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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Donald McNellis
Review Completion Date	November 19, 2010
Established Name	Testosterone solution for transdermal use
(Proposed) Trade Name	Axiron
Therapeutic Class	Testosterone replacement
Applicant	Acrux Pharma Pty Ltd
Formulation(s)	Solution for transdermal use
Dosing Regimen	Once daily
Indication(s)	Male Hypogonadism
Intended Population(s)	Males \geq 18 years of age with hypogonadism

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, Axiron testosterone solution for transdermal use should be approved for the indication of “hypogonadism” in adult males.

This recommendation is based on the demonstration of substantial evidence of effectiveness in producing a serum testosterone within the normal range in hypogonadal men and an acceptable safety profile.

1.2 Risk Benefit Assessment

A comprehensive review of NDA 22,504 was carried out. This NDA submission has provided substantial evidence from adequate studies that the Sponsor’s testosterone solution will have the effect claimed in labeling. This claim is that this solution is an effective treatment for men with hypogonadism. This testosterone solution was efficacious in achieving its primary endpoint and two of three secondary efficacy endpoints. No significant safety issues were detected.

The phase 3 efficacy study, MTE08, was an open-label titration trial to evaluate the effectiveness and safety of different doses of a dermal application of Axiron in hypogonadal men. Men were deemed to be hypogonadal based on two screening total testosterone levels that were <300 ng/dL. The primary objective for MTE08 was to establish that the percentage of subjects with C_{AVG} total testosterone levels within the normal range (300-1050 ng/dL) on Day 120 of the study was greater than 75%. The study showed that 84.1% of subjects had a normal testosterone on Day 120.

There were three secondary objectives of the study, all evaluated at Day 120.

- Establish the percentage of subjects with $C_{max} > 1500$ ng/dL. This should be less than 15% of subjects; the study result showed this to be 5.2%.
- Establish the percentage of subjects with C_{max} between 1800 and 2500 ng/dL. This should be less than 5% of subjects; the study result showed this to be 3.0%.
- Establish the percentage of subjects with a C_{max} greater than 2500 ng/dL. This should be 0%; the study result showed this to be 0.7% (1 of 135 subjects).

Axiron has been shown to be generally safe for its intended use as recommended in the label by all tests reasonably applicable to assessment of safety. The pattern of adverse events is similar to other drugs in the class. The most common adverse events (seen in

>2% of subjects) were: application site erythema and irritation, nasopharyngitis, increase in hematocrit, headache, diarrhea and vomiting.

The potential for transferring testosterone to another individual by direct contact was evaluated by the Sponsor. This evaluation showed that skin-to-skin contact resulted in significant transfer. However, a clothing barrier was shown to be effective in preventing clinically significant transfer.

The ability to wash the product from the skin was also evaluated. This study showed that approximately 5% of the applied testosterone remained on the skin following washing the application site with soap and water.

In summary, the information that has been submitted by the Sponsor is adequate to allow the reasonable conclusion that Axiron is an effective and safe treatment for men with hypogonadism. The data also provide an adequate basis for labeling the product so that it can be used in a safe and effective manner.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

A Medication Guide should be required. This guide is necessary to communicate to patients the measures they should use to assure that the product is used safely. As with other transdermal testosterone products, transfer of testosterone to another individual is possible. Patients need to be aware of the measures to be taken to minimize the risk of this transfer.

1.4 Recommendations for Postmarketing Requirements and Commitments

No postmarketing requirement and/or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution. Male hypogonadism results from insufficient production of testosterone and is characterized

by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis.

The 2010 Endocrine Society guidelines suggest that the diagnosis of testosterone deficiency in adult men should be based on a comprehensive review of patient symptoms and signs, and measurement of serum testosterone levels by a reliable assay. The exact prevalence of androgen deficiency in men is not known. Although serum total and free testosterone concentrations decline in men with advancing age, the significance of age-related decline in testosterone concentration is incompletely understood.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050 ng/dL). These replacement therapies are ideally based on short term titration regimens that result in an optimal dose of product for a particular patient.

Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range. Currently available treatment options for hypogonadism include intramuscular injections, subdermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels which are applied with the hands to the shoulders and upper arms and/or abdomen.

The Axiron formulation is a simple single-phase solution containing 2 % w/v testosterone, and a permeation enhancer, octisalate (b) (4) together with povidone (b) (4), ethanol (b) (4) and isopropanol.

The product is applied via a metered-dose pump with a nozzle which is designed to deliver a unit volume of the formulation uniformly to an applicator which is then used to apply the product to the skin of the axilla.

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Approved Medications for the Treatment of Male Hypogonadism

Trade Name	Dose	Sponsor	Route of Administration	NDA Number	Date of Approval
Androderm	2.5mg & 5mg	Watson Labs	Transdermal Patch	20,489	September 29, 1995
Androgel 1%	1.25gm, 2.5gm & 5 gm	Unimed Pharma	Transdermal gel	21,015	February 28, 2000
Testim 1%	5gm	Auxilium Pharma	Transdermal gel	21,454	October 31, 2002
Testopel	75mg	Slate Pharma	Pellet for implantation	ANDA 80,911	Prior to January 1, 1982
Striant	30mg	Columbia Labs	Extended Release tablet, buccal	21,543	June 19, 2003
Testosterone cypionate	200mg/ml	Paddock	Injection	ANDA 40,530	January 31, 2005
Depo-Testosterone	100 & 200mg/ml	Pharmacia & Upjohn	Injection	ANDA 85,635	Prior to January 1, 1982
Testosterone cypionate	100 & 200mg/ml	Sandoz	Injection	ANDA 40,615	August 10, 2006
Testosterone cypionate	200mg/ml	Synerx Pharma	Injection	ANDA 40,652	December 11, 2006
Testosterone cypionate	200mg/ml	Watson Labs	Injection	ANDA 86,030	Prior to January 1, 1982
Delatestryl	200mg/ml	Endo Pharma	Injection	9,165	Prior to January 1, 1982
Testosterone enanthate	200mg/ml	Paddock	Injection	ANDA 40,575	June 14, 2006
Testosterone enanthate	200mg/ml	Synerx Pharma	Injection	ANDA 40,647	October 5, 2009
Testosterone enanthate	200mg/ml	Watson Labs	Injection	ANDA 85,598	Prior to January 1, 1982

2.3 Availability of Proposed Active Ingredient in the United States

Testosterone is currently available in the United States as a buccal tablet, a subcutaneous implant, a transdermal patch, a transdermal gel and a parenteral injection.

2.4 Important Safety Issues with Consideration to Related Drugs

Labeled risks of testosterone administration in hypogonadal men include erythrocytosis, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity, and acne. Two major areas of concern in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease.

Transdermal testosterone preparations, which are applied to the skin, have been associated with secondary exposure of testosterone in women and children via direct skin to skin transference. The exposed women and children have experienced significant clinical sequela which prompted the FDA to mandate a Boxed Warning for all transdermal testosterone products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND No. 70,516 was submitted to the Division of Reproductive and Urologic Drug Products on August 11, 2006 by Acrux Pharma. Under this IND, their transdermal testosterone metered-dose lotion (Testosterone MD-Lotion®) was to be evaluated as a therapy for males with conditions associated with a deficiency or absence of endogenous testosterone.

An end-of-phase 2 meeting between Acrux and the Division was held on March 13, 2008. At this meeting, the design of Acrux's planned phase 3 study was discussed, including the dose titration scheme, the primary and secondary endpoints and the safety monitoring for the trial.

Prior to this meeting, Acrux had completed studies evaluating their product and the effect of deodorant use, application site washing, and person to person transfer. These initial studies had been conducted using a 1% formulation of the product rather than the 2% formulation that the Sponsor intends to market. This change in formulation was discussed and the Division indicated that, while it is unlikely that these trials would need to be repeated using the new formulation, a final decision would only be possible after review of the study reports.

A number of Chemistry, Manufacturing and Control issues were also discussed.

On August 31, 2009, a pre-NDA meeting was held between Acrux and the Division. The content and format of the submission was discussed. A number of issues regarding possible labeling were discussed and the Division indicated that no decisions on these issues would be possible until the submission was reviewed. The need for a clinical study evaluating the ability of soap and water to remove the product from the skin was discussed. Several Chemistry, Manufacturing and Control issues were also discussed.

2.6 Other Relevant Background Information

The Sponsor submitted the MTE11 study report, evaluating the ability of soap and water to wash testosterone from the skin. The results of this study are incorporated into this review.

During the review, the review team believed that the absence of a study evaluating person-to-person transfer using the to-be-marketed formulation (2% testosterone) was a significant deficiency. The study that was submitted with the application evaluated a 1% solution. This was discussed with the Sponsor who agreed to perform the necessary study. The Sponsor submitted this study report, MTE12, and the results have been incorporated in this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Sponsor has in place standard operating procedures that are consistent with ICH Good Clinical Practice. These include archiving of source data, data validation of CRF data, internal audits, and documentation of qualifications of investigators.

As part of this review, an assessment of the datasets and Case Report Forms (CRF) of Studies MTE08 and MTE09 was done and did not reveal miscoding or discrepancies between the data recorded on the CRFs and the datasets.

3.2 Compliance with Good Clinical Practices

The Sponsor has indicated that their studies were carried out according to the Declaration of Helsinki, the Code of Federal Regulations and the Notes for Guidance on Good Clinical Practice (2000) (CPMP/ICH/135/95), the ICH GCP Guidelines and the EU Clinical Trials Directive (2001/20/EC).

3.3 Financial Disclosures

The Sponsor has certified that the compensation of all clinical investigators was independent of the study outcome. They have also certified that no investigator had a financial interest in the product or the Sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A Chemistry review of the application has been conducted. The Chemistry reviewer has concluded that the sponsor has provided sufficient information on drug substance controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The sponsor has also provided sufficient stability information on the drug product to assure strength, purity and quality of the drug product during the expiration dating period.

The reviewer has also concluded that the labels have adequate information as required. They note that an overall acceptable recommendation has been made by the Office of Compliance.

The reviewer recommends approval of this NDA from a CMC perspective.

4.2 Clinical Microbiology

A Microbiology review of the application has been conducted. The reviewer has concluded that there are no microbiological deficiencies or impediments to approval.

4.3 Preclinical Pharmacology/Toxicology

A Toxicology review of the application has been conducted. The sponsor submitted no new nonclinical information, and is relying on published studies of testosterone. The overall toxicological profile of testosterone is well established. Nonclinical toxicities are not relevant for approval due to the preponderance of clinical data for testosterone that supersedes any nonclinical findings.

The formulation contains octisalate, an excipient not present in previously approved testosterone products. Octisalate is a penetration enhancer that is widely used in dermatological products including sunscreens and cosmetics and it has been found to be safe at concentrations up to 5%.

Dimethicone oil from the pump was detected in drug product following the first few pump actuations. The ubiquitous presence of dimethicone in cosmetics, in the clinical batch, and its known low dermal toxicity represents a low human safety risk in this testosterone 2% solution.

The toxicology reviewer's opinion is that the nonclinical data support approval of testosterone 2% solution for topical testosterone replacement in hypogonadal men.

4.4 Clinical Pharmacology

A clinical pharmacology review of the application has been conducted. The reviewer has concluded that the information supplied supports the approval of the application.

A formal consult to the Division of Scientific Investigations (DSI) was made for clinical and bioanalytical study sites inspections and there are no unresolved issues related to the approvability of Axiron.

No post-marketing requirements or commitments were recommended by the reviewer.

4.4.1 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.

4.4.2 Pharmacodynamics

There were no pharmacodynamic assessments conducted.

4.4.3 Pharmacokinetics

The reviewer evaluated the pharmacokinetics of Axiron from a phase 1 study as well as the pharmacokinetic results of the phase 3 efficacy trials. In addition, a study evaluating the effects of deodorants and antiperspirants on the pharmacokinetics of Axiron, a study evaluating the effect of application site washing on the pharmacokinetics of Axiron, a

study of the application site residual following washing, and a study of the potential for interpersonal transfer of testosterone from the application site were each reviewed by the clinical pharmacology reviewer.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Listing of all Clinical Studies

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
pK	DDS08	pK following single transdermal dose of Testosterone Lotion or Androgel	Randomized, two way, single-dose crossover	3ml Testosterone Solution and 5gm Androgel	6	Hypogonadal Males
pK	DDS15	PK following single transdermal dose of two different formulations of Testosterone	Randomized, two-way, single-dose, crossover	3 mL Testosterone Solution (1% testosterone) with (b) (4) octisalate applied to the inner arm	9	Healthy Women
pK	DDS16	PK following single transdermal dose of Testosterone Lotion	Randomized, two-way, single-dose, crossover	1 mL Testosterone Solution (1% testosterone, (b) (4) octisalate) applied to the inner arm or axilla	10	Healthy Women
pK	MTE04	Steady state PK of different doses/ formulations of Testosterone Lotion vs. Androgel	Randomized, open-label 4-way crossover	3 ml of 1% testosterone (b) (4) octisalate, 6 ml 1% testosterone (b) (4) octisalate, 6 ml 1% testosterone (b) (4) octisalate applied to axilla, or 5 g Androgel (1%	16	Healthy Males with chemically suppressed testosterone levels

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
				testosterone) applied to the shoulder, abdomen and upper arm.		
pK	MTE05	Steady state PK of 30 mg and 60 mg doses of Testosterone Lotion 1%	Randomized, open-label 2-way crossover	30 mg and 60 mg Testosterone Solution (1% testosterone/ ^{(b) (4)} 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 Solution Parts B and C/Effect of Deodorant and Antiperspirant and Washing: 3ml Testosterone Solution 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 Lotion (1% and 2%).	Randomized 4-way crossover	Axillary application of 30mg and 60 mg of 1% and 2% Testosterone Solution	21	Hypogonadal Males
Efficacy & Safety	MTE08	Confirm efficacy and safety of Testosterone 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	155	Hypogonadal Males

Type of Study	Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
				Solution		
Safety	MTE09	Assess skin safety of continuous use of the Testosterone 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 Solution	52	Hypogonadal Males
Safety	MTE10	Evaluate impact of washing and deodorant or antiperspirant use on absorption	Randomized, single dose, parallel group	Testosterone Solution containing 2% testosterone	36	Healthy Females
Safety	MTE11	Evaluate the effect of washing	Open label, single dose	Testosterone Solution containing 2% testosterone	10	Healthy Males
Safety	MTE12	Evaluate interpersonal transfer of testosterone	Open label, single dose	Testosterone Solution containing 2% testosterone	10 male/female pairs	Healthy Males and Females

5.2 Review Strategy

Study MTE08 was reviewed for the purpose of establishing the efficacy of Axiron. Study MTE10 was reviewed to evaluate the effect of using deodorant or antiperspirant on the efficacy of Axiron and also to evaluate the effect of washing the application site on efficacy.

Study MTE06 was evaluated for antiperspirant use and site washing. However, study MTE06 was performed using a 1% formulation of testosterone solution rather than the 2% solution contained in Axiron. Also, study MTE06 did not contain a true control group. For these reasons, study MTE10 was reviewed as the primary source of data regarding antiperspirant use and application site washing. Study MTE12 was reviewed as the primary source of data regarding the ability of a clothing barrier to block the interpersonal transfer of testosterone.

Studies MTE07, MTE08, MTE09, MTE10, MTE11 and MTE12 are the major source of safety information since they were done using the to-be-marketed 2% Testosterone solution. Studies DDS08, DDS15, DDS16, MTE04, MTE05, and MTE06 were considered as supportive since they used formulations that differed from the to-be-marketed formulations.

5.3 Discussion of Individual Studies/Clinical Trials

Primary Efficacy Trial – MTE08

Trial MTE08 was a Phase III open-label titration trial to evaluate the effectiveness and safety of a dermal application of Axiron Testosterone Lotion in hypogonadal men. It was carried out at 25 sites in Australia, France, Germany, Sweden, the United Kingdom and the United States.

Inclusion Criteria

Subjects who met all of the following criteria were eligible for entry into the trial:

- Male subjects greater than 18 years 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, and
 - Screening serum testosterone of ≤ 300 ng/dL (based on the average of two morning samples taken at least 30 minutes apart),
- Were currently receiving treatment (buccal, oral, transdermal or intramuscular androgen replacement) for hypogonadism in accordance with approved labeling, or in the Investigator's opinion are eligible to receive such treatment,
- Body Mass Index (BMI) < 35.0 kg/m²,
- Hemoglobin levels at screening ≥ 11.5 g/dL,
- Adequate venous access on left or right arm to allow collection of a number of samples by venipuncture,
- Ability to communicate with the trial staff, understand the Trial Information Sheet and sign the Written Informed Consent Forms; willing to follow the Protocol requirements and comply with Protocol restrictions and procedures.

Exclusion Criteria

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

- Current use of long acting testosterone injectables such as Nebido,
- Any significant history of allergy and/or sensitivity to the drug products or their excipients, including any history of sensitivity to testosterone and/or sunscreens,
- 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 trial subject in the trial and/or that in the Investigator's opinion, would interfere with the trial objectives or safety of the subject,

- Chronic skin disorder (e.g. eczema, psoriasis) likely to interfere with transdermal drug absorption,
- Men with suspected reversible hypogonadism (i.e. due to medications, stress),
- Any man in whom testosterone therapy was contraindicated, which included those with:
 - Known or suspected carcinoma (or history of carcinoma) of the prostate or clinically significant symptoms of benign prostatic hyperplasia and/or clinically significant symptoms of lower urinary obstruction and IPSS scores of ≥ 19 ,
 - Known or suspected carcinoma (or history of carcinoma) of the breast,
 - Severe liver disease (i.e. cirrhosis, hepatitis or liver tumors or liver function tests >2 times the upper limit of the normal range values),
 - Active deep vein thrombosis, thromboembolic disorders or a documented history of these conditions,
 - Current significant cerebrovascular or coronary artery disease,
 - Untreated sleep apnea,
 - Hematocrit of > 51 ,
 - Untreated moderate to severe depression,
- Men with clinically significant prostate exam (such as irregularities or nodules palpated) or clinically significant elevated serum Prostate Specific Antigen (PSA) levels (> 4 ng/mL), or age adjusted reference range of PSA values,
- 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),
- Men taking concomitant medications (prescribed or over-the-counter) that would affect SHBG or testosterone concentrations or metabolism, warfarin, insulin, opiates, gonadotropin-releasing hormone analogues, 5 alpha reductase inhibitors, propranolol, oxyphenbutazone, corticosteroids (except for physiological replacement doses), estradiol,
- Men involved in sport in which there is screening for anabolic steroids,
- Men with uncontrolled diabetes ($HbA1c \geq 10\%$),
- Men currently taking any investigational product, or have received an investigational product within 28 days prior to screening or 5 half-lives (whichever is the longer),
- Any contraindication to blood sampling,
- Subjects intending to have any surgical procedure during the course of the trial,
- Subjects with a partner of child bearing potential who are not willing to use adequate contraception for the duration of the trial,
- Subjects whose partners are pregnant.

Treatment

Subjects who met all inclusion criteria and had no excluding criteria were then begun on treatment with Axiron. The initial dose was 3ml (60mg) administered as 1.5ml to each axilla, once daily.

On day 15 and again on day 60, subjects underwent 24 hour pharmacokinetic evaluation which allowed calculation of C_{AVG} testosterone concentration. On day 45 and day 90, the Axiron dose was titrated according to the following:

- If C_{AVG} was in the normal range (300 – 1050 ng/dL), the dose was not changed.
- If C_{AVG} was <300 ng/dL, the dose was increased by 30mg to 90mg or 120mg.
- If C_{AVG} was >1050 ng/dL, the dose was decreased by 30mg. If their dose had previously been decreased to 30mg, this meant that they were discontinued from the trial.

Efficacy Endpoints

Primary Endpoint

In this trial, as in other trials for testosterone products, pharmacokinetic parameters were used as efficacy endpoints. The primary efficacy endpoint for MTE08 was to achieve a C_{AVG} for total testosterone in the defined normal range (300-1050 ng/dL). As agreed upon with the Division, the product would be considered to have achieved this endpoint if $\geq 75\%$ of subjects, with the lower bound of the 90% confidence interval $>66.8\%$, had C_{AVG} within this range on day 120.

Secondary Endpoints

The following secondary efficacy endpoints were evaluated.

- The proportion of subjects with total testosterone $C_{MAX} < 1500$ ng/dL. As agreed upon with the Division, the product would be considered to have achieved this endpoint if $>85\%$ of subjects had $C_{MAX} < 1500$ ng/dL on day 120.
- The proportion of subjects with total testosterone C_{MAX} between 1800 ng/dL and 2500 ng/dL. As agreed upon with the Division, the product would be considered to have achieved this endpoint if 5% of subjects had C_{MAX} in this range on day 120.
- The proportion of subjects with total testosterone $C_{MAX} > 2500$ ng/dL. As agreed upon with the Division, the product would be considered to have achieved this endpoint if no subjects had $C_{MAX} > 2500$ ng/dL on day 120.
- The proportion of subjects with total testosterone $C_{MIN} < 300$ ng/dL.
- Quality of Life Assessments
 - SF-36 mental and physical components.
 - Psychosexual Social Questionnaire evaluating sexual desire and enjoyment, mood, sexual activity and sexual performance.

Safety Evaluation

Clinic visits occurred at baseline and on days 15, 45, 60, 90 and 120. The following safety variables were assessed during the study: Complete medical history and physical

examination at baseline and study completion, review of concomitant medications at each visit, vital signs were taken at each visit, application site inspection for Draize score at each visit, hematology, chemistry and urine evaluation at baseline and study completion, recording adverse events at each visit. For subjects continuing into study MTE09, final physical exam and laboratory evaluation occurred at the completion of that study rather than on day 120 of study MTE08.

Safety Extension Trial – MTE09

Study MTE09 was a Phase III open-label extension of the MTE08 trial to evaluate skin-safety and adverse events. It was carried out at 25 sites in Australia, France, Germany, Sweden, the United Kingdom and the United States.

Inclusion Criteria

Subjects were eligible for trial MTE09 if they:

- Had completed the MTE08 trial up to and including Day 120/121 in a compliant manner,
- Were able to communicate with the trial staff, understand the Trial Information Sheet and sign the Written Informed Consent Forms; were willing to follow the Protocol requirements and comply with Protocol restrictions and procedures.

Exclusion Criteria

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

- Any clinically significant chronic illness or finding and/or laboratory testing that would interfere with the trial objectives or safety of the subject,
- Any man in whom testosterone therapy was contraindicated, which included those with:
 - Known or suspected carcinoma (or history of carcinoma) of the prostate or clinically significant symptoms of benign prostatic hyperplasia and/or clinically significant symptoms of lower urinary obstructions and with a IPSS score of ≥ 19 ,
 - Known or suspected carcinoma (or history of carcinoma) of the breast,
 - Severe liver disease (i.e. cirrhosis, hepatitis or liver tumors or liver function tests >2 times the upper limit of the normal range values,
 - Active deep vein thrombosis, thromboembolic disorders or a documented history of these conditions,
 - Current significant cerebrovascular or coronary artery disease,
 - Untreated sleep apnea,
 - Hematocrit of $>54\%$,
 - Untreated moderate to severe depression,

- Men with clinically significant prostate exam or clinically significant elevated serum Prostate Specific Antigen (PSA) level (> 4 ng/mL) or age adjusted reference range of PSA values,
- Men taking concomitant medications (prescribed or over-the-counter) that would affect SHBG or testosterone concentrations (excluding Axiron) or metabolism such as warfarin, insulin, opiates, gonadotropin-releasing hormone analogues, 5 alpha reductase inhibitors, propranolol, oxyphenbutazone, corticosteroids (except for physiological replacement doses), estradiol,
- Men with uncontrolled diabetes (HbA1c \geq 10%),
- Subjects intending to have any surgical procedure during the course of the trial,
- Subjects with a partner of child bearing potential who are not willing to use adequate contraception for the duration of the trial,
- Subjects whose partners are pregnant.

Treatment

Subjects were to continue to apply the dose of Axiron that they were using at Day 120 of the MTE08 trial. This could vary from 30mg/day to 120mg/day. This treatment was continued for two months following the completion of trial MTE08, resulting in exposure to Axiron of six months for those completing trial MTE09.

Trial Endpoints

No efficacy evaluation was done in trial MTE09. The primary objective of MTE09 was to assess the skin-safety of Axiron for an additional two months of continuous use (i.e. a total of 6 months).

The secondary objective for MTE09 was to collect adverse event and concomitant medication information over an additional two-month trial period. Study MTE09 compared the data collected at the study completion visit with the screening data in the MTE08 trial for the following variables:

- Fasting Insulin and Fasting Glucose levels.
- Prostate Specific Antigen (PSA) levels
- LH, Estradiol and FSH levels
- Hemoglobin and hematocrit levels
- Total Testosterone, free testosterone, DHT, DHT:T ratio levels at Day 187-190.

Study Evaluating Person-to-Person Transfer – MTE06

Study MTE06 was 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 solution.

Reviewer's Comment: *This study was carried out using a 1% solution of testosterone rather than the to-be-marketed 2% solution. The effect of deodorants, antiperspirants, and site washing on testosterone pharmacokinetics was re-evaluated, in study MTE10, using the 2% solution and study MTE10 provides the primary information regarding those factors. Initially it was planned to use study MTE06 as the primary source of information regarding person-to-person transfer of testosterone. However, during the course of the review it was decided that this safety issue should be evaluated using the product that is intended to be marketed. This was discussed with the sponsor, and the sponsor agreed to conduct an additional study, MTE12, which would evaluate person-to-person transfer with the Axiron 2% solution.*

Study Design

The study had three independent parts. Part A was designed to evaluate the potential for transfer of testosterone from healthy male subjects using testosterone solution 1% (60mg applied to axilla) to female partners. Four cohorts, with 6 partners in each cohort, were studied. Each cohort had 15 minutes of skin-to-skin contact at 2, 6 or 12 hours after the application of the solution. The fourth cohort evaluated transfer at 2 hours after application when the male partner wore a shirt. All female partners had pharmacokinetics evaluated for 24 hours following the contact.

Part B evaluated the impact of application of deodorant (Period I) or antiperspirant (Period II) on absorption of testosterone, when applied pre-application of testosterone 1% solution and immediately after, 30 minutes and 8 hours post application of testosterone 1% solution. This part of the study was divided into 2 study periods, Period I where subjects received an application of deodorant in addition to the study drug, and Period II where subjects received an application of antiperspirant in addition to the study drug.

Part C evaluated the impact of washing the application site 30 minutes, 2, 6, or 8 hours post application of testosterone 1% solution on the absorption of testosterone. The group where subjects washed the application site 8 hours after application of Testosterone 1% solution was used as a control group for both Parts B and C.

Reviewer's Comment: *Parts B and C of this study were repeated, using the to-be-marketed 2% testosterone solution, in study MTE10. That study will be reviewed as the primary source of data regarding the effects of deodorant use and application site washing effects on testosterone pharmacokinetics. Part A was repeated in study MTE12 which will serve as the primary source of data regarding the effect of a clothing barrier on interpersonal transfer.*

Inclusion Criteria

Subjects were included in Part A of the study if they met the following criteria:

- Healthy subjects ≥ 18 and ≤ 45 years of age,
- Males with a BMI ≥ 19 kg/m² and ≤ 30 kg/m², females with a BMI of 19-28 kg/m²,

- Females must be willing to undergo frequent blood sampling and have adequate venous access on their left or right arm to allow collection of a number of samples by venous cannulation and/or venipuncture,
- Had passed the required laboratory and physical screening tests,
- Refrained from consumption of grapefruit juice (an inducer of cytochrome p450 CYP3A), for 14 days preceding study and throughout the course of the study,
- Were willing to use a medically acceptable method of contraception for 14 days preceding study and throughout the course of the study.
- Agreed not to use any prescribed, over-the-counter or complementary medication during the 7 days preceding the study and throughout the course of the study, unless approved by both the Principal Investigator and the Sponsor,
- Males had hemoglobin levels at screening ≥ 135 g/L, females ≥ 115 g/L,
- Females had SHBG levels at screening $<$ twice the upper limit of normal,
- Females had negative serum pregnancy test taken at screening,
- Were 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, and
- Were willing to stop shaving, waxing or using depilatory products on the hair on their armpits for 1 week prior to dosing and for the study duration.

Exclusion Criteria

Subjects who met any of the following criteria were excluded:

- Had any significant history of allergy and/or sensitivity to the drug products or their excipients, including any history of sensitivity to testosterone and/or sunscreens,
- Had 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 subject in the study and/or that in the Investigator's opinion, would interfere with the study objectives,
- Had a chronic skin disorder (e.g. eczema, psoriasis) likely to interfere with transdermal drug absorption,
- Anyone in whom testosterone therapy was contraindicated, which included those with a history or the presence of:
 - Known or suspected carcinoma (or history of carcinoma) of the prostate or breast 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 tumours),
 - 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,

- Had any history of malignancy except non-melanotic skin cancer,
- Had current or prior history of drug or alcohol abuse (according to Canadian standards),
- Were taking concomitant medications (prescribed or over-the-counter) that would affect SHBG, prolactin or testosterone metabolism, or that are known to be cytochrome P450 inducers or inhibitors, anti-coagulants (warfarin) or diabetic medications (insulin) or anti-histamines within two weeks of dosing,
- Were taking any investigational product, or had received an investigational product within 28 days prior to screening or 5 half-lives (whichever is the longer),
- Had any contraindication to blood sampling,
- Had donated 400 mL or more of blood or had significant blood loss during the 8 weeks preceding dosing or a plasma donation within 14 days prior to dosing,
- Were involved in a sport for which there is screening for anabolic steroids,
- Study subjects who intended to have any surgical procedure during the course of the study,
- Women who were planning to become pregnant during the study duration, who did become pregnant during the study or who were breast feeding; Male subjects whose partners were pregnant, or were planning to become pregnant,
- Heavy smokers (> 10 cigarettes per day) who were unable to refrain from smoking during the confinement periods in this study,
- Difficulty abstaining from food and/or beverages that contain caffeine and/or other xanthines for 24 hours prior to testosterone administration and for the duration of confinement at the study centre,
- Were positive for HIV antibodies, Hepatitis B surface antigen or Hepatitis C antibodies,
- Men with clinically significant prostate exam or clinically significant elevated serum Prostate Specific Antigen (PSA) level, or age adjusted reference range of PSA values,
- Had current or prior history of a diagnosed psychiatric illness.
- Women who used androgen therapy within 30 days of dosing (e.g. testosterone implant, oral testosterone or tibolone, oral dehydroepiandrosterone, testosterone cream or troches),
- Women with current or past history of moderate to severe hirsutism or acne or any androgenic alopecia.

Study Procedures

Four cohorts of subjects were studied. Each cohort consisted of six male/female pairs. In each cohort the male partner had 60mg of 1% testosterone solution applied to an axilla. The female partners forearm had contact with the treated male axilla for 15 minutes at either 2, 6 or 12 hours after application. The forth cohort had this contact at 2 hours after application, but the male partner wore a shirt and the contact was between the female forearm and the clothed male axilla. For each cohort, the female partner then had pharmacokinetic evaluation for 24 hours following contact.

Study Objective

The objective was to evaluate testosterone transfer from the treated male to the untreated female. Blood samples were collected from the female partners at -30 min, 0, 30 min, 1, 2, 4, 8, 12, 16, 24, 36, 48, and 72 hours after contact. Testosterone pharmacokinetics were used as the measure of testosterone transfer. AUC_{0-72} , C_{MAX} , and C_{MIN} were considered the primary parameters evaluated. T_{MAX} and T_{MIN} were also evaluated.

Safety Evaluation

During screening, the following assessments were performed: physical examination (including blood pressure, heart rate, temperature and respiration rate), medical and medication history, breast examination and pelvic examination (for female subjects, unless a pap smear was performed within 12 months), ECG, Draize assessment, biochemistry (including hormone testing, hepatitis B-surface antigen, hepatitis C, HIV, renal function screens, and serum β -HCG testing on female subjects), hematology, urinalysis, drugs of abuse (urine), and alcohol (breathalyzer) screens.

After check-in for the study, the following were performed on all subjects:

- Testing for drugs of abuse (urine);
- Testing for alcohol (breathalyzer);
- Body temperature;
- Vital sign measurements;
- Draize skin assessment: Both axillas for male subjects and both forearms for female subjects.
- Serum β -HCG testing on all female subjects.

AEs were monitored and documented throughout the confinement portion of the study.

Seven days after drug application or at the time of withdrawal from the study, each subject was required to return to the clinical facility, for the following assessments:

- Physical examination
- Vital signs measurements (including blood pressure, heart rate, temperature and respiration rate)
- ECG
- Draize Assessment
- Laboratory tests (biochemistry, haematology, hormone testing and renal function screen)
- Documentation of concomitant medications and AEs

Study Evaluating the Effect of Application Site Washing or Deodorant Use on Testosterone Pharmacokinetics – MTE10

Study MTE10 was a phase I trial 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 (cutaneous solution). It was a randomized, open label, single-center, parallel group, single dose study.

Inclusion Criteria

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

- Healthy premenopausal female subjects ≥ 18 and ≤ 45 years of age,
- Body Mass Index (BMI) 19-30 kg/m²,
- Willing to undergo frequent blood sampling,
- Passed the required laboratory and physical screening tests,
- Adequate venous access on left or right arm to allow collection of a number of samples by venous cannulation and/or venipuncture,
- Willing to refrain from consumption of products containing grapefruit (an inducer of cytochrome p450 CYP3A), for 14 days preceding trial and throughout the course of the trial,
- Willing to use a medically acceptable method of contraception for 14 days preceding trial and throughout the course of the trial,
- Agreed not to use any prescribed, over-the-counter or complementary medication during the 7 days preceding the trial and throughout the course of the trial, unless approved by both the PI and the Sponsor,
- Had hemoglobin levels at screening ≥ 115 g/L,
- Had SHBG levels within the reference range for their age group,
- Was able to communicate with the trial staff, understand the Trial Information Sheet and sign the Written Informed Consent Form; was willing to follow the Protocol requirements and comply with Protocol restrictions and trial procedures,
- Had negative serum pregnancy test taken at screening,
- Was willing to stop shaving, waxing or using depilatory products on the hair on their armpits for 1 week prior to dosing and for the treatment period (i.e. 72 hours).

Exclusion Criteria

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

- Had a significant history of allergy and/or sensitivity to the drug products or their excipients, including any history of sensitivity to testosterone and/or sunscreens,
- Had a clinically significant finding on screening physical exam, including breast exam, pap smear (conducted within <12 months of screening) and/or laboratory testing that made it undesirable for the Investigator to enroll the subject in the

trial and/or that in the Investigator's opinion, would interfere with the trial objectives,

- Had a chronic skin disorder (e.g. eczema, psoriasis) likely to interfere with transdermal drug absorption,
- Any woman in whom testosterone 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 years,
 - 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,
- Had any history of malignancy except non-melanotic skin cancer,
- Had a history of drug or alcohol abuse (more than 2 standard drinks per day) and/or abnormal liver function tests considered clinically significant
- Women who were taking concomitant medications (prescribed or over-the-counter) that would affect SHBG, prolactin or testosterone metabolism, or that was known to be cytochrome P450 inducers or inhibitors, Cyclosporin, anti-coagulants (warfarin) or diabetic medications (insulin) or anti-histamines within 14 days of dosing,
- 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),
- Had any contraindication to blood sampling, or had donated 400 mL or more of blood or had significant blood loss during the eight weeks preceding dosing or a plasma donation within 14 days prior to dosing,
- Women involved in a sport for which there was screening for anabolic steroids,
- Subjects intending to have any surgical procedure during the course of the trial,
- Women who were planning to become pregnant during the trial duration, who did become pregnant during the trial or who were breast feeding,
- Heavy smokers (>10 cigarettes per day) who were unable to refrain from smoking during the confinement periods in the trial,
- 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 hours post dose),
- Were positive for Human Immunodeficiency Virus (HIV) antibodies, Hepatitis B surface antigen or Hepatitis C antibodies,

- Had used androgen therapy within 30 days of dosing (e.g. testosterone implant, oral testosterone or tibolone, oral dehydroepiandrosterone, testosterone cream or troches),
- Had current or prior history of a diagnosed psychiatric illness,
- Women with current or past history (within the last 5 years) of moderate to severe hirsutism or acne or any androgenic alopecia,
- Women on hormonal contraceptive.

Study Procedure

Thirty-six subjects were randomized to one of six treatment groups on a 1/1/1/1/1/1 basis.

- Group 1: Antiperspirant/deodorant stick was applied 2 minutes prior to Testosterone 2% solution application.
- Group 2: Antiperspirant/deodorant spray was applied 2 minutes prior to Testosterone 2% cutaneous solution application.
- Group 3: Deodorant spray was applied 2 minutes prior to Testosterone 2% cutaneous solution application.
- Group 4: Control group applied Testosterone 2% cutaneous solution at the nominated time.
- Group 5: Application site washing procedure was performed 2 hours post Testosterone 2% cutaneous solution application.
- Group 6: Application site washing procedure was performed 6 hours post Testosterone 2% cutaneous solution application.

Pharmacokinetic sampling was conducted for all subjects at 30 minutes, 1, 2, 4, 8, 12, 16, 24 and 36 hours post application to measure testosterone and DHT levels and to calculate free testosterone. SHBG was also measured in the 24 hour sample.

Study Objectives

- To evaluate the impact of application of antiperspirant and deodorant on absorption of testosterone, when applied prior to Testosterone 2% solution.
- To evaluate the impact of washing the application site on the absorption of testosterone, when washed following Testosterone 2% solution application.
- To assess the safety and tolerability of Testosterone 2% solution following single dose application.

Safety Evaluation

During screening, the following assessments were performed: physical examination (including blood pressure, heart rate, temperature and respiration rate), medical and medication history, breast examination and pelvic examination (unless a pap smear was performed within 12 months), ECG, biochemistry (including hormone testing, hepatitis B-surface antigen, hepatitis C, HIV, renal function screens, and serum β -HCG), hematology, urinalysis, drugs of abuse (urine), and alcohol (breathalyzer) screens.

After check-in for the study, the following were performed on all subjects:

- Testing for drugs of abuse (urine);
- Testing for alcohol (breathalyzer);
- Body temperature;
- Vital sign measurements;
- Serum β -HCG testing.

AEs were monitored and documented throughout the confinement portion of the study.

Seven days after drug application or at the time of withdrawal from the study, each subject was required to return to the clinical facility, for the following assessments:

- Physical examination
- Vital signs measurements (including blood pressure, heart rate, temperature and respiration rate)
- ECG
- Draize Assessment
- Laboratory tests (biochemistry, hematology, hormone testing and renal function screen)
- Documentation of concomitant medications and AEs

Study Evaluating the Ability to Wash Axiron from the Application Site – MTE11

Study MTE11 was a healthy volunteer, single dose, phase I trial to determine the amount of testosterone remaining after washing an axilla to which Testosterone 2% solution had been applied. It was an open label study that was performed at a single center.

Inclusion Criteria

To be eligible for the trial, subjects must meet the following criteria:

- Healthy male subjects ≥ 18 and ≤ 70 years of age,
- BMI 19-35 kg/m²,
- Agreed not to use any prescribed, over-the-counter or complementary medication during the seven days preceding Day 1 of the study and throughout the course of the study, unless approved by both the Principal Investigator and the Sponsor,
- Have hemoglobin levels at screening ≥ 135 g/L,
- Have passed the required laboratory and physical screening tests,
- Be willing to use a medically acceptable method of contraception for 14 days preceding Day 1 and throughout the course of the study.

- Be able to communicate with the study staff, understand the Study Information Sheet and sign the Written Informed Consent Form; be willing to follow the Protocol requirements and comply with Protocol restrictions and study procedures,
- Have not shaved, waxed or used depilatory products on the hair of the axilla for the three months prior to the screening period.

Exclusion Criteria

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

- Have any significant history of allergy and/or sensitivity to the drug product or excipients, including any history of sensitivity to testosterone and/or sunscreens,
- Have any clinically significant finding on screening physical exam, and/or laboratory testing that makes it undesirable for the Investigator to enroll the subject in the study and/or that in the Investigator's opinion, would interfere with the study objectives,
- Have a chronic skin disorder (eg. eczema, psoriasis) likely to interfere with transdermal drug absorption,
- Any subject in whom Testosterone therapy is contraindicated, which includes those with a history or the presence of:
 - Known or suspected carcinoma (or history of carcinoma) of the prostate or clinically significant symptoms of benign prostatic hyperplasia and/or clinically significant symptoms of lower urinary obstruction and International Prostate Symptoms Score (IPSS) scores of ≥ 19 .
 - 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 years,
 - Severe liver damage ie. cirrhosis, hepatitis or liver tumors,
 - Active deep vein thrombosis, thromboembolic disorders or a documented history of these conditions,
 - Current significant cerebrovascular or coronary artery disease
 - Known or suspected sleep apnea,
 - Hematocrit $>51\%$,
 - Confirmed or suspected androgen-dependent neoplasia,
 - Untreated moderate to severe depression,
- Have any history of malignancy except non-melanotic skin cancer,
- Have a history of drug or alcohol abuse (more than 2 standard drinks per day) and/or abnormal liver function tests considered clinically significant,
- 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),
- Subjects intending to have any surgical procedure during the course of the study,
- Have current or prior history of a diagnosed psychiatric illness,

- Any contraindication to blood sampling,
- Heavy smokers (> 10 cigarettes per day) who are unable to refrain from smoking during the confinement periods in this study,
- Men with clinically significant elevated serum Prostate Specific Antigen (PSA) level, or age adjusted reference range of PSA values,
- Men taking concomitant medications (prescribed or over-the-counter) that would affect SHBG or testosterone concentrations or metabolism, or that are known to be cytochrome P450 inducers or inhibitors, anti-coagulants (warfarin), or diabetic medications (insulin),
- Men involved in a sport in which there is screening for anabolic steroids,
- Men who have used any self tanning lotions or sprays in the month preceding the screening period.
- Study subjects whose partners are pregnant.

Study Objectives

- To evaluate the amount of testosterone remaining on the axilla in healthy males who undergo a washing procedure after applying Testosterone 2% solution.
- To assess the safety and tolerability of Testosterone 2% solution.

Study Procedures

This trial was a single dose trial in healthy male subjects. Eligible subjects reported to the Phase I unit and had a shower.

A 3.0ml (2 x 1.5mL) of Testosterone 2% solution, was applied to each axilla by trained site staff and allowed to dry (equivalent to a 60mg dose to each axilla). After the Testosterone MD-Lotion® 2% had dried (5 minutes after application of the second dose), the left axilla was wiped with alcohol towelettes which were assayed for testosterone content.

Subjects were asked to shower following a standardized procedure with soap and water 30 minutes after application. The right axilla was then wiped with alcohol towelettes which were assayed for testosterone content.

For each axilla, the wiping procedure was standardized and a total of ten towelettes was used on each axilla. Each towelette is assayed for testosterone independently.

Safety Evaluation

During screening, the following assessments were performed: physical examination (including blood pressure, heart rate, temperature and respiration rate), medical and medication history, ECG, biochemistry (including hormone testing, hepatitis B-surface antigen, hepatitis C, HIV, and renal function screens), hematology, urinalysis, drugs of abuse (urine), and alcohol (breathalyzer) screens.

AEs were monitored and documented throughout the confinement portion of the study.

Seven days after drug application or at the time of withdrawal from the study, each subject was required to return to the clinical facility, for the following assessments:

- Physical examination
- Vital signs measurements
- ECG
- Laboratory tests (biochemistry, haematology, hormone testing and renal function screen)
- Documentation of concomitant medications and AEs

Study Evaluating Interpersonal Transfer of Axiron through a Clothing Barrier – MTE12

The original study of interpersonal testosterone transfer, MTE06, had been conducted using a 1% testosterone solution. During the application review, it was determined that the ability of a clothing barrier to protect from transfer should be evaluated using the to-be-marketed formulation of 2%. The Sponsor evaluated this in study MTE12.

Study MTE12 was a single center, open label study to evaluate the potential for interpersonal transfer of testosterone following a single dose application of 2% testosterone solution. The transfer would be evaluated with the site of application covered with a cotton shirt.

This trial was a single dose study in healthy male and female subjects. Ten pairs of subjects were enrolled. Female (recipient) subjects underwent baseline intensive pharmacokinetic sampling during the 24 hour period prior to the transfer procedure to establish their baseline levels of testosterone and DHT. Testosterone and DHT were measured and free testosterone calculated at 0 minutes, 30 minutes, 1, 2, 4, 8, 10, 12, 16, and 24 hours on the day prior to the transfer procedure. SHBG was measured in samples collected at 24 hours. Eligible healthy male (donor) subjects received a 120mg dose (2 x 1.5mL to each axilla), of 2% testosterone solution. Female study subjects underwent 15 minutes of vigorous contact at 2 hours post dose application of 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 pharmacokinetic sampling post the transfer procedure. Testosterone and DHT were measured and free testosterone calculated at 30 minutes, 1, 2, 4, 8, 10, 12, 16, 24, 48 and 72 hours post transfer procedure. SHBG was measured in samples collected at 24, 48 and 72 hours post transfer.

Single dose testosterone and DHT pharmacokinetic parameters (AUC_{0-24} and AUC_{0-72} , C_{max} , C_{min} and t_{max}) were calculated. Single dose free testosterone pharmacokinetic

parameters (AUC_{0-24} , AUC_{0-72} , C_{max} , C_{min} and t_{max}) were calculated using SHGB levels collected daily. Mean, standard deviation (SD) and Coefficient of Variation (CV) were calculated for serum concentrations of testosterone, free testosterone and DHT at each time point for pharmacokinetic parameters. Changes from baseline were analyzed using a paired Student's t test for DHT, total testosterone and calculated free testosterone.

Adverse events, concomitant medications, vital signs, physical examination, Draize scores, clinical laboratory parameters and ECGs were tabulated and summarized.

Other Studies

Safety Information from the following pharmacokinetic studies was reviewed:

- DDS08 – pK following a single transdermal dose of testosterone 1% solution or Androgel. N = 6.
- DDS15 – pK following a single dose of two different formulations of testosterone 1% solution. N = 9.
- DDS16 – pK following a single transdermal dose of testosterone 1% solution. N = 10.
- MTE04 – Steady state pK following different doses and formulations of testosterone 1% solution or Androgel. N = 16.
- MTE05 – Steady state pK following 30mg and 60mg doses of testosterone 1% solution. N = 41.
- MTE07 – Comparison of steady state pK following testosterone 1% solution and testosterone 2% solution. N = 21.

6 Review of Efficacy

Efficacy Summary

The Sponsor has conducted one clinical trial (MTE08), evaluating the efficacy of their testosterone transdermal solution in producing serum testosterone levels within the normal range when the solution is used in hypogonadal men. This trial was adequately designed and evaluated accepted endpoints for testosterone products. The trial has shown that this medication has significant efficacy for the treatment of hypogonadism.

In addition, the Sponsor has conducted a clinical trial (MTE10), evaluating the effect of underarm deodorant use and the effect of application site washing on product efficacy. This study, together with Study MTE08, indicates that, while deodorant use or washing the application site lowers the testosterone exposure, it remains an effective treatment for hypogonadism.

6.1 Indication

It is indicated for testosterone replacement therapy in males having conditions associated with a deficiency or absence of endogenous testosterone.

6.1.1 Methods

The design of study MTE08 was reviewed in Section 5.3.

6.1.2 Demographics

The MTE08 study was conducted at 26 clinical research centers in Australia, the United States, the United Kingdom, Germany, Sweden and France. The following cohorts of subjects were defined:

- Safety Set – 155 subjects who received at least one dose of study drug. This set is the basis for the safety evaluation.
- Completer Set – 138 subjects who completed the study through the day 120 visit plus any subjects that withdrew prior to day 120 for reasons of efficacy or adverse event. This set is the basis for the primary efficacy evaluation.
- Full Analysis Set – 143 subjects who received at least one dose of study drug and had on-treatment data for at least one efficacy variable. Analyses based on this set were considered as supportive.
- Per-protocol Set – 123 subjects who completed study MTE08 with no protocol violations. Analyses based on the Per-Protocol Set were considered as supportive for the primary efficacy endpoint.

Disposition of all screened subjects for MTE08 and MTE09 (a safety extension) is summarized by center in Table 3 and by maintenance dose in

Table 4.

Table 3. Study Participants by Site

Site Number	Location	Screened Subjects	MTE08				MTE09
			Safety Set ¹ N(%)	Full Analysis Set ² N(%)	Completer Set ³ N(%)	Per Protocol Set ⁴ N(%)	Safety Set N(%)
101	AUS	2	1 (0.6)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
102	AUS	6	4 (2.6)	4 (2.8)	4 (2.9)	4 (3.3)	0 (0.0)
103	AUS	4	3 (1.9)	3 (2.1)	3 (2.2)	3 (2.4)	0 (0.0)
104	AUS	5	2 (1.3)	2 (1.4)	2 (1.4)	2 (1.6)	0 (0.0)
201	USA	15	8 (5.2)	8 (5.6)	8 (5.8)	5 (4.1)	8 (11.3)
202	USA	17	8 (5.2)	7 (4.9)	7 (5.1)	6 (4.9)	5 (7.0)
203	USA	34	9 (5.8)	9 (6.3)	9 (6.5)	8 (6.5)	9 (12.7)

Site Number	Location	Screened Subjects	MTE08				MTE09
			Safety Set ¹ N(%)	Full Analysis Set ² N(%)	Completer Set ³ N(%)	Per Protocol Set ⁴ N(%)	Safety Set N(%)
204	USA	9	3 (1.9)	2 (1.4)	2 (1.4)	2 (1.6)	1 (1.4)
205	USA	33	13 (8.4)	11 (7.7)	11 (8.0)	10 (8.1)	8 (11.3)
206	USA	23	4 (2.6)	4 (2.8)	4 (2.9)	3 (2.4)	4 (5.6)
207	USA	26	13 (8.4)	13 (9.1)	13 (9.4)	11 (8.9)	10 (14.1)
208	USA	25	9 (5.8)	7 (4.9)	6 (4.3)	5 (4.1)	4 (5.6)
209	USA	10	9 (5.8)	7 (4.9)	7 (5.1)	5 (4.1)	5 (7.0)
210	USA	16	8 (5.2)	8 (5.6)	8 (5.8)	8 (6.5)	8 (11.3)
211	USA	30	13 (8.4)	12 (8.4)	10 (7.2)	10 (8.1)	4 (5.6)
212	USA	22	7 (4.5)	6 (4.2)	5 (3.6)	5 (4.1)	5 (7.0)
301	GBR	6	5 (3.2)	4 (2.8)	4 (2.9)	3 (2.4)	0 (0.0)
302	GBR	4	3 (1.9)	3 (2.1)	3 (2.2)	3 (2.4)	0 (0.0)
303	GBR	7	2 (1.3)	2 (1.4)	2 (1.4)	2 (1.6)	0 (0.0)
401	DEU	5	4 (2.6)	4 (2.8)	4 (2.9)	4 (3.3)	0 (0.0)
402	DEU	2	1 (0.6)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)
403	DEU	4	4 (2.6)	4 (2.8)	4 (2.9)	4 (3.3)	0 (0.0)
501	SWE	7	6 (3.9)	6 (4.2)	5 (3.6)	5 (4.1)	0 (0.0)
502	SWE	9	5 (3.2)	5 (3.5)	5 (3.6)	5 (4.1)	0 (0.0)
601	FRA	11	8 (5.2)	8 (5.6)	8 (5.8)	8 (6.5)	0 (0.0)
602	FRA	8	3 (1.9)	3 (2.1)	2 (1.4)	2 (1.6)	0 (0.0)
Total		340	155	143	138	123	71

Source: NDA 22504 submission, Module 5.3.5.2, Table 14.1.1.1

Table 4 Study Participants by Final Testosterone Dose

Maintenance Dose of Testosterone Solution	MTE08 Safety Set ¹ N(%)	Full Analysis Set ² N(%)	Completer Set ³ N(%)	Per Protocol Set ⁴ N(%)	MTE09 Safety Set N(%)
30 mg	3 (1.9)	3 (2.1)	3 (2.2)	3 (2.4)	2 (2.8)
60 mg	117 (75.5)	105 (73.4)	100 (72.5)	88 (71.5)	49 (69.0)
90 mg	25 (16.1)	25 (17.5)	25 (18.1)	22 (17.9)	12 (16.9)
120 mg	10 (6.5)	10 (7.0)	10 (7.2)	10 (8.1)	8 (11.3)
Overall	155 (100.0)	143 (100.0)	138 (100.0)	123 (100.0)	71 (100.0)

Source: NDA 22504 submission, Module 5.3.5.2, Table 14.1.1.2

[1] Safety Set = Any subject who entered the study and received at least one dose of investigational product.

[2] Full Analysis Set = All subjects who entered the trial, received at least one dose of investigational product, and have on-treatment data for at least one efficacy variable.

[3] Completer Set = All subjects in the Full Analysis Set who also completed the Day 120 Visit. Subjects who withdrew prior to Day 120 due to either lack of efficacy or an adverse event will also be included in the Completer Set.

[4] Per Protocol Set = All subjects who completed the trial without any significant protocol deviations or violations.

The demographic characteristics, and also the baseline characteristics, of the safety set are shown in Table 5.

Table 5. Demographic and Baseline Characteristics for Safety Set

Maintenance Dose of Testosterone Solution					
	30 mg (N=3)	60 mg (N=117)	90 mg (N=25)	120 mg (N=10)	All Doses (N=155)
Age (years)					
Mean (sd)	57.3 (7.1)	51.3 (13.4)	52.9 (10.9)	48.7 (9.4)	51.5 (12.7)
Min, Max	51, 65	19, 78	25, 75	30, 62	19, 78
Race					
Asian	0	1 (0.9%)	0	0	1 (0.7%)
Caucasian	2 (66.7%)	94 (86.2%)	19 (86.4%)	7 (70.0%)	122 (84.7%)
African American	0	2 (1.8%)	3 (13.6%)	1 (10.0%)	6 (4.2%)
Hispanic	1 (33.3%)	10 (9.2%)	0	2 (20.0%)	13 (9.0%)
Other	0	2 (1.8%)	0	0	2 (1.4%)
Weight (kg)					
Mean (sd)	83.4 (6.0)	94.5 (15.2)	94.6 (12.0)	95.1 (14.1)	94.4 (14.5)
Min, Max	79.4, 90.3	59.1, 126.1	75.5, 119.7	75.9, 123.6	59.1, 126.1
BMI (kg/m)					
Mean (sd)	28.1 (5.4)	29.6 (3.7)	29.7 (3.0)	29.1 (3.9)	29.5 (3.6)
Min, Max	24.8, 34.4	18.2, 38.9	24.6, 35.0	23.9, 34.8	18.2, 38.9
Baseline Testosterone (ng/dL)					
Mean (sd)	138.8 (137.3)	204.0 (89.6)	169.9 (97.2)	197.9 (68.2)	196.7 (91.0)
Min, Max	24, 291	6.8, 419	42, 341	108, 280	6.8, 419

Source: NDA 22504 submission, Module 5.3.5.2, Table 14.1.2.1

Reviewer's Comment: *The baseline testosterone values are the average of the first series of two screening testosterone determinations. Several subjects had averages greater than 300 on this first screening. They underwent additional screening and were only enrolled if the subsequent values averaged less than 300 ng/dL. Table 5 does not include the subsequent values that qualified the patients for the study. This explains the >300 values seen in this Table – they are the first screening values, not necessarily the qualifying values.*

85.8% of the safety set cohort patients had at least one prior treatment for hypogonadism. The prior treatments are summarized in Table 6.

Table 6. Prior Treatment for Hypogonadism

Route of Administration	Maintenance	Dose	Of	Testosterone	Lotion
	30 mg (N=3)	60 mg (N=117)	90 mg (N=25)	120 mg (N=10)	Overall (N=155)
Subjects with at least one prior treatment for hypogonadism	3 (100%)	98 (83.8%)	22 (88.0%)	10 (100%)	133 (85.8%)
Oral Formulation	0	9 (7.7%)	3 (12.0%)	1 (10.0%)	13 (8.4%)
Intramuscular Injection	0	44 (37.6%)	8 (32.0%)	2 (20.0%)	54 (34.8%)
Subdermal implant	0	5 (4.3%)	0	1 (10.0%)	6 (3.9%)
Transdermal patch	0	14 (12.0%)	2 (8.0%)	1 (10.0%)	17 (11.0%)
Buccal Patch	0	1 (0.9%)	0	0	1 (0.6%)
Topical Gel	3 (100%)	66 (56.4%)	13 (52.0%)	6 (60.0%)	88 (56.8%)
Other	0	4 (3.4%)	3 (12.0%)	0	7 (4.5%)

Source: NDA 22504, Module 5.3.5.2, Table 14.1.3.3, page 171

Table 7 shows the baseline medical conditions present in >3% of the safety set.

Table 7. Baseline Medical Conditions, Safety Set

Preferred Term	Number	Percentage
Hypertension	55	35.5
Erectile Dysfunction	42	27.1
Hypercholesterolemia	40	25.8
GI Reflux	23	14.8
Depression	21	13.5
Diabetes Mellitus Type II	18	11.6
Hyperlipidemia	15	9.7
Asthma	14	9.0
Diabetes Mellitus Type I	13	8.4
Osteoarthritis	12	7.7
BPH	11	7.1
Sleep Apnea	9	5.8
Klinefelter's Syndrome	5	3.2

Source: NDA 22504, Module 5.3.5.2.3, Table 14.1.3.7

6.1.3 Subject Disposition

One hundred fifty-five subjects were enrolled in study MTE08. Twenty subjects were subsequently withdrawn from the study. The reasons for withdrawal are shown in Table 8.

Table 8. Reasons for Withdrawal from Study MTE08

Reason for Withdrawal	Number of Subjects
Withdrew consent	9
Non-compliance with study drug	3
Lost to follow-up	2
Non-compliance with site directives	1
Sponsor request	1
Screening Testosterone level >300 ng/dL	1
AE: Superficial thrombophlebitis	1
AE: Melanoma of scalp	1
AE: Emotional changes	1

Source: NDA 22504 submission, Module 5.3.5.2, Table 10-1

Reviewer's comment: The emotional changes leading to withdrawal in one subject were judged to be possibly related to study drug, although, the subject experienced on going emotional behavioral changes prior to and during the clinical trial. Testosterone therapy in my opinion might have precipitated already existing emotional state of mind in this subject. The phlebitis and melanoma were believed to be unrelated to the study medication.

6.1.4 Analysis of Primary Endpoint(s)

The primary assessment of efficacy, as specified in the end-of-phase 2 meeting, was based on the proportion of subjects with C_{AVG} (0-24h) total testosterone within the normal range (300 – 1050 ng/dL) on day 120 of the trial. In order to be considered an effective treatment, this proportion had to be $\geq 75\%$, with the lower bound of the 95% confidence interval $> 66.8\%$.

Table 9 shows the proportion of subjects having C_{AVG} total testosterone within the normal range at three time points.

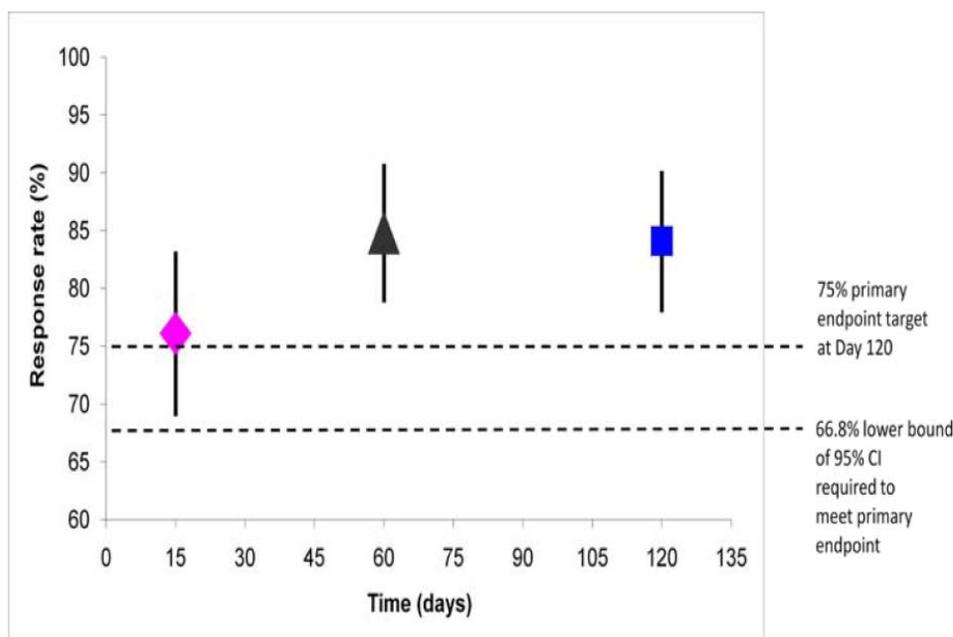
Table 9. Proportion of Subjects with Serum Total Testosterone C_{AVG} in the Range of 300 – 1050 ng/dL (Percent, 95% CI, N)

Data Set	Day 15/16	Day 60/61	Day 120/121
Completer Set (N=138)	76.1% (69.0 – 83.2) 105/138	84.8% (78.8 – 90.8) 117/138	84.1% (78.0 – 90.2) 116/138
Full Analysis Set (N=143)	77.6% 111/143	86.2% 119/138	84.1% 116/138

Source: NDA 22504, Module 5.3.5.2, Table 11-1, page 92.

This is shown graphically for the Completer set in Figure 1.

Figure 1. Proportion of Subjects with Serum Total Testosterone C_{AVG} in the Range of 300 – 1050 ng/dL



Source: NDA 22504, Module 5.3.5.2, Figure 11-1, page 92

Reviewer’s comment: *The Sponsor has demonstrated that their Testosterone solution (Axiron) is effective in normalizing serum testosterone levels in men who are hypogonadal. They have also shown that they were able to achieve the pre-specified criteria for efficacy after a single titration, 15 days following initiation of therapy. The second titration at 60 days did not meaningfully change the proportion of subjects having serum testosterone within the normal range.*

Dihydrotestosterone levels similarly increased with treatment. The arithmetic mean DHT concentration at the time of enrollment was 18.7 ng/dL. This increased to 90.5 ng/dL on day 120.

Free testosterone levels were calculated using total testosterone, SHBG and albumin levels. As a calculated fraction of total testosterone levels, free testosterone levels (C_{avg} , C_{max} and C_{min}) as well as the t_{max} mirrored those of total testosterone. The geometric mean levels increased from 56.7 pg/ml prior to initiation of drug treatment to 121 pg/ml on day 120.

6.1.5 Analysis of Secondary Endpoints(s)

Table 10 shows the data for four secondary endpoints that are based on pharmacokinetic data.

Table 10. Secondary Serum Total Testosterone Pharmacokinetic Endpoints (Completer Set)

Data	Target	Day 15/16	Day 60/61	Day 120/121
$C_{MAX} < 1500$ ng/dL	> 85%	95.6% 130/136	91.2% 124/136	94.5% 128/135
$C_{MAX} > 2500$ ng/dL	0	1.5% 2/136	1.5% 2/136	0.7% 1/135
$C_{MAX} > 1800$ and ≤ 2500 ng/dL	< 5%	2.2% 3/136	4.4% 6/136	3.0% 4/135
$C_{MIN} < 300$ ng/dL	No prespecified Target value	71.3% 97/136	69.1% 94/136	64.4% 87/135

Source: NDA 22504, Module 5.3.5.2, Table 11-2, page 93

Proportion of subjects with C_{MAX} less than 1500 ng/dL

At each PK sampling period the number of subjects in the Completer Set with C_{max} below 1500 ng/dL was always greater than 90% and at Day 120 it was 94.8%. At all time points, the trial target of more than 85% of subjects with their C_{max} below 1500 ng/dL was achieved. Across the entire trial 87.5% of subjects had a $C_{max} < 1500$ ng/dL.

Proportion of subjects with Serum Total Testosterone C_{MAX} between 1800 ng/dL and 2500 ng/dL

At each of the intensive PK sampling days this target was met and at Day 120 the number of subjects who fell into this category numbered 4 out of 135 or 3.0%. Of the four subjects at Day 120 who fell into this category only one had a reasonably sustained level of testosterone between 1800 and 2500 ng/dL and this was mirrored by increases in DHT as well.

Proportion of subjects with Serum Total Testosterone C_{MAX} greater than 2500 ng/dL

During the course of the trial five patients had a $C_{MAX} > 2500$ ng/dL at some point. These patients are shown in Table 11.

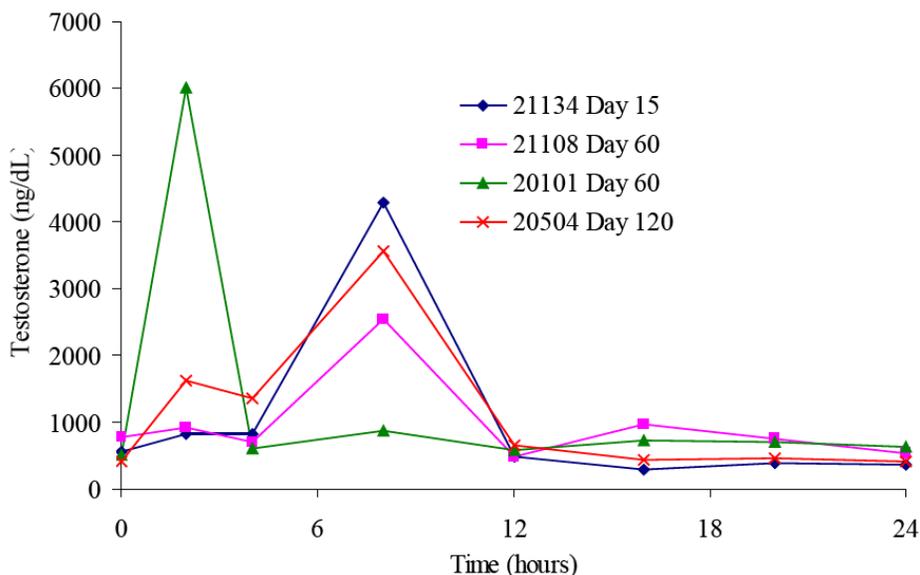
Table 11. Subjects with Serum Total Testosterone C_{MAX} >2500 ng/dL

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

Source: NDA 22504, Module 5.3.5.2, Table 11-3, page 94

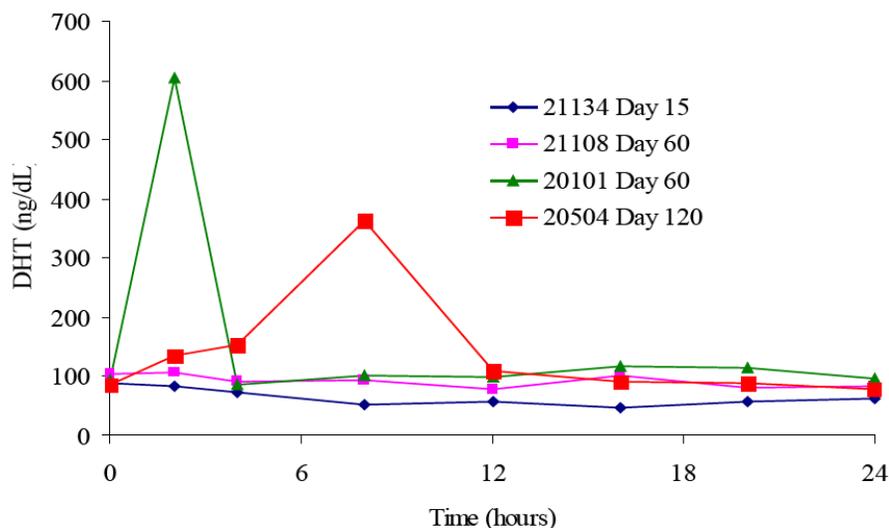
An analysis of the pharmacokinetic data for the five subjects shows that, in four of the five, the elevated value is a single point that appears to be out of line with respect to the data points on either side of it. Figure 2 and Figure 3 show a graphical representation of the testosterone and DHT pK data for these four subjects on the day on which the elevated C_{MAX} was seen.

Figure 2. Serum Total Testosterone pK Profiles for Four Subjects having C_{MAX} >2500 ng/dL



Source Data: [Report on Pharmacokinetic Assessment, Appendix 12.0 Individual PK Profiles \(Appendix 16.1.9\)](#)

Figure 3. Serum DHT pK Profiles for Four Subjects having Testosterone C_{MAX} >2500 ng/dL



Source Data: [Report on Pharmacokinetic Assessment, Appendix 12.0 Individual PK Profiles \(Appendix 16.1.9\)](#)

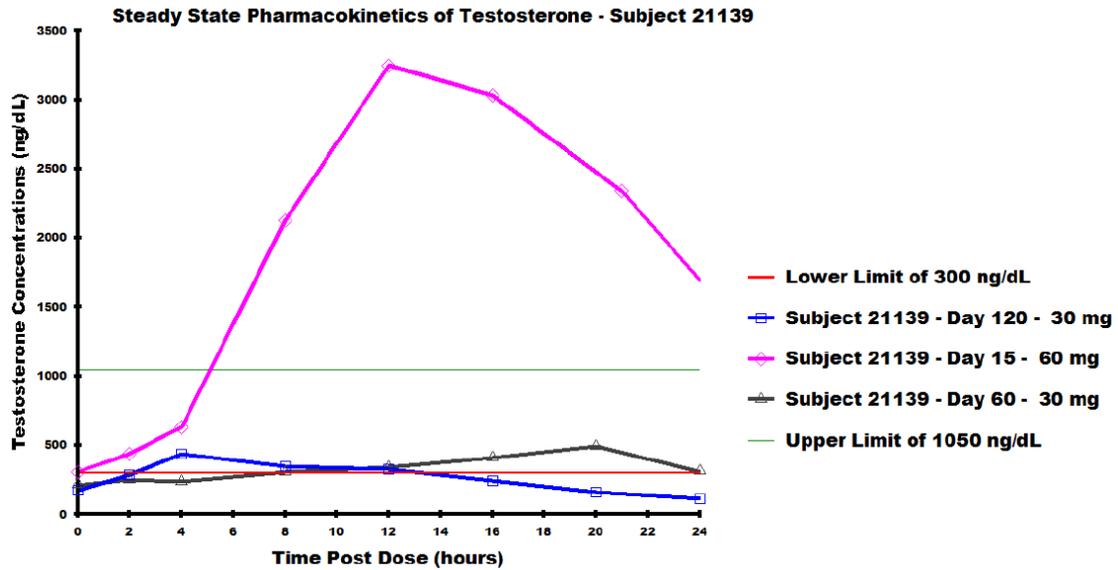
In two of the four subjects, 21134 and 21108, the testosterone elevation was not accompanied by any significant elevation of DHT. This suggests that in these subjects the testosterone elevation was likely secondary to contamination of the blood sample.

The Sponsor's analysis of the other two subjects in whom the elevated testosterone level was accompanied by an elevated DHT level is:

The two cases (20101 and 20504) where the high levels of testosterone were mimicked by a high level of DHT suggest systemic exposure to these levels of testosterone for short periods of time (< 4 hours). However, the transient and incongruous nature of this exposure with respect to the remaining dataset in each case, suggests contamination of the blood draw site with testosterone and subsequent absorption from this contamination. This likely occurred via testosterone on the skin surface coming into contact with the blood sampling port and is anatomically quite feasible given the relative proximity of the dosing site and blood draw site.

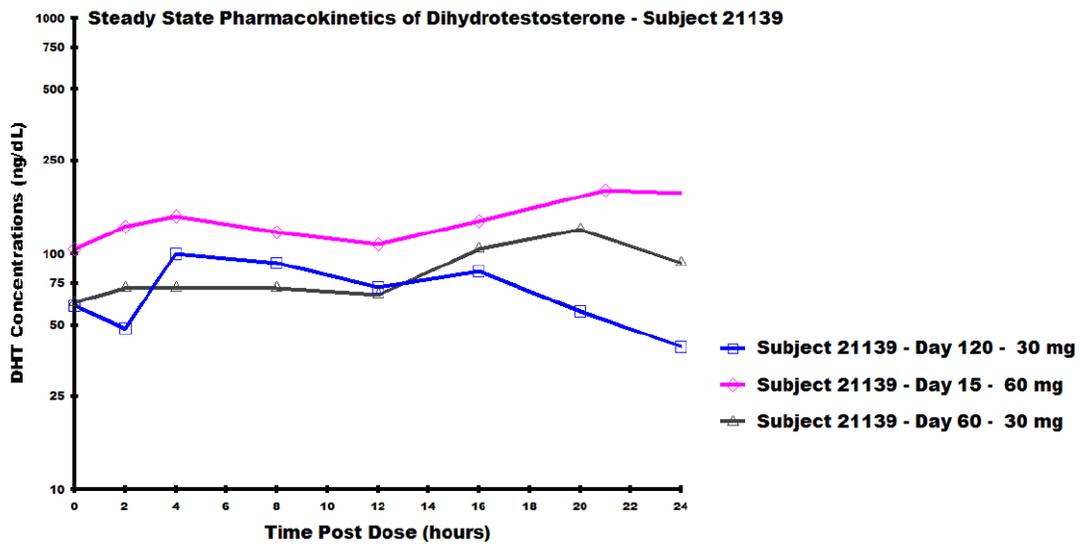
The fifth subject in whom there was a C_{MAX} > 2500 ng/dL is subject 21139. The pK profile for testosterone and DHT is shown in Figure 4 and Figure 5.

Figure 4. Subject 21139 Total Testosterone Concentration



Source: NDA 22504, Module 5.3.5.2.12, page 444

Figure 5. Subject 21139 DHT Concentration



Source: NDA 22504, Module 5.3.5.2.12, page 445

The Sponsor's analysis of this subject is:

The incident of a C_{max} >2500 ng/dL that occurred in Subject 21139 was associated with a pattern of apparently sustained exposure. However, this apparent increase in testosterone was not accompanied by a parallel increase in DHT suggesting that contamination of the sample set for this subject must have occurred after the samples were taken. Indeed, comparison of Figure ...4 and Figure ...5 indicate a decline in DHT at the time the testosterone levels are rising in Subject 21139.

Reviewer's Comment: *The Sponsor's analysis attributes all five instances of C_{MAX} >2500 ng/dL to specimen contamination. In the case of subjects 21134 and 21108 this is a very likely explanation, given the spike in testosterone concentration that is not accompanied by a rise in DHT concentration.*

Subject 20101 *had a spike in testosterone concentration at 2 hours to approximately 6000 that was accompanied by a spike in DHT concentration to approximately 600. At 4 hours, the testosterone concentration had declined to approximately 700 and the DHT to approximately 75. The concentrations remained in this range for the remainder of the 24 hour period. Given the markedly elevated testosterone that rapidly declined to normal, it is reasonable to attribute this elevation, despite the concomitant DHT rise, to likely specimen contamination.*

Subject 20504 *had 2, 4, 8 and 12 hour testosterone levels of approximately 1500, 1300, 3500 and 750. The corresponding DHT levels were approximately 130, 150, 375 and 100. The 8 hour testosterone value, 3500 ng/dL, could reasonably be considered to be out of line with the 2, 4 and 12 hour values of 1500, 1300 and 750. In the opinion of this clinical reviewer, it is reasonable to also consider this value to probably be related to specimen contamination.*

Subject 21139 *had a sustained elevation of testosterone concentration. He had a gradual increase to the peak concentration of 3247 ng/dL at 12 hours followed by a gradual fall in concentration. However at 24 hours the level remained approximately 1750 ng/dL. In this subject, I do not believe that the elevation can reasonably be attributed to ongoing specimen contaminations, despite the lack of concomitant DHT elevation. However, this elevation occurred at the Day 15 evaluation, and after titration to a lower dose of testosterone solution, this subject had acceptable testosterone levels on Days 60 and 120 (Figure 4).*

In summary, for five subjects having a C_{MAX} >2500 ng/dL, I believe that three of five are likely to be secondary to specimen contamination and one is probably related to specimen contamination. The remaining subject has testosterone values that are unlikely to be related to contamination and should be considered as a true elevation above 2500 ng/dL. However, this subject subsequently had acceptable testosterone levels after titration to a lower dose.

Proportion of subjects with Serum Total Testosterone C_{MIN} below 300 ng/dL

The percentage of subjects who had C_{MIN} values below the lower limit of 300 ng/dL were 71.3%, 69.1% and 64.4% on days 15/16, 60/61 and 120/121, respectively. The C_{MIN} often occurred at pre-dose or at the end of the dosing interval. This was reflected in a relatively short duration that subjects had total testosterone levels below this lower limit. On day 15/16, over the 24 hr period the arithmetic mean duration below 300 ng/dL was 6.67 hrs (120 %CV, N = 143), which reduced further to 5.05 hrs (123 % CV, N = 138) on day 60/61 and 4.61 hrs (146% CV, N = 135) by day 120/121 (Source: Module 5.3.5.2, Table 14.2.6). The C_{MIN} observed in the hypogonadal subjects in this study after testosterone administration mimics the lower serum testosterone levels observed during the trough of diurnal variation in healthy adult men.

6.1.6 Other Endpoints

The Sponsor also evaluated Quality of Life Issues. The SF-36 Health Survey mental and physical component scores were evaluated. There was a statistically significant increase in both parameters from Day 1 to Day 60 and from Day 1 to Day 120. The mean physical component score increased from 50.55 on Day 1 to 52.58 on Day 60 ($P=0.0082$) and 52.3 on Day 120 ($p=0.254$), while the mean mental component score increased from 46.79 on Day 1 to 51.28 on Day 60 ($P<0.0001$), and 51.26 on Day 120 ($p<0.001$).

The Psychosexual Social Questionnaire was also administered to subjects. The data is presented in Table 12 for the following parameters of this questionnaire:

- Sexual Desire,
- Sexual Activities (Total Score),
- Satisfaction with Erection,
- Positive Mood Summary Score,
- Negative Mood Summary Score

Table 12. Psychosexual Daily Questionnaire: Changes from Baseline to Day 120 (Mean, SD)

Parameter	Baseline	Day 120				
		30 mg N=1-3	60 mg N= 90- 131	90 mg N= 25- 29	120 mg N=10	All Doses
Dose	All N= 131	30 mg N=1-3	60 mg N= 90- 131	90 mg N= 25- 29	120 mg N=10	All Doses
Sexual Desire	1.9 (1.47)	2.29 (2.10)	1.37 (1.83)	1.95 (2.00)	1.19 (1.36)	1.49 (1.84)
Overall Sexual Activity	0.93 (1.00)	0.93 (1.00)	1.31 (1.28)	0.86 (1.42)	1.19 (1.46)	1.02 (1.62)
Erection Maintained Satisfactorily ¹	3.12 (1.99)	1.33 (NA)	0.99 (2.10)	1.72 (2.04)	0.73 (1.13)	1.11 (2.0)
Positive Mood ²	4.31 (1.19)	0.54 (0.81)	0.51 (1.33)	0.63 (1.23)	0.81 (0.55)	0.56 ³ (1.25)
Negative Mood ²	1.95 (1.24)	-0.41 (1.61)	-0.47 (1.33)	-0.57 (1.49)	-0.59 (0.96)	-0.50 ³ (1.33)

Source: NDA 22504, Module 5.3.5.2, Table 11-6, page 102

1. The variable, 'Erection Maintained for a Satisfactory Duration?' is recorded on an ordinal scale from 0 to 7 where 0 = Not satisfactory and 7 = Very Satisfactory.

2. Individual mood variables are rated on an ordinal scale from 0 to 7 where 0 = Not at all true and 7 = Very true. Positive mood is the sum of the four positive mood variables-alert, full of pep/energetic, friendly, and well/good.

Negative mood is the sum of the five negative mood variables angry, irritable, sad or blue, tired, and nervous.

3. p <0.0001.

Reviewer's comment: *There is a slight tendency towards improvement in sexual desire and overall sexual activity while on treatment, however, it is not clinically meaningful, since there was no placebo control and no correlation of serum testosterone with the survey response.*

6.1.7 Subpopulations

The subpopulations that did or did not use deodorant and those that did or did not wash the application site were evaluated. The results are discussed in the following section.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Sponsor investigated two areas that could potentially influence dosing recommendations: the effect of underarm deodorant use and the effect of washing the application site on product efficacy. They evaluated this in a separate study, MTE10, and also by means of a subgroup analysis of subjects in study MTE08.

Study MTE10 was a phase I trial 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 solution (Axiron). The design of this study is discussed in section 5.3 Discussion of Individual Studies/Clinical Trials.

This trial was a single dose, parallel group trial in healthy female subjects. A total of 36 subjects were enrolled and were randomized into one of the following six treatment groups:

- Group 1: Antiperspirant/deodorant stick applied 2 minutes prior to Testosterone solution.
- Group 2: Antiperspirant/deodorant spray applied 2 minutes prior to Testosterone solution.
- Group 3: Deodorant spray applied 2 minutes prior to Testosterone solution.
- Group 4: Control group: Testosterone solution with no deodorant or washing.
- Group 5: Application site washed 2 hours post Testosterone solution application.
- Group 6: Application site washed 6 hours post Testosterone solution application.

Each treatment group underwent intensive blood sampling for a period of 72 hours for pharmacokinetic analysis.

In study MTE08, the Sponsor evaluated subgroups that did and did not use deodorant or antiperspirant, and subgroups that did or did not wash the site (two or more hours following application of testosterone solution) on the day of pharmacokinetic evaluation.

The Effect of Deodorant/Antiperspirant Use on Efficacy

Table 13 shows the pharmacokinetic results of Study MTE10 for the control group that did not use deodorant, and the three groups that used either deodorant or antiperspirant 2 minutes prior to testosterone solution application.

Table 13. Study MTE10 Pharmacokinetic Results – Deodorant Use

Parameter		Group 1 Stick Antiperspirant N=6	Group 2 Spray Antiperspirant N=6	Group 3 Spray Deodorant N=5	Group 4 Control N=6
Baseline corrected Testosterone	T _{max} (h)	18.2	13.7	19.3	25.5
	C _{max} (ng/dL)	236.3	245.5	227.5	322.5
Testosterone	AUC ₀₋₇₂ (h*ng/dL)	7355.7	6797.9	6638.3	9568.4
Calculated Free Testosterone	T _{max} (h)	16.8	13.7	17.7	25.5
	C _{max} (ng/dL)	5.0	4.3	3.7	6.1
Testosterone	AUC ₀₋₇₂ (h*ng/dL)	166.9	136.1	112.6	184.6
Baseline corrected DHT	T _{max} (h)	24.9	19.6	20.9	21.5
	C _{max} (ng/dL)	55.6	53.3	61.7	73.2
DHT	AUC ₀₋₇₂ (h*ng/dL)	1786.9	1635.0	1880.2	2330.3

Source: NDA 22504, Module 5.3.5.4, Table 6, page 48

Subjects with the pre-application of antiperspirant/deodorant stick or spray or deodorant spray demonstrated numerically lower concentrations of baseline corrected testosterone (C_{max} 236.3, 245.5 and 227.5 compared to 322.5 ng/dL), free testosterone (C_{max} 5.0, 4.3 and 3.7 compared to 6.1 ng/dL), and baseline corrected DHT (C_{max} 55.6, 53.3 and 61.7 compared to 73.2) compared to the control group. The following were the statistical results:

- Group 1 (Stick Antiperspirant) – There were no pharmacokinetic parameters that were significantly different from the control values.
- Group 2 (Spray Antiperspirant) - Significant changes in free testosterone AUC₀₋₇₂, compared to control were observed, but not for C_{max} or T_{max}. Significant changes in DHT AUC₀₋₇₂, compared to control were observed, but not for C_{max} or T_{max}.
- Group 3 (Spray Deodorant) - Significant changes in free testosterone AUC₀₋₇₂ and C_{max} compared to control were observed but not for T_{max}.

Reviewer’s comment: *Despite the lack of consistent, statistically significant differences between treatment and control groups, distinctly lower concentrations of testosterone, and DHT were seen in all treatment groups as compared to control. The small group size may have contributed to the statistical findings.*

Table 14 summarizes the proportion of subjects in the Study MTE08 Completer Set having C_{AVG} total testosterone within the normal range by use of antiperspirant/deodorant.

Table 14. Proportion (percentage) of Subjects with C_{AVG} in the Normal Range

Group	Antiperspirant/ Deodorant Use	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)	39/47 (83.0%) (72.2 – 93.7)	42/47 (89.4%) (80.6 – 98.2)
C	Did not use everyday since last visit	42/48 (87.5%) (78.1 – 96.9)	52/61 (85.2%) (76.4 – 94.2)	53/60 (88.3%) (80.2 – 96.5)
D	Used everyday since last visit	42/61 (68.9%) (57.2 – 80.5)	56/65 (86.2%) (77.8 – 94.6)	59/71 (83.1%) (74.4 – 91.8)

Source: NDA 22504, Module 5.3.5.2 Table 11-4, page 99

The most pertinent comparison to make is between those subjects who did not use a deodorant or an antiperspirant since their last visit (row B) and those who used a deodorant or antiperspirant every day (row D). At day 120 there was no significant difference between the response rate in those subjects who did not use an antiperspirant/deodorant since their last visit (89.4%) and those who used a deodorant or antiperspirant every day (83.1%). The response rates at day 120 was greater than 75% for those who did and those who did not use antiperspirant/deodorant and furthermore the lower bounds of the 95% confidence limits associated with the response rates are above 66.8%.

Reviewer’s comment: *This data indicates that at day 120 there was no evidence that the use of an antiperspirant or deodorant had a significant effect on testosterone concentration. Group that used deodorant everyday and the group that did not use deodorant at all, satisfied the criteria of having >75% within the normal range with the lower bound of the 95% CI > 66.8%.*

Overall, a reasonable conclusion from Studies MTE08 and MTE10 is that the use of antiperspirant or deodorant results in a somewhat lower testosterone exposure, but an exposure that can still be considered an effective one in treating hypogonadism.

The Effect of Application Site Washing on Efficacy

This effect was evaluated directly in Study MTE10 and by means of subgroup analysis in Study MTE08. Table 15 shows the pharmacokinetic results of Study MTE10 for the control group, that did not use deodorant, and the two groups that washed the application site following product application.

Table 15. Study MTE10 Pharmacokinetic Results – Site Washing

Parameter		Group 4 Control N=6	Group 5 Washed 2 Hr post dose N=6	Group 6 Washed 6 Hr post dose N=6
Baseline corrected Testosterone	T _{max} (h)	25.5	14.2	12.8
	C _{max} (ng/dL)	322.5	200.1	257.0
	AUC ₀₋₇₂ (h*ng/dL)	9568.4	5571.3	6409.4
Calculated Free Testosterone	T _{max} (h)	25.5	18.2	112.8
	C _{max} (ng/dL)	6.1	3.5	4.7
	AUC ₀₋₇₂ (h*ng/dL)	184.6	107.8	138.1
Baseline corrected DHT	T _{max} (h)	21.5	19.5	13.4
	C _{max} (ng/dL)	73.2	43.7	47.3
	AUC ₀₋₇₂ (h*ng/dL)	2330.3	1273.8	1219.8

Source: NDA 22504, Module 5.3.5.4, Table 6, page 48

Washing the application site 2 and 6 hours following Testosterone solution application resulted in numerically lower concentrations of testosterone (C_{max} 220.6 and 279.7 compared to 341.9 ng/dL), baseline corrected testosterone (C_{max} 200.1 and 257.0 compared to 322.5 ng/dL), free testosterone (C_{max} 3.5 and 4.7 compared to 6.1 ng/dL), DHT (C_{max} 54.4 and 56.8 compared to 83.5 ng/dL) and baseline corrected DHT (C_{max} 43.7 and 47.3 compared to 73.2) compared to the control group. Statistical significance was reached for:

- Group 5 (wash 2 hours post-dose) - free testosterone AUC₀₋₇₂, and baseline corrected DHT AUC₀₋₇₂.
- Group 6 (wash 6 hours post-dose) - baseline corrected DHT AUC₀₋₇₂.

Reviewer's comment: *Despite the lack of consistent statistically significant difference between treatment and control groups, distinctly lower concentrations of testosterone, and DHT were seen in all treatment groups as compared to the control group. The small group size may be a factor in the statistical findings.*

In Study MTE08, subjects were asked, whether they showered or washed during the 24 hour period following application of Testosterone solution on days 15, 60 and 120, i.e.

did they wash while the 24 hour PK profile was being determined. The data is summarized in Table 16. This shows that showering or washing the application site did not adversely affect the efficacy of the product, i.e. the response rate for those who washed the application site (two hours or more after dosing) during the 24 hour intensive PK sampling was not significantly different from those that did or from the overall response rate.

Table 16. Proportion (percentage) of subjects with C_{avg} in the normal range by incidence of washing (Completer Set Study MTE08)

	Day 15	Day 60	Day 120
Subject washed the application site while in the pK unit	13/19 (68.4%)	23/25 (92.0%)	28/34 (82.4%)
Subject did not wash the application site while in the pK unit	35/48 (72.9%)	53/65 (81.5%)	86/99 (86.9%)

Source: NDA 22504, Module 5.3.5.2, Table 11-5, page 100

Reviewer’s comment: *These data show that washing the application site 2 or more hours after application of the testosterone solution did not significantly affect the efficacy of the product.*

Overall, a reasonable conclusion from Studies MTE08 and MTE10 is that washing the application site 2 or more hours after application, results in a somewhat lower testosterone exposure, but an exposure that can still be considered an effective one in treating hypogonadism.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

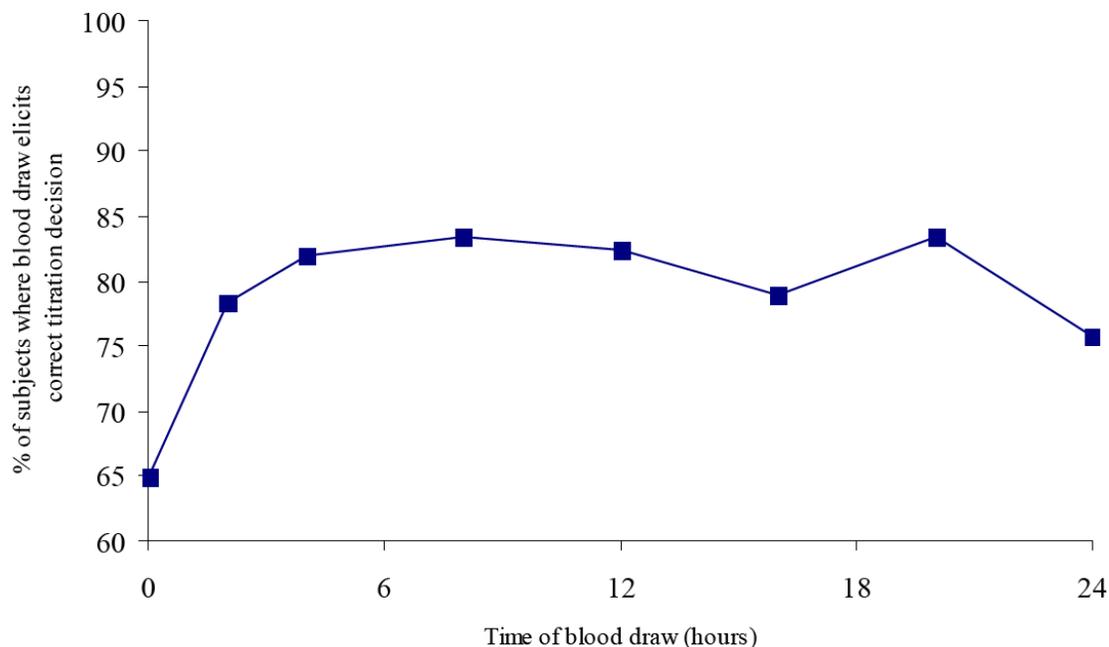
There was no evaluation of tolerance or persistence of efficacy beyond 120 days.

6.1.10 Additional Efficacy Issues/Analyses

During Study MTE08, all dose titration decisions were made based on C_{AVG} of total testosterone values. In clinical practice, dose titration decisions are made based on single values of total testosterone concentration. Therefore, the Sponsor has provided an analysis of the data from Study MTE08 to assess the relationship between single testosterone concentration values done at various times after dose application and the eventual 24 hour C_{AVG} values. They evaluated the likelihood that a single value at time x after application would result in a “correct” titration decision. For purposes of this analysis, a “correct” decision is the one that is the same as the decision that would be made if it were based on the C_{AVG} value.

Figure 6 shows the percentage of titration decisions made on the basis of a single testosterone value that are correct.

Figure 6. Percentage of subjects at each time point where use of that single value would lead to a correct titration decision

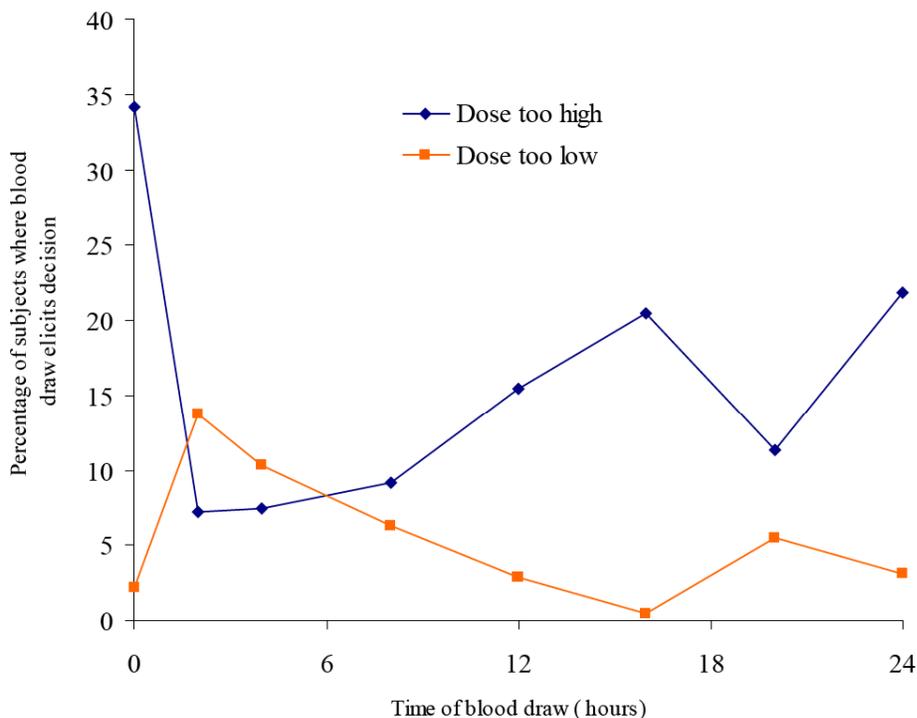


Source Data: Report 434: Justification for the timing of the blood draw used to make dose titration decisions for Axiron™, (Appendix 16.1.9)

Reviewer’s Comment: Decisions made on the basis of a single draw in the range of 4 to 12 hours after application would agree with the decision made on the basis of C_{AVG} approximately 83% of the time.

The Sponsor then evaluated the incorrect decisions that would be made when using a single draw. They determined if the decision would result in a dose that was higher or lower than the “correct” dose. Figure 7 shows the results of this analysis.

Figure 7. Percentage of blood draws that would elicit decisions resulting in doses that were too high or too low



Source Data: Report 434: Justification for the timing of the blood draw used to make dose titration decisions for Axiron™, (Appendix 16.1.9)

Reviewer’s comment: Decisions made on the basis of blood draws done 2 – 4 hours after application minimize the likelihood of titrating to a dose that is “too high” as compared to the titration that would be done based on C_{AVG} . As time after application increases, the likelihood of “too high” decisions increases while the likelihood of “too low” decisions decreases.

Based on this analysis, the Sponsor recommends that titration decisions be made based on blood draws done 2 – 8 hours after product application, with 4 hours being the optimal time.

Reviewer’s comment: The Sponsor’s recommendation for titrating the dose based on a single testosterone value drawn 2 – 8 hours after application of the product appears to be reasonable as it approximates a decision made based on C_{AVG} values while minimizing the likelihood of titration to a dose higher than one that was based on C_{AVG} values. A single value drawn at 4 hours after application appears to be the optimum single draw on which to base a titration decision.

7 Review of Safety

Safety Summary

The Sponsor has conducted one phase 3 clinical trial evaluating Axiron, an extension of this trial to provide for six months of exposure, and two phase 1 trials of Axiron. Review of adverse events, vital signs, hematology and chemistry data indicate that this medication is safe for use as a treatment for testosterone deficiency in appropriately selected men greater than 18 years of age.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies MTE07, MTE08, MTE09, MTE11 and MTE12 are the major source of safety information. These studies were done using the to-be-marketed 2% Testosterone solution. Studies DDS08, DDS15, DDS16, MTE04, MTE05, MTE06, and MTE10 evaluated testosterone formulations different from the to-be-marketed formulation but still contributed to the safety database.

7.1.2 Categorization of Adverse Events

The Sponsor has categorized adverse events using MEDRA version 11.1.

7.1.3 Pooling of Data across Clinical Trials to Estimate and Compare Incidence

Safety data from studies MTE08 and MTE09 were pooled. Studies MTE07 and MTE11 were evaluated individually.

7.2 Adequacy of Safety Assessments

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

Exposure

Table 17 shows the number of patients with exposure to the medication in Studies MTE08 and MTE09.

Table 17. Exposure to Testosterone Solution – Studies MTE08 and MTE09

Dose	Number of Patients With Exposure to Solution for			
	≥30 Days	≥90 Days	≥120 Days	≥180 Days
Any Dose	149	147	134	51
30 mg/Day	3	2	0	0
60 mg/Day	137	107	97	40
90 mg/Day	34	8	5	0
120 mg/Day	9	3	0	0

Source: MO Analysis of Module 5.3.5.2.25.3.1, Analysis Dataset ADSL

Reviewer’s Comment: *Exposure to testosterone solution appears to be adequate. The sponsor has achieved the goal that was specified at the End-of-Phase 2 meeting. The sponsor was asked to have at least 50 subjects exposed to the solution for 180 days, which they did.*

In Study MTE07, 21 male subjects received a daily dose of testosterone solution for seven days. In Study MTE11, 10 male subjects received a single dose of testosterone solution.

Demographics

Table 18 shows the demographics of the safety population for Studies MTE08/MTE09 by maintenance dose of testosterone solution.

Table 19 shows the demographics of the population for Studies MTE7, MTE11 and MTE12.

Table 18. Demographics - Study MTE08 and MTE09

	Maintenance Dose of Testosterone Solution				
	All Doses N=155	30 mg N=3	60 mg N=117	90 mg N=25	120 mg N=10
Age					
Mean	51.5	57.3	51.3	52.9	48.7
Range	19 – 78	51 – 65	19 – 78	25 – 75	30 – 62
Race					
Asian	1 (0.7%)	0	1 (0.9%)	0	0
Caucasian	122 (84.7%)	2 (66.7%)	94 (86.2%)	19 (86.4%)	7 (70%)
African American	6 (4.2%)	0	2 (1.8%)	3 (13.6%)	1 (10.0%)
Hispanic	13 (9.0%)	1 (33.3%)	10 (9.2%)	0	2 (20.0%)
Other	2 (1.4%)	0	2 (1.8%)	0	0
Weight (kg)					
Mean	94.4	83.4	94.5	94.6	95.1
Range	59.1 – 126.1	79.4 – 90.3	59.1 – 126.1	75.5 – 119.7	75.9 – 123.6
BMI (kg/m ²)					
Mean	29.5	28.1	29.6	29.7	29.1
Range	18.2 – 38.9	24.8 – 34.4	18.2 – 38.9	24.6 – 35.0	23.9 – 34.8

Source: Module 5.3.5.2.3, Table 14.1.2.1

Reviewer's Comment: *The subjects requiring only a 30 mg/day dose of testosterone are lighter in weight, and with a lower BMI than other subjects. Overall, the demographics of the study population appear to be representative of the target population for this medication.*

Table 19 shows the demographics of the subjects in Studies MTE07 and MTE11.

Table 19. Demographics - Study MTE07 and MTE11

	Study		
	MTE07	MTE11	MTE12
Age (years)			
Mean	47.3	23.3	
Range	20, 71	-	
Race			
Caucasian	17/21	10/10	
African American	4/21	0	
Weight (kg)			
Mean	96.6	85.5	
Range	77, 132	-	
BMI (kg/m ²)			
Mean	30.1	25.1	
Range	22, 35	-	

Source: NDA 22504, MTE07 and MTE11 Study Reports.

Table 20 shows the baseline testosterone levels for the subjects in Study MTE08.

Table 20. Baseline Testosterone Levels – Study MTE08

	Maintenance Dose of Testosterone Solution				
	All Doses N=155	30 mg N=3	60 mg N=117	90 mg N=25	120 mg N=10
Baseline Testosterone (ng/dL)					
Mean	196.7	138.8	204.0	169.9	197.6
Median	213.2	102.1	223.5	168.2	217.8

Source: Module 5.3.5.2.3, Table 14.1.2.1

Reviewer’s Comment: *These baseline values are the average of the first series of two screening testosterone determinations. Several subjects had averages greater than 300 on this first screening. They underwent additional screening and were only enrolled if the subsequent values averaged less than 300 ng/dL.*

7.2.2 Explorations for Dose Response

The Sponsor’s phase three study included dose titration based on C_{avg} values 15 days and 60 days after start of treatment. Therefore, the dose response in individual patients was adequately evaluated.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was requested for this product.

7.2.4 Routine Clinical Testing

The numbers of patients exposed to the product, and the safety monitoring employed in the studies appears to be adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific metabolic, clearance or interaction evaluations were requested for this product.

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

Transdermal testosterone products are known to present a risk for interpersonal transfer of testosterone. The Sponsor therefore has performed studies evaluating person to person transfer (MTE06 using a 1% solution and MTE12 using a 2% solution) and a study evaluating the ability to wash the product from the skin (MTE11). These studies are discussed in section 7.6.

7.3 Major Safety Results

7.3.1 Deaths

There were no subject deaths during the clinical studies evaluating this product.

7.3.2 Nonfatal Serious Adverse Events

Table 21 shows the serious adverse events reported during studies MTE08 and MTE09. There were no serious adverse events reported in studies MTE06, MTE07, MTE11 or MTE12.

Table 21. Serious Adverse Events

Study	Subject Number	Testosterone Dose	Event (Medra PT)
MTE08	20203	120 mg	Appendicitis
MTE08	20530	90 mg	Scalp Melanoma
MTE09	20711	60 mg	Hepatitis C
MTE09	21016	60 mg	Prostate Cancer

Source: NDA 22504, Module 5.3.5.2.3, Table 12-9

Each subject's case narrative is discussed individually.

Subject 20203 A 54 year old man who was diagnosed with hypogonadism in 1999, had received Androgel treatment for hypoandrogenism prior to entry into MTE08. The subject's screening total testosterone level was 120.25 ng/dL and his baseline ECG, safety blood examination and urinalysis were unremarkable.

His Medical History included;

- Hypercholesterolemia onset 1999
- Hypertension onset 1999
- Erectile Dysfunction, onset 2007
- Acid reflux secondary to concomitant medication treatment for Erectile Dysfunction, onset 2008

His concomitant medications were Pravachol, Cialis, Pepcid and Altace.

His first dose of testosterone solution was applied on July 26, 2008. His last dose prior to the event was applied November 1, 2008.

The serious adverse event, Appendicitis, was diagnosed on November 2, 2008. It was graded as severe in intensity and was not believed to be related to the investigational product by the Investigator. He underwent an appendectomy and the event resolved without sequela. He resumed testosterone solution on November 4, 2008. He completed study MTE08 and his C_{AVG} on Day 120 was 515 ng/dL.

Reviewer's comment: *This event is unrelated to the study medication.*

Subject 20530 A 60 year old man who was diagnosed with hypogonadism in 2002 and had received Depo Testosterone, Androderm and Androgel treatment for hypogonadism prior to entry into MTE08. At screening his total testosterone was 287.0 ng/dL and his ECG, blood work and urinalysis were unremarkable.

His Medical History included;

- Erectile Dysfunction, onset 2002
- Chronic Sinusitis onset 1983
- Arthritis onset 1980
- Hyperlipidemia onset 2006
- Occasional headaches onset 1955
- GERD onset 2003

His concomitant medications were lisinopril, omeprazole, Zyrtec, Protonix, and Advil.

His first dose of testosterone solution was applied on December 5, 2008. He was titrated to the 90mg dose at the Day 45 study visit. At the Day 90 visit, on March 5, 2009, he informed the investigator that [REDACTED] (b) (6) a suspicious mole on his scalp had been removed by a doctor and he had been informed [REDACTED] (b) (6) that the mole was malignant (melanoma). He was scheduled to have the margins removed and a split thickness skin graft placed [REDACTED] (b) (6).

The Sponsor requested that the subject discontinue his treatment and an early withdrawal visit was performed on the March 11, 2009. At the time of study withdrawal, the subject's ECG and his safety blood and urinalysis profiles were unremarkable.

On a follow up visit on March 26, 2009, the subject's skin graft was healing and all of the removed margins were reported as being positive for malignant melanoma in situ.

The investigator believed that the adverse event was not related to the investigational product.

Reviewer's comment: *In the opinion of this clinical reviewer, the scalp melanoma is not likely to be related to the investigational product.*

Subject 20711 A 65 year old man who was diagnosed with hypogonadism in 2006 but had received no treatment for hypogonadism prior to entry into the MTE08 study. At screening, he had a total testosterone level of 264 ng/dL. His safety blood work and urinalysis were unremarkable. His baseline ECG showed an anterior fascicular block that was deemed abnormal but not clinically significant by the Investigator.

His Medical History included;

- Muscle Pain onset 1992
- Benign Prostatic Hypertrophy from 2006 with an end date of 2006
- Bone Fracture in 2006

His only concomitant medication was Motrin.

His first dose of testosterone solution was applied on October 3, 2008. He was maintained on the 60mg daily dose of the testosterone solution and he completed Study MTE08 on January 30, 2009. He rolled over into the MTE09 study on January 31, 2009. His last dose prior to the event was applied on March 31, 2009.

At the subject's MTE08 screening visit performed on September 25, 2008, his liver function test results were: ALT 32U/L (6-43 U/L), AST 36 U/L (11-36 U/L), GGT 13 U/L (10-50 U/L), and LDH 258U/L (53-234 U/L). These results were within range or not-clinically significant.

At the subject's Day 120 MTE09 'rollover' visit (February 1, 2009), his liver function test results were: ALT 64U/L (6-43 U/L), AST 50U/L (11-36 U/L), GGT 12U/L (10-50 U/L), and LDH 248U/L (53-234 U/L). All results were within range or deemed not-clinically significant by the Investigator.

The subject completed the MTE09 study on March 31, 2009.

At the subject's MTE09 follow up visit on April 7, 2009, his liver function test results were: ALT 557 U/L (6-43 U/L), AST 323 U/L (11-36 U/L), GGT 86 U/L (10-50 U/L), and LDH 293 U/L (53-234U/L). On April 10, 2009 a hepatitis set of blood tests were drawn. These were negative and/or non-reactive for Hepatitis A IGM, Hepatitis B surface antigen, and Hepatitis B core Ab, however his Hepatitis C Virus Ab was positive at 22.8IU/mL (normal range <1.00IU/mL).

The diagnosis of Hepatitis C was made on the basis of these results and he was contacted by office staff to attend the clinic for an evaluation. He stated that he felt fine and refused a visit. Staff attempted several times to contact the patient.

On June 10, 2009 the subject contacted the clinic and was urged by staff to go for a consultation regarding the Hepatitis C diagnosis. The patient stated to the nurse that his job is more important than his life and "if he dies he dies."

There was no action taken with respect to the trial drug, as the patient had completed the MTE08 and MTE09 trials prior to the serious adverse event. In the opinion of the Investigator, the positive Hepatitis C Virus Ab was mild in intensity and not related to trial drug.

Reviewer's comment: *This clinical reviewer concurs with the investigators conclusion that Hepatitis C in this subject does not appear to be related to his transdermal product (Axiron).*

Subject 21016 A 55 year old man who was diagnosed with hypogonadism in 2007 and had received Testim treatment for hypogonadism prior to entry into MTE08. At screening, the subject's testosterone level was 207 ng/dL. The subject had an ECG that showed sinus bradycardia that was deemed abnormal but not clinically significant by the Investigator. The subject also had an elevated fasting glucose and bacteria in the urine at screening.

His medical history included:

- Asthma onset 1963
- Bee allergy onset 1963
- Dust and mold allergy onset 1956

He was taking no concomitant medications.

His first dose of testosterone solution was applied on October 28, 2008. He was maintained on the initial 60mg dose for the entire 120 days of treatment and completed the MTE08 study on February 24, 2009. He was then enrolled in Study MTE09. His last dose of the investigational product prior to the event was on February 26, 2009.

His MTE08 screening visit was on October 7, 2008 and a Prostate Specific Antigen (PSA) was 1.27ng/mL (normal range <4ng/mL). As part of the MTE09 'rollover' on February 24, 2009, a PSA sample was collected and was reported as 7.28ng/mL. A repeat sample was collected, and the result was 6.36ng/mL.

On February 28, 2009 the subject was instructed by the Investigator to cease investigational product application and was advised to make an appointment with a urologist. (b) (6) the subject saw the urologist. A repeat PSA at that time was 3.2 ng/mL. A prostate biopsy was performed and revealed adenocarcinoma Gleason score 6. He was scheduled for surgery. The results of the surgery are not available.

In the opinion of the Investigator, the prostate cancer was moderate in intensity and not related to investigational product.

Reviewer's comment: *The prostate cancer is not likely to be related to the testosterone solution. Its use may have been a factor in the PSA rise which led to the diagnosis.*

7.3.3 Dropouts and/or Discontinuations

Table 8 shows the disposition of the patients who were enrolled in Study MTE08. Of the 20 subjects who discontinued the study, three did so because of adverse events. The remainder discontinued because of withdrawal of consent, lack of compliance, or being lost to follow-up. Those subjects that discontinued because of adverse events are discussed below. There were no dropouts or discontinuations from studies MTE07 or MTE11.

Subject 20530 A 60 year old man who withdrew because of the diagnosis of a scalp melanoma. A full discussion of this subject is provided in 7.3.2.

Subject 10101 A 59 year old man who was diagnosed with hypogonadism in 2003. Prior to entry into Study MTE08 he had received the following treatments for hypogonadism; androderm patches, androderm cream and testosterone implants.

His medical history included:

- Atrophic calcified left Kidney, onset 1950

- Right Testicular Cancer, 1995
- Left Testicular Cancer, 1995
- Asthma, onset 1998
- GERD, onset 2002
- Varicose Veins, onset 1988
- Erectile Dysfunction, onset 1994
- Esophagitis, onset 2002

His concomitant medications were: Ventolin puffer for asthma, Viagra for erectile dysfunction, aspirin for superficial thrombophlebitis was started on January 9, 2009 and stopped on January 29, 2009.

He had the Day 1 study visit on January 8, 2009 and was started on the 60mg dose of Investigational product. He saw a vascular surgeon (b) (6) for evaluation of varicose veins. The patient was diagnosed with superficial thrombophlebitis (blood clot). The Vascular Surgeon started the subject on Aspirin 200mg BD and scheduled surgery for repair of the varicose veins. The surgery would require post-operative medications classified as opiates which were prohibited in this study. He was therefore withdrawn from the study. The last dose of study medication was administered January 20, 2009.

Reviewer's comment: *It is clear that the subject withdrawal actually occurred because of a pre-existing condition. There is no clinical evidence that suggests that the thrombophlebitis was related to the investigational product.*

Subject 20907 A 28 year old man who was diagnosed with hypogonadism in 2001. He had received Testim and Delatestryl treatment for hypogonadism prior to entry into Study MTE08. At screening, he had a testosterone level of 209 ng/dL. His baseline ECG, blood panel and urinalysis were unremarkable.

His Medical History included;

- Seizures, from 1982 to 1994
- Epilepsy, onset 1982
- Concussion, in 1994
- Hernia surgery, right inguinal in 2008
- Vitamin D deficiency, onset 2001

His concomitant medications were depakote for seizures and antacid for heartburn.

The subject started Day 1 of the MTE08 study on October 2, 2008.

The subject did not return for his Day 15 visit on October 17, 2008. When he was contacted by the investigator, he informed him that he had been to the Emergency Room (b) (6)

He reported that within the week prior to going to the hospital he had been under a lot of stress and had broken up with his girlfriend. The reason for the Emergency visit was that he was very angry and very emotional. The subject's mother had called an emergency line as she was afraid of his behavior. He was not treated at the hospital but he was observed for several hours. He stated to the hospital personnel that he thought that the way he was feeling was due to the investigational product. The hospital staff told him to stop the treatment. The subject reported that after two days off the investigational product he "felt better". He reported neither past psychological problems nor having seen a psychologist previously.

Reviewer's comment: *The association between the investigational product and the emotional episode appears to be a weak one, but can not be ruled out.*

Following completion of Study MTE08, 71 subjects were enrolled in the safety extension Study MTE09. Twenty of these subjects withdrew from MTE09. Table 22 shows the reasons for withdrawal.

Table 22. Reason for Withdrawal from Study MTE09

Reason for Withdrawal	Number of Subjects
Day 120 C _{avg} outside normal range	9
Elevated Hgb or Hct	4
Elevated PSA	1
Elevated HbA1c	1
Skin reaction	2
Lost to follow up	1
Withdrew consent	2

Source: NDA 22504, Module 5.3.5.2.3, Table 10-2

Fifteen of the twenty withdrawals occurred because the subjects had bloodwork that had been drawn at the Day 120 visit for Study MTE08 and showed the subject to have a value that excluded them from continuing in Study MTE09. Only two subjects discontinued because of an adverse event; both skin related. These are discussed below.

Subject 20205 A 54 year old man who was diagnosed with hypogonadism in 2005. He had received Testim treatment for Hypogonadism prior to entry into MTE08. The subject's screening testosterone level was 54 ng/dL and his ECG showed sinus bradycardia that was deemed not clinically significant by the Investigator. The subject's baseline safety blood profile and urinalysis was unremarkable.

His Medical History included:

- Azoospermia, onset 2005

- Seasonal Allergies, onset 2007
- Sciatica, onset 2007
- Left buttock/leg pain, onset 2005

His concomitant medications were: aspirin (81mg, orally QD for cardiac health), Aleve (PRN for Sciatica, Left buttock/leg pain), a daily Multivitamin, Claritin for rhinitis, and Benedryl for rhinitis.

He began the study medication on August 23, 2008. He was titrated to the 90mg dose at the Day 45 study visit. He completed the MTE08 study on December 20, 2008 and rolled over into Study MTE09 on December 21, 2008 receiving the 90mg dose. His last dose prior to the adverse events leading to study withdrawal was on February 8, 2009 (Day 170).

He reported generalized dry skin on the torso area which started on January 15, 2009. He also reported a burning sensation in both axillae which began on February 7, 2009. These AEs were mild in intensity and only the burning sensation in the axillae was classified as possibly being related to study medication by the Investigator. The investigational product was permanently discontinued, and the subject's last dose was on February 8, 2009. The burning sensation resolved on February 9, 2009. His Draize score was recorded as zero at every study visit for both the MTE08 and the MTE09 studies.

Reviewer's comment: *The axillary burning is likely related to the investigational product. However, the very short duration of discomfort, 2 days that occurred after 170 days of treatment, raises the possibility that it may have been a transient effect and could have resolved without the product discontinuation.*

Subject 20203 A 54 year old man who was diagnosed with hypogonadism in 1999 and had received Androgel treatment for hypoandrogenism prior to entry into MTE08. The subject's screening total testosterone level was 120.25ng/dL and his baseline ECG, safety blood examination and urinalysis were unremarkable.

His Medical History included;

- Hypercholesterolemia onset 1999
- Hypertension onset 1999
- Erectile Dysfunction, onset 2007
- Acid reflux secondary to concomitant medication treatment for Erectile Dysfunction, onset 2008

His concomitant medications were Pravachol, Cialis, Pepcid and Altace.

His first dose of testosterone solution was applied on July 26, 2008. He experienced a serious adverse event, appendicitis, (b) (6). This is discussed in section 7.3.2 Nonfatal Serious Adverse Events above.

He completed study MTE08, using 120 mg/day of testosterone, on November 22, 2008. His C_{AVG} on Day 120 was 515 ng/dL. He was enrolled in Study MTE09 on November 22, 2008.

The Subject experienced very slight erythema at the application site (bilateral axilla) from December 12, 2008 to December 23, 2008 which was graded as mild in intensity and possibly related to the investigational product. The Draize score was 1. The Subject also experienced both dry and red skin of the torso from December 12, 2008 to December 23, 2008. Both events were mild and were classed as not being related to the investigational product. The last date of investigational product application by the subject occurred on December 16, 2008. The investigational product was permanently discontinued and the Subject was withdrawn from the MTE09 study on December 17, 2008 due to the non-specific skin rash.

Reviewer's comment: *The mild axillary erythema may have been related to the investigational product. However, the rash involving the torso, which appears to have been the reason for his withdrawal from the study, is unlikely to be related to this product.*

7.3.4 Significant Adverse Events

No drug-related significant adverse events were seen during the development of this product.

7.3.5 Submission Specific Primary Safety Concerns

The issue of transfer of testosterone from a patient using a transdermal product to another individual via person-to-person transfer has been shown to be a significant safety issue with transdermal testosterone gel products. This was discussed at a Pediatric Advisory Committee meeting held on June 23, 2009. Transdermal testosterone gel product labels were revised in 2009 to incorporate a boxed warning concerning this potential transfer.

To evaluate the potential for interpersonal transfer the Sponsor conducted two trials. Study MTE06 was a study evaluating person to person transfer and Study MTE11 evaluated the ability to wash Axiron from the skin using soap and water. The design of both studies is discussed in section 5.3 Discussion of Individual Studies/Clinical Trials.

Person-to-Person Transfer – Studies MTE06 and MTE12

These studies evaluated the transfer of testosterone from male subjects, to whom the product was applied, to female subjects who had contact with the application area. The measure of transfer was the testosterone pharmacokinetics in the female subject. In study MTE06, four cohorts of subjects were evaluated, each cohort being composed of six male/female pairs. One cohort underwent 15 minutes of contact between the

female's forearm and the male's axilla 2 hours after the product had been applied to the male. A second cohort had the contact at the same time, but with the male wearing a shirt. The third and fourth cohorts had the contact, without a shirt, at six hours and 12 hours after application of the product. Study MTE06 evaluated this transfer using a 1% testosterone solution.

Table 23 shows study MTE06 pharmacokinetic results for total testosterone and
 Table 24 shows study MTE06 results for total testosterone that has been corrected for the female's baseline testosterone concentration.

Table 23. Pharmacokinetics for Total Testosterone in Female Subjects Following contact with the Application Site of a Male Subject. MTE06

Parameter	Mean ± SD			
	Contact at 2 hr without shirt N=6	Contact at 2 hr with shirt N=6	Contact at 6 hr without shirt N=6	Contact at 12 hr without shirt N=6
AUC ₀₋₇₂ (ng/dL*hr)	5050 ± 2793	2135 ± 911	4790 ± 3416	5827 ± 1761
C _{MAX} (ng/dL)	225 ± 185	47 ± 26	165 ± 116	496 ± 383
C _{MIN} (ng/dL)	20 ± 5.7	23 ± 12.1	30 ± 22.0	31 ± 7.9
T _{MAX} (hr)	12	12	10	4.5

Source: NDA 22504, Module 5.3.5.4.3, Table 11.4.1.3.1.1

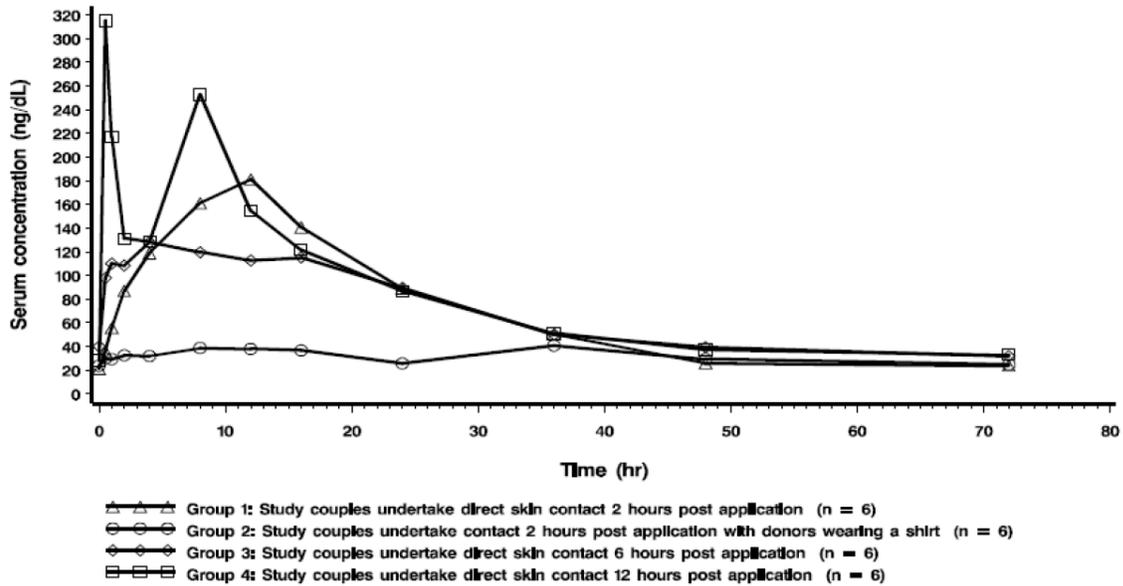
Table 24. Pharmacokinetics for Baseline-corrected Total Testosterone in Female Subjects Following contact with the Application Site of a Male Subject. MTE06

Parameter	Mean ± SD			
	Contact at 2 hr without shirt N=6	Contact at 2 hr with shirt N=6	Contact at 6 hr without shirt N=6	Contact at 12 hr without shirt N=6
AUC ₀₋₇₂ (ng/dL*hr)	3830 ± 2957	565 ± 377	2849 ± 1855	4436 ± 1587
C _{MAX} (ng/dL)	204 ± 185	21 ± 15.8	123 ± 92	467 ± 381
C _{MIN} (ng/dL)	1.1 ± 1.7	0 ± 0	2.7 ± 4.5	3.7 ± 5.1
T _{MAX} (hr)	12	12	10	4.5

Source: NDA 22504, Module 5.3.5.4.3, Table 11.4.1.3.1.2

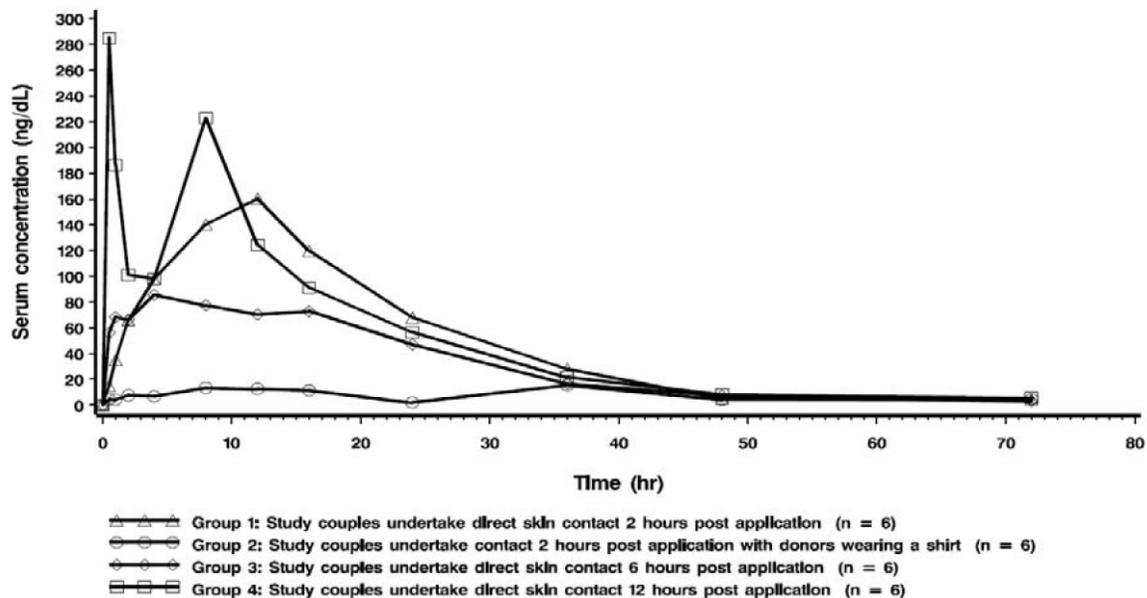
Figure 8 and Figure 9 show the results graphically.

Figure 8. Mean Serum Testosterone Concentration in Female Subjects Following contact with the Application Site of a Male Subject



Source: NDA 22504, Module 5.3.5.4.3, Figure 11.4.1.2.1.1

Figure 9. Mean Serum Total Testosterone (Baseline-corrected) Concentration in Female Subjects Following contact with the Application Site of a Male Subject



Source: NDA 22504, Module 5.3.5.4.3, Figure 11.4.1.2.1.2

The pharmacokinetic results for free testosterone and dihydrotestosterone were similar. Because Study MTE06 was carried out using a 1% testosterone solution, the Sponsor was asked to evaluate the ability of a clothing barrier to block the transfer of the to-be-marketed 2% testosterone solution. This was evaluated in Study MTE12.

In Study MTE12, ten male/female pairs were evaluated. The female partners had baseline testosterone pharmacokinetics evaluated with blood draws for 24 hours prior to contact. The male subject had a single 120 mg dose of 2% testosterone solution applied (60 mg to each axilla) on the day of contact. Two hours after the application, while wearing a long-sleeved cotton shirt, the partners had 15 minutes of contact between the female's forearm and the male's axilla. The female partner had blood draws for testosterone pharmacokinetics for 72 hours after the contact.

One female partner was dropped from the study for a major protocol violation – she was enrolled in another clinical study simultaneously. The results are based on an analysis of nine female subjects.

Table 25 shows the results of MTE12 and the results are shown graphically in Figure 10.

Table 25. Summary of Arithmetic Mean (SD) Pharmacokinetic Parameter Estimates for Total Testosterone Before (Baseline) and Following Transfer Procedure in Study MTE12

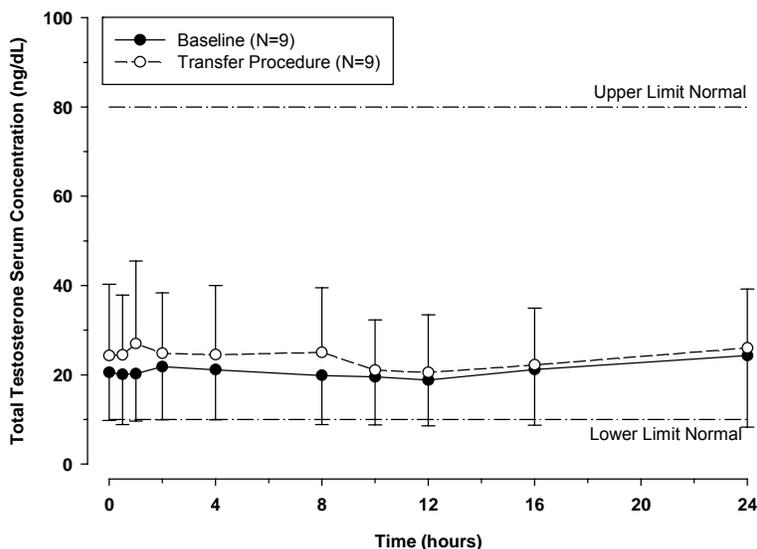
Parameter	Baseline (A) (N=9)	After transfer procedure (B) (N=9)	Ratio of arithmetic means	Ratio of geometric LS means (B:A) ^a	90% CI for the ratio (B:A) ^a
AUC _{0-24hr} (ng.h/dL)	501±281 480±273 ^b	558±307 531±302 ^b	1.11	1.13	1.06, 1.20
C _{avg} (ng/dL)	20.9±11.7 20.0±11.4 ^b	23.3±12.8 22.1±12.6 ^b	1.11	1.13	1.06, 1.20

^a A mixed effects model with $\log(\text{PK}) = \text{TREATMENT (fixed effect)} + \text{SUBJECT (random effect)} + \text{RANDOM ERROR}$ was fitted to the log transformed pharmacokinetic parameters of testosterone. Geometric least squares (LS) mean ratios (and 90% confidence intervals (CI)) for comparisons between baseline and post transfer procedure were determined for the per-protocol set (N=9).

^b All subjects (N=10)

Source: NDA 22504, Report of Study MTE12, Table 11.

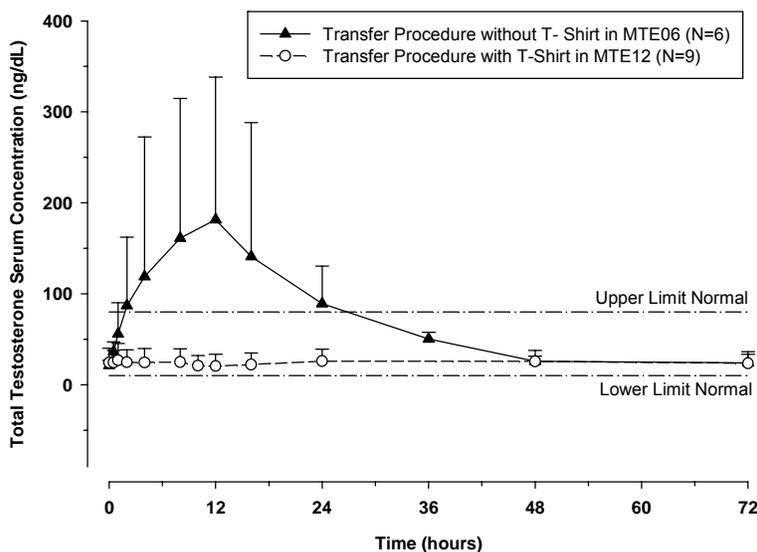
Figure 10. Arithmetic mean (SD) total testosterone serum concentrations in females before and following the MTE12 transfer procedure



Source: NDA 22504, Report of Study MTE12, Figure 9.

Figure 11 shows the transfer information without a shirt, from Study MTE06, with the information with a shirt, from Study MTE12.

Figure 11. Mean (SD) total testosterone serum concentration-time profiles in females following transfer procedure with t-shirt covering the application area in MTE12 and without a t-shirt (MTE06).



Source: NDA 22504, Report of Study MTE12, Figure 13.

Reviewer's comment: *These results show that there is a significant potential for testosterone to transfer from the application site of an individual to another individual via direct skin-to-skin contact. However, a clothing barrier significantly reduces this transfer. Following skin to clothed application site contact, the mean testosterone values of the female subjects 24 hours following contact as compared to the 24 hours prior to contact are well within the normal limit of testosterone level for a female.*

Although, there is a slight increase over the baseline, the serum testosterone concentrations remained well within normal limits^{1,2} following this clothed contact whereas they rose above the upper limit of normal following direct skin-to-skin contact. Therefore, it is reasonable to conclude that a clothing barrier does not completely eliminate testosterone transfer, but does provide adequate protection from clinically meaningful transfer.

Washing Testosterone from the Skin – Study MTE11

This study evaluated the ability to wash testosterone from the skin. This ability is a significant one in properly advising patients concerning the safe use of the product.

The study enrolled ten subjects who applied a 60 mg dose of testosterone solution to each axilla. One axilla was wiped with ten alcohol towlettes. The subject then showered and washed the opposite axilla with a standard washing procedure. The second axilla was then wiped with ten alcohol towlettes. The total amount of testosterone recovered after the second wiping procedure, when compared to the amount recovered from the first wiping procedure, provides a measure of the extent of removal of testosterone by washing.

Table 26 shows the testosterone recovery before and after washing for each subject.

Table 26. Testosterone Recovery, by Ten Alcohol Towlettes, from an Unwashed and a Washed Axilla

Subject	Unwashed Recovery (mg)	Washed Recovery (mg)	Effectiveness of Washing In Removing Testosterone (% removed)
1	42.8	2.1	95.1
2	43.8	4.2	90.4
3	37.0	4.2	88.7
4	45.4	2.3	95.0
5	36.8	0.9	97.5

1 Luthold WW, Borges MF et al. Serum Testosterone Fractions in Women: Normal and Abnormal Clinical States. *Metabolism* 1993 42(5):638-643.

2 Stanczyk FZ. Diagnosis of hyperandrogenism: Biochemical criteria. *Best Practice and Research Clinical Endocrinology and Metabolism* 2006 20(2):177-191.

Subject	Unwashed Recovery (mg)	Washed Recovery (mg)	Effectiveness of Washing In Removing Testosterone (% removed)
6	47.0	2.9	93.8
7	40.8	1.2	97.1
8	41.8	10.4	75.2
9	37.7	1.0	97.3
10	48.4	2.3	95.3
Mean ± SD	42.1 ± 4.1	3.1 ± 2.8	92.5 ± 6.7

Source: NDA 22504, Module 5.3.5.4.3, Table 4, Table 6, MO Analysis

Reviewer's comment: Recovery of testosterone using ten alcohol wipes must be considered an overestimation of the amount of testosterone that would be available for interpersonal transfer. Since only 3.1 mg of the applied 60 mg was recoverable using this methodology, I believe that the Sponsor has adequately demonstrated that washing the application site effectively reduces the potential for interpersonal transfer of testosterone.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The data from the phase 3 primary efficacy trial, MTE08, is presented in Table 27. The data from the safety extension study, MTE09, is presented in Table 28. The most common adverse events were application site erythema/irritation/edema, increased hematocrit, headache, diarrhea, vomiting, increased PSA and nasopharyngitis.

Table 27. Common Treatment-emergent Adverse Events (>2%) occurring in Study MTE08

Medra SOC Preferred Term	Dose of Testosterone Solution				
	30mg N (%)	60mg N (%)	90mg N (%)	120mg N (%)	Overall N (%)
Subjects with at least one TEAE	3 (75%)	71 (45.8%)	13 (37.1%)	5 (50.0%)	81 (52.3%)
Total number of TEAEs	4	177	31	8	220
General Disorders and Administrative Site Conditions					
Application site erythema	0	8 (5.2%)	0	0	8 (5.2%)
Application site irritation	0	10 (6.5%)	1 (2.9%)	1 (10%)	12 (7.7%)
Infections and Infestations					
Nasopharyngitis	0	5 (3.2%)	1 (2.9%)	0	6 (3.9%)
Investigations					
Hematocrit increased	0	5 (3.2%)	1 (2.9%)	0	6 (3.9%)
Nervous System Disorders					
Headache	0	8 (5.2%)	0	0	8 (5.2%)
Gastrointestinal Disorders					
Diarrhea	0	2 (1.3%)	2 (5.7%)	0	4 (2.6%)
Vomiting	0	3 (1.9%)	1 (2.9%)	0	4 (2.6%)

Source: NDA 22504, Module 5.3.5.2.3, Table 12-3.

Table 28. Common Treatment-emergent Adverse Events (>2%) occurring in Study MTE09

Medra SOC Preferred Term	Dose of Testosterone Solution				
	30mg N (%)	60mg N (%)	90mg N (%)	120mg N (%)	Overall N (%)
Subjects with at least one TEAE	2 (66.7%)	36 (50.7%)	10 (50.0%)	4 (50.0%)	45 (63.4%)
Total number of TEAEs	6	92	23	11	132
General Disorders and Administrative Site Conditions					
Application site erythema	0	4 (5.6%)	0	1(12.5%)	5 (7.0%)
Application site irritation	0	5 (7.0%)	1 (5.0%)	0	6 (8.5%)
Application site edema	0	2 (2.8%)	0	0	2 (2.8%)
Infections and Infestations					
Fungal Infection	0	2 (2.8%)	0	0	2 (2.8%)
Herpes Zoster	0	1 (1.4%)	1 (5.0%)	0	2 (2.8%)
Upper Respiratory Infection	0	1 (1.4%)	0	1(12.5%)	2 (2.8%)
Investigations					
Hematocrit increased	0	5 (7.0%)	0	0	5 (7.0%)
PSA Increased	0	2 (2.8%)	1 (5.0%)	0	3 (4.2%)
Nervous System Disorders					
Headache	0	3 (4.2%)	0	0	3 (4.2%)
Gastrointestinal Disorders					
Diarrhea	0	2 (2.8%)	1 (5.0%)	0	3 (4.2%)
Vomiting	0	2 (2.8%)	1 (5.0%)	0	3 (4.2%)
Skin and Subcutaneous Tissue Disorders					
Dry Skin	0	0	1 (5.0%)	1(12.5%)	2 (2.8%)
Hyperkeratosis	0	1 (1.4%)	0	1(12.5%)	2 (2.8%)
Rash	0	2 (2.8%)	0	0	2 (2.8%)
Musculoskeletal and Connective Tissue Disorders					
Back pain	0	1 (1.4%)	1 (5.0%)	0	2 (2.8%)
Vascular Disorders					
Hypertension	0	2 (4.1%)	0	0	2 (2.8%)

Source: NDA 22504, Module 5.3.5.2.3, Table 12-4.

Reviewer's comment: This reviewer considers the application site events, the increased hematocrit and the PSA change to be reasonably likely to be drug related. Most skin reactions were mild and did not require discontinuation of medication. However, two subjects withdrew from Study MTE09 because of application site events. These subjects, 20203 and 20205, are discussed in section 7.3.3 Dropouts and/or Discontinuations. Application site reactions are discussed more fully in section 7.4.5 Special Safety Studies/Clinical Trials. The hematocrit and PSA changes are discussed in section 7.4.2 Laboratory Findings.

A review of the adverse events seen by subjects in the phase 1 studies MTE07 and MTE11 did not reveal events that differed from those seen in studies MTE08 and MTE09.

7.4.2 Laboratory Findings

There were ten subjects who reported at least one abnormal and clinically significant laboratory value in the MTE08 and MTE09 studies. These are shown in Table 29. No hematology or clinical chemistry abnormalities were seen in the subjects participating in studies MTE07 or MTE11.

Table 29. Abnormal Laboratory Results Reported as Adverse Events in Studies MTE08 and MTE09

	Dose of Testosterone Solution				
	30 mg	60 mg	90 mg	120 mg	Overall
Elevated PSA (>4 ng/ml)	0	2 (1.7%)	1 (4.0%)	0	3 (1.9%)
Elevated Hematocrit (>54%)	0	6 (5.1%)	1 (4.0%)	0	7 (4.5%)
Elevated Hemoglobin (>18.1)	0	2 (1.7%)	0	0	2 (1.3%)
Elevated RBC (>6.4)	0	1 (0.9%)	0	0	1 (0.6%)
Elevated Hemoglobin A1c	0	0	0	1 (10%)	1 (0.6%)

Source: NDA 22504, Module 5.3.5.2.3, Table 12-14.

PSA Elevation

Three subjects had a PSA elevation during the study.

Subject 202-01 A 56 year old male had a baseline PSA of 0.79 on July 14, 2008. He began testosterone solution on July 26, 2008 and was titrated to 90 mg on October 24, 2008. His PSA at the end of Study MTE08 was 1.05 on November 28, 2008. His testosterone C_{AVG} at that time was 313 ng/dL with a C_{MAX} of 525. He was enrolled in Study MTE09 and received his final dose of testosterone on January 21, 2009. His end-of-Study MTE09 PSA was 10.28 on January 28, 2009. This was repeated, twice, on February 2, 2009 with values of 4.36 and 3.38.

Reviewer's comment: *The reason for the elevation on January 28 is not clear. The PSA had been stable for the initial 120 days of testosterone therapy. The rapid decline from approximately 10 to approximately 4 over 5 days suggests the possibility of a transient inflammatory process. There is no further follow-up information available.*

Subject 203-21 A 67 year old male had a baseline PSA of 3.9 on September 26, 2008. He began testosterone therapy on October 13, 2008 and remained on 60 mg throughout the study. His PSA at the end of MTE08 was 4.36 on February 9, 2009. It was repeated on February 19, 2009 and was 3.87. His end of MTE08 testosterone C_{AVG} was 122 with a C_{MAX} of 133.

Reviewer's comment: *The PSA values throughout this study are not significantly different.*

Subject 210-16 A 54 year old male had a baseline PSA of 1.27 on October 7, 2008. He began testosterone therapy on October 28, 2008 and remained on 60 mg throughout the study. His end-of-study PSA was 7.28 on February 24, 2009 and 6.36 on February 26, 2008. He was withdrawn from study MTE09 and his last dose was on February 26, 2009. He was referred for a Urology evaluation and a repeat PSA on [REDACTED] (b) (6) was 3.2. A prostate biopsy showed prostate carcinoma. This subject has been discussed in section 7.3.2 Nonfatal Serious Adverse Events.

Reviewer's comment: *In the opinion of this clinical reviewer, the underlying prostate cancer is not likely to be related to the four months of testosterone therapy. However, the PSA elevation is likely to be related to the testosterone therapy. Therefore, it is my impression that testosterone therapy lead to an increase of PSA that prompted further urological evaluation and as a result, a prostate biopsy was obtained to confirm the diagnosis of prostate cancer. It is my strong belief that the patient had an underlying low grade prostate cancer that got diagnosed with a significant elevation of PSA during this trial.*

Current guidelines of The Endocrine Society³ recommend that men 40 years of age and older have a baseline PSA followed by a second 3 - 6 months after the start of therapy and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient. These are reasonable guidelines that should be incorporated into the product label.

Elevated Hematocrit

The mean hematocrit at screening was 44%. After 120 days of testosterone therapy the mean hematocrit increased 1% with a standard deviation of 4%. After 180 days of treatment the mean hematocrit increased 3% with a standard deviation of 4%. Seven Subjects had a hematocrit >54% during the course of Studies MTE08/MTE09. They are shown in Table 30.

³ Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. 2010.

Table 30. Subjects with Hematocrit >54%

Subject	Screening Hct	Maximal Hct	Final Hct	Screening Testosterone	Day 120 C _{AVG}	Maintenance Dose of Testosterone Solution
202-11	48	61	57	271	945	90 mg
203-21	51	57	53	26	697	60 mg
207-02	50	58	54	324	889	60 mg
210-05	48	55	53	256	256	60 mg
210-07	51	58	57	241	362	60 mg
211-26	45	61	61	280	433	60 mg
212-03	45	55	54	301	650	60 mg

Source: MO Analysis

Reviewer’s comment: *The rise of hematocrit with testosterone therapy is well known⁴. This study excluded the enrollment of subjects with a hematocrit >51%. There was only one subject with hematocrit that rose to 61% and was determined after completion of study MTE08. This subject did not participate in the extension study MTE09. All the subjects with elevated hematocrit did not need any further medical intervention.*

The current guidelines of The Endocrine Society consider a hematocrit >50% to be a relative contraindication to testosterone therapy and they recommend that the hematocrit should be monitored 3 – 6 months after the start of therapy and then yearly. The guidelines also recommend that if the hematocrit rises to >54%, therapy should be stopped until the hematocrit decreases to a level considered safe for the patient. Physicians should evaluate the patient for hypoxia and sleep apnea; and reinstate therapy with a reduced dose. These are reasonable guidelines for the safe use of testosterone replacement therapy.

Other Clinical Laboratory Findings

The effect of treatment on serum electrolytes, cholesterol, LDL, HDL, triglycerides, AST, ALT, bilirubin, creatinine, WBC and platelet count was evaluated. No significant changes in these parameters were observed.

7.4.3 Vital Signs

Analysis of the safety data for pulse rate, seated diastolic and systolic blood pressure, respiratory rate and temperature demonstrated no significant changes from screening to the follow up visits (either after 120 days of treatment in the MTE08 study or after 180

⁴ Hajjar RR, Kaiser FE, Morley JE Outcomes of Long-Term Testosterone Replacement in Older Hypogonadal Males: A Retrospective Analysis. J Clin Endocrinology and Metabolism 82(11):3793-3796 1997.

days of testosterone treatment in the MTE09 study). Similarly, no significant changes in vital signs was seen in the subjects participating in studies MTE07 and MTE11.

7.4.4 Electrocardiograms (ECGs)

ECGs were undertaken for every subject at screening and again at the follow up visit (post treatment) at either the end of 120 days of testosterone treatment (MTE08) or 180 days of testosterone treatment (MTE09). Analysis of the data revealed that at screening, 51% of subjects had normal ECGs and 49% had abnormal, non-clinically significant ECGs. After 120 days of treatment, 61.5% of subjects had normal ECGs and 38.5% had abnormal, non-clinically significant ECGs. After 180 days of treatment, 58.8% of subjects had normal ECGs and 41.2% had abnormal, non-clinically significant ECGs.

Reviewer's comment: *The majority of the abnormal ECGs, both at baseline and follow up, showed minor abnormalities of rhythm such as sinus bradycardia.*

7.4.5 Special Safety Studies/Clinical Trials

Application Site Reactions

In studies MTE08 and MTE09, the effect of this topical product on the application site was evaluated using a categorical (Draize) scale with definitions of erythema as: 0 = no erythema, 1 = very slight erythema (barely perceptible), 2 = well defined erythema, 3 = moderate to severe erythema, and 4 = severe erythema (deep/dark red erythema) to slight eschar formation (injuries in depth).

In addition, the Draize definitions used for edema: erythema as: 0 = no edema, 1 = very slight edema (barely perceptible), 2 = slight edema (edges well defined with definitive raising, 3 = moderate edema (area raised approximately 1mm), and 4 = severe erythema (raised more than 1mm and extending beyond area of exposure). There was a possible total score of 8.

During both Study MTE08 and MTE09, the site of application was evaluated at every study visit. The majority of subjects did not register a Draize score of greater than zero at any time point.

At Days 15 and 16, three subjects registered a Draize score of 3 and one subject registered a Draize score of 2 (which resolved by day 16).

On Day 45 four subjects registered a Draize score of 1 and one subject registered a Draize score of 3.

On Days 60 and 61 and 90, no subject reported a Draize score of greater than zero.

On Day 120 and 121 one subject registered a Draize score of 1. During MTE09, only one subject registered a score of 2 (at the Day 180 visit).

All Draize scores of greater than zero were reported at the 60 mg dose and all events were transient in nature. The change in Draize score from screening to end of the 180 days of treatment was 0.1 ± 0.55 which was not significant. The change was not related to time or dose of study drug.

In addition to the above objective measurements of skin irritation, AEs related to the sensation of irritation reported by the subjects at each study visit were recorded.

In MTE08, 7/155 subjects (4.5%; six at the 60 mg dose and one at the 120 mg dose) reported Application Site Irritation (transient burning sensation at the site of application). In the MTE09 study, one subject (on the 90 mg dose) experienced this type of event and the subject withdrew from the study (Subject 20205 discussed in section 7.3.3 Dropouts and/or Discontinuations).

Such events, which the Sponsor believes to be a sensation attributable to the application of the alcoholic solution, were transient and resolved without intervention.

Reviewer's comment: *Application site reactions and irritation do not appear to be a significant clinical issue with this product.*

7.4.6 Immunogenicity

Testosterone is a substance that has a long history of human use with no immunogenicity issues. No studies of immunogenicity were done to support this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Table 27 shows adverse events by maintenance dose of drug. No clinically significant trend attributing the frequency of adverse events to the testosterone solution dose was found. There was also no evidence of a relationship between dose of testosterone solution and discontinuations from the studies.

7.5.2 Time Dependency for Adverse Events

There appears to be no time dependency for either serious adverse events or common adverse events when comparing studies MTE08 (days 1-120) and MTE09 (days 120-180).

Elevations of hematocrit were detected at day 120, which was the first evaluation of these parameters following the baseline. No subject with a normal hematocrit on day 120 was found to have an abnormal value on day 180.

Of the three subjects that were found to have an abnormal PSA, two were seen at day 120. One subject, 202-01, had a normal baseline and day 120 PSA but an abnormal value on day 180. This subject is discussed in section 7.4.2 Laboratory Findings.

Reviewer's comment: Overall, there does not appear to be any evidence of increasing adverse events with time-on-medication.

7.5.3 Drug-Demographic Interactions

The age distribution for the 155 subjects in the safety cohort of Study MTE08 is shown in Table 31.

Table 31. Age Distribution – Safety Cohort of Study MTE08

Age Group	Number of Subjects	Percentage of Subjects
<45	47	30.3
45 – 54	37	23.9
55 – 64	48	31.0
≥65	23	14.8
Total	155	100.0

Source: MO Analysis

A review of TEAEs, Serious AEs, discontinuations, and laboratory abnormalities does not suggest a significant relationship between those events and subject age.

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies or analyses were performed.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There are several lines of evidence that suggest the potential for a relation between testosterone and prostate cancer development.

Firstly, the clinical incidence of prostate cancer varies significantly across the world, with the highest incidence occurring in African-Americans (79 per 100 000) and the lowest in Japanese males (4 per 100 000)⁵. Ross et al.⁶ have demonstrated that at the time of puberty African American males have 10 to 15% higher levels of circulating testosterone than their Caucasian counterparts, but equal levels compared with Japanese men, who because of a genetic deficiency of 5 α -reductase actually have lower DHT levels in the prostate. In addition, differences in the function of 5 α -reductase genes affecting the AR and androgen metabolism contribute to an increased risk of prostate cancer in African-American men.⁷

Secondly, prostate cancer can be induced in rats to whom large amounts of testosterone have been administered.⁸ Thirdly, men castrated prior to puberty do not develop prostate cancer.⁹ A reduced risk of this cancer has been also been associated with hyperoestrogenic states (e.g. cirrhosis cases)¹⁰, and estrogen therapy has a palliative role in advanced prostate cancer because it competes with testosterone in the hypothalamus and suppresses gonadotropin production. Finally, prostate cancer may be successfully treated by surgical or medical androgen ablation.

Despite these suggestions of a relationship between testosterone and the development of prostate cancer, there is no evidence that suggests that elevated levels of testosterone or testosterone treatment of hypogonadal men is associated with an increase in prostate cancer.^{11,12} A recent meta-analysis¹³ examined 51 placebo

5 Oesterling J, Fuks Z, Lee CT. Cancer of the Prostate. in : Devita V, Hellman S, Rosenberg S, editors. Cancer: principles and practices in Oncology. 5th ed. Lippincott-Raven 1997.

6 Ross R, Bernstein L, Lobo R. 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. *Lancet* 1992; 339: 887-9

7 Devgan SA, Henderson BE, Yu MC, et al. Genetic variation of 3 beta-hydroxysteroid dehydrogenase type II in three racial/ethnic groups: implications for prostate cancer risk. *Prostate* 1997; 33 (1): 9-12

8 Nobel R. The development of prostatic adenocarcinoma in Nb rats, following prolonged sex hormone administration. *Cancer Res* 1977; 37: 1929-33

9 Huggins C, Hodges C. Studies on prostatic cancer 1: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941; 1: 293-7

10 Glantz C. Cirrhosis and carcinoma of the prostate gland. *J Urol* 1964; 91: 291-3

11 Eaton NE, Reeves GK, Appleby PN et al. Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies. *Brit J of Cancer* 1999; 80(7): 930-934.

12 Hsing AW, Comstock GW. Serological Precursors of Cancer: Serum Hormones and Risk of

controlled trials of testosterone therapy. The conclusion was that, although the quality of the evidence was low to medium, “testosterone therapy had no significant effects on all-cause mortality, (or) prostatic ... outcomes...”

There have, however, been numerous reports of the effect of testosterone therapy resulting in an occult prostate carcinoma becoming clinically manifest^{14,15,16}. The possibility of “unmasking” an occult tumor with testosterone therapy is something that prescribers should be made aware of.

Reviewer’s comment: *The best evidence at this time is that, despite the known effects of testosterone on established prostate cancer, there is no evidence to suggest that there is a relationship between testosterone therapy and the development of prostate cancer.*

7.6.2 Human Reproduction and Pregnancy Data

Axiron is not intended for use by, and should not be used by pregnant or lactating women. Safety information is not available for use in pregnancy and lactation. The amount of applied testosterone that would appear in human milk is unknown. It is known that exposure of a fetus to androgens may result in varying degrees of virilization.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of Axiron in males <18 years old has not been established. Use in prepubertal males would have the potential to result in premature closure of the epiphyses. Axiron is not indicated for use in this population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no experience with overdosage in the development program for Axiron. A non-clinical report¹⁷ of the effect of testosterone overdose in hamsters shows that, at high doses, testosterone causes central autonomic depression. There is a testosterone overdosage reported in the label of a testosterone gel, Androgel – “There is one report

Subsequent Prostate Cancer. *Cancer Epidemiology* 1993; 2: 27-32.

13 Fernandez-Balsells M, Murad MH, Lane M et al. Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis. *J Clin Endo Metab.* 2010; 96(6): 2560-2575.

14 Loughlin KR, and Richie JP: Prostate cancer after exogenous testosterone treatment for impotence. *J Urol* 157: 1845, 1997.

15 Morgenthaler A, Bruning CO III, and DeWolf WC: Incidence of occult prostate cancer in men with low total or free serum testosterone. *JAMA* 276: 1904–1906, 1996.

16 Curran MJ, and Bihrlle W. Dramatic rise in prostate-specific antigen after androgen replacement in a hypogonadal man with occult adenocarcinoma of the prostate. *Urology* 53: 423–424, 1999.

17 Peters KD, Wood RI. Androgen dependence in hamsters: overdose, tolerance, and potential opioidergic mechanisms. *Neuroscience* 130(4): 971-981. 2005

of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone levels of up to 11,400 ng/dL with a cerebrovascular accident.” This reviewer is unaware of any further details of this case. Treatment of overdosage would consist of discontinuation of testosterone treatment together with appropriate symptomatic and supportive care.

Androgenic steroids are drugs of abuse. They are taken in large quantities by athletes and others to increase performance, with negative health consequences. As a result, in 1991 testosterone and related androgenic steroids were declared controlled substances.

No information on testosterone withdrawal or rebound is available.

7.7 Additional Submissions / Safety Issues

There were no additional submissions or safety issues beyond those discussed earlier in this review.

8 Postmarketing Experience

There is no postmarketing experience with this new product.

9 Appendices

9.1 Literature Review/References

Shown as footnotes.

9.2 Labeling Recommendations

- The boxed warning that has been adopted by other topical testosterone products should be included in the Axiron label. This warning should discuss the potential for interpersonal transfer of testosterone and the consequences of that transfer.
- The phase three study of Axiron used a dose titration design based on average testosterone concentrations over a 24 hour period. In clinical practice, titration will be done based on single values. The results of the Sponsor's analysis of the best time to draw these single values, 2 – 8 hours after application, should be included in the label. The need for titration of the dose, and the method of doing so should be discussed.
- The label should indicate that Axiron is contraindicated in men with breast or prostate carcinoma. It should also include a contraindication for women who are, or may become, pregnant.
- The label should include warnings concerning the effects of testosterone on BPH, fertility, edema, gynecomastia and sleep apnea. Warnings concerning interpersonal transfer should be included. Methods of minimizing the risk of transfer such as hand and site washing, and covering the application site with clothing should be discussed.
- The potential for significant rise in red cell mass should be emphasized. In accordance with recent Endocrine Society Guidelines¹⁸, the label should discuss that appropriate monitoring would include a baseline measure of red cell mass such as hematocrit, and that the effect of the product on this should be assessed with a repeat measurement several months after the start of treatment.
- Because of the potential for an occult tumor becoming clinically apparent, discussed in section 7.6.1 Human Carcinogenicity, the label should advise

¹⁸ Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. 2010.

evaluation for prostate carcinoma in appropriate individuals at baseline and 3-6 months after the start of therapy. This recommendation would be in accordance with the Endocrine Society's 2010 Guidelines regarding testosterone therapy.

- The responder rates for Days 15, 60 and 120 should be incorporated into the clinical section of the label. The Day 15 rate demonstrates the response without any titration. However, the Day 60 and Day 120 response rates show the effect of one or two titrations on the overall response rate. This information will be useful to the prescribing physicians and will demonstrate the importance of titration.
- The label should not include reference to secondary endpoints such as increased libido, less erectile dysfunction, etc. The phase three study was not designed to evaluate these endpoints and there was no control group to provide context to the changes seen.

9.3 Advisory Committee Meeting

Topical testosterone products have been used since 2000 and other formulations for many years prior to that time. The safety issues associated with testosterone therapy are well known. There did not appear to be a need to evaluate this product with an advisory committee.

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/s/

DONALD R MCNELLIS
11/19/2010

SURESH KAUL
11/19/2010

Clinical Review Addendum

Regarding: NDA 22,504, Axiron, Labeling

Date: November 19, 2010

This memorandum addresses two aspects of the AXIRON label

Responder Rates

I believe that Days 15, 60 and 120 responder rates should be included in section 14 of the AXIRON label. I believe that it will be useful to prescribing physicians to include this data.

The 15 day 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. This will emphasize the importance of the titration procedures recommended in the label.

Having the 60 day data included in the label will demonstrate to the physician that a single titration will often be sufficient to achieve normal levels. This is useful and accurate clinical information and has been reviewed and accepted by the biometrics team.

Figure showing Mean (\pm SD) Steady-State Serum Testosterone Concentrations on Day 120

The Sponsor has requested that a Figure showing both the Day 15 and Day 120 pharmacokinetic profiles be included in section 14 of the AXIRON label. The clinical team had no objections to this inclusion. The clinical pharmacology team believed that this Figure should not be included.

A telephone conference between the review teams was held on November 17, 2010. After considerable discussion, the clinical pharmacology team indicated that, while they favored removal of the Figure, inclusion would be acceptable if only the Day 120 data was shown. This was communicated to the Sponsor on November 17, 2010. The sponsor agreed to remove the 15 day data from the Figure in the Clinical Section, 14.1, of the label.

I believe the Day 120 data in the Figure is accurate, not misleading, and worthwhile information for physicians to see and is the most reasonable way to reach a final agreement on the label between the Sponsor and the two review teams.

Donald McNellis
Medical Officer
Division of Reproductive and Urologic Products

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/s/

DONALD R MCNELLIS
11/19/2010

SURESH KAUL
11/19/2010

NDA 22,504

Testosterone 2% transdermal solution (Axiron)

Medical Officer's Filing Review Memorandum

Application Letter Date: January 25, 2010

45-Day Filing Review Date: March 26, 2010

PDUFA Goal Date: November 25, 2010

Sponsor: Acrux Pharma Pty Ltd

Product and Dose: Testosterone 2% transdermal solution

Indication: Hypogonadism in males

1. Executive Summary Objective: This review is conducted to fulfill a regulatory requirement of reviewing **NDA 22504** (testosterone 2% transdermal solution) to determine its suitability for filing under 21 CFR 314.50. This document will also serve as the basis for communicating to the sponsor the review issues identified during the initial filing period.

Recommendation: Following a preliminary review of results from the pivotal pharmacokinetic study, as well as the safety data, it is the impression of the clinical reviewer that the application is sufficiently complete to permit a substantive clinical review and should be filed.

2. NDA Filing Review

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Male hypogonadism results from insufficient production of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without impotence, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis. The Endocrine Society guidelines suggest that the diagnosis of testosterone deficiency in adult men should be based on a comprehensive review of patient symptoms and signs, and measurement of serum testosterone levels by a reliable assay.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050

ng/dL). Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range.

Currently available treatment options for hypogonadism include intramuscular injections, sub dermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels which are applied with the hands to the shoulders and upper arms and/or abdomen.

The testosterone formulation that has been developed by the Sponsor of this application is a (b) (4) solution containing 2 % w/v testosterone, and a permeation enhancer, octisalate (b) (4) together with povidone (b) (4) ethanol (b) (4) and IPA. The product is applied via a metered-dose pump utilizing a standard manual pump and nozzle which is designed to deliver a unit volume of the formulation uniformly to an applicator which is then used to apply the product to the skin of the axilla.

Criteria for Filing: This review is based on the three criteria proposed in the FDA Guidance “New Drug Evaluation Guidance Document: Refusal to File” (July 12, 1993), which represents FDA’s interpretation of 21 CFR 314.50. These criteria are:

- Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner
- Failure to include evidence of effectiveness compatible with the statute and regulations
- Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Question 1: Does this NDA omit a section required under CFR 314.50 or was a particular section presented in such a manner to render it incomplete for clinical review?

Answer: No

This NDA contains the critical sections in sufficient detail to permit a substantive Clinical review. As requested by the Division, the Sponsor has submitted the report of a Phase 3 study demonstrating that the use of their product results in a serum testosterone within the normal range in an acceptable proportion of subjects. They have also submitted safety data that is consistent with ICH requirements, labeling, and Safety/Efficacy summaries.

This application is a 505(b)(2) submission. The Sponsor will rely on published literature for nonclinical information. They will not rely on any information from other products applications, therefore there is no Reference Listed Drug.

Question 2: Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:

- **Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints**
- **Presentation or what appears to be only a single adequate and well-controlled trial without adequate explanation**
- **Use of study design clearly inappropriate**

Answer: No

Testosterone products have historically been approved based on pharmacokinetic criteria. As per the requirement of the Agency, the sponsor submitted data from an adequate Phase 3 trial (MTE08). The trial design and endpoint was appropriate and consistent with those of the Phase 3 trials used for the initial approval of other transdermal testosterone products. The trial was a multi-center trial to determine the efficacy and safety of the Sponsor's testosterone formulation in producing a serum testosterone level within the normal range in men with baseline serum testosterone levels in the hypogonadal range. Trial MTE09 was a safety extension of the MTE08 trial evaluating safety over a six month exposure to the formulation.

Trial Design

This trial evaluated the efficacy and safety of their testosterone 2% solution, used transdermally, as a treatment for male hypogonadism. Trial MTE08 was carried out at 26 centers in Australia, the United States, the United Kingdom, Germany, France and Sweden. A total of 155 patients were enrolled into trial MTE08 and received at least one dose of study treatment.

Trial MTE09 enrolled 71 subjects who had completed trial MTE08. These subjects continued study medication and were evaluated for safety during a total period of exposure to the medication of six months.

Subjects entered into study MTE08 all received a starting dose of 60 mg of Testosterone 2% solution on Day 1. At Days 15 and 60, subjects underwent intensive pharmacokinetic sampling and C_{AVG} was determined. This was then used to titrate subsequent dosing. The dose changes were done were made on days 45 and 90. The dose could be titrated down to 30 mg or upward to 90 mg or 120 mg.

Subjects participating in the MTE09 study were to continue to apply the dose that they were taking at the Day 120 visit of the MTE08 study. This study did not involve dose titrations.

Diagnosis and main criteria for inclusion:

Men, 18 years-of-age or older with a documented diagnosis of hypogonadism as evidenced by a serum testosterone of ≤ 300 ng/dL (based on the average of two morning samples taken at least 30 minutes apart).

Primary Endpoint

The primary efficacy endpoint for MTE08 was the percentage of subjects having C_{avg} total testosterone on day 120 that is within the normal range (300-1050 ng/dL). The trial would

demonstrate effectiveness of the medication if >75% of subjects were within this normal range.

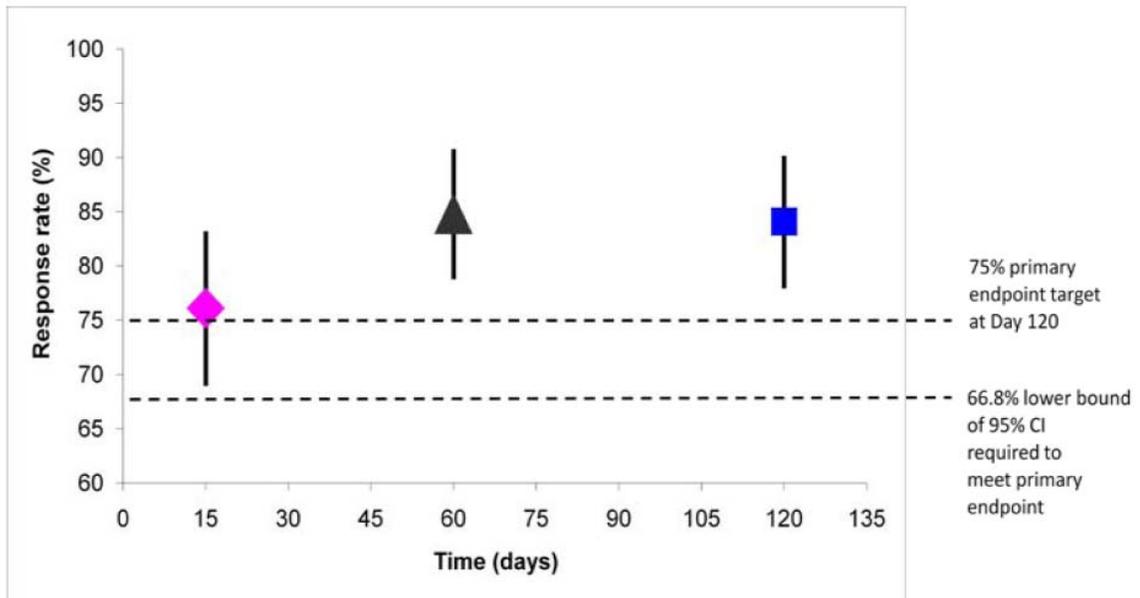
Secondary Endpoints

The following key secondary endpoints were evaluated:

- Proportion of subjects with Serum Total Testosterone C_{max} less than 1500 ng/dL. A target of 85% of subjects in this range was pre-specified.
- Proportion of subjects with Serum Total Testosterone C_{max} between 1800 ng/dL and 2500 ng/dL. A target of <5% of subjects in this range was pre-specified.
- Proportion of subjects with Serum Total Testosterone C_{max} greater than 2500 ng/dL. A target of no subjects in this range was pre-specified.

Efficacy

The following figure demonstrates the proportion of subjects having C_{AVG} within the normal range.



The secondary endpoint results are shown in the following table.

Endpoint	Target	Day 120 Result
Proportion of subjects with Serum Total Testosterone C _{max} less than 1500 ng/dL	>85%	128/135 (94.8%)
Proportion of subjects with Serum Total Testosterone C _{max} between 1800 ng/dL and 2500 ng/dL	<5%	4/135 (3.0%)
Proportion of subjects with Serum Total Testosterone C _{max} greater than 2500 ng/dL	0%	1/135 (0.7%)

Comment: One subject had a C_{MAX} on day 120 of >2500 ng/dl. This will be a review issue.

The Sponsor has provided an extensive analysis of the dose titrations that were done and, based on this analysis, has proposed a plan for titration based on a single serum value as opposed to the C_{AVG} that was used for titration in the phase 3 study.

Question 3: Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:

- **Total patient exposure at relevant doses that is clearly inadequate to evaluate safety**
- **Clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets**
- **Absence of comprehensive analysis of safety data**
- **Absence of an analysis of data supporting the proposed dose and dose interval**

Answer: No

In study MTE08, 155 men were enrolled and 135 men completed the 120 day treatment period. 71 of these subjects were followed in study MTE09 for a total exposure of six months. All of the subjects were men >18 years of age. This patient population is adequate given the long prior experience with testosterone products.

Altogether 20 subjects prematurely discontinued the phase 3 study. The most common reasons for premature termination were withdrawal of consent (9 subjects), non-compliance (4 subjects) and lost to follow-up (2 subjects). Three subjects withdrew because of adverse events – superficial thrombophlebitis (1), melanoma (1) and emotional changes (1). There were no deaths in the phase 3 studies.

The Sponsor has provided an analysis of adverse events. The following table shows adverse events occurring in >2% of subjects.

System Organ Class MedDRA Preferred Term	Dose of Testosterone MD-Lotion® 2%				
	30mg n (%)	60mg n (%)	90mg n (%)	120mg n (%)	Overall n (%)
Subjects with at least one TEAE	3 (75%)	71 (45.8%)	13 (37.1%)	5 (50.0%)	81(52.3%)
Total Number of reported TEAEs	4	177	31	8	220
General Disorders and Administration Site Conditions					
Application Site Erythema	0 (0%)	8 (5.2%)	0 (0%)	0 (0%)	8 (5.2%)
Application Site Irritation	0 (0%)	10 (6.5%)	1 (2.9%)	1 (10%)	12 (7.7%)
Infections and Infestations					
Nasopharyngitis	0 (0%)	5 (3.2%)	1 (2.9%)	0 (0%)	6 (3.9%)
Investigations					
Haematocrit Increased	0 (0%)	5 (3.2%)	1 (2.9%)	0 (0%)	6 (3.9%)
Nervous System Disorders					
Headache	0 (0%)	8 (5.2%)	0 (0%)	0 (0%)	8 (5.2%)
Gastrointestinal Disorders					
Diarrhoea	0 (0%)	2 (1.3%)	2 (5.7%)	0 (0%)	4 (2.6%)
Vomiting	0 (0%)	3 (1.9%)	1 (2.9%)	0 (0%)	4 (2.6%)

The subjects with increased hematocrit will be a review issue.

Preliminary review of a study evaluating the possibility of transfer of testosterone from a user of this product to another person via skin-to-skin contact shows that this transfer is possible, as it is with other transdermal products. This product should be subject to the labeling requirements adopted for transdermal testosterone products in 2009.

3. Reviewer's Conclusions

A preliminary review of the Sponsor's submission indicates that they have submitted adequate evidence of efficacy. This is provided by a single study, involving 155 subjects, that appears to be well-designed with respect to inclusion criteria, exclusion criteria, treatment, endpoints and analysis.

The Sponsor has submitted data to allow a substantive review of the safety of testosterone 2% solution to be conducted. The requested washing study has been completed by the Sponsor, but the results have not yet been submitted. This information is required for a complete safety submission.

4. Recommended Regulatory Action

The Sponsor should be notified, in the 74-day letter, that the application will be filed. The Sponsor should be informed that, from a clinical standpoint, there are three review issues:

1. Subjects who had a $C_{max} > 2500$ ng/dl at any time point.
2. Subjects with elevated hematocrit/hemoglobin.
3. The report of the yet to be submitted washing study.

Also, the Sponsor should be informed that the labeling standards, including a black box warning regarding person-to-person transfer, adopted in 2009 for other transdermal testosterone products will be expected in the label for this product.

Donald McNellis
 Medical Officer
 Division of Reproductive and Urological Products

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		Requested washing study has been completed. Results will be submitted as discussed at pre-NDA meeting
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver request included
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

- 1. Subjects having a C_{max} >2500 ng/dl will be a review issue.**
- 2. Subjects having elevated hematocrit and/or hemoglobin will be a review issue.**
- 3. The results of the washing study will be a review issue.**

Donald McNellis

March 11, 2010

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

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/s/

DONALD R MCNELLIS
03/12/2010

SURESH KAUL
03/17/2010