

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022504Orig1s000**

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

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## OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

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NDA: 022504	Submission Dates: 1/25/2010, 5/12/2010, 5/20/2010, 8/16/2010, 9/24/2010, 10/14/2010, and 11/19/2010
Brand Name	Axiron™
Generic Name	Testosterone (T)
Reviewer	Chongwoo Yu, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Acrux Pharma
Relevant IND	070516
Submission Type	505(b)(2) Original
Formulation, Strength, Regimen	30, 60, 90, and 120 mg T (30 mg per pump actuation), Starting dose at 60 mg T (2 pump actuations) once daily and dose adjust appropriately
Indication	Treatment of male hypogonadism

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The purpose of this addendum is to address the Office of Clinical Pharmacology (OCP)'s recommendations on the Sponsor's proposed product labeling and on the relevance of the Division of Scientific Investigation (DSI) consult recommendations that were not addressed in the original Clinical Pharmacology reviews of NDA 022504 dated November 1, 2010 and November 17, 2010 in DARRTS.

### **1. OCP's Recommendations on the Product Labeling**

#### **1.1. Responder Rate Information**

In Section 14.1 of the Full Prescribing Information (FPI) of the product labeling, the Sponsor proposed to include the percentage (%) responder rates of Days 15 and 60 (in Table 3 in the product labeling) which are not the primary endpoint days. The primary efficacy endpoint was assessed on Day 120.

**Table 3:** Proportion of subjects who had an average Serum Total T in the range 300 to 1,050 ng/dL and completed 120 days of treatment (N=138<sup>a</sup>)

Evaluation Time	Statistics	Value
Baseline Testosterone	Mean (SD)	194.6 ng/dL (92.9 ng/dL)
Day 15	Normal <sup>b</sup>	76.1% <sup>c</sup>
	95% CI	(69.0%, 83.2%)
Day 60	Normal <sup>b</sup>	84.8%
	95% CI	(78.8%, 90.8%)
Day 120	Normal <sup>b</sup>	84.1%
	95% CI	(77.9%, 90.2%)

<sup>a</sup> Three patients who withdrew from the study due to adverse reactions are included as treatment failures.

<sup>b</sup> Normal represents the percentage of patients with average testosterone concentration in the range of 300 – 1,050 ng/dL.

<sup>c</sup> On Day 15, 72.2% of the 90 subjects in the US study population had an average serum testosterone in the range of 300 ng/dL – 1,050 ng/dL.

The Clinical Pharmacology review team does not agree with the Sponsor’s proposal. Currently, there are 2 approved T gels (Testim<sup>®</sup> [NDA 021514, approved on October 31, 2002] and AndroGel<sup>®</sup> [NDA 021015, approved on February 28, 2000]) being marketed in the U.S. Under Section 14 of the AndroGel<sup>®</sup> label or under Clinical Studies Section of Testim<sup>®</sup> label, only the primary endpoint data in terms of % responders are included (e.g., 74% achieved an average serum T within the normal range on Day 90 for Testim<sup>®</sup>; 87% achieved an average serum T within the normal range on Day 180 for AndroGel<sup>®</sup>). In the AndroGel<sup>®</sup> product labeling, there is a statement that mean peak, trough and average serum T concentrations within the normal range (298-1,043 ng/dL) were achieved on the first day of treatment with doses of 5 g and 10 g. While the approved T products had different clinical trial designs and there were several titration time points (e.g., titrated on Day 60 for Testim<sup>®</sup> based on the 24 hr averaged serum T concentrations obtained on Day 30), only the % responders on the primary endpoint date were included in these product labels.

The Clinical Pharmacology review team is concerned that including the % responder information of Days 15 and 60 under the Section 14.1 of the label may potentially be used to promote that Axiron<sup>™</sup> works fast to achieve normal T concentrations. As addressed in text of Section 12.3 of the product labeling, in general, steady-state serum T concentrations were achieved by approximately 14 days of daily dosing. In addition, Figure 1 under the Section 12.3 addressed the dose-response of different T strengths on Day 7. A detail examination of Table 4 under the Section 14.1 revealed that the number of subjects on each dose continued to change on each titration date (i.e., Days 15, 60, and 120). While the steady-state serum T concentrations are achieved by approximately 14 days of daily dosing in general, this observation underlines the fact that the individual response to Axiron<sup>™</sup> is different and therefore, cannot be generalized. For example, some patients who achieved the “normal” T range between 300 and 1,050 ng/dL on non-primary endpoint days (i.e., Day 15 or 60) did not meet this primary endpoint on Day 120 (e.g., Patient ID 211-39).

Patient ID	Study Day	Axiron <sup>™</sup> Dose (mg)	C <sub>avg</sub> (ng/dL)
211-39	15	60	2067
	60	30	343
	120	30	275
210-09	15	60	845
	60	60	1218
	120	30	749
203-08	15	60	875
	60	60	1394
	120	30	456

\* These 3 patients reflect N=3 under Table 4 in Section 14.1 (30 mg, Day 120 group) of the Axiron<sup>™</sup> product labeling

Other examples are listed below:

Patient ID	Study Day	Axiron™ Dose (mg)	C <sub>avg</sub> (ng/dL)	Patient ID	Study Day	Axiron™ Dose	C <sub>avg</sub> (ng/dL)
103-01	15	60	425	206-21	15	60	182
	60	60	495		60	90	321
	120	60	243		120	90	213
201-01	15	60	307	208-09	15	60	313
	60	60	1128		60	60	275
	120	60	555		120	90	418
202-02	15	60	325	208-11	15	60	689
	60	60	482		60	60	363
	120	60	269		120	60	283
202-10	15	60	280	209-08	15	60	146
	60	90	322		60	90	327
	120	90	265		120	90	293
203-26	15	60	208	209-10	15	60	448
	60	90	319		60	60	440
	120	90	209		120	60	272
205-04	15	60	942	210-05	15	60	510
	60	60	923		60	60	477
	120	60	1182		120	60	256
205-15	15	60	380	211-16	15	60	305
	60	60	426		60	60	336
	120	60	269		120	60	229
212-14	15	60	249	403-02	15	60	442
	60	90	325		60	60	538
	120	90	246		120	60	157
601-10	15	60	928				
	60	60	866				
	120	60	1126				

Therefore, the Clinical Pharmacology review team believes that including the % responder information of Days 15 and 60 is misleading and unacceptable.

However, the Clinical reviewer, Dr. Donald McNellis, believes that Days 15, 60, and 120 % responder rates should be included in Section 14 of the product labeling. Briefly, he believes that the Day 15 data, in comparison to the data from later time points, will demonstrate to the prescribing physicians the magnitude of the improvement in response that is achieved with titration. He states that this will emphasize the importance of the titration procedures recommended in the label. Having the Day 60 data included in the product labeling will demonstrate to the physician that a single titration will often be sufficient to achieve “normal” T concentrations. He states that this is useful and accurate clinical information and has been reviewed and accepted by the biometrics team. Reference is made to Dr. Donald McNellis’ Clinical review addendum dated November 19, 2010 in DARRTS.

At the teleconference with the Sponsor held on November 15, 2010 to discuss the product labeling, while the Clinical Pharmacology review team conveyed the recommendation of deleting the % responder information of Days 15 and 60, the Clinical team conveyed to the Sponsor that they accept the inclusion of the Day 60 data (i.e., % responder information) but the inclusion of the Day 15 data is unacceptable since the U.S. population did not meet the primary efficacy endpoint. During the teleconference, the Clinical review team offered an alternative approach of

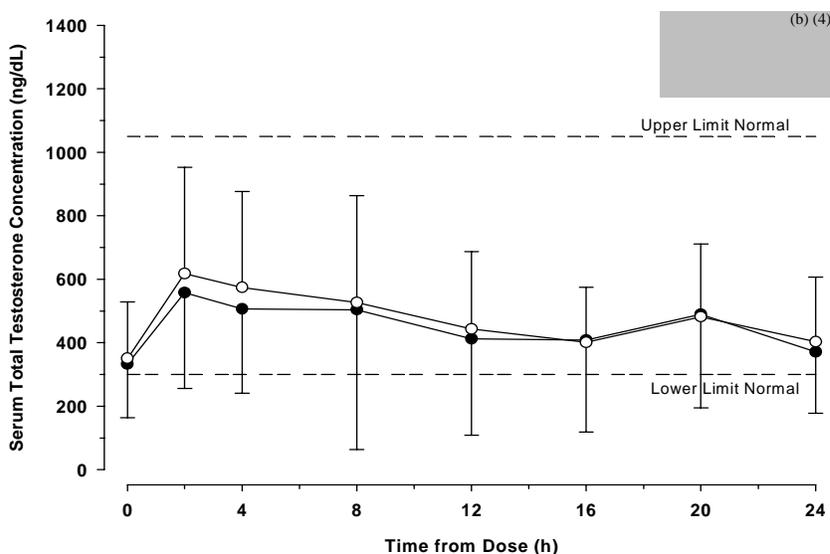
including the % responder information of Day 15 (b) (4)

On November 16, 2010, the Sponsor accepted the Clinical review team's recommendation and a decision was made by the DRUP to include the % responder information of Days 15 and 60 with a footnote stating that "On Day 15, 72.2% of the 90 subjects in the US study population had an average serum testosterone in the range of 300 ng/dL - 1,050 ng/dL."

**1.2. Figure showing Mean ( $\pm$ SD) Steady-State Serum T Concentrations on Days 15 and 120**

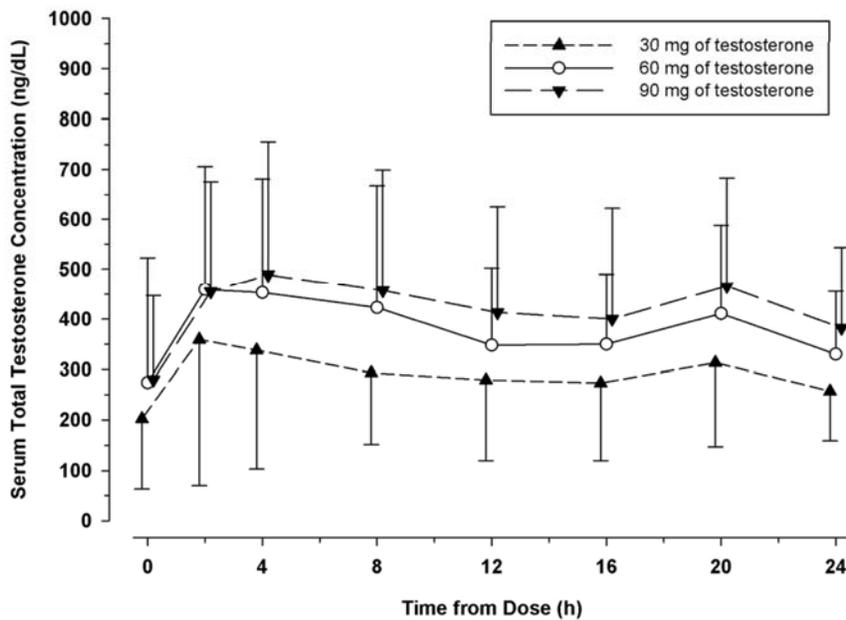
The Sponsor originally proposed to include figure below (b) (4) in Section 12.3 of the product labeling.

Mean ( $\pm$  SD) Steady-State Serum T Concentrations on (b) (4) Day 120 (30, 60, 90 or 120 mg T) in Patients Who Completed 120 Days (N=135) of Axiron<sup>™</sup> Once-Daily Treatment



The Clinical Pharmacology team recommended removing this figure and proposed to include a figure of steady state PK (Figure 1 in Section 12.3 of the product labeling).

**Figure 1:** Mean ( $\pm$ SD) Serum T Concentrations on Day 7 in Patients Following Axiron™ Once-Daily Application of 30 mg, 60 mg, or 90 mg of T



Sponsor accepted the Clinical Pharmacology review team's proposal.

(b) (4)

The Clinical Pharmacology review team believes that this figure with the 24 hr PK profile on Days 15 and Day 120 of T following a daily Axiron™ application should not be included in Section 14.1. First concern is that while the entire study population was on one dose (i.e., 60 mg T) on Day 15, the Day 120 profile is a mean of everyone on different doses at each time-matched point. In addition, there were many patients who were above or below the "normal range" on Day 15.

**Table 4:** Baseline-unadjusted Arithmetic Mean ( $\pm$ SD) Steady-State Serum T Concentrations on Days 15, 60 and 120 in Patients Who Completed 120 Days of Treatment

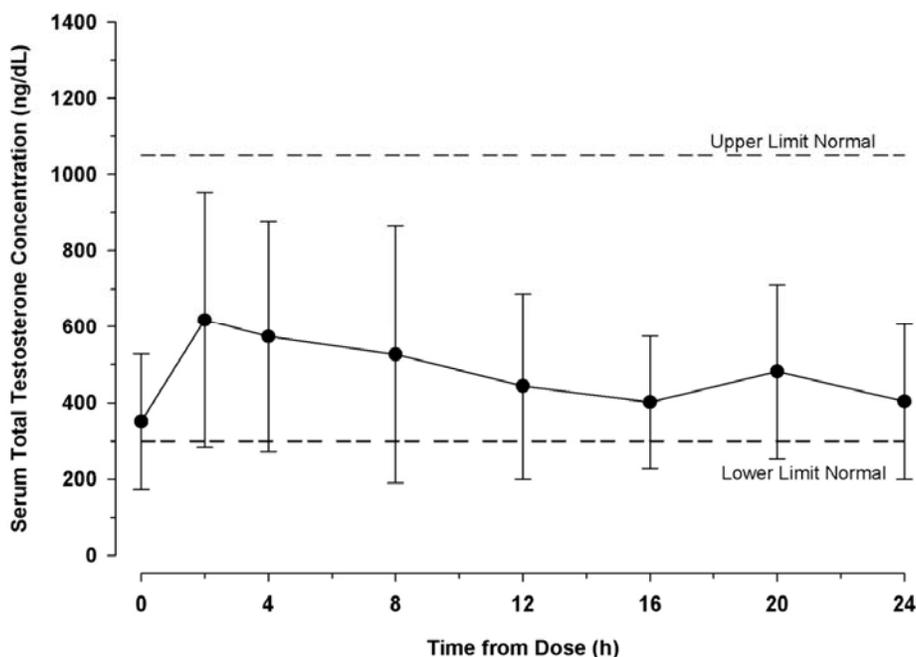
	Dose of AXIRON				Overall
	30 mg	60 mg	90 mg	120 mg	
<b>Day 15</b>	[N=0]	[N=135]	[N=0]	[N=0]	[N=135]
$C_{avg}$ (ng/dL)	--	456 ( $\pm$ 226)	--	--	456 ( $\pm$ 226)
$C_{max}$ (ng/dL)	--	744 ( $\pm$ 502)	--	--	744 ( $\pm$ 502)
<b>Day 60</b>	[N=1]	[N=105]	[N=29]	[N=0]	[N=135]
$C_{avg}$ (ng/dL)	343 (--)	523 ( $\pm$ 207)	368 ( $\pm$ 138)	--	488 ( $\pm$ 204)
$C_{max}$ (ng/dL)	491 (--)	898 ( $\pm$ 664)	646 ( $\pm$ 382)	--	840 ( $\pm$ 620)
<b>Day 120</b>	[N=3]	[N=97]	[N=25]	[N=10]	[N=135]
$C_{avg}$ (ng/dL)	493 ( $\pm$ 239)	506 ( $\pm$ 175)	415 ( $\pm$ 165)	390 ( $\pm$ 160)	480 ( $\pm$ 177)
$C_{max}$ (ng/dL)	779 ( $\pm$ 416)	839 ( $\pm$ 436)	664 ( $\pm$ 336)	658 ( $\pm$ 353)	792 ( $\pm$ 417)

A detail examination of Table 4 in Section 14.1 of the product labeling reveals that the number of subjects on each dose continues to change on each titration date (i.e., Days 15, 60, and 120). While the steady-state serum T concentrations are achieved by approximately 14 days of daily dosing in general, this observation underlines the fact that the individual response to Axiron™ is different and therefore, cannot be generalized. The mean of their T measurements at each time point on Day 15 basically evens out and the profile looks similar to Day 120 which can be misleading. Second, the primary efficacy endpoint in the U.S. population was not met on Day 15. By showing these two profiles, it can be misinterpreted that Day 15 would have as good efficacy as Day 120. Therefore, the Clinical Pharmacology review team concludes that the inclusion of this figure is unacceptable.

The Clinical review team had no objections to the Sponsor's proposal. The Clinical reviewer, Dr. Donald McNellis, believes the Day 120 data in the Figure is accurate, not misleading, and worthwhile information for physicians to see. Reference is made to Dr. Donald McNellis' Clinical review addendum dated November 19, 2010 in DARRTS.

During the internal discussion held between the Clinical Pharmacology and Clinical review teams held on November 17, 2010, the Clinical Pharmacology review team's recommendation of deleting this figure was conveyed and both review teams agreed to inform the Sponsor of such recommendation. If further discussion was needed with the Sponsor, the review teams agreed to hold a teleconference with the Sponsor.

**Figure 2:** Mean ( $\pm$  SD) Steady-State Serum T Concentrations on Day 120 (30, 60, 90 or 120 mg T) in Patients Who Completed 120 Days (N=135) of Axiron™ Once-Daily Treatment



However, the DRUP made a decision to accept the insertion of this figure (i.e., Figure 2 in Section 14.1 of the product labeling) with only the Day 120 data shown. The DRUP's recommendation was communicated to the Sponsor on November 17, 2010 and the Sponsor agreed to remove the Day 15 data from Figure 2 in Section 14.1 of the product labeling.

### 1.3. OCP's Overall Recommendation on the Product Labeling

The final agreed upon product labeling between the Sponsor and the DRUP was submitted by the Sponsor on November 19, 2010 (Supporting Document Number: 17). There are no outstanding Clinical Pharmacology issues.

## 2. OCP's Recommendation on the Relevance of DSI Consult Recommendations

Following inspection of the bioanalytical sites, DSI recommended that for Study MTE06 (b) (4) the total T, dihydrotestosterone (DHT), and sex hormone binding-globulin (SHBG) samples identified from Study MTE06 should be excluded and the remaining data re-evaluated. Many analytical runs had > 33.3% of the total QCs and/or > 50% of the QCs at the same concentration with deviations > 15% (for MS-based assays) or 20% (for liquid-based assays) from the nominal concentrations or mean pooled QC concentrations. These analytical runs are listed below:

- Total T: Runs 07060694, 07062970, 07062971, 07063073, 07070796, and 07080981
- DHT: Runs 07062884, 07070704, 07070806, 07080742, 07081156, and 07081875
- SHBG: Run 07060745

DSI recommended that for the studies conducted (b) (4), the SHBG data from studies MTE07, MTE08, MTE09, and MTE10 are not acceptable for review. Additionally, incurred sample reproducibility (ISR) should be evaluated for the total testosterone assay.

Other than the concerns noted above, DSI concluded that the remaining data audited during the inspections are acceptable for review. Reference is made to the DSI Consult Memorandum dated October 29, 2010 in DARRTS.

**Reviewer's Comment:** *Following a detail examination of the Study MTE06 data, it was found that samples of 2 subjects (i.e., Subjects 19 and 20 of Run 07080981) of Part A (interpersonal transfer study) were part of the runs identified with deficiencies. However, data from these subjects were not used in making any conclusions of the study or any recommendations on the product labeling. Therefore, it does not affect OCP's final recommendation on the product approval.*

*As noted in the Clinical Pharmacology Individual Study Review dated November 17, 2010 in DARRTS, SHBG was not the primary analyte of interest and was not reviewed in detail. Therefore, the deficiency of SHBG data mentioned above does not affect OCP's recommendation on the product approval.*

*ISR assessment is a good practice that the Agency is recommending to Sponsors since the February 8, 2008 Crystal City meeting (on GLP Bioanalysis) held in Arlington, VA and it provides confidence in the assay reproducibility for analyses of subject samples. However, given that the bioanalytical method validation and bioanalytical study performance of the studies mentioned above had no major deficiencies observed, the lack of ISR assessment data alone should not delay approval as the studies listed above are not pivotal BE studies. It should be noted that while the Bioanalytical Method Validation Guidance is currently being updated with recommendations of ISR assessments, currently it does not require the submission of the ISR assessment data.*

**3. Recommendation**

The Division of Clinical Pharmacology 3, OCP finds NDA 022504 acceptable from a Clinical Pharmacology perspective.

**4. Post-Marketing Requirements / Commitments**

None

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/s/  
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CHONGWOO YU  
11/22/2010

MYONG JIN KIM  
11/22/2010

EDWARD D BASHAW  
11/22/2010

**CLINICAL PHARMACOLOGY  
INDIVIDUAL STUDY REVIEW**

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<b>NDA:</b>	022504
<b>Type/Category:</b>	505(b)(2)/Original
<b>Brand Name:</b>	Axiron
<b>Generic Name:</b>	Testosterone
<b>Relevant IND:</b>	IND 70516
<b>Indication:</b>	Treatment of male hypogonadism
<b>Dosage Form:</b>	Solution
<b>Route of Administration:</b>	Transdermal
<b>Dosing Regimen and Strength:</b>	Starting dose at 60 mg testosterone (2 pump actuations) once daily and dose adjust appropriately, 2% (30, 60, 90, and 120 mg)
<b>Sponsor:</b>	Acrux Pharma
<b>OCP Division:</b>	Division of Clinical Pharmacology 3
<b>OND Division:</b>	Division of Reproductive and Urologic Products (DRUP)
<b>Submission Dates:</b>	January 25, 2010, May 12, 2010, May 20, 2010, August 16, 2010, September 24, 2010, and October 14, 2010
<b>Reviewer:</b>	Chongwoo Yu, Ph.D.
<b>Team Leader:</b>	Myong-Jin Kim, Pharm.D.

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## 1. Individual Study Reviews

### 1.1 Study MTE08 and MTE09

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**Study MTE08: A Phase III open-label titration study to evaluate the effectiveness and safety of different doses of a dermal application of Testosterone MD-Lotion<sup>®</sup> (cutaneous solution) in hypogonadal men**

**Study MTE09: A Phase III open-label extension of the MTE08 study (A Phase III open-label titration study to evaluate the effectiveness and safety of different doses of a dermal application of Testosterone MD-Lotion<sup>™</sup> (cutaneous solution) in hypogonadal men) to evaluate skin-safety**

**Phase:** 3

**Principal Investigator:** Drs. Christina Wang and Stefan Arver

**Clinical Study Centers:** 26 study centers (international)

**Clinical Study Dates:** July 30, 2008 - August 31, 2009

**Analytical Study Facility:**

(b) (4)

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#### OBJECTIVES

- **MTE08:** To confirm the efficacy and safety of 4 different dose levels of Axiron<sup>™</sup> for use by hypogonadal men via the axilla to achieve a  $C_{avg}$  for total testosterone (T) in the defined normal range (i.e., 300-1,050 ng/dL)
- **MTE09:** To assess the occurrence of skin safety events for additional 2 months of continuous use of Axiron<sup>™</sup> (i.e., up to a total of 6 months).

#### STUDY ENDPOINTS

The primary endpoints were:

- **MTE08:** The proportion of subjects with  $C_{avg}(0-24)$  of total T within the normal range at Day 120. The study was to be deemed successful if 75% or more of subjects had a  $C_{avg}(0-24)$  in the normal range on Day 120. Per agreement with the Division, the value of the lower limit of the two-sided 95% Wald confidence interval (CI) also had to exceed 66.8% in order to establish definitive evidence of efficacy in the study.
- **MTE09:** To observe the change in subject Draize Score (Day 1 to Day 180) after 6 months of continuous use of Axiron<sup>™</sup>.

Secondary endpoints were:

##### **MTE08:**

- Proportion of subjects with  $C_{max} < 1,500$  ng/dL (at least 85% of subjects should have had a  $C_{max} < 1,500$  ng/dL).
- Proportion of subjects with  $C_{max}$  between 1,800 ng/dL and 2,500 ng/dL (< 5% of subjects).
- Proportion of subjects with  $C_{max} > 2,500$  ng/dL (no subjects).
- Proportion of subjects with  $C_{min} < 300$  ng/dL.
- Changes from baseline in the following clinical endpoints:
  - Psychosexual Daily Questionnaire
  - SF-36 questionnaire
  - Fasting Insulin and Glucose levels
  - Prostate Specific Antigen (PSA) levels
  - Luteinizing hormone (LH), follicle stimulation hormone (FSH), and estradiol (E2) levels
  - Hemoglobin and Hematocrit levels
- Confirm the safety of different doses of Axiron<sup>™</sup>.

### **MTE09:**

- To collect adverse event (AE) and concomitant medication information over the 2 month study period.
- To compare the following data collected at the MTE09 follow up visit with the screening data collected in the MTE08 study:
  - Fasting Insulin and Fasting Glucose levels
  - PSA levels
  - LH, E2, and FSH levels
  - Hemoglobin and Hematocrit levels
  - Total T and dihydrotestosterone (DHT) concentrations, and DHT:T ratio levels at Day 187-190

## **STUDY DESIGN**

### **MTE08**

The study was an open label, multi-centre, titration study. 155 subjects were enrolled. Subjects were qualified for the study if they had total T levels < 300 ng/mL. Men with a prior definitive diagnosis of hypoandrogenism as evidenced by documentation meeting the following were recruited:

- Hypothalamic, pituitary or testicular disorder or age related idiopathic hypogonadism,
- A screening serum T of  $\leq 300$  ng/dL (based on the average of two morning samples drawn between 07:00 and 10:00 am and taken at least 30 min apart), and
- Receipt of treatment (buccal, oral, transdermal, or intramuscular [IM] androgen replacement) for hypoandrogenism in accordance with approved labeling, or in the Investigator's opinion are eligible to receive such treatment

Eligible subjects taking T therapy at the time of screening were required to cease their current therapy. Assessment of their baseline levels of T occurred after a washout period of up to 7 days after ceasing their current buccal, oral, or transdermal therapies and after a washout period of up to 30 days for subjects on IM therapies (only T enanthate or short acting T). Subjects were to complete the Psychosexual Daily Questionnaire for the 7 days preceding the Day 1 visit. On Day 1, subjects were started on their daily treatment dose of 60 mg (i.e., one pump actuation [1.5 mL] applied to each axilla) of Axiron™ among the following treatments:

- **Treatment A:** 30 mg of Axiron™ applied daily by 1 pump actuation to the axilla (30 mg to one axilla).
- **Treatment B:** 60 mg of Axiron™ applied daily by 2 pump actuations to the axilla (30 mg to each axilla).
- **Treatment C:** 90 mg of Axiron™ applied daily by 3 pump actuations to the axilla (2 x 30 mg to one axilla and 1 x 30 mg to the other axilla).
- **Treatment D:** 120 mg of Axiron™ applied daily by 4 pump actuations to the axilla (2 x 30 mg to each axilla).
- **Lot or Batch Numbers:** BN0481, BN0481, BN0483, BN0484, BN0489, BN0490, BN0481B, BN0482B, BN0483B, BN0484B, BN0483D, BN0491, BN0492.

**Application Instructions:** The exact application procedure instructions were as follows:

1. Remove the cap and the applicator cup from the bottle. Carefully depress the pump fully once and direct the lotion into the applicator cup.
2. Make sure the axilla is clean, dry with no broken skin. Simply wipe the applicator cup steadily up and down into the axilla as if applying a deodorant. If the dose drips or runs back up with the applicator cup.
3. Repeat the application process from step 2 to the other axilla. Once again wipe the applicator cup steadily up and down into the axilla as if applying a deodorant.
4. Carefully wash the applicator cup by rinsing under warm running water for at least 15 sec before drying with a tissue.

- Allow the solution to dry on the skin for completely (a few min) before applying clothing. Replace the applicator cup and cap back on the bottle before storing safely. Refrain from washing or swimming for 2 hr post-dose.

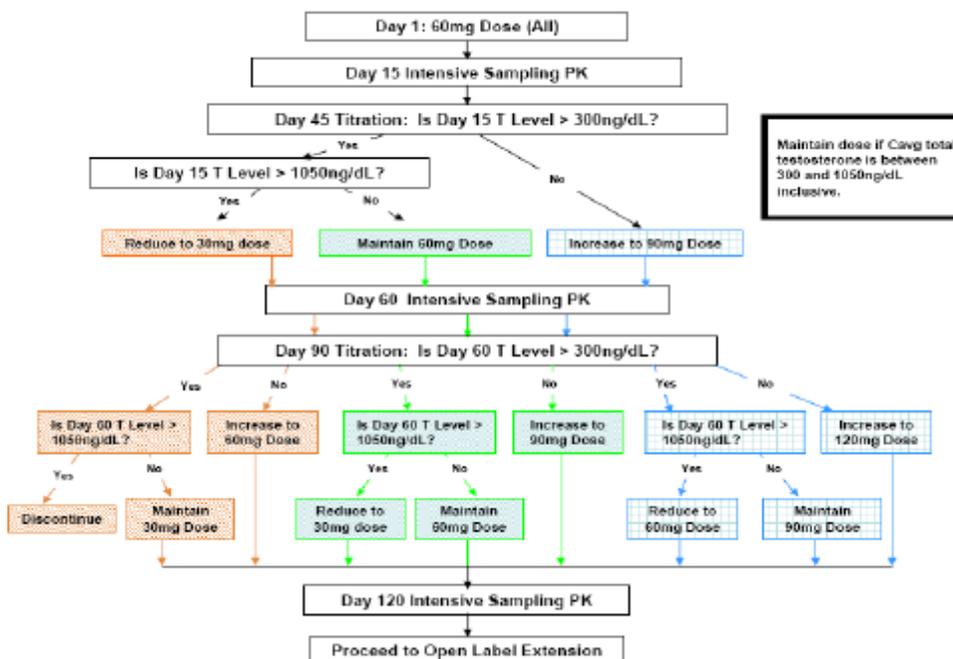
When repeat application to the same axilla was required (i.e., subjects on the 90 mg [i.e., 3 pump actuation] or 120 mg [i.e., 4 pump actuations] dose), subjects were instructed to wait until the axilla was dry before more product was applied. Following completion of the application procedure, subjects were instructed to wait a few min until the application site was dry before dressing.

**Reviewer’s Comment:** While the Sponsor instructed subjects to wait until the application site was dry before dressing the length of time (i.e., for how many minutes) was not reported in the study report.

**Dosing Titration:** During Study MTE08, decisions regarding the titration of subjects onto higher or lower doses of the product were made using  $C_{avg}(0-24)$  data (i.e., the average serum concentration of T across a 24 hr period). On Days 15 and 60, subjects underwent intensive pharmacokinetic (PK) sampling over a 24 hr period. Total serum T and DHT were measured and free T was calculated at pre-dose (0), 2, 4, 8, 12, 16, 20, and 24 hr post-dose. Sex hormone binding globulin (SHBG) was measured in samples collected at pre-dose (0) and at 24 hr post-dose on Days 15, 60, and 120. The ratio of DHT:T was also assessed at each time point during the intensive sampling periods (on Days 15, 60, and 120). On Days 45 and 90, subjects returned to the study centre and were titrated to a lower dose, a higher dose or remained on their current dose, depending on their serum total testosterone PK profile ( $C_{avg}$ ). Dosing titrations were conducted with the following rules:

- Subjects with a  $C_{avg}$  of 300-1,050 ng/dL were maintained on their current dose
- Subjects on the 30 mg dose with a  $C_{avg}$  of < 300 ng/dL were titrated to a 60 mg dose
- Subjects on the 30 mg dose with a  $C_{avg}$  of > 1050 ng/dL were withdrawn from the study
- Subjects on the 60 mg dose with a  $C_{avg}$  of < 300 ng/dL were titrated to a 90 mg dose
- Subjects on the 60 mg dose with a  $C_{avg}$  of > 1050 ng/dL, were titrated to a 30 mg dose
- Subjects on the 90 mg dose with a  $C_{avg}$  of < 300 ng/dL, were titrated to a 120 mg dose
- Subjects on the 90 mg dose with a  $C_{avg}$  of > 1050 ng/dL were titrated to a 60 mg dose

Figure A-1-1: Dose Titration Strategy



Subjects also underwent intensive PK sampling over a 24 hr period on Day 120 with the same PK sampling time points being assessed as on Days 15 and 60. The primary endpoint of the study was assessed based on the  $C_{avg}$  data collected on Day 120. Data allowing the assessment of other efficacy endpoints were collected using daily subject diaries and the PK sampling undertaken at Days 15, 60, and 120. On a daily basis, subjects recorded the application time and dose as well as use of antiperspirant or deodorant in a diary. In addition, subjects recorded any deviations from the protocol such as application of deodorants or antiperspirants after application of study drug, missed doses, and medications that were taken. Whilst in the PK unit, note was taken of if and when a subject showered or washed after dose application. The study involved a screening period of up to 40 days; a treatment period of 120 days and a follow-up period at 7-10 days after the last dose.

### **MTE09**

Study MTE09 was an open label, multi-centre, extension, continuous use study intended to evaluate the skin safety of Axiron™ for an additional 60 days (i.e., for a total of 180 days from the start of Study MTE08). For continuity, subjects visit days were counted from their Day 1 in the MTE08 study. Subjects were enrolled and rolled over into the MTE09 study on Day 120 of the MTE08 study. As such, if it was subsequently found that subjects did not meet all of the entry criteria for the MTE09 study, they were withdrawn.

- Roll over phase: Informed consent was obtained from subjects on or prior to Day 120 (of Study MTE08).
- Treatment period: In accordance with MTE08 study procedures subjects were confined on the evening of Day 120. On Day 120/121 subjects were assessed for compliance with the inclusion and exclusion criteria (including confirming the International Prostate Symptoms Score [IPSS] was not  $\geq 19$ ) and were rolled over to MTE09. Subjects continued to apply Axiron™ daily for 2 months (until Day 180) as per their Day 120 dosing regimen. There were to be no titrations in this study. The dose of Axiron™ was applied on the morning (nominally at 8:00 am) of Day 121 under the supervision of study staff prior to discharge from the site. Subjects reported to the study site prior to dosing on Day 150 and Day 180. During these visits the subjects had their vital signs assessed, concomitant medications, and AEs recorded and a Draize score assessment undertaken.
- Follow up visit/Early withdrawal visit: All subjects were to return to the clinic 7-10 days after the final dose of Axiron™ (Day 187-190) for the follow-up visit or at the time of early withdrawal from the study. During this visit all subjects underwent an update of their medical history, physical examination including evaluation of vital signs, Draize score, and an ECG. A urinalysis was performed during this visit. All AE and concomitant medications were recorded.

### **PK Blood Sampling**

#### **MTE08**

Blood samples for PK measurements were taken at the following time points:

#### *Total T and DHT*

- Days 15, 60, and 120: pre-dose, 2, 4, 8, 12, 16, 20, and 24 hr post-dose

#### *SHBG*

- Days 15, 60, and 120: pre-dose and 24 hr post-dose

#### **MTE09**

No PK blood sampling was carried out for this study.

### **STUDY SITES, POPULATION, AND SAMPLE SIZE**

Study MTE08 involved 26 sites: 12 sites in the US, 4 sites in Australia, 3 sites in the UK, 2 sites in Sweden, 2 sites in France and 3 sites in Germany. The open label continuous use study (MTE09) involved only subjects from the 12 US sites. The MTE08 study enrolled 155 subjects and the MTE09 study enrolled 71 subjects.

In Study MTE08, of the 363 subjects enrolled, 208 were screen failures. 155 subjects were started on the 60 mg dose and received at least one dose of Axiron™. The majority of the subjects were Caucasian (84.7%), with a mean age of  $51.5 \pm 12.7$  yr and an age range of 18-78 yr. 21 out of 155 subjects (13.5%) enrolled were 65 yr or older. Subjects with body mass index (BMI) of higher than  $35 \text{ kg/m}^2$  were excluded from the study. The mean BMI was  $29.5 \pm 3.6 \text{ kg/m}^2$ . BMI for all individuals enrolled were  $< 35 \text{ kg/m}^2$  at randomization. However, there were 4 subjects with BMI higher than  $35 \text{ kg/m}^2$  on Day 120 due to modest elevation in increase in body weight during the course of the study. It should be noted that body weight was not assessed on Day 90. There was a subject with the baseline serum total T concentration higher than 300 ng/dL due to the use of incorrect screening total T concentrations (i.e., from other subject) for enrollment decision. These individuals (n=5) were excluded from the primary efficacy analysis.

Of the 155 subjects enrolled, 135 subjects have completed the study. There were 20 withdrawals (12.9%) from the study for the following reasons:

- 4 for non compliance (2.58%),
- 1 for having screening T concentration  $> 300 \text{ ng/dL}$  (0.65%)
- 2 lost to follow up (1.29%),
- 3 due to an AE (pre-existing superficial thrombophlebitis, melanoma, and angry emotional changes) (1.94%),
- 9 withdrew consent (5.81%); and
- 1 per Sponsor's request (1.29%).

Reference is made to the minutes of the End of Phase 2 (EOP2) meeting held between DRUP and the Sponsor on March 13, 2008. DRUP responded to the Sponsors inquiry that in addition to the anticipated 107 completers for the measurement of the primary endpoint in Study MTE08, a minimum of 50 subjects should be exposed to Axiron™ for at least 6 months to determine skin safety in Study MTE09. 138 subjects completed Study MTE08 and 71 subjects were included in the skin safety analysis of Study MTE09. Therefore, the number of subjects in Studies MTE08 and MTE09 are sufficient. The reason for the Sponsor's request for withdrawal of 1 subject mentioned above is unknown.

In Study MTE09, the median age of subjects in the safety set was 53 yr old, with an age range of 21-78 yr. Of the 71 subjects in the safety set, 54 (76.1%) were Caucasian, 10 (14.1%) were Hispanic, 6 (8.5%) were African Americans, and 1 (1.4%) had race recorded as "Other". The mean BMI was  $29.78 \text{ kg/m}^2$ .

## **FORMULATION**

Axiron™ was to be supplied in a bottle fitted with a 1.5 mL (30 mg) metered dose pump. The dosing used in the studies was determined by the number of pump actuations: 30 mg (1 pump actuation), 60 mg (2 pump actuation), 90 mg (3 pump actuation), and 120 mg (4 pump actuation) of the bottle. The dose of the Axiron™ was applied using a specially designed applicator that was supplied with the bottle.

## **INCLUSION AND EXCLUSION CRITERIA**

### **Inclusion Criteria**

Inclusion criteria of Studies MTE08 and MTE09 included the following:

### **MTE08**

1. Male subjects equal or greater than 18 yr of age with a prior documented definitive diagnosis of hypogonadism as evidenced by previously documented:
  - Hypothalamic, pituitary or testicular disorder or age related idiopathic hypogonadism,
  - Screening serum testosterone of  $\leq 300 \text{ ng/dL}$  (based on the average of two morning samples taken at least 30 min apart),

2. Were currently receiving treatment (buccal, oral, transdermal, or IM androgen replacement) for hypogonadism in accordance with approved labeling, or in the Investigator's opinion were eligible to receive such treatment,
3. BMI < 35.0 kg/m<sup>2</sup>,
4. Hemoglobin levels at screening  $\geq$  11.5 g/dL

### **MTE09**

1. Completed Study MTE08 up to and including Day 120/121 in a compliant manner
2. Ability to communicate with the study staff, understand the study information sheet and sign the written informed consent forms; willing to follow the protocol requirements and comply with protocol restrictions and procedures

### **Exclusion Criteria**

Exclusion criteria of Studies MTE08 and MTE09 included the following:

### **MTE08 and MTE09**

1. Current use of long acting T injectables such as Nebido<sup>®</sup>,
2. Any significant history of allergy and/or sensitivity to the drug products or their excipients, including any history of sensitivity to T and/or sunscreens,
3. Any clinically significant chronic illness or finding on screening physical exam and/or laboratory testing that makes it undesirable for the investigator to enroll the study subject in the study and/or that in the investigator's opinion, would interfere with the study objectives or safety of the subject,
4. Chronic skin disorder (e.g., eczema, psoriasis) likely to interfere with transdermal drug absorption,
5. Men with suspected reversible hypogonadism (i.e., due to medications or stress),
6. Any man in whom T therapy is contraindicated,
7. Men with clinically significant prostate exam (such as irregularities or nodules palpated) or clinically significant elevated serum PSA levels (> 4 ng/mL), or age adjusted reference range of PSA values,
8. Current or history of drug or alcohol abuse (more than 4 standard drinks per day and/or abnormal liver function tests > 2 times the upper limit of the normal range values),
9. Men taking concomitant medications (prescribed, over-the-counter (OTC) or complementary) that would affect SHBG, T concentrations, or metabolism such as warfarin, insulin, opiates, gonadotropin releasing hormone (GnRH), 5 alpha reductase inhibitors, propranolol, oxyphenbutazone, corticosteroids (except for physiological replacement doses), E2,
10. Men with uncontrolled diabetes (HbA1c  $\geq$  10%),
11. Men currently taking any investigational product, or who have received an investigational product within 28 days prior to screening, or 5 half-lives (whichever is the longer),
12. Subjects with a partner of child bearing potential who are not willing to use adequate contraception for the duration of the study,
13. Subjects whose partners are pregnant.

### **Concomitant Therapy**

The medications listed in the exclusion criteria above were prohibited. All concomitant medications taken from the time of consent and those used during the study were to be recorded in the Case Report Form (CRF).

### **Compliance Assessment**

For treatment compliance monitoring regarding application, patients were required to complete a daily dosing chart, which required them to record the dose and time of study drug application each day. This information allowed for measurement of compliance against the correct dose for each subject. When subjects returned to a site for a scheduled study visit, they were instructed to apply the drug product under the direct observation of trained site staff to monitor consistent dosing technique and application within acceptable application area.

## SAFETY ASSESSMENTS

The following procedures were used to evaluate safety in both Studies MTE08 and MTE09:

- AEs/reactions
- Serious AEs (SAEs)
- ECG
- Vital signs
- Physical examination, including a digital rectal examination
- Draize score
- Clinical laboratory parameters, including PSA, biochemistry (lipids, glucose, insulin), hematology (including hematocrit, hemoglobin A1C), hormonal assessments (T, DHT, free T, LH, FSH, and E2), urinalysis.

## BIOANALYTICAL METHODS

### Determination of Total T and DHT Concentrations

A liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay was utilized for the analysis of both total T and DHT. T, DHT, and the internal standard (b) (4) were extracted from human serum samples by liquid-liquid extraction (LLE). After evaporation under (b) (4), the residue was reconstituted and analyzed. Dynamic ranges for T and DHT in human serum were 20.0-5,000 and 5.00-1,250 ng/dL and calibration curves were generated using a weighted ( $1/x^2$ ) linear least-squares regression.

Phosphate buffer saline (PBS) was used as a substitute to human serum to avoid any endogenous concentrations of the tested analytes, for the preparation of the calibration curve per the validated method. When preparing QC samples in human serum, the endogenous concentrations of T and DHT in human serum were evaluated by analyzing 6 replicates of the serum matrix (processed as unknown samples). The endogenous concentrations of the analytes were calculated using the calibration standards prepared in PBS.

*Stability:* In order to confirm long term storage stability longer than that of the study samples from collection to analysis, stability of QC samples after storage in a freezer set to maintain -10 to -30°C for at least 387 days was required. Stability of QC samples after storage in a freezer set to maintain -10 to -30°C for 463 days was established and reported in the method validation report. The 387 days for stability was calculated to represent the longest possible duration of storage Day 1 sample collection July 9, 2008 to the end of analysis July 31, 2009.

### Determination of SHBG Concentrations

The SHBG analyses in the current study were undertaken by a central laboratory using an enzyme immunoassay. For the MTE08 and MTE09 studies, the central laboratory used was (b) (4). Acceptance criteria and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance*.

### Calculation of Free T Concentrations

The concentrations of free T were calculated using the literature method outlined below (Vermeulen *et al.*, 1999).

$$\text{Free Testosterone} = \text{Total T} * \left[ \frac{1}{1 + K_{\text{SHBG}} * [\text{SHBG}] + n * K_{\text{ALB}} * [\text{ALB}]} \right]$$

Where,

- SHBG values were reported as nmol/L and converted to mol/L or Molar concentration (multiplied by a factor of  $10^{-9}$ ).
- $K_{\text{SHBG}}$  for T (association constant for binding to SHBG) is  $0.6 \times 10^9 \text{ M}^{-1}$ .

- For the calculation of free T concentration from 0 to 20 hrs, SHBG reported at time “0” and for 24 hr and beyond, the SHBG values at 24 hr were used.
- $n \cdot KALB$  (the product of the number of binding sites per molecule and the association constant for albumin) is  $4 \times 10^4 M^{-1}$
- The plasma albumin values reported for each subject (reported in g/L and converted to molar concentrations by dividing with the molecular weight of albumin, 69,000 Da) were used in the Sponsor’s calculations
- The free T concentrations were reported in units of pg/ml.

## STATISTICAL METHODS

### MTE08

The following non-baseline and baseline corrected PK parameters were to be determined from serum concentrations of total T, DHT, calculated free T, and DHT:T ratio: AUC(0-24),  $C_{min}$ ,  $C_{max}$ ,  $C_{avg}$ ,  $T_{max}$ , and Degree of Fluctuation (DF).

Mean, standard deviation (SD), and coefficient of variation (CV) were to be calculated for PK parameters. Analyses of linearity of dosing (e.g., ANOVA of log transformed dose normalized AUC data) were also assessed.

## PROTOCOL DEVIATIONS

In total, there were 35 major deviations noted in 27 subjects, which fell into the following 4 categories:

- There were 15 instances in 12 subjects of prohibited medications being taken at some point during the study, including a subject that was on prohibited medication upon entry into the study. That subject (Subject 20401) was subsequently withdrawn from the study once the prohibited medication was discovered.
- There were 13 instances in 9 subjects of failure to dose consistently for the 3 days before an intensive sampling period (either Days 15, 60, or 120).
- There were 5 instances in 5 subjects of failure to titrate the dose according to the protocol. In 1 case, subject 20101 was titrated down to 30 mg according to his  $C_{avg}$  but subsequently titrated back up based on the Sponsor’s decision, so that a repeat profile could be undertaken at the original dose. 2 subjects were incorrectly titrated at the site level on Day 90 (Subject 20531 and 60207) but were quickly rectified to their correct dose within 1 and 4 days, respectively, of their visit. Subject 20713 was titrated based on  $C_{avg}$  data received by the Sponsor (1 data time point was missing). When the final data was received in the form of listings and tables, the titration error was discovered. Lastly, Subject 20908 had the 24 hr PK blood draw after applying study drug on Day 61. The 24 hr PK data on Day 61 was included in the  $C_{avg}$  calculation and thus the subject was incorrectly titrated.
- 2 subjects did not fulfill all inclusion and exclusion criteria (Subjects 20102 [i.e., enrolled in another clinical study using a different investigational product] and 20902 [i.e., used incorrect screening total T concentration for enrollment. These subjects should not have been enrolled in the study]). Subject 20902 was withdrawn from the study before Day 15 and Subject 20102 remained in the study for 117 days but has not completed the study. Both subjects were not included in the complete set (described below) that was used for the primary efficacy analyses.

## DATA SETS ANALYZED

Analysis sets for MTE08 included safety, full analysis, completer, and per-protocol population sets. The completer set was the primary analysis set for the efficacy analysis. All analyses for MTE09 used the MTE09 safety set.

### *Safety Set*

The safety sets for Study MTE08 and Study MTE09 included all subjects who received at least 1 dose of Axiron™ in each study, respectively. The safety set for Study MTE09 is a subset of the MTE08 Safety Set. All analyses for MTE09 were conducted using the MTE09 Safety Set. The Safety Set comprises 155 subjects.

### ***Full Analysis Set***

The full analysis set included all subjects who entered the study, received at least 1 dose of Axiron™, in MTE08, and had on-treatment data for at least 1 efficacy variable. Analyses based on the full analysis set were considered as supportive for the primary efficacy analysis. The full analysis set comprises 143 subjects.

### ***Completer Set***

The Completer Set included all subjects who were included in the full analysis set and who completed the Day 120 visit. The Completer Set also included subjects who withdrew from Study MTE08 prior to Day 120 due to either an AE or efficacy. Subjects who withdrew from MTE08 for these reasons were considered as treatment failures in the primary efficacy analysis. 135 subjects completed the study with 20 withdrawals, 3 of which were due to AEs. The 3 subjects that withdrew due to an AE are classed as treatment failures (as agreed with the Division) and are thus included in the primary analysis of the completer set. Subjects who withdrew from MTE08 prior to Day 120 for reasons other than an AE or efficacy were not included in the Completer Set. Therefore, the Completer Set on which the primary endpoint is calculated contained 138 subjects. Note that for some of the PK analysis the Completer Set does not contain 138 subjects because PK data does not exist at all time points (days) for the 3 subjects who withdrew due to an AE.

### ***Per Protocol Set***

The Per Protocol Set included all subjects who completed MTE08 without any significant protocol violations or deviations as defined prior to database lock. Any subject who withdrew due to an AE or efficacy was considered a treatment failure for the primary efficacy analysis and was included in the Per Protocol Set. There were a total of 32 subjects who were excluded from the Per Protocol population of data for various reasons:

- 6 subjects took prohibited medications that may have affected the Day 120 (and thus primary endpoint) data
- 18 subjects withdrew from the study before Day 120 and thus did not complete the study
- 2 subjects did not respect all of the inclusion and exclusion entry criteria
- 4 subjects were not compliant with regards to their dosing schedule for the 3 days before an intensive sampling period (either Days 15, 60, or 120)
- 2 subjects were incorrectly titrated

## **STUDY RESULTS**

### **Primary Efficacy Analysis**

**Study MTE08:** Reference is made to the letter that the Division sent to the Sponsor on November 10, 2008 under IND 70516. The Sponsor was advised that for the primary efficacy analysis, the Division would consider dropouts that occurred as a result of AEs, to be failures. The Sponsor incorporated this into their primary efficacy analysis. In addition, for the primary efficacy analysis, the Sponsor was advised that the Division would consider the treatment effect to be statistically and clinically significant if the proportion of subjects with a  $C_{avg}(0-24)$  value within the normal range of 300-1,050 ng/dL on Day 120 is equal to or greater than 75% and the lower bound of the 95% CI associated with this point estimate is greater than approximately 67%.

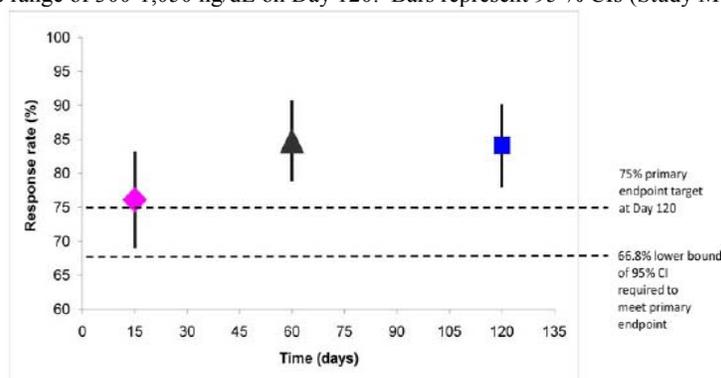
As mentioned above, the primary efficacy analysis was conducted on the completer set (N=138 subjects) at Day 120. The Completer Set included all subjects who completed the Day 120 visit. 135 subjects completed the study with 20 withdrawals, including 3 of which were due to AEs. The 3 subjects that withdrew due to an AE were classed as treatment failures (as agreed with the Division) and were thus included in the primary efficacy analysis (i.e., 135 completers + 3 AE withdrawals = 138 subjects). Subjects that withdrew from MTE08 prior to Day 120 for reasons other than an AE or efficacy were not included in the primary efficacy analysis. Note that for some of the PK analysis the completer set did not contain all 138 subjects. This is because 3 subjects who withdrew from the study due to an AE did not have blood drawn at all PK time points (days).

The primary endpoint of the study was assessed based on the  $C_{avg}(0-24)$  data collected on Day 120. As shown in Table A-1-1, the proportion of subjects with a  $C_{avg}(0-24)$  value in the normal range of 300-1,050 ng/dL on Day 120 in the Completer Set was 84.1% (i.e., 116 out of 138 subjects). The lower bound of the 95% CI associated with the proportion was 78.0% ( $p < 0.001$ ). While the reason was unknown, 17 of the 19 nonresponders had a  $C_{avg}(0-24)$  value below 300 ng/dL while the other 2 had a  $C_{avg}(0-24)$  value above 1,050 ng/dL on Day 120. It is noted that 75% (87/116) of the responders were on the 60 mg dose, while 2% (2/116), 17% (20/116), and 6% (7/116) were on the 30 mg, 90 mg, and 120 mg, respectively, on Day 120. Among the 19 nonresponders, 1, 10, 5, and 3 subjects were on the 30 mg, 60 mg, 90 mg, and 120 mg dose, respectively, on Day 120.

**Table A-1-1:** Primary Efficacy Endpoint Analysis: Proportion of Responders who had steady-state Serum Total T  $C_{avg}$  in the range 300 to 1,050 ng/dL at Day 120 (Study MTE08)

Data Set	Day 120	
	Responders	Proportion of Responders (95% CI)
Completer Set (N=138)	116/138	84.1% (78.0-90.2)
Per Protocol Set (N=123)	106/123	86.2% (80.1-92.3)
Full Analysis Set (N=143)	116/138	84.1%, (NR)

**Figure A-1-2:** Primary endpoint analysis: proportion of subjects who had steady-state Serum Total T  $C_{avg}$  in the range of 300-1,050 ng/dL on Day 120. Bars represent 95 % CIs (Study MTE08)



**Reviewer's Comment:** The primary efficacy analysis was based on the Completer Set. As shown in Table A-1-1, the primary efficacy endpoint was met regardless of which population (i.e., Completer Set, Per Protocol Set, or Full Analysis Set) was used for analysis.

### Secondary Endpoint Analysis

**Study MTE08:** Secondary endpoints are considered to be met if they met the following:

- More or equal to 85% having total T  $C_{max}$  less than 1,500 ng/dL
- Less than 5% having total T  $C_{max}$  in the range of 1,800-2,500 ng/dL
- No subjects having total T  $C_{max}$  higher than 2,500 ng/dL

Secondary endpoint analysis data is summarized in Table A-1-2 below.

**Table A-1-2:** Serum Total T PK Secondary Endpoints

Data Set	Day 15	Day 60	Day 120
$C_{max} < 1,500$ ng/dL	95.6% (130/136)	91.2% (124/136)	94.8% (128/135)
$C_{max} > 1,800$ and $\leq 2,500$ ng/dL	2.2% (3/136)	4.4% (6/136)	3.0% (4/135)
$C_{max} > 2,500$ ng/dL	1.5% (2/136)	1.5% (2/136)	0.7% (1/135)

It should be noted that out of the 138 patients included in the completer set for efficacy analysis, 2 subjects withdrew before Day 15 and 1 subject withdrew after Day 60.

Secondary endpoints of  $C_{max}$  being less than 1,500 ng/dL in at least 85% of subjects and less than 5% of subjects having a  $C_{max}$  between 1,800 ng/dL and 2,500 ng/dL, were met.

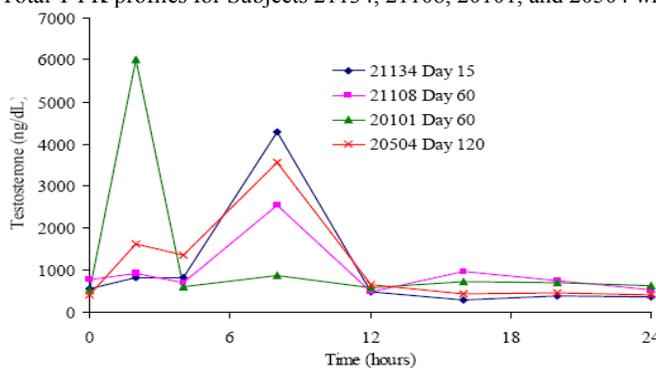
However, one of the secondary endpoints was that there should be no subjects with  $C_{max} > 2,500$  ng/dL at Day 120 was not met. A closer examination of data revealed that 5 out of 136 subjects had a  $C_{max}$  greater than 2,500 ng/dL at some point during the study. 2 of these occurred at Day 15, 2 at Day 60 and 1 at Day 120. The 5 subjects that exhibited  $C_{max}$  values greater than 2,500 ng/dL are listed in Table A-1-3.

**Table A-1-3:** Subjects with Serum Total T  $C_{max} > 2,500$  ng/dL

Subject #	$C_{max}$ (ng/dL)	$T_{max}$ (hr)	PK Sampling Day	Dose on PK Day with $C_{max} > 2,500$ ng/dL (mg)
21134	4280	8	15	60
21139	3247	12	15	60
21108	2554	8	60	60
20101	5996	2	60	60
20504	3457	8	120	60

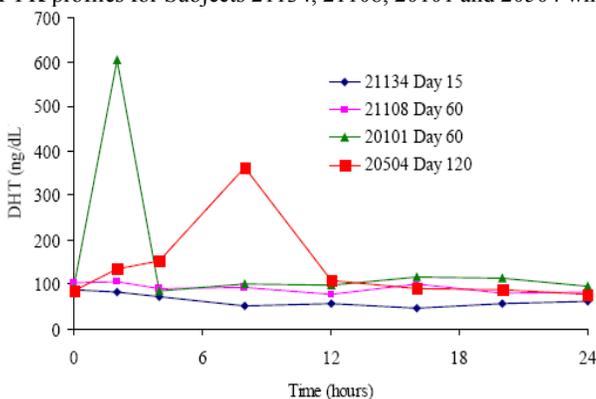
Figure A-1-3 depicts the profiles for Subjects 21134, 21108, 20101, and 20504 on the days where a  $C_{max} > 2,500$  ng/dL was observed. In 2 of these cases (Subjects 21134 and 21108) the apparent increase in T concentrations was not accompanied by proportionate increases in DHT concentrations (Figure A-1-4). In all cases, the serum total T and DHT reanalysis results were confirmatory of the original values seen.

**Figure A-1-3:** Serum Total T PK profiles for Subjects 21134, 21108, 20101, and 20504 where  $C_{max} > 2,500$  ng/dL



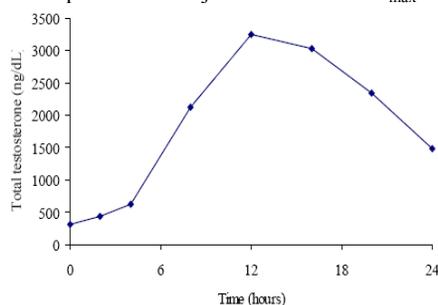
In 2 cases (Subjects 20101 and 20504), the high T concentrations were mimicked by a spike to a high concentration of DHT. However, it was noted that these spikes were only observed at a single time point.

**Figure A-1-4:** Serum DHT PK profiles for Subjects 21134, 21108, 20101 and 20504 where the T  $C_{max} > 2500$  ng/dL

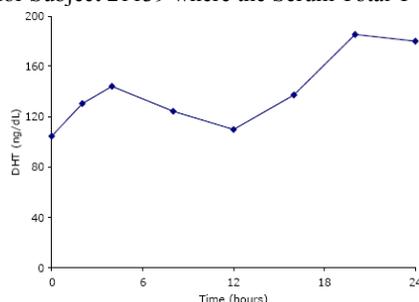


The remaining incident of a  $C_{max} > 2,500$  ng/dL occurred in Subject 21139 and was associated with a pattern of apparently sustained exposure (Figure A-1-5). However, this apparent increase in T was not accompanied by parallel increase in DHT (Figure A-1-6). Comparison of Figure A-1-5 and Figure A-1-6 indicate a decline in DHT at the time the T concentrations are rising in Subject 21139.

**Figure A-1-5:** Serum Total T PK profile for subject 21139 where  $C_{max} > 2,500$  ng/dL (Study MTE08)



**Figure A-1-6:** DHT PK profile for Subject 21139 where the Serum Total T  $C_{max} > 2,500$  ng/dL (Study MTE08)



In addition, a closer look at individual T PK profiles showed that T and DHT concentrations at each time point across different days (i.e., Days 15, 60, and 120) were comparable except the one time point spike of T concentrations observed in each of these 5 subjects, respectively. While the third secondary endpoint was not met and the cause of the spikes of T concentration is unknown, at least there was no consistent trend of  $C_{max}$  spikes observed.

### **PK Parameters**

**Total T PK:** A responder was defined as a subject who had a  $C_{avg}(0-24)$  in the defined normal range for Total T of 300-1,050 ng/dL on Day 120 of treatment. At the time of enrollment the arithmetic mean (SD) baseline T concentrations in the safety set (N=155), was  $196.7 \pm 91$  ng/dL. The increases in  $C_{avg}(0-24)$  observed between Day 15 and Day 60 are reflected in the proportion of subjects in the normal range that also increased from Day 15 (76.1%) to Day 60 (84.8%) (Table 20). The increment in  $C_{avg}(0-24)$  observed between Day 60 and Day 120 was minimal, as was the change in the proportion of subjects in the normal range between these days (84.8% and 84.1% at Days 60 and 120, respectively). It should be noted that only the 135 completers are included in Table A-1-4 below.

**Table A-1-4:** Baseline-unadjusted Arithmetic Mean ( $\pm$ SD) Steady-state Serum T concentrations on Days 15, 60, and 120 in patients who completed 120 days of treatment

Parameter	Dose of AXIRON				Overall
	30 mg	60 mg	90 mg	120 mg	
<b>Day 15</b>		N= 135			N= 135
Cavg (ng/dL)	-	456 (225)	-	-	456 (225)
Cmax (ng/dL)	-	743 (500)	-	-	743 (500)
Cmin (ng/dL)	-	257 (106)	-	-	257 (106)
<b>Day 60</b>	N= 1	N= 105	N= 29		N= 135
Cavg (ng/dL)	343 (ND)	521 (208)	369 (138)	-	487 (104)
Cmax (ng/dL)	491 (ND)	893 (662)	646 (382)	-	837 (619)
Cmin (ng/dL)	213 (ND)	280 (123)	212 (79)	-	265 (118)
<b>Day 120</b>	N= 3	N= 97	N= 25	N= 10	N= 135
Cavg (ng/dL)	493 (239)	506 (175)	415 (165)	390 (160)	480 (177)
Cmax (ng/dL)	779 (416)	839 (436)	664 (336)	658 (353)	792 (417)
Cmin (ng/dL)	290 (175)	288 (115)	230 (119)	262 (111)	275 (117)

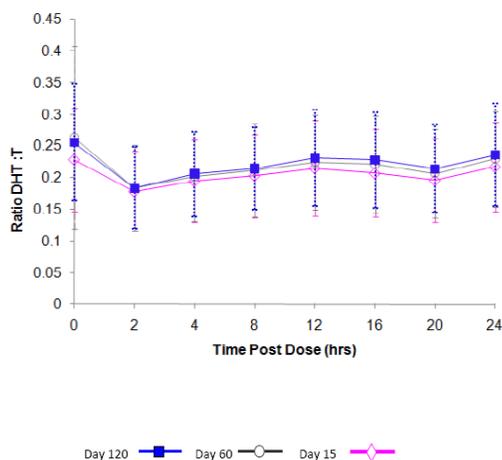
**PK of other analytes:** The measured DHT concentrations and calculated free T concentrations increased as total T concentrations increased showing the PK of these analytes mirrored those of total T. The DHT/T ratios on Days 15, 60, and 120 (N=135), showed a reasonably constant arithmetic mean DHT/T ratio ranging between 0.17-0.26 a 24 hr period (Figure A-1-7). Typically, the DHT/T ratio is normally in the range of 0.05-0.33 (Diver *et al.*, 2003)

The baseline-unadjusted arithmetic mean of steady-state PK parameters of T, free T, and DHT following daily administration of Axiron™ for 15, 160, and 120 days, respectively, are summarized in Table A-1-5 below.

**Table A-1-5:** Baseline-unadjusted Arithmetic mean (±SD) of steady-state PK parameters of T, free T, and DHT following daily administration of Axiron™ for 15, 160, and 120 days, respectively

PK Sampling Day	PK Parameter	ANALYTE		
		Testosterone AM (±SD)	Free Testosterone AM (±SD)	DHT AM (±SD)
Day 15 (N = 136)	C <sub>max</sub>	743 (500)	207(144)	114(48.8)
	C <sub>avg</sub>	456 (225)	126 (59.4)	84.9(36.9)
	C <sub>min</sub>	257 (106)	71.2 (27.8)	58.7(28.8)
	Degree of fluctuation	99.9 (50.3)	100 (50.5)	65.8 (25.3)
	AUC <sub>0-24</sub> (conc*hr)	10966 (5547)	3030 (1463)	2035 (885)
	T <sub>max</sub> (hrs)	9.75 (8.20)	9.59 (8.10)	10.6 (8.40)
Day 60 (N = 136)	C <sub>max</sub>	837 (619)	239.3 (214)	135(71.0)
	C <sub>avg</sub>	487 (204)	137 (62.6)	96.2 (40.2)
	C <sub>min</sub>	265 (118)	74.2 (33.2)	64.4 (31.6)
	Degree of fluctuation	109 (62.97)	108 (62.0)	73.8 (47.9)
	AUC <sub>0-24</sub> (conc*hr)	11633 (4908)	3271 (1508)	2299(965)
	T <sub>max</sub> (hrs)	8.66 (7.67)	8.97 (7.86)	8.82(7.95)
Day 120 (N = 135)	C <sub>max</sub>	792 (417)	215 (122)	134 (59.5)
	C <sub>avg</sub>	480 (177)	130 (49.3)	98.7 (41.2)
	C <sub>min</sub>	275 (117)	73.6 (31.1)	66.5 (31.4)
	Degree of fluctuation	104 (47.2)	103 (46.8)	68.4 (31.1)
	AUC <sub>0-24</sub> (conc*hr)	11510 (4208)	3103 (1175)	2365 (980)
	T <sub>max</sub> (hrs)	8.72 (8.14)	8.71 (8.08)	10.66 (8.65)

**Figure A-1-7:** Steady-state Ratio of DHT:T (Arithmetic Mean  $\pm$  SD) in Subjects who Completed the Clinical Study (N=135)



### Selection and Justification for the Timing of a Single Blood Draw to be Used in Dose Titration Decisions

Reference is made to the minutes of the EOP2 meeting held between DRUP and the Sponsor on March 13, 2008. DRUP recommended that the dose titration should be based on a single blood draw since a dose titration scheme incorporating multiple blood draws over 24 hr is not clinically feasible. Sponsor was asked to propose and justify the timing of serum T determination for dose titration. Per DRUP’s request, the Sponsor submitted their proposal of conducting dose titration based on the serum T concentration from a single blood draw 2–8 hr after applying Axiron™ and at least 7 days after starting treatment with their justification.

During Study MTE08, dose titration decisions were made based on  $C_{avg}(0-24)$  (i.e., the average serum T concentration across a 24 hr period). The Sponsor conducted a comparison between the titration recommendation made based on the total T concentration ( $C_x$ ) from a single blood draw and the titration recommendation made based on  $C_{avg}(0-24)$ . Figure A-1-8 represents the theoretical outcomes (correct or incorrect titration) of using a single blood draw to predict the  $C_{avg}$  during a 24 hr period at different blood draw time points. In this figure, X could be 0, 2, 4, 8, 12, 16, 20, or 24 hr after dosing (i.e., any of the time points at which blood was drawn) to construct the serum T concentration profile from which  $C_{avg}(0-24)$  was then calculated. Note that regions where the  $C_x$ -based and  $C_{avg}(0-24)$ -based titration recommendations were different are notated as “incorrect” while regions where the titration recommendations were identical are notated as “correct”.

**Figure A-1-8:** Possible outcomes from a titration decision based on a single blood draw

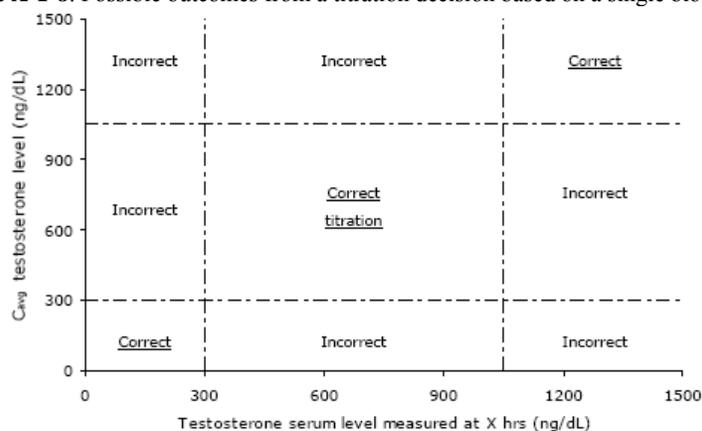
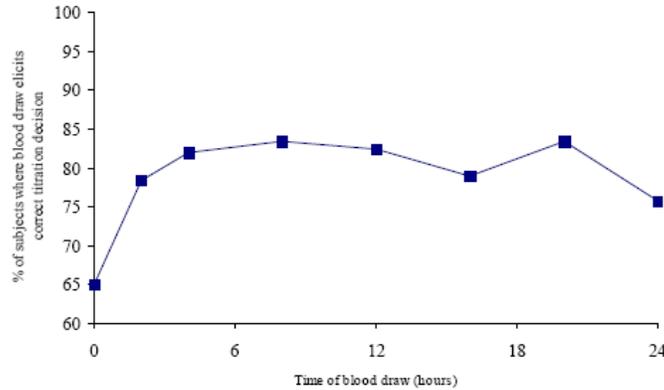


Figure A-1-9 suggests that dose titrations based on single blood draws between 2 and 20 hr after dosing gives the best match with  $C_{avg}(0-24)$ -based dose titration recommendations (79-85%).

**Figure A-1-9:** Percentage of subjects at each time point where use of the blood draw would lead to a correct titration decision



There are 6 regions in Figure A-1-8 that represents incorrect (i.e., different) titration decisions based on a single blood draw. In order to determine the number of titration decisions that would result in doses that were higher than necessary or lower than necessary, the following questions were asked:

- A: Is the measured serum level less than 300 ng/dL, but the  $C_{ave}$  greater than 1,050 ng/dL?
- B: Is the measured serum level in the normal range, but the  $C_{ave}$  greater than 1,050 ng/dL?
- C: Is the measured serum level less than 300 ng/dL, but the  $C_{ave}$  in the normal range?
- D: Is the measured serum level in the normal range, but the  $C_{ave}$  less than 300 ng/dL?
- E: Is the measured serum level greater than 1,050 ng/dL, but the  $C_{ave}$  in the normal range?
- F: Is the measured serum level greater than 1,050 ng/dL, but the  $C_{ave}$  less than 300 ng/dL?

In situations described in questions A, B, and C, the single blood draw based titration recommendation will result in a dose higher than necessary while in situations described in questions D, E, and F, the single blood draw based titration recommendations will result in a dose lower than necessary. The occurrence of each case is summarized in Table A-1-6.

**Table A-1-6:** Potentially Incorrect Dose Decisions by Time of Analysis of Serum Sample

Time (hr)	0	2	4	8	12	16	20	24
$C_x < C_{avg}$ : Higher titration than necessary (%)	34	7.2	7.5	9.1	15	20	11	22
$C_x > C_{avg}$ : Lower titration than necessary (%)	2.2	14	10	6.8	2.9	0.5	5.5	3.1

**Figure A-1-10:** Percentage of Incorrect Titration Decisions based on a Single Blood Draw

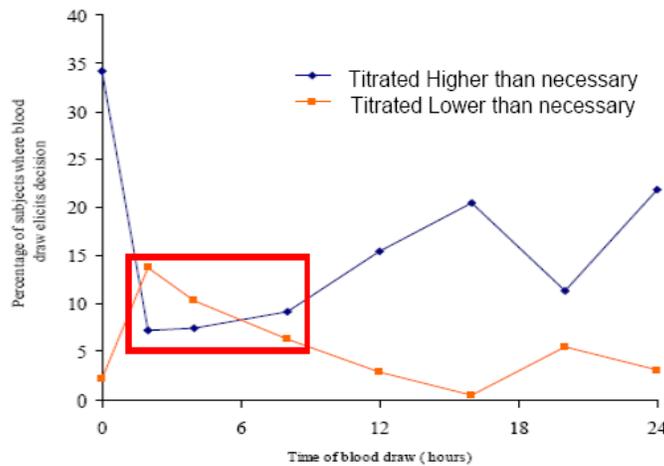


Figure A-1-10 illustrates the percentage of incorrect titration decisions based on a single blood draw resulting in doses that were higher or lower than necessary. As Figure A-1-10 suggests, it is reasonable to suggest that subjects should be titrated based on blood draws taken between 2 and 8 hr after administration of the drug.

It should be noted that data used in the analysis was obtained at least 14 days after initiation of Axiron™ treatment or dose adjustment in the pivotal Phase 3 study (MTE08). In conclusion, dose titration should be based on the serum total T concentrations from a single blood draw 2-8 hr after dosing and at least 14 days after initiation of therapy or dose adjustment. This titration scheme recommendation is reflected in the product labelling.

### Effect of Antiperspirant/Deodorant Use on Total T

Table A-1-7 summarizes the proportion of subjects in the MTE08 completer set with  $C_{avg}(0-24)$  total T within the normal range by use of antiperspirant/deodorant. This data was collected after the study had commenced and therefore the total observations in each data set are not the same, although at Day 120 the deodorant/antiperspirant usage was captured for 131 subjects out of a possible 138.

**Table A-1-7:** Proportion (%) of subjects with  $C_{avg}$  in the normal range by use of deodorant and antiperspirant (Completer Set)

Use of antiperspirant or deodorant		Subjects with $C_{avg}$ in normal range		
		Day 15	Day 60	Day 120
A	Used since the last visit	50/70 (71.4%) (60.9%-82.0%)*	69/79 (87.3%) (80.0%-94.7%)*	70/84 (83.3%) (75.4%-91.3%)*
		B	Did not use since the last visit	34/39 (87.2%) (76.7%-97.7%)*
C	Did not use everyday since last visit			42/48 (87.5%) (78.1%-96.9%)
		D	Used everyday since their last visit	42/61 (68.9%) (57.2%-80.5%)*

\*values represent 95% CI on percentage response rates

The response rates at Day 120 were greater than 75% and comparable for those who did and did not use antiperspirant/deodorant.

**Reviewer's Comment:** *This data only shows the portion of the population in the normal T range but does not show the actual effect of deodorant and/or antiperspirants on the change of total T concentrations. The effect on the actual total T concentration change is unknown. There was a dedicated study (i.e., Study MTE 10) to assess this aspect. Please refer to the review on that study for detail information.*

### Effect of Showering/Washing on Total T

Table A-1-8 shows the proportion of subjects in Study MTE08 with total T  $C_{avg}(0-24)$  within the normal range by shower/washing data. It should be noted that the number of subjects in this analysis is not representative of the entire completer set because, as with the antiperspirants and deodorants, the analysis was implemented after the study had begun. However, the data collected at Day 120 represented 96% of the completer set (133 subjects out of a possible 138). Subjects were asked whether they showered or washed during the 24 hr period following application of Axiron™ (i.e., did they wash whilst the 24 hr PK profile was being determined?) on Days 15, 60, and 120. The data is summarized in Table A-1-8 shows that the response rate for those that showered or washed the application site (2 hr or more after dosing) during the 24 hr intensive PK sampling was comparable with those that did not.

**Table A-1-8:** Proportion (%) of subjects with Total T  $C_{avg}$  in the normal range by incidence of washing (Completer Set)

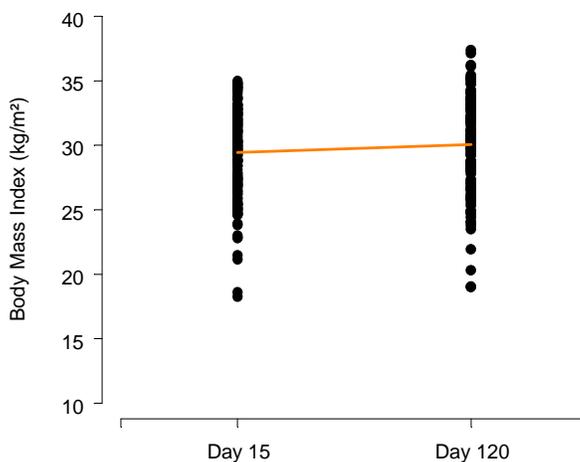
Did the subject wash the application site whilst in the PK unit?	Subjects with $C_{avg}$ in normal range		
	Day 15	Day 60	Day 120
Yes	13/19 (68.4%)	23/25 (92.0%)	28/34 (82.4%)
No	35/48 (72.9%)	53/65 (81.5%)	86/99 (86.9%)

**Reviewer’s Comment:** From this study one can only conclude that washing did not affect the number of subjects that maintained the normal range of total T concentration but not the effect on the actual total T concentration. Considering that Subjects were instructed to refrain from washing or swimming for 2 hr post-dose, efficacy of Axiron™ should not be interfered as long as the users refrain from showering and washing for at least 2 hr, the efficacy. There was a dedicated study (i.e., Study MTE 10) to assess this aspect. Please refer to the review on that study for detail information.

**Effect of Body Mass Index (BMI) on T exposure**

Only men with BMI < 35.0 kg/m<sup>2</sup> were enrolled in Studies MTE08 and MTE09. The prevalence of subjects categorized as being overweight (25 to 30 kg/m<sup>2</sup>) or obese (30 to 35 kg/m<sup>2</sup>) in MTE08 at study entry was 42% and 48%, respectively. Only a single subject was classified as being underweight (<18.5 kg/m<sup>2</sup>) and thus data from this subject were included in the normal weight category (18.5 to 25 kg/m<sup>2</sup>) for the purposes of visual examinations, as appropriate. Individuals with BMI > 35 kg/m<sup>2</sup> were specifically excluded from enrollment in Studies MTE08 and MTE09. Hence, clinical experience in a population of severely or morbidly obese (BMI ≥ 35 kg/m<sup>2</sup>) men is limited; consistent with the inclusion criteria, the BMI in these individuals were all < 35 kg/m<sup>2</sup> at randomization in Study MTE08 and any modest elevation in their BMI resulted from a minor increase in body weight during the course of the study (i.e., after Day 60). The representation of normal weight (11%), overweight (36%) and obese (44%) was essentially similar at the conclusion (Day 120) of Study MTE08 compared to study entry with mean (range) being 29 kg/m<sup>2</sup> (18-35 kg/m<sup>2</sup>) for Day 15 and 30 kg/m<sup>2</sup> (19-37 kg/m<sup>2</sup>) at Day 120. It should be noted that body weight was assessed on Days 15, 60, and 120 but not on Day 90. As illustrated in Figure A-1-11 below, there were no subjects with BMI > 35.0 kg/m<sup>2</sup> at randomization as well on Day 15.

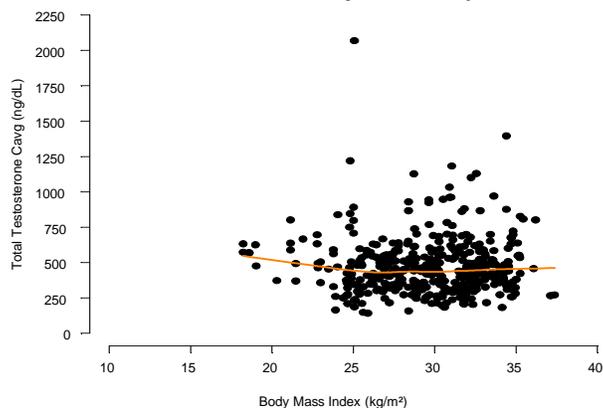
**Figure A-1-11:** BMI represented in the PK population of Study MTE08 at Day 15 (N=143) and 120 (N=135)



The potential influence of body fat, as measured by BMI, on total T systemic exposure ( $C_{avg}$ ) was explored; whereby individual estimates of  $C_{avg}$  (N=416) across the entire study (Days 15, 60, and 120) were examined. To evaluate any pattern of influence of BMI, if any, on total T exposure, all individual data were combined (Days 15, 60, and 120) across the BMI continuum (Figure A-1-12). Application of a nonparametric regression method

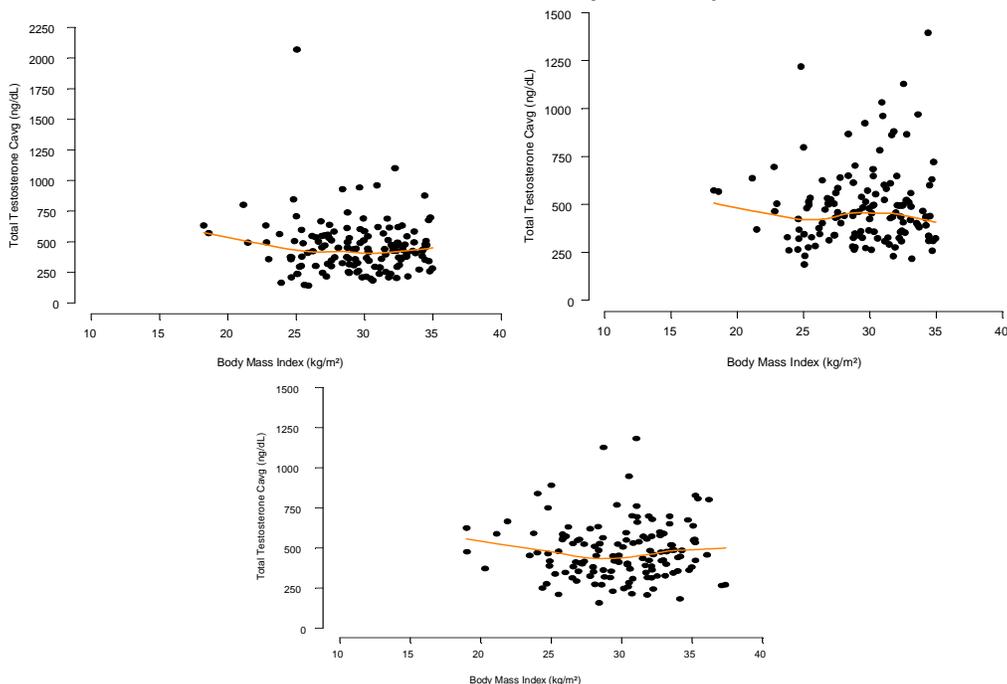
(LOESS) to investigate the influence of BMI did not reveal any systematic pattern and demonstrated an absence of any influence of BMI on total T exposures.

**Figure A-1-12:** Individual total T  $C_{avg}$  estimates (Days 15, 60, and 120) vs. BMI for all PK observations for subjects in Study MTE08



Further analyses according to the continuous measure of BMI were conducted to explore trends between total T exposure and BMI on each day (Days 15, 60, and 120) (Figure A-1-13) recognizing that dose may have been time-varying, leading to commensurate alterations in total T concentrations. No systematic pattern for higher exposures in those having a lower BMI compared to those having higher BMI (in the range of 18-37  $\text{kg}/\text{m}^2$ ) was discerned from an examination of the  $C_{avg}$  estimates.

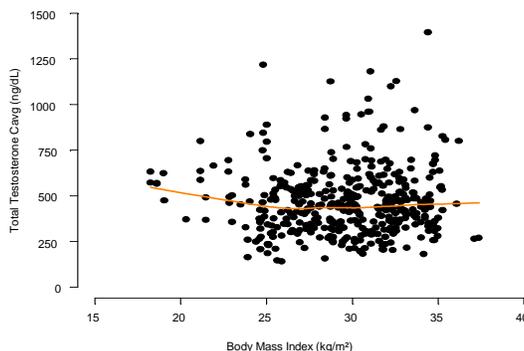
**Figure A-1-13:** Individual total T  $C_{avg}$  estimates on each of Days 15 (upper left panel), 60 (upper right panel) and 120 (lower panel) vs. BMI for all PK observations for subjects in Study MTE08



Relative to the majority of subjects in the PK analysis, a single subject (21139) with a reported BMI of 25  $\text{kg}/\text{m}^2$  was considered to be an outlier based on an estimated  $C_{avg}$  (2,067.25 ng/dL) on Day 15 that significantly exceeded those for the remaining subjects. It should be noted that Subject 21139 was one of the outliers with a  $C_{max}$  of 3,247 ng/dL at 12 hr on Day 15 that was discussed above in the secondary endpoint analysis. Hence, this datum was excluded from the visual comparisons to assess any potential influence on the overall

interpretation of the results (Figure A-1-14). No discernible trend between BMI and individual total T exposures, either across all observations or excluding the datum identified above, was apparent.

**Figure A-1-14:** Individual total T  $C_{avg}$  estimates (Days 15, 60, and 120) vs. BMI for all PK observations in Study MTE08, excluding outlier (Subject 21139).



Although obesity may be expected to influence total T disposition, in Study MTE08, no systematic pattern of BMI effect on T exposures was observed. In consideration of the exclusion criterion applied across the studies, there is scarce data establishing safety and efficacy in subjects with a BMI > 35 kg/m<sup>2</sup>. The product labeling states that safety and efficacy of Axiron™ in men with BMI > 35 kg/m<sup>2</sup> has not been established.

#### **Effect of Age on the Efficacy of Axiron™**

There was not been sufficient number of geriatric patients involved in controlled clinical studies utilizing Axiron™ to determine whether efficacy in those over 65 years of age differs from younger subjects. Only 21 geriatric patients of over 65 years of age (out of a total of 155 patients) were enrolled in Study MTE08 utilizing Axiron™. The mean age was 51.5 ± 12.7 yr and age ranged between 18 and 78 yr. Additionally, there is insufficient long-term safety data in geriatric patients utilizing Axiron™ to assess a potential incremental risk of cardiovascular disease and prostate cancer. This information is reflected in the product labeling.

#### **Effect of Axillary Hair on T Absorption**

The potential effects of axillary hair on T absorption were not assessed in Studies MTE08 or MTE09. In the 74-day letter sent to the Sponsor on April 9, 2010, the Clinical Pharmacology reviewer requested clarification from the Sponsor if potential effects of axillary hair on T absorption were assessed in Studies MTE08 and MTE09. In addition, the Sponsor was asked to provide any literature or scientific information to address this if this was not assessed in the Phase 3 studies. The MTE08 study was a global study that involved hypogonadal men from 5 countries (United States, Australia, France, Sweden, and United Kingdom) and ages ranging between 19-78 yr. Sponsor believes that a normal distribution of axillary hair was associated with the study population and the extent of impact would be rather dependent on physio-chemical property of the drug. There is only limited information available in published literature that assesses the impact of the presence or absence of hair on the absorption of drugs through the skin. Nevertheless, there were no specific restrictions regarding axillary hair in the inclusion/exclusion criteria of the Phase 3 studies and the potential effect of axillary hair, if any, would have been accounted for in the dose titrations in the Phase 3 study.

#### **Drying Time following Application**

Drying time following application was not assessed during the MTE08 and MTE09 studies. For drying time, patients were instructed to wait until the axilla was dry before a repeat application of product, or clothing was applied.

In the Sponsor's *in vitro* testing employing weight measurements following application, it was shown that Axiron™ dried quicker than the other products (i.e., Testim®, AndroGel®, and Tostran®, a 2% T gel indicated for male hypogonadism and is marketed in the European countries but not marketed in the U.S.) evaluated. For

each product listed in Table A-1-9, a glass cover slip was tared on a 5 decimal place balance. The product was dosed on to the glass cover slip and spread to an area of approximately 1 cm<sup>2</sup>. Using the BalanceLink software set to take a reading every 5 sec, the weight of the dose was recorded over a period of 10 min. For Treatment 2, the dose weight was recorded after the second dose of Axiron™ was applied. This experiment was performed in triplicate for each treatment. As the products dry due to evaporation of the volatile components (such as isopropyl alcohol and ethanol) the measured weight declines. The products were deemed ‘dry’ when this weight loss ceased. The weight measurements were plotted as a percentage of the initial weight.

**Table A-1-9:** Experimental Design used for the Determination of the Drying Times of various T Products

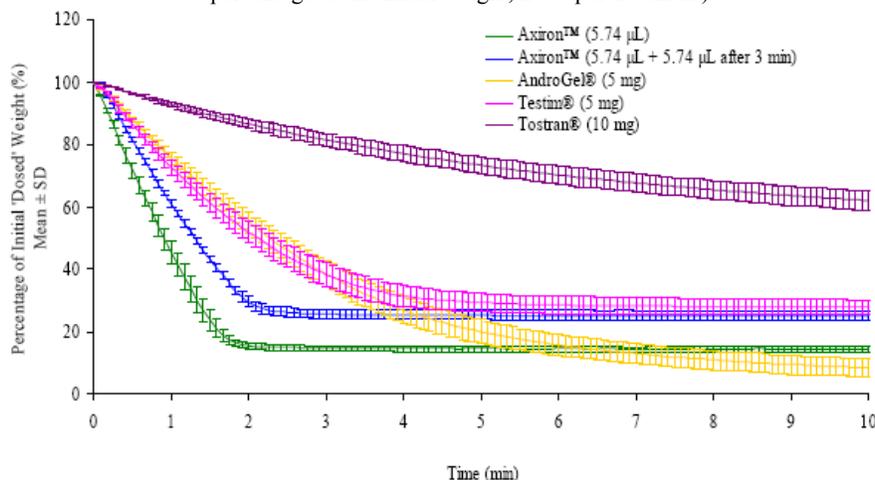
Treatment	Product	Dose of Product Applied (per cm <sup>2</sup> )	Dose of TES Applied (per cm <sup>2</sup> )
1	AXIRON™	5.74 µL (equivalent to 4.7 mg) <sup>†</sup>	115 µg
2	AXIRON™	5.74 µL + 5.74 µL 3 min after the 1 <sup>st</sup> dose (4.7 mg + 4.7 mg 3 min after the 1 <sup>st</sup> dose)	230 µg
3	AndroGel®	5 mg	50 µg
4	Testim®	5 mg	50 µg
5	Tostran®	10 mg	200 µg

<sup>†</sup> Density of AXIRON™ = 0.8193 g/mL<sup>5</sup>

**Reviewer’s Comment:** *It should be noted that there were no justification regarding the basis of dose of each product applied per cm<sup>2</sup> submitted. The Sponsor told the Division that Axiron™ has a dosing area of 261-522 cm<sup>2</sup> while AndroGel® or Testim has 600-1,000 cm<sup>2</sup>. Reference is made to the minutes of the pre-NDA meeting held between the Division and the Sponsor on August 31, 2009.*

The weight of the dosed product expressed as a percentage of the initial weight, for the 5 treatments over a 10 min period, are presented in Figure A-1-15 below.

**Figure A-1-15:** Drying profiles of various T products over 10 min (Mean weight ± SD) as a percentage of the initial weight, n = 3 per treatment).



Axiron™ was dry within 2 min of application for both treatments (single and repeat dose). The weight of the dried residual was ~14% of the initial dose after a single dose and ~25% after two doses of 5.74 µL. Testim® was dry in approximately 4-5 min after application. The residual weight was 26% of the initial dose. AndroGel®

was dry at 10 min after application. The residual weight was 8% of the initial dose. Tostran<sup>®</sup> was not dry after 10 min. The residual weight at 10 min was 62% of the initial dose.

### Safety Results

In Studies MTE08 and MTE09, AEs following Axiron<sup>™</sup> were consistent with the known common effects of transdermal T therapy, and few subjects discontinued treatment due to drug-related AEs. Within the range of doses studied in these studies, there were no dose-related safety concerns.

In Study MTE08, 20 subjects were withdrawn from treatment meaning 135 subjects completed the study. The reasons for discontinuations are shown in Table A-1-10.

**Table A-1-10:** Subject Disposition in Study MTE08

Reason for withdrawal	Number of subjects (n=20)
Withdrew consent	9
Non-compliance of study drug	3
Lost to follow-up	2
Non-compliance with site directives	1
Sponsor request	1
Screening testosterone levels >300 ng/dL	1
AE: Superficial Thrombophlebitis	1
AE: Melanoma	1
AE: Angry, emotional changes	1

In Study MTE09, of the 20 withdrawals, 2 were due to AEs. 1 subject withdrew due to AEs of red skin torso, dry skin torso, very slight erythema bilateral axilla. The AEs of red skin torso and dry skin torso were considered not related to study drug, while the AE of very slight erythema bilateral axilla was considered to be possibly related to study drug. Another subject withdrew due to an AE of application site irritation (burning sensation bilateral axilla), which was considered to be possibly related to study drug. The majority of study withdrawals were related to the eligibility criteria for the study (n=15).

**Table A-1-11:** Subject Disposition in Study MTE09

Reason for withdrawal	Number of subjects (n=20)
Day 120 C <sub>max</sub> (0-24h) Total Testosterone <300 ng/dL*	8
Withdrew consent	2
HCT>54%*	3
Day 120 C <sub>max</sub> (0-24h) Total Testosterone >1050ng/dL*	1
Lost to follow-up	1
HbA <sub>1c</sub> >10%*	1
Elevated HCT, HGB, RBC*	1
Elevated PSA*	1
AE: Red skin torso, dry skin torso, very slight erythema bilateral axilla	1
AE: Application site irritation (burning sensation bilateral axilla)	1

\*Eligibility criteria for the MTE09 study.

A total of 3 SAEs were reported, 1 in MTE08 and 2 in MTE09. Of the 3 subjects who experienced SAEs, one was on a 120 mg maintenance dose and the remaining 2 were on a 60 mg maintenance dose. None of the SAEs were considered to be treatment related by the Investigator. There were no deaths reported in the MTE08 or MTE09 studies.

**Application Site Reactions:** In Study MTE09, there was no change in the overall Draize score over time (from baseline to 180 days of treatment) or in relation to the dose given. Erythema and edema at the application site was evaluated using a categorical scale (i.e., Draize score) with definitions of erythema and edema, respectively, as:

- 0 = no erythema; no edema,
- 1 = very slight erythema (barely perceptible); very slight edema (barely perceptible),
- 2 = well defined erythema; slight edema (edges well defined with definitive raising),
- 3 = moderate to severe erythema; moderate edema (area raised approximately 1 mm),
- 4 = severe erythema (deep/dark red erythema) to slight eschar formation (injuries in depth); severe erythema (raised more than 1mm and extending beyond area of exposure)

There was a possible total score of 8. During the studies, the site of application was evaluated at every study visit. The majority of subjects did not register a Draize score of greater than 0 at any time point. Table A-1-12 summarizes the registered Draize Scores (only when registered).

**Table A-1-12:** Summary of Registered Draize Scores during Study MTE08 and MTE09

Days	Draize Score	Number of Subjects
15	2	1
	3	3
45	1	4
	3	1
120	1	1
180	2	1

In conclusion, the overall mean change in Draize score from Day 1 to end of the 180 days of treatment was  $0.1 \pm 0.55$  which was not significant. In summary, Studies MTE08 and MTE09 demonstrated an acceptable safety and tolerability profile for the administration of Axiron™ for up to 180 days in hypogonadal men.

**Reviewer’s Comment:** *There was no evidence showing the Draize score change was related to time or dose of study drug. Per Clinical reviewer, Dr. Don McNellis, Draize score is used commonly in the Division of Dermatology and Dental products.*

**CONCLUSION**

In conclusion, Axiron™ has successfully met the primary efficacy endpoint of maintaining the total T concentration in the range of 300-1,050 ng/dL at Day 120 of treatment in hypogonadal men. While the third secondary endpoint (i.e., having no patients with total T  $C_{max} > 2,500$  ng/dL) was not met and the cause of the spikes of T concentration is unknown, at least there was no consistent trend of  $C_{max}$  spikes observed. While Subject 21139 was associated with a pattern of apparently sustained exposure, this apparent increase in T was not accompanied by parallel increase in DHT. Studies MTE08 and MTE09 showed an acceptable safety and tolerability profile for the administration of Axiron™ for up to 180 days in hypogonadal men.

## A.1.2. Study MTE07

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### A Phase 2, Randomised, Four-way Cross-over Study to Compare the Steady-state Pharmacokinetics of Testosterone following Application of Different Testosterone Metered Dose lotion<sup>®</sup> Formulations and Doses in Hypogonadal Men.

**Protocol No:** MTE07  
**Phase:** 2  
**Principal Investigator:** Dr. Christina Wang  
**Clinical Study Center:** Multi-center study (4 centers in US)  
**Clinical Study Dates:** October 15, 2007 - January 14, 2008  
**Analytical Study Facility:** (b) (4)

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#### OBJECTIVE

- **Primary:** To determine and compare the steady-state PK of different doses and formulations of Axiron<sup>™</sup>.
- **Secondary:** To assess the safety and tolerability of Axiron<sup>™</sup> after multiple doses.

#### STUDY DESIGN

The study was a multi-centre, multiple-dose, open label, randomized, four-way cross over study of Axiron<sup>™</sup> applied to the axilla of hypogonadal men. The study was designed to determine and compare the PK of 4 different doses/formulations of Axiron<sup>™</sup> applied transdermally to the axilla. All study participants were dosed with each of the 4 study treatments. The comparison was between pooled data obtained from each study participant.

Prospective study participants attended the study centre for an initial screening visit within 30 days of commencement of the study. Assessment of baseline levels of T occurred within 10 days of ceasing buccal, oral or transdermal therapies and within 30 days for study participants on intramuscular therapies. Two blood samples (taken at least 30 min apart) for T measurement were drawn between 07:00 and 10:00 am. Study participants with T levels  $\leq 300$  ng/dL were randomized into the study. Study participants with T levels  $> 300$  ng/dL were considered screen failures.

Eligible study participants were randomized prior to Day 1 to a sequence of 4 study treatments. Each treatment period was 7 days long. There was no washout period between each treatment period considering that the steady-state of T is reached within 7 days of application based on the Sponsor's prior experience with the drug.

Study participants were trained on how to apply the study drug, were provided with dose application instructions and a daily dosing chart. The first dose of study treatment was applied in the morning (nominally 8:00 am) at the study centre with the assistance and supervision of study staff. Then, study participants were dosed daily with one of the treatments for 7 days in each of 4 treatment periods. The 2% T study drug used was the to-be-marketed (TBM) formulation and was supplied in a bottle fitted with a metered dose pump. Once dispensed, the study drug was applied by a specifically designed applicator that was supplied with the bottle.

- Treatment A: 30 mg (2 pump actuations) of 1% T lotion applied daily for 7 days to both axilla (15 mg to each axilla) - Batch Number: BN0433
- Treatment B: 30 mg (1 pump actuation) of Axiron<sup>™</sup> (2% T) applied daily for 7 days to 1 axilla - Batch Number: BN0450
- Treatment C: 60 mg (2 pump actuations) of Axiron<sup>™</sup> (2% T) applied daily for 7 days to both axilla (30 mg) to each axilla - Batch Number: BN0450
- Treatment D: 90 mg (3 pump actuations) of Axiron<sup>™</sup> (2% T) applied daily for 7 days (2 x 30 mg to one axilla and 1 x 30 mg to the other axilla) - Batch Number: BN0450

On the morning of Days 7, 14, 21, and 28, study participants were admitted for an overnight stay at the study centre for a 24 hr period of intensive blood sampling. Multiple dose PK parameters of the different treatments were assessed on Days 7, 14, 21, and 28. All study participants attended a follow up visit 7-10 days following the last dose of study drug. Table A-2-1 summarizes the study schedule of hormone testing for PK assessment.

Table A-2-1: Schedule of PK Assessment

	Screening Visit (Up to 30 Days)	Day 1 Day 8 Day 15 Day 22	Day 7 Day 14 Day 21 Day 28	Follow-Up Visit Days 35-38
Report to study centre			X	X
Confinement at study centre			X	
Testosterone	X	X (0/24 hours)*	X (0, 2, 4, 8, 12, 16, 20 hours)	X
DHT		X (0/24 hours)*	X (0, 2, 4, 8, 12, 16, 20 hours)	X
SHBG		X (0/24 hours)*	X (0 hour)	X

\* Days 8, 15 and 22 were 24 hour post-dose samples

\* 2 blood samples were taken at least 30 min apart at the screening visit and as the pre-dose blood samples on Day 1

The safety of each treatment cohort was assessed in all study participants by evaluating the following safety data: AEs, SAEs, ECG, vital signs, application site reactions (Draize score), and clinical laboratory parameters (biochemistry and hematology).

The study population consisted of hypogonadal adult males aged 20-71 yr (mean: 47.3, SD: 12.3) with a BMI < 35 kg/m<sup>2</sup>. This study enrolled 21 hypogonadal male study participants. 4 study participants were African-American and 17 were Caucasian. The baseline T concentrations of study participants ranged from 48.08-295.78 ng/dL (mean 193.20 ng/dL, SD 73.90).

The data from all 21 study participants were analyzed for safety and the data from 18 study participants were analyzed for PK parameters.

### INCLUSION CRITERIA

Study participants who met all of the following criteria were eligible for entry into the study:

1. Male study participants between the ages of 18 and 70 yr with a prior documented definitive diagnosis of hypoandrogenism as evidenced by previously documented:
  - Hypothalamic, pituitary or testicular disorder
  - Serum T of ≤ 300 ng/dL.
2. Were receiving, or in the Investigator's opinion were eligible to receive treatment (buccal, oral, transdermal, or IM androgen replacement) for hypoandrogenism in accordance with the manufacturers licensed information
3. BMI < 35 kg/m<sup>2</sup>.
4. Passed the required laboratory and physical screening tests.
5. Hemoglobin levels at screening ≥ 13.0 g/dL.
6. Adequate venous access on left or right arm to allow collection of a number of samples by venipuncture.
7. Able to communicate with the study staff, understand the Study Information Sheet and sign the Written Informed Consent Forms; willing to follow the Protocol requirements and comply with Protocol restrictions and study procedures.

### EXCLUSION CRITERIA

Study participants who met any of the following criteria were not eligible for participation in this study:

1. Any significant history of allergy and/or sensitivity to the drug products or their excipients, including any history of sensitivity to T and/or sunscreens.
2. Any clinically significant chronic illness or finding on screening physical exam and/or laboratory testing that made it undesirable for the Investigator to enroll the study participant in the study and/or that in the Investigator's opinion, interfered with the study objectives.

3. Chronic skin disorder (e.g., eczema, psoriasis) likely to interfere with transdermal drug absorption.
4. Men with suspected reversible hypoandrogenism (i.e., due to medications, stress).
5. Any man in whom T therapy is contraindicated, which included those with:
  - Known or suspected carcinoma (or history of carcinoma) of the prostate or symptoms of benign prostatic hyperplasia and/or symptoms of lower urinary obstruction,
  - Known or suspected carcinoma (or history of carcinoma) of the breast,
  - Severe liver damage i.e., cirrhosis, hepatitis or liver tumors,
  - Active deep vein thrombosis, thromboembolic disorders or a documented history of these conditions,
  - Significant cerebrovascular or coronary artery disease,
  - Known or suspected sleep apnea,
  - Hematocrit > 51%.
6. Men with clinically significant prostate exam or clinically significant elevated serum PSA level, or age adjusted reference range of PSA values.
7. Current history of drug or alcohol abuse (more than 4 standard drinks per day and/or abnormal liver function tests 3 times the upper limit of the normal range values).
8. Men taking concomitant medications (prescribed, OTC or complementary) that affect SHBG or T concentrations or metabolism, or that were CYP inducers or inhibitors, anti-coagulants (e.g., warfarin), or diabetic medications (e.g., insulin), anti-histamines.
9. Men involved in sport in which there was screening for anabolic steroids.
10. Men with uncontrolled diabetes (HbA1c  $\geq$  10%).
11. Men taking any investigational product, or who had received an investigational product within 28 days prior to screening or 5 half-lives (whichever was the longer).
12. Any contraindication to blood sampling.
13. Study participants who planned to have a surgical procedure during the course of the study.
14. Study participants with a partner of child bearing potential who was not willing to use adequate contraception (e.g., condoms) for the duration of the study.
15. Study participants whose partners were pregnant.

## **STUDY RESTRICTIONS**

### **Dietary**

Study participants were asked to refrain from the consumption of grapefruit juice for the entirety of the study duration.

### **Concomitant Medication**

The following (prescribed, OTC or complementary) concomitant medications prevented a study participant from being entered into this study:

- antihistamines could not be used for the duration of the study
- medications that affect SHBG, prolactin, or T metabolism
- medications known to be inducers of CYP, for example: barbiturates, carbamazepine, glucocorticoids at supraphysiological doses, modafinil, phenobarbital, or phenytoin
- medications known to be inhibitors of CYP, for example: oral azole antifungal agents, protease inhibitors, or cimetidine.

All concomitant medications taken from the time of consent and those used during the study were recorded in the CRF.

### **Washing**

Study participants were instructed to refrain from washing the application site(s) for at least 8 hr after each dose of study drug.

### **Physical Contact**

Direct skin to skin contact was not to be made with the site of application to prevent transfer to other people, e.g., women and children, unless the application site had first been washed thoroughly with soap (no less than 8 hr after dosing). Loose clothing that covered the application area/s was worn to prevent transfer of T to other people. Clothing worn during the study was washed as per normal fabric care instructions. Study participants with partners of child bearing potential used adequate contraceptive precautions (e.g., condoms) for the duration of the study.

### Use of Anti-perspirant, Deodorant, and Body Lotions

Study participants were asked to refrain from using deodorants and anti-perspirants during the treatment periods. If the study participant was distressed with symptoms of sweating they could apply deodorant to the axilla(s) once the study drug had dried (i.e., defined drying time as 3 min for this study). If study participants did apply deodorant to the axilla(s), this was recorded in the Daily Dosing Chart. Study participants were instructed not to apply any sunscreen containing octisalate or body lotions to the application site(s) during the treatment periods.

## DATA ANALYSIS

### PK Analysis

The PK analysis involved calculation of median, mean, SD, and CV of serum concentrations of T and DHT summarized by treatment and time point. Free T concentrations at each time point was calculated by using the Vermeulen equation:

$$Free\ Testosterone = T * \left( \frac{1}{1 + k_{SHBG} * [SHBG] + n * k_{Alb} * [Alb]} \right)$$

where:

- T is the measured total testosterone concentration
- $k_{SHBG}$  (the association constant for binding to SHBG) is  $0.6 \times 10^9 \text{ M}^{-1}$  and
- $n \cdot k_{Alb}$  (the product of the number of binding sites per molecule and the association constant for albumin) is  $4 \times 10^4 \text{ M}^{-1}$ . The calculation assumes an albumin (Alb) concentration of 43 g/L ( $6.2 \times 10^{-4} \text{ mol/L}$ ).

The following PK parameters were determined from serum T and DHT, and for calculated free T: AUC,  $C_{max}$ ,  $C_{min}$ ,  $T_{max}$ ,  $C_{avg}$ , and DF.

In addition, The following PK parameters were assessed:

- Proportion of study participants with total T  $C_{avg}$  in the normal range for each dose of Axiron™ on Days 7, 14, 21, and 28
- Steady-state total T PK parameters measured on Day 7, 14, 21, and 28
- Proportion of study participants with  $C_{min}$  in the normal range for each dose of Axiron™ on Days 7, 14, 21, and 28
- Proportion of study participants with  $C_{max}$ :  $> 1500 \text{ ng/dL}$ ,  $> 1500 \text{ ng/dL}$  and  $< 1800 \text{ ng/dL}$ ,  $> 1800 \text{ ng/dL}$  and  $< 2500 \text{ ng/dL}$ ,  $> 2500 \text{ ng/dL}$  on Days 7, 14, 21, and 28
- DHT PK parameters
- DHT:T ratio ( $C_{avg}$ )
- Free T PK parameters (calculated using SHBG collected at 0 and 24 hr)
- Assessments of steady-state.

### Statistical Analysis

The study examined the hypothesis that the steady-state PK for the 1% T formulation was statistically different to the Axiron™ (2% T formulation) in a hypogonadal population. Descriptive statistics, including mean, SD and CV were calculated for serum concentrations of T and DHT at each time point for PK parameters.

AUC(0-24) and  $C_{max}$  were analyzed using Analysis of Variance of Log-transformed data. A non-parametric method was used to analyze  $T_{max}$  data. Analysis of linearity of dosing was performed (e.g., ANOVA of log transformed dose normalized AUC data).

### **Bioanalytical Methods**

A LC-MS/MS bioanalytical method was employed for the determination of T and DHT in human serum. Calibration curves for both analytes were prepared in PBS. Liquid-liquid extraction (LLE) was employed for sample preparation. Following evaporation under (b) (4) the residue was reconstituted for sample analysis. The dynamic range for T and DHT was 20-5,000 ng/dL and 5-1,250 ng/dL, respectively. Calibration curves were generated using a weighted ( $1/x^2$ ) linear least-squares regression.

The study period from sample collection to sample analysis was 93 days. Stability of QC samples after storage in a freezer set to maintain -10 to -30 °C for 463 days was established. Stability of PBS QC samples after storage in a freezer set to maintain -10 and -30 °C for 195 days was established.

## **RESULTS**

### **Protocol Deviations**

3 study participants had a protocol deviation related to blood sampling:

- Study participant 0109: The CRF recorded that 2 blood samples were taken at screening for determination of baseline total T, however only 1 sample was received by the laboratory. The T level for this sample was 68 ng/dL. This study participant was deemed to have met the entry criterion for the study of a screening average testosterone level  $\leq 300$  ng/dL, and the Sponsor authorized randomization of the study participant.
- Study participant 0303: Samples not obtained due to an AE during Treatment B (Period 4) at 12 and 16 hr post-dose.
- Study participant 0304: Sample not obtained due to staff error during Treatment B (Period 1) at 24 hr post-dose.

3 study participants had deviations from the protocol with regard to treatments administered:

- Study participant 0903: The planned randomization schedule was for this study participant to be dosed in sequence order CDAB. However, on Day 15, this study participant was provided with Treatment B for self-administration in Period 3, and so the randomization for this study participant was changed to sequence order CDBA.
- Study participant 0304: The study participant was dosed incorrectly during Period 1. He was randomized to Treatment B, but was incorrectly instructed to apply 1 pump to each axilla instead of 1 pump to 1 axilla. PK samples were obtained as scheduled on Days 7 and 8. The study participant continued with the original randomization sequence, and received Treatment C in Period 2.
- Study participant 0906: In Period 1, the study participant incorrectly dosed on Days 2 to 6, applying 2 pumps to each axilla, with a total of 4 pumps instead of 2 for Treatment A. The error was not discovered until Day 7, when the study participant attempted to continue dosing after a pump had been applied to each axilla while observed by site staff.

4 study participants did not comply with restrictions on the use of deodorant/anti-perspirant throughout the study period. 2 study participants did not comply with restrictions on washing/bathing for 8 hr after dose application throughout the study period, however all study participants refrained from washing/bathing for at least 6 hr after dose application.

### **PK Results**

The PK parameters were characterized in all study participants who completed the study without any significant protocol violations or deviations. 3 study participants were omitted from the Per Protocol analysis set. These 3 study participants had deviations from the protocol with regard to treatments administered (Study participants

0304, 0903, and 0906). All study participants were included in the PK evaluable analysis set, with the following notations:

- Study participant 0304: Not included in any analyses dependent on the T or DHT concentration at 24 hr, such as AUC(0-24),  $C_{avg}$ , and comparison of the pre-dose with 24 hr post-dose, since a 24 hr blood sample was not collected (in Treatment B [Period 1]).
- Study participant 0303: Missing values were at intermediate sampling times, and all parameters were estimable from the available concentrations (Treatment B [Period 4]).

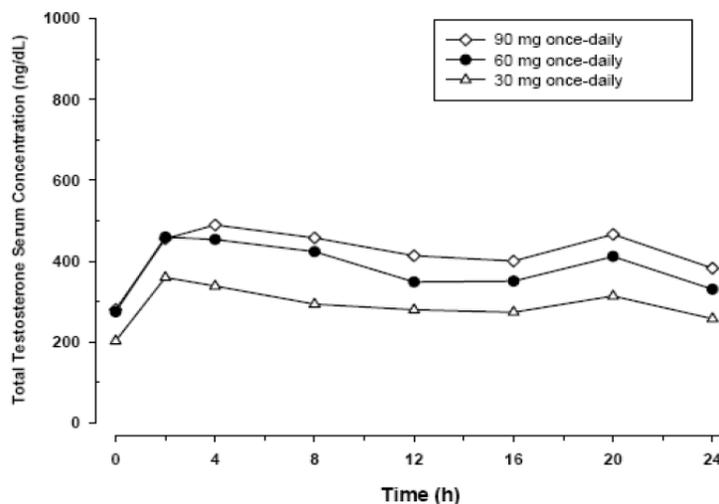
The PK of the different treatment cohorts were determined by measuring total T and DHT concentrations in serum, and calculating free T. The PK parameters of total T for each treatment are as follows (Table A-2-2):

**Table A-2-2:** Arithmetic Mean (SD) PK Parameters of Total T by Treatment (Per Protocol analysis; N=18)

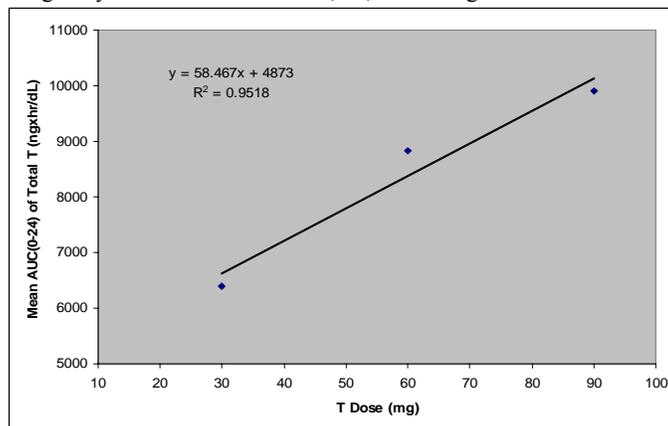
Treatment	$C_{ave}$ (ng/dL)	AUC(0-24) (ng·hr/dL)	$C_{max}$ (ng/dL)	$C_{min}$ (ng/dL)	$T_{max}^a$ (hr)
A: 30 mg 1% T	325 (75)	7809 (1786)	537 (261)	166 (63)	11.95 (1.93, 24)
B: 30 mg Axiron™	267 (100)	6399 (2405)	395 (216)	161 (50)	16.00 (1.95, 23.93)
C: 60 mg Axiron™	368 (131)	8837 (3131)	547 (242)	214 (99)	4.13 (0, 20)
D: 90 mg Axiron™	413 (173)	9907 (4145)	588 (223)	239 (123)	12.01 (1.92, 23.97)

<sup>a</sup> Median (min, max)

**Figure A-2-1:** Arithmetic mean total T serum concentrations following 7 days of once-daily administration of 30 mg, 60 mg, and 90 mg Axiron™ (Study MTE07)



**Figure A-2-2:** Dose Linearity Assessment for Mean AUC(0-24) of Total T following daily administration with 30, 60, and 90 mg of the Axiron™ for 7 days



**Reviewer's comment:** As shown in Figure A-2-1, after an initial plateau of serum total T concentration was observed between 2 and 4 hr post-dose, a second plateau that is comparable was observed at approximately 20 hr post-dose. While the cause of having two plateaus is unknown, it should be noted that this trend was observed consistently in the PK profiles of Axiron™ throughout this study. The 60 mg Axiron™ group had 10 individuals with  $T_{max} \leq 4.25$  hr while the 30 mg and 90 mg Axiron™ group had 8 individuals with  $T_{max} \leq 4.25$  hr. Considering that 8-10 individuals are approximately half of the population (N=18) included in the final analysis and the fact that  $T_{max}$  was equal or longer than 16 hr in majority of the remaining individuals in each treatment group may lead to an explanation of the different median  $T_{max}$  values across the treatment groups. As shown in Figures A-2-2, mean AUC(0-24) of total T following daily administration with 30, 60, and 90 mg of Axiron™ for 7 days are not dose proportional but exposure increased with increasing the dose. This would also be the case for  $C_{avg}$  since it is derived by dividing AUC(0-24) by 24.

There were no study participants with  $C_{avg}$  above the normal range ( $> 1,050$  ng/dL) in any dose group of investigational product. The highest average concentration of serum total T for any dose of Axiron™ after daily dosing for 7 days was 722 ng/mL, for study participant 0403 in Treatment D (90 mg). The  $C_{max}$  of serum total T for any dose of Axiron™ after daily dosing for 7 days was 1,289 ng/mL, for study participant 0908 in Treatment C (60 mg). There were no study participants with  $C_{max}$  greater than 1,500 ng/dL in any dose group of the investigational product.

While this study used both 1% and 2% (TBM) T formulations, the utility of this study was providing the multiple-dose total T PK profile of the Axiron™ TBM formulation. Therefore, the PK profile of free T and DHT as well as the DHT:T ratio ( $C_{avg}$ ) were not reviewed. In addition, DSI recommends that the SHBG data from Studies MTE07, MTE08, MTE09, and MTE10 (b) (4) are not acceptable for review and therefore, was not reviewed. Reference is made to the DSI Consult Memorandum that is attached to this review.

## CONCLUSIONS

Hypogonadal male study participants received 7 daily doses of 3 different Axiron™ strengths (i.e., 30, 60, and 90 mg) as well as 30 mg doses of a 1% T formulation. Multiple dose PK and safety of different treatment cohorts were characterized. A dose dependent absorption was observed among the 3 different Axiron™ strengths administered.

### A.1.3. Study MTE10

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#### **A Phase I Study to Determine the Impact of Application of Antiperspirant and Deodorant as well as Washing the Application site, on the Pharmacokinetics of Testosterone following Single Dose Applications of 2% Testosterone MD-Lotion® (cutaneous solution).**

**Protocol No:** MTE10  
**Phase:** 1  
**Principal Investigator:** Dr Joanne Marjason  
**Clinical Study Center:** Q-Pharm, Herston, Australia  
**Clinical Study Dates:** January 21, 2009 - March 27, 2009  
**Analytical Study Facility:** (b) (4)

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#### **OBJECTIVE**

##### Primary:

- To evaluate the impact of application of antiperspirant and deodorant on absorption of T, when applied prior to application of Axiron™.
- To evaluate the impact of washing the application site on the absorption of T, when washed following application of Axiron™.

##### Secondary:

- To assess the safety and tolerability of Axiron™ following single dose application.

#### **STUDY DESIGN, TREATMENT, AND SUBJECTS**

This study was a single dose, parallel group study in healthy female subjects. Subjects were randomized into 1 of the following 6 treatment groups:

- Group 1: Antiperspirant/deodorant stick applied 2 min prior to Axiron™ application
- Group 2: Antiperspirant/deodorant spray applied 2 min prior to Axiron™ application
- Group 3: Deodorant spray applied 2 min prior to Axiron™ application
- Group 4: Control group - Axiron™ only.
- Group 5: Application site washed 2 hr after Axiron™ application using a Dove® soap bar
- Group 6: Application site washed 6 hr after Axiron™ application using a Dove® soap bar

Each treatment group underwent intensive blood sampling for a period of 72 hr for PK analysis. Subjects were admitted to the study centre where they remained until the completion of the 36 hr period of intensive blood sampling. All dosed subjects returned for a follow-up visit 7 to 10 days following dose administration.

The study was designed to determine the impact of application of antiperspirant and deodorant as well as washing the application site, on the PK of T following single dose application of Axiron™ (i.e., 2% T solution).

#### **TREATMENT PRODUCTS AND FORMULATION**

A single application of 30 mg (1 pump actuation) was applied topically to 1 axilla of each subject by the site staff, using an applicator. The batch number of Axiron™ was BN0492 (expiry: February 2010).

- Group 1 applied Speed Stick Anti-Perspirant Deodorant Solid Unscented (3 Ounces, Colgate-Palmolive Co, product code: 031525): 2 min prior to Axiron™ application
- Group 2 applied Right Guard Sport Anti-Perspirant Deodorant Spray Unscented (6 ounces, Gillette, Product code: 678369): 2 min prior to Axiron™ application
- Group 3 applied Right Guard Sport Deodorant Spray Original (10 Ounces, Gillette, Product Code: 852113): 2 min prior to Axiron™ application.

#### **STUDY POPULATION AND STUDY RESTRICTIONS**

### **Inclusion Criteria**

1. Healthy premenopausal female subjects  $\geq 18$  and  $\leq 45$  years of age,
2. BMI 19-30 kg/m<sup>2</sup>,
3. Willing to refrain from consumption of products containing grapefruit (an inducer of cytochrome P450 [CYP] 3A), for 14 days preceding study and throughout the course of the study,
4. Willing to use a medically acceptable method of contraception for 14 days preceding study and throughout the course of the study. Medically acceptable methods of contraception included; abstinence, diaphragm with vaginal spermicide, Intrauterine Device, condom with vaginal spermicide, surgical sterilization, or vasectomy (> 6 months),
5. Was willing to stop shaving, waxing, or using depilatory products on the hair on their axillas for 1 week prior to dosing and for the treatment period (i.e. 72 hr).

### **Exclusion Criteria**

1. Any woman in whom T therapy was contraindicated, which included those with a history or the presence of:
  - Known or suspected carcinoma (or history of carcinoma) of the breast, or a first degree relative with a history of breast cancer under the age of 50 yr,
  - Severe liver damage (i.e. cirrhosis, hepatitis, or liver tumors)
  - Active deep vein thrombosis, thromboembolic disorders, or a documented history of these conditions,
  - Cerebrovascular or coronary artery disease
  - Known or suspected sleep apnea,
  - Hematocrit > 0.51 L/L,
  - Confirmed or suspected androgen-dependent neoplasia,
2. Had a history of drug or alcohol abuse (i.e., > 2 standard drinks per day) and/or abnormal liver function tests considered clinically significant
3. Women who were taking concomitant medications (prescribed, OTC or complementary) that would affect SHBG, prolactin, or T metabolism, or that was known to be CYP inducers or inhibitors, Cyclosporin, anti-coagulants (e.g., warfarin), or diabetic medications (e.g., insulin) or anti-histamines within 14 days of dosing,
4. Women who were taking any Investigational Product, or had received an investigational product within 28 days prior to screening or 5 half-lives (whichever was the longer),
5. Heavy smokers (>10 cigarettes per day) who were unable to refrain from smoking during the confinement periods in the study,
6. Had difficulty refraining from more than 3 beverages (per day) that contained caffeine and/or other xanthines for the duration of the treatment period (i.e., 72 hr post dose),
7. Had used androgen therapy within 30 days of dosing (e.g., T implant, oral T or tibolone, oral dehydroepiandrosterone, T cream or troches),
8. Women on hormonal contraceptive.

### **Subject Disposition**

36 of the screened subjects met the inclusion and exclusion criteria, and were enrolled into the study. A total of 32 (88.9%) subjects were Caucasian with the following exceptions: 1 (16.7%) subject in Group 1 (antiperspirant/deodorant stick) was Indian, 1 (16.7%) subject in Group 2 (antiperspirant/deodorant spray) was Latino, 1 (16.7%) subject in Group 3 (deodorant spray) was Latino, and 1 (16.7%) subject in Group 4 (control) was Asian.

### **Concomitant Therapy**

The following (prescribed, OTC, or complementary) concomitant medications prevented a subject from being entered into this study:

- Those medications that would affect SHBG, prolactin or T metabolism

- Warfarin
- Insulin therapy
- Cyclosporine therapy
- Opiates
- GnRH analogues
- Oxyphenbutazone
- Propanolol
- Corticosteroids (except for physiological replacement doses)
- 5 alpha reductase inhibitors
- Estradiol
- Antihistamines

### **Dietary**

Subjects refrained from consumption of grapefruit products for 14 days prior to the study and throughout the duration of the study, until the follow-up visit. Subjects refrained from having more than 3 beverages (per day) that contained caffeine and/or other xanthines for the duration of the treatment period (i.e., 72 hr post-dose). Subjects did not consume alcohol for the duration of the confinement period, and were limited to two standard drinks per day during the study.

### **Smoking:**

Smoking or the use of nicotine products was not permitted while confined at the study centre.

### **Washing Application Site(s):**

Subjects were unable to wash the application sites for at least 36 hr following application of Axiron™. Subjects allocated to Groups 5 and 6 underwent a washing procedure, performed by the site staff.

### **Physical Contact:**

Direct skin to skin contact was not made with the site of application to prevent transfer to other people (e.g., partners and children). Loose clothing that covered the application area was worn to prevent transfer of T to other people. Clothing worn during the study was washed as per normal fabric care instructions.

### **Use of Antiperspirant, Deodorant, Sunscreen, and Body Lotions:**

Subjects refrained from using antiperspirant and deodorants until the completion of the treatment period (i.e., 72 hr). Subjects randomized to Groups 1, 2, and 3 had deodorant/antiperspirant or deodorant applied by the site staff. In addition, Subjects did not apply any sunscreen containing octisalate or body lotions to the application site(s) during the study.

### **Shaving/Waxing/Depilatory Products:**

From 1 week prior to dosing and for the duration of the treatment period (i.e., 72 hr post-dose), subjects refrained from shaving, waxing, or using depilatory products on the hair on their axillas.

### **Perfume Usage:**

Subjects could apply perfume during the study period; however they were instructed not to apply perfume to the axilla or to the blood sampling area.

### **Spray Tan Usage:**

Use of any self tanning lotions or sprays was not allowed for the duration of the treatment period.

## **PROCEDURES**

### **Antiperspirant and Deodorant Application**

#### *Antiperspirant stick application directions*

The site staff carried out the application while wearing gloves. New gloves were worn for each subject. The procedure was as consistent between subjects as possible. Ideally, the same staff member performed specific procedures for every subject. Instructions to the site staff were:

1. Put on gloves and wear gloves during the application process.
2. Apply the antiperspirant stick to the skin using **two** strokes. A single stroke constituted wiping the antiperspirant stick in a downward or upward motion along the axilla.
3. Take off and dispose of gloves.
4. Do not allow the subject to cover the axilla with clothing between application of the antiperspirant and Axiron™.
5. According to the randomization schedule, the site staff applied the Axiron™ to the axilla at the specified time.
6. Allow the area to dry before covering with loose clothing.

#### ***Antiperspirant and Deodorant Spray application directions***

The site staff carried out the application while wearing gloves. New gloves were worn for each subject. The procedure was as consistent between subjects as possible. Ideally, the same staff member performed specific procedures for every subject. Instructions to the site staff were:

1. Put on gloves and wear gloves during the application process.
2. Hold can **6 inches** (15 cm) from axilla, point arrow, press down nozzle and spray for **two** consecutive seconds.
3. Take off and dispose of gloves.
4. Do not allow the subject to cover the axilla with clothing between application of antiperspirant or deodorant spray and Axiron™.
5. According to the randomization schedule, the site staff applied the Axiron™ to the axilla at the specified time.
6. Allow the area to dry before covering with loose clothing.

#### **Washing the Application Site**

The washing procedure was performed by the site staff. At the nominal time the site staff washed the application site on the subjects. Washing was consistent between subjects. Ideally, the same staff member performed specific procedures for every subject. Dove soap bar was used for washing. Instructions to the site staff were:

1. Put on gloves and wear gloves during the washing process
2. Evenly rinse the application site with warm water
3. Gently rub the application site twice with the soap solution
4. Rinse the application site with warm water
5. Dry the application site gently with a fresh towel

**Reviewer's Comment:** *The total duration of the washing process was not reported.*

#### **PK Measurements**

The primary objective for the study were assessment and comparison of PK parameters of T characterized from blood samples taken at 0.5 hr pre-dose, 0, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, and 72 hr post-dose. The dose of Axiron™ was made in the morning (normally at 08:00 am). The pre-dose baseline PK sampling was collected within 30 min prior to Axiron™ application. Free T was calculated using the formula below.

$$\text{Free Testosterone} = T * \left( \frac{1}{1 + k_{SHBG} * [SHBG] + n * k_{Alb} * [Alb]} \right)$$

Where T is the measured total testosterone concentration,  $k_{SHBG}$  (the association constant for binding to SHBG) is  $0.6 \times 10^9 \text{ M}^{-1}$  and  $n * k_{Alb}$  (the product of the number of binding sites per molecule and the association constant for albumin) is  $4 \times 10^4 \text{ M}^{-1}$ . The calculation assumed an albumin (Alb) concentration of 43 g/L ( $6.2 \times 10^{-4} \text{ mol/L}$ ).

Blood samples for PK analysis were collected by venipuncture or cannula/butterfly needle or equivalent.

### Bioanalytical Method

A LC-MS/MS method was employed for the determination of T and DHT in human serum. Calibration curves for both analytes were prepared in PBS. LLE was employed for sample preparation. Following evaporation under (b) (4), the residue was reconstituted for sample analysis. The dynamic range for T and DHT was 20-5,000 ng/dL and 5-1,250 ng/dL, respectively. Calibration curves were generated using a weighted (1/x<sup>2</sup>) linear least-squares regression.

The study period from sample collection to sample analysis was 93 days. Stability of QC samples after storage in a freezer set to maintain -10 to -30 °C for 463 days was established. Stability of PBS QC samples after storage in a freezer set to maintain -10 and -30 °C for 735 days was established.

### CRITERIA FOR EVALUATION

#### PK Parameters

The study aimed to determine and compare the single dose PK of T, when Axiron™ was applied in conjunction with antiperspirant/deodorant, and when the application site was washed 2 and 6 hr post-dose administration.

#### Statistical Methods

Single dose T PK parameters (AUC(0-72), C<sub>max</sub>, C<sub>min</sub>, and T<sub>max</sub>) were calculated. Single dose free T PK parameters (AUC(0-72), C<sub>max</sub>, C<sub>min</sub>, and T<sub>max</sub>) were calculated using SHBG levels collected daily. Single dose DHT PK parameters (AUC(0-72), C<sub>max</sub>, C<sub>min</sub>, and T<sub>max</sub>) were calculated. Mean, SD, and CV were calculated for serum concentrations of T and DHT at each time point for PK parameters.

For the PK analysis, AUC(0-72), C<sub>max</sub>, and T<sub>max</sub> were determined for total T, baseline corrected T, free T, total DHT, and baseline corrected DHT. AUC(0-72) and C<sub>max</sub> were log-transformed and analyzed using a one-way Analysis of Variance. The assumptions of normality were satisfied for log-transformed AUC(0-72) and C<sub>max</sub>. T<sub>max</sub> was analyzed nonparametrically using a Kruskal-Wallis test.

### PK RESULTS

#### Effect of Antiperspirant/deodorant use on T absorption following Axiron™ application

2 pre-dose baseline PK blood samples were collected, 1 within 30 min prior to Axiron™ administration and 1 right before Axiron™ administration. Individual pre-dose baseline total T concentrations ranged between 20.0 and 38.3 ng/dL and were comparable between each group (i.e., mean T baseline of each group were 27.5, 28.9, 23.3, and 26.2 ng/dL, respectively). Demographic and other baseline characteristics (i.e., age, race, height, weight, BMI, smoking habits, and alcohol consumption) among the treatment groups were comparable and no significant differences were noted.

Mean total T PK parameters obtained from subjects in Groups 1 to 3, with pre-application of antiperspirant/deodorant stick or spray or deodorant spray, were compared to the control group (Group 4).

**Table A-3-1:** Summary of Baseline-uncorrected Mean (SD) Total T PK Parameters

Parameter	Group 1 A/D Stick (N=6)	Group 2 A/D Spray (N=6)	Group 3 D Spray (N=6)	Group 4 Control (N=6)
AUC(0-72) (ng-hr/dL)	9098.0 (2003.4)	8399.8 (1416.5)	7380.1 (2016.2)	10975.6 (3178.1)
C <sub>max</sub> (ng/dL)	260.4 (110.3)	271.0 (73.7)	238.0 (47.9)	341.9 (133.5)

Please note that this Table only shows treatment groups that were used in evaluating the antiperspirant/deodorant effects.

The study results showed that the pre-application of antiperspirants/deodorant products has reduced the total T concentrations (e.g., up to 32.8% AUC(0-72) reduction in Group 3) in all 3 groups compared to the control group (Group 4).

**Reviewer’s Comment:** *It should be noted that response to a certain dose would be different in each individual. Therefore, given that this is a parallel group study, it is unknown whether the AUC(0-72) values observed in this study are confounded by different individual responses to T and/or by the effect from using these antiperspirant/deodorant products. No information on active ingredients of these antiperspirant/deodorant products was submitted and the cause of the AUC(0-72) reduction is unknown.*

Per the Biostatistic reviewer, Dr. Xin Fang, the statistical analysis revealed that the difference of AUC(0-72) between Group 4 (control) vs. Group 3 is statistically significantly different (p-value = 0.011). The following results are obtained using log of AUC(0-72) and log of C<sub>max</sub> through an ANOVA model. The ANOVA model only included fixed effect of group. The Sponsor’s p-value of 0.058 is for overall comparison of AUC(0-72) between 5 treatments and control. Statistical comparison of AUC(0-72) and C<sub>max</sub> between each individual treatment is summarized in Tables A-3-2 and A-3-3 below, respectively:

**Table A-3-2:** Statistical Comparison of AUC(0-72) between Individual Treatment Groups

Treatment	Estimate	Standard Error	DF	t-value	p-vlaue
Group 4 vs. 1	0.1745	0.1373	29	1.27	0.2140
Group 4 vs. 2	0.2443	0.1373	28	1.78	0.0875
Group 4 vs. 3	0.3905	0.1440	29	2.71	0.0112

**Table A-3-3:** Statistical Comparison of C<sub>max</sub> between Individual Treatment Groups

Treatment	Estimate	Standard Error	DF	t-value	p-vlaue
Group 4 vs. 1	0.2799	0.2100	29	1.33	0.1930
Group 4 vs. 2	0.2027	0.2100	29	0.97	0.3424
Group 4 vs. 3	0.3173	0.2203	29	1.44	0.1605

The limitation of this study is that it was conducted in a parallel fashion in premenopausal women. While they are comparable, it was noted that the mean baseline T concentration of Group 3 (23.3 ng/dL) was slightly lower than the control, Group 4 (26.2 ng/dL) while Groups 1 and 2 had a slightly higher mean baseline T concentration (27.5 and 28.9 ng/dL, respectively) compared to Group 4. However, the impact of this on the statistical analysis results is unknown. The Phase 3 studies were conducted with no restrictions of antiperspirant/deodorant use. Only 42 out of 138 subjects have refrained from using these products concomitantly. While it is difficult to estimate the extent of impact of antiperspirant/deodorant application on T absorption when applied prior to Axiron™ application in hypogonadal men, the use of antiperspirant/deodorant products as part of a regular program for personal hygiene should not interfere with the efficacy of Axiron™ in treating male hypogonadism. Therefore, despite the observed influence of antiperspirant/deodorant application on T absorption, restriction of antiperspirant/deodorant application prior to Axiron™ application appears to be unnecessary. If patients use antiperspirant/deodorant products (e.g., stick, roll-on, or spray), then it should be applied at least 2 min prior to the application of Axiron™ to avoid contamination of the stick or roll-on product. This information will be reflected in the product labeling.

Effect of Washing the Application Site on total T Exposure following Axiron™ application

2 pre-dose baseline PK blood samples were collected, 1 within 30 min prior to Axiron™ administration and 1 right before Axiron™ administration. Pre-dose baseline total T concentrations ranged between 18.18 and 38.28 ng/dL and were comparable between each group (i.e., mean T baseline of each group were 26.2, 23.8, and 26.0 ng/dL, respectively). Demographic and other baseline characteristics (i.e., age, race, height, weight, BMI, smoking habits, and alcohol consumption) among the treatment groups were comparable and no significant differences were noted. The washing procedure was performed by the site staff as described above. .

Mean total T PK parameters obtained from subjects in Groups 5 and 6, with application site washed 2 hr or 6 hr after Axiron™ application, respectively, were compared to the control group (Group 4).

**Table A-3-4:** Summary of Baseline-uncorrected Mean PK Parameters

Parameter	Group 4 Control (N=6)	Group 5 Washing 2 hr after application (N=6)	Group 6 Washing 6 hr after application (N=6)
AUC(0-72) (ng·hr/dL)	10975.6 (3178.1)	7097.9 (1392.5)	8108.8 (2041.9)
C <sub>max</sub> (ng/nL)	341.9 (133.5)	220.6 (89.0)	279.7 (115.7)

The study results showed that washing the application site 2 hr or 6 hr using a Dove<sup>®</sup> soap bar after Axiron<sup>™</sup> application reduced the total T concentrations (e.g., up to 35.3% AUC(0-72) reduction in Group 5) compared to the control group (Group 4).

**Reviewer's Comment:** *It is unknown whether the AUC(0-72) values observed in this study are confounded by different individual responses to T and/or by the effect of washing the application site.*

Per the Biostatistic reviewer, Dr. Xin Fang, the statistical analysis showed that the difference of AUC(0-72) between Group 4 (control) vs. Group 5 is statistically significant. The following results were obtained using log of AUC(0-72) and log of C<sub>max</sub> through an ANOVA model. The ANOVA model only included fixed effect of group. The Sponsor's p-value of 0.058 is for overall comparison of AUC(0-72) between 5 treatments and control. Statistical comparison of AUC(0-72) and C<sub>max</sub> between each individual treatment is summarized in Tables A-3-5 and A-3-6 below, respectively:

**Table A-3-5:** Statistical Comparison of AUC(0-72) between Individual Treatment Groups

Group	Estimate	Standard Error	DF	t-value	p-value
Group 4 vs. 5	0.4187	0.1373	29	3.05	0.0049
Group 4 vs. 6	0.2938	0.1373	29	2.14	0.0410

**Table A-3-6:** Statistical Comparison of C<sub>max</sub> between Individual Treatment Groups

Group	Estimate	Standard Error	DF	t-value	p-value
Group 4 vs. 5	0.4438	0.2100	29	2.11	0.0433
Group 4 vs. 6	0.2158	0.2100	29	1.03	0.3127

As mentioned above, the limitation of this study is that it was conducted in a parallel fashion in premenopausal women. In addition, the effect of washing the application site was only evaluated with the lowest proposed dose, 30 mg. It was noted that the mean baseline T concentration of Group 5 (23.8 ng/dL) was lower than the control, Group 4 (26.2 ng/dL) while Group 6 had a comparable mean baseline T concentration of 26.0 ng/dL compared to Group 4. However, the impact of this on the statistical analysis results is unknown. Considering that subjects were instructed to refrain from washing or swimming for 2 hr post-dose in the Phase 3 study (MTE08), efficacy of Axiron<sup>™</sup> should not be interfered as long as the users refrain from showering and washing for at least 2 hr, the efficacy. Axiron<sup>™</sup> users should avoid swimming or washing the application site for 2 hr after Axiron<sup>™</sup> application. However, to reduce the likelihood of interpersonal transfer of T, the application site should always be washed prior to any skin-to-skin contact regardless of the length of time since application. This information will be reflected in the product labeling.

**Reviewer's Comment:** *While PK of free T and DHT were also characterized, these were not reviewed given that the primary objective of the study was to determine the impact of antiperspirant/deodorant product use as well as washing the application site, on the PK of total T following single dose application of Axiron<sup>™</sup>.*

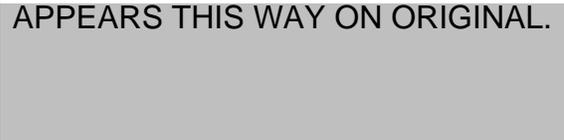
## CONCLUSIONS

The study results demonstrate that the pre-application of antiperspirants/deodorant products as well as washing the application site has reduced the total T concentrations. However, despite the observed influence of antiperspirant/deodorant application on T absorption, restriction of antiperspirant/deodorant application prior to Axiron<sup>™</sup> application appears to be unnecessary. If patients use an antiperspirant/deodorant products (e.g., stick,

roll-on, or spray), then it should be applied at least 2 min prior to the application of Axiron™ to avoid contamination of the stick or roll-on product.

Based on this study, Axiron™ users should avoid swimming or washing the application site for 2 hr after Axiron™ application. However, to reduce the likelihood of interpersonal transfer of T, the application site should always be washed prior to any skin-to-skin contact regardless of the length of time since application.

APPEARS THIS WAY ON ORIGINAL.



#### A.1.4. Study MTE11

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#### A Healthy Volunteer, Single dose, Phase I Study to Determine the Amount of Axiron™ Remaining on the Axilla after Washing.

**Protocol No:** MTE11  
**Phase:** 1  
**Principal Investigator:** Dr. Joanne Marjason  
**Clinical Study Center:** Q-Pharm, Herston, AUSTRALIA  
**Clinical Study Dates:** December 14, 2009 – January 14, 2010  
**Analytical Study Facility:** (b) (4)

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#### OBJECTIVE

- Primary: To evaluate the amount of residual T remaining on the axilla in healthy males who undergo a post Axiron™ dose washing procedure.
- Secondary: To assess the safety and tolerability of Axiron™.

#### STUDY ENDPOINT

- T assessment: The study aimed to determine and compare the T collected from each axilla using the towelettes. The T content of the towelettes used for each axilla was pooled and the mean and median T recovery calculated for the washed and unwashed axilla.
- Safety assessment: The study aimed to determine the safety and tolerability of Axiron™.

#### STUDY DESIGN

After showering on Day 1, all subjects received 120 mg Axiron™ in total (equivalent to a 60 mg dose per axilla). Axiron™ was allowed to dry for 5 min and the left axilla was wiped with alcohol towelettes which were assayed for T content. Subjects were required to shower with soap and water 30 min after application. The right axilla was then wiped with alcohol towelettes which were assayed for T content.

Vital signs, concomitant medications, and AEs were recorded. Subjects remained at the Phase I unit for up to 24 hr post application. The treatment length of this study was 1 day. All dosed subjects returned for a follow-up visit 7-10 days following dose administration.

#### SUBJECTS

The study was conducted in healthy Caucasian male subjects between the ages of  $\geq 18$  and  $\leq 70$  with a mean age  $\pm$  SD of  $23.3 \pm 1.9$  yrs and mean BMI  $\pm$  SD of  $25.1 \pm 3.42$  kg/m<sup>2</sup>. 10 subjects were enrolled and completed the study.

#### DETERMINATION OF SAMPLE SIZE

No formal sample size calculation was performed. Sufficient subject numbers were chosen, to allow for evaluation of major differences between the treatment of the left and right axilla with regards to the residual T content. The left axilla acted as a control for each subject.

#### TREATMENT PRODUCT AND FORMULATION

60 mg of Axiron™ was applied topically to each axilla of each subject by the site staff, using an applicator. The batch number of Axiron™ was BN0492K, expiry October 2010.

#### INCLUSION CRITERIA

Subjects who met all of the following criteria were entered into the study:

1. Healthy male subjects  $\geq 18$  and  $\leq 70$  yr of age,

2. BMI 19-35 kg/m<sup>2</sup>,
3. Agreed not to use any prescribed, OTC or complementary medication during the 7 days preceding Day 1 of the study and throughout the course of the study, unless approved by both the Principal Investigator and the Sponsor,
4. Have not shaved, waxed or used depilatory products on the hair of the axilla for the 3 months prior to the screening period.

### EXCLUSION CRITERIA

Subjects who met any of the following criteria were not eligible for participation in this study:

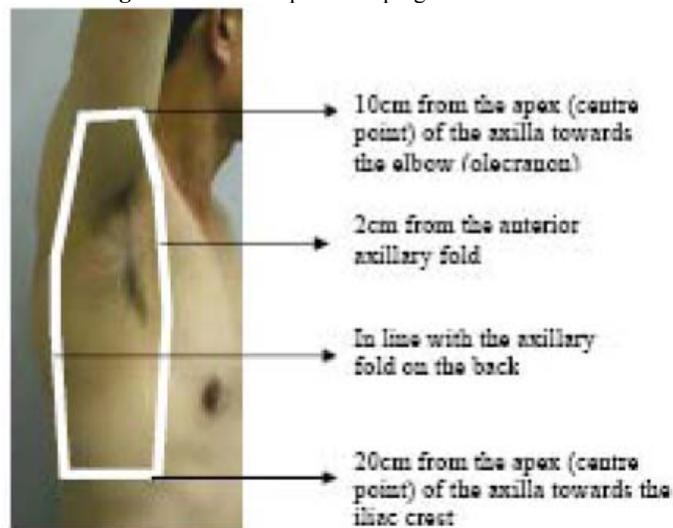
1. Have a chronic skin disorder (e.g., eczema, psoriasis) likely to interfere with transdermal drug absorption,
2. Any subject in whom T therapy is contraindicated,
3. Any subject currently taking any investigational product, or who has received an investigational product within 28 days prior to screening or 5 half-lives of the Investigational Product (whichever is the longer),
4. Men taking concomitant medications (prescribed, over-the-counter or complementary) that would affect SHBG or T concentrations or metabolism, or that are known to be CYP inducers or inhibitors, anti-coagulants (e.g., warfarin), or diabetic medications (e.g., insulin),

### TREATMENT PROCEDURE

Prior to the application of Axiron™ to the axilla: An area was marked on all subjects to define the outer boundary of where the subjects were to be wiped for collection of T (“Wiping Area”). This was done using a suitable marker and a template provided Instructions to the site staff were:

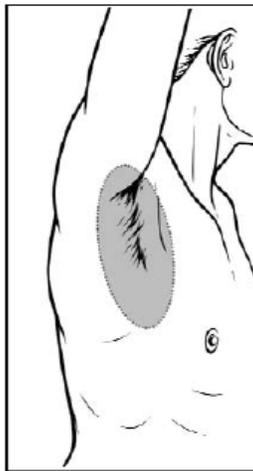
1. Using a suitable marker and the template provided, mark on each subject the upper border of this area 10 cm from the apex (centre point) of the axilla towards the elbow.
2. Mark the lower border by measuring 20 cm from the apex (centre point) of the axilla towards the iliac crest.
3. An anterior vertical boundary marked 2 cm in front of the anterior axillary fold and a posterior vertical boundary taken in line with the posterior axillary fold will complete the area.
4. Ensure that the boundary is marked on each patient’s axilla. Figure A-2-1 below shows the outer boundary of this area.
5. The Wiping Area must be marked in both the subjects’ left and right axilla.

**Figure A-4-1:** Acceptable Wiping Area for Axiron



6. The application area of Axiron™ is shown in Figure A-4-2 below:

**Figure A-4-2:** Acceptable Application Area for Axiron



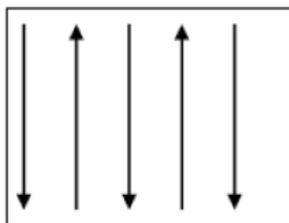
Application of Axiron™ by trained site staff:

1. Gloves were on during the application of Axiron™.
2. 60 mg (2 pump actuation) application was applied to the each axilla.
3. The second application of Axiron™ was done after the skin was dry.
4. Subjects were reminded not to apply any clothing until after showering and final wiping step.

Wiping left axilla: 5 min after the last application of Axiron™, the wiping area around the **left** axilla was wiped with Liv-Wipes®. Liv-Wipes® are towelettes impregnated with 70% isopropyl alcohol and were supplied by the Sponsor. Instructions to the site staff were:

1. Ensure a fresh pair of gloves is applied prior to wiping the axilla.
2. Fold a Liv-Wipe towelette into quarters. Wipe the wiping area with the folded Liv-Wipe towelette using 5 strokes up and down as shown in Figure A-4-3. Fold the Liv-Wipe towelette in half again so it is now an eighth of its original size and wipe the Wiping Area with another 5 strokes. Ensure the entire Wiping area marked by the boundaries as defined in Figure A-4-1 is wiped with the Liv-Wipe towelette.

**Figure A-4-3:** Schematic Diagram of Wiping Technique on Wiping Area



3. Place the Liv-Wipe towelette into a labelled 100 mL glass bottle. Wipe the wiping area using the same procedure an additional 9 times, using a new Liv-Wipe towelette each time and placing each Liv-wipe into a pre-labelled bottle.
4. Remove the gloves (outer side facing out) and place into a 250 mL bottle (for T recovery from the gloves)

Showering: 30 min after the last application of Axiron™, subjects were required to take a shower. The showering procedure (instructions to the site staff) was follows:

1. Turn on warm shower.
2. Subjects are required to stand under the shower and raise their arms for 5 sec to wet skin.
3. Subjects are then to stand away from the flow of water.
4. Subjects will dispense the entire volume of the syringe, containing 3.0 mL of shower gel (Zest® Ocean Energy Body Wash) onto their hand.

5. The subjects will then rub the shower gel over the entire application area of the **right** axilla for 30 sec.
6. Rinse the soap off the skin using a hand to rub water on the skin for 30 sec. Ensure all foam from the soap is removed.
7. Subjects are to repeat steps 5 to 7 washing the wiping area of the **left** axilla.
8. Turn off the shower.
9. Dry the skin (including both axilla areas) with a towel.

Wiping right axilla: The same wiping procedures applied to the left axilla (as described above) were applied in wiping the right axilla.

### **CONCOMITANT MEDICATIONS**

Subjects were prohibited from taking the same concomitant medication as in Study MTE10 (refer to the review of MTE10).

### **Other Study Restrictions**

- Same dietary and smoking restrictions applied to subjects as in Study MTE10.
- Clothing and skin contact: Direct skin to skin contact was not made with the site of application to prevent transfer to other people. From the time the subject had their first shower until the time of the last wipe after the second shower subjects were not be allowed any clothing on their torso. After study procedures were complete (i.e., the second set of wiping had occurred) loose clothing that covered the application area was worn to prevent transfer of T to other people.
- Use of body lotions: Subjects were instructed not to apply any sunscreen containing octisalate or body lotions to the application site(s) during the study.
- Aftershave/Perfume Usage: Subjects were able to apply perfume during the study period; however they were instructed to refrain from applying perfume to the axilla or to the blood sampling area.

### **TESTOSTERONE ASSESSMENTS**

The T content was assayed from each collected alcohol towelette (Liv-wipe<sup>®</sup>). The T result from each of the towelettes collected (i.e., 10 from each axilla) was pooled to make up the total T obtained from that axilla. The left axilla of the subject acted as the control. The left axilla was wiped. 5 min after Axiron<sup>™</sup> had dried. The right axilla was wiped after showering. The Liv-wipes were assayed to determine the amount of T that could be recovered from the right axilla after showering. Mean, median, SD, and CV were calculated for recovered T. The actual time of collection of Liv-wipe<sup>®</sup> was recorded in the CRF.

### **Statistical Analysis**

The T content was assayed from each collected alcohol towelette. The T content was pooled for all of the towelettes used for each axilla. Mean, SD, CV, and medians were calculated for T concentrations and data compared for the left and right axilla.

### **Bioanalytical method**

*Sample preparation:* The towelettes and gloves were diluted with appropriate volumes of absolute ethanol to ensure the injected samples were within the dynamic range of the bioanalytical method. After dilution of absolute ethanol, the lid was secured to the bottle and vigorously shaken. The bottle was then (b) (4) extract the T from the towelette and gloves. The bottle was then shaken vigorously again before transferring to a glass vial for sample analysis. If required, a serial dilution was performed for samples that were above the validated dynamic range.

*Bioanalytical method:* The T concentrations extracted from Liv-Wipes<sup>®</sup> and from nitrile powder-free gloves samples taken during the Study MTE11 were determined by reversed phase high performance liquid chromatography (HPLC) using ultraviolet (UV) detection at 240 nm employing a (b) (4)

The calibration curve and system suitability data indicated that the method met the acceptance criteria

for all samples tested. The bioanalytical method was adequately validated in compliance with the *Bioanalytical Method Validation Guidance*.

## RESULTS

### T Recovery Analysis

The T recovery from the unwashed (Table A-4-1) and the washed (Table A-4-2) axilla (washed with soap and water 30 min after application of the 60 mg dose) is summarized below:

**Table A-4-1:** T Recovery (mg) in Liv-Wipes and Glove used to wipe Unwashed Axilla

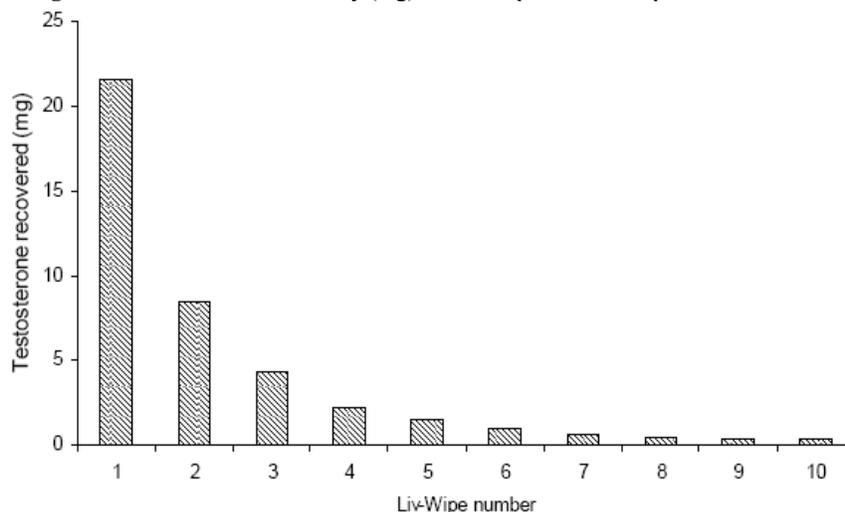
Subject	Liv-Wipe number										Gloves	Total
	1	2	3	4	5	6	7	8	9	10		
1	(b) (4)										0.19	42.8
2											0.26	43.8
3											0.20	37.0
4											0.53	45.4
5											0.26	36.8
6											0.52	47.0
7											0.21	40.8
8											0.70	41.8
9											0.17	37.7
10											0.38	48.4
Mean	22.1	8.56	4.44	2.33	1.52	0.99	0.65	0.47	0.40	0.36	0.34	42.1
SD	6.8	1.51	1.08	0.88	0.63	0.47	0.34	0.27	0.23	0.24	0.18	4.1
Median	21.6	8.39	4.38	2.13	1.45	0.96	0.62	0.43	0.37	0.32	0.26	42.3

**Table A-4-2:** T Recovery (mg) in Liv. Wipes and Glove used to Wipe Washed Axilla

Subject	Liv-wipe number										Gloves	Total
	1	2	3	4	5	6	7	8	9	10		
1	(b) (4)										0.01	2.1
2											0.04	4.2
3											0.02	4.2
4											0.04	2.3
5											0.01	0.9
6											0.06	2.9
7											0.01	1.2
8											0.15	10.4
9											0.02	1.0
10											0.07	2.3
Mean	1.2	0.64	0.39	0.25	0.18	0.13	0.10	0.07	0.06	0.05	0.04	3.1
SD	1.2	0.54	0.32	0.22	0.18	0.11	0.11	0.08	0.08	0.05	0.04	2.8
Median	1.0	0.52	0.25	0.15	0.10	0.07	0.05	0.05	0.03	0.03	0.03	2.3

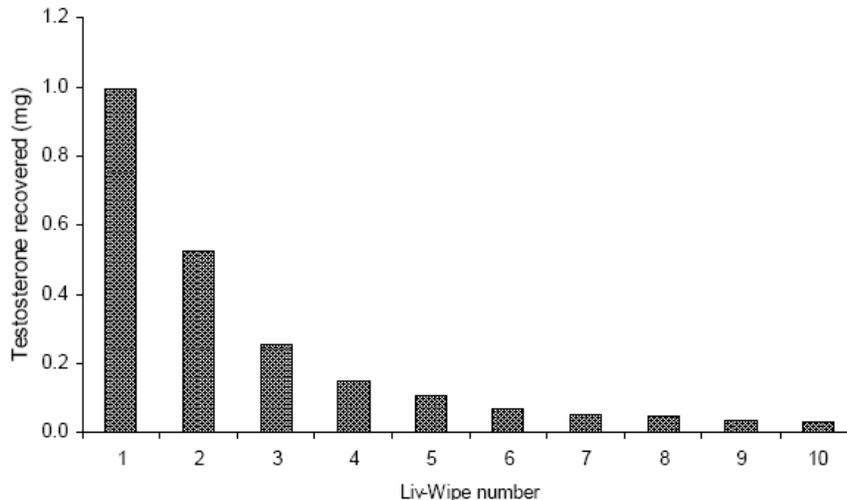
The recovery decreased rapidly as the number of wipes increased from 1 to 10 with an average of 22.1 mg being recovered in the first wipe and 0.36 mg in the last. Indeed, the sum of the content of the last 4 wipes equated to less than 10% of the content of the first.

**Figure A-4-4:** Median T Recovery (mg) in Liv-Wipes used to wipe unwashed Axilla



As for recovery from the unwashed axilla, the T recovered from the washed axilla was largely found in the first few wipes and the fifth wipe contained less than 10% of the first.

**Figure A-4-5:** Median T Recovery (mg) in Liv. Wipes used to Wipe Washed Axilla



The total mean T recovered from the unwashed axilla (including the small amount recovered from the gloves) was  $42.1 \pm 4.1$  mg of T which equates to  $70.2 \pm 6.9$  % of the applied dose of 60 mg from the axilla). The total mean T recovered from the axilla that was washed with soap and water was  $3.1 \pm 2.8$  mg which equates to  $5.2 \pm 4.7$ % of the applied dose of 60 mg. The study results showed a 92.6% of reduction of residual T on the axilla ( $[(42.1 \text{ mg} - 3.1 \text{ mg}) / 42.1 \text{ mg}] \times 100 = 92.6$  %) following washing with soap and water compared to when axilla was not washed. This information will be reflected in the product labeling.

### Safety Results

A total of 4 treatment emergent AEs were reported by 4 subjects during the study. All 4 treatment emergent AEs were deemed to be mild in severity and not related to the Axiron™. Only 1 of the 4 AEs required a concomitant medication (i.e., Subject R03 experienced a sore throat) and all events resolved. There were no serious treatment emergent AEs reported during the study.

### CONCLUSION

The study results showed a 92.6% of reduction of residual T on the axilla following washing with soap and water compared to when axilla was not washed indicating that washing the application site helps preventing unintended secondary exposure of T.

### A.1.5. Study MTE12

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#### A Phase 1 Study to Evaluate the Potential for Interpersonal Transfer of Testosterone following Single Dose Application of 2% Testosterone Metered Dose (MD) Lotion

**Protocol No:** MTE12  
**Phase:** 1  
**Principal Investigator:** Dr. Joanne Marjason  
**Clinical Study Center:** Q-Pharm, Herston, Australia  
**Clinical Study Dates:** August 5, 2010 – September 9, 2010  
**Analytical Study Facility:** (b) (4)

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#### OBJECTIVE

- To evaluate the potential for interpersonal transfer from healthy male subjects using Axiron™ to healthy female subjects, when contact is made 2 hr post application of Axiron™ when the application area is covered with a 100% cotton long sleeve T-shirt prior to the transfer procedure.

#### STUDY DESIGN

This was a single dose study in healthy male and female subjects. Female (recipient) subjects underwent baseline intensive PK sampling during the 24 hr period prior to the transfer procedure to establish their baseline concentrations of T and DHT. T and DHT were measured and free T calculated at 0, 0.5, 1, 2, 4, 8, 10, 12, 16, and 24 hr on the day prior to the transfer procedure. SHBG was measured in samples collected at 24 hr. Eligible healthy male (donor) subjects received a 120 mg dose (60 mg, 2 pump actuations to each axilla) of Axiron™. Female subjects underwent 15 min of vigorous contact at 2 hr post dose application of the male subjects. Male subjects were required to wear the long sleeve 100% cotton T-shirt (that they put on during following dosing) during the transfer procedure. Female subjects were involved in further intensive PK sampling post the transfer procedure. T and DHT were measured and free T calculated at 0.5, 1, 2, 4, 8, 10, 12, 16, 24, 48, and 72 hr post transfer procedure. SHBG was measured in samples collected at 24, 48 and 72 hr post transfer. No PK characterization was performed in male subjects. All subjects were detained for the 24 hr following completion of the transfer procedure.

#### STUDY SUBJECTS

The study population consisted of healthy premenopausal female subjects and male subjects aged 18-45 yr, with BMI 19-28 kg/m<sup>2</sup> for the females and BMI 19-30 kg/m<sup>2</sup> for males. No subjects withdrew from the study. The Per-Protocol population included subjects without any significant protocol violations or deviations. 1 subject (Subject R-04) was excluded from the Per-Protocol population and the PK analyses due to eligibility violation (was enrolled in another clinical study taking a different investigational product).

#### TREATMENTS

The Investigational Product was Axiron™ which contains 2% T. A single dose of 120 mg (60 mg, 2 pump actuation to each axilla) Axiron™ was applied to male subjects at 2 hr prior to the transfer procedure by the site staff, using the applicator. The highest of dose level of Axiron™ was investigated in this study as this represents the worst case scenario in terms of interpersonal transfer. The batch number of the Investigational Product was BN0492, expiry October 2010.

#### TRANSFER PROCEDURE

The following instructions were given and overseen by the clinical staff:

- 1 Ensure that the forearms of female subjects are exposed. Male subjects must be still wearing the 100% cotton long-sleeve T-shirt that they put on following dosing with the investigational product. The female must be wearing a protective covering over the cannula (or equivalent) site to prevent contamination.

- 2 Instruct the male subject to lift both arms out to his side at a 45° angle. Instruct the female to place her forearms (wrist facing down) under the male armpits, such that the cannula site is not in contact with the male skin. Instruct the male subject to gently allow his arms to relax down over the female forearms, and to move his arms as if he were walking, so that his armpits rub vigorously against the female forearms.
- 3 The male and female will hold their arms together in this way for 15 min whilst continuing the rubbing procedure throughout. Observe the subjects throughout the contact period to ensure that contact is not broken.
- 4 On completion of the transfer procedure, remove the protective covering from the female and replace with a clean one.
- 5 Do not allow the female to wash the area until 24 hr after transfer procedure. Do not allow the male subject to wash the area until the transfer procedure is complete.

**Reviewer's Comment:** *It appears that the females had the protective covering on during the transfer process. It is unknown whether there was any T transfer to the protective covering.*

### EVALUATION PARAMETERS

- PK: Blood samples were collected for determination of serum PK parameters (i.e., AUC(0-24), AUC(0-72), C<sub>max</sub>, C<sub>min</sub>, and T<sub>max</sub>) of total T, DHT, and SHBG.

### INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria and exclusion criteria were same as Studies MTE10, MTE11 and were found to be acceptable.

### STUDY RESTRICTIONS

- **Washing Application Site(s):** Male subjects were instructed to wash the application site following completion of the transfer procedure. Female (recipient) subjects were instructed to refrain from washing the transfer sites for at least 24 hr following completion of the transfer procedure.
- **Physical Contact:** Subjects were instructed that no direct skin to skin contact should be made with the application site. From their last shower/wash prior to check in, study subjects were instructed not to apply any sunscreen, body lotions, moisturizers, deodorant sprays, perfumes or any other cosmetic preparation to the application site/s, (male subjects) and to the forearms (female subjects) during the study treatment period.

**Reviewer's Comment:** *Taking the washing restrictions in account, interpersonal transferability was based on AUC(0-24) and C<sub>max</sub> while PK blood sampling was conducted up to 72 hr post-dose.*

### Bioanalytical Methods

Validated assays were utilized for the analysis of both T and DHT (b) (4) using serum collected from the blood samples. LC-MS/MS methods were used for both total T and DHT measurements. The dynamic range was 2.5-5,000 ng/dL for total T and 1.0-500 ng/dL for DHT, respectively. The SHBG analysis in the current study was performed (b) (4) using a validated immunoradiometric assay.

The concentrations of free T were calculated using the method and formula outlined below:

$$\text{Free Testosterone} = \text{Total T} * \left[ \frac{1}{1 + K_{\text{SHBG}} * [\text{SHBG}] + n * K_{\text{ALB}} * [\text{ALB}]} \right]$$

Where:

- SHBG values were reported as nmol/L and converted to mol/L or Molar concentration (multiplied by a factor of 10<sup>-9</sup>)
- K<sub>SHBG</sub> for T (association constant for binding to SHBG) is 0.6 x 10<sup>9</sup> M<sup>-1</sup>

- For the calculation of free T concentration from 0 to 20 hrs, SHBG reported at time “0” and for 24 hrs and beyond, the SHBG values at 24 hrs were used
- $n \cdot K_{ALB}$  (the product of the number of binding sites per molecule and the association constant for albumin) is  $4 \times 10^4 M^{-1}$
- The plasma albumin values reported for each subject (reported in grams/Liter and converted to molar concentrations by dividing with the molecular weight of albumin, 69,000 Da) were used in the calculations
- The free T concentrations were reported in units of pg/mL

Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range.

## STUDY RESULTS

### Pharmacokinetics Results

Table A-5-1 presents a summary of the PK parameters for total T.

**Table A-5-1:** Summary PK parameters for Total T (Pre and Post-transfer)

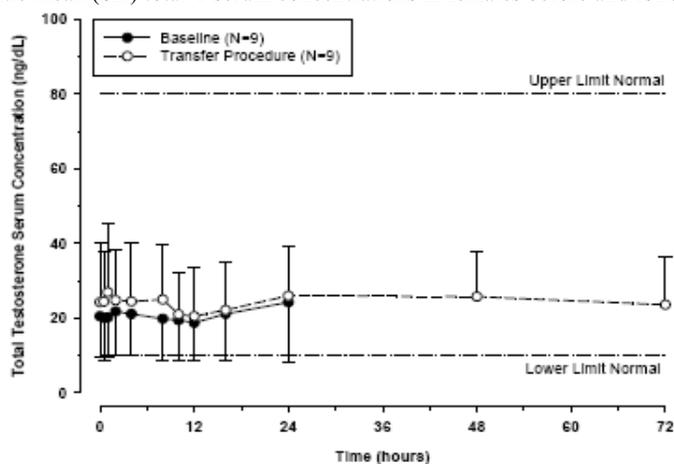
Statistic	24 hr Pre-Transfer				First 24 hr Post-Transfer			
	T <sub>max</sub> 0-24 hr	C <sub>max</sub> 0-24 ng/dL	C <sub>min</sub> 0-24 ng/dL	AUC <sub>0-24</sub> hr*ng/dL	T <sub>max</sub> 0-24 hr	C <sub>max</sub> 0-24 ng/dL	C <sub>min</sub> 0-24 ng/dL	AUC <sub>0-24</sub> hr*ng/dL
Mean	14.6	25.5	17.1	501	5.02	29.8	18.2	558
std dev	11.0	16.3	10.3	281	7.52	18.0	10.8	307
Median	23.8	20.0	14.0	412	2.12	24.0	16	497
Min	2.0	9.4	5.7	192	0.5	12	6.1	215
Max	24.0	62	34	1035	24.0	62	41	1217
P value					0.078 <sup>#</sup>	0.117 <sup>#</sup>	0.359 <sup>*</sup>	0.023 <sup>*</sup>

\*paired Students T-Test  
<sup>#</sup> Wilcoxon signed-rank test

**Reviewer’s Comment:** The mean pre-dose total T concentration (N=9) was  $20.5 \pm 10.8$  ng/dL.

The arithmetic mean serum concentration-time profiles for total T (n=9) in females at baseline and following the transfer procedure over the entire sampling period (and the putative dosing interval) are illustrated in Figures A-5-1. Following the transfer procedure, mean total T concentrations were higher than those at baseline. Despite the increase over baseline in mean total T concentrations following the transfer procedure, serum levels remain within the normal range for females of approximately 10-80 ng/dL (Javanbakht *et al.*, *J. Clin. Endocrinol. Metabol.*, 2000).

**Figure A-5-1:** Arithmetic mean (SD) total T serum concentrations in females before and following transfer procedure



Tables A-5-2 and A-5-3 presents a summary of the PK parameters for DHT and free T, respectively.

**Table A-5-2: Summary PK parameters for DHT (Pre and Post-transfer)**

Statistic	24 hr Pre-Transfer				First 24 hr Post-Transfer			
	T <sub>max</sub> 0-24 hr	C <sub>max</sub> 0-24 ng/dL	C <sub>min</sub> 0-24 ng/dL	AUC <sub>0-24</sub> hr*ng/dL	T <sub>max</sub> 0- 24 hr	C <sub>max</sub> 0- 24 ng/dL	C <sub>min</sub> 0- 24 ng/dL	AUC <sub>0-24</sub> hr*ng/dL
Mean	10.8	7.38	5.67	158	10.3	8.1	5.4	162
Std dev	10.9	4.11	3.31	89.8	10.5	4.33	3.2	87.5
Median	4	8.7	7	181	4.05	8.3	4.4	161
Min	0.5	2.4	2.2	57	0.5	3.4	2.2	70.2
Max	24	13	11	286	24	14	9.7	274
p-value					0.820 <sup>#</sup>	0.251*	0.557*	0.439*

\*paired Students T-Test  
# Wilcoxon signed-rank test

**Table A-5-3: Summary PK parameters for Free T (Pre and Post-transfer)**

Statistic	24 hr Pre-Transfer				First 24 hr Post-Transfer			
	T <sub>max</sub> 0-24 hr	C <sub>max</sub> 0-24 pg/mL	C <sub>min</sub> 0-24 pg/mL	AUC <sub>0-24</sub> hr*pg/mL	T <sub>max</sub> 0-24 hr	C <sub>max</sub> 0-24 pg/mL	C <sub>min</sub> 0-24 pg/mL	AUC <sub>0-24</sub> hr*pg/mL
Mean	11.3	3.32	3.08	67.8	7.45	3.86	2.34	72.2
Std dev	10.4	1.34	2.04	26.1	9.69	1.45	0.87	24.6
Median	4.00	3.30	2.50	71.5	4.00	4.00	2.40	71.2
Min	2.0	1.5	0.9	29.1	0.5	1.6	1.1	32.9
Max	23.8	6.0	8.0	119	24.0	6.5	4.0	115
p-value					0.570 <sup>#</sup>	0.073*	0.316 <sup>#</sup>	0.126*

\*paired Students T-Test  
# Wilcoxon signed-rank test

The PK parameters of both DHT and free T were comparable between pre- and post-transfer process.

As shown in Table A-5-4, the study result showed a 13% and 17% increase in T exposure (AUC[0-24]) and C<sub>max</sub>, respectively, compared to baseline in females.

**Table A-5-4: Summary of Arithmetic Mean (SD) PK Parameter Estimates for Total T Before (baseline) and Following Transfer Procedure (Study MTE12)**

Parameter	Baseline (A) (N=9)	After Transfer Procedure (B) (N=9)	Ratio of Geometric LS Means (B:A) <sup>a</sup>	90% CI for the Ratio (B:A) <sup>a</sup>
AUC(0-24) (ng·h/dL)	501 ± 281 <sup>b</sup>	558 ± 307 <sup>b</sup>	1.13	1.06, 1.20
C <sub>max</sub> (ng/dL)	25.5 ± 16.3 <sup>b</sup>	29.8 ± 18.0 <sup>b</sup>	1.17	NR <sup>c</sup>

<sup>a</sup> A mixed effect model with log(PK)=TREATMENT(fixed effect) + SUBJECT (random effect) + RANDOM ERROR was fitted to the log transformed PK parameters of T. Geometric least squares (LS) mean ratio (and 90% CI) for comparisons between baseline and post transfer procedure were determined for the subjects without any protocol violation (N=9).

<sup>b</sup> From subjects without any protocol violation (N=9)

<sup>c</sup> Not reported

**Reviewer's Comment:** *The geometric mean ratio of the pre- and post-transfer procedure (B:A) were reported by the Sponsor but the actual geometric means used in the calculation were not. However, the arithmetic mean ratio of the pre- and post-transfer procedure (B:A) were 1.11 and 1.17 for AUC(0-24) and C<sub>max</sub>, respectively, and were comparable to the geometric mean ratio.*

There was no study conducted to assess direct skin-to-skin effect transfer potential using Axiron<sup>TM</sup> (i.e., 2% T).

## CONCLUSIONS

Slight increases in total T exposure following the transfer procedure compared to that at baseline were observed.

### A.1.6. Study MTE06

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#### **A Phase I, Three Part Study To Evaluate The Potential for Interpersonal Transfer, and to Determine the Impact of Application of Antiperspirant and Deodorant, and the Impact of Washing the Application Site, on the Pharmacokinetics of Testosterone Following Single Dose Applications of Testosterone Metered Dose (MD)-Lotion®**

**Protocol No:** MTE06  
**Phase:** 1  
**Principal Investigator:** Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.  
**Clinical Study Center:** Biovail Contract Research, Toronto, Canada  
**Clinical Study Dates:** May 23, 2007 – August 3, 2007  
**Analytical Study Facility:** (b) (4)

---

**NOTE:** This study consists of 3 parts (i.e., evaluation of effect of antiperspirant/deodorant use, effect of washing application site, and interpersonal transferability) conducted using a 1% T solution formulation. The Sponsor assessed the other two aspects in Study MTE10 which was conducted with the TBM formulation. Therefore, this review will only cover Part A (evaluation of interpersonal transferability).

#### **OBJECTIVE**

To evaluate the potential for transfer from healthy male subjects using 1% T solution (60 mg applied to male subjects) to female partners, when contact was made 2 (with or without a T-shirt on), 6, or 12 hr post application of the 1% T solution.

#### **STUDY DESIGN**

The study followed a randomized, open-label study design in healthy male and female subjects. Male subjects received a single 3 mL dose of 1% T solution to each axilla (60 mg [6 mL] total dose) according to the randomization schedule and engaged in 15 min of direct skin (axilla of males) to skin (forearms of females) contact at 2 (either with or without wearing a shirt), 6, or 12 hr post-dose. Healthy male and female subjects participating in the study were randomized to 1 of the following treatment groups (N=6 couples per group):

- Group 1: Study couples engaged in 15 min of direct skin (axilla of the donor) to skin (forearms of the recipient) contact 2 hr post dose application.
- Group 2: Study couples engaged in 15 min of contact 2 hr post dose application. Donors were required to wear a shirt during the 15 min of contact with recipients, but donors did not wear a shirt during the drug application procedure.
- Group 3: Study couples engaged in 15 min of direct skin (axilla of the donor) to skin (forearms of the recipient) contact 6 hr post dose application.
- Group 4: Study couples engaged in 15 min of direct skin (axilla of the donor) to skin (forearms of the recipient) contact 12 hr post dose application.

During the study period, 13 blood samples for PK at -0.5, 0, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, and 72 hr post-dose of the study drug were taken from each female subject. No blood samples were taken from male subjects for PK analyses.

**Reviewer's Comment:** *In the study report, Sponsor states that pre-dose PK samples were collected at -0.5 and 0 (right before dosing) hr. However, while raw data at these pre-dose two time points were reported, baseline concentrations that the Sponsor used in calculating the baseline adjusted PK parameters were not reported. Nevertheless, considering that a baseline in this study is not generated based on the ideal 24 hr intensive PK sampling, the relevance of the baseline corrected PK data reported is unknown.*

#### **STUDY SUBJECTS**

24 male subjects had the study treatment applied, and 24 female subjects underwent the transfer procedure (i.e., 6 couples per treatment cohort). All subjects completed the study, and the data obtained from all 24 female subjects were used for the PK and statistical analyses. Demographic and other baseline characteristics (i.e., age, race, height, weight, BMI, smoking habits, and alcohol consumption) among the treatment groups were comparable and no significant differences were noted.

## TREATMENTS

The following investigational drug was used in this study:

- Name: Testosterone MD-Lotion<sup>®</sup>
- Manufacturer: Acrux Pharma Pty. Ltd., Australia
- Batch #: BN0441
- Date of Manufacture: January 31, 2007
- Retest date: (b) (4)

The study drug, 1% T solution, was applied as a 3 mL dose applied to each axilla using the metered dose mechanism of the bottle to apply 2 pump actuations (1.5 mL per pump actuation) dose towards the top part of each axilla (i.e., 60 mg [6 mL] total dose).

## TRANSFER PROCEDURE

The following instructions were given and overseen by the clinical staff:

- 1 Ensure that the forearms of female (recipient) subjects are exposed. Male donor subjects must be still wearing the 100% cotton long-sleeve T-shirt that they put on following dosing with the investigational product. The female (recipient) must be wearing a protective covering over the cannula (or equivalent) site to prevent contamination.
- 2 Instruct the male (donor) subject to lift both arms out to his side at a 45° angle. Instruct the female (recipient) to place her forearms (wrist facing down) under the male (donor) armpits, such that the cannula site is not in contact with the male (donor) skin. Instruct the male (donor) subject to gently allow his arms to relax down over the female (recipient) forearms, and to move his arms as if he were walking, so that his armpits rub vigorously against the female (recipient) forearms.
- 3 The male (donor) and female (recipient) will hold their arms together in this way for 15 min whilst continuing the rubbing procedure throughout. Observe the subjects throughout the contact period to ensure that contact is not broken.
- 4 On completion of the transfer procedure, remove the protective covering from the female (recipient) and replace with a clean one.
- 5 Do not allow the female (recipient) to wash the area until 24 hr after transfer procedure. Do not allow the male (donor) subject to wash the area until the transfer procedure is complete.

**Reviewer's Comment:** *It appears that the females had the protective covering on during the transfer process. It is unknown whether there was any transfer to the protective covering.*

## EVALUATION PARAMETERS

- PK: Blood samples were collected for determination of serum PK parameters (i.e., AUC(0-24), AUC(0-72), C<sub>max</sub>, C<sub>min</sub>, and T<sub>max</sub>) of total T, DHT, and SHBG.

## INCLUSION CRITERIA

Inclusion criteria and exclusion criteria were same as Studies MTE10, MTE11 and were found to be acceptable.

## STUDY RESTRICTIONS

**Washing Application Site(s):** Male subjects were instructed to wash the application site following completion of the transfer procedure. Female subjects were instructed to refrain from washing the transfer sites for at least 24 hr following completion of the transfer procedure.

## Bioanalytical Methods

Validated assays were utilized for the analysis of both T and DHT by (b) (4) using serum collected from the blood samples. T was measured by liquid chromatography with mass spectrometry detection after addition of an internal standard (b) (4). Extracts and samples were separated, dried, and reconstituted. The reconstituted material was analyzed via LC-MS/MS. DHT was extracted with (b) (4). DHT was then measured by radioimmunoassay. The SHBG analysis in the current study was performed (b) (4) using a validated immunoradiometric assay. The concentrations of free T were calculated using the method and formula outlined below:

$$\text{Free Testosterone} = \text{Total T} * \left[ \frac{1}{1 + K_{\text{SHBG}} * [\text{SHBG}] + n * K_{\text{ALB}} * [\text{ALB}]} \right]$$

Where T was the measured total T concentration,  $K_{\text{SHBG}}$  (the association constant for binding to SHBG) is  $0.6 \times 10^9 \text{ M}^{-1}$  and  $n * K_{\text{ALB}}$  (the product of the number of binding sites per molecule and the association constant for albumin) is  $4 \times 10^4 \text{ M}^{-1}$ . The calculation assumed an albumin (Alb) concentration of 43 g/L ( $6.2 \times 10^{-4} \text{ mol/L}$ ).

## STUDY RESULTS

### Pharmacokinetics Results

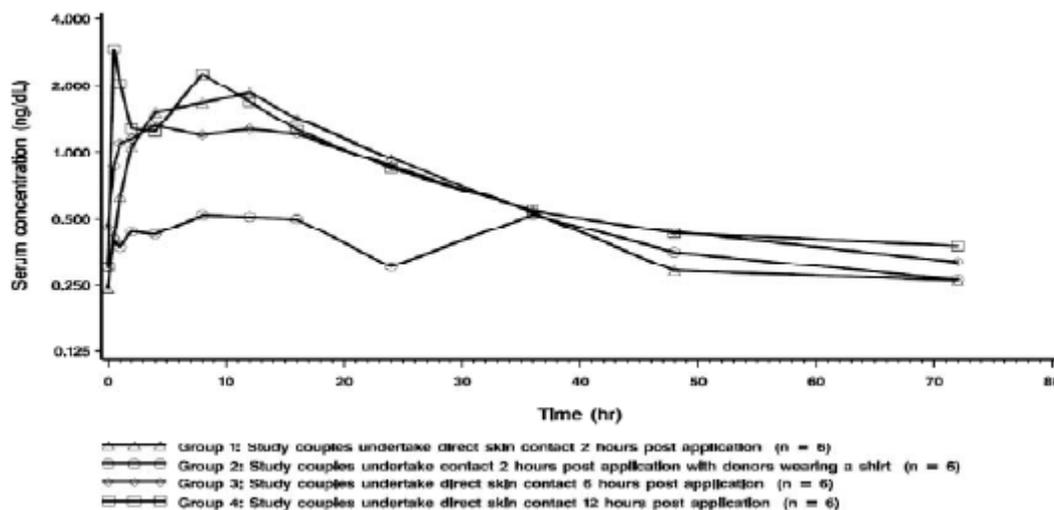
Table A-6-2 presents a summary of the PK parameters for total T. Considering the study objective, PK parameters of DHT and free T are not shown here.

**Table A-6-2:** Summary Baseline Uncorrected PK parameters for Total T

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean $\pm$ SD			
	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
<b>AUC<sub>0-72</sub></b> (ng/dL-hr)	4521.18 (55.31) 5050.73 $\pm$ 2793.61	1954.83 (42.68) 2135.72 $\pm$ 911.52	3861.69 (71.32) 4790.59 $\pm$ 3416.82	5614.30 (30.23) 5827.23 $\pm$ 1761.34
<b>C<sub>max</sub></b> (ng/dL)	166.72 (82.11) 225.17 $\pm$ 184.90	42.03 (56.21) 47.00 $\pm$ 26.42	125.85 (70.35) 165.00 $\pm$ 116.08	388.76 (77.09) 496.83 $\pm$ 382.99
<b>C<sub>min</sub></b> (ng/dL)	19.88 (27.49) 20.67 $\pm$ 5.68	20.12 (52.73) 22.97 $\pm$ 12.11	25.66 (72.21) 30.50 $\pm$ 22.02	30.04 (25.74) 30.83 $\pm$ 7.94
<b>T<sub>max</sub></b> (hr)*	12.00 (4.00 - 12.00)	12.00 (2.00 - 36.25)	10.00 (0.50 - 12.00)	4.53 (0.50 - 12.00)
<b>T<sub>min</sub></b> (hr)*	60.04 (0.50 - 72.00)	13.00 (0.50 - 72.00)	72.00 (0.50 - 72.07)	72.00 (0.50 - 72.05)

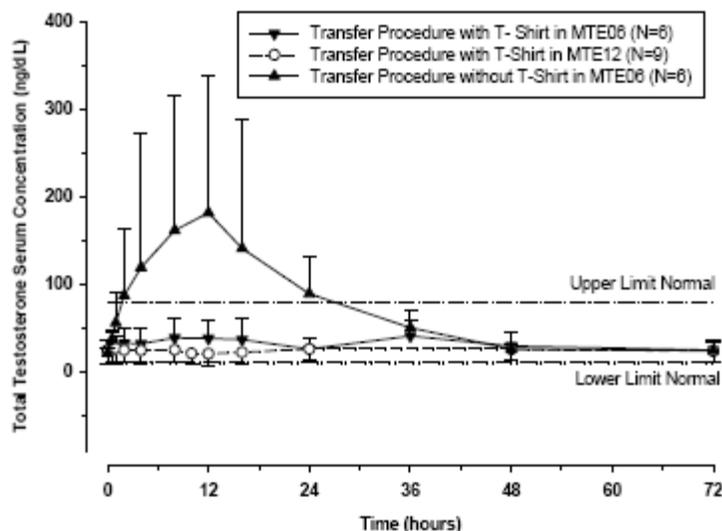
\* median (min - max)

**Figure A-6-1:** Arithmetic mean serum concentrations of total T (non-baseline corrected) in healthy female subjects for Groups 1, 2, 3 and 4 [semi-logarithmic scales]



As shown in Figure A-6-1, the addition of a shirt significantly reduced the transfer of T when female subjects made contact 2 hr post application (with and without a donor wearing a shirt) of 1% T solution with male subjects.

**Figure A-6-2:** Mean (SD) total T serum concentration-time profiles in females following transfer procedure with clothing covering the application area in Studies MTE12 and MTE06 and without clothing covering the application area (Study MTE06)



**Reviewer's Comment:** *The limitation of this study is that it was conducted in a parallel fashion and the actual baseline T concentrations used in calculating the PK parameters were not reported. Another limitation of the study is the lack of a 24 hr PK based T baseline. The mean pre-dose total T concentration of Group 1 (i.e., skin-to-skin contact 2 hr post-dose) and Group 2 (i.e., transfer with a T shirt barrier on 2 hr post-dose) were  $21.3 \pm 5.5$  ng/dL and  $23.8 \pm 11.4$  ng/dL, respectively. These values are comparable to the mean pre-dose total T concentration of  $20.5 \pm 10.8$  ng/dL reported in Study MTE12. In addition, female subjects were instructed to refrain from washing for 24 hr post-transfer process and the status of whether they washed after 24 hr was not reported. Therefore, the relevance of the 72 hr PK parameters (e.g., AUC(0-72)) is unknown.*

*Regardless of the 72 hr PK profile relevance, Figure A-6-2 shows that direct skin-to-skin contact without a T-shirt barrier resulted in a substantially higher T transfer compared to when having a T-shirt on even by just accounting for the first 24 hr where females were instructed to refrain from washing.*

## CONCLUSIONS

After female subjects made contact 2 hr post application (with and without a donor wearing a shirt) of 1% T solution with male subjects, it was shown that the addition of a shirt significantly reduced the transfer of T.

Pages 53 to 64 has been withheld as a duplicate copy of the original "Review of EIR Covering NDA-22-504" dated 10/28/10 which can be found in the "Other Review" section of this redacted Approval Package.

Pages 65 to 72 has been withheld as a duplicate copy of the original "Clinical Pharmacology Filing Memo" which can be found at the end of this "Clinical Pharmacology and Biopharmaceutical Review".

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHONGWOO YU  
11/17/2010

MYONG JIN KIM  
11/17/2010

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA:</b>	022504
<b>Type/Category:</b>	505(b)(2)/Original
<b>Brand Name:</b>	Axiron
<b>Generic Name:</b>	Testosterone
<b>Relevant IND:</b>	IND 70516
<b>Indication:</b>	Treatment of male hypogonadism
<b>Dosage Form:</b>	Solution
<b>Route of Administration:</b>	Transdermal
<b>Dosing Regimen and Strength:</b>	Starting dose at 60 mg testosterone (2 pump actuations) once daily and dose adjust appropriately, 2% (30, 60, 90, and 120 mg)
<b>Sponsor:</b>	Acrux Pharma
<b>OCP Division:</b>	Division of Clinical Pharmacology 3
<b>OND Division:</b>	Division of Reproductive and Urologic Products (DRUP)
<b>Submission Dates:</b>	January 25, 2010, May 12, 2010, May 20, 2010, August 16, 2010, September 24, 2010, and October 14, 2010
<b>Reviewer:</b>	Chongwoo Yu, Ph.D.
<b>Team Leader:</b>	Myong-Jin Kim, Pharm.D.

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## 1 EXECUTIVE SUMMARY

The Sponsor submitted a 505(b)(2) application for Axiron™. Axiron™ is non-sterile, transdermally applied testosterone (T) solution for treatment of male hypogonadism associated with deficiency or absence of endogenous T. Axiron™ is to be administered transdermally once daily to clean, dry, intact skin of the axilla (1 or 2 armpits) by use of an applicator cup, preferably at the same time each morning. The product is applied via a metered-dose pump designed to deliver 60 pump actuations of 30 mg (i.e., 1 pump actuation) of T to an applicator cup which is then used to apply T to skin of the axilla. The recommended start dose is 60 mg (i.e., 2 pump actuations) of T. Dose adjustment is recommended if the serum total T concentration is outside of the pre-specified T normal range of 300-1,050 ng/dL. The daily dose should be increased from 60 mg to 90 mg or from 90 mg to 120 mg if the serum total T concentration is below 300 ng/dL. The daily dose should be reduced from 60 mg to 30 mg daily if serum total T concentration is above 1,050 ng/dL.

The Sponsor submitted 12 Biopharmaceutics/Clinical Pharmacology and Clinical studies including multiple-dose pharmacokinetics (PK) (MTE07), evaluation of the effect of antiperspirant/deodorant applications and the effect of application site washing (MTE06 with 1% T and MTE10 with 2% T), evaluation of application site washing on residual T (Study MTE11), and evaluation of interpersonal transferability (MTE12 with 2% T and MTE06 with 1% T), and 2 pivotal Phase 3 clinical studies (MTE08 and MTE09) to support the approval of Axiron™. Study MTE08 was an open-label titration study to evaluate the safety and efficacy of various doses of Axiron™ in hypogonadal men for 120 days while Study MTE09 was a open-label extension of Study MTE08 to 180 days to evaluate skin safety.

Out of the 12 studies submitted, 7 studies containing relevant information acquired during the Axiron™ product development were reviewed. Studies not reviewed include studies conducted under development programs using different formulation (i.e., T 1% solution) and using different patient populations (e.g., healthy females with low T for single dose studies or healthy men with chemically suppressed T levels to simulate hypogonadism). A formal consult to the Division of Scientific Investigations (DSI) was made for clinical and bioanalytical study sites inspections (signed off by Dr. E. Dennis Bashaw in DARRTS on March 18, 2010) and there are no unresolved issues related to the approvability of Axiron™.

### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 22504 submitted on January 25, 2010, May 12, 2010, May 20, 2010, August 16, 2010, September 24, 2010, and October 14, 2010. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language.

### 1.2 POST-MARKETING REQUIREMENTS / COMMITMENTS

None

### 1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

#### Formulation:

Axiron™ was originally developed as a 1% solution formulation. However, Sponsor developed a 2% solution as the to-be-marked (TBM) formulation in order to deliver the same amount of T in smaller volumes in order to prevent dripping and assure that adequate amount of Axiron™ can be applied to the axilla. Study MTE06 was conducted with the 1% solution formulation while multiple-dose PK of both 1% and 2% (i.e., Axiron™) T solution formulations were characterized in Study MTE07 (except the 120 mg dose of Axiron™). Studies MTE08, MTE09, MTE10, MTE11, and MTE12 were conducted with the TBM formulation (i.e., Axiron™).

## Absorption

The following PK profiles of total T were obtained with a daily dose of 30 mg, 60 mg, and 90 mg Axiron™ applied to the axilla(s) of hypogonadal men for 7 days. PK of the 120 mg dose was not characterized in this study. PK of Axiron™ was not dose proportional but dose-dependent.

**Table 1:** Arithmetic Mean (SD) PK Parameters of Total T by Treatment (N=18)

Treatment	C <sub>avg</sub> (ng/dL)	AUC(0-24) (ng·hr/dL)	C <sub>max</sub> (ng/dL)	C <sub>min</sub> (ng/dL)	T <sub>max</sub> <sup>a</sup> (hr)
30 mg Axiron™	267 (100)	6399 (2405)	395 (216)	161 (50)	16.00 (1.95, 23.93)
60 mg Axiron™	368 (131)	8837 (3131)	547 (242)	214 (99)	4.13 (0, 20.00)
90 mg Axiron™	413 (173)	9907 (4145)	588 (223)	239 (123)	12.01 (1.92, 23.97)

<sup>a</sup> Median (min, max)

## Distribution, Metabolism, and Excretion

Based on the similarities of Axiron™ to other transdermal T agents, specific studies describing the distribution, metabolism, or excretion of T absorbed from Axiron™ have not been conducted.

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

*Metabolism:* There is considerable variation in the half-life of T as reported in the literature, ranging from 10 to 100 min. T is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of T are estradiol and dihydrotestosterone (DHT). DHT concentration increased in parallel with T concentration during Axiron™ treatment. The mean steady state DHT/T ratio remained within normal limits and ranged from 0.17 to 0.26 across all doses (i.e., 30, 60, 90, and 120 mg) on Days 15, 60, and 120.

*Excretion:* About 90% of a dose of T given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of T and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of T occurs primarily in the liver. When Axiron™ treatment is discontinued after achieving steady state, serum T concentrations return to their pretreatment concentrations by 7-10 days after the last application (Study MTE07).

## Primary Efficacy Analysis

The Sponsor submitted 1 Phase 3 safety/efficacy study and 1 Phase 3 skin safety study to support the approval of Axiron™. Study MTE08 was an open-label titration study to evaluate the safety and efficacy of various doses (i.e., 30 mg, 60 mg, 90 mg, or 120 mg) of Axiron™ in 155 hypogonadal men for 120 days while Study MTE09 was a open-label extension of Study MTE08 to 180 days to evaluate skin safety. The primary endpoint of the study was assessed based on the C<sub>avg</sub>(0-24) data collected on Day 120. Efficacy was to be deemed established if 75% or more of patients had a C<sub>avg</sub>(0-24) in the normal range on Day 120. Per agreement with the Division, the value of the lower limit of the two-sided 95% Wald confidence interval (CI) also had to exceed 66.8% in order to establish definitive evidence of efficacy in the study. As shown in Table 2, the proportion of patients with a C<sub>avg</sub>(0-24) value in the normal range of 300-1,050 ng/dL on Day 120 in the completer set was 84.1% (i.e., 116 out of 138 patients). It should be noted that there were 20 withdrawals including 3 due to adverse events (AE). Per agreement with the Division, these 3 individuals were included in the 138 subjects for primary efficacy analysis (i.e., completer set) since they were considered to be treatment failures. The lower bound of the 95% CI associated with the proportion was 78.0% (p < 0.001).

**Table 2: Primary Efficacy Endpoint Analysis: Proportion of Responders who had steady-state Serum Total T C<sub>avg</sub> in the range 300 to 1,050 ng/dL at Day 120 (Study MTE08)**

Data Set	Day 120	
	Responders	Proportion of Responders (95% CI)
Completer Set (N=138) <sup>b</sup>	116/138	84.1% (78.0-90.2)
Per Protocol Set (N=123) <sup>c</sup>	106/123	86.2% (80.1-92.3)
Full Analysis Set (N=143) <sup>a</sup>	116/138	84.1%, (NR)

<sup>a</sup> Full analysis set included all subjects who entered the study, received at least 1 dose of Axiron™ and had on-treatment data for at least 1 efficacy variable.

<sup>b</sup> Completer set included all subjects who were included in the full analysis set and who completed the Day 120 visit. The completer set also included subjects who withdrew from Study MTE08 prior to Day 120 due to either an AE or efficacy.

<sup>c</sup> Per-protocol set included all subjects who completed Study MTE08 without any significant protocol violations or deviations.

### Secondary Endpoint Analysis

In Study MTE08, secondary endpoints related to safety are considered to be met if they meet the following:

- More than or equal to 85% having total T C<sub>max</sub> less than 1,500 ng/dL
- Less than 5% having total T C<sub>max</sub> in the range of 1,800-2,500 ng/dL
- No patients having total T C<sub>max</sub> higher than 2,500 ng/dL

**Table 3: Serum Total T PK Secondary Endpoints**

Data Set	Day 15	Day 60	Day 120
C <sub>max</sub> < 1,500 ng/dL	95.6% (130/136)	91.2% (124/136)	94.8% (128/135)
C <sub>max</sub> > 1,800 and ≤ 2,500 ng/dL	2.2% (3/136)	4.4% (6/136)	3.0% (4/135)
C <sub>max</sub> > 2,500 ng/dL	1.5% (2/136)	1.5% (2/136)	0.7% (1/135)

It should be noted that out of the 138 patients included in the completer set for efficacy analysis, 2 subjects withdrew before Day 15 and 1 subject withdrew after Day 60.

As shown in Table 3, secondary endpoints of C<sub>max</sub> being less than 1,500 ng/dL in at least 85% of patients and less than 5% of patients having a C<sub>max</sub> between 1,800 ng/dL and 2,500 ng/dL, were met on all 3 PK days (i.e., Days 15, 60, and 120). However, the third secondary endpoint to have no patients with C<sub>max</sub> > 2,500 ng/dL was not met on all 3 days (i.e., Days 15, 60, and 120).

In Study MTE09 (a safety study continued from MTE08), erythema and edema at the application site was evaluated using a categorical (i.e., Draize score) scale. There was a possible total score of 8. During the study, the site of application was evaluated at every study visit. The majority of subjects did not register a Draize score of greater than 0 at any time point. Table 4 summarizes the registered Draize Scores (only when registered).

**Table 4: Summary of Registered Draize Scores during Study MTE09**

Days	Draize Score	Number of Subjects
15	2	1
	3	3
45	1	4
	3	1
120	1	1
180	2	1

Draize score had definitions of erythema and edema, respectively, as:

0 = no erythema; no edema,

1 = very slight erythema (barely perceptible); very slight edema (barely perceptible),

2 = well defined erythema; slight edema (edges well defined with definitive raising),

3 = moderate to severe erythema; moderate edema (area raised approximately 1 mm),

4 = severe erythema (deep/dark red erythema) to slight eschar formation (injuries in depth); severe erythema (raised more than 1mm and extending beyond area of exposure)

There was no change in the overall Draize score over time (from baseline to 180 days of treatment) or in relation to the dose given. Within the range of doses studied in these studies, there were no dose-related safety concerns.

### Effects of Deodorant and Antiperspirants

In a single dose, parallel group study conducted in healthy premenopausal female subjects to evaluate the impact of antiperspirant/deodorant application on T absorption when applied prior to application of 30 mg Axiron™,

results showed numerically lower concentrations (e.g., up to 32.8% reduction in AUC(0-72) of total T) when antiperspirant/deodorant stick or spray products were applied 2 minutes prior to Axiron™ application compared to control group.

**Table 5:** Summary of Baseline-uncorrected Mean (SD) PK Parameters (Study MTE10)

Parameter	Group 1 (N=6)	Group 2 (N=6)	Group 3 (N=6)	Group 4 (N=6)
AUC(0-72) (ng·hr/dL)	9098.0 (2003.4)	8399.8 (1416.5)	7380.1 (2016.2)	10975.6 (3178.1)
C <sub>max</sub> (ng/dL)	260.4 (110.3)	271.0 (73.7)	238.0 (47.9)	341.9 (133.5)

Group 1: Antiperspirant/deodorant stick applied 2 min prior to Axiron™ application  
 Group 2: Antiperspirant/deodorant spray applied 2 min prior to Axiron™ application  
 Group 3: Deodorant spray applied 2 min prior to Axiron™ application  
 Group 4: Control group - Axiron™ only

The limitation of this study is that it was conducted in a parallel fashion in premenopausal women which is not the target population of Axiron™. This study has used the lowest available Axiron™ dose strength (i.e., 30 mg) in order to minimize unnecessary exposure of T to women. In addition, it would probably show the worst case impact of antiperspirant/deodorant application on T absorption compared to when using higher dose strengths of Axiron™. It is noted that the normal T baseline in premenopausal women ranges between 20 and 80 ng/dL that is in the range of the T baseline (< 300 ng/dL) in hypogonadal men. Despite the existence of impact on T absorption from antiperspirant/deodorant application, restriction of antiperspirant/deodorant application prior to Axiron™ application appears to be unnecessary since this will be accounted for in the clinical dose titration process as there were no restrictions in the as the Phase 3 studies. The potential of T contamination when using stick products following Axiron™ application has not been evaluated.

### Effects of Application Site Washing

In a single dose, parallel group study conducted in healthy premenopausal female subjects to evaluate the impact of washing the application site on T absorption at 2 hr (Group 5) and 6 hr (Group 6) following a single application of 30 mg (1 pump actuation) Axiron™ to 1 axilla of each subject. Study results showed numerically lower concentrations (e.g., up to 35.3% AUC(0-72) reduction of total T) in Groups 5 and 6 compared to Group 4 (which only applied 30 mg Axiron™ but had no washing).

**Table 6:** Summary of Baseline-uncorrected Mean (SD) PK Parameters (Study MTE10)

Parameter	Group 4 (N=6)	Group 5 (N=6)	Group 6 (N=6)
AUC(0-72) (ng·hr/dL)	10975.6 (3178.1)	7097.9 (1392.5)	8108.8 (2041.9)
C <sub>max</sub> (ng/dL)	341.9 (133.5)	220.6 (89.0)	279.7 (115.7)

Group 4: Control group - Axiron™ only  
 Group 5: Application site washed 2 hr post Axiron™ application  
 Group 6: Application site washed 6 hr post Axiron™ application

The limitation of this study is that it was conducted in a parallel fashion in premenopausal women which is not the target population of Axiron™. According to the Biostatistic reviewer, Dr. Xin Fang, the difference of AUC(0-72) between Group 4 (control) vs. Group 5 is statistically significant (p-value = 0.005). The treatment group that washed the application site 6 hr following application of Axiron™ (Group 6) still showed a reduction in total T exposure but to a smaller extent. Subjects were instructed to refrain from washing or swimming for 2 hr after Axiron™ application on PK days in the Phase 3 study (MTE08) and washing the application site after 2 hr or more was accounted for in the dose titration recommendation. Axiron™ users should avoid swimming or washing the application site for 2 hr after Axiron™ application.

### Application Site Residual Evaluation following Washing

One of the safety concerns with topical hormonal products is potential of interpersonal transfer. A clinical study was conducted to evaluate the amount of residual T remaining on the axilla in 10 healthy Caucasian males. All subjects received 60 mg Axiron™ on each axilla. Axiron™ was allowed to dry for 5 min and the left axilla was wiped with alcohol towelettes which were assayed for T content. Subjects were required to shower following a predefined procedure with soap and water 30 min after application. The right axilla was then wiped with

alcohol towelettes which were assayed for T content. A mean of  $3.1 \pm 2.8$  mg T was recovered using alcohol towelettes. This amount equals to a 93.6% decrease of residual T recovered from the axilla without washing ( $42.1 \pm 4.1$  mg T). Study results showed that the use of a showering procedure utilizing soap and water reduced the residual T on axilla and washing the application site can reduce the risk of potential interpersonal transfer.

### Interpersonal Transfer Potential

A single dose clinical study was conducted to evaluate the potential for interpersonal transfer from healthy male subjects using Axiron™ to healthy female subjects when vigorous contact was made for 15 min at 2 hr post-application of 120 mg Axiron™. 10 males and 10 females between the ages of 18 and 45 yr were enrolled. The application site was covered with a 100% cotton long sleeve T-shirt prior to the transfer procedure. Female subjects underwent intensive PK sampling for a 24 hr period for baseline characterization. Study results showed approximately 13% and 17% increase in both mean total T AUC(0-24) and C<sub>max</sub> values, respectively, following the transfer procedure.

**Table 7:** Summary of Arithmetic Mean (SD) PK Parameter Estimates for Total T Before (baseline) and Following Transfer Procedure (Study MTE12)

Parameter	Baseline (A) (N=9)	After Transfer Procedure (B) (N=9)	Ration of Geometric LS Means (B:A)	90% CI for the Ratio (B:A)
AUC(0-24) (ng-h/dL)	501 ± 281 <sup>a</sup>	558 ± 307 <sup>a</sup>	1.13	1.06, 1.20
C <sub>max</sub> (ng/dL)	25.5 ± 16.3 <sup>a</sup>	29.8 ± 18.0 <sup>a</sup>	1.17	NR <sup>b</sup>

<sup>a</sup> From subjects without any protocol violation (N=9)

<sup>b</sup> Not reported

In another clinical study (Study MTE06) conducted in a similar fashion, interpersonal transferability was evaluated after 30 mg 1% T solution was applied to each axilla. After female subjects made contact 2 hr post application (with and without a donor wearing a shirt), it was shown that transfer of T was significantly reduced by wearing a T-shirt.

**Table 8:** Summary of Arithmetic Mean (SD) PK Parameters for Total T following Transfer Procedures with or without T-shirts on (Study MTE06)

Parameter	Skin-to-skin transfer (N=6)	Transfer with T-shirts on 2 hr after application (N=6)
AUC(0-72) (ng-h/dL)	5050.7 ± 2793.6	2135.7 ± 911.5
C <sub>max</sub> (ng/dL)	225.2 ± 184.9	47.0 ± 26.4

### Drug-Drug Interactions

No drug-drug interaction (DDI) studies were conducted with Axiron™. Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement. Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy. The concurrent use of T with adreno-corticotrophic Hormone (ACTH) or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal, or hepatic disease.

### Use in Specific Populations and Waiver Request for Pediatrics

#### Pediatric Use and Pediatric Study Waiver Request

No pediatric studies were conducted. Safety and efficacy of Axiron™ has not been established in males < 18 years of age. Improper use may result in acceleration of bone age premature closure of epiphyses. Precaution should be taken for unintentional secondary exposure.

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

#### Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing Axiron™ to determine whether efficacy in those over 65 yr of age differs from younger subjects. Only 21 geriatric patients of over 65 yr of age (out of a total of 155 patients) were enrolled in the pivotal Phase 3 clinical study. Additionally, there are insufficient long-term safety data in geriatric patients utilizing Axiron™ to assess a potential incremental risk of cardiovascular disease and prostate cancer.

#### Renal / Hepatic Impaired Patients

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

#### Effect of Body Mass Index (BMI)

Only men with BMI < 35.0 kg/m<sup>2</sup> were enrolled in Studies MTE08 and MTE09. However, modest elevation in BMI resulted from a minor increase in body weight during the course of the study (i.e., after Day 60) in 4 patients. The potential influence of body fat, as measured by BMI, on total T systemic exposure (C<sub>avg</sub>) was explored; whereby individual estimates of C<sub>avg</sub> across the entire study (Days 15, 60, and 120) were examined. No systematic pattern for higher exposures in those having a lower BMI compared to those having higher BMI was discerned from an examination of C<sub>avg</sub>. Safety and efficacy of Axiron™ in males with BMI > 35.0 kg/m<sup>2</sup> has not been established.

#### **Bioanalytical Methods**

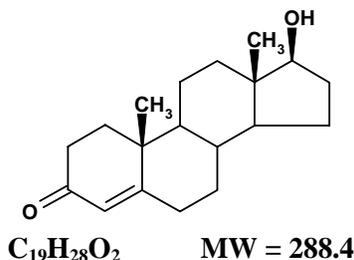
Serum samples were analyzed for total T and DHT by validated bioanalytical methods including radioimmunoassays (RIA), liquid chromatography-mass spectrometry (LC-MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The determination of SHBG for the Phase 3 study samples was performed using an enzyme immunoassay. Acceptance criteria and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance* and therefore found to be acceptable. A formal DSI consult on the clinical and bioanalytical study sites has been signed off in DARRTS by Dr. Dennis Bashaw on March 18, 2010 and DSI's memorandum reveals that there are no unresolved issues that would affect the approvability of Axiron™ (refer to DSI's memorandum in DARRTS dated October 29, 2010).

## 2. QUESTION BASED REVIEW

### 2.1 General Attributes

#### 2.1.1 What is Axiron™ and its active pharmacological ingredient?

Axiron™ is a clear, colourless, single phase solution containing 2% T for topical administration through the axilla. The active pharmacologic ingredient in Axiron™ 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:



The inactive ingredients are ethanol, isopropyl alcohol, octisalate, and povidone.

#### 2.1.2 What clinical data and related information is submitted to support the approval of Axiron™?

The Sponsor submitted 12 Biopharmaceutical/Clinical Pharmacology and Clinical studies including multiple-dose PK (MTE07), evaluation of the effect of antiperspirant/deodorant applications and the effect of application site washing (MTE06 with 1% T and MTE10 with 2% T), evaluation of application site washing on residual T (MTE11), and evaluation of interpersonal transferability (MTE12 with 2% T and MTE06 with 1% T), and 2 pivotal Phase 3 clinical studies (MTE08 and MTE09) to support the approval of Axiron™. Study MTE08 was an open-label titration study to evaluate the safety and efficacy of various doses of Axiron™ in hypogonadal men for 120 days while Study MTE09 was an open-label extension of Study MTE08 to 180 days to evaluate skin safety. In addition, the Sponsor submitted the following information:

- Draft labeling in PLR format
- Bioanalytical study reports and method validation reports
- Request of waiver for pediatric studies

### 2.2 General Clinical Pharmacology and Biopharmaceutics

#### 2.2.1 What is the proposed mechanism of action?

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

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

Axiron™ was developed with an aim to ensure that the desired serum T concentrations (i.e., 300–1,050 ng/dL) are achieved in hypogonadal men following treatment with Axiron™.

### **2.2.2 What is the dosing regimen and dose titration scheme?**

The recommended starting dose of Axiron™ is 60 mg (2 pump actuations) applied once daily. To ensure proper dosing, serum T concentrations should be measured after initiation of therapy to ensure that the desired levels (i.e., 300–1,050 ng/dL) are achieved. Clinical studies with Axiron™ have shown that dose titration should be conducted based on the serum total T concentration from a single blood draw 2-8 hr after dosing and at least 15 days after initiation of therapy.

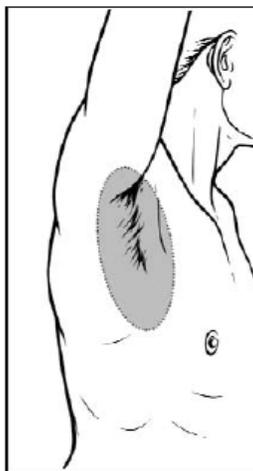
If the measured serum T concentration is below 300 ng/dL, the daily Axiron™ dose may be increased from 60 mg (2 pump actuations) to 90 mg (3 pump actuations) or from 90 mg to 120 mg (4 pump actuations). If the serum T concentration exceeds 1,050 ng/dL, the daily Axiron™ dose should be decreased, from 60 mg (2 pump actuations) to 30 mg (1 pump actuation) as instructed by a physician. If the serum T concentration consistently exceeds 1,050 ng/dL at the lowest daily dose of 30 mg (1 pump actuation), Axiron™ therapy should be discontinued.

### **2.2.3 What are the administration instructions?**

Axiron™ is applied to the skin of the axilla, preferably at the same time each morning, to clean, dry, intact skin. Users should not apply Axiron™ to other parts of the body. After applying the solution, the application site should be allowed to dry completely prior to dressing. User should avoid fire, flames, or smoking until the solution has dried since alcohol based products, including Axiron™, are flammable.

Axiron™ is applied to the axilla using an applicator. When using Axiron™ for the first time, patients must be instructed to prime the pump by depressing the pump 3 times, discard any product dispensed directly into a basin, sink, or toilet and then wash the liquid away thoroughly. This priming should be done only prior to the first use of each pump. After priming, users should completely depress the pump 1 time (i.e., 1 pump actuation) to dispense 30 mg of product. To dispense the solution, position the nozzle over the applicator cup and carefully depress the pump fully once. Users should ensure that the liquid is directed into the cup. The cup should be filled with no more than 30 mg (1 pump actuation) of product. When dosing Axiron™ that requires greater than 1 pump actuation, it must be applied in increments of 30 mg as shown in Table 8. Keeping the applicator upright, users should place it up into the axilla and wipe steadily up and down into the axilla. If the solution drips or runs, it can be wiped back up with the applicator cup. The solution should not be rubbed into the skin with fingers or hand. The process is then repeated with application of 30 mg (1 pump actuation) to the other axilla to achieve a total of 60 mg of Axiron™ applied. For users prescribed the 90 mg dose, the procedure is the same, but 3 axilla applications are required. To dose 120 mg, 4 axilla applications are required alternating left and right for each application as per Table 8. Acceptable application area is illustrated in Figure 2.

**Figure 2:** Acceptable Application Area for Axiron™



**Table 9:** Application Technique for Axiron™

Daily Prescribed Dose	Number of Pump Actuations	Application
30 mg	1 (once daily)	Apply once to one axilla only (left OR right)
60 mg	2 (once daily)	Apply once to the left axilla and then apply once to the right axilla.
90 mg	3 (once daily)	Apply once to the left and once to the right axilla, wait for the product to dry, and then apply again once to the left OR right axilla.
120 mg	4 (once daily)	Apply once to the left and once to the right axilla, wait for the product to dry, and then apply again once to the left AND once to the right axilla.

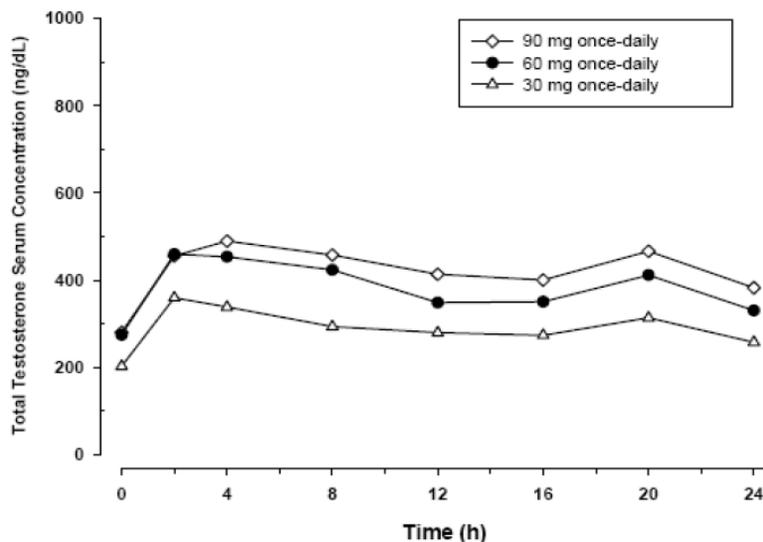
When repeat application to the same axilla is required, the axilla area should be allowed to dry completely before more Axiron™ is applied. The application site should be allowed to dry prior to dressing. Hands should be washed thoroughly with soap and water after Axiron™ has been applied. After use, the applicator should be rinsed under room temperature, running water and then patted dry with a tissue. The applicator and cap are then replaced on the bottle for storage.

#### 2.2.4 What are the multiple dose PK parameters of total T?

Multiple-dose PK of total T was characterized in an open label, randomized, 4 way cross-over study of Axiron™ applied to the axilla of hypogonadal men. The PK profiles of total T were obtained with a daily dose of 30 mg, 60 mg, and 90 mg Axiron™ as well as 30 mg of the old formulation (i.e., 1% T solution) applied to the axilla(s) of 21 hypogonadal men for 7 days in each of the 4 treatment periods. All study participants were dosed with each of the 4 study treatments (i.e., cross-over study). On the first day of each treatment period (i.e., Days 1, 8, 15, and 22), study participants reported to the clinic and the study drug was applied in the morning (normally at 8 am) at the study center with the assistance and supervision of the study staff. On the other days, study participants applied the drug once daily at approximately the same time each morning at home and recorded each administration on a daily dosing chart. 24 hr period of intensive blood sampling (i.e., at 0, 2, 4, 8, 12, 16, 20, 24 hr post-dose) occurred on Days 7, 14, 21, and 28. There was no washout period between each treatment period considering that the steady-state of T is reached within 7 days of application. PK of the 120 mg dose was not characterized in this study. PK parameters in Table 9 were calculated in the population that completed the study without any significant protocol violations or deviations (N=18). 3 study participants (i.e., Study participants 0304, 0903, and 0906) that had deviations from the protocol with regard to treatments administered were omitted from the final analysis set.

**Table 10:** Arithmetic Mean (SD) PK Parameters of Total T by Treatment

Treatment	C <sub>ave</sub> (ng/dL)	AUC(0-24) (ng·hr/dL)	C <sub>max</sub> (ng/dL)	C <sub>min</sub> (ng/dL)	T <sub>max</sub> <sup>a</sup> (hr)
30 mg Axiron™	267 (100)	6399 (2405)	395 (216)	161 (50)	16.00 (1.95, 23.93)
60 mg Axiron™	368 (131)	8837 (3131)	547 (242)	214 (99)	4.13 (0, 20.00)
90 mg Axiron™	413 (173)	9907 (4145)	588 (223)	239 (123)	12.01 (1.92, 23.97)

<sup>a</sup> Median (min, max)**Figure 3:** Arithmetic mean total T serum concentrations following 7 days of once-daily administration of 30 mg, 60 mg, and 90 mg Axiron™ (Study MTE07)

As shown in Figure 3, after an initial plateau of serum total T concentration was observed between 2 and 4 hr post-dose, a second plateau that is comparable or even higher than the first one was observed between approximately 16 and 20 hr post-dose. While the cause of having two plateaus is unknown, it should be noted that this trend was observed consistently in the PK profiles of Axiron™. A more careful examination of the individual PK data shows that the 60 mg Axiron™ group had 10 individuals with  $T_{max} \leq 4.25$  hr while the 30 mg and 90 mg Axiron™ group had 8 individuals with  $T_{max} \leq 4.25$  hr. Considering that 8-10 individuals are approximately half of the population (N=18) included in the final analysis and the fact that  $T_{max}$  was equal or longer than 16 hr in majority of the remaining individuals in each treatment group may lead to an explanation of the different median  $T_{max}$  values across the treatment groups. Mean  $C_{avg}$  and AUC(0-24) of total T following daily administration with 30, 60, and 90 mg of Axiron™ for 7 days are not dose proportional but exposure increased with increasing the dose.

### 2.2.5 Does application of antiperspirant/deodorants prior to Axiron™ application affect the absorption of T following Axiron™ application?

A single dose, parallel group study (Study MTE10) was conducted in healthy premenopausal female subjects randomized into 3 treatment groups to evaluate the impact of antiperspirant/deodorant application on T absorption when applied prior to application of 30 mg Axiron™. 2 pre-dose baseline PK blood samples were collected, 1 within 30 min prior to Axiron™ administration and 1 right before Axiron™ administration. Individual pre-dose baseline total T concentrations ranged between 18.18 and 43.62 ng/dL with the exception of Subject 001035 (Group 3) that had baseline T concentrations of 91.37 and 72.46 ng/dL and were comparable between each group (i.e., mean T baseline of each group were 27.5, 28.9, 23.3, and 26.2 ng/dL, respectively). Demographic and other baseline characteristics (i.e., age, race, height, weight, BMI, smoking habits, and alcohol

consumption) among the treatment groups were comparable and no significant differences were observed. Subjects were randomized into 1 of the following treatment groups:

- Group 1: Antiperspirant/deodorant stick for men (i.e., Speed Stick Antiperspirant deodorant solid unscented [3 oz, Colgate-Palmolive Co., product code: 031525]) applied 2 min prior to Axiron™ application. Stick product was applied to skin using 2 strokes. A single stroke constituted wiping the stick in a downward or upward motion along the axilla.
- Group 2: Antiperspirant/deodorant spray (i.e., Right Guard Sport Antiperspirant deodorant spray unscented [6 oz, Gillette, product code: 678369]) applied 2 min prior to Axiron™ application. Spray product was applied by holding the spray product can 6 inches (15 cm) from the axilla and by pressing down the nozzle and spraying for 2 consecutive sec.
- Group 3: Deodorant spray (i.e., Right Guard Sport deodorant spray original [10 oz, Gillette, product code: 852113]) applied 2 min prior to Axiron™ application. Spray product was applied by holding the spray product can 6 inches (15 cm) from the axilla and by pressing down the nozzle and spraying for 2 consecutive sec.
- Group 4: Control group - Axiron™ only.

Mean total T PK parameters obtained from subjects in Groups 1 to 3, with pre-application of antiperspirant/deodorant stick or spray or deodorant spray, were compared to the control group (Group 4).

**Table 11:** Summary of Baseline-uncorrected Mean (SD) Total T PK Parameters (Study MTE10)

Parameter	Group 1 A/D Stick (N=6)	Group 2 A/D Spray (N=6)	Group 3 D Spray (N=6)	Group 4 Control (N=6)
AUC(0-72) (ng-hr/dL)	9098.0 (2003.4)	8399.8 (1416.5)	7380.1 (2016.2)	10975.6 (3178.1)
p-value for AUC(0-72) (vs. Group 4)	0.214	0.086	0.011	-
C <sub>max</sub> (ng/dL)	260.4 (110.3)	271.0 (73.7)	238.0 (47.9)	341.9 (133.5)

Please note that this Table only shows treatment groups that were used in evaluating the antiperspirant/deodorant effects.

The study results showed that the pre-application of antiperspirants/deodorants has reduced the total T concentrations (e.g., up to 32.8% AUC(0-72) reduction in Group 3) in all 3 groups compared to the control group (Group 4).

Per the Biostatistic reviewer, Dr. Xin Fang, the statistical analysis revealed that the difference of AUC(0-72) between Group 4 (control) vs. Group 3 is statistically significantly different (p-value = 0.011). The following results are obtained using log of AUC(0-72) and log of C<sub>max</sub> through an ANOVA model. The ANOVA model only included fixed effect of group. The Sponsor's p-value of 0.058 is for overall comparison of AUC(0-72) between 5 treatments and control. Statistical comparison of AUC(0-72) and C<sub>max</sub> between each individual treatment is summarized in Tables 12 and 13 below, respectively:

**Table 12:** Statistical Comparison of AUC(0-72) between Individual Treatment Groups

Treatment	Estimate	Standard Error	DF	t-value	p-value
Group 4 vs. 1	0.1745	0.1373	29	1.27	0.2140
Group 4 vs. 2	0.2443	0.1373	28	1.78	0.0875
Group 4 vs. 3	0.3905	0.1440	29	2.71	0.0112

**Table 13:** Statistical Comparison of C<sub>max</sub> between Individual Treatment Groups

Treatment	Estimate	Standard Error	DF	t-value	p-value
Group 4 vs. 1	0.2799	0.2100	29	1.33	0.1930
Group 4 vs. 2	0.2027	0.2100	29	0.97	0.3424
Group 4 vs. 3	0.3173	0.2203	29	1.44	0.1605

The limitation of this study is that it was conducted in a parallel fashion in premenopausal women. It was noted that the mean baseline T concentration of Group 3 (23.3 ng/dL) was lower than the control, Group 4 (26.2

ng/dL) while Groups 1 and 2 had a slightly higher mean baseline T concentration (27.5 and 28.9 ng/dL, respectively) compared to Group 4. However, the impact of this on the statistical analysis results is unknown. In addition, the Phase 3 studies were conducted with no restrictions of antiperspirant/deodorant use. Only 42 out of 138 subjects have refrained from using these products concomitantly. While it is difficult to estimate the extent of impact of antiperspirant and deodorant application on T absorption when applied prior to Axiron™ application in hypogonadal men, the impact of antiperspirant and deodorant use will be accounted for in the clinical dose titration process. Therefore, despite the observed influence of antiperspirant/deodorant application on T absorption, restriction of antiperspirant/deodorant application prior to Axiron™ application appears to be unnecessary. If patients use an antiperspirant or deodorant products (e.g., stick, roll-on, or spray), then it should be applied at least 2 min prior to the application of Axiron™ to avoid contamination of the stick or roll-on product. This information is reflected in the product labeling.

## 2.2.6 Does washing the application site after Axiron™ application affect the total T exposure?

A single dose, parallel group study (Study MTE10) was conducted in healthy premenopausal female subjects (18-45 yr old with BMI of 19-30 kg/m<sup>2</sup>) to evaluate the impact of washing the application site on T absorption at 2 hr (Group 5) and 6 hr (Group 6), respectively, following application of 30 mg Axiron™. 2 pre-dose baseline PK blood samples were collected, 1 within 30 min prior to Axiron™ administration and 1 right before Axiron™ administration. Pre-dose baseline total T concentrations ranged between 18.18 and 38.28 ng/dL and were comparable between each group (i.e., mean T baseline of each group were 26.2, 23.8, and 26.0 ng/dL, respectively). Demographic and other baseline characteristics (i.e., age, race, height, weight, BMI, smoking habits, and alcohol consumption) among the treatment groups were comparable and no significant differences were noted. Subjects were randomized into 1 of the following treatment groups:

- Group 4: Control group - Axiron™ only.
- Group 5: Application site washed 2 hr after Axiron™ application using a Dove® soap bar
- Group 6: Application site washed 6 hr after Axiron™ application using a Dove® soap bar

The washing procedure was performed by the site staff. At the nominal time the site staff washed the application site on the subjects to ensure consistency. The washing procedure involved evenly rinse the application site with warm water, gently rubbing the application site twice with Dove® soap solution, rinse the application site with warm water, and drying the application site gently with a fresh towel.

Mean total T PK parameters obtained from subjects in Groups 5 and 6, with application site washed 2 hr or 6 hr after Axiron™ application, respectively, were compared to the control group (Group 4).

**Table 14:** Summary of Baseline-uncorrected Mean PK Parameters (Study MTE10)

Parameter	Group 4 Control (N=6)	Group 5 Washing 2 hr after application (N=6)	Group 6 Washing 6 hr after application (N=6)
AUC(0-72) (ng·hr/dL)	10975.6 (3178.1)	7097.9 (1392.5)	8108.8 (2041.9)
p-value for AUC(0-72) (vs. Group 4)	-	0.005	0.041
C <sub>max</sub> (ng/nL)	341.9 (133.5)	220.6 (89.0)	279.7 (115.7)

The study results demonstrate that washing the application site 2 hr or 6 hr using a Dove® soap bar after Axiron™ application has reduced the total T concentrations (e.g., up to 35.3% AUC(0-72) reduction in Group 5) compared to the control group (Group 4).

Per the Biostatistic reviewer, Dr. Xin Fang, the statistical analysis reveals that the difference of AUC(0-72) between Group 4 (control) vs. Group 5 is statistically significant. The following results are obtained using log of AUC(0-72) and log of C<sub>max</sub> through an ANOVA model. The ANOVA model only included fixed effect of group. The Sponsor's p-value of 0.058 is for overall comparison of AUC(0-72) between 5 treatments and

control. Statistical comparison of AUC(0-72) and  $C_{max}$  between each individual treatment is summarized in Tables 15 and 16 below, respectively:

**Table 15:** Statistical Comparison of AUC(0-72) between Individual Treatment Groups

Group	Estimate	Standard Error	DF	t-value	p-value
Group 4 vs. 5	0.4187	0.1373	29	3.05	0.0049
Group 4 vs. 6	0.2938	0.1373	29	2.14	0.0410

**Table 16:** Statistical Comparison of  $C_{max}$  between Individual Treatment Groups

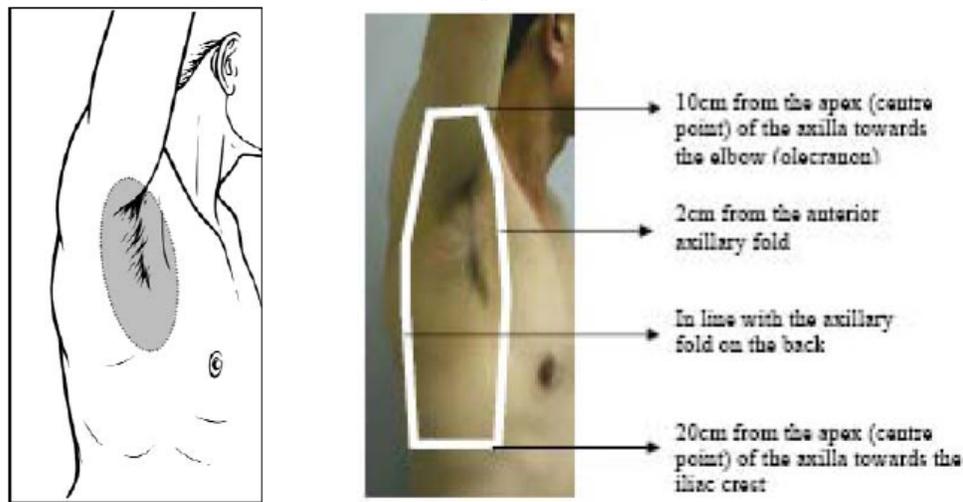
Group	Estimate	Standard Error	DF	t-value	p-value
Group 4 vs. 5	0.4438	0.2100	29	2.11	0.0433
Group 4 vs. 6	0.2158	0.2100	29	1.03	0.3127

The limitation of this study is that it was conducted in a parallel fashion in premenopausal women. It was noted that the mean baseline T concentration of Group 5 (23.8 ng/dL) was lower than the control, Group 4 (26.2 ng/dL) while Group 6 had a comparable mean baseline T concentration of 26.0 ng/dL compared to Group 4. However, the impact of this on the statistical analysis results is unknown. Subjects were instructed to refrain from washing or swimming for 2 hr after Axiron™ application on PK days in the Phase 3 study (MTE08) and washing the application site after 2 hr or more was accounted for in the dose titration recommendation. Axiron™ users should avoid swimming or washing the application site for 2 hr after Axiron™ application. However, to reduce the likelihood of interpersonal transfer of T, the application site should always be washed prior to any skin-to-skin contact regardless of the length of time since application. This information is reflected in the product labeling.

### 2.2.7 What are the findings from residual amount determination before and after washing the application site after Axiron™ application?

A clinical study was conducted in 10 healthy Caucasian male subjects (18-70 yr old) to evaluate the residual T on the axilla following before and after application site washing after Axiron™ application. After showering on Day 1, all subjects received 120 mg Axiron™ to each axilla (equivalent to a 60 mg dose per axilla). Axiron™ was allowed to dry for 5 min and the left axilla was wiped with 10 alcohol towelettes (Liv-wipe®) which were assayed for T content. Subjects were required to shower with soap (i.e., 3 mL of Zest® Ocean Energy Body Wash shower gel) and water 30 min after application. The right axilla was then wiped with 10 alcohol towelettes (Liv-wipe®) which were assayed for T content. The left axilla of the subject acted as the control.

**Figure 4:** Acceptable Application Area (Left) and Wiping Area (Right) of Axiron™



The total mean T recovered from the unwashed axilla (including the small amount recovered from the gloves) was  $42.1 \pm 4.1$  mg of T which equates to  $70.2 \pm 6.9$  % of the applied dose of 60 mg 9from the axilla). The total mean T recovered from the axilla that was washed with soap and water was  $3.1 \pm 2.8$  mg which equates to  $5.2 \pm 4.7\%$  of the applied dose of 60 mg. The study results showed a 92.6% of reduction of residual T on the axilla ( $[(42.1 \text{ mg} - 3.1 \text{ mg}) / 42.1 \text{ mg}] \times 100 = 92.6 \%$ ) following washing with soap and water compared to when axilla was not washed. This information is reflected in the product labeling.

### 2.2.8 What is the interpersonal transferability potential of T from Axiron™?

A single dose clinical study to evaluate the interpersonal transferability potential from healthy male subjects using Axiron™ to healthy female subjects was conducted. The study population consisted of healthy premenopausal female subjects and male subjects aged 18-45 yr., with BMI 19-28 kg/m<sup>2</sup> for the females and BMI 19-30 kg/m<sup>2</sup> for males. Female subjects underwent baseline intensive PK sampling during a 24 hr period prior to the transfer procedure to establish their baseline levels of T and DHT. Eligible healthy male subjects received a 120 mg dose (2 pump actuation to each axilla) of Axiron™. Female study subjects underwent 15 min of vigorous contact at 2 hr after application of Axiron™ to the male subjects. Male (donor) subjects were required to wear a long sleeve 100% cotton T-shirt during the transfer procedure. Female (recipient) subjects were involved in further intensive PK sampling following the transfer procedure. Subject S05/R04/NLB was concurrently enrolled in another clinical trial at another institution. This subject was excluded from the final data analysis. As shown in Table 17, the study result showed a 13% and 17% increase in T exposure (AUC[0-24]) and C<sub>max</sub>, respectively, compared to baseline in females.

**Table 17:** Summary of Arithmetic Mean (SD) PK Parameter Estimates for Total T Before (baseline) and Following Transfer Procedure (Study MTE12)

Parameter	Baseline (A) (N=9)	After Transfer Procedure (B) (N=9)	Ration of Geometric LS Means (B:A) <sup>a</sup>	90% CI for the Ratio (B:A) <sup>a</sup>
AUC(0-24) (ng·h/dL)	501 ± 281 <sup>b</sup>	558 ± 307 <sup>b</sup>	1.13	1.06, 1.20
C <sub>max</sub> (ng/dL)	25.5 ± 16.3 <sup>b</sup>	29.8 ± 18.0 <sup>b</sup>	1.17	NR <sup>c</sup>

<sup>a</sup> A mixed effect model with  $\log(\text{PK}) = \text{TREATMENT}(\text{fixed effect}) + \text{SUBJECT}(\text{random effect}) + \text{RANDOM ERROR}$  was fitted to the log transformed PK parameters of T. Geometric least squares (LS) mean ratio (and 90% CI) for comparisons between baseline and post transfer procedure were determined for the subjects without any protocol violation (N=9).

<sup>b</sup> From subjects without any protocol violation (N=9)

<sup>c</sup> Not reported

There was no study conducted to assess direct skin-to-skin effect transfer potential using Axiron™ (i.e., 2% T). In a separate clinical study (MTE06) conducted with 30 mg of a 1% T formulation on each axilla under similar conditions, direct skin-to-skin transfer showed a 2.3-fold and 4.0-fold increase in T AUC(0-72) and T C<sub>max</sub>, respectively, compared to when men had a T-shirt on.

**Table 18:** Summary of Arithmetic Mean (SD) PK Parameters for Total T following Transfer Procedures with or without T-shirts on (Study MTE06)

Parameter	Skin-to-skin transfer (N=6)	Transfer with T-shirts on 2 hr after application (N=6)
AUC(0-72) (ng·h/dL)	5050.7 ± 2793.6	2135.7 ± 911.5
C <sub>max</sub> (ng/dL)	225.2 ± 184.9	47.0 ± 26.4

**Figure 5:** Mean (SD) total T serum concentration-time profiles in females following transfer procedure with clothing covering the application area in Studies MTE12 and MTE06 and without clothing covering the application area (Study MTE06)

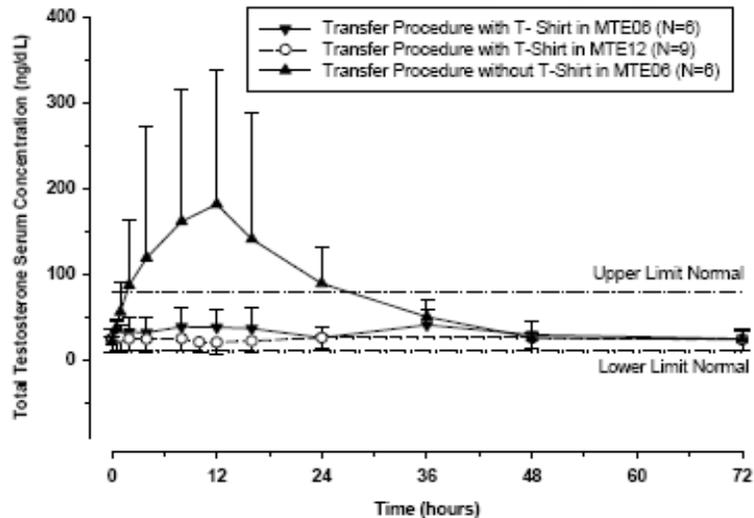


Figure 5 shows that direct skin-to-skin contact without a T-shirt barrier resulted in a substantially higher T transfer compared to when having a T-shirt on. While interpersonal T transfer from Axiron™ can occur with a T-shirt on, it has been shown that transfer can be highly reduced by wearing a T-shirt. This information is reflected in the product labeling.

### 2.2.9 How was the safety and efficacy Axiron™ assessed?

Axiron™ was developed aiming the circulating total T concentrations to be within the range of 300-1,050 ng/dL in adult males for conditions associated with a deficiency or absence of endogenous T. The Sponsor submitted a pivotal Phase 3 safety and efficacy clinical study (MTE08) and a clinical skin safety study (MTE09) to support the approval of Axiron™. Study MTE08 was an open-label titration study to evaluate the safety and efficacy of various doses (i.e., 30 mg, 60 mg, 90 mg, or 120 mg) of Axiron™ in hypogonadal men for 120 days while Study MTE09 was an open-label extension of Study MTE08 to 180 days to evaluate skin safety. The primary endpoints were:

- Study MTE08: The proportion of subjects with  $C_{avg}(0-24)$  of total T within the normal range at Day 120. The study was to be deemed successful if 75% or more of subjects had a T  $C_{avg}(0-24)$  in the range of 300-1,050 ng/dL on Day 120. The value of the lower limit of the two-sided 95% Wald confidence interval had also to exceed 66.8%.
- Study MTE09: To observe the change in subject Draize Score (Day 1 to Day 180) after 6 months of continuous use of Axiron™.

#### Study Sites, Population, and Sample Size

Study MTE08 involved 26 sites: 12 sites in the US, 4 sites in Australia, 3 sites in the UK, 2 sites in Sweden, 2 sites in France and 3 sites in Germany. The open label continuous use study (MTE09) involved only subjects from the 12 US sites. The MTE08 study enrolled 155 subjects and the MTE09 study enrolled 71 subjects.

In Study MTE08, of the 363 subjects enrolled, 208 were screen failures. 155 subjects were started on the 60 mg dose and received at least one dose of Axiron™ in Study MTE08. The majority of the subjects were Caucasian (84.7%), with a mean age of  $51.5 \pm 12.7$  yr and an age range of 18-78 yr. 21 out of 155 subjects enrolled were 65 yr or older. Subjects with BMI of higher than  $35 \text{ kg/m}^2$  were excluded from the study. The mean BMI was  $29.5 \pm 3.6 \text{ kg/m}^2$ . BMI for all individuals enrolled were  $< 35 \text{ kg/m}^2$  at randomization in Study MTE08. However, there were 4 subjects with BMI higher than  $35 \text{ kg/m}^2$  on Day 120 due to modest elevation in increase in body weight during the course of the study. It should be noted that body weight was not assessed on Day 90. There was a subject with the baseline serum total T concentration higher than 300 ng/dL due to the use of incorrect

screening total T concentrations (i.e., from other subject) for enrollment decision. These individuals were excluded from the primary efficacy analysis.

Of the 155 subjects enrolled, 135 subjects have completed the study. There were 20 withdrawals (12.9%) from the MTE08 study for the following reasons:

- 4 for non compliance (2.58%),
- 1 for having screening T levels > 300 ng/dL (0.65%)
- 2 lost to follow up (1.29%),
- 3 due to an AE (pre-existing superficial thrombophlebitis, melanoma, and angry emotional changes) (1.94%),
- 9 withdrew consent (5.81%); and
- 1 per Sponsor's request (1.29%).

Reference is made to the minutes of the End of Phase 2 (EOP2) meeting held between DRUP and the Sponsor on March 13, 2008. DRUP responded to the Sponsors inquiry that in addition to the anticipated 107 completers for the measurement of the primary endpoint in Study MTE08, a minimum of 50 subjects should be exposed to Axiron™ for at least 6 months to determine skin safety in Study MTE09. 138 subjects completed Study MTE08 and 71 subjects were included in the skin safety analysis of Study MTE09. Therefore, the number of subjects in Studies MTE08 and MTE09 are sufficient to demonstrate efficacy and skin safety, respectively. The reason for the Sponsor's request for withdrawal of 1 subject mentioned above is unknown.

In Study MTE09, the median age of subjects in the safety set was 53 yr old, with an age range of 21-78 yr. Of the 71 subjects in the safety set, 54 (76.1%) were Caucasian, 10 (14.1%) were Hispanic, 6 (8.5%) were African Americans, and 1 (1.4%) had race recorded as "Other". The mean BMI was 29.78 kg/m<sup>2</sup>.

#### Study Design

**Study MTE08:** On Day 1, subjects started their daily treatment with a dose of 60 mg Axiron™ (i.e., one pump actuation [1.5 mL] applied to each axilla). During Study MTE08, decisions regarding the titration of subjects onto higher or lower doses of the product were made using C<sub>avg(0-24)</sub> data (i.e., the average serum concentration of T across a 24 hr period.) obtained on Days 15 and 60. On these days, subjects underwent intensive PK sampling over a 24 hr period. Total serum T and DHT were measured and free T calculated at pre-dose (0), 2, 4, 8, 12, 16, 20, and 24 hr post-dose. SHBG was measured in samples collected at pre-dose (0) and at 24 hr post-dose. The ratio of DHT:T was also assessed at each time point during the intensive sampling periods. The concentrations of free T were calculated using the literature method outlined below (Vermeulen *et al.*, 1999).

$$\text{Free Testosterone} = \text{Total T} * \left[ \frac{1}{1 + K_{\text{SHBG}} * [\text{SHBG}] + n * K_{\text{ALB}} * [\text{ALB}]} \right]$$

Where,

- SHBG values were reported as nmol/L and converted to mol/L or Molar concentration (multiplied by a factor of 10<sup>-9</sup>).
- K<sub>SHBG</sub> for T (association constant for binding to SHBG) is 0.6 x 10<sup>9</sup> M<sup>-1</sup>.
- For the calculation of free T concentration from 0 to 20 hrs, SHBG reported at time "0" and for 24 hr and beyond, the SHBG values at 24 hr were used.
- n\*KALB (the product of the number of binding sites per molecule and the association constant for albumin) is 4 x 10<sup>4</sup> M<sup>-1</sup>
- The plasma albumin values reported for each subject (reported in g/L and converted to molar concentrations by dividing with the molecular weight of albumin, 69,000 Da) were used in the Sponsor's calculations
- The free T concentrations were reported in units of pg/ml.

On Days 45 and 90, subjects returned to the study centre and were titrated to a lower dose, a higher dose or remained on their current dose, depending on their serum total T  $C_{avg}(0-24)$  values measured on Day 15 and 60, respectively. Dosing titrations were conducted with the following rules:

- Subjects with a  $C_{avg}(0-24)$  of 300-1,050 ng/dL were maintained on their current dose
- Subjects on the 30 mg dose with a  $C_{avg}(0-24)$  of < 300 ng/dL were titrated to a 60 mg dose
- Subjects on the 30 mg dose with a  $C_{avg}(0-24)$  of > 1050 ng/dL were withdrawn from the study
- Subjects on the 60 mg dose with a  $C_{avg}(0-24)$  of < 300 ng/dL were titrated to a 90 mg dose
- Subjects on the 60 mg dose with a  $C_{avg}(0-24)$  of > 1050 ng/dL, were titrated to a 30 mg dose
- Subjects on the 90 mg dose with a  $C_{avg}(0-24)$  of < 300 ng/dL, were titrated to a 120 mg dose
- Subjects on the 90 mg dose with a  $C_{avg}(0-24)$  of > 1050 ng/dL were titrated to a 60 mg dose

**Study MTE09:** This was an open label, multi-centre, extension, continuous use study intended to evaluate the skin safety of Axiron™ for an additional 60 days (i.e., for a total of 180 days from the start of Study MTE08). For continuity, subjects visit days were counted from their Day 1 in the MTE08 study. Subjects were enrolled and rolled over into the MTE09 study on Day 120 of the MTE08 study. As such, if it was subsequently found that subjects did not meet all of the entry criteria for the MTE09 study, they were withdrawn. No PK blood sampling was carried out for this study.

#### *Protocol Deviations*

In total, there were 35 major deviations noted in 27 subjects, which fell into the following 4 categories:

- There were 15 instances in 12 subjects of prohibited medications being taken at some point during the study, including a subject that was on prohibited medication upon entry into the study. That subject (Subject 20401) was subsequently withdrawn from the study once the prohibited medication was discovered.
- There were 13 instances in 9 subjects of failure to dose consistently for the 3 days before an intensive sampling period (either Days 15, 60, or 120).
- There were 5 instances in 5 subjects of failure to titrate the dose according to the protocol. In 1 case, subject 20101 was titrated down to 30 mg according to his  $C_{avg}$  but subsequently titrated back up based on the Sponsor's decision, so that a repeat profile could be undertaken at the original dose. 2 subjects were incorrectly titrated at the site level on Day 90 (Subject 20531 and 60207) but were quickly rectified to their correct dose within 1 and 4 days, respectively, of their visit. Subject 20713 was titrated based on  $C_{avg}$  data received by the Sponsor (1 data time point was missing). When the final data was received in the form of listings and tables, the titration error was discovered. Lastly, Subject 20908 had the 24 hr PK blood draw after applying study drug on Day 61. The 24 hr PK data on Day 61 was included in the  $C_{avg}$  calculation and thus the subject was incorrectly titrated.
- 2 subjects did not fulfill all inclusion and exclusion criteria (Subjects 20102 [i.e., enrolled in another clinical study using a different investigational product] and 20902 [i.e., used incorrect screening total T concentration for enrollment. This subject should not have been enrolled in the study]).

#### *Primary Efficacy Analysis*

**Study MTE08:** Reference is made to the letter that the Division sent to the Sponsor on November 10, 2008 under IND 70516. The Sponsor was told that for the primary efficacy analysis, the Division will consider dropouts that occur as a result of AEs, to be failures. The Sponsor has incorporated this into their primary efficacy analysis. In addition, for the primary efficacy analysis, the Sponsor was told that the Division will consider the treatment effect to be statistically and clinically significant if the proportion of subjects with a  $C_{avg}(0-24)$  value within the normal range of 300-1,050 ng/dL on Day 120 is equal to or greater than 75% and the lower bound of the 95% CI associated with this point estimate is greater than approximately 67%.

As mentioned above, the primary efficacy analysis was conducted on the completer set (N=138 subjects) at Day 120. The completer set included all subjects who completed the Day 120 visit. 135 subjects completed the study with 20 withdrawals, including 3 of which were due to AEs. The 3 subjects that withdrew due to an AE

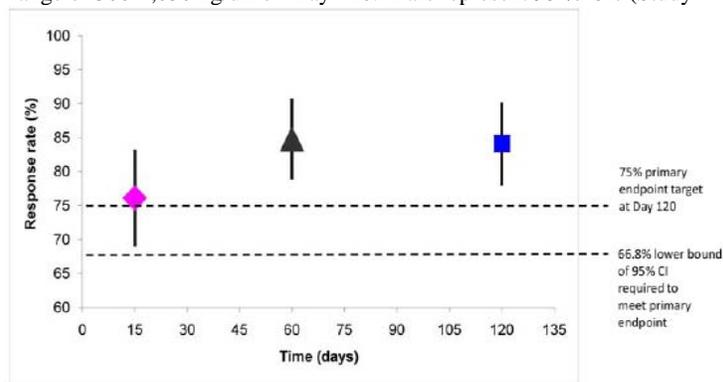
are classed as treatment failures (as agreed with the Division) and are thus included in the primary efficacy analysis (i.e., 135 completers + 3 AE withdrawals = 138 subjects). Subjects who withdrew from MTE08 prior to Day 120 for reasons other than an AE or efficacy were not included in the primary efficacy analysis. Note that for some of the PK analysis the completer set does not contain 138 subjects because PK data does not exist at all time points (days) for the 3 subjects who withdrew due to an AE.

The primary endpoint of the study was assessed based on the  $C_{avg}(0-24)$  data collected on Day 120. As shown in Table 19, the proportion of subjects with a  $C_{avg}(0-24)$  value in the normal range of 300-1,050 ng/dL on Day 120 in the completer set was 84.1% (i.e., 116 out of 138 subjects). The lower bound of the 95% CI associated with the proportion was 78.0% ( $p < 0.001$ ). While the reason was unknown, the nonresponders had a  $C_{avg}(0-24)$  value below 300 ng/dL on Day 120. It was noted that 75% (87/116) of the responders were on the 60 mg dose, while 2% (2/116), 17% (20/116), and 6% (7/116) were on the 30 mg, 90 mg, and 120 mg, respectively, on Day 120.

**Table 19:** Primary Efficacy Endpoint Analysis: Proportion of Responders who had steady-state Serum Total T  $C_{avg}$  in the range 300 to 1,050 ng/dL at Day 120 (Study MTE08)

Data Set	Day 120	
	Responders	Proportion of Responders (95% CI)
Completer Set (N=138)	116/138	84.1% (78.0-90.2)
Per Protocol Set (N=123)	106/123	86.2% (80.1-92.3)
Full Analysis Set (N=143)	116/138	84.1%, (NR)

**Figure 6:** Primary endpoint analysis: proportion of subjects who had steady-state Serum Total T  $C_{avg}$  in the range of 300-1,050 ng/dL on Day 120. Bars represent 95 % CIs (Study MTE08)



### PK Parameters

**Total T PK:** A responder was defined as a subject who had a  $C_{avg}(0-24)$  in the defined normal range for Total T of 300-1,050 ng/dL on Day 120 of treatment. At the time of enrollment the arithmetic mean baseline T levels in the safety set (N=155), was  $196.7 \pm 91$  ng/dL. The increases in  $C_{avg}(0-24)$  observed between Day 15 and Day 60 are reflected in the proportion of subjects in the normal range that also increased from Day 15 (76.1%) to Day 60 (84.8%) (Table 20). The increment in  $C_{avg}(0-24)$  observed between Day 60 and Day 120 was minimal, as was the change in the proportion of subjects in the normal range between these days (84.8% and 84.1% at Days 60 and 120, respectively).

**Table 20:** Baseline-unadjusted Arithmetic Mean ( $\pm$ SD) Steady-state Serum T concentrations on Days 15, 60, and 120 in patients who completed 120 days of treatment

Parameter	Dose of AXIRON				Overall
	30 mg	60 mg	90 mg	120 mg	
<b>Day 15</b>		N= 136			N= 136
Cavg (ng/dL)	-	456 (225)	-	-	456 (225)
Cmax (ng/dL)	-	743 (500)	-	-	743 (500)
Cmin (ng/dL)	-	257 (106)	-	-	257 (106)
<b>Day 60</b>	N= 1	N= 106	N= 29		N= 136
Cavg (ng/dL)	343 (ND)	521 (208)	369 (138)	-	487 (104)
Cmax (ng/dL)	491 (ND)	893 (662)	646 (382)	-	837 (619)
Cmin (ng/dL)	213 (ND)	280 (123)	212 (79)	-	265 (118)
<b>Day 120</b>	N= 3	N= 97	N= 25	N= 10	N= 135
Cavg (ng/dL)	493 (239)	506 (175)	415 (165)	390 (160)	480 (177)
Cmax (ng/dL)	779 (416)	839 (436)	664 (336)	658 (353)	792 (417)
Cmin (ng/dL)	290 (175)	288 (115)	230 (119)	262 (111)	275 (117)

**PK of other analytes:** The measured DHT concentrations and calculated free T concentrations increased as total T concentrations increased showing the PK of these analytes mirrored those of total T. The DHT/T ratios on Days 15, 60, and 120 (N=135), showed a reasonably constant arithmetic mean DHT/T ratio ranging between 0.17-0.26 a 24 hr period. Typically, the DHT/T ratio is normally in the range of 0.05-0.33 (Diver *et al.*, 2003)

#### Safety Analysis

**Study MTE08:** Secondary endpoints that are safety related are considered to be met if they meet the following:

- More or equal to 85% having total T  $C_{max}$  less than 1,500 ng/dL
- Less than 5% having total T  $C_{max}$  in the range of 1,800-2,500 ng/dL
- No subjects having total T  $C_{max}$  higher than 2,500 ng/dL

Secondary endpoint analysis data is summarized in Table 21 below.

**Table 21:** Serum Total T PK Secondary Endpoints

Data Set	Day 15	Day 60	Day 120
$C_{max} < 1,500$ ng/dL	95.6% (130/136)	91.2% (124/136)	94.8% (128/135)
$C_{max} > 1,800$ and $\leq 2,500$ ng/dL	2.2% (3/136)	4.4% (6/136)	3.0% (4/135)
$C_{max} > 2,500$ ng/dL	1.5% (2/136)	1.5% (2/136)	0.7% (1/135)

It should be noted that out of the 138 patients included in the completer set for efficacy analysis, 2 subjects withdrew before Day 15 and 1 subject withdrew after Day 60.

Secondary endpoints of  $C_{max}$  being less than 1,500 ng/dL in at least 85% of subjects and less than 5% of subjects having a  $C_{max}$  between 1,800 ng/dL and 2,500 ng/dL, were met.

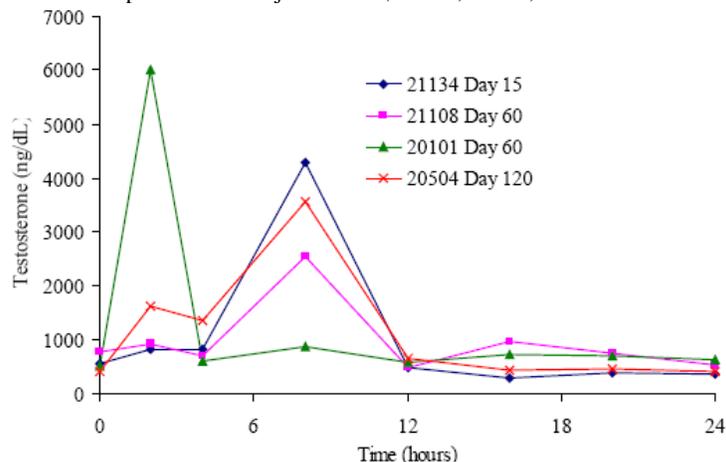
However, one of the secondary endpoints was that there should be no subjects with  $C_{max} > 2,500$  ng/dL at Day 120 was not met. A closer examination of data revealed that 5 out of 136 subjects had a  $C_{max}$  greater than 2,500 ng/dL at some point during the study. 2 of these occurred at Day 15, 2 at Day 60 and 1 at Day 120. The 5 subjects that exhibited  $C_{max}$  values greater than 2,500 ng/dL are listed in Table 22.

**Table 22:** Subjects with Serum Total Testosterone  $C_{max} > 2500$  ng/dL

Subject	$C_{max}$ (ng/dL)	$T_{max}$ (hours)	PK sampling day
21134	4280	8	Day 15
21139	3247	12	Day 15
21108	2554	8	Day 60
20101	5996	2	Day 60
20504	3457	8	Day 120

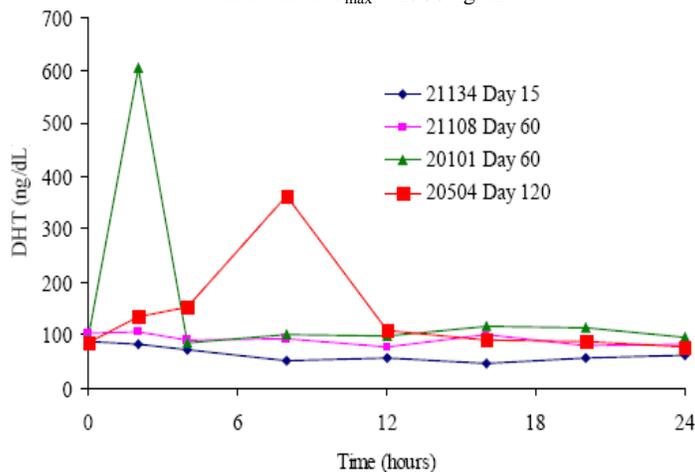
Figure 7 depicts the profiles for Subjects 21134, 21108, 20101, and 20504 on the days where a  $C_{max} > 2,500$  ng/dL was observed. In 2 of these cases (Subjects 21134 and 21108) the apparent increase in T levels was not accompanied by proportionate increases in DHT levels (Figure 8). In all cases, the serum total T and DHT reanalysis results were confirmatory of the original values seen.

**Figure 7:** Serum Total T PK profiles for Subjects 21134, 21108, 20101, and 20504 where  $C_{max} > 2,500$  ng/dL



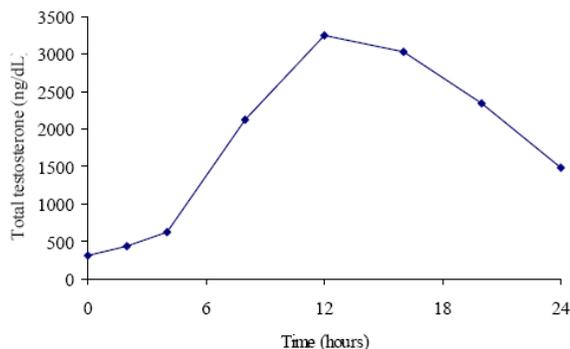
In 2 cases (Subjects 20101 and 20504), the high levels of T were mimicked by a spike to a high level of DHT. However, it was noted that these spikes were only observed at a single time point.

**Figure 8:** Serum DHT PK profiles for Subjects 21134, 21108, 20101 and 20504 where the  $T C_{max} > 2500$  ng/dL

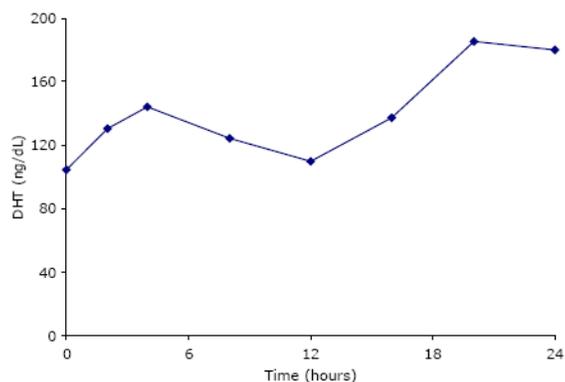


The remaining incident of a  $C_{max} > 2,500$  ng/dL occurred in Subject 21139 and was associated with a pattern of apparently sustained exposure (Figure 9). However, this apparent increase in T was not accompanied by parallel increase in DHT (Figure 10). Comparison of Figure 9 and Figure 10 indicate a decline in DHT at the time the T levels are rising in Subject 21139.

**Figure 9:** Serum Total T PK profile for subject 21139 where  $C_{max} > 2,500$  ng/dL (Study MTE08)



**Figure 10:** DHT PK profile for Subject 21139 where the Serum Total T  $C_{max} > 2,500$  ng/dL (Study MTE08)



In addition, a closer look at individual T PK profiles showed that T and DHT concentrations at each timepoint across different days (i.e., Days 15, 60, and 120) were comparable except the one timepoint spike of T concentrations observed in each of these 5 subjects, respectively. While the third secondary endpoint was not met and the cause of the spikes of T concentration is unknown, at least there was no consistent trend of  $C_{max}$  spikes observed.

#### 2.2.10 What is the Sponsor's justification for dose titration time point and scheme proposed in the product labeling?

Reference is made to the minutes of the End of Phase 2 (EOP2) meeting held between DRUP and the Sponsor on March 13, 2008. DRUP has recommended that the dose titration should be based on a single blood draw since a dose titration scheme incorporating multiple blood draws over 24 hr is not clinically feasible. Sponsor was asked to propose and justify the timing of serum T determination for dose titration. Per DRUP's request, the Sponsor has submitted their proposal of conducting dose titration based on the serum T concentration from a single blood draw 2–8 hours after applying Axiron™ and at least 7 days after starting treatment with their justification.

During Study MTE08, dose titration decisions were made based on  $C_{avg}(0-24)$  (i.e., the average serum level of T across a 24 hr period). A closer examination of data collected in Study MTE08 allowed an assessment of the most appropriate timing of a single blood draw to use as a basis of dose titration. The Sponsor conducted a comparison between the titration recommendation made based on the total T concentration ( $C_x$ ) from a single blood draw and the titration recommendation made based on  $C_{avg}(0-24)$ . Figure 11 represents the theoretical outcomes (correct or incorrect titration) of using a single blood draw to predict the  $C_{avg}$  during a 24 hr period at different blood draw timepoints. In this figure, X could be 0, 2, 4, 8, 12, 16, 20, or 24 hr after dosing (i.e., any of the timepoints at which blood was drawn) to construct the serum level T profile from which  $C_{avg}(0-24)$  was then calculated. Note that regions where the  $C_x$ -based and  $C_{avg}(0-24)$ -based titration recommendations were

different are notated as “incorrect” while regions where the titration recommendations were identical are notated as “correct”.

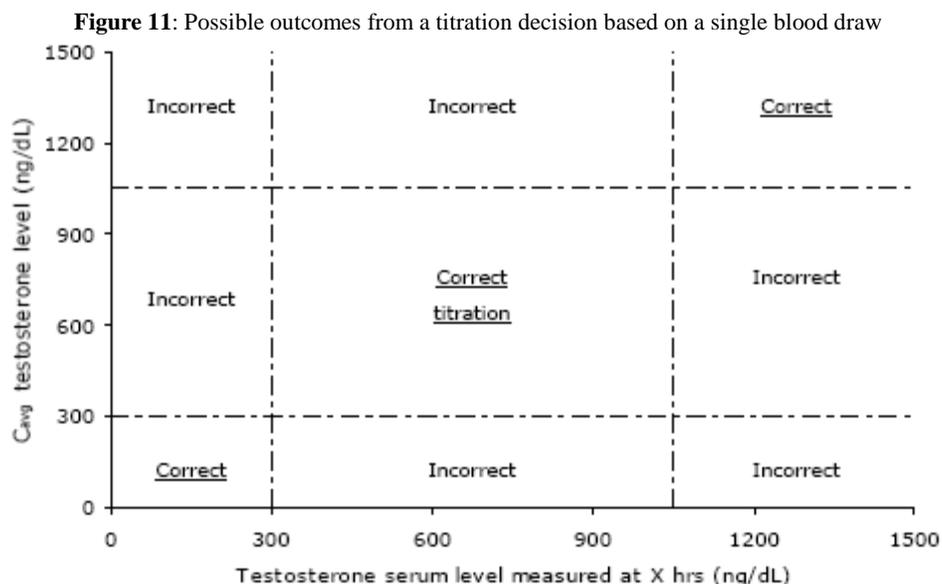
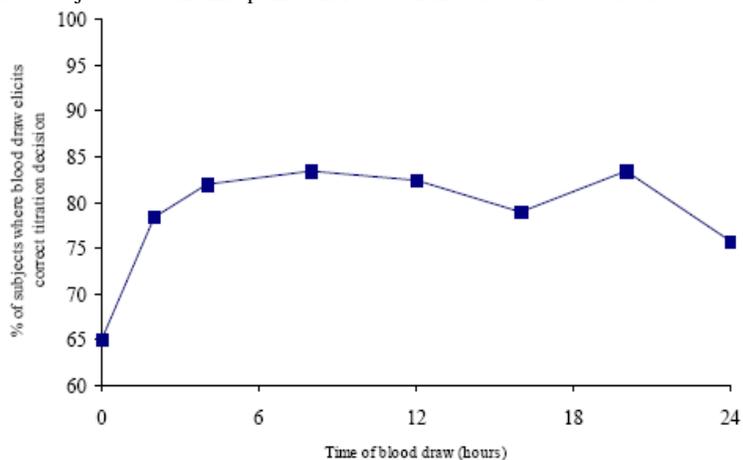


Figure 12 suggests that dose titrations based on single blood draws between 2 and 20 hr after dosing gives the best match with  $C_{avg}(0-24)$ -based dose titration recommendations (79-85%).

**Figure 12:** Percentage of subjects at each time point where use of the blood draw would lead to a correct titration decision



There are 6 regions in Figure 11 that represents incorrect (i.e., different) titration decisions based on a single blood draw. In order to determine the number of titration decisions that would result in doses that were higher than necessary or lower than necessary, the following questions were asked:

- A: Is the measured serum level less than 300 ng/dL, but the  $C_{ave}$  greater than 1,050 ng/dL?
- B: Is the measured serum level in the normal range, but the  $C_{ave}$  greater than 1,050 ng/dL?
- C: Is the measured serum level less than 300 ng/dL, but the  $C_{ave}$  in the normal range?
- D: Is the measured serum level in the normal range, but the  $C_{ave}$  less than 300 ng/dL?
- E: Is the measured serum level greater than 1,050 ng/dL, but the  $C_{ave}$  in the normal range?
- F: Is the measured serum level greater than 1,050 ng/dL, but the  $C_{ave}$  less than 300 ng/dL?

In situations described in questions A, B, and C, the single blood draw based titration recommendation will result in a dose higher than necessary while in situations described in questions D, E, and F, the single blood

draw based titration recommendations will result in a dose lower than necessary. The occurrence of each case is summarized in Table 23.

**Table 23:** Potentially Incorrect Dose Decisions by Time of Analysis of Serum Sample

Time (hr)	0	2	4	8	12	16	20	24
$C_x < C_{avg}$ : Higher titration than necessary (%)	34	7.2	7.5	9.1	15	20	11	22
$C_x > C_{avg}$ : Lower titration than necessary (%)	2.2	14	10	6.8	2.9	0.5	5.5	3.1

**Figure 13:** Percentage of Incorrect Titration Decisions based on a Single Blood Draw

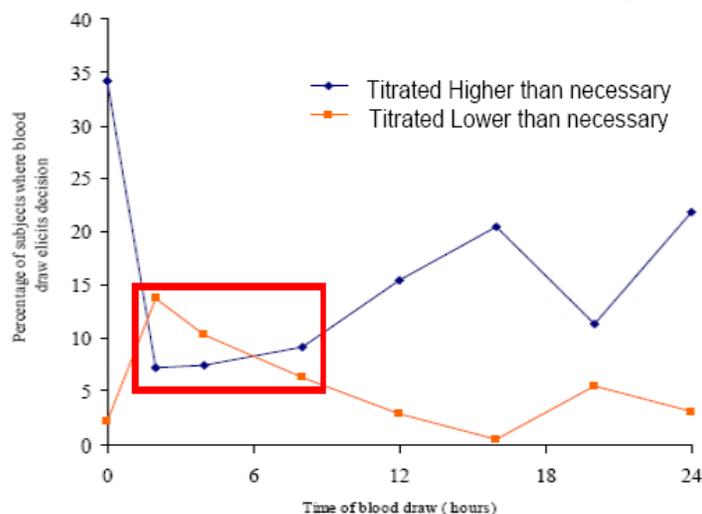


Figure 13 illustrates the percentage of incorrect titration decisions based on a single blood draw resulting in doses that were higher or lower than necessary. As Figure 13 suggests, it is reasonable to suggest that subjects should be titrated based on blood draws taken between 2 and 8 hr after administration of the drug.

It should be noted that data used in the analysis was obtained at least 14 days after initiation of Axiron™ treatment or dose adjustment in the pivotal Phase 3 study (MTE08). In conclusion, dose titration should be based on the serum total T concentrations from a single blood draw 2-8 hr after dosing and at least 14 days after initiation of therapy or dose adjustment. This titration scheme recommendation is reflected in the product labelling.

## 2.3 Intrinsic Factors

### 2.3.1 Was there any age effect observed in the efficacy of Axiron™?

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing Axiron™ to determine whether efficacy in those over 65 years of age differs from younger subjects. Only 21 geriatric patients of over 65 years of age (out of a total of 155 patients) were enrolled in the pivotal clinical study utilizing Axiron™. The mean age was  $51.5 \pm 12.7$  yr and age ranged between 18 and 78 yr. Additionally, there is insufficient long-term safety data in geriatric patients utilizing Axiron™ to assess a potential incremental risk of cardiovascular disease and prostate cancer. This information is reflected in the product labeling.

### 2.3.2 What is the Sponsor's justification of the pediatric waiver request and is it acceptable?

T production is dormant until the time of puberty, at which time endogenous T levels increase, leading to secondary male sex characteristics. Therefore, there is no therapeutic use for T in the neonate, infant, or child.

No pediatric studies were conducted. A full pediatric waiver to include children from birth to age 18 yr for Axiron™ was requested by the Sponsor for the reasons listed above.

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

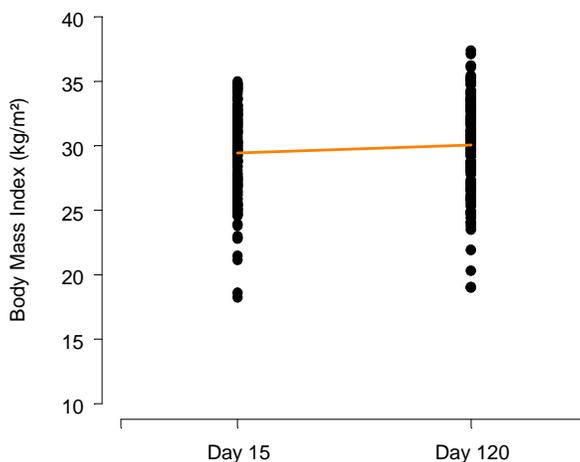
### 2.3.3 Did the Sponsor conduct PK studies in population with renal or hepatic impairment?

No. The Sponsor did not conduct studies in renal and/or hepatic impaired patients. No additional information is available in the labeling of topical drugs in the same drug class (i.e., Testim® or AndroGel®) regarding this aspect.

### 2.3.4 Was there any effect of BMI on T exposure observed?

Only men with BMI < 35.0 kg/m<sup>2</sup> were enrolled in Studies MTE08 and MTE09. The prevalence of subjects categorized as being overweight (25 to 30 kg/m<sup>2</sup>) or obese (30 to 35 kg/m<sup>2</sup>) in MTE08 at study entry was 42% and 48%, respectively. Only a single subject was classified as being underweight (<18.5 kg/m<sup>2</sup>) and thus data from this subject were included in the normal weight category (18.5 to 25 kg/m<sup>2</sup>) for the purposes of visual examinations, as appropriate. Individuals with BMI > 35 kg/m<sup>2</sup> were specifically excluded from enrollment in Studies MTE08 and MTE09. Hence, clinical experience in a population of severely or morbidly obese (BMI ≥ 35 kg/m<sup>2</sup>) men is limited; consistent with the inclusion criteria, the BMI in these individuals were all < 35 kg/m<sup>2</sup> at randomization in Study MTE08 and any modest elevation in their BMI resulted from a minor increase in body weight during the course of the study (i.e., after Day 60). The representation of normal weight (11%), overweight (36%) and obese (44%) was essentially similar at the conclusion (Day 120) of Study MTE08 compared to study entry with mean (range) being 29 kg/m<sup>2</sup> (18-35 kg/m<sup>2</sup>) for Day 15 and 30 kg/m<sup>2</sup> (19-37 kg/m<sup>2</sup>) at Day 120. It should be noted that body weight was assessed on Days 15, 60, and 120 but not on Day 90. As illustrated in Figure 14 below, there were no subjects with BMI > 35.0 kg/m<sup>2</sup> at randomization as well on Day 15.

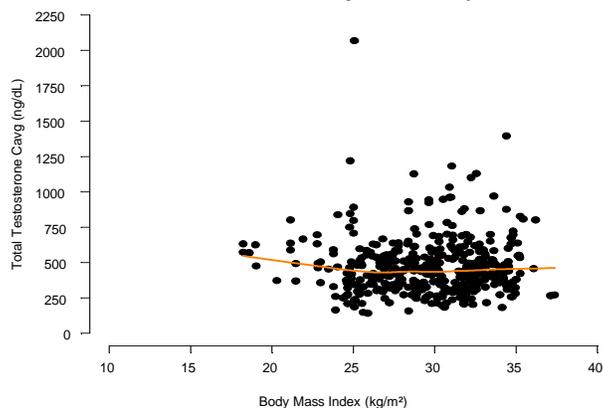
**Figure 14:** BMI represented in the PK population of Study MTE08 at Day 15 (N=143) and 120 (N=135)



The potential influence of body fat, as measured by BMI, on total T systemic exposure ( $C_{avg}$ ) was explored; whereby individual estimates of  $C_{avg}$  (N=416) across the entire study (Days 15, 60, and 120) were examined. To evaluate any pattern of influence of BMI, if any, on total T exposure, all individual data were combined (Days 15, 60, and 120) across the BMI continuum (Figure 15). Application of a nonparametric regression method

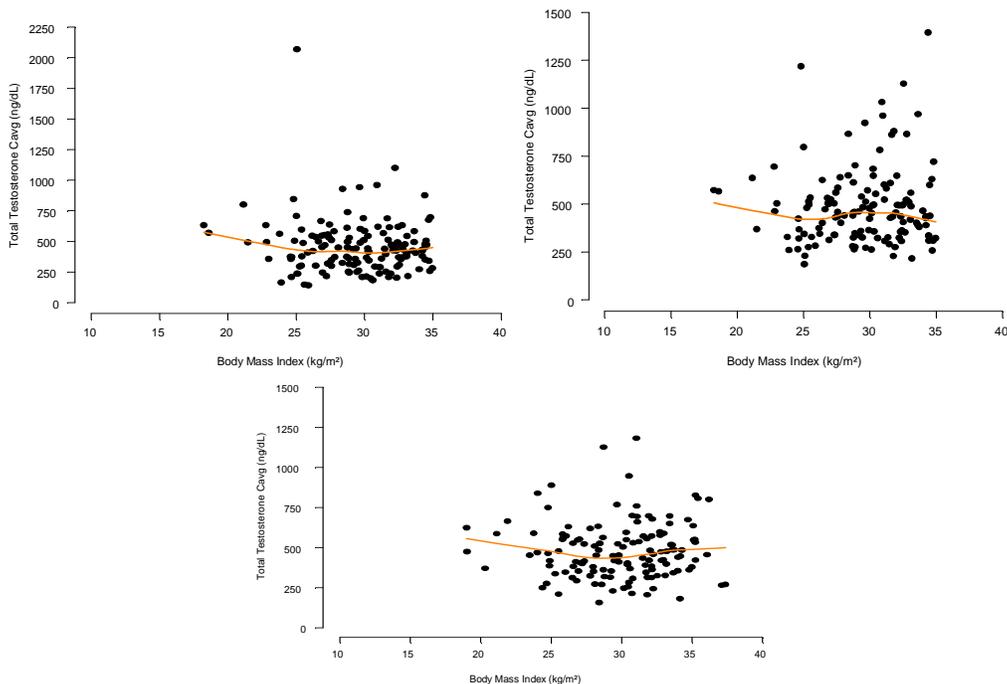
(LOESS) to investigate the influence of BMI did not reveal any systematic pattern and demonstrated an absence of any influence of BMI on total T exposures.

**Figure 15:** Individual total T  $C_{avg}$  estimates (Days 15, 60, and 120) vs. BMI for all PK observations for subjects in Study MTE08



Further analyses according to the continuous measure of BMI were conducted to explore trends between total T exposure and BMI on each day (Days 15, 60, and 120) (Figure 16) recognizing that dose may have been time-varying, leading to commensurate alterations in total T concentrations. No systematic pattern for higher exposures in those having a lower BMI compared to those having higher BMI was discerned from an examination of the  $C_{avg}$  estimates.

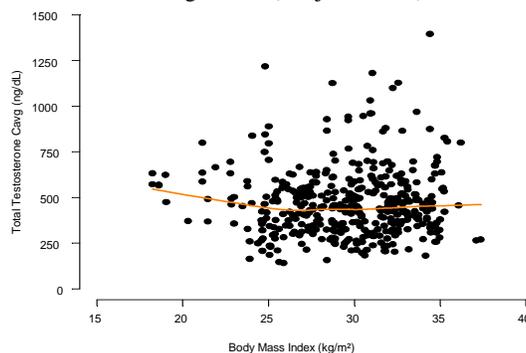
**Figure 16:** Individual total T  $C_{avg}$  estimates on each of Days 15 (upper left panel), 60 (upper right panel) and 120 (lower panel) vs. BMI for all PK observations for subjects in Study MTE08



Relative to the majority of subjects in the PK analysis, a single subject (21139) with a reported BMI of 25 kg/m<sup>2</sup> was considered to be an outlier based on an estimated  $C_{avg}$  (2,067.25 ng/dL) on Day 15 that significantly exceeded those for the remaining subjects. It should be noted that Subject 21139 was one of the outliers with a  $C_{max}$  of 3,247 ng/dL at 12 hr on Day 15 that was discussed above in the secondary endpoint analysis. Hence, this datum was excluded from the visual comparisons to assess any potential influence on the overall

interpretation of the results (Figure 17). No discernible trend between BMI and individual total T exposures, either across all observations or excluding the datum identified above, was apparent.

**Figure 17:** Individual total T  $C_{avg}$  estimates (Days 15, 60, and 120) vs. BMI for all PK observations in Study MTE08, excluding outlier (Subject 21139).



Although obesity may be expected to influence total T disposition, in Study MTE08, no systematic pattern of BMI effect on T exposures was observed. In consideration of the exclusion criterion applied across the studies, there is scarce data establishing safety and efficacy in subjects with a BMI > 35 kg/m<sup>2</sup>. The product labeling states that safety and efficacy of Axiron™ in men with BMI > 35 kg/m<sup>2</sup> has not been established.

### 2.3.5 Did the Sponsor evaluate the potential effects of axillary hair on the T observed?

The potential effects of axillary hair on T absorption were not assessed in Studies MTE08 or MTE09. In the 74-day letter sent to the Sponsor on April 9, 2010, the Clinical Pharmacology reviewer has requested clarification from the Sponsor if potential effects of axillary hair on T absorption were assessed in Studies MTE08 and MTE09. In addition, the Sponsor was asked to provide any literature or scientific information to address this if this was not assessed in the Phase 3 studies. The MTE08 study was a global study that involved hypogonadal men from 5 countries (United States, Australia, France, Sweden, and United Kingdom) and ages ranging between 19-78 yr. It is the Sponsor's assumption that a normal distribution of axillary hair is associated with the study population. Sponsor thinks that the extent of impact would be rather dependent on physio-chemical property of each drug. There is only limited information available in published literature that assesses the impact of the presence or absence of hair on the absorption of drugs through the skin. Nevertheless, there were no specific restrictions regarding axillary hair in the inclusion/exclusion criteria of the Phase 3 studies and the potential effect of axillary hair, if any, would have been accounted for in the dose titrations in the Phase 3 study. Therefore, it appears that axillary hair would not affect the efficacy of Axiron™.

## 2.4 Extrinsic Factors

### 2.4.1 Did the Sponsor conduct any DDI studies?

No DDI studies were conducted with Axiron™. Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement. Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy. The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal, or hepatic disease.

## 2.5 General Biopharmaceutics

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

Axiron™ is a clear, colourless, single phase solution containing 2% T for topical administration through the axilla. The active pharmacologic ingredient in Axiron™ is T. T USP is a white to practically white crystalline powder. The inactive ingredients are ethanol, isopropyl alcohol, octisalate, and povidone.

**Table 24:** Comparison of Formulation Ingredients

Ingredients	1% T solution	Axiron™ (2% T solution)
Testosterone	1% w/v	2% w/v
Octisalate		(b) (4)
Povidone		
Isopropyl Alcohol (IPA)		

(b) (4)

(b) (4)

Axiron™ was originally developed as a 1% solution formulation. However, Sponsor developed a 2% solution as the to-be-marked (TBM) formulation in order to deliver the same amount of T in smaller volumes in order to prevent dripping and assure that adequate amount of Axiron™ can be applied to the axilla without any other complications. Study MTE06 was conducted with the 1% solution formulation while multiple-dose PK of both 1% and 2% (i.e., Axiron™) T solution formulations were characterized in Study MTE07 (except the 120 mg dose of Axiron™). Studies MTE08, MTE09, MTE10, MTE11, and MTE12 were conducted with the TBM formulation (i.e., Axiron™).

## 2.6 Analytical Section

### 2.6.1 Did the Sponsor use validated bioanalytical methods to generate the study data?

Validated analytical methods were used in clinical studies. Serum samples were analyzed for total T and DHT by validated bioanalytical methods including radioimmunoassays (RIA), liquid chromatography-mass spectrometric (LC-MS), and liquid chromatography-tandem mass spectrometric (LC-MS/MS) methods. The determination of SHBG for the Phase 3 study samples was performed using an enzyme immunoassay. Acceptance criteria and assay performance for each analyte were in compliance with the *Bioanalytical Method Validation Guidance* and therefore found to be acceptable. A formal DSI consult on the clinical and bioanalytical study sites has been signed off in DARRTS by Dr. Dennis Bashaw on March 18, 2010. DSI's memorandum reveals that there are no unresolved issues that would affect the approvability of Axiron™ (refer to DSI's memorandum in DARRTS dated October 29, 2010). Bioanalytical methods are summarized in Table 25.

**Table 25:** Summary of Bioanalytical Methods

Study Number	Study Title	Biological Matrix	Analyte	Method	LLOQ
MTE07	Multiple-dose PK	Serum	Total T	LC-MS/MS	20 ng/dL
			DHT		5 ng/dL
MTE08/09	Pivotal Efficacy/Safety Study (Phase 3)	Serum	Total T	LC-MS/MS	20 ng/dL
			DHT		5 ng/dL
MTE10	Assessment of antiperspirant/deodorant application as well as washing application site	Serum	Total T	LC-MS/MS	20 ng/dL
			DHT		5 ng/dL
MTE11	Application site residual washing study	Alcohol towelettes	Total T	HPLC-UV	0.12 µg/mL
MTE12	Interpersonal transferability Study	Serum	Total T	LC-MS/MS	3 ng/dL
			DHT		1 ng/dL
MTE06	Assessment of washing application site	Serum	Total T	LC-MS/MS	2.5 ng/dL
			DHT	RIA	2 ng/dL

**LABELING**

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

(b) (4)



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHONGWOO YU  
11/01/2010

MYONG JIN KIM  
11/01/2010

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

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

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

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

	described in the WR?				
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?** \_\_\_ Yes \_\_\_

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Provide us information on application surface area evaluated in Studies MTB08 and MTB09.
- Provide information on the exact application procedure instructions in Studies MTB08 and MTB09.
- Clarify if drying time following application and treatment compliance regarding application area were assessed in Studies MTB08 and MTB09. If this was assessed, provide information regarding these aspects.
- Clarify if potential effects of underarm hair on testosterone absorption were assessed in Studies MTB08 and MTB09. If this was not assessed in your Phase 3 studies, provide any literature or scientific information to address the potential effect of underarm hair on testosterone absorption.
- The following will be review issues:
  - Effect of body mass index (BMI) on the systemic testosterone exposure
  - The dose titration time point and scheme
  - The results of transfer studies and the results of your washing study that you submitted on April 2, 2010 will be a review issue. The potential for secondary exposure of testosterone to women and children will be further considered. Additional information in labeling may be needed, including information directed to patients to assure safe use.

*Chongwoo Yu*

*3/11/2010*

Reviewing Clinical Pharmacologist

Date

*Myong Jin Kim*

*3/11/2010*

Team Leader/Supervisor

Date

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

## Filing Memo

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### Clinical Pharmacology Review

**NDA:** 022504  
**Compound:** Axiron™ (Testosterone solution, 2%)  
**Sponsor:** Acrux Pharma  
  
**Date:** 3/11/2010  
**Reviewer:** Chongwoo Yu, Ph.D.

#### Introduction:

Acrux Pharma submitted New Drug Application (NDA) 022504 for Axiron (testosterone solution, 2%) on January 25, 2010 to seek an approval for the treatment of hypogonadism.

Axiron is non-sterile, transdermally applied solution for testosterone replacement therapy in hypogonadal men. It is designed to deliver “physiologic” amounts of testosterone, aiming to normalize circulating total testosterone concentrations that approximate “normal” levels (300-1050 ng/dL) in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Axiron is to be administered transdermally once daily to clean, dry intact skin of the axilla or armpit (one or two armpits) by use of an applicator cup, preferably at the same time each morning following showering. The product is applied via a metered-dose pump designed to deliver 90 mL, or 60 metered doses of 1.5 mL (30 mg of testosterone) of the formulation per actuation to an applicator cup which is then used to apply testosterone to skin of the axilla or armpit. Keeping the applicator upright, patients should place it up into the armpit and wipe steadily up and down into the armpit. If the solution drips or runs, it can be wiped back up with the applicator cup. The solution should not be rubbed into the skin with fingers or hand. The application site should be allowed to dry prior to dressing. Hands should be washed thoroughly with soap and water after Axiron has been applied. The recommended start dose is 3 mL (60 mg of testosterone).

Dose adjustment is recommended if the serum total testosterone concentration ( $C_{ave}$  over 24 hr) is below the pre-specified range of 300-1050 ng/dL: increase from 3 mL (60 mg) to 4.5 mL (90 mg) or from 4.5 mL to 6 mL (120 mg). The dose may be reduced from 3 mL (60 mg) to 1.5 mL (30 mg) daily if serum total testosterone concentrations are above 300-1050 ng/dL.

#### Regulatory History

The following meetings were held between the Division of Reproductive and Urologic Products (DRUP) and the Sponsor:

Pre-IND meeting: November 5, 2004  
End of Phase 2 meeting: March 13, 2008  
Pre-NDA meeting: August 31, 2009

#### Clinical Development of Axiron

The clinical development of Axiron consists of 11 studies:

- 5 Phase 1 PK studies using the 1% formulation (DDS08, DDS15, DDS16, MTE04, and MTE06): In Study MTE06, the potential for dermal testosterone *transfer* between males dosed with Axiron and untreated females and the impact of *washing* (the application site) and *deodorant/antiperspirant use* was evaluated
- 1 Phase 2 PK study using the 1% formulation
- 1 Phase 2 PK study using the 1% and 2% (TBM) formulation (MTE07)
- 1 pivotal Phase 3 study (MTE08) with a skin sub-study (MTE09) using the 2% formulation: The efficacy and safety of Axiron in the treatment of hypogonadism was assessed in this single pivotal, Phase 3, open label 3-month study (MTE08). In this study, the primary endpoint was the proportion of subjects with  $C_{avg}$  (0-24 hr) total testosterone within the normal range (300–1050 ng/dL) at Day 120.
- 1 washing (the application site) and deodorant/antiperspirant use study using the 2% formulation (MTE10)
- 1 residual washing study using the 2% formulation (MTE11): As discussed at the August 31, 2009 pre-NDA meeting, DRUP stated that it was preferred to have this report submitted with the original NDA submission but it would not be considered as a fileability issue if it was not included. The MTE11 study protocol was submitted

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under IND 70516 on December 2, 2009 (SN069) and the final MTE11 clinical study report was submitted on April 2, 2010.

These studies are summarized in the Table below:

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Product(s)	N	Type of Subjects
PK	DDS08	PK following single transdermal dose of Testosterone MD-Lotion® or AndroGel®	Randomized, two way, single-dose, crossover PK	3 mL Testosterone MD-Lotion® (1% testosterone, (b) octisalate) and AndroGel® (5g) applied to the forearm.	6	Hypogonadal Males
PK	DDS15	PK following single transdermal dose of two different formulations of Testosterone MD-Lotion®	Randomized, two way, single-dose, crossover PK study	3 mL Testosterone MD-Lotion® (1% testosterone) with (b) (4) octisalate applied to the inner arm.	9	Healthy Women
PK	DDS16	PK following single transdermal dose of Testosterone MD-Lotion®	Two way, randomized, single-dose, crossover PK study	1 mL Testosterone MD-Lotion® (1% testosterone, (b) octisalate) applied to the inner arm or axilla	10	Healthy Women
PK	MTE04	Steady state PK of different doses/ formulations of Testosterone MD-Lotion vs. AndroGel	Randomized, open-label 4-way crossover	3 ml of 1% testosterone/ (b) octisalate, 6 ml 1% testosterone/ (b) octisalate, 6 ml 1% testosterone/ (b) octisalate applied to axilla, or 5 g AndroGel (1% testosterone) applied to the shoulder, abdomen and upper arm.	16	Healthy Males with chemically suppressed testosterone levels
PK	MTE05	Steady state PK of 30 mg and 60 mg doses of Testosterone MD-Lotion 1%	Randomized, open label, 2-way crossover	30 mg and 60 mg Testosterone MD-Lotion® (1% testosterone/ (b) octisalate) applied to the axilla	41	Hypogonadal Males
Safety	MTE06	Evaluate transfer to female partners, impact of washing and deodorant or antiperspirant use on absorption	Randomized, open-label, 3 part study design in normal, healthy, male and female subjects.	Single Axillary Application: Part A/Transfer: 6 ml Testosterone MD-Lotion® Parts B and C/Effect of Deodorant and Antiperspirant and Washing: 3ml Testosterone MD-Lotion® to one axilla	96	Part A: 24 Healthy Males/24 Healthy Females Part B:24 Healthy Females Part C:24 Healthy Females
PK	MTE07	Compare steady state PK of different doses and formulations of Testosterone MD-Lotion (1% and 2%).	Randomized 4-way crossover	Axillary application of 30mg and 60 mg of 1% and 2% Testosterone MD-Lotion®	21	Hypogonadal Males
Efficacy and Safety	MTE08	Confirm efficacy and safety of Testosterone MD-Lotion 2%	Open label titration	Dermal application of 30 mg applied to 1 axilla once, 60 mg daily to both axilla, 90 mg x 3, and 120 mg x 4 (2% testosterone) Testosterone MD-Lotion®.	155	Hypogonadal Males
Safety	MTE09	Assess skin safety of continuous use of the Testosterone MD-Lotion® 2% after completion of the MTE08 trial	Open label titration	Dermal application of 30 mg applied to 1 axilla once, 60 mg daily to both axilla, 90 mg x 3, and 120 mg x 4 (2% testosterone) Testosterone MD-Lotion®.	52	Hypogonadal Males
Safety	MTE10	Evaluate impact of washing and deodorant or antiperspirant use on absorption.	Randomized, single dose, parallel group design.	Testosterone MD Lotion® containing 2 % testosterone.	36	Healthy Females
Safety	MTE11	Evaluate the impact of washing on absorption.	Open label, single-dose	Testosterone MD-Lotion containing 2% testosterone	10-12	Healthy Volunteers

**Pediatric Waiver Request**

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This NDA contains an amendment of the pediatric waiver request submitted to IND 70516 (SN: 047) on December 22, 2008. Sponsor states that although exogenous testosterone might be used in a depot formulation for small number of pediatric patients with primary hypogonadism, there is almost no therapeutic use for testosterone in the neonate, infant, or child. In addition, the Sponsor believes compliance is unreliable (i.e., the use of a daily transdermal product administered via the axilla would be impractical in adolescents). For these reasons, a full pediatric waiver to include children from birth to age 18 for Axiron (testosterone solution 2%) is requested.

**Drug Product Formulation:**

The formulations used in clinical studies are summarized in the Table below. Study MTE07 serves as a relative BA study between testosterone solution 1% and 2%. Studies MTE 08, MTE09, MTE10, and MTE 11 were conducted with the TBM (testosterone solution 2%) formulation.

Study Description	Formulations					
	Human single dose PK study	Human single dose PK study	Human Multidose steady state PK study Comparator (8% OSAL)	Phase 2 Multidose steady state PK study	Phase 2 1% and 2% formulation comparability study.	Pivotal Phase 3 (08) and Safety extension (09)
Study No.	DDS08	DDS16	MTE04	MTE05	MTE07	MTE08/09
<b>Ingredients</b>						
Testosterone	1% w/v	1% w/v	1% w/v	1% w/v	2%w/v	2%w/v
Octisalate	(b) (4)					
Povidone						
Isopropyl Alcohol (IPA)						

(b) (4)

**Absorption**

Axiron is designed to normalize circulating testosterone concentrations to approximately 300-1050 ng/dL in adult males for conditions associated with a deficiency or absence of endogenous testosterone. On the skin, the ethanol and isopropanol quickly evaporate leaving a depot of testosterone and octisalate which is absorbed by the upper layers of the skin. This forms a ‘depot within the skin’ from which testosterone diffuses into the systemic circulation.

With single daily applications of Axiron, The overall average (± SD) daily testosterone concentration produced by Axiron in patients responding to treatment was reported to be 504±139 ng/dL.

**Distribution, Metabolism, and Excretion**

Based on the similarities of Axiron to other transdermal testosterone agents, specific studies describing the distribution, metabolism, or excretion of testosterone absorbed from Axiron have not been conducted. The Sponsor is proposing to use the publically available information for their product.

**Drug-Drug Interactions:**

No DDI studies were conducted with Axiron

**Specific Populations and Waiver Request for Pediatrics:**

- Pediatric use: No pediatric studies were conducted and pediatric waiver request was submitted

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- Geriatric use: Sponsor did not stratify the studies to rule out whether efficacy and safety in those over 65 yr of age would differ from younger subjects. Hypogonadal males aged 19-78 yr were enrolled in the Phase 3 studies, MTB08 and MTB09.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant or breast feeding women
- Warnings and Precaution for children and women for secondary exposure

## **Bioanalytical Method validation:**

Serum samples were analyzed for total testosterone and dihydrotestosterone by validated bioanalytical methods. A validated radioimmunoassay method was used in Study DDS08. In Studies DDS15, DDS16, MTE04, and MTE05, a validated liquid chromatography-mass spectrometry (LC-MS) detection after nonpolar solvent extraction was used. Testosterone was measured by a validated LC-MS method (b) (4). Dihydrotestosterone was measured by radioimmunoassay after extraction and oxidation. A validated LC-MS/MS method was used in all other studies (MTE07, MTE08 and MTE09). The LC-MS/MS analysis of the Phase 3 (MTE08) trial samples was conducted (b) (4). The determination of sex hormone binding globulin (SHBG) for the Phase 3 samples was performed (b) (4) using an enzyme immunoassay.

## **Recommendation:**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 22504 is fileable.

## **Comments for the Sponsor:**

- *Provide us information on application surface area evaluated in Studies MTB08 and MTB09.*
- *Provide information on the exact application procedure instructions in Studies MTB08 and MTB09.*
- *Clarify if drying time following application and treatment compliance regarding application area were assessed in Studies MTB08 and MTB09. If this was assessed, provide information regarding these aspects.*
- *Clarify if potential effects of underarm hair on testosterone absorption were assessed in Studies MTB08 and MTB09. If this was not assessed in your Phase 3 studies, provide any literature or scientific information to address the potential effect of underarm hair on testosterone absorption.*
- *The following will be review issues:*
  - *Effect of body mass index (BMI) on the systemic testosterone exposure*
  - *The dose titration time point and scheme*
  - *The results of transfer studies and the results of your washing study that you submitted on April 2, 2010 will be a review issue. The potential for secondary exposure of testosterone to women and children will be further considered. Additional information in labeling may be needed, including information directed to patients to assure safe use.*

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<i>Office of Clinical Pharmacology</i> <i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA Number	22504	Brand Name	Axiron	
OCP Division	DCP3	Generic Name	Testosterone	
Medical Division	DRUP	Drug Class	Steroid	
OCP Reviewer	Chongwoo Yu, Ph.D	Indication(s)	Treatment of male hypogonadism	
OCP Team Leader	Myong Jin Kim, Pharm. D.	Dosage Form	Solution 2%, (30, 60, 90, and 120 mg)	
Secondary Reviewer	Myong Jin Kim, Pharm. D.	Dosing Regimen	Starting dose at 3 ml (60 mg testosterone) and dose adjust appropriately	
Date of Submission	January 25, 2010	Route of Administration	Transdermal	
Estimated Due Date of OCP Review	September 25, 2010	Sponsor	Acrux Pharma	
PDUFA Due Date	November 25, 2010	Priority Classification	Standard	
Division Due Date	November 4, 2010			
<u>Clin. Pharm. and Biopharm. Information</u>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	6		DDS08, DDS15, DDS16, MTE06, MTE10, MTE11
multiple dose:	X	3		MTE04, MTE05, MTE07
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	NA			Pediatric waiver request
geriatrics:				
renal impairment:				

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hepa ic impairment:				
<b>PD:</b>				
Phase 1:				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2		MTE08, MTE09
<b>Population Analyses -</b>				
PK:				
PD:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Immunogenicity profile</b>				
<b>Thorough QT study</b>				
<b>Literature References</b>	X			
<b>Total Number of Studies</b>		11		
<b>Other comments</b>				
	<b>Comments</b>			
<b>QBR questions (key issues to be considered)</b>	<ol style="list-style-type: none"> <li>1. Starting dose and titration scheme</li> <li>2. Acceptability of primary efficacy</li> <li>3. Assessment of transfer potential, washing potential, and sunscreen effect</li> <li>4. DSI inspection on clinical and bioanalytical sites</li> <li>5. Acceptability of bioanalytical assay validation and performance</li> </ol>			
<b>Other comments or information not included above</b>	<ul style="list-style-type: none"> <li>• Application surface area evaluated in Studies MTE08 and MTE09</li> <li>• A formal DSI consult on clinical and bioanalytical study sites have been signed off in DARTS by Dr. Dennis Bashaw on March 18, 2010.</li> </ul>			

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22504	ORIG-1	ACRUX PHARMA PTY LTD	TESTOSTERONE

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/s/

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CHONGWOO YU  
04/08/2010

MYONG JIN KIM  
04/08/2010