuals in Cmax over baseline	4.2 – 51.9 ng/dL	2.4- 5.6 ng/dL	0.20- 16.0 ng/dL
Cmax fold-changes over baseline Mean (Range)	1.53 [0.9-3.63]	0.80 [0.37-1.36]	1.08 [0.67-1.74]

APPENDIX 2: Pharmacokinetic data from a subgroup of phase 3 patients

Table 1: Testosterone PK in a subgroup from study S176.3.104 on days when gel application occurred on multiple sites (i.e. 3 sites for 3.75 g or 4 sites for 5.0 g doses)

Day	Dose (g)	ID	Sites used	Cmax (ng/dL)	Cavg (ng/dL)
56	3.75 g	007-001	3	972	779
		007-005	3	706	427
		013-015	3	552	450
		034-013	3	470	389
		044-003	3	303	246
		044-007	3	539	407
		063-005	3	761	678
		067-001	3	1440	519
182	3.75 g	013-015	3	866	574
		015-005	3	379	331
		047-005	3	1140	711
	Average (ng/dL)			**738.9**	**501**
56	5.0 g	021-010	4	309	292
		031-003	4	492	243
		031-010	4	720	489
		034-021	4	653	462
		053-004	4	121	93.2
		063-006	4	682	473
56	5.0 g	049-034	4	789	535
		050-008	4	754	619
112	5.0 g	021-010	4	505	270
		031-003	4	466	261
		042-013	4	1860	1180
		049-034	4	1050	865
		050-008	4	648	494
		064-006	4	1940	1160
182	5.0g	031-003	4	567	356
		042-013	4	1700	1180
		049-023	4	672	509
		049-034	4	1190	802
		050-016	4	430	392
		053-004	4	272	177
		053-005	4	619	566
		053-010	4	738	419
		050-008	4	1280	596
	Average (ng/dL)			**802.48**	**540.57**

- Data from 17 out of 41 patients originally presented by the sponsor were not considered as dose application to multiple sites in those patients did not align to the (b) (4) (revised) application instructions.
- Individuals who had more than one PK record using multiple site usage (N = 6 patients) are color coded. Most patients (rows not highlighted in the table above; N = 17) had only one PK record that documents correct use of multiple-site usage over the 180 day study period.

Table 2: Average testosterone Cavg and Cmax values based on the application site(s) used on the day before and/or day of PK sampling, across all PK days post-titration during the 180 day study period of study S176.3.104:

	Dose	Arms/Shoulders	Abdomen	Both sites
Cmax [ng/dL]	3.75 g	886	672	739
	5.0 g	772	813	802
Cavg [ng/dL]	3.75 g	600	464	501
	5.0 g	494	554	540
N = number of post-titration PK values contributed by study patients (i.e. based on PK profiles from days 56, 112 and 182)				
N = 120, 9, 11 respectively for Arms/Sho, Abdomen and Both sites (3.75 g dose);				
N = 190, 11, 24 respectively for Arms/Sho, Abdomen and Both sites (5.0 g dose)				

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Appendix 3: DSI consult review

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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

/s/

SANDHYA K APPARAJU
03/04/2010

MYONG JIN KIM
03/04/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-309	Submission Date(s): 02/11/2009; 05/14/2009; 09/02/2009; 09/17/2009
Brand Name	AndroGel®
Generic Name	Testosterone gel
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology III (DCP3)
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Solvay Pharmaceuticals on behalf of Unimed Pharmaceuticals, LLC
Relevant IND(s)	50,377
Submission Type	Original
Formulation; Strength(s)	Topical gel; 1.62 %
Indication	Testosterone replacement in hypogonadal males

A required inter-divisional OCP briefing for NDA 22-309 was held on October 6, 2009 from 3.30 – 4.30 PM in WO Bldg 51 Conf Room 4300. Attendees included Drs. Dennis Bashaw, Hae Young Ahn, Myong Jin Kim, Mark Hirsch, Roger Wiederhorn, Mehul Mehta, Brian Booth, Chandra Sahajwalla, Gilbert Burckart, Donny Tran, Jee Eun Lee, Julia Cho, Dilara Jappar, Ting Eng Ong, Chinmay Shukla, Elimika Pfuma, Li Zhang and Sandhya Apparaju.

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1 Executive Summary

1.1 Recommendation

NDA 22-309 is acceptable from a Clinical Pharmacology perspective provided an agreement can be reached with the sponsor with respect to the labeling language.

An inspection of the Phase 3 Bioanalytical site (b) (4)) by the Division of Scientific Investigations (DSI) is pending at this time. An addendum to this review will be entered in DARRTS when the results of this inspection are available.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The subject of this new NDA 22-309 is AndroGel® (testosterone gel) 1.62 % a new testosterone gel formulation developed by Solvay Pharmaceuticals, Inc. The proposed indication for AndroGel 1.62% is testosterone replacement in adult males for conditions associated with a deficiency or absence of endogenous testosterone such as primary or secondary hypogonadism. Sponsor has conducted several Clinical and Clinical Pharmacology studies to support their new formulation.

Currently the AndroGel® testosterone gel 1% formulation is approved in the U.S. *[NDA 21015; approved 02/28/2000; Unimed Pharmaceuticals, a Solvay Pharmaceuticals Inc. company]*. The approved 1 % formulation necessitates use of 4 – 8 actuations of the pump (1.25 g gel per actuation) for topical application of 5 g – 10 g gel doses (equivalent to 50 mg – 100 mg testosterone). The proposed AndroGel 1.62% gel formulation requires 1 – 4 pump actuations (of 1.25 g each) for topical application of 1.25 g – 5g gel doses equivalent to ~ 20.25 mg- 81 mg of testosterone.

The proposed starting dose for Androgel 1.62 % gel formulation is 2.5 g (equivalent to 40.5 mg testosterone) applied once daily to clean, dry, healthy, intact skin of either the shoulders/upper arms (b) (4). Dose can subsequently be increased or decreased in 1.25 g (or 20.25 mg testosterone) increments within the range of 1.25 g – 5.0 g (equivalent to 20.25 mg – 81 mg testosterone).

In phase 3 clinical trial of Androgel 1.62 % gel, all patients started at a 2.5 g gel dose and three subsequent up or down dose titrations in 1.25 g increments were allowed as needed in the 1.25 g and 5 g range. Dose adjustment was based on pre-dose measurement of serum total testosterone in the patients after two weeks on treatment. If pre-dose value was < 350 ng/dL the dose was increased by 1.25 g (or 20.25 mg testosterone) increments and if pre-dose serum testosterone was > 750 ng/dL the dose was reduced by 1.25 g increments, within the 1.25 g – 5.0 g range. If patient has a serum pre-dose testosterone value between 350 – 750 ng/dL, the current dose level was maintained.

NDA 22-309 includes various phase 1 studies and one phase 3 clinical trial in hypogonadal males. With the exception of the transfer studies, all clinical studies were conducted in the target hypogonadal male population. Study results are summarized:

Pivotal phase 3 trial: The efficacy and safety of a testosterone gel 1.62% were evaluated in the phase 3 clinical trial S176.3.104 following administration of active gel treatment or placebo to 279 hypogonadal men for a period of 182 days. Patients started at a dose of 2.5 g applied once-daily to clean, intact skin of either shoulders/upper arms or abdomen. Patients returned to clinic for pre-dose blood-draws for serum testosterone assessment on days 14, 28 and 42 (titration days) during the study. Patients returned within 2 days for potential dose titrations. If the pre-dose testosterone on titration days was < 350 ng/dL dose was up-titrated. If levels were > 750 ng/dL, dose was down-titrated. If the pre-dose testosterone value stayed within the 350 – 750 ng/dL range, patients remained on their current dose level. Overall three dose titrations were allowed. Patients remained on their final titrated dose level from ~day 42 onwards till the remainder of the study. Patients also returned for extensive PK sampling over 24 hours on day 14, day 56 and day 112 (day of pivotal efficacy evaluation) during the pivotal phase of the trial.

Efficacy: Success in the study was defined as ≥75% of subjects on active treatment with Cavg (average total testosterone levels over the dosing interval) within the normal serum testosterone concentration range of 300-1000 ng/dL on day 112. In addition, the 95 % confidence interval surrounding the treatment mean for responders was to be at least 65 %.

A critical secondary endpoint was to evaluate total testosterone observed maximum serum concentration (Cmax) values during the first 182 days of the study. The individual total testosterone Cmax values were to be in the following ranges:

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

Results: On day 112 (i.e. primary efficacy endpoint evaluation), the proportion of responders for the active treatment groups was 81.6 % [146/179; 95 % CI: 75.1 – 87.0], thus fulfilling the pre-defined primary endpoint success criteria. This rate was significantly different compared to 37 % responder rate observed in the placebo group (p < 0.0001). The number and percentage of subjects achieving target range for average testosterone (Cavg) by day and treatment in the full analysis (FA) sample are shown:

Population	Study Day	Testosterone gel 1.62%		Placebo		p-value
		n/N (%)	95% CI	n/N (%)	95% CI	
FA	14	138/210 (65.7)	(58.9, 72.1)	11/37 (29.7)	(15.9, 47.0)	<0.0001
	56	151/183 (82.5)	(76.2, 87.7)	11/32 (34.4)	(18.6, 53.2)	<0.0001
	112	146/179 (81.6)	(75.1, 87.0)	10/27 (37.0)	(19.4, 57.6)	<0.0001
	182	139/169 (82.2)	(75.6, 87.7)	8/28 (28.6)	(13.2, 48.7)	<0.0001

Cmax-based secondary endpoint: Overall, across all PK days (14, 56, 112 and 182 days), in the full analysis sample 93.9 % of patients had Cmax values ≤ 1500 ng/dL; 3 % of patients had Cmax values between 1800-2500 ng/dL and 0.8 % of patients had Cmax values > 2500 ng/dL (data regardless of dose) . Ten patients had a total of 11 observations of total testosterone concentration > 2500 ng/dL during the double blind phase of the study. These instances of testosterone outliers were infrequent, random and generally attributable to either sample contamination or potential compliance issues with the dose and/or regimen based on narratives submitted for each of these individuals.

Safety: The overall incidence of adverse events was higher in the active treatment group (55.6 %) compared to the placebo group (37.5 %). The most common (≥2% in the testosterone gel 1.62% groups) treatment-emergent adverse events in the active group were increased PSA (23/234, 9.8% vs. no subject in the placebo), upper respiratory tract infection, (11/234, 4.7% vs. no subject), back pain (7/234, 3.0% vs. no subject), headache (7/234, 3% vs. 2/40, 5.0%), insomnia (7/234, 3.0% vs. 1/40, 2.5%), hypertension (6/234, 2.6% vs. no subject), and diarrhea, nasopharyngitis, myalgia, and dermatitis contact (5/234, 2.1% vs. no subject for placebo).

Overall, results from the phase 3 clinical trial S176.3.104 support the use of a 2.5 g (i.e. 40.5 mg testosterone) starting dose of AndroGel 1.62 % gel in hypogonadal male patients. Information from this trial supports pre-dose testosterone -based titration to individual efficacious doses in the 1.25 g – 5.0 g dose range (equivalent to 20.25 – 81 mg testosterone doses).

Pharmacokinetics: Single dose and multiple dose pharmacokinetics of testosterone, and its metabolites dihydrotestosterone (DHT) and estradiol (E2) following once daily doses of Androgel 1.62 % gel have been adequately characterized over a dose range of 1.25 g to 6.25 g (20.25 -101.25 mg testosterone doses). Steady state pharmacokinetics of total testosterone (observed) from the multiple dose PK study S176.1.002 are shown:

Day 14	1.25 g (n = 9-11)	2.5 g (n = 10-11)	3.75 g (n = 11)	5.0 g [n = 7-8]	6.25 g (n = 10)
Cavg ng/dL	345 ± 137	377 ± 183	463 ± 117	624 ± 309	623 ± 170
Cmax ng/dL	463 ± 159	503 ± 220	721 ± 181	1030 ± 340	1020 ± 355
AUC24 ng h/dL	8280 ± 3300	9050 ±4390	11100 ± 2810	15000 ± 7410	15000 ± 4100
Tmax h	4.0 [0 - 24.0]	8.0 [0.5 - 24.0]	8.0 [1.0 - 10.0]	0.8 [0.5 -16.0]	6.0 [0.5 - 24.0]
RAUC	1.14 [0.5 – 2.28]	0.986 [0.68 – 1.35]	1.39 [0.8 – 3.6]	1.36 [0.8 – 3.06]	1.41 [0.88 – 2.49]
RCmax	1.19 [0.55 – 1.95]	1.02 [0.7 – 1.43]	1.46 [0.8 -2.37]	1.8 [0.66 – 3.42]	1.67 [0.86 – 3.53]

Mean baseline (Day -1) concentrations of observed testosterone ranged from 202 to 306 ng/dL, compared to a normal range of 300 to 1000 ng/dL. On day 1, testosterone concentrations increased from hypogonadal baseline values to eugonadal (300 – 1000 ng/dL) range within few hours post-dose in all dose groups. By day 14, observed

testosterone levels were relatively stable and were maintained within the normal (eugonadal) range for most individuals throughout the dosing interval.

Systemic exposure of testosterone increased linearly with dose in the 1.25 g – 5.0 g dose range although the increase was less than dose proportional, with significant overlap at the higher doses. Steady-state was achieved within 2 days of dosing when drug was applied to a single application site (abdomen or shoulders/upper arms); regimens where drug application site was rotated between the two sites required 4-5 days for achieving steady-state. Mean accumulation based on Cmax or AUC data was negligible at the lower doses (1.25 g – 2.5 g), while some drug accumulation was evident at higher doses, and was on average 1.5-1.7 fold compared to day 1 exposure.

Mean baseline (Day -1) concentrations of observed dihydrotestosterone ranged from 13.3 to 27.0 ng/dL and were in general within the normal range established for DHT. By day 14, mean DHT levels were in general stable during the 24 hour period and remained within the normal range, with the exception of few individuals that demonstrated values exceeding this range at some of the time points.

Mean baseline (Day -1) concentrations of observed estradiol ranged from 12.9 to 19.3 pg/mL and were within the normal range. Mean data for serum estradiol suggest an increase from baseline with active treatment but generally remaining within the normal range (10-40 pg/ml) on both day 1 and day 14.

Transfer potential: The magnitude of testosterone transfer from male patients applying the 1.62 % gel formulation to non-dosed female partners was evaluated in two separate phase 1 studies (S176.1.003 and S176.1.008). In addition, the effect of washing in removing residual drug from the skin was evaluated using tape stripping analysis in study S176.1.005. Together, these studies yielded important information related to transfer potential for this new gel formulation and possible risk minimization strategies.

S176.1.003: In this study, female partners underwent 15 minutes of supervised contact once-daily for 7 days with males who applied 5.0 g of testosterone gel 1.62 % to their abdomens. Treatment groups (N = 16 couples per group) were as follows:
A: Direct skin contact occurred 2 h post-dose;
B: Contact occurred 2 h post-dose with the male wearing a t-shirt;
C: Direct skin contact occurred 12 h post-dose

Results: Female subjects in Treatment A [direct skin-to-skin contact at 2h post-dose] and Treatment C [direct skin-to-skin contact at 12 h post-dose] had an approximate 2.0- to 2.7-fold increase from their baseline Cavg on Days 1 and 7. Female subjects in treatment B [2 h contact /with t-shirt on male] had a 1.5- and 1.9-fold increase from baseline Cavg for Days 1 and 7.

Summary of fold-changes from baseline [Arithmetic mean (ranges)] are shown:

	Day 1		Day 7	
Treatment	Cmax	Cavg	Cmax	Cavg
A	2.72 (1.14-5.86)	2.40 (1.12-4.05)	3.12 (1.04-5.79)	2.67 (1.04-4.56)
B	1.53	1.58	1.96	1.93

	(0.9 -3.63)	(0.83-3.18)	(0.58-6.65)	(0.68-6.56)
C	2.86 (1.05-6.87)	2.51 (1.08-6.09)	2.26 (0.57-4.24)	2.02 (0.55-3.52)

All treatments employed 5 g dose on the abdominal site of application
Trt A: direct contact at 2 h post-dose; Trt B: contact at 2 h post-dose/T-shirt on male; Trt C: direct contact at 12 h

Significant partner-to-partner transfer of testosterone occurs from AndroGel 1.62 % gel *(abdominal application of 5.0 g dose)* as evident from a statistically significant increase from baseline in systemic testosterone concentrations in non-dosed females. Covering the application site with a clothing barrier reduced the magnitude of transfer in such individuals but did not eliminate it completely.

S176.1.008: The effects 1) of a lower testosterone gel dose (2.5 g), 2) of washing the gel application site in males prior to contact and 3) of two different gel application sites on the transfer potential were evaluated in this study.

Treatments: N = 24 couples (or 48 total subjects; 24 male, 24 female; 18-80 years inclusive; healthy) randomized to one of the following treatment groups (Groups I, II, III). Within each treatment group, subjects received two single dose treatments in a randomized order.

- Group **I** *[2.5 g dose; **A:** direct skin contact at 2h post-dose; **B:** contact at 2h post-dose with clothing barrier to cover application site]*
- Group **II** *[5.0 g dose; **C:** direct skin contact at 2 h post-dose**; D:** direct skin contact at 2h post-dose after the male showered]*
- Group **III** *[5.0 g dose; **E:** direct skin contact at 2 h post-dose-gel applied to shoulders/upper arms; **F:** direct skin contact at 2h- gel applied to abdomen]*

Each single dose/contact was separated by a 1-week washout period. Dose application and subsequent skin contact occurred on Days 1 and 8 of the study. Each couple engaged in a total of 15 minutes of supervised contact in a vertical position.

- In group I (2.5 g; abdomen), the magnitude of transfer to females upon direct skin contact with males (Trt A) was ~ 1.3 fold (average increase over baseline Cavg) and a clothing barrier (Trt B) to cover the male application site prevented the transfer. Small increases in Cavg over baseline were still observed in four females (ranging from 1.11 – 1.27-fold).
- In group II (5.0 g dose; abdomen) direct skin contact with males resulted in a mean increase over baseline Cavg of 1.6-fold (Trt C) in the females. When contact occurred after males showered (with soap and water), the magnitude of transfer to females was much lower on average (1.09-fold over baseline Cavg). Four females still had Cavg values that were somewhat higher than their baseline Cavg (ranging from 1.04 -1.33 fold).
- In group III, direct contact at 2 h post-dose demonstrated that the transfer potential was significant irrespective of site of gel application.

Results from study S176.1.008 are briefly summarized; Data shown are fold-changes in Cavg over baseline in each of the treatments [mean (range)]:

	Group I		Group II		Group III	
	Trt A	Trt B	Trt C	Trt D	Trt E	Trt F
Fold changes in Cavg over baseline [mean (range)]	1.32 [0.7-1.73]	1.00 [0.51-1.27]	1.61 [0.91-2.78]	1.09 [0.95-1.32]	6.15 [1.65-23.9]	2.48 [1.06-5.55]
Group I: 2.5g; abdomen Trt A: direct contact at 2h; Trt B: contact at 2 h with T-shirt on male Group II: 5 g; abdomen Trt C: direct contact at 2 h; Trt D: direct contact at 2h after male washing Group III: 5 g; two sites Trt E: direct contact at 2 h; gel on shoulders; Trt F: direct contact at 2h; gel on abdomen]						

S176.1.005: Results of this study suggested that while washing of the application site (followed by tape stripping) resulted in removal of at least 80 - 88 % of residual testosterone from the application site, the systemic absorption of testosterone was not markedly affected. Results from this study also support the conclusion that systemic exposure of testosterone was only modestly affected (Cavg lower by 9 -11 %) when skin is washed at or after 2 h post-dose. Therefore, skin application sites can be allowed to be washed at or after 2 hours post-dose during clinical use.

Overall results suggest that significant transfer of testosterone to non-dosed individuals (e.g. females, children) can occur upon direct skin-to-skin contact with the AndroGel 1.62 % gel application site in males. The magnitude of transfer was higher with higher doses of the gel (5.0 g vs. 2.5 g). Clothing barrier reduces the transfer but does not eliminate it completely at the higher gel dose where mean increases in Cavg over baseline of ~ 58 % were noted despite clothing. Therefore clothing alone shouldn't be considered as a means to prevent transfer from AndroGel 1.62 %. Washing with soap and water in the shower was largely effective in removing residual testosterone from the skin and was effective in reducing the magnitude of transfer in females when used with high dose (5 g).

Labeling should caution regarding transfer potential (both direct and through clothing barrier); patients should be advised that clothing alone doesn't prevent transfer and that washing with soap and water preferably followed by covering the skin with clothing barrier should be diligently followed to prevent transfer especially when interacting with children.

Site of application: The impact of drug application site (abdomen vs. shoulders/upper arms vs. combination of both sites) on PK has been adequately characterized in study S176.1.007. Data suggests that drug application to shoulders/upper arms provided greater systemic exposure compared to abdominal application. On day 7, mean Cmax and AUC values for the abdominal site were 37 % and 33 % lower compared to that of shoulders/upper arms. Phase 3 clinical trial for the 1.62 % gel utilized both the application sites (shoulders/upper arms or abdomen) and rotation between the two sites was allowed. Thus clinical safety and efficacy for these sites of applications has been adequately evaluated.

Moisturizer/Sunscreen product use: Use of moisturizing lotion or sunscreen on the same application site 1 h after use of Androgel 1.62 % gel caused modest increases in the Cmax and Cavg of testosterone (S176.1.006). Mean increases in Cavg over the control treatment (1.62 % gel alone) were 1.15-fold and 1.10-fold for the moisturizer and sunscreen products, respectively. Impact of moisturizer or sunscreen application at other time points relative to gel application or at gel doses larger than 2.5 g has not been evaluated.

Bioanalytical data: The serum levels of testosterone, dihydrotestosterone and estradiol has been adequately determined using validated LC-MS/MS methodologies. Parameters assessed included precision, accuracy, sensitivity, selectivity, dilution parallelism, recovery, cross-analyte interference, carryover analyte stability in thawed matrix and reinjection reproducibility of stored sample extracts. Validation parameters were found to be within pre-determined acceptable ranges. DSI inspection of the Bioanalytical facility used in phase 3 analyses (b) (4)) is pending. Sufficient stability of stored samples has been demonstrated to justify complete sample re-analysis. Based on stability information obtained by analyzing quality controls (QC) prepared in human serum (frozen in April- May 2003 at -20^{0}C and reanalyzed using a freshly prepared calibration curve in August 2008), it appears that extended storage at -20^{o}C had no impact on T, DHT or E2 concentrations in serum.

2 Question-Based Review

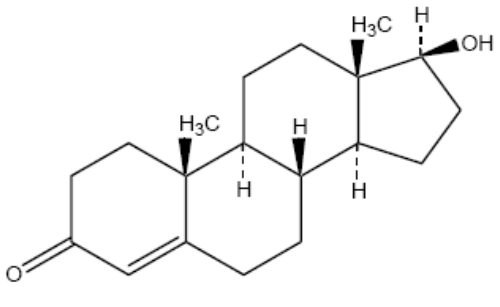
2.1 General Attributes

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

AndroGel® (testosterone gel) 1 % was approved in February, 2000 (NDA 21-015) for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The subject of this new NDA 22-309 is a new testosterone gel formulation AndroGel 1.62 %. Sponsor has conducted several Clinical and Clinical Pharmacology studies to support the new formulation.

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?

AndroGel 1.62% is a clear, colorless hydroalcoholic gel containing 1.62% testosterone. The AndroGel 1.62% doses, 1.25 g, 2.5 g, 3.75 g, or 5 g, contain 20.25 mg, 40.5 mg, 60.75 mg, or 81 mg of testosterone, respectively, and are to be applied daily to the skin's surface. The active pharmacologic ingredient in AndroGel 1.62% 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:



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

Figure 1: Testosterone chemical structure

Inactive ingredients in AndroGel 1.62% are carbopol 980, ethyl alcohol (b) (4), isopropyl myristate, purified water, and sodium hydroxide. These ingredients are not pharmacologically active.

2.1.3. What is the proposed mechanism of action and therapeutic indication?

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; and 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.

AndroGel 1.62%, an androgen, is indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary Hypogonadism (Congenital or Acquired) – e.g., testicular failure due to 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 levels and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Secondary Hypogonadism (Congenital or Acquired) – e.g., idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum levels, but have gonadotropins in the normal or low range.

2.1.4. What are the proposed dosage(s) and route(s) of administration?

AndroGel 1.62% is supplied in a pump. The recommended starting dose of AndroGel 1.62% is 2.5 g once daily (equivalent to 40.5 mg testosterone) preferably applied at the same time every day to clean, dry, healthy, intact skin of either the shoulders/upper arms (b) (4). To ensure proper dosing, serum testosterone levels should be measured and the dose should be adjusted to achieve and maintain serum testosterone levels in the normal range (300 -1000 ng/dl). If serum testosterone levels are above or below the normal range, adjust dose in 1.25 g increments to a daily dose between 1.25 g and 5 g (i.e. 20.25 mg – 81 mg testosterone doses).

Table 1: Dosing information for the proposed AndroGel® 1.62 % gel formulation

Number of Pump Actuations	Prescribed Daily Dose	Amount of Testosterone
1 (once daily)	1.25 g	20.25 mg
2 (once daily)	2.5 g	40.5 mg
3 (once daily)	3.75 g	60.75 mg
4 (once daily)	5 g	81 mg

2.2 General Clinical Pharmacology

2.2.1 What clinical pharmacology and clinical studies were conducted in support of dosing or claims?

NDA 22-309 includes 7 phase 1 studies and one phase 3 clinical trial in hypogonadal males. With the exception of the transfer studies, all clinical studies were conducted in the target hypogonadal male population. Doses evaluated in these studies included 0, 1.25, 2.5, 3.75, 5.0 and 6.25 g of the gel product, providing topical testosterone doses of approximately 0, 20.25, 40.5, 60.75, 81 and 101.25 mg, respectively. The dose range of Androgel 1.62 % gel proposed for clinical usage (and evaluated in the phase 3 clinical trial) is 1.25 g -5.0 g gel applied once-daily to shoulders/upper arms or abdomen. Each individual patient will be titrated to their effective dose level, after first starting at 2.5 g.

Phase 3 Clinical Trial

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

Phase 1 Studies:

S176.1.001: The multiple dose pharmacokinetics and comparative bioavailability of testosterone after administration of 1.25 g, 2.5 g and 3.75 g dose levels of investigational testosterone hydro-alcoholic gel formulations in hypogonadal male volunteers.

S176.1.002: The single and multiple dose pharmacokinetics of testosterone after administration of 1.62 % hydro-alcoholic gel at dose levels of 1.25, 2.50, 3.75, 5.00 and 6.25 g in hypogonadal males.

S176.1.003: A Randomized, Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-dosed Females after Skin Contact with a Male Partner Dosed with Testosterone Gel 1.62%.

S176.1.005: A randomized, Open-label, three-way crossover pharmacokinetic study to evaluate the effects of skin washing after administration of testosterone gel 1.62 % in hypogonadal males

S176.1.006: A randomized, open-label, three-way crossover multiple dose pharmacokinetic study on the effect of moisturizer lotion or sunscreen application on the serum levels of testosterone in hypogonadal males administered testosterone gel 1.62 %.

S176.1.007: A single and multiple dose pharmacokinetic and comparative bioavailability study of testosterone absorption after administration of testosterone gel 1.62 % to the abdomen, upper arms/shoulders, or via a rotation schedule in hypogonadal males.

S176.1.008 A Randomized, Open-Label, Parallel Group Study to Evaluate the Effects of Dose, Post-dose Washing, and Application Site on the Transfer Potential of Testosterone Gel 1.62% from Dosed Males to a Non-dosed Female Partner.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint and the key secondary endpoints for this indication are based on achieving total testosterone levels within predetermined 'normal' ranges. Therefore, pharmacokinetic data are pivotal in this NDA for defining success of the active treatment. Since subjects were titrated to their individual 'effective' dose level, efficacy endpoints (Cavg and Cmax) for defining success are interpreted without regard to the dose level. Primary and secondary endpoints for the pivotal phase 3 clinical trial S176.3.104 are listed below.

- Primary: Success in the study was defined as ≥75% of subjects on active treatment within the normal serum testosterone concentration range of 300-1000 ng/dL. In addition, the lower bound of the 95% confidence interval (CI) was to be not less than 65% based on the Day 112 PK results for the pivotal phase of the trial.

The secondary objectives of this study were as follows:

- A critical secondary endpoint was to evaluate total testosterone observed

maximum serum concentration (Cmax) values during the first 182 days of the study. The individual total testosterone Cmax values were to be in the following ranges:

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

- Secondary parameters included measurement of sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and selected serum inflammatory and cardiovascular risk markers (tumor necrosis factor-α [TNF-α], interleukin 6 [IL-6], interleukin-10 [IL-10], high sensitivity C-reactive protein (hs-CRP), matrix metalloprotease-9 [MMP-9], high-density lipoprotein [HDL]2, HDL3, d-dimer, fibrinogen, and vascular cell adhesion molecule [VCAM]), waist-to-hip ratio, as well as serum markers of bone metabolism (bone-specific alkaline phosphatase and type 1 cross linked c-telopeptide), and the Short Form-36 (SF-36).

2.2.3 What were the primary and secondary efficacy outcomes for the pivotal phase 3 clinical trial?

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

This was a phase 3, multi-center, randomized, double-blind, placebo-controlled study of four different doses of testosterone gel 1.62 % (1.25 g, 2.5g, 3.75 g, and 5 g equivalent to 20.25, 40.5, 60.75 and 81 mg testosterone, respectively) in hypogonadal males (18-80 years; baseline morning serum testosterone level < 300 ng/dL based on the average of two morning blood draws). The efficacy and safety of testosterone gel 1.62% were evaluated following administration of active treatment or placebo to hypogonadal men for a period of 182 days. Study medication was applied to intact dry skin once-daily in the morning to shoulders/upper arms or abdomen after showering. Over a7-day period, study gel could be rotated between the upper arms/shoulders or abdomen (e.g., four days upper arms/shoulders; three days abdomen) as long as drug was applied to shoulders/upper arms during PK visits.

All subjects started at 2.50 g of testosterone gel 1.62% or matching placebo on Day 1 of the study. Subjects returned to the clinic at Day 14 (Week 2), Day 28 (Week 4), and Day 42 (Week 6) for pre-dose serum total testosterone assessments for potential dose-titrations in 1.25 g increments within the 1.25 g – 5.0 g range. Dose titration was based on total testosterone concentrations at pre-dose (Ctrough). Subjects were up-titrated if Ctrough was < 350 ng/dL, down-titrated if Ctrough was > 750 ng/dL or remained on the same dose if Ctrough was within 350- 750 ng/dL range. Subjects were maintained at their respective Day 42 (Week 6) dose until Day 112 (Week 16).

PK sampling was conducted over 24 hours on days 14, 56, 112 (end point) during the double-blind phase for assessment of T, DHT and E2. Non-compartmental methods were used for the computation of PK parameters. Statistical analyses on the PK data were performed on the full analysis sample (i.e. subjects who had data for at least one post-baseline assessment of any efficacy measurement; N = 251). Overall, 179 subjects had PK data on the final 'efficacy' day 112.

Results:

Primary efficacy endpoint: The primary efficacy parameter was the percentage of subjects (i.e. responders) with serum total testosterone time-averaged concentration over the dosing interval of 24 hours (Cavg[0-24] or Cavg) within the normal range of 300-1000 ng/dL at day 112.

Success in the study was defined as ≥75% of subjects on active treatment within the normal serum testosterone concentration range of 300-1000 ng/dL. In addition, the lower bound of the 95% confidence interval (CI) was to be not less than 65% based on the Day 112 PK results for the pivotal phase of the trial.

On day 112, the proportion of responders for the active treatment groups was 81.6 % [146/179; 95 % CI: 75.1 – 87.0], thus fulfilling the pre-defined primary endpoint success criteria. This was significantly different compared to 37 % responder rate observed in the placebo group ($p < 0.0001$).

Table 2: Number of percentage of subjects achieving target range for testosterone Cavg by day and treatment in the full analysis (FA) sample

Population	Study Day	Testosterone gel 1.62%		Placebo		p-value
		n/N (%)	95% CI	n/N (%)	95% CI	
FA	14	138/210 (65.7)	(58.9, 72.1)	11/37 (29.7)	(15.9, 47.0)	<0.0001
	56	151/183 (82.5)	(76.2, 87.7)	11/32 (34.4)	(18.6, 53.2)	<0.0001
	112	146/179 (81.6)	(75.1, 87.0)	10/27 (37.0)	(19.4, 57.6)	<0.0001
	182	139/169 (82.2)	(75.6, 87.7)	8/28 (28.6)	(13.2, 48.7)	<0.0001

Secondary variables:

A critical secondary endpoint was to evaluate total testosterone observed maximum serum concentration (Cmax) values during the first 182 days of the study. The individual total testosterone Cmax values were to be in the following ranges:
- Cmax ≤1500 ng/dL in ≥85% of the subjects
- Cmax between 1800-2500 ng/dL in ≤5% of the subjects
- Cmax >2500 ng/dL in none of the subjects.

Table 3: Number and percentage of subjects achieving target Cmax range

Study Pop	Day	n / N (%) for Subjects Achieving Testosterone C_{max} Range					
		Testosterone gel 1.62%			Placebo		
		≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL	≤1500 ng/dL	1800-2500 ng/dL	>2500 ng/dL
FA	Overall[1]	696/741 (93.9)	22/741 (3.0)	6/741 (0.8)	123/124 (99.2)	0/124	0/124
	14	203/210 (96.7)	5/210 (2.4)	1/210 (0.5)	37/37 (100.0)	0/37	0/37
	56	178/183 (97.3)	1/183 (0.5)	2/183 (1.1)	32/32 (100.0)	0/32	0/32
	112	159/179 (88.8)	10/179 (5.6)	2/179 (1.1)	26/27 (96.3)	0/27	0/27
	182	156/169 (92.3)	6/169 (3.6)	1/169 (0.6)	28/28 (100.0)	0/28	0/28

Overall, across all PK days (14, 56, 112 and 182 days), in the FA sample 93.9 % of patients had Cmax values ≤ 1500 ng/mL; 3 % of patients had Cmax values between 1800-2500 ng/dL and 0.8 % of patients had Cmax values > 2500 ng/dL.

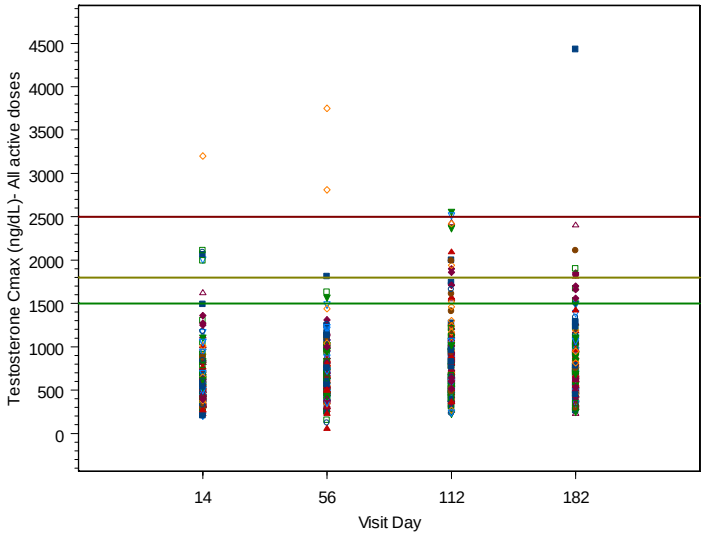


Figure 2: Scatter plot of observed total testosterone concentrations in the phase 3 trial. Horizontal lines represent Cmax cut-off values of 1500 ng/dL, 1800 ng/dL and 2500 ng/dL.

Testosterone outliers: There were a total of 10 patients that had a total of 11 observations of total testosterone concentration > 2500 ng/dL during the double blind phase of the study. With the exception of one subject (049/008) who had two observations exceeding 2500 ng/dL on two separate days, no other subject demonstrated high T concentration on more than one occasion. 6 out of 11 high T concentrations were noted at times post-dose, while the remaining were observed pre-dose and hence were not included in PK analyses for Cmax calculation. There was no apparent trend for increased incidence of T outliers with increasing dose of testosterone gel.

A review of the case reports for subjects with T values > 2500 ng/dL suggests sample contamination and over-compliance (excessive dose/frequency of application) as the predominant causes of the random T increases. Sponsor submitted the following listing of subjects with testosterone concentrations > 2500 ng/dL and their causal attribution.

Table 4: Testosterone outliers (> 2500 ng/dL) over the duration of the phase 3 clinical trial and causal attribution.

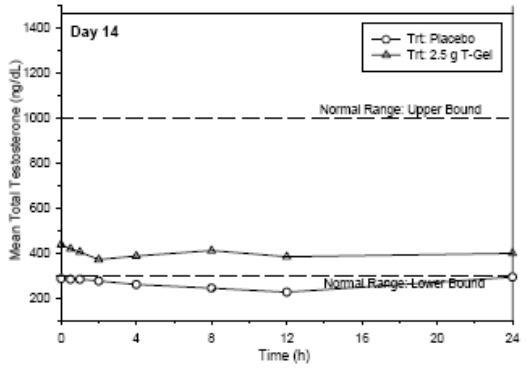
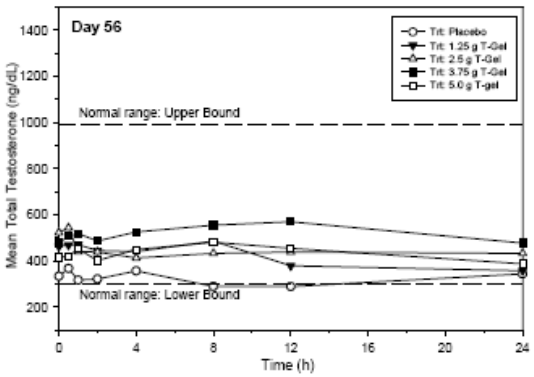
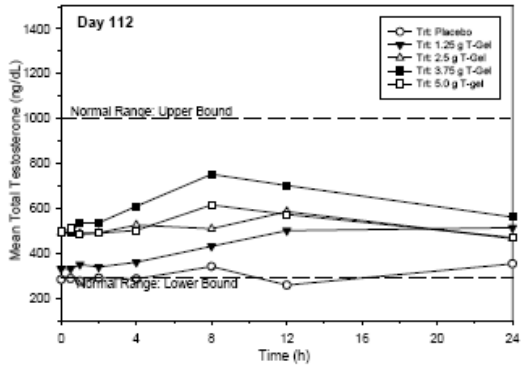
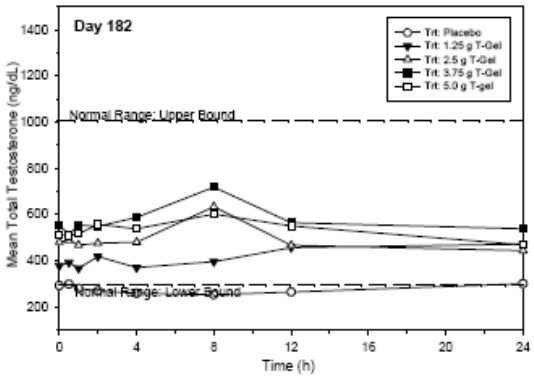
Subject Number	Dose (g/day)	Day	Timepoint	Total Testosterone (ng/dL)	DHT (ng/dL)	DHT/T ratio	E2 (pg/mL)
Cases of Suspected Blood Sample Contamination by Venipuncture Artifact Influencing PK Profiles							
003-008	N/A	1	Baseline Day 1	3270	18	0.006	48
039-009	5.00	56	1 hour	3750	43	0.011	14
012-008	5.00	182	2 hour	4430	77	0.017	22
005-028	3.75	28	Pre-dose	3867*	100	0.026	No value
044-005	2.50	14	Pre-dose	2850	193	0.068	No value
Cases of Acute Increases in Systemic Absorption Primarily Influencing PK Profiles							
007-006	5.0	112	8 hour	2550	137	0.054	16
058-006	5.00	112	2 hours	2510	237	0.094	43
067-001	3.75	112	Pre-dose	2730	267	0.098	64
015-005	2.5	14	Pre-dose	3290	341	0.104	31
049-008	2.50	56	0.5 hours	2810	354	0.126	35
	2.50	14	0.5 hours	3200	414	0.129	17

* This concentration reflect[s] (b) (4) alue measured with RIA and was not confirmed b[y] (b) (4) methodology.
Note: Dose listed is the dose at the time of testosterone concentration >2500 ng/dL

Reviewer concurs with the sponsor's interpretation of the testosterone outliers and finds that the instances of testosterone outliers were infrequent, random and usually attributable to either sample contamination or potential compliance issues with the dose and/or regimen.

Effectiveness of the dose titration regimen: The percentage of responders (Cavg within the normal range) increased from day 14 of the titration phase (65.7 %) to day 56 (i.e. after 2 weeks on the final titrated dose) and beyond (maintenance phase; 81.6 – 82.5 %). This suggests that a pre-dose (Ctrough) based titration (conducted on days 14, 28 and 42) in this study was successful in identifying non-responders or supra-responders and titrating these patients to their efficacious doses. % patients with Cavg in the normal range were 66.6 %, 82.5 %, 82.13 % and 83.4 % on days 14, 56, 112 and 182 respectively. Based on subjects' last titrated dose, allocation to testosterone gel 1.62% treatment was as follows: 17 subjects to 1.25 g, 60 subjects to 2.50 g, 66 subjects to 3.75 g, and 91 subjects to 5.00 g.

Mean concentration vs. time profiles for total T are shown by treatment & visit. Plots show the efficacy of active treatments over placebo in achieving normal ranges of testosterone (shown as dashed lines).
Figure 3: Mean testosterone concentrations vs. time profiles by treatment and visit day.

Day 14	Day 56
	
Day 112	**Day 182**
	

Note: On Day 14 all subjects in the active treatment group were on 2.50 g Testosterone gel 1.62%

Secondary endpoints: Several exploratory secondary pharmacodynamic endpoints were evaluated in this clinical trial. These included serum SHBG, LH, FSH, inflammatory and cardiovascular risk markers (TNF-a, IL-6, IL-10, hs-CRP, MMP-9, HDL2, HDL3, d-Dimer, Fibrinogen etc), and bone metabolism markers (bone-specific alkaline phosphatase, Type 1 cross-linked C telepeptide).

Statistically significant difference relative to placebo was observed for LH and FSH on both days 84 and 182 and for SHBG on day 84 only:

- For LH, a mean decrease of 3.47 IU/L and 3.5 IU/L was observed with testosterone treatment on Day 84 and Day 182, which was significantly different from placebo ($p<0.0001$).

- For FSH, a mean decrease of 4.39 IU/L and 4.09 IU/L was observed on Day 84 and Day 182 with testosterone treatment, which was significantly different from placebo ($p<0.0001$).
- For SHBG, a mean decrease of -2.7 nmol/L and -0.7 nmol/L was observed on Day 84 and Day 182. The difference from baseline was statistically significant relative to placebo on day 84.

Statistically significant decrease in IL-10 was noted on day 84 relative to placebo. All other changes to secondary efficacy parameters were not significant.

Subgroup analyses for Testosterone in the Phase 3 clinical trial S176.3.104:

Subgroup analyses of phase 3 data using various baseline demographic variables suggest that a greater percentage of white patients achieved the target range Cavg than non-whites. Data also indicate that a greater percentage of subjects in the age category >45 years achieved the target range Cavg concentration in comparison to subjects <45 years. Subgroup analyses of PK parameter Cavg by BMI ranges showed no clear trends. Due to the differences in sample sizes across the various subgroups and because no formal statistical analysis was performed to distinguish between the categories, it is not possible to conclude on the intrinsic factor effects on PK. No clear trend in the impact of dose application site prior to PK day was observed for Ctrough (shown) or other PK parameters.

Overall conclusions: Androgel 1.62 % gel formulation was successful in achieving eugonadal (300- 1000 ng/dL) testosterone concentrations in the target population. The primary efficacy endpoint (% responders with Cavg in the normal range) and key secondary endpoints (Cmax criteria) have been met. While 0.8 % of the patient population had Cmax values > 2500 ng/dL, the incidence of these outliers was sporadic, random and could be explained either as due to sample contamination or overcompliance.

2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Testosterone and its major metabolites dihydrotestosterone and Estradiol were adequately evaluated in the serum samples using validated LC-MS/MS methodologies.

2.2.5 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The primary efficacy outcomes of the study are based on pharmacokinetics i.e. achievement of 'normal' or eugonadal ranges of testosterone (Cavg). Since patients are

titrated to their effective dose regimen, the efficacy outcomes should be interpreted without regard to dose. For exploratory purposes, reviewer has summarized the dose-response relationships from the phase 3 clinical trial:

Efficacy endpoints (Cavg and Cmax-based) by various dose subgroups:

Cavg criterion: The average testosterone concentrations were within the normal range (300-1000 ng/dL) in at least 75 % of patients by day 112 in all dose groups of the active treatment. This proportion was somewhat higher in the larger dose groups ranging 2.5 to 5 g (81-83 %), compared to the smallest evaluated gel dose of 1.25 g (75 %). The 3.75 g dose of testosterone 1.62 % gel had the least proportion of patients that had Cavg values below 300 ng/dL.

Table 5: Primary efficacy endpoint (Cavg) by dose group

% of patients	N = 27	N = 12	N = 36	N = 53	N = 78
	0 g	**1.25 g**	**2.5 g**	**3.75 g**	**5 g**
< 300 ng/dL	62.96	16.67	13.89	5.66	11.54
300-1000 ng/dL	37.04	75.00	83.33	81.13	82.05
> 1000 ng/dL	0.00	8.33	2.78	13.21	6.41

Cmax criterion: All Cmax values during the double-blind phase of the study were considered in this analysis by treatment dose:

Table 6: Secondary endpoint (Cmax ranges) by dose group

% of patients	N = 124	N = 57	N = 183	N = 273	N = 227
	Placebo	**1.25 g**	**2.5 g**	**3.75 g**	**5 g**
< 1500 ng/dL	99.19	96.49	96.17	93.77	93.39
1501-1800 ng/dL	0.81	1.75	3.83	5.86	5.29
>2500 ng/dL	0	1.75	0	0.37	1.32
N = number of Cmax observations available on all PK days combined					

On PK days (i.e. using available data from days 14, 56, 112 and 182), majority of Cmax values were within 1500 ng/dL (93-96 %) in each of the active treatment groups. In the two lower active dose groups (1.25 g, and 2.5 g) the proportion of Cmax values between 1500-1800 ng/dL was within 5 %. This proportion exceeded 5 % in the two higher dose groups (3.75 g, 5g). There was no apparent relationship to dose in the % of patients with testosterone > 2500 ng/dL.

The relationship between Cmax and Cavg,ss and the change from baseline values for all PD endpoints were also explored statistically. The relationship was assessed using simple linear least squares regression and the null hypothesis of no linear relationship was tested

at the 0.05 significance level. Significant correlations between Cavg or Cmax and the decrease in LH or FSH were noted.

Table 7: Luteinizing hormone (LH)

Testosterone Pharmacokinetic Parameter (unit)	Slope			Intercept		
	Estimate	95% Confidence Interval	p-value	Estimate	95% Confidence Interval	p-value
Cav (ng/dL)	-0.9970	(-1.741 , -0.2530)	0.0089	5.723	(-0.8428 , 12.29)	0.0872
Cmax (ng/dL)	-0.8361	(-1.484 , -0.1886)	0.0117	4.728	(-1.317 , 10.77)	0.1245

Table 8: Follicle-stimulating hormone (FSH)

Testosterone Pharmacokinetic Parameter (unit)	Slope			Intercept		
	Estimate	95% Confidence Interval	p-value	Estimate	95% Confidence Interval	p-value
Cav (ng/dL)	-1.670	(-2.685 , -0.6545)	0.0014	10.97	(2.009 , 19.93)	0.0167
Cmax (ng/dL)	-1.265	(-2.153 , -0.3768)	0.0055	8.046	(-0.2463 , 16.34)	0.0571

2.2.4.2 ***What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?***

The overall incidence of adverse events was higher in the active treatment group (55.6 %) compared to the placebo group (37.5 %). A higher proportion of subjects in the testosterone gel 1.62% groups compared with the placebo group experienced treatment-emergent adverse events (TEAEs) that led to permanent discontinuation of study medication (25/234, 10.7% versus no subject). The most common AE leading to discontinuation was PSA increased (17 subjects), which was pre-specified in the protocol as a discontinuation criterion (>4.0 ng/mL and/or change from Baseline >0.75 ng/mL).

Table 9: Summary of adverse events in phase 3 clinical trial (Drug vs. Placebo)

Primary SOC PT	Statistic	Placebo (N=40)	T-Gel 1.62% (N=234)
Number of Subjects With at Least One TEAE	n (%)	15 (37.5%)	130 (55.6%)
GASTROINTESTINAL DISORDERS	n (%)	3 (7.5%)	14 (6.0%)
DIARRHOEA	n (%)	0	5 (2.1%)
INFECTIONS AND INFESTATIONS	n (%)	5 (12.5%)	37 (15.8%)
NASOPHARYNGITIS	n (%)	0	5 (2.1%)
UPPER RESPIRATORY TRACT INFECTION	n (%)	0	11 (4.7%)
INVESTIGATIONS	n (%)	0	34 (14.5%)
PROSTATIC SPECIFIC ANTIGEN INCREASED	n (%)	0	23 (9.8%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	n (%)	3 (7.5%)	20 (8.5%)
MYALGIA	n (%)	0	5 (2.1%)
BACK PAIN	n (%)	0	7 (3.0%)
NERVOUS SYSTEM DISORDERS	n (%)	3 (7.5%)	13 (5.6%)
HEADACHE	n (%)	2 (5.0%)	7 (3.0%)
PSYCHIATRIC DISORDERS	n (%)	1 (2.5%)	14 (6.0%)
INSOMNIA	n (%)	1 (2.5%)	7 (3.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	n (%)	2 (5.0%)	16 (6.8%)
DERMATITIS CONTACT	n (%)	0	5 (2.1%)
VASCULAR DISORDERS	n (%)	0	11 (4.7%)
HYPERTENSION	n (%)	0	6 (2.6%)

The most common (≥2% in the testosterone gel 1.62% groups) TEAEs were increased PSA (23/234, 9.8% versus no subject in the placebo), upper respiratory tract infection, (11/234, 4.7% versus no subject), back pain (7/234, 3.0% versus no subject), headache

(7/234, 3% versus 2/40, 5.0%), insomnia (7/234, 3.0% versus 1/40, 2.5%), hypertension (6/234, 2.6% versus no subject), and diarrhea, nasopharyngitis, myalgia, and dermatitis contact (5/234, 2.1% versus no subject for placebo).

Summary of adverse events by dose: There was a greater incidence with dose in number of subjects with PSA increase, and in the incidence of hypertension. There was also a greater incidence of testicular disorders (e.g. testicular pain), headache, dizziness, and myalgia at the highest dose evaluated. Other AEs did not demonstrate a discernible trend with dose.

Table 10: Adverse events by dose

Adverse event	1.25 g	2.5 g	3.75 g	5.0 g
Gastrointestinal (e.g. diarrhea)	0	3.3 %	9.1 %	6.6 %
Infections and Infestations	23.5 %	10 %	22.7 %	13.2 %
Musculoskeletal (e.g. myalgia, backpain)	17.6 %	10 %	7.6 %	6.6 %
Nervous system (e.g. headache)	5.9 %	5 %	6.1 %	5.5 %
Psychiatric (e.g. aggression, insomnia)	17.6 %	6.7 %	6.1 %	3.3 %
PSA increased	5.9 %	3.3 %	15.2 %	11.0 %
Reproductive system/breast Disorders	5.9 %	1.7 %	4.5 %	4.4 %
Skin (e.g. dermatitis)	11.8 %	3.3 %	7.6 %	7.7 %
Hypertension	0	0	1.5 %	4.4 %

TEAEs by highest measured testosterone concentration category: The proportion of subjects with at least one TEAE across testosterone concentration categories is shown:

≤1500 ng/dL: 96/183 (52.5%)
1501 to <1800 ng/dL: 9/16 (56.3%)
1800 to ≤2500 ng/dL: 17/25 (68.0%)
>2500 ng/dL: 8/10 (80.0%)

Due to the small sample size of most of the categories, it is difficult to comment on whether there is a definitive pattern of increasing incidence of adverse events with higher testosterone concentration category.

2.2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes. Results from the phase 3 clinical trial S176.3.104 support the use of a 2.5 g starting dose of Androgel 1.62 % gel in all hypogonadal male patients. Information from this trial supports pre-dose total testosterone level based titration to individual efficacious dose in 1.25 g dose increments in the 1.25 g – 5.0 g dose range.

2.2.6 Pharmacokinetics

2.2.6.1 What are the single dose and multiple dose PK characteristics of the drug and its major metabolites?

Pharmacokinetics of testosterone and its primary metabolites dihydrotestosterone (DHT), and Estradiol (E2) were evaluated in phase 1 and phase 3 studies.

Testosterone (T):

Phase 3 Clinical Trial S176.3.104: The PK of total testosterone was evaluated over 24 hours on Day 14, 56, 112, and Day 182 in the placebo and active treatment groups. Key pharmacokinetic variables Cavg and Cmax were used in the primary and secondary efficacy analyses as explained earlier.

PK summary of total testosterone for Day 112 is shown. Data shows that the active gel treatment was efficacious at all doses compared to placebo in bringing T levels to normal ranges (300-1000 ng/dL). The time to maximum concentration (tmax) ranged from 4 to12 hours across study days for testosterone treatment. A dose-related increase in exposure parameters is observed in the 1.25 to 3.75 g range of testosterone gel.

Table 11: Pharmacokinetics of observed testosterone on day 112 of Phase 3 trial

	Mean (SD)					
	Placebo	**1.25 g**	**2.50 g**	**3.75 g**	**5.00 g**	**All active**
Day 112						
C_{av} (ng/dL)	303 (135)	457 (275)	524 (228)	643 (285)	537 (240)	561 (259)
C_{max} (ng/dL)	450 (349)	663 (473)	798 (439)	958 (497)	815 (479)	845 (480)
t_{max} (h)[a]	4.0 (0.5, 25.50)	8.0 (0.45, 24.0)	8.0 (0.5, 24.0)	8.01 (0.25, 24.02)	8.0 (0.42, 24.08)	8.0 (0.25, 24.08)
C_{min} (ng/dL)	215 (102)	242 (58.4)	312 (141)	371 (179)	333 (148)	334 (155)
t_{min} (h)[a]	8.0 (0.50, 12.02)	3.97 (0.42, 24.0)	7.99 (0.5, 24.22)	2.02 (0.48, 24.02)	3.92 (0.42, 24.05)	3.97 (0.42, 24.22)
AUC_{0-24} (ng*h/dL)	7280 (3230)	10900 (6460)	12600 (5470)	15400 (6830)	12900 (5790)	13500 (6210)
C_{trough} (ng/dL)	283 (133)	332 (86.4)	497 (256)	494 (390)	495 (307)	484 (317)
PTF (%)	68.0 (77.4)	82.5 (34.1)	87.7 (49.2)	87.4 (36.0)	87.0 (49.6)	86.9 (44.6)

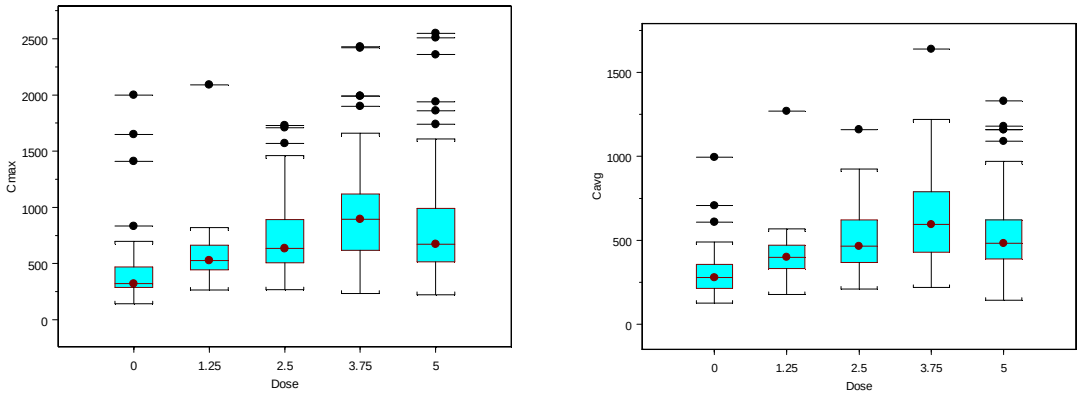


Figure 4: Box plots of testosterone Cmax and Cavg on day 112.

Box plots of key pharmacokinetic parameters for testosterone on the efficacy day (112) are shown above. Data indicate a trend for dose-related increases in Cmax and Cavg up to 3.75 g dose of the gel.

Phase 1 PK study S176.1.002: The Single and Multiple Dose Pharmacokinetics of Testosterone After Administration of 1.62% Hydro-Alcoholic Gel at Dose Levels of 1.25, 2.50, 3.75, 5.00, and 6.25 g in Hypogonadal Males

Design: This study was a single center, open-label, randomized, single and multiple dose, parallel group study in hypogonadal male subjects. A total of 56 subjects were randomized to one of 5 treatment groups.

Treatments: Each subject received single (Day 1) and multiple (Days 2-14) doses of 1.62% T-gel over a 14-day treatment period. Study drug was applied topically once daily in the morning. Subjects were confined to the clinic for the entire 17-day study period. Dose was applied after showering and the site of application was rotated over the 14-day period across the shoulders/upper arm (on days 1, 2, 5 – 9, 12-14) and abdomen (on days 3, 4, 10, 11) sites. Extensive PK sampling was conducted on day 1 and day 14 for evaluation of serum T, DHT and E2; trough samples were obtained on the days in between.

Achievement of steady-state: Based on graphical evaluation and statistical analyses conducted by the sponsor (time of earliest p value > 0.05 when comparing trough levels of earlier to later treatment days), steady-state T levels across dose groups were achieved typically after 2 -6 days of daily dosing.

Pharmacokinetic results: Mean baseline (Day -1) concentrations of observed testosterone ranged from 202 to 306 ng/dL, compared to a normal range of 300 to 1000 ng/dL. On day 1, testosterone concentrations increased from below normal baseline values to eugonadal range by ~8 hours post-dose in all dose groups. Mean profiles for all dose groups on day 1 demonstrate continued maintenance of T levels within the normal range through the 24 hour period.

By day 14, observed testosterone levels (observed) were relatively stable and within the normal (eugonadal) range throughout the dosing interval. Dose-related increases in systemic T concentrations were noted, although some overlap was apparent across the dose levels.

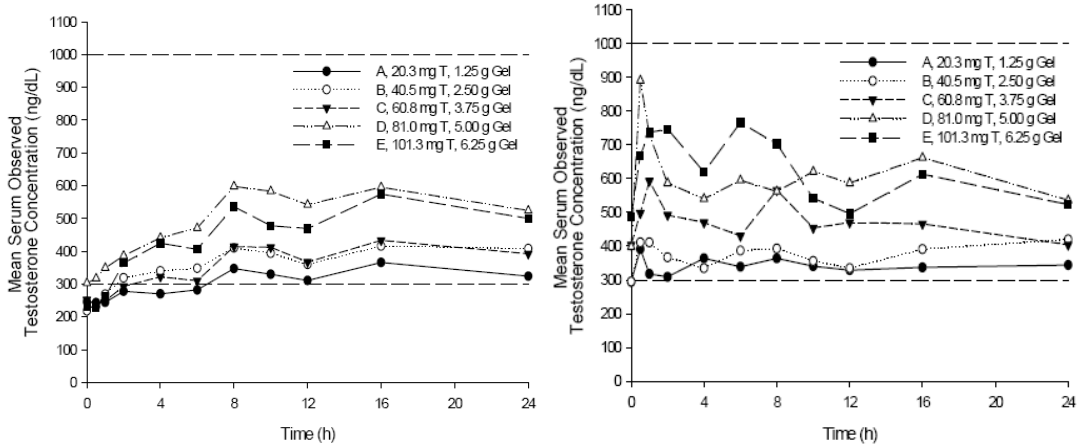


Figure 5: Observed testosterone concentrations on day 1 and day 14 of PK study 002

Mean day 1 pharmacokinetic parameters for serum total testosterone (observed) are shown in the table below. Mean data do not suggest a dose proportional increase in PK parameters. Significant overlap is observed between the PK parameters for the various treatment groups. There were no Cmax values > 1500 ng/dL or Cavg values > 1000 ng/dL in any of the dose groups.

Table 12: PK parameters on day 1 of AndroGel 1.62 % in PK study S176.1.002

Day 1	1.25 g	2.5 g	3.75 g	5.0 g	6.25 g
C_{avg} ng/dL	318 ± 80	389 ± 124	373 ± 125	521 ± 134	471 ± 119
C_{max} ng/dL	404 ± 104	498 ± 162	533 ± 210	737 ± 229	654 ± 194
C_{min} ng/dL	203 ± 62	215 ± 77	227 ± 83	264 ± 77	210 ± 49
AUC_{24} ng h/dL	7580 ± 1910	9270 ± 2960	8900 ± 2980	12400 ± 3190	11200 ± 2830
T_{max} h	12.0 [2.0 - 24.0]	10.0 [4.0 - 24.0]	10.0 [8.0 - 24.0]	12.0 [6.0 - 24.0]	16.0 [8.0 - 24.0]
PTF %	64 ± 23	80 ± 12	83 ± 52	89 ± 31	92 ± 24

Mean day 14 pharmacokinetic parameters for total testosterone are shown below. Cavg, Cmax, Cmin and AUC values in general increased (though not proportionately) with dose in the 1.25 – 3.75 g range. The mean data for 5.0 g and 6.25 g doses were generally indistinguishable. There were no Cmax values exceeding 1500 ng/dL or Cavg values exceeding 1000 ng/dL in the three lower dose groups or at the highest dose level (6.25 g).

Mean accumulation based on Cmax or AUC data was negligible at the lower doses (1.25 g – 2.5 g), although one individual in each of these dose groups demonstrated accumulation of 1.5 to 2-fold at these doses. Accumulation at steady-state was larger at the three higher doses (1.5 – 1.7 fold) with at least one individual in each of these groups demonstrating much greater accumulation than others (up to 3.0- 3.5 fold).

Table 13: PK parameters of serum total testosterone (observed) on day 14

Day 14	1.25 g (n = 9-11)	2.5 g (n = 10-11)	3.75 g (n = 11)	5.0 g [n = 7-8]	6.25 g (n = 10)
C_{avg} ng/dL	345 ± 137	377 ± 183	463 ± 117	624 ± 309	623 ± 170
C_{max} ng/dL	463 ± 159	503 ± 220	721 ± 181	1030 ± 340	1020 ± 355
C_{min} ng/dL	226 ± 97	266 ± 154	315 ± 106	422 ± 182	356 ± 50
C_{trough} ng/dL	294 ± 112	295 ± 152	404 ± 142	398 ± 57	487 ± 178
AUC_{24} ng h/dL	8280 ± 3300	9050 ±4390	11100 ± 2810	15000 ± 7410	15000 ± 4100
T_{max} h	4.0 [0 - 24.0]	8.0 [0.5 - 24.0]	8.0 [1.0 - 10.0]	0.8 [0.5 -16.0]	6.0 [0.5 - 24.0]
PTF %	71 ± 15	65 ± 15	89 ± 31	106 ± 48	102 ± 36
R_{AUC}	1.14 [0.5 – 2.28]	0.98 [0.68 – 1.35]	1.39 [0.8 – 3.6]	1.36 [0.8 – 3.06]	1.41 [0.88 – 2.49]
R_{Cmax}	1.19 [0.55 – 1.95]	1.02 [0.7 – 1.43]	1.46 [0.8 -2.37]	1.8 [0.66 – 3.42]	1.67 [0.86 – 3.53]

Mean Cavg values in this phase 1 study were ~18- 38 % lower at corresponding dose levels compared to PK data collected on day 112 from the phase 3 clinical trial S176.3.104. The reason for this discrepancy is not clear although differences in sample sizes may partly explain this. In both studies on PK days drug was applied to the shoulders/upper arm site that has been shown to provide approximately 30-40 % higher exposure compared to the abdominal site of application.

Dihydrotestosterone (DHT):

Phase 3 trial S176.3.104: Testosterone is partially metabolized to its active metabolite, DHT by the enzyme 5α-reductase. DHT was measured in the serial PK samples collected for measurement of total testosterone on each PK assessment day. Mean baseline DHT values were 22 ng/dL and 18.9 ng/dL in the placebo and active treatment groups respectively.

The mean concentrations of DHT in the placebo group remained generally similar to the baseline (pre-treatment) values. Mean DHT levels in the 1.25 g, 2.5 g, and 5 g active treatment groups increased with active treatment but were within the eugonadal reference range (11.2 – 95.5 ng/dL) on all study days. For the 3.75 g testosterone gel 1.62% treatment, mean DHT levels over the concentration profile were somewhat higher than

the upper limit of the eugonadal reference range. Mean DHT concentration profiles generally paralleled the changes seen in testosterone profiles.

Mean (SD) for DHT/T ratios for the testosterone gel 1.62% group was 0.167 (0.0619) with 95% prediction intervals of 0.074-0.330 and was 0.077 (0.034) for placebo with 95% prediction intervals of 0.034-0.151, which is within the normal range reported in the literature for this ratio ((0.05– 0.33). DHT/T ratios for each of the dose levels (all days) were: Placebo: 0.076; 1.25 g: 0.147; 2.5 g: 0.156; 3.75 g: 0.184; 5.0 g: 0.172. All active treatment groups demonstrated ~ 2-fold increase in DHT/T ratio from baseline.

Phase 1 PK study S176.1.002: On day 1, DHT concentrations increased from baseline parallel to the observed T increases for up to 8-10 hours post-dose after which they generally leveled off to pre-dose values. Individual data (not identified by dose in the plot below) suggests that some of the individual concentrations exceeded the accepted normal range around the peak on day 1.

Mean DHT levels on day 14 were in general stable during the 24 hour period and remained within the normal range, with the exception of few individuals that demonstrated values exceeding this range at some of the time points.

Day 1 Day 14

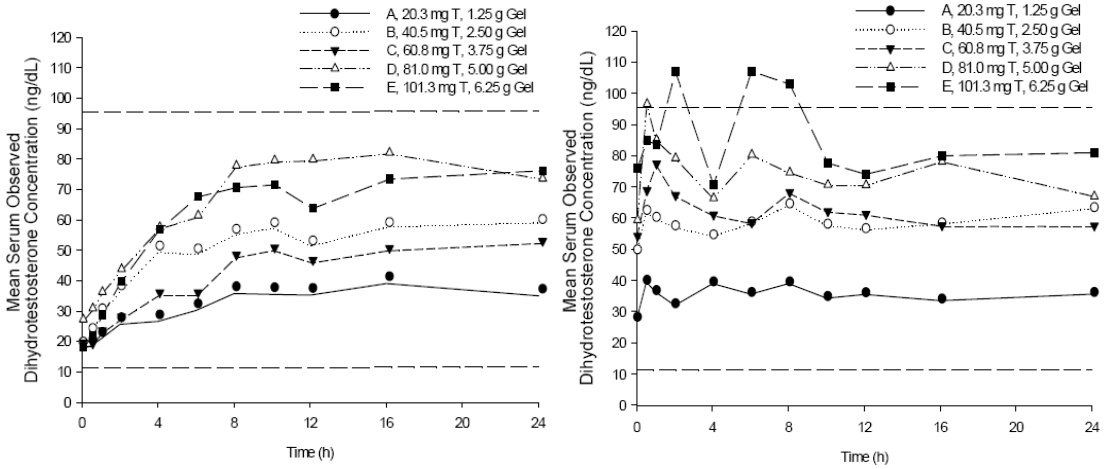


Figure 6: Serum DHT concentration-time profiles on days 1 and 14 of study S176.1.002

Table 14: Mean observed and baseline-adjusted pharmacokinetic parameters of DHT

Parameter	Treatment Group [a]	Day 1				Day 14			
		Observed		Baseline-adjusted [b]		Observed		Baseline-adjusted [b]	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
AUC_{0-24}	A	10	786 (259)	9	377 (158)	11	863 (387)	11	415 (324)
(ng*h/dL)	B	10	1260 (659)	9	787 (510)	11	1390 (994)	11	910 (840)
	C	11	999 (326)	10	558 (284)	11	1440 (454)	11	1040 (455)
	D	12	1610 (588)	10	982 (589)	8	1780 (442)	8	1180 (557)
	E	11	1460 (788)	10	1070 (726)	10	2060 (1290)	10	1680 (1190)
C_{av}	A	10	33 (11)	9	16 (7)	11	36 (16)	11	17 (14)
(ng/dL)	B	10	53 (28)	9	33 (21)	11	58 (41)	11	38 (35)
	C	11	42 (14)	10	23 (12)	11	60 (19)	11	43 (19)
	D	12	67 (25)	10	41 (25)	8	74 (18)	8	49 (23)
	E	11	61 (33)	10	45 (31)	10	86 (54)	10	70 (50)
C_{max}	A	11	44 (13)	11	27 (9)	11	47 (21)	11	30 (20)
(ng/dL)	B	11	64 (35)	11	45 (27)	11	71 (46)	11	51 (40)
	C	11	60 (25)	11	43 (23)	11	84 (28)	11	67 (27)
	D	12	96 (36)	12	70 (36)	8	109 (25)	8	86 (26)
	E	11	84 (39)	11	65 (36)	10	127 (83)	10	113 (81)
t_{max} [c]	A	11	12.0 (4.0, 24.0)	11	12.0 (4.0, 24.0)	11	4.0 (0.0, 24.0)	11	6.0 (0.0, 16.0)
(h)	B	11	12.0 (8.0, 24.0)	11	16.0 (8.0, 24.0)	11	8.0 (0.5, 24.0)	11	8.0 (0.5, 24.0)
	C	11	16.0 (8.0, 24.0)	11	16.0 (8.0, 24.0)	11	8.0 (1.0, 16.0)	11	4.0 (0.5, 12.0)
	D	12	10.0 (8.0, 24.0)	12	16.0 (8.0, 24.0)	8	1.3 (0.5, 10.0)	8	1.3 (0.50, 10.0)
	E	11	16.0 (4.0, 24.0)	11	10.0 (4.0, 24.0)	10	6.0 (0.5, 24.0)	10	6.0 (0.5, 24.0)
C_{min}	A	11	16 (5)	11	0.002 (3)	11	26 (13)	11	7.7 (3.9)
(ng/dL)	B	11	18 (9)	11	-1.2 (3)	11	45 (35)	11	25 (30)
	C	11	16 (7)	11	-1.0 (3)	11	46 (17)	11	29 (18)
	D	12	23 (12)	12	1.0 (5)	8	65 (25)	8	28 (20)
	E	11	15 (8)	11	-0.1 (4)	10	59 (35)	10	42 (28)
PTF	A	10	82 (11)	9	185 (53)	11	61 (17)	11	1280 (3790)
(%)	B	10	93 (14)	9	159 (26)	11	50 (13)	11	86 (35)
	C	11	100 (32)	10	173 (34)	11	64 (21)	11	98 (38)
	D	12	107 (27)	10	165 (33)	8	72 (21)	8	143 (104)
	E	11	113 (20)	10	154 (24)	10	77 (30)	10	100 (36)

SD = standard deviation.
[a] Gel (Testosterone) dose: Treatment A = 1.25 g (20.3 mg); Treatment B = 2.50 g (40.5 mg); Treatment C = 3.75 g (60.8 mg); Treatment D = 5.00 g (81.0 mg); Treatment E = 6.25 g (101.3 mg).
[b] Sample sizes for Baseline-adjusted parameters may be lower than for Observed parameters, due to missing baseline or post-treatment concentrations.
[c] Median (min, max) presented for t_{max}.

Estradiol (E2):

Phase 3 clinical trial S176.3.104: Baseline E2 values were 19.4 and 19.8 pg/ml in the placebo and active groups, respectively. The mean concentration profiles for estradiol for all treatment groups (placebo and testosterone gel doses) were generally within the normal range of 10-40 pg/mL for Day 14 Day 56, Day 112 and Day 182 except for the placebo and 1.25 g group on Day 56 which was slightly above the upper limit of the normal range at a single time point.

Phase 1 PK study S176.1.002: Mean baseline (Day -1) concentrations of observed estradiol ranged from 12.9 to 19.3 pg/mL and were within the normal range. Mean data for serum estradiol (plots above) suggest an increase from baseline with active treatment but generally remaining within the normal range (10-40 pg/ml) on both day 1 and day 14.

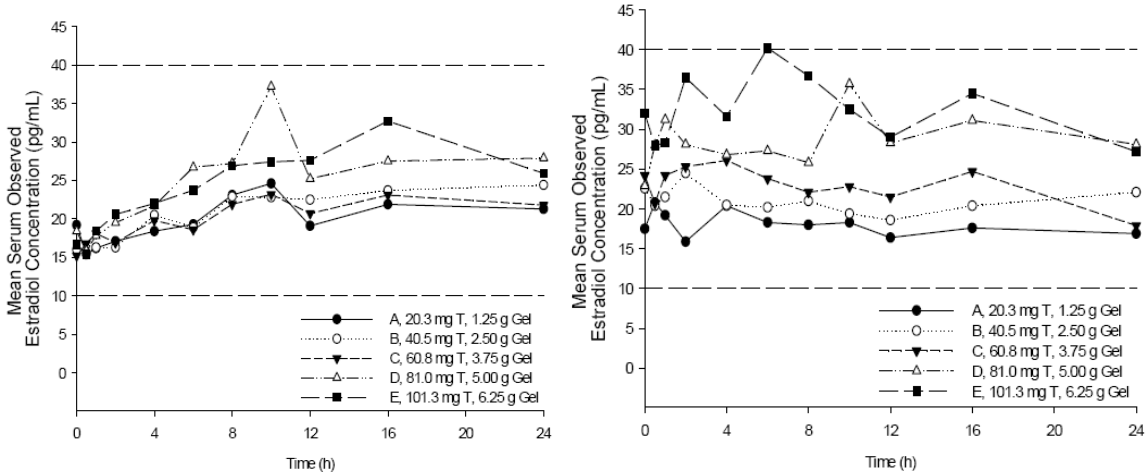


Figure 7: Serum estradiol concentrations on days 1 and 14 of PK study S176.1.002

Table 15: Mean estradiol PK parameters (observed and baseline-adjusted)

Parameter	Treatment Group [a]	Day 1				Day 14			
		Observed		Baseline-adjusted [b]		Observed		Baseline-adjusted [b]	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
AUC_{0-24}	A	10	786 (259)	9	377 (158)	11	863 (387)	11	415 (324)
(ng*h/dL)	B	10	1260 (659)	9	787 (510)	11	1390 (994)	11	910 (840)
	C	11	999 (326)	10	558 (284)	11	1440 (454)	11	1040 (455)
	D	12	1610 (588)	10	982 (589)	8	1780 (442)	8	1180 (557)
	E	11	1460 (788)	10	1070 (726)	10	2060 (1290)	10	1680 (1190)
C_{av}	A	10	33 (11)	9	16 (7)	11	36 (16)	11	17 (14)
(ng/dL)	B	10	53 (28)	9	33 (21)	11	58 (41)	11	38 (35)
	C	11	42 (14)	10	23 (12)	11	60 (19)	11	43 (19)
	D	12	67 (25)	10	41 (25)	8	74 (18)	8	49 (23)
	E	11	61 (33)	10	45 (31)	10	86 (54)	10	70 (50)
C_{max}	A	11	44 (13)	11	27 (9)	11	47 (21)	11	30 (20)
(ng/dL)	B	11	64 (35)	11	45 (27)	11	71 (46)	11	51 (40)
	C	11	60 (25)	11	43 (23)	11	84 (28)	11	67 (27)
	D	12	96 (36)	12	70 (36)	8	109 (25)	8	86 (26)
	E	11	84 (39)	11	65 (36)	10	127 (83)	10	113 (81)
t_{max} [c]	A	11	12.0 (4.0, 24.0)	11	12.0 (4.0, 24.0)	11	4.0 (0.0, 24.0)	11	6.0 (0.0, 16.0)
(h)	B	11	12.0 (8.0, 24.0)	11	16.0 (8.0, 24.0)	11	8.0 (0.5, 24.0)	11	8.0 (0.5, 24.0)
	C	11	16.0 (8.0, 24.0)	11	16.0 (8.0, 24.0)	11	8.0 (1.0, 16.0)	11	4.0 (0.5, 12.0)
	D	12	10.0 (8.0, 24.0)	12	16.0 (8.0, 24.0)	8	1.3 (0.5, 10.0)	8	1.3 (0.50, 10.0)
	E	11	16.0 (4.0, 24.0)	11	10.0 (4.0, 24.0)	10	6.0 (0.5, 24.0)	10	6.0 (0.5, 24.0)
C_{min}	A	11	16 (5)	11	0.002 (3)	11	26 (13)	11	7.7 (3.9)
(ng/dL)	B	11	18 (9)	11	-1.2 (3)	11	45 (35)	11	25 (30)
	C	11	16 (7)	11	-1.0 (3)	11	46 (17)	11	29 (18)
	D	12	23 (12)	12	1.0 (5)	8	65 (25)	8	28 (20)
	E	11	15 (8)	11	-0.1 (4)	10	59 (35)	10	42 (28)
PTF	A	10	82 (11)	9	185 (53)	11	61 (17)	11	1280 (3790)
(%)	B	10	93 (14)	9	159 (26)	11	50 (13)	11	86 (35)
	C	11	100 (32)	10	173 (34)	11	64 (21)	11	98 (38)
	D	12	107 (27)	10	165 (33)	8	72 (21)	8	143 (104)
	E	11	113 (20)	10	154 (24)	10	77 (30)	10	100 (36)

SD = standard deviation.
[a] Gel (Testosterone) dose: Treatment A = 1.25 g (20.3 mg); Treatment B = 2.50 g (40.5 mg); Treatment C = 3.75 g (60.8 mg); Treatment D = 5.00 g (81.0 mg); Treatment E = 6.25 g (101.3 mg).
[b] Sample sizes for Baseline-adjusted parameters may be lower than for Observed parameters, due to missing baseline or post-treatment concentrations.
[c] Median (min, max) presented for t_{max}.

PK conclusions:

- *Single dose and multiple dose pharmacokinetics of testosterone, DHT and E2 from Androgel 1.62 % gel have been adequately characterized.*
- *Systemic exposure increased linearly with dose although the increase was less than dose proportional.*
- *Steady-state was achieved within 2 days of dosing when drug was applied to a single application site (abdomen or shoulders/upper arms); regimens where drug application site was rotated between the two sites required 4-5 days for achieving steady-state.*
- *Testosterone concentrations at steady-state were sustained in the eugonadal range at all dose levels.*
- *Drug accumulation was evident at most doses, and was on average 1.5-1.7 fold over day 1 exposure.*

2.2.7 Transfer and Secondary Exposure Potential

2.2.7.1 How was the secondary exposure potential (transfer to non-dosed individuals) for Androgel® (testosterone gel) 1.62 % evaluated?

The magnitude of testosterone transfer from male patients applying the 1.62 % gel formulation to non-dosed female partners was evaluated in two separate phase 1 studies (S176.1.003 and S176.1.008). In addition, the effect of washing in removing residual drug from the skin was evaluated using tape stripping analysis in study S176.1.005. Together, these studies yielded important information related to transfer potential for this new gel formulation and possible risk minimization strategies.

Study S176.1.003: A Randomized, Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-dosed Females after Skin Contact with a Male Partner Dosed with Testosterone Gel 1.62%.

This study was a single center, open-label, randomized, single and multiple exposure, parallel group study in N = 16 healthy male and female couples per treatment cohort. In each treatment group, 5.00 g testosterone gel 1.62% (81 mg testosterone) was applied by each male subject to his abdomen once daily for seven days (Days 1-7).

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

Following drug application to the abdomen in the male, each couple engaged in a total of 15 minutes of contact in a vertical position. Male subjects in Treatment B were given a 100% cotton t-shirt to wear that fully covered the abdomen. Female subjects did not shower or bathe until just prior to the next dose application.

Whole blood samples for measurement of serum testosterone, dihydrotestosterone, and estradiol concentrations were collected over 24 hours for PK assessments from each female subject at baseline (day -1), and at the end of the 15 minute contact period on day 1 and day 7.

Results:

Table 16: Mean (% CV) observed testosterone pharmacokinetic parameters in female volunteers in each of the treatment groups and days of transfer evaluation study S176.1.003

		Trt A	Trt B	Trt C
C_{max}	Day -1	30.75 (39 %)	29.7 (57.5 %)	32.6 (65 %)
	Day 1	77.7 (44 %)	49.2 (68.5%)	85 (75 %)
	Day 7	88.1 (41 %)	51.4 (66 %)	68.6 (66 %)
C_{avg}	Day -1	25.5 (39%)	23.8 (57.6%)	26.2 (62 %)
	Day 1	52.8 (47 %)	34.4 (57.2%)	62.4 (71 %)
	Day 7	61.7 (33.5 %)	38.9 (60 %)	50 (69 %)
AUC	Day -1	611 (39 %)	573 (57 %)	631 (62 %)
	Day 1	1245 (47%)	812 (57 %)	1475 (71 %)
	Day 7	1454 (34 %)	918 (60 %)	1174 (69 %)

A: direct contact at 2h post-dose; B: contact at 2 h post-dose /T-shirt on male; C: direct contact at 12 h post-dose

Table 17: PK parameters for <u>baseline-adjusted</u> testosterone data in female subjects [mean(%CV)]

		Trt A	Trt B	Trt C
C_{max}	Day 1	53.1 (63 %)	17.1 (89 %)	53.1 (97 %)
	Day 7	60.8 (59 %)	25 (119 %)	37.4 (91 %)
C_{avg}	Day 1	29.3 (71 %)	8.61 (115 %)	25.1 (58 %)
	Day 7	35.8 (55 %)	10.5 (170 %)	16.2 (84 %)
AUC	Day 1	690 (71 %)	204 (115 %)	595 (57 %)
	Day 7	844 (55 %)	247 (171 %)	382 (84 %)

A: direct contact at 2h post-dose; B: contact at 2 h post-dose /T-shirt on male; C: direct contact at 12 h post-dose

Statistically significant differences in testosterone PK parameters among treatments were not observed at baseline in female subjects. Mean observed Baseline (Day -1) Cavg values, which ranged from 23.9-26.3 ng/dL, were similar for all treatments and were within the normal range (8-75 ng/dL). Mean observed Baseline (Day -1) Cmax values, which ranged from 29.7-32.6 ng/dL, were similar for all treatments and were within the normal range (8-75 ng/dL).

The plots below summarize the observed and baseline-adjusted testosterone concentration-time profiles within the three treatment groups:

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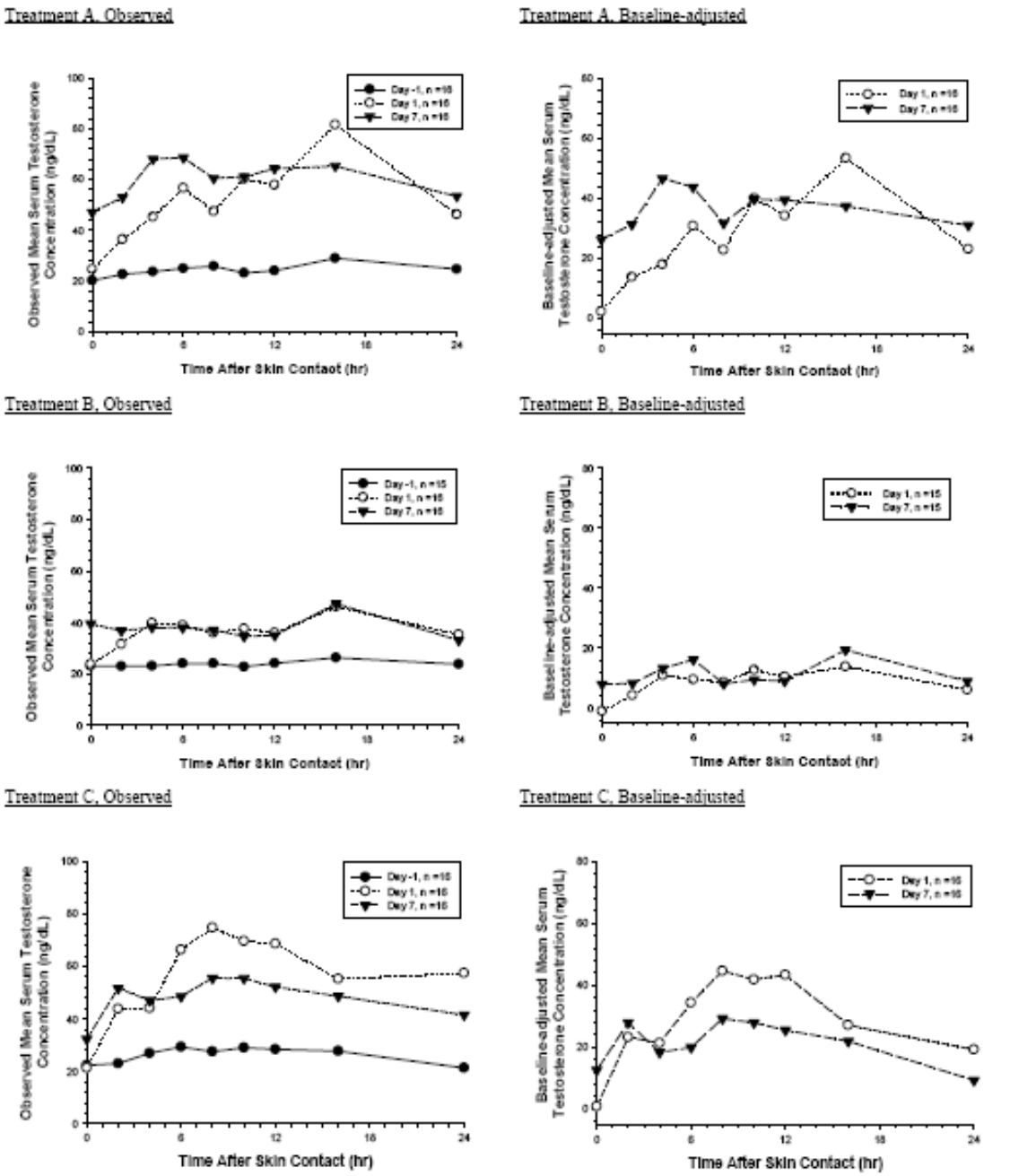


Treatment A: Direct skin contact occurred 2 hours postdose (no t-shirt), Treatment B: Skin contact occurred 2 hours postdose (with the male wearing a t-shirt), Treatment C: Direct skin contact occurred 12 hours postdose (no t-shirt).

Supporting documentation: Table 10.2.1 and Table 10.2.4.

Figure 1. Arithmetic Mean Observed and Baseline-adjusted Testosterone Serum Concentration versus Time Profiles on Linear Scales for each Treatment

Figure 8: Observed and baseline-adjusted serum total testosterone in S176.1.003

Female subjects in Treatment A [direct skin-to-skin contact at 2h post-dose] and Treatment C [direct skin-to-skin contact at 12 h post-dose] had an approximate 2.0- to 2.7-fold increase from their baseline Cavg on Days 1 and 7.

Female subjects in treatment B [2 h contact /with t-shirt on male] had a 1.5- and 1.9-fold increase from baseline Cavg was observed for Days 1 and 7.

Table 18: Summary of fold-changes from baseline in testosterone PK [mean (range)]

	Day 1		Day 7	
Treatment	Cmax	Cavg	Cmax	Cavg
A	2.72 (1.14-5.86)	2.40 (1.12-4.05)	3.12 (1.04-5.79)	2.67 (1.04-4.56)
B	1.53 (0.9 -3.63)	1.58 (0.83-3.18)	1.96 (0.58-6.65)	1.93 (0.68-6.56)
C	2.86 (1.05-6.87)	2.51 (1.08-6.09)	2.26 (0.57-4.24)	2.02 (0.55-3.52)

A: direct contact at 2 h post-dose; B: contact at 2 h post-dose/T-shirt on male; C: direct contact at 12 h post-dose

Statistical comparisons within each treatment group suggest a significant increase from baseline (day -1) in AUC, Cavg and Cmax of testosterone in female subjects on both day 1 and day 7 of supervised contact sessions ($p < 0.05$).

Additional comparisons between treatment groups suggest significant differences ($p < 0.05$) in the PK parameters between female subjects of treatment group B (contact at 2 h with T-shirt) to that in treatments A (contact at 2 h without T-shirt) or C (contact at 12 h without T-shirt). There was no significant difference between PK parameters in treatments A and C suggesting that the timing of direct contact (2h or 12 h) did not make a difference with regard to testosterone transfer from dosed males to non-dosed female partners.

Individual concentration-time data within each treatment group are shown. Data suggest a consistent trend for an increased testosterone levels over baseline in individual females following all transfer regimens (direct skin-to-skin contact with male partners (treatments A and C) or contact with clothing covering the male application site (treatment B)). The overall magnitude of transfer was lower in treatment B but transfer was not completely eliminated when the application site was covered with clothing.

Figure 9: Individual testosterone plots in treatment A [S176.1.003]

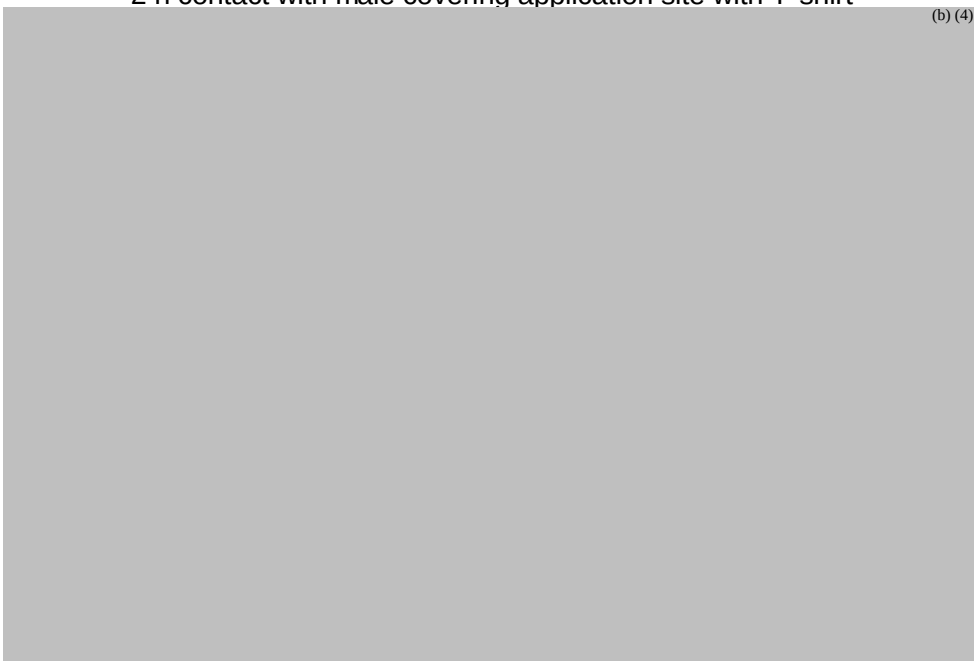


Figure 10: Individual plots in treatment B [S176.1.003]

Figure 11: Individual plots in Treatment C [study S1761.003]

Table 19: Individual listing of fold-changes in Cavg of testosterone in females is shown:

Trt A		Trt B		Trt C	
Subject ID	Cavg Day 1/ Day -1	Subject ID	Cavg Day1/ Day -1	Subject ID	Cavg Day 1/ Day -1
26385		26387	1.21	26386	
26390	2.17	26388	1.95	26389	
26392	1.61	26391	1.25	26393	2.79
26394		26396	1.28	26395	2.26
26397	1.72	26399	2.08	26398	1.56
26400	4.05	26401	2.80	26402	1.85
26403		26404	1.46	26405	
26407	3.51	26406	1.28	26408	4.50
26411	1.84	26410		26409	2.17
26412	2.07			26413	1.53
26416	2.66	26415	3.18	26417	6.09
26419	1.61	26418		26420	1.62
26421	2.26	26422	0.96	26423	1.88
26426	1.12	26425	0.83	26424	
26427	3.90	26428	1.01	26429	1.08
26430	2.67	26431	1.27	26432	2.75
Average change	**2.40**		**1.58**		**2.51**

<u>Note on cyclical variation of testosterone levels in pre-menopausal women</u>: Literature data suggests that testosterone levels in females vary over the menstrual cycle. Values are typically reported to be higher during the luteal phase compared to the follicular phase, with peak testosterone levels appearing around ovulation.

In the present study S176.1.003, baseline T levels in female subjects were determined on day -1. For obtaining fold-changes over baseline, these values were subtracted from corresponding values obtained after male to female contact sessions on days 1 or 7. Since at study entry females were not controlled for their menstrual cycle phase, it is anticipated that baseline testosterone levels would be changing throughout the study duration and particularly so from day -1 to day 7. This was apparent in some individuals who demonstrated day 7 observed T levels that were lower than those seen on day 1 probably due to differences in endogenous T levels.

Therefore, use of a baseline obtained 7 days earlier would not allow accurate assessment of treatment-related increases in serum testosterone levels. For this purpose, only the fold changes in systemic testosterone following single dose exposure (day 1) from this study will be used for assessing transfer potential. The distribution (box plot) of the relative fold changes in testosterone PK from baseline to day 1 are shown for the three treatment groups:

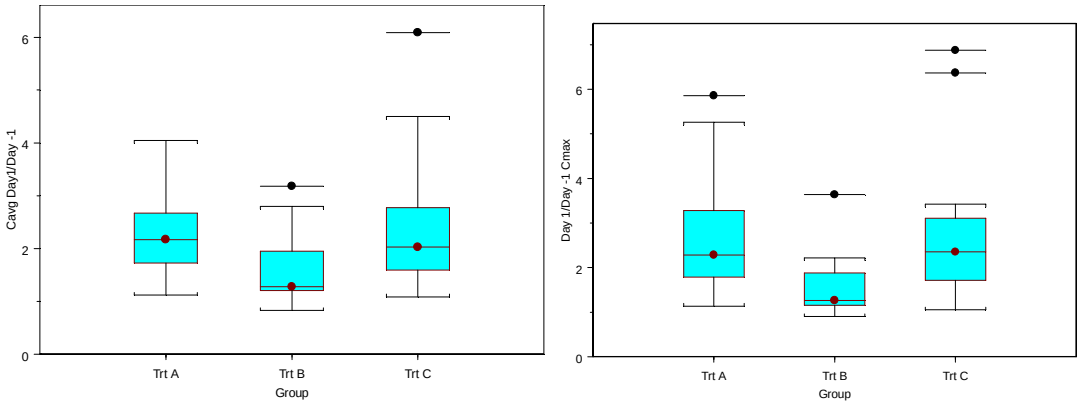


Figure 12: Box plots representing distribution of fold changes over baseline in Cmax and Cavg total testosterone in study S176.1.003

Conclusions:

Significant partner-to-partner transfer of testosterone occurs from Androgel 1.62 % gel (abdominal application of 5.0 g gel dose equivalent to 81 mg testosterone) as evident from a statistically significant increase from baseline in systemic testosterone concentrations in non-dosed females. Covering the application site with clothing reduced the magnitude of transfer in such individuals but did not eliminate it completely.

Patients should be advised of this risk. Cautionary language should be included in the product labeling to communicate this risk to physicians/patients and appropriate

precautions to minimize transfer should be taken (e.g. hand-washing after dose application, covering of the application site with clothing, avoiding direct contact with the product or with the drug application site in dosed individuals, washing of the drug application site if a direct contact is anticipated, etc). A combination of such measures may be needed to minimize transfer.

Study S176.1.008: A Randomized, Open-Label, Parallel Group Study to Evaluate the Effects of Dose, Post-dose Washing, and Application Site on the Transfer Potential of Testosterone Gel 1.62% From Dosed Males to a Non-dosed Female Partner

Treatments: N = 24 couples (or 48 total subjects; 24 male, 24 female; 18-80 years inclusive; healthy) randomized to one of the following treatment groups (I, II, III). Within each treatment group, subjects received two single dose/exposure treatments in a randomized order. Each single dose/contact was separated by a 1-week washout period. Dose application and subsequent skin contact occurred on Days 1 and 8 of the study.

- Group **I** *[2.5 g dose; Trt **A:** direct skin contact at 2h post-dose; Trt **B:** contact at 2h post-dose with clothing barrier to cover application site]*
- Group **II** *[5.0 g dose; Trt **C:** direct skin contact at 2 h post-dose; Trt **D:** direct skin contact at 2h post-dose after the male showered]*
- Group **III** *[5.0 g dose; Trt **E:** direct skin contact at 2 h post-dose-gel applied to shoulders/upper arms; Trt **F:** direct skin contact at 2h- gel applied to abdomen]*

Note that the 2.5 g and 5.0 g gel doses of AndroGel 1.62 % provide topical testosterone doses equivalent to 40.5 mg and 81 mg respectively. Each couple engaged in a total of 15 minutes of contact in a vertical position. Male subjects in Treatment B were given a 100% cotton t-shirt to wear that fully covered the abdomen. For Treatment D only, male subjects showered and thoroughly washed the application site with soap and water 15 minutes prior to the scheduled contact time. Female subjects did not shower or bathe until 24 hours after the contact period. Blood samples for serum analyses of T, DHT and E2 were collected at various time points on day -1, day 1 and day 8.

Results:

Table 20: Observed PK parameters of testosterone across all groups (S176.1.008)

Observed testosterone PK Mean (SD)	C_{max} ng/dL	C_{avg} ng/dL	AUC_{0-24} ng.h/dL
Group I- Baseline	35.96 (18.1)	21.6 (8.2)	519 (197)
Trt A	44.65 (24.6)	27.7 (12.8)	666 (309)
Trt B	24.03 (7.42)	20.6 (8.0)	495 (191)
Group II- Baseline	20.96 (7.26)	16.4 (4.2)	393 (101)
Trt C	36.6 (16.1)	25.3 (8.7)	606 (208)
Trt D	24.2 (9.13)	18.2 (5.9)	436 (142)
Group III- Baseline	39.7 (37.08)	18.5 (10.3)	445 (247)

Trt E	103.6 (29.4)	56.3 (17.2)	1350 (413)
Trt F	57.5 (34.3)	38.9 (26.6)	933 (640)

Group I: 2.5g, abdomen; Trt A: direct contact at 2h; Trt B: contact at 2 h with T-shirt on male
Group II: 5 g, abdomen; Trt C: direct contact at 2 h; Trt D: direct contact at 2h after male washing
Group III: 5 g, two sites; Trt E: direct contact at 2 h; gel on shoulders; Trt F: direct contact at 2h; gel on abdomen]

Table 21: Baseline-adjusted PK parameters across all treatments (S1761.008)

Mean (SD)	C_{max} ng/dL	C_{avg} ng/dL	AUC_{0-24} ng.h/dL
Group I			
Trt A	28.4 (21.8)	5.71 (9.58)	137 (230)
Trt B	7.64 (6.09)	-1.14 (6.97)	-27.3 (167)
Group II			
Trt C	22.3 (16.1)	8.74 (8.36)	209 (200)
Trt D	9.03 (6.33)	1.72 (2.44)	41.3 (58.5)
Group III			
Trt E	89.8 (28.6)	37.4 (19.1)	898 (459)
Trt F	43.1 (34.4)	20.0 (22.7)	481 (545)

Group I: 2.5g, abdomen; Trt A: direct contact at 2h; Trt B: contact at 2 h with T-shirt on male
Group II: 5 g, abdomen; Trt C: direct contact at 2 h; Trt D: direct contact at 2h after male washing
Group III: 5 g, two sites; Trt E: direct contact at 2 h; gel on shoulders; Trt F: direct contact at 2h; gel on abdomen]

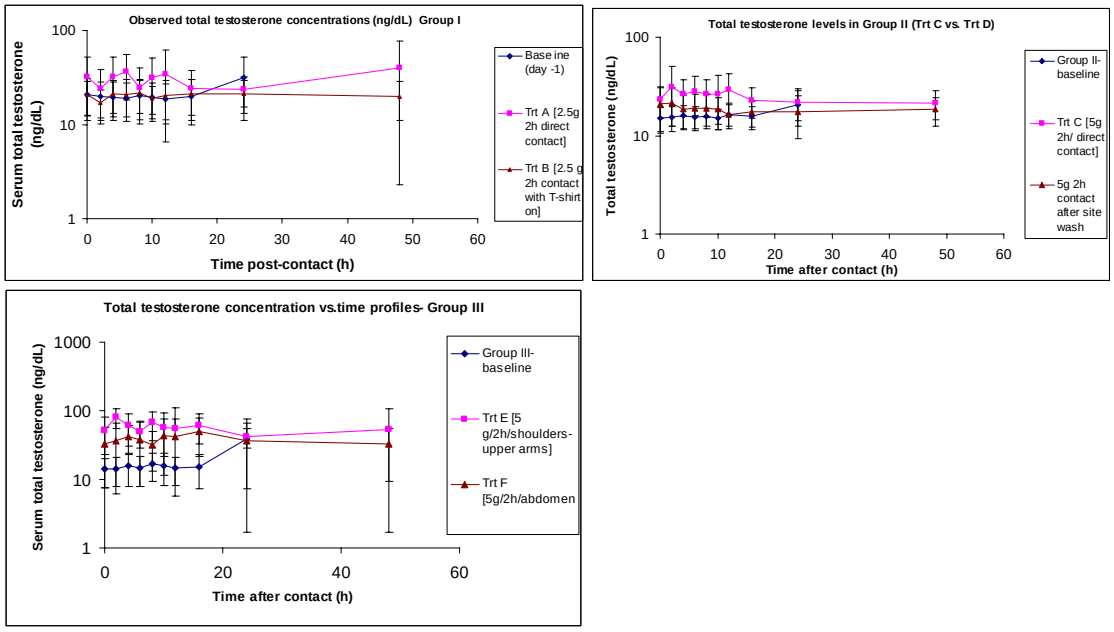


Figure 13: Mean observed testosterone concentration vs. time profiles in the various treatment groups (compared to baseline) in study S1761.008

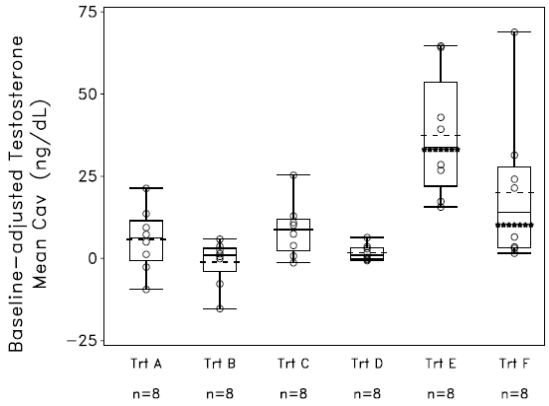


Figure 14: Box plots of baseline-adjusted total testosterone Cavg in study S1761.008

Table 22: Fold changes in testosterone exposure over baseline in female subjects [mean (range)] in the various treatment groups of transfer evaluation study S176.1.008

Mean fold-changes (Range)	Group I		Group II		Group III	
	Trt A	Trt B	Trt C	Trt D	Trt E	Trt F
C_{max}	1.26	0.80	1.86	1.17	5.01	2.21
	[0.9-1.58]	[0.37-1.36]	[0.89-3.27]	[0.96-1.91]	[1.0-11.07]	[0.77-7.97]
C_{avg}	1.32	1.00	1.61	1.09	6.15	2.48
	[0.7-1.73]	[0.51-1.27]	[0.91-2.78]	[0.95-1.32]	[1.65-23.9]	[1.06-5.55]
Group I: 2.5g, abdomen; Trt A: direct contact at 2h; Trt B: contact at 2 h with T-shirt on male Group II: 5 g, abdomen; Trt C: direct contact at 2 h; Trt D: direct contact at 2h after male washing Group III: 5 g, two sites; Trt E: direct contact at 2 h; gel on shoulders; Trt F: direct contact at 2h; gel on abdomen]						

Table 23: Individual fold-changes from baseline across various treatment groups are shown:

Fold changes over baseline in various PK parameters						
	Group I		Group II		Group III	
	Trt A	Trt B	Trt C	Trt D	Trt E	Trt F
C_{max}	0.90	0.51	2.57	1.33	2.27	1.87
	1.22	0.37	1.37	1.07	10.52	7.97
	1.48	0.69	3.27	1.00	5.57	1.91
	1.58	1.36	1.70	0.96	1.00	0.77
	1.15	0.91	1.12	1.91	11.07	1.48
	1.03	0.98	2.71	1.15	1.29	1.23
	1.51	1.15	1.34	0.96	3.42	1.23
	1.21	0.46	0.89	1.01	4.97	1.28
Average	1.26	0.80	1.87	1.17	5.01	2.22
C_{avg}	0.70	0.51	1.83	1.22	4.18	4.52
	1.54	0.72	1.34	1.08	10.38	5.55
	1.73	1.20	2.78	0.98	2.21	1.27

	1.53	1.27	1.55	1.32	2.22	1.75
	0.90	1.02	1.04	1.17	23.92	2.66
	1.09	1.11	2.22	1.04	1.65	1.81
	1.39	1.20	1.26	0.95	1.74	1.06
	1.68	1.00	0.91	0.99	2.94	1.26
Average	1.32	1.00	1.62	1.10	6.15	2.49

Group I: 2.5g, abdomen; Trt A: direct contact at 2h; Trt B: contact at 2 h with T-shirt on male
Group II: 5 g, abdomen; Trt C: direct contact at 2 h; Trt D: direct contact at 2h after male washing
Group III: 5 g, two sites; Trt E: direct contact at 2 h; gel on shoulders; Trt F: direct contact at 2h; gel on abdomen]

Group I: 7 out of 8 individuals demonstrated an increase in Cavg levels over baseline during treatment A (2.5 g; direct contact); these increases ranged from 9 %- 73 % over baseline. In treatment B (2.5 g; male T-shirt), small increases in Cavg over baseline were still apparent in few of the individuals (4 out of 8 individuals; ranging 11 % – 27%). Similar trends were seen with Cmax.

The fold changes over baseline T following direct contact at 2 h post-dose in treatment A (using 2.5 g of the gel dose) were lower compared to a 2.72- fold (Cmax) and 2.4-fold (AUC) observed at a 5 g dose in a different transfer study (003). The reason for this difference is not understood, and could potentially involve a dose factor (i.e. lower doses might result in lesser transfer) as lesser amount of drug is available at the application site with a smaller dose.

Statistical analyses of change from baseline suggest that for treatment A (direct contact at 2h), significant change over baseline at the 2.5 g gel dose was observed in females only for Cmax ($p < 0.05$), while the increase was not significantly greater for other parameters. For treatment B (T-shirt), no significant increases from baseline were noted.

Table 24: Statistical analysis of changes over baseline in PK in various treatment group I

Parameter (unit)	Treatment [a]	Study Day [b]	N	Arithmetic Mean	Geometric Least Squares Mean	95% Confidence Interval	Comparisons: Pair [b]	Ratio(%)	90% Confidence Interval	p-value
AUC0-24 (ng·h/dL)	A	Base	8	519	485	(340.8 , 690.9)				
		Post	8	666	614	(431.1 , 873.9)	Post/Base	126.5	(101.6 , 157.5)	0.0820
	B	Base	8	519	485	(350.1 , 672.5)				
		Post	8	495	469	(338.6 , 650.4)	Post/Base	96.7	(78.4 , 119.4)	0.7723
Cav (ng/dL)	A	Base	8	21.6	20.2	(14.2 , 28.8)				
		Post	8	27.7	25.6	(18.0 , 36.4)	Post/Base	126.6	(101.6 , 157.7)	0.0816
	B	Base	8	21.6	20.2	(14.6 , 28.0)				
		Post	8	20.6	19.5	(14.1 , 27.1)	Post/Base	96.6	(78.2 , 119.3)	0.7667
Cmax (ng/dL)	A	Base	8	36.0	31.6	(20.6 , 48.4)				
		Post	8	44.7	39.1	(25.5 , 60.0)	Post/Base	123.8	(108.4 , 141.3)	0.0185
	B	Base	8	36.0	31.6	(22.1 , 45.2)				
		Post	8	24.0	23.2	(16.2 , 33.2)	Post/Base	73.4	(53.7 , 100.4)	0.1037

Group II: 7 out of 8 individuals demonstrated an increase in Cavg levels over baseline during treatment C (5.0 g; direct contact) ranging from 5 %-178 % increases. In the treatment group D (5.0 g; direct contact after washing application site), 4 out of 8 individuals still had an increase in Cavg over baseline ranging from 4 % to 33 %. Similar trends were seen with Cmax.

Statistical analyses of change from baseline suggest that statistically significant increases from baseline were observed in female partners for all PK parameters following treatment C (direct contact), but not for treatment D (contact after washing).

Table 25: Statistical analysis of change over baseline in PK in various treatment group II

Parameter (unit)	Treatment [a]	Study Day [b]	N	Arithmetic Mean	Geometric Least Squares Mean	95% Confidence Interval	Comparisons Pair [b]	Ratio(%)	90% Confidence Interval	p-value
AUC0-24 (ng·h/dL)	C	Base	8	393	380	(289.6 , 497.8)				
		Post	8	606	575	(439.0 , 754.4)	Post/Base	151.5	(117.7 , 195.1)	0.0169
	D	Base	8	393	380	(300.5 , 479.7)				
		Post	8	436	413	(327.2 , 522.2)	Post/Base	108.9	(100.7 , 117.7)	0.0786
Cav (ng/dL)	C	Base	8	16.4	15.8	(12.1 , 20.7)				
		Post	8	25.3	24.0	(18.3 , 31.4)	Post/Base	151.7	(117.7 , 195.3)	0.0169
	D	Base	8	16.4	15.8	(12.5 , 20.0)				
		Post	8	18.2	17.2	(13.6 , 21.8)	Post/Base	108.9	(100.7 , 117.7)	0.0774
Cmax (ng/dL)	C	Base	8	21.0	19.8	(14.1 , 27.9)				
		Post	8	36.7	33.7	(23.9 , 47.5)	Post/Base	170.1	(124.5 , 232.4)	0.0146
	D	Base	8	21.0	19.8	(15.1 , 25.9)				
		Post	8	24.2	22.6	(17.3 , 29.6)	Post/Base	114.2	(97.6 , 133.7)	0.1529

Group III: All individuals demonstrated an increase in baseline with direct contact at 2 h after drug application to shoulders/upper arms (treatment E) or abdomen (treatment F), with the fold changes on average being lower in the latter treatment group, probably due to one individual that demonstrated a 24-fold increase over baseline. This individual # 27409 was post-menopausal and had negligible serum testosterone values at baseline (Cavg of 1.82 ng/dL); subject experienced a Cavg of 44 ng/dL with drug application on shoulders/upper arms (E) which was within normal range for pre-menopausal females; however, subject had very low systemic T levels after drug application to the abdomen (5 ng/dL).

Statistical analyses within group III suggest that statistically significant increases from baseline in testosterone PK parameters were observed in females following contact with male partners applying drug to either shoulders/upper arms (E) or abdomen (F), with the exception of Cmax following abdominal application.

Table 26: Statistical analysis of change over baseline in PK in various treatment group III

Parameter (unit)	Treatment [a]	Study Day [b]	N	Arithmetic Mean	Geometric Least Squares Mean	95% Confidence Interval	Comparisons Pair [b]	Ratio(%)	90% Confidence Interval	p-value
AUC0-24 (ng·h/dL)	E	Base	8	445	369	(212.4 , 641.4)				
		Post	8	1350	1400	(805.9 , 2433.4)	Post/Base	379.4	(204.9 , 702.5)	0.0046
	F	Base	8	445	391	(200.8 , 761.4)				
		Post	8	933	816	(419.0 , 1588.9)	Post/Base	208.7	(138.4 , 314.7)	0.0116
Cav (ng/dL)	E	Base	8	18.5	15.4	(8.8 , 26.7)				
		Post	8	56.3	58.4	(33.6 , 101.4)	Post/Base	379.5	(204.9 , 703.0)	0.0046
	F	Base	8	18.5	16.3	(8.4 , 31.7)				
		Post	8	38.9	34.0	(17.4 , 66.2)	Post/Base	208.6	(138.4 , 314.4)	0.0115
Cmax (ng/dL)	E	Base	8	39.7	30.2	(18.4 , 49.5)				
		Post	8	104	111	(67.5 , 181.2)	Post/Base	366.2	(211.3 , 634.8)	0.0029
	F	Base	8	39.7	32.1	(19.3 , 53.5)				
		Post	8	57.6	53.9	(32.3 , 89.9)	Post/Base	167.9	(105.7 , 266.7)	0.0718

Conclusions:

Group I: Results from this group suggest that clothing to cover the application site may aid in minimizing the overall transfer at the 2.5 g dose level, although it may not completely eliminate transfer to non-dosed individuals.

Group II: Overall washing of the application site prior to contact appears to minimize (but not completely eliminate) transfer to non-dosed individuals. Use of washing in conjunction with clothing to cover the application site may further reduce the degree of transfer to non-dosed individuals. The washing protocol in this study included soap and water and sponsor notes that use of a wash-cloth could've potentially removed more of the drug from the application site. Patient instructions could potentially incorporate this as an additional measure to mitigate transfer.

Group III: Results from this group demonstrate that transfer potential to non-dosed individuals upon direct skin contact is significant for testosterone 1.62 % gel formulation regardless of the site of application. Appropriate precautionary measures should be used to minimize transfer.

Issue of cyclical variation in serum testosterone during menstrual cycle phases: It is known from literature that endogenous testosterone in female varies during the menstrual cycle with higher values typically observed the luteal phase compared to the follicular phase and a likely peak around ovulation. Since this study was not controlled with respect to menstrual cycle phase of the females, it is likely that the baseline T levels may have changed over the course of the study duration, which could potentially confound accurate determination of treatment effect. This may be particularly so with data collected on day 8 of each treatment group since baseline subtraction was done using values obtained 8 days on day -1.

Hence data resulting from this study were interpreted with caution as the confounding influence of changing T baseline during the study couldn't be ruled out. There were two treatments within each group of this study. Subjects were randomized to receive either of these treatments in a crossover manner on day 1 or day 8. For example, based on their randomization, in group II half of the subjects would've received treatment C on day 1 while the other half would receive treatment D on this day. Since, the impact of baseline variation can theoretically be of the most concern to day 8 data, subgroup analyses of data from this study was done using only that data obtained from day 1 of each study and comparing it to each subject's baseline at day -1. Therefore in this analysis, there were four subjects per treatment cohort since day 8 data was not considered. Fold changes from baseline to day 1 in the testosterone Cmax and Cavg of these individuals are shown below:

A: 2.5 g; 2h; direct contact
B: 2.5 g 2h; male wearing T-shirt
C: 5.0 g; 2h; direct contact
D: 5.0 g; 2h; direct contact after male washing the site of application
E: 5.0 g; 2h; direct contact after gel application to shoulders/upper arms
F: 5.0 g; 2h; direct contact after gel application to abdomen

Table 27: Observed fold-changes over baseline in C_{max} and C_{avg} after deleting day 8 data for each treatment group

Group I	Subject	C_{max}	C_{avg}
Trt A on day 1	27400	1.22	1.54
	27403	1.48	1.73
	27410	1.15	0.90
	27419	1.21	1.68
		1.27	1.46
Trt B on day 1	27398	0.51	0.51
	27407	1.36	1.27
	27412	0.98	1.11
	27415	1.15	1.20
		1.00	1.02

Group II	Subject	C_{max}	C_{avg}
Trt C on day 1	27402	1.37	1.34
	27405	1.70	1.55
	27411	1.12	1.04
	27416	1.34	1.26
		1.38	1.30
Trt D on day 1	Subject	Cmax	C_{avg}
	27399	1.33	1.22
	27404	1.00	0.98
	27413	1.15	1.04
	27417	1.01	0.99
		1.12	1.06

Group III	Subject	C_{max}	C_{avg}
Trt E on day 1	27397	2.27	4.18
	27406	5.57	2.21
	27408	1.00	2.22
	27414	1.29	1.65
		2.53	2.56
Trt F on day 1	Subject	C_{max}	C_{avg}
	27401	7.97	5.55
	27409	1.48	2.66
	27418	1.23	1.06
	27420	1.28	1.26
		2.99	2.63

Above data incorporating PK collected from day 1 alone suggests similar trends in C_{max} and C_{avg} changes from baseline, with the clothing barrier (2.5 g dose; abdomen; Treatment B) and washing the application site (5.0 g dose; abdomen; Treatment D) minimizing the overall magnitude of transfer relative to direct skin-to-skin contact.

Results from another phase 1 study S176.1.005 (skin stripping results to be discussed below) provide additional information on the effect of washing on residual testosterone on skin that can be used in conjunction with the results of these transfer studies.

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

Note: only results from the skin stripping analysis to determine effect of washing on residual testosterone are discussed here. Results of the effect of washing on bioavailability are discussed elsewhere.

Design: Single center, open-label, randomized, three-way crossover study in 24 hypogonadal male volunteers. 5.00 g testosterone gel 1.62% (81 mg testosterone) was applied topically once daily in the morning to the shoulders/upper arms for 7 days during each of three consecutive treatment periods, for a total of 21 days of dosing. There was no washout period between treatment periods. On the seventh dosing day of each treatment period, skin washing with soap and water occurred at the following times:

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

The skin washing occurred in the shower using commercially available Ivory Bar soap and water on the shoulder/upper arms with a soap lather time of approximately 2 minutes followed by a thorough rinse. The site of application was then thoroughly dried. Tape stripping procedures were conducted at 30 minutes after the projected or actual wash time on the sixth (control) and seventh (washed) days of each treatment period to evaluate the presence of any residual testosterone remaining in the stratum corneum with or without washing. For tape stripping, at the same skin site 10 strips total were applied and removed. The drug was extracted from the 10 strips in two samples. The first sample contained strips 1-3 and the second sample contained strips 4-10.

Results: Tape stripping: Residual testosterone on skin

Data suggests that the recovered amount was markedly decreased on the days when skin was washed (i.e. 2 h, 6h or 10 h post-dose on day 7) compared to day 6 when no washing was done. In total (strips 1-10; surface and deeper skin layer combined), the amount of testosterone recovered was decreased by 84.0%, 87.2%, and 81.3% after post-dose skin washing (Day 7) compared to no post-dose skin washing (Day 6) for Treatments A, B, and C, respectively.

For surface stripping alone (strips 1-3), the amount was decreased by 86.9%, 88.7%, and 82.9% after post-dose skin washing in Treatments A, B, and C, respectively. For stripping of the deep skin layer (strips 4-10), the amount remaining after strips 1-3 was reduced by 50.6%, 77.3%, and 63.9% in Treatments A, B, and C, respectively.

Table 28: Results of tape stripping analyses in study S176.1.005

	Trt Group	Treatment Day 6[a] Amount (µg) n	Mean (SD)	Treatment Day 7 Amount (µg) n	Mean (SD)	Difference[b] (µg) Mean (SD)	Change[c] (%) Mean (SD)	Ratio[d] Mean (SD)
First sample collection (stripping 1-3)	A	21	18.550 (14.247)	20	2.459 (3.279)	-16.356 (13.664)	-86.9 (13.5)	0.131 (0.135)
	B	21	17.081 (10.639)	21	2.043 (2.138)	-15.038 (9.913)	-88.7 (9.5)	0.113 (0.095)
	C	22	11.803 (8.247)	22	1.838 (2.059)	-9.965 (7.710)	-82.9 (17.7)	0.171 (0.177)
Second sample collection (stripping 4-10)	A	21	2.456 (1.729)	20	1.032 (1.161)	-1.409 (1.619)	-50.6 (79.0)	0.495 (0.791)
	B	21	3.494 (2.753)	21	0.702 (0.575)	-2.792 (2.529)	-77.3 (15.4)	0.227 (0.154)
	C	22	3.134 (2.427)	22	0.868 (0.695)	-2.266 (2.021)	-63.9 (33.6)	0.361 (0.336)
Total sample collection (stripping 1-10)	A	21	21.006 (15.534)	20	3.491 (4.267)	-17.765 (14.590)	-84.0 (15.4)	0.160 (0.154)
	B	21	20.575 (12.885)	21	2.744 (2.591)	-17.831 (11.909)	-87.2 (9.8)	0.128 (0.098)
	C	22	14.937 (9.949)	22	2.706 (2.598)	-12.231 (9.042)	-81.3 (16.9)	0.187 (0.169)

[a] On Day 6, no skin washing; on Day 7, the skin washing occurred.

[b] Difference=(value of Day 7-value of Day 6); positive difference indicates increase; negative difference indicates decrease.

[c] Change (%)=(value of Day 7-value of Day 6)/value of Day 6*100; positive change indicates increase; negative change indicates decrease.

[d] Ratio=(value of Day 7)/(value of Day 6).

Treatment A=testosterone gel 1.62% applied once daily for 7 days followed by skin washing 2 hours postdose on Treatment Day 7.

Treatment B=testosterone gel 1.62% applied once daily for 7 days followed by skin washing 6 hours postdose on Treatment Day 7.

Treatment C=testosterone gel 1.62% applied once daily for 7 days followed by skin washing 10 hours postdose on Treatment Day 7.

Study conclusions:

Results of this study suggest that while washing of the application site resulted in removal of at least 80 % of residual testosterone from the application site, the systemic absorption of testosterone was not markedly affected. Thus skin application sites can be allowed to be washed at or after 2 hours post-dose during clinical use.

While tape stripping results showed that residual testosterone on the skin can be removed (by at least 80 %) by washing the site with soap and water, washing did not completely remove all traces of drug from the skin.

Conclusions on the transfer potential from Androgel 1.62 %:

- *Results from studies S176.1.003, S176.1.005 and S176.1.008 suggest that significant secondary exposure of testosterone in non-dosed individuals (e.g. females, children) can occur when direct skin-to-skin contact with the Androgel 1.62 % application site occurs.*
- *Clothing barrier reduces but does not eliminate transfer and thereby secondary exposure. Therefore, clothing alone shouldn't be used as a sole means of transfer minimization.*
- *Washing with soap and water was effective in removing most of the residual testosterone from the skin and by far appears to be the most effective way to minimize transfer (combining the results from studies S176.1.005 and S176.1.008). Sponsor notes in a subsequent correspondence (09/17/09) to the division that use of a washcloth, rather than using only soap and water, may potentially remove additional testosterone from the surface of the skin due to desquamation of the outer layers of the skin. Although this was not evaluated clinically, use of a washcloth may be incorporated as an additional measure to avoid transfer. Patients should however avoid sharing washcloths with their spouses or other family members.*
- *Washing coupled with a clothing barrier to cover the application site would likely have the most benefit in the clinical setting to prevent transfer. Washing at or after 2 h post-dose been shown not to adversely influence the systemic exposure in the male patient and therefore will not compromise efficacy. However, patients should be advised to wash at any time post-dose if contact with non-dosed individuals is anticipated and unavoidable.*
- *If direct contact does occur on accident, it is important that the contact site is immediately and thoroughly washed with soap and water to minimize systemic absorption. Data from S176.1.008 suggests that transfer and thereby secondary exposure to non-dosed individuals occurs very rapidly as evidenced by high systemic T levels at time 0 in group C, which marks the end of the 15-minute contact session.*

2.3 General Biopharmaceutics

2.3.1 What is the effect of the site of drug application on the systemic pharmacokinetics of testosterone from Androgel (testosterone gel) 1.62 %?

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

Design: This study was a single center, open-label, randomized, three-way crossover study in 36 hypogonadal male volunteers. Subjects received 5.00 g of testosterone gel 1.62% once daily for each of three 7-day treatment regimens. There was a 5-day washout period between treatments.
Dosing occurred once daily in the morning on Days 1-7, Days 12-18, and Days 23-29 as indicated by treatment randomization.

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

Blood sampling for PK: Whole blood samples for measurement of testosterone, dihydrotestosterone, and estradiol concentrations were collected at Baseline (Day -1), Days 1, 12, and 23, and Days 7, 18, and 29 for pharmacokinetic (PK) assessments; and Days 3-6, 14-17, and 25-28 for predose assessments.

Results:

Achievement of steady-state: Graphical and statistical assessment of pre-dose concentrations demonstrate that steady-state was achieved by day 2 post-dose in groups A (application to shoulders/upper arms only) and B (application to abdomen only). In case of treatment C (abdomen for 3 days, followed by shoulders/upper arms for 4 days), two different plateaus of trough concentrations are noted, one around day 3 (abdominal application) and another around day 6 (during shoulders/upper arms application). The trough levels during the first three days were lower compared to those seen during the last four days when drug was applied to shoulders/upper arms. Statistical analyses show steady-state achievement by day 5.

On day 1 of treatment, serum total testosterone concentrations rose from hypogonadal baseline concentrations to 'normal' (eugonadal; > 300 ng/dL) range within 2 hours of dosing with androgel 1.62 % gel dose. Highest concentrations were observed with treatment B (shoulders/upper arms alone), while treatment groups A and C that employed the abdomen as drug application site on day 1 demonstrated comparable systemic exposure on day 1. Baseline-adjusted data demonstrated similar trends.

On day 7, systemic exposure was the lowest for the treatment group A (abdominal application), while it was comparable for groups B and C both of which utilized shoulders/upper arms (during the last 4 days for treatment C). Day 7 data suggest relatively steady systemic concentrations of testosterone that were within the eugonadal range (300-1000 ng/dL).

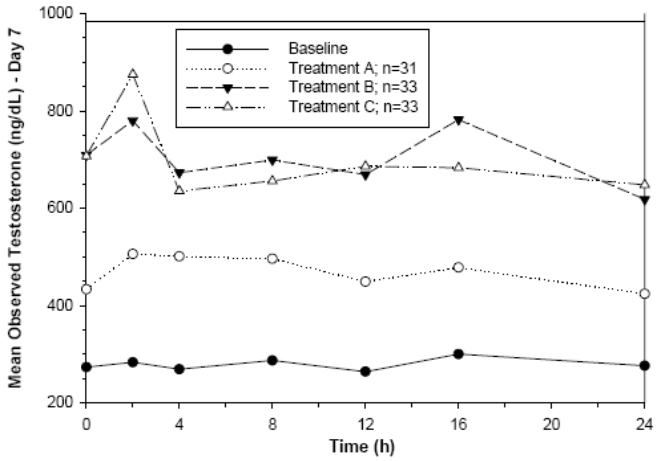


Figure 15: Mean observed testosterone on day 7 in the site of application study S176.1.007 (A: abdomen; B: shoulders/upper arms; C: rotation of both sites)

Pharmacokinetic data:

Table 29: Mean (SD) data for the various treatment groups and days

	Treatment A (N = 32)		Treatment B (N = 33)		Treatment C N = 33)	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/dL)	511 (220)	680 (387)	837 (453)	1090 (440)	536 (254)	1080 (703)
T_{max} (h)	16	4	16	8	16	6
C_{avg} (ng/dL)	383 (171)	468 (177)	545 (192)	704 (219)	401 (168)	706 (347)
AUC_{0-24} (ng h/dl)	9170 (4100)	11200 (4240)	13100 (4600)	16900 (5250)	9600 (4020)	16900 (8310)
C_{min} (ng/dL)	214 (136)	331 (110)	240 (93.8)	470 (159)	227 (98.6)	449 (172)
$R_{AUC0-24}$	-	1.35 (0.54)	-	1.3 (0.38)	-	1.84 (0.795)
$R_{Cmax0-24}$	-	1.5 (1.0)	-	1.43 (0.6)	-	2.11 (0.98)
Trt A: 5.0 g gel applied to abdomen; Trt B: 5.0 g gel applied to shoulders/upper arms; C: 5.0 g applied to abdomen and to shoulders/upper arms on a rotation basis over 7 d						

Mean data suggests greater systemic exposure with drug application to shoulders/upper arms compared to the abdominal site. On day 7, mean Cmax and AUC values for the abdominal site were 37 % and 33 % lower compared to that of shoulders/upper arms.

Systemic exposure with the mixed schedule (treatment C) was comparable to that of treatment B, as the PK data on day 7 is again predominantly from the shoulders/upper arms site in this group.

Drug accumulation was observed in all groups, with predominant accumulation noted in the treatment C (rotation schedule), since site of application on day 1 (abdomen) and day 7 (shoulders/upper arms) were different in this group. With single application sites, accumulation was 1.3- 1.5 fold.

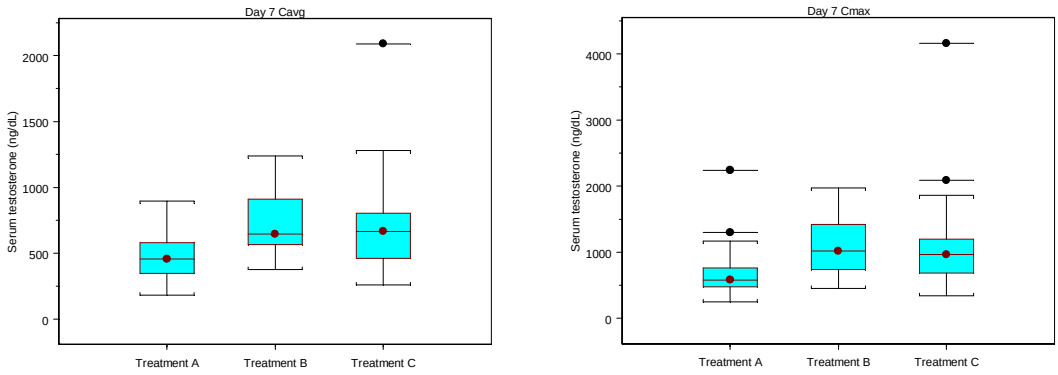


Figure 16: Box plots representing the distribution of observed testosterone Cmax and Cavg across the various application sites [A: abdomen; B: shoulders/upper arms; C: rotation]

Concentrations returned to baseline on average by 48 hours post-dose for treatment A and by 72 hours in treatment groups B and C.

- Overall conclusions: The impact of drug application site (abdomen vs. shoulders/upper arms vs. combination of both sites) on PK has been adequately characterized. Data strongly suggests that drug application to shoulders/upper arms provided greater systemic exposure (~ 30 – 40 %) compared to abdominal application.
- Phase 3 clinical trial for the 1.62 % gel utilized both the application sites (shoulders/upper arms or abdomen) and rotation between the two sites was allowed. Thus clinical safety and efficacy for these site of applications has been adequately evaluated.

1.3.3. What is the effect of moisturizer or sunscreen products on the systemic exposure of testosterone in males using Androgel (Testosterone gel) 1.62 %?

S176.1.006: A Randomized, Open-Label, Three-way Crossover, Multiple Dose Pharmacokinetic Study on the Effect of Moisturizer Lotion or Sunscreen Application on the Serum Levels of Testosterone in Hypogonadal Males Administered Testosterone Gel 1.62%

Design: This study was a single center, open-label, randomized, three treatment, three period, six sequence, crossover study in 18 hypogonadal male volunteers (18-80 years inclusive; serum T < 300 ng/dL).

Treatments: Each subject participated in three sequential treatment periods in randomized order.

- Treatment A: once daily application of 2.50 g testosterone gel 1.62% to the upper arms/shoulders for 7 days. Each day, 1 hour after testosterone gel 1.62%

administration, a 6.0 g application of Lubriderm Daily Moisture Lotion was applied to the same application site.

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

PK sampling was conducted at various time points over 24 hours on day -1 (baseline), days 7, 14, and 21 (treatment day 7) and pre-dose on days in between.

Results: Mean observed testosterone concentration-time profiles are shown for the three treatment groups [Treatment C: Control].

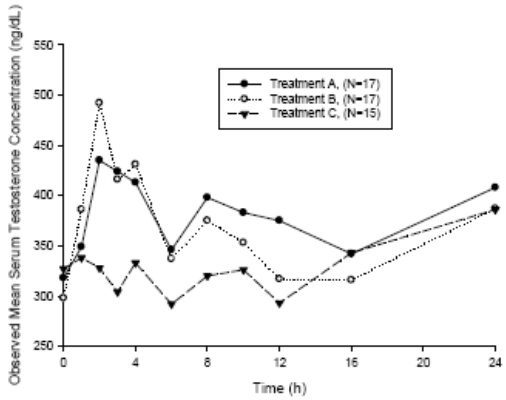


Figure 17: Observed testosterone concentration-time profiles in the various treatments of study S176.1.006 [Trt A: Moisturizer applied at 1 h post-dose; Trt B: Sunscreen applied at 1h post-dose; Trt C: AndroGel 1.62 % gel alone]

Data suggests a greater systemic T exposure in the groups A and B where moisturizer lotion or sunscreen was applied at 1 h post-dose. Presence of (b) (4) (b) (4) in these products may have enhanced the transdermal absorption of T from the 1.62 % gel product. Pharmacokinetic parameters for observed T levels are summarized below for the various treatment groups. Data suggests a modest increase in serum T exposure in treatment groups A (6.0 g moisturizer at 1 h post-dose) and B (6.0 g sunscreen at 1 h post-dose).

Table 30: Mean testosterone PK from study S176.1.006

	A (Moisturizer) (n = 17)	B (Sunscreen) (n = 17)	C (Control) (n = 15)
C_{max} (ng/dL)	549 (91)	542 (148)	477 (115)
T_{max} (h) [range]	8.0 [0-23.75]	2.0 [1-23.75]	10.0 [0 - 23.75]
C_{avg} (ng/dL)	378 (88)	363 (74)	332 (71)
AUC_{24} (ng.h/dL)	8990 (2090)	8620 (1764)	7870 (1673)
C_{min} (ng/dL)	261 (81)	253 (79)	222 (58)
$FAUC_{24}$ % [ref = C]	115 (18)	110 (29)	-
FC_{max} % [ref = C]	119 (27)	119 (42)	-

Treatment A (moisturizer lotion applied 1 h after dose application):

- Mean increase in Cavg was 1.15-fold. Increase in Cavg over the reference group was seen in 10 out of 14 individuals. Increases were generally in the range of 3 % to 51 %.
- Mean increase in Cmax was 1.19-fold. Increase in Cmax was seen with moisturizer treatment in 9 out of 15 individuals. Increases were in the range of 9 to 78 %.

Treatment B (sunscreen lotion applied 1 h after dose application):

- Mean increase in Cavg was 1.10-fold. Increase over the reference group (C) was seen in 8 out of 14 individuals, with increases ranging from 3 % to 65 %.
- Mean increase in Cmax was 1.19 fold. Increase over the reference group C was seen with sunscreen product in 8 out of 15 individuals, with increases ranging from 7 % to 114 %.

None of the patients experienced individual testosterone concentrations above the eugonadal range (300- 1000 ng/dL) during this study.

Table 31: Statistical comparison of the treatment groups

Analysis	Parameter	Treatment Group [a]	N	Geometric LS Mean	Pair	Ratio (%)	95% CI	p-value
Observed	AUC_{0-24}	A	17	8790	A/B	104.7	(93.3, 117.7)	0.4204
	(ng*h/dL)	B	17	8400	B/C	108.8	(96.1, 123.2)	0.1747
		C	14	7720	A/C	114.0	(100.6, 129.1)	0.0401
	C_{max}	A	17	542	A/B	103.8	(90.3, 119.3)	0.5875
	(ng/dL)	B	17	522	B/C	113.0	(97.8, 130.6)	0.0938
		C	15	462	A/C	117.3	(101.5, 135.6)	0.0322

[a] Treatment A=2.5 g testosterone gel 1.62% followed by 6.0 g of moisturizer 1 hour postdose;
Treatment B=2.5 g testosterone gel 1.62% followed by 6.0 g of sunscreen 1 hour postdose;
Treatment C=2.5 g testosterone gel 1.62%

Thus, application of moisturizer 1 hour post-dose resulted in a small but significant increase in the systemic testosterone levels. Mean testosterone AUC0-24 and Cmax increased by 14.0% and 17.3% compared to Treatment C (reference; 2.5 g T-gel 1.62 %). The 95 % CI values fell outside the 80-125 % range for both Cmax and AUC for this interaction, while in case of the sunscreen administration at 1 hour post-dose, only the Cmax value fell outside this range. However, this difference was not statistically significant.

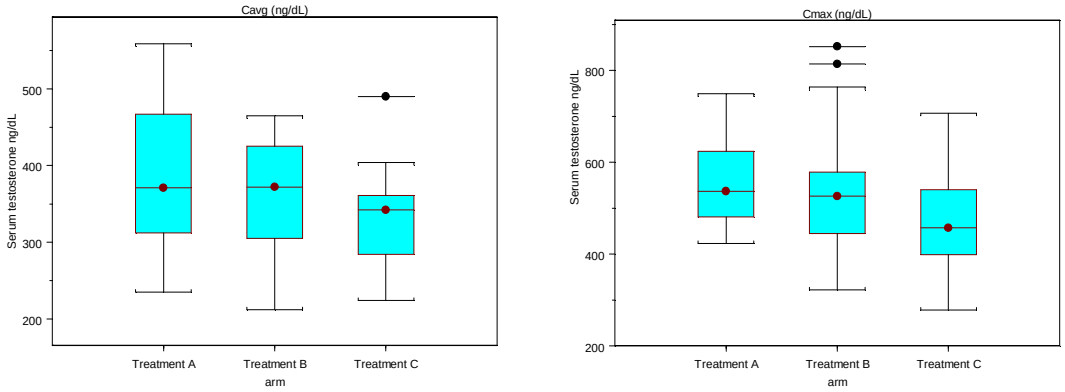


Figure 18: Box plots of Cavg and Cmax
A: Moisturizer at 1 hour post-dose; B: Sunscreen at 1 hour post-dose; C: 1.62% gel alone

Conclusions: Use of moisturizing lotion or sunscreen on the same application site 1 h after use of Androgel 1.62 % gel caused modest increases in the Cmax and Cavg of testosterone. At the dose evaluated (2.5 g) no subjects experienced testosterone concentrations above 'normal' range (300- 1000 ng/dL). Hence clinically relevant effects on testosterone were not observed in this study. Impact of moisturizer or sunscreen application at other time points relative to gel application or at gel doses larger than 2.5 g has not been evaluated.

2.3.3. What is the effect of washing on the systemic pharmacokinetics of testosterone from Androgel 1.62 % gel?

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

Design: Single center, open-label, randomized, three-way crossover study in 24 hypogonadal male volunteers. 5.00 g testosterone gel 1.62% (81 mg testosterone) was applied topically once daily in the morning to the shoulders/upper arms for 7 days during each of three consecutive treatment periods, for a total of 21 days of dosing. There was no washout period between treatment periods. On the seventh dosing day of each treatment period, skin washing with soap and water occurred at the following times:

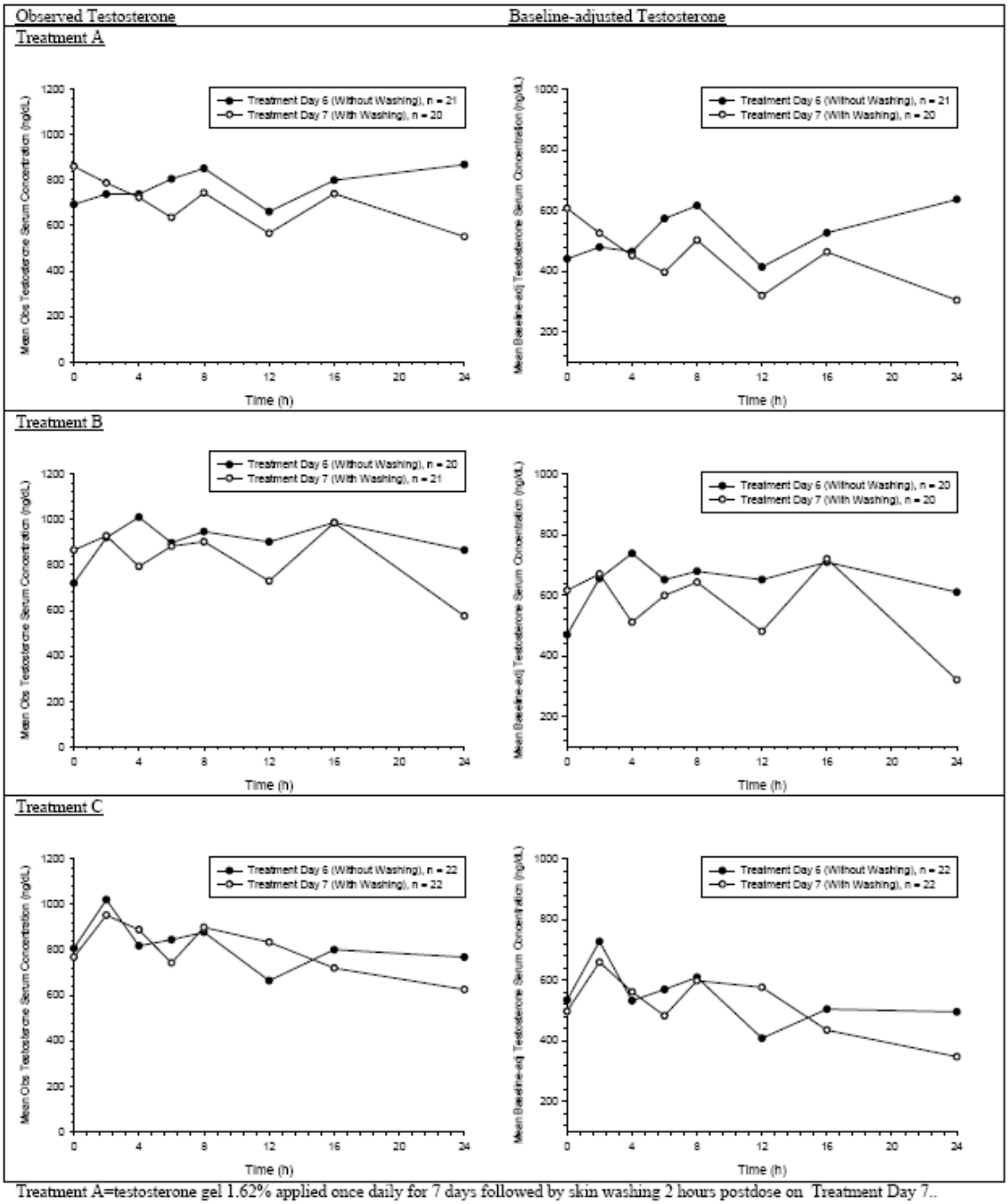
Treatment A: 2 hours post-dose
Treatment B: 6 hours post-dose
Treatment C: 10 hours post-dose

The skin washing occurred in the shower using commercially available Ivory Bar soap and water on the shoulder/upper arms with a soap lather time of approximately 2 minutes followed by a thorough rinse. The site of application was then thoroughly dried. Tape stripping procedures were conducted at 30 minutes after the projected or actual wash time on the sixth (control) and seventh (washed) days of each treatment period to evaluate the

presence of any residual testosterone remaining in the stratum corneum with or without washing. Whole blood samples were collected for serum determination of total testosterone, dihydrotestosterone, and estradiol at various timepoints on day -1 (baseline), days 6, 13, 20 (treatment day 6) and on days 7, 14, and 21 (treatment day 7) and at pre-dose on days in between.

Results: Steady -state for serum total testosterone was achieved in general by days 4-6 during once-daily treatment with 5.0 g of T-gel 1.62 %.

Figure 19: Mean concentration-time profiles for serum total testosterone for both observed and baseline-corrected data in study S176.1.005.



Treatment A=testosterone gel 1.62% applied once daily for 7 days followed by skin washing 2 hours postdose on Treatment Day 7..

Treatment B= testosterone gel 1.62% applied once daily for 7 days followed by skin washing 6 hours postdose on Treatment Day 7..

Treatment C=testosterone gel 1.62% applied once daily for 7 days followed by skin washing 10 hours postdose on Treatment Day 7.

With treatment A (skin washing at 2 hours post-dose on day 7), a decrease in the serum T levels was observed at all time points post-washing relative to the unwashed control period on day 6. With treatment B (skin washing at 6 hours post-dose on day 7) and treatment C (skin washing at 10 hours post-dose on day 7) an effect of washing on serum T levels was not readily apparent.

Mean dihydrotestosterone and estradiol concentration-time profiles suggest a trend for DHT similar to that observed for T, with a lower serum profile observed with treatment A, and an inconclusive effect of treatments B & C. In general, there was no marked effect of skin washing at various time points post-dose on the serum E2 levels.

Table 32: Pharmacokinetic parameters for testosterone in study S176.1.005

		Observed			
	Trt [a]	Treatment Day 6		Treatment Day 7	
Parameter		n	Mean (SD)	n	Mean (SD)
AUC_{0-24} (ng*h/dL)	A	21	18500 (6000)	19	16100 (5320)
	B	20	21800 (7140)	20	19300 (5250)
	C	21	19100 (6570)	20	19100 (5620)
C_{av} (ng/dL)	A	21	771 (250)	19	671 (222)
	B	20	911 (297)	20	806 (220)
	C	21	797 (274)	20	795 (236)
C_{max} (ng/dL)	A	21	1250 (679)	20	1240 (764)
	B	20	1400 (520)	21	1360 (680)
	C	21	1200 (521)	22	1250 (418)
t_{max} [b] (h)	A	21	6.00 (0.00, 16.08)	20	2.98 (0.00, 23.95)
	B	20	6.00 (2.00, 24.05)	21	8.00 (0.00, 16.03)
	C	21	4.00 (0.00, 23.95)	22	6.00 (2.00, 16.00)

Treatment A: During treatment A (2 h post-dose washing on day 7) serum testosterone Cavg (& AUC) values were on average lower by 11 % on day 7 compared to day 6 (no washing control). This difference though modest was statistically significant at $p < 0.05$. The Cmax values were comparable on days 6 and 7.

Treatment B: During treatment B (i.e. skin washing at 4 h post-dose on day 7), a modest decrease was observed in Cavg (9 %) which was not statistically significant compared to day 6 ($p > 0.05$). Cmax values were again comparable on days 6 and 7 of treatment B.

Treatment C: Cavg values were comparable during treatment C (skin washing at 10 h post-dose on day 7) relative to day 6 (unwashed control). Cmax values were also comparable. Differences were not statistically significant.

Conclusions: Overall, the results of this study suggest that while washing of the application site resulted in removal of at least 80 % of residual testosterone from the application site, the systemic absorption of testosterone was not markedly affected. Thus patients may wash at or after 2 hours post-dose during clinical use of Androgel 1.62 % gel.

2.4 Analytical section

A bioanalytical method has been developed and validated by (b) (4) for the analysis of testosterone (T) and dihydrotestosterone (DHT) in human serum. The method is applicable to the quantitation of testosterone and dihydrotestosterone within a

nominal range of 50.0 to 10000 pg/mL or (5-1000 ng/dL) and requires a 150-µL human serum aliquot. Samples are kept frozen at -20°C or colder prior to analysis.

Method Description for Assay of T and DHT: A 150-µL matrix aliquot is fortified with 50 µL of testosterone-d3 and dihydrotestosterone-d3 internal standard working solution. Analytes are isolated through supported liquid extraction using an ISOLUTE SLE+ 200-mg extraction plate and eluted with 1.6 mL of dichloromethane. The eluent is evaporated under a nitrogen stream at approximately 50 °C, and the remaining residue is reconstituted with 200 µL of 50:50 methanol / water v/v with 0.1% formic acid. The final extract is analyzed via UPLC with MS/MS detection.

Method validation: Validation experiments for T and DHT were done at (b) (4) in August 2008. Parameters assessed included precision, accuracy, sensitivity, selectivity, dilution parallelism, recovery, cross-analyte interference, carryover analyte stability in thawed matrix and reinjection reproducibility of stored sample extracts. *Validation parameters were found to be within pre-determined acceptable ranges.*

Table 33: validation parameters for testosterone and DHT assays

Validation Parameters	**Testosterone**	**DHT**
Linearity and calibration	Standards : Average R^2 = 0.9981 % CV = < 8 % % bias: ±2 %	Standards : Average R^2 = 0.9980 % CV = < 9 % % bias: -6 to 3 %
Precision (% CV) & Accuracy (% nominal)		
Intra-assay	Precision (% CV): < 15 % Accuracy: ± 15 % of nominal	Precision (% CV): < 15 % except at LLOQ (18 %) Accuracy: ± 15 % of nominal
Inter-assay	Precision (% CV): < 10 % Accuracy: 0.8 to -7 % of nominal	Precision (% CV): < 15 % Accuracy: 3 to -9 % of nominal

Quantitation of Estrone, Equilin, and 17ß-Estradiol in Human Serum via HPLC with MS/MS Detection:

A bioanalytical method has been validated by (b) (4) for the analysis of estrone, equilin, and 17ß-estradiol in human serum. The method is applicable to the quantitation of estrone and equilin within a nominal
range of 5.00 to 500 pg/mL and 17ß-estradiol within a nominal range of 1.00 to 100 pg/mL and requires a 500-µL aliquot of human serum.

Method Description for E2 Assay: A 500-µL sample aliquot is fortified with 25 µL of internal standard working solution. Analytes are isolated through (b) (4) with 5.0 mL of 10:90 ethyl acetate/hexane, v/v. The solvent is evaporated under a stream

of nitrogen at 40 to 50 ^{0}C and the remaining residue is derivatized with dansyl chloride. The derivatized analytes are extracted into 3.0 mL of 10:90 ethyl acetate/hexane, the solvent is evaporated, and the remaining residue is reconstituted with 150 µL of acetonitrile and 200 µL of water. The final extract is analyzed via HPLC with MS/MS detection.

Method validation: Parameters assessed included precision, accuracy, sensitivity, selectivity, dilution parallelism, recovery, cross-analyte interference, carryover analyte stability in thawed matrix and reinjection reproducibility of stored sample extracts. *Validation parameters were found to be within pre-determined acceptable ranges.*

Table 34: Validation parameters for E2 assay

Validation Parameter	Results for Estradiol
Linearity and Calibration	Standards: $R^2 = 0.9994$ % diff from theoretical: ± 10 %
Precision & Accuracy	% CV: < 15 %; < 20 % at LLOQ % bias: within ± 15 %

Regulatory history relevant to Bioanalytical issues

(b) (4) initially served as the analytical laboratory for most of the phase 1 studies and the phase 3 study evaluating the safety and efficacy of AndroGel 1.62% in hypogonadal men. Serum samples were originally assayed at this facility using HPLC-MS/MS methods for the measurement of testosterone and estradiol, and a radioimmunoassay for the measurement of DHT. (b) (4) In November of 2007, (b) (4) was issued an FDA Form 483 after a routine bioresearch monitoring inspection by the Division of Scientific Investigations (DSI) revealed issues with analytical methods used in testosterone and DHT assays. (b) (4)

Solvay at that time conducted an independent assessment that revealed that several inspection findings which affected the (b) (4) (b) (4) phase 1 studies and the phase 3 study (S176.3.104) for the AndroGel 1.62% program. Therefore in August, 2008 Solvay met with FDA to discuss the path forward for filing the Androgel 1.62 % NDA. At that time it was concluded that the data generated by (b) (4) would not meet the Food and Drug Administration (FDA) standards for bioanalytical data, thus rendering the testosterone, DHT, and estradiol data

invalid (see minutes in DARRTS dated 09/11/2008 regarding a face-to-face meeting with Solvay on August 13, 2008 in this regard). The following deficiencies were cited:

1. Assay Run Acceptance / Rejection Criteria: DRUP is concerned that the standard operating procedures (SOPs) for run acceptance/rejection criteria for samples in support of NDA 22-309, at the time of the analysis of the study samples, were not strictly adhered to by (b) (4) and were deficient. Consistent with what was stated by DMEP in the May 16, 2008, End-of Review meeting, DRUP also does not agree with the revision of acceptance/rejection criteria for already completed runs.

2. Method validation: DRUP does not agree that the post-study validation experiments (i.e., accuracy and precision) necessarily reflect assay performance during the analysis of the samples from the corresponding studies. Our concerns are summarized below:

- For the DHT assay, the specificity/selectivity evaluations conducted post-study do not necessarily reflect the condition of sample analysis at the time of the analysis of the study samples. For instance, earlier inspection findings included (but are not limited to): *lack of documentation on calibration standard stock solution and lots of antiserum used, replicate Quality Controls (QC) being rejected without justification, and revision of QC tables at least 3 times due to errors.*
- The pre-NDA briefing documents submitted to the division state that a review of the documentation associated with the testosterone LC-MS/MS method validation revealed that changes to the method occurred during the course of the method validation. It is unclear from the documentation whether the same method was used for study sample analysis. (b) (4) proposes to conduct a revalidation of the testosterone method to address this ambiguity. However, it cannot be assured that the performance of the revalidated method reflects the performance of the testosterone assay used to analyze the study samples.

Because a significant portion of the study samples were available for re-assay (98 % per the sponsor), the Division agreed to accept results from a complete re-assay of all available samples from all NDA studies for the three critical analytes (T, DHT and E2) at (b) (4) as an appropriate means of resolving the pending deficiencies. Efficacy and safety analyses would be based on the new (b) (4) results. The Sponsor was reminded that the NDA submission should provide data supporting acceptable stability of the re-assayed samples.

Thus the retained samples were subsequently transferred by the sponsor to (b) (4) (b) (4) *) for re-assay of testosterone, DHT, and estradiol using validated HPLC-MS/MS methods. Testosterone, DHT, and estradiol data from* (b) (4) *are the primary data for this submission.*

Long term stability of analytical samples:

Additional stability information was presented in NDA 22-309 to support complete re-analysis of the stored samples at (b) (4) after initial analysis by (b) (4) was deemed invalid.

Based on stability information obtained by analyzing quality controls (QC) prepared in human serum (frozen in April- May 2003 at -20^{0}C and reanalyzed using a freshly prepared calibration curve in August 2008), it appears that extended storage at -20^{o}C had no impact on T, DHT or E2 concentrations in serum. The long term storage stability data (>=1919 days) appear to cover the longest storage period at -20°C between sample collection and reanalysis a (b) (4) (maximally 878 days for samples from study S176.1.002).

For testosterone, long-term stability assessment was carried out on frozen QC samples with theoretical concentrations of 229 pg/ml and 7940 pg/ml stored for 1919 days at -20^{o}C. No apparent abnormalities associated with long-term storage were observed. The precision (% CV) values of 3.46 and 2.23 %, and accuracy (% nominal) values of 1.66 and -0.969 % respectively at 229 pg/ml and 7940 pg/ml concentrations of testosterone QCs were found to be acceptable.

For DHT, long-term stability in frozen human serum was evaluated for frozen QC samples with theoretical concentrations of 52.9 pg/ml and 803 pg/ml stored for 1919 days at -20^{o}C. While the high-level DHT stability samples (803 pg/mL) were acceptable, evaluation of the results from the low level stability samples was confounded by the fact that each of the low level samples (52.9 pg/mL) quantified below the validated LLOQ. However, DHT has been shown to be stable in frozen human serum at 54.5 and 755 pg/mL using (b) (4) GC/MS (gas chromatography/mass spectrometry) Method MS 57 for a period of 2019 days at -20 °C.

For E2, stability in frozen human serum has been evaluated by analyzing stability samples stored under the same conditions as study samples. Stability samples in charcoal stripped human serum were prepared on 10 April 2003 and analyzed on 28 October 2004 versus freshly prepared calibration standards. Results indicate a frozen-state stability of approximately 567 days at approximately –20 °C or colder. Low-level stability samples in unstripped, untreated human serum were prepared on 25 April 2003 and analyzed on 28 August 2008 versus freshly prepared calibration standards. Low-level, frozen-state stability was demonstrated for approximately 1952 days at approximately –20 °C in unstripped, untreated human serum. High-level stability samples in unstripped, untreated human serum were prepared on 25 April 2003 and analyzed on 29 August 2008. High-level, frozen-state stability was demonstrated for approximately 1953 days at approximately –20 °C in unstripped, untreated human serum.

Thus, overall there appears to be adequate stability data to support the age of the reanalyzed samples in this NDA submission.

Freeze-thaw stability: In response to an information request from Clinical Pharmacology discipline, the sponsor clarified that 'maximum' number of freeze/thaw (F/T) cycles that any one study sample was subjected to while at (b) (4), Solvay and/or (b) (4) was eleven. Stability of the analytes to 11 F/T cycles has therefore been evaluated for T and DHT.

Testosterone: 100, 7500 pg/ml (surrogate QCs); 7620 pg/ml (serum QC); 6 F/T
Precision (% CV): 2 – 6 %; Accuracy (% nominal): -4.8 to 0.1 %
115 pg/ml serum QC (10 F/T): % CV: 6.91 % and % nominal: -4.94 %

DHT: 100, 7500 pg/ml (surrogate QCs); 7530 pg/ml (serum QC); 6 F/T
% CV: < 10 % and % nominal: within - 7 %
205 pg/ml serum QC (10 F/T): % CV: 9.64 % and % nominal: 4.28 %

The precision and accuracy of the F/T QCs were found to be within acceptable limits. Based on the information provided by the sponsor, it appears that freeze/thaw stability has been adequately assessed for T and DHT for the maximum number of F/T cycles encountered during sample processing at both (b) (4)

3 Labeling Recommendations

(b) (4)

4 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/TS) FOLLOWING THIS PAGE

4 Appendix

4.1 OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-309**	**Brand Name**	**Androgel 1.62 %**
OCP Division	**DCP3**	**Generic Name**	**Testosterone gel 1.62 %**
Medical Division	**DRUP**	**Drug Class**	**Steroid**
OCP Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**Testosterone replacement in males**
OCP Team Leader	**Myong Jin Kim, Pharm. D.**	**Dosage Form**	**Topical gel**
		Dosing Regimen	**Once daily**
Date of Submission	**02/12/2009**	**Route of Administration**	**Topical (skin)**
Estimated Due Date of OCP Review	**10/12/2009**	**Sponsor**	**Unimed Pharma/Solvay**
PDUFA Due Date	**12/12/2009**	**Priority Classification**	**Standard**
Division Due Date		**Related IND**	**50,377**

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**	**9**		**8 Phase 1 studies and 1 Phase 3 trial.**
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**17**		NDA includes 17 assay reports including validation reports, and long-term stability reports for T, DHT and E2
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		Study S176.1.008 Single dose assessment of male to female transfer potential; includes evaluation of effect of dose, skin washing and application site on transfer
multiple dose:	X	1		Study S176.1.003; multiple dose male to female transfer assessment study
Patients-				
single dose:	X			
multiple dose:	X	1		S176.1.002: Single and multiple dose PK study of T gel 1.62 % at 1.25 g, 2.5 g, 3.75 g, 5 g and 6.25 g doses
Dose proportionality -				

fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		S176-.1.006 Moisturizer or sunscreen interaction study
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	**X**	1		S176.3.104: Phase 3 clinical trial of testosterone gel 1.62 % with primary efficacy based on T levels within normal range.
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics			APPEARS THIS WAY ON ORIGINAL	S176.1.005: Effect of post-dose skin washing on PK S176.1.001: Comparative BA of various formulation strengths 1.22 %, 1.42 % and 1.62 % and in comparison to reference 1 % gel. S176.1.007: Site of application BA study
Absolute bioavailability:				
Relative bioavailability -	**X**	**3**		
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	**X**	**1**		PD.176.7.08R.CRO: In vitro study using human biomaterial for assessing permeability characteristics to optimize formulation selection
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	**X**			Waiver requested
Literature References				
Total Number of Studies		**26**		
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Adequacy of stability data provided in support of complete sample re-analysis Transfer potential and labeling Sunscreen/moisturizer interaction and labeling Effect of washing on systemic bioavailability of testosterone and labeling Higher bioavailability from shoulders/upper arms and following a rotational schedule compared to abdomen alone; labeling implications Testosterone outliers- patients with Cmax > 2500 ng/dL**	
Other comments or information not included above	**DSI inspection o (b) (4) has been requested in relation to pivotal phase 3 clinical trial S176.3.104 (see DFS entry signed by Dr. Hae Young Ahn, on 04/07/2009).**	
Primary reviewer Signature and Date	**Sandhya Apparaju**	
Secondary reviewer Signature and Date		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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

/s/

SANDHYA K APPARAJU
10/22/2009

MYONG JIN KIM
10/26/2009

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-309**	**Brand Name**	**Androgel 1.62 %**
OCP Division	**DCP3**	**Generic Name**	**Testosterone gel 1.62 %**
Medical Division	**DRUP**	**Drug Class**	**Steroid**
OCP Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**Testosterone replacement in males**
OCP Team Leader	**Myong Jin Kim, Pharm. D.**	**Dosage Form**	**Topical gel**
		Dosing Regimen	**Once daily**
Date of Submission	**02/12/2009**	**Route of Administration**	**Topical (skin)**
Estimated Due Date of OCP Review	**10/12/2009**	**Sponsor**	**Unimed Pharma/Solvay**
PDUFA Due Date	**12/12/2009**	**Priority Classification**	**Standard**
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Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
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HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**17**		NDA includes 17 assay reports including validation reports, and long-term stability reports for T, DHT and E2
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		Study S176.1.008 Single dose assessment of male to female transfer potential; includes evaluation of effect of dose, skin washing and application site on transfer
multiple dose:	X	1		Study S176.1.003; multiple dose male to female transfer assessment study
Patients-				
single dose:	X			
multiple dose:	X	1		S176.1.002: Single and multiple dose PK study of T gel 1.62 % at 1.25 g, 2.5 g, 3.75 g, 5 g and 6.25 g doses
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		S176-.1.006 Moisturizer or sunscreen interaction study
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	**X**	1		S176.3.104: Phase 3 clinical trial of testosterone gel 1.62 % with primary efficacy based on T levels within normal range.
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				[redacted]S176.1.005: Effect of post-dose skin washing on PK S176.1.001: Comparative BA of various formulation strengths 1.22 %, 1.42 % and 1.62 % and in comparison to reference 1 % gel. S176.1.007: Site of application BA study
Absolute bioavailability:				
Relative bioavailability -	**X**	**3**		
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	**X**	**1**		PD.176.7.08R.CRO: In vitro study using human biomaterial for assessing permeability characteristics to optimize formulation selection
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	**X**			Waiver requested
Literature References				
Total Number of Studies		**26**		

APPEARS THIS WAY ON ORIGINAL

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	**Adequacy of stability data provided in support of complete sample re-analysis Transfer potential and labeling Sunscreen/moisturizer interaction and labeling Effect of washing on systemic bioavailability of testosterone and labeling Higher bioavailability from shoulders/upper arms and following a rotational schedule compared to abdomen alone; labeling implications Testosterone outliers- patients with Cmax > 2500 ng/dL**			
Other comments or information not included above	**DSI inspection of (b) (4) has been requested in relation to pivotal phase 3 clinical trial S176.3.104 (see DFS entry signed by Dr. Hae Young Ahn, on 04/07/2009).**			
Primary reviewer Signature and Date	**Sandhya Apparaju**			
Secondary reviewer Signature and Date				

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 22-309
Compound: Testosterone gel 1.62 %
Sponsor: Solvay Pharmaceuticals

Date: 03/16/2009
Reviewer: Sandhya Apparaju, Ph.D.

Background: AndroGel® (testosterone gel) 1 % was approved in 2000 (NDA 21-015) for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The subject of this NDA 22-309 is a new testosterone gel formulation AndroGel 1.62 % developed to have (b) (4), a reduced volume of application, and improved (b) (4) compared to AndroGel 1%. Sponsor has conducted several Clinical and Clinical Pharmacology studies to support the new formulation:

- *Clinical Pharmacology Studies: Pharmacokinetics in Healthy Subjects*

S176.1.003	A Randomized, Open-Label, Parallel Group Study of Serum Testosterone Levels in Non-dosed Females after Skin Contact with a Male Partner Dosed with Testosterone Gel 1.62%
S176.1.008	A Randomized, Open-Label, Parallel Group Study to Evaluate the Effects of Dose, Post-dose Washing, and Application Site on the Transfer Potential of Testosterone Gel 1.62% from Dosed Males to a Non-dosed Female Partner

- *Clinical Pharmacology Studies: Pharmacokinetics in Hypogonadal Subjects*

S176.1.001 and amendment	The Multiple Dose Pharmacokinetics and Comparative Bioavailability of Testosterone After Administration of 1.25, 2.5, and 3.75 g Dose Levels of Investigational Testosterone Hydro-Alcoholic Gel Formulations in Hypogonadal Male Volunteers
S176.1.002	The Single and Multiple Dose Pharmacokinetics of Testosterone After Administration of 1.62% Hydro-Alcoholic Gel at Dose Levels of 1.25, 2.50, 3.75, 5.00, and 6.25 g in Hypogonadal Males
S176.1.005	A Randomized, Open-Label, Three-Way Crossover Pharmacokinetic Study to Evaluate the Effects of Skin Washing After Administration of Testosterone Gel 1.62% in Hypogonadal Males
S176.1.006	A Randomized, Open-Label, Three-Way Crossover, Multiple Dose Pharmacokinetic Study on the Effect of Moisturizer Lotion or Sunscreen Application on the Serum Levels of Testosterone in Hypogonadal Males Administered Testosterone Gel 1.62%
S176.1.007	A Single and Multiple Dose Pharmacokinetic and Comparative Bioavailability Study of Testosterone Absorption after Administration of Testosterone Gel 1.62% to the Abdomen, Upper Arms/Shoulders, or via a Rotation Schedule in Hypogonadal Males

- *Clinical Pharmacology Studies: Pharmacokinetics under Conditions of Clinical Use*

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

Clinical vs. To-be-marketed formulation: The following statements appear in the clinical overview, which suggest that the clinical and TBM formulations are same:
"A final gel formulation containing 1.62% testosterone was selected for further human studies as it provided comparable exposure to AndroGel 1% and offered the greatest potential for application volume reduction. No changes were made to the formulation during clinical development"
"The to-be-marketed formulation was used in the Phase III clinical study".

The sponsor also clarified during a pre-NDA meeting that the formulation used in the phase 1 and phase 3 clinical trials is same as the to-be-marketed formulation.

Bioanalytical reports: Assay reports and method validation reports could be located in the submission.

Datasets: Individual subject serum analyte concentration-time data (T, DHT and E2) as well as individual PK parameters are provided for all studies in the NDA submission; see location: (M5: Datasets: Tabulations: Study ID: PC.XPT; concentrations and PP.XPT; PK parameters).

Regulatory history: Bioanalytical issues

Section 2.7.1.1.2 Overview of Bioanalytical Methods describes the bioanalytical methods that were instituted to support the clinical development of testosterone gel 1.62%. The analytes measured during the clinical studies were total testosterone (T), dihydrotestosterone (or DHT), and 17β-estradiol (estradiol or E2).

Serum samples from S176.1.002, S176.1.003, S176.1.005, S176.1.006, S176.1.007, S176.1.008, and S176.3.104) were originally assayed by (b) (4), using HPLC-MS/MS methods for the measurement of testosterone and estradiol, and a radioimmunoassay for the measurement of DHT. It was subsequently determined that the data generated by (b) (4) would not meet the Food and Drug Administration (FDA) standards for bioanalytical data, thus rendering the testosterone, DHT, and estradiol data invalid (see minutes in DARRTS dated 09/11/2008 regarding a face-to-face meeting with Solvay on August 13, 2008 in this regard). The remaining retained samples were returned to Solvay Pharmaceuticals, Inc and subsequently transferred to (b) (4)) for assay of testosterone, DHT, and estradiol using the validated HPLC-MS/MS methods described in Section 2.7.1.1.2.3 and Section 2.7.1.1.2.4. The testosterone, DHT, and estradiol data from (b) (4) are the primary data for this submission. The testosterone, DHT, and estradiol data from (b) (4) are not included in this submission as they are considered invalid.

T and DHT: Validation and additional stability evaluation are presented in Appendix D to Report S176.1.002.B1. Validation experiments were done prior to sample reanalysis in eight separate validation runs beginning on 08 August 2008 and ending on 14 August 2008. This method was applicable to the quantitation of total T within a nominal range of 50-10000 pg/ml (5-1000 ng/dL) and total DHT within a nominal range of 50-10000 pg/ml and required a 150 µl human serum aliquot.

Sponsor notes that because T and DHT are endogenous steroid compounds, measurable levels are expected to be present in the blood from all human donors. The validation was conducted using samples prepared in two matrices: human serum and a surrogate matrix of 5.0 mg/mL bovine serum albumin (BSA) in phosphate buffered saline (PBS). Use of the surrogate matrix

reportedly allowed for creation of a calibration curve with an LLOQ below the lowest levels typically found in human serum. The calibration standards and QC pools (QC0 to 5) used in this validation were prepared in surrogate matrix. Additional QCs were prepared in human serum.

Reviewer notes: Use of a surrogate matrix for calibration standards is reasonable due to the endogenous nature of the analytes, especially since additional QCs in both surrogate and human serum matrix were run with all analytical batches. Since the analytical methodology for T is validated for a range of 5-1000 ng/dL, it should be checked during review whether any study samples exceeded this range and if so how they were analyzed (i.e. whether they were diluted to within the validated range and whether appropriate diluted QCs were included in such runs).

Based on additional stability information obtained by analyzing quality controls (QC) prepared in human serum *(frozen in April- May 2003 and reanalyzed using a freshly prepared calibration curve in August 2008),* sponsor suggests that neither extended storage at -20°C nor excessive freeze/thaw cycles had any impact on T, DHT or E2 concentrations in serum. Sponsor notes that the long term storage stability data (>=1919 days) cover the longest storage period at -20°C between sample collection and reanalysis a (b) (4) (maximally 878 days for samples from study S176.1.002). The theoretical concentrations of QC samples tested in the stability assessment are as follows:

- Testosterone: Long-term stability assessment was carried out on frozen QC samples with theoretical concentrations of 229 pg/ml and 7940 pg/ml stored for 1919 days at -20°C. Freeze/thaw stability assessment was carried out on QC samples with theoretical T concentrations of 115 pg/ml (for 10 cycles) and 7620 pg/ml (for 6 cycles).
- DHT: Long-term stability in frozen human serum was evaluated for frozen QC samples with theoretical concentrations of 52.9 pg/ml and 803 pg/ml stored for 1919 days at -20°C. Freeze/thaw stability assessment was carried out on QC samples with theoretical DHT concentrations of 205 pg/ml (for 10 cycles) and 7530 pg/ml (for 6 cycles).
- E2: Long term stability in frozen human serum was demonstrated using QC samples with theoretical concentrations of 27.6 pg/ml and 228 pg/ml. Additional freeze-thaw stability for 10 cycles was demonstrated using QC samples in human serum with theoretical concentrations of 2.47 pg/ml, 24.4 pg/ml, and 77.5 pg/ml.

All freeze/thaw samples were derived from the surrogate matrix and human serum QC pools used during the validation with the exception of the low-level surrogate matrix freeze/thaw samples, which were prepared separately prior to the validation.

Reviewer comments: The source of the frozen QC samples used for evaluating long-term storage stability is not clear. Sponsor should clarify whether frozen human serum QCs were from (b) (4) *(i.e. stored along with the study samples under identical conditions) or whether* (b) (4) *employed QCs that they had in their storage.*

The following are the sponsor's comments/conclusions from the stability assessments provided in support of sample re-analyses *(pending review)*:

All sample shipments (including shipments from the clinical sites to (b) (4) to Solvay, and Solvay to (b) (4)) contained dry ice. Samples were stored at each location at approximately -20°C (b) (4) has stability data on file that address the extended storage conditions at -20°C and additional freeze/thaw cycles encountered by these samples as a result of the re-analyses.

T and DHT: Long-term analyte stability in frozen human serum was evaluated by analyzing quality controls which were prepared on 08 May 2003 and stored at -20 °C for 1919 days prior to analysis with a freshly prepared calibration curve on 08 August 2008.

- For testosterone, no apparent abnormalities associated with long-term storage for up to 1919 days at -20 °C were observed.
- The high-level DHT stability samples (803 pg/mL) were acceptable, however, evaluation of the results from the low level stability samples was confounded by the fact that each of the low level samples (52.9 pg/mL) quantified below the validated LLOQ. Using extrapolated values, the low level stability samples had an estimated mean negative bias (-67.7%) that was not acceptable.
- Sponsor notes that stability of DHT in the testosterone gel 1.62% study samples is not of concern as DHT has been shown to be stable in frozen human serum at 54.5 and 755 pg/mL using (b) (4) GC/MS (gas chromatography/mass spectrometry) Method MS 57 for a period of 2019 days at -20 °C. Data are stored on file at (b) (4) Additional data demonstrating the stability of DHT in frozen human serum is being obtained by (b) (4) using LC/MS (liquid chromatography/mass spectrometry) methodology and will be submitted to this report as an addendum.
- Adequate stability was demonstrated under various conditions, including freeze/thaw stability (six freeze/thaw cycles for surrogate matrix and serum QC samples and 10 freeze/thaw cycles for low-level serum QC samples), stability of thawed samples at room temperature (46 hours), reinjection reproducibility after storage at 2-8°C after initial injection, and post-preparative extract stability for up to 140 hours at 2-8°C.

Estradiol (E2): The validation of LCMSD 350.1 is described in an Appendix D to Report S176.1.002.B2. Additional freeze/thaw serum, long-term serum, and post-preparative extract stability experiments were conducted following the partial validation using untreated human serum QCs prepared on April 25, 2003 and stored at -20°C for 1952 days prior to analysis with a freshly prepared calibration curve on 28 August 2008. These details are included as Validation Report Addenda in Report S176.1.002.B2.

- Adequate stability was demonstrated under various conditions including freeze/thaw stability (eleven freeze/thaw cycles for low- and high-level serum QC samples).
- Adequate stability of untreated serum samples for up to 1952 days when frozen at -20°C was demonstrated.

Filing comments: The sponsor appears to have included adequate stability information in support of the sample re-analyses. Information that couldn't be verified readily during the filing review will be sent to the sponsor for additional clarification (see IR comments further below).

A brief description of study outcomes *(pending final review)* from the Phase 1 and Phase 2 Clinical Pharmacology Studies is presented below:

S176.1.005: For Treatments A and B, skin washing at 2 and 6 hours post-dose caused a small decrease in bioavailability compared to when there was no post-dose wash. AUC0-24 decreased by 14% on average for Treatment A (p=0.0029) and 10% on average for Treatment B (p=0.0240). No effect of skin washing was observed for Treatment C (10 h skin wash; p=0.8617). Skin washing had no effect on Cmax for any treatment. Based on skin stripping results, the amount of testosterone remaining on the skin of the application site decreased at least 80% with skin washing 2-10 hours post dose.

S176.1.006: Small increases in AUC0-24 and Cmax were observed when moisturizer lotion and sunscreen were applied [1h] after testosterone gel 1.62% application, compared to application of testosterone gel 1.62% alone (Treatment C). For moisturizer treatment (Treatment A), mean testosterone AUC0-24 and Cmax increased by 14.0% and 17.3% compared to Treatment C, and the 95% CIs exceeded the upper limit of an 80-125% range for both parameters. For sunscreen treatment (Treatment B), the 95% CI for testosterone AUC0-24 was completely contained within an 80-125% limit; however mean Cmax increased by 13.0% compared to Treatment C, and the 95% CI for this parameter exceeded the upper limit of an 80-125% range.

S176.1.007: Treatment A: Abdomen only; Treatment B: Shoulders/upper arms; Treatment C: Fixed rotation (abdomen and shoulders/upper arms).
On Treatment Day 1, bioavailability was lower following abdominal application (Treatments A and C), and was higher following application to the upper arms/shoulders (Treatment B). Mean AUC0-24 and Cmax values for Treatment A were 33% and 38% lower than Treatment B, respectively. AUC0-24 and Cmax values for Treatment C were 28% and 35% lower than Treatment B, respectively.
On Treatment Day 7, bioavailability was similar between Treatments B and C. AUC0-24 values for Treatment A were 34% and 32% lower than Treatments B and C, respectively. Similar results were observed for Cmax, with Treatment A providing 39% and 35% lower Cmax values compared to Treatments B and C, respectively.

S176.1.003: Transfer potential evaluation from male volunteers who applied 5 g of 1.62 % on abdomen to female partners after 2 h direct contact (A), contact at 2 h with male wearing T-shirt (B) and direct contact at 12 h post dose application; Mean AUC0-24 (observed testosterone) on Days 1 and 7 was 105-143% higher for Treatment A, 41-57% higher for Treatment B, and 118-83% higher for Treatment C, respectively, when compared to Day -1.
Similarly, mean Cmax (observed testosterone) on Days 1 and 7 was 144-85% higher for Treatment A, 47-58% higher for Treatment B, and 138-105% higher for Treatment C, when compared to Day -1. Mean AUC0-24 (observed testosterone) was decreased by 40-43% on Days 1 and 7, when a T-shirt was used (Treatment B) instead of direct skin contact (Treatment A). Similarly, mean Cmax (observed testosterone) was decreased by 43-48% on Days 1 and 7, for Treatment B compared to Treatment A. The timing of direct skin contact did not significantly affect testosterone exposure.

S176.1.008: Second transfer potential evaluation study (to assess effect of dose, site of application, skin washing, T-shirt use on transfer to females);
After direct abdominal skin contact of a female with the abdominal application site on a male partner dosed with 2.50 g of testosterone gel 1.62%, an increase from Baseline levels was observed although this increase was within the normal range. A t-shirt barrier eliminated transfer in this study.
• After direct abdominal skin contact of a female with the application site on a male partner dosed with 5.00 g of testosterone gel 1.62%, transfer of testosterone was observed; however, mean testosterone concentrations remained within the normal range. After washing, overall exposure (AUC0-24 and Cav) was comparable to Baseline and Cmax was only slightly increased (i.e., 14%) above Baseline, and all testosterone levels remained within the normal range. Thus, washing the dosed application site prior to direct skin contact resulted in minimal transfer of testosterone.
• After direct abdominal or upper arms/shoulders skin contact of a female with the corresponding application site on a male partner dosed with 5.00 g of testosterone gel 1.62%, an increase in

testosterone was observed, indicating that transfer occurred.
Overall, mean testosterone Cav remained within the normal range for both contact sites; however, mean Cmax increased above the upper limit of normal following upper arms/shoulders contact. Testosterone transfer was higher for the upper arms/shoulders contact site compared to the abdomen.

S176.1.001: Formulation selection; dose-ranging study; subjects received 1.22 %, 1.42 % or 1.62 % at three different dose levels (site of application?); Dose proportionality or linearity in testosterone exposure, based on AUC0-24 and Cmax, was not demonstrated for any gel strength. Of the three T-gel strengths evaluated, the 1.62% strength was the most comparable to AndroGel® 1% (5.00 g). Comparable exposure to reference was observed at the 2.50 and 3.75 g dose levels based on the 24-hour concentration profiles, Cav, Cmax and proportion comparisons.

S176.1.002: Single and multiple dose (14 days) PK dose ranging (1.25 g- 6.25 g) of T-gel 1.62 % in male hypogonadal subjects; The site of application was rotated over the 14-day treatment period. Study drug was applied to the shoulder/upper arm on Days 1, 2, 5 to 9, and 12 to 14 and applied to the abdomen on Days 3, 4, 10, and 11.
Following multiple dose applications of 1.62% T-gel for 14 days at dose levels ranging from 1.25 to 6.25 g, observed testosterone mean Cav was within the eugonadal range (300 to 1000 ng/dL) for all treatments. Mean Cmax was below the upper eugonadal limit of 1000 ng/dL for the 1.25 to 3.75 g dose levels. At the dose levels of 5.00 g and 6.25 g, there was a greater incidence of individual Cmax values exceeding the upper eugonadal limit.
Observed testosterone AUC0-24 and Cmax increased with dose from 1.25 to 5.00 g following single dose application and over the entire dose range of 1.25 to 6.25 g following multiple dose applications. Statistical analysis did not indicate that steady state had been achieved, although graphical assessment of mean and median trough concentrations indicated that steady state was achieved by Day 2 for all treatments. No accumulation of observed testosterone was seen at the 1.25 g and 2.50 g doses, and <2-fold accumulation was seen at the 3.75 g to 6.25 g doses, following multiple dosing for 14 days.

Division of Scientific Investiations (DSI) Consult: An informal email/telephone discussion with Drs' C.T. Vishwanathan and Dr. Jacqueline O'Shaughnessy of DSI revealed that the Bioanalytical facility (b) (4) employed for 100 % sample re-analysis has been issued FDA Form 483 on few occasions in the past. Given this inspection history, and given that the primary endpoints are PK-based (i.e. total serum testosterone within normal range), the Office of Clinical Pharmacology has requested an inspection of (b) (4) in relation to the pivotal Phase 3 Clinical trial S176.3.104. A consult has been sent to DSI on 04/07/2009.

Note to Project Manager: Please send the following Clinical Pharmacology related information requests and potential review issues to the sponsor. Please include a timeline for response to the information requests as noted below (i.e. within a month of receiving this communication).

Information requests to sponsor *(response requested within a month of receiving this communication)*:

1. You've noted in your submission that "DHT has been shown to be stable in frozen human serum at 54.5 and 755 pg/mL using (b) (4) GC/MS (gas chromatography/mass spectrometry) Method MS 57 for a period of 2019 days at -20 °C. Data are stored on file at (b) (4). Provide relevant data in this regard.

2. You've noted in your submission that "additional data demonstrating the stability of DHT in frozen human serum is being obtained by (b) (4) using LC/MS (liquid chromatography/mass spectrometry) methodology and data will be submitted to this report as an addendum". Clarify the anticipated date of this submission to the NDA.
3. For each of the analytes, confirm whether the range of quality controls evaluated in freeze/thaw and long-term stability studies would encompass the observed range of analyte concentrations in patients during the completed clinical trials for AndroGel 1.62 %.
4. Quality controls (QCs) available in storage since May 2003 were reportedly used for assessment of freeze/thaw and long-term stability (conducted in August 2008). Clarify the source of these QCs and their storage location until the time of reanalysis (i.e. at (b) (4), Solvay, (b) (4)). Comment on whether these were stored along with and under the same conditions as the study samples.
5. What is the maximum number of freeze/thaw cycles that the study samples were subjected to while at (b) (4), Solvay (b) (4) Clarify whether the available freeze/thaw stability data would encompass these sample handling conditions.
6. For the study S176.3.104, submit the serum testosterone pre-dose concentrations obtained during the titration phase on days 14, 28 and 42 for all subjects (analyzed by (b) (4) using RIA). Alternatively, provide their location in your NDA, if previously submitted. Clarify whether on dose titration days that overlapped with 24-hour PK days, pre-dose serum concentrations were assessed by both RIA (b) (4)) and LC-MS/MS assays (b) (4)).
7. What percentage of total serum samples were available for re-analysis at (b) (4) Were there any missing samples from each study?
8. Serum analysis of the analyte SHBG appears to have been done by (b) (4) Please elaborate on why these samples were not reanalyzed at (b) (4) along with other analytes.

Potential review issues:

- The adequacy of the stability data provided in support of the 100 % sample re-analysis at (b) (4) will be a review issue.
- Significant transfer potential exists for this drug product. Results of the transfer studies as well as labeling will be a review issue.
- Differences in systemic exposure appear to exist across the two gel application sites (shoulders/upper arms vs. abdomen). Specific dosing instructions as they relate to the site of application will be a review issue.
- Specific labeling instructions related to application site washing, moisturizer or sunscreen use will be a review issue.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 find that the Human Pharmacokinetics and Bioavailability section for NDA 22-309 is fileable.

Sandhya Apparaju, Ph.D. _____
Date

_____ _____
Myong Jin Kim, Pharm.D., Team Leader Date

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

/s/

Sandhya Apparaju
4/8/2009 09:19:23 AM
BIOPHARMACEUTICS

Myong-Jin Kim
4/8/2009 09:23:35 AM
BIOPHARMACEUTICS