CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022504Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-504/N0000
Drug Name:	AXIRON™ (Testosterone MD-Lotion 2%)
Indication(s):	Testosterone replacement therapy for conditions associated with androgen deficiency
Applicant:	Acrux Pharma PTY, Inc
Date(s):	Date of submission: 01/25/2010
	PDUFA due date: 11/25/2010
	Review completion date: 11/19/2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Xin Fang, Ph.D., Primary Reviewer
Concurring Reviewers:	Mahboob Sobhan, Ph.D. Team Leader
Medical Division:	Division of Reproductive and Urologic Products
Clinical Team:	Donald McNellis, M.D., Medical Reviewer
	Suresh Kaul, M.D., Team Leader
Project Manager:	Jeannie M. Roule

Keywords: NDA review, Clinical studies, Confidence Interval.

We agreed to include day 15 efficacy data in Table 3 of section 14.1 of the label.

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/s/

XIN FANG
11/19/2010

MAHBOOB SOBHAN
11/19/2010

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Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from one study (Study MET08) support the efficacy of AXIRON™ as testosterone replacement therapy in hypogonadal men. The proportion of subjects with C_{avg} total serum testosterone within the normal range (300-1050 ng/dL) at day 120 was 84.1% with the lower bound of the associated 95% confidence interval of 78%, greater than 66.8% limit pre-specified in the protocol.

From a statistical perspective, the efficacy has been demonstrated in support of the transdermally applied 2% testosterone solution (Axiron™) as the testosterone replacement therapy for conditions associated with androgen deficiency.

1.2 Brief Overview of Clinical Studies

The applicant, Acrux Pharma PTY, Inc, reported efficacy and safety data from a single clinical trial MTE08/09 (Study MTE08 with its safety extension MTE09) to support transdermally applied 2% testosterone solution (AXIRON™) as the testosterone replacement therapy for conditions associated with androgen deficiency. Study MTE08 was a single-arm, open-label, dose-titration trial conducted multinationally in 26 sites across 6 countries. Healthy adult subjects with total circulating testosterone < 300 ng/mL were enrolled into the study and received a fixed starting dose of 3 mL (60 mg) AXIRON™. Following the initial treatment, subjects were titrated to lower dose or higher dose on Day 45 and on Day 90 based on their total circulating testosterone data on Day 15 and on Day 60, respectively. The treatment duration was 120 days.

The protocol specified primary efficacy endpoint was the proportion of subjects with average total serum testosterone concentration (C_{avg}) in the normal range (300-1050 ng/dL) on Day 120. The secondary endpoints included, but not limited to, (1) the proportion of subjects with C_{avg} in the defined normal range on Day 15 and Day 60, (2) the proportion of subjects with minimum serum concentration (C_{min}) < 300 ng/dL, and (3) the proportion of subjects with maximum serum concentration (C_{max}) <1500 ng/dL, between 1800 ng/dL and 2500 ng/dL, and >2500 ng/dL.

The objective of study MTE08 was to establish the efficacy and safety of Axiron™ when used by hypogonadal men. The planned sample size was 150 with 107 completers. At the end of the study, 155 subjects were enrolled and 135 subjects completed the study. In addition, 3 discontinued subjects due to adverse event were considered treatment failure and were included in the completer set. At the end, the primary analysis set included 138 subjects.

1.3 Statistical Issues and Findings

There was no statistical issue noted regarding either dataset or analysis.

2. INTRODUCTION

2.1 Overview

The sponsor, Acrux Pharma PTY Inc, is seeking approval of Axiron™ for the treatment of hypogonadism. AXIRON™ has been developed to deliver physiological amounts of testosterone to produce circulating testosterone concentrations within approximate normal levels (300-1050 ng/dL) in healthy adult men. AXIRON™ is administered transdermally once daily to axilla or armpit and the advantages of using this product included (1) ease of application (2) quick drying and no visible residual on the skin, (3) request for smaller skin area and volume than existing relevant transdermal products, and (4) a low level of skin irritation.

To support the safety and efficacy of AXIRON™, clinical data from a single Phase-3, open-label study MTE08/09 (Study MTE08 with its safety extension MTE09) was submitted. The study of MTE08 was entitled "A Phase III open-label titration trial to evaluate the effectiveness and safety of different doses of a dermal application of Testosterone MD-Lotion® (cutaneous solution) in hypogonadal men with an extension to evaluate skin-safety". Our review will focus on the efficacy data from this study summarized in Table 2.1.

Table 2.1 Summary of Study

Study	Study Site	Study Design	Number Randomized/ Study Regimens	Duration of Treatment
MTE08/09	Australia (4) Germany (3) France (2) UK (3) Sweden (2) USA (12)	Multi-nation, Open-label, Titration	**Planned**: 150 (one group only) **Analyzed**: 155	120 days for MTE08 Additional 60 days for MTE09

2.2 Data Sources

The study report and additional information were submitted electronically. The data quality of the submission was within the acceptable limit. Analysis datasets and associated definition files were listed in Table 2.2.

Table 2.2 Data Sources

Study	File	Location
MTE08/09	Datasets	\\CDSESUB1\EVSPROD\NDA022504\0000\m5\datasets\study-report-mte08-mte09\analysis\
	Definition	\\CDSESUB1\EVSPROD\NDA022504\0000\m5\datasets\study-report-mte08-mte09\analysis\define.pdf
	Datasets	\\CDSESUB1\EVSPROD\NDA022504\0000\m5\datasets\study-report-mte08-mte09\tabulations\
	Definition	\\CDSESUB1\EVSPROD\NDA022504\0000\m5\datasets\study-report-mte08-mte09\tabulations\define.pdf

2.3 Indication

AXIRON™ is indicated for the treatment of male hypogonadism.

3. STATISTICAL EVALUATION

3.1 Overview of Study MTE08/09

3.1.1 Design and Objectives

Design: Study MTE08 was a multinational Phase III, open-label, titration trial to evaluate the efficacy and safety of AXIRON™ in the treatment of hypogonadal men, while Study MTE09 was the extension of Study MTE08 with additional 60-day administration of final titration dose to evaluate the skin safety. Study MTE08/09 was conducted in 26 centers across 6 countries: 4 centers in Australia, 3 centers in Germany, 2 centers in France, 3 centers in UK, 2 centers in Sweden, and 12 centers in USA. All eligible subjects started with one starting dose of 3 mL (60 mg) and were titrated to a lower dose or a higher dose twice during the study.

Subjects with total testosterone levels of < 300 ng/mL and who satisfied other inclusion/exclusion criteria received starting dose of 3 mL (60 mg) at the beginning of the study. Two titrations on Day 45 and on Day 90 were performed after the initial treatment. On Day 15, all subjects were to undergo intensive pharmacokinetic (PK) sampling. On Day 45 if a subject's day-15 total testosterone was within the normal range (300-1050 ng/dL), he was to continue on the starting 60 mg dose, otherwise, he was to be titrated to either the lower dose (30 mg) or to the higher dose (90 mg) on Day 45. On Day 60, PK samples were repeated. On Day 90, subjects with their day-60 total testosterone out of normal range received a final dose titration. All subjects remained in their final titrated dose until Day 120. On Day 120, the final efficacy data of intensive PK samplings were taken.

Immediately after Day 120, about 71 subjects continued their maintained dose for additional 60 days. On Day 150 and Day 180, their vital signs, concomitant medication, adverse events and a Draize score were taken. The follow-up visit for Study MTE08/09 were between Day 7 to Day 10 after the final dose.

The treatment duration was 120 days for Study MTE08 and 60 days for Study MTE09. The primary objective of the Study MTE08 was to determine the proportion of subjects having C_{avg} total testosterone levels within the normal range (300-1050 ng/dL) on Day 120.

Primary Efficacy Endpoints: The primary endpoint was the proportion of subjects with C_{avg} (0-24 hours) total testosterone in the normal range (300-1050 dg/dL) on Day 120. In order to claim trial success, the following three conditions must be satisfied (1) the minimum number of completers was 107, (2) the observed response rate was at least 75%, and (3) the lower limit of the two sided 95% confidence interval (CI) was at least 66.8%.

Secondary Efficacy Endpoints: The secondary objectives included:

- the proportion of subjects with C_{max} < 1500 ng/dL (at least 85% of subjects should have C_{max} less than 1500 ng/dL)

- the proportion of subjects with C_{max} between 1800 and 2500 ng/dL (less than 5% of subjects should have C_{max} between 1800 ng/dL and 2500 ng/dL)
- the proportion of subjects with C_{max} > 2500 ng/dL (no subjects expected)
- the proportion of subjects with C_{min} < 300 ng/dL
- confirm the safety of different doses of Axiron™ (cutaneous solution)
- the changes from baseline in the following clinical endpoints:
  - Psychosexual Daily Questionnaire
  - SF-36 Questionnaire
  - Fasting Insulin and Glucose Levels
  - Prostate Specific Antigen Levels
  - LH, FSH and Estradiol levels
  - Hemoglobin and hematocrit level

Determination of Sample Size: Assuming an observed response rate of 75%, a total of 107 completers were needed to provide a 95% CI with a lower limit of at least 66.8%. With a dropout rate of 28.5%, 150 subjects were required to enroll in the study. For the extension phase of the study, 50 subjects were needed to complete continuous use of the product for 6 months.

Definition of Analysis Data Sets: Four analysis data sets were defined in the protocol: safety data set (SS), full analysis data set (FAS), the completers data set (CS) and the per protocol data set (PP). The primary analysis set was the completer data set. The SS included all subjects who received at least one dose of AXIRON™. The Full Analysis Set (FAS) included all subjects who received at least one dose of study drug and had on-treatment data for at least one efficacy variable. The FAS data set was considered supportive for the primary efficacy analysis. The CS included all subjects in FAS who completed the Day 120 visit or withdrew from the study prior to Day 120 due to either an adverse event or lack of efficacy. Subjects who withdrew from study prior to Day 120 for the above reasons were considered treatment failure and were included in the CS. Subjects who withdrew for other reasons were not included in the CS. The PP data set included all subjects in CS having no significant protocol violations or deviations as defined prior to database lock. In addition, subjects who withdrew due to an AE or efficacy were considered as treatment failure and were included in the PP data set.

Handling of Missing Data: Missing data other than missing PK data were not imputed. For PK data with 3 or more missing concentration values, AUC values were set to missing. If initial PK concentration was missing, then a partial AUC was reported such as (AUC_{2-24} or AUC_{0-20}).

Pool of Sites: All sites were pooled for the primary analysis.

Statistical Methods: The statistical method included estimation of the proportion of subjects with C_{avg} in the normal range (300-1050 ng/dL) on Day 120 and the associated 95% CI using completer's data set. In addition, similar statistics were presented using PP data set as a sensitivity analysis.

All secondary endpoints were summarized using descriptive statistics.

Multiple Comparisons/Multiplicity: No adjustments for multiplicity were made.

3.1.2 Reviewer's Comments on the Design

The Study design was adequate to assess the efficacy in hypogonadal men in terms of proportion of patients with normally ranged total testosterone C_{avg} on Day 120. A total of 107 completers were also adequate to rule out a lower bound of the 95% confidence interval of the point estimate below 67% with at least 80% power.

3.2 Results: Study MTE08/09

3.2.1 Subject Disposition

The study was conducted in 26 centers across 6 countries. A total of 155 patients were enrolled in study MTE08 for efficacy and safety evaluation, of which 71 patients continued into study MTE09 for skin safety evaluation. There were 135 completers and 20 discontinuations as shown in Table 3.2.1. The major reason for discontinuation was withdrawal (6 %), followed by adverse events (AE), and non-compliance to study drug.

Table 3.2.1 Subject Disposition

Category	N (%)
Total Enrolled/ Safety Set	155 (100%)
Completed Study	135 (87%)
Discontinuations:	20 (13%)
Adverse Events	3 (2%)
Non-compliance	3 (2%)
Lost to Follow-up	2 (1%)
Voluntary Withdrawal	9 (6%)
Other	3 (2%)
Full Analysis Set	143
Primary Efficacy Set (Completer Set)	138
Per Protocol Set	123

3.2.2 Subject Demographics and Baseline Characteristics

The baseline characteristics such as age, race, and body mass index (BMI) were similar based on the Primary Efficacy Set (PES) in Study MTE08 (Table 3.2.2). The primary efficacy set contained 138 subjects, out of which 100 subjects (72%) maintained at the 60 mg dose. Also, it seems the younger the subjects, the higher the maintained dose. The body mass indexes were comparable among the maintained dose groups.

Table 3.2.2 Demographic Characteristics by Maintenance Doses					
Demographic Variables	Testosterone MD-Lotion 2%				Total N=138
	30 mg N=3	60 mg N=100	90 mg N=25	120 mg N=10	
Age (SD)	57.3 (7.09)	51.5(13.62)	52.9(10.91)	48.7 (9.43)	51.7 (12.77)
Body Mass Index (SD)	28.1 (5.46)	29.5 (3.66)	29.7 (3.05)	29.1 (3.87)	29.5 (3.58)
Race [N (%)]					
Caucasian	2 (66.7%)	79 (79.0%)	19 (76.0%)	7 (70.0%)	107 (77.5%)
African American	0	2 (2.0%)	3 (12.0%)	1 (10.0%)	6 (4.4%)
Asian	0	1 (1.0%)	0	0	1 (0.7%)
Hispanic	1 (33.3%)	10 (10.0%)	0	2 (20.0%)	13 (9.4%)
Other	0	8 (8.0%)	3 (12.0%)	0	11 (8.0%)

Source: Reviewer's analysis
Note:

- Other race included subjects having missing value in race.
- Dose was titrated as needed and was not a fixed block design to assess dose-response.

3.2.3 Primary Efficacy

The primary efficacy data set (PES) is the completer set (CS) which contained 138 subjects including three withdrawals (MTE08-101-01, MTE08-205-30, MTE08-209-07) due to AE. As described in the protocol, they were all included in the CS data set as treatment failures. However, not all of the three withdrawals were included in the FAS. Only one of them (MTE08-205-30) had on treatment efficacy measurement on Days 15 and 60 and was included in the FAS data set. Our primary analyses were based on these 138 subjects (in CS) although there were more observed data (belonged to dropouts) on Days 15 and 60. Sensitivity analyses were based on FAS and PS data sets.

All study subjects had a baseline serum total testosterone (sTT) <300 ng/dL measured either on screening day or study Day 1. The baseline values were the average of two morning samples taken at least 30 minutes apart at screening time. For thirteen subjects, repeated screening measurements were taken, because the first measurement was >300 ng/dL. The primary and secondary efficacy results were shown in Table 3.2.3. On Day 120, the overall estimate of the proportion of subjects having normal sTT was 84.1% with lower bound of the associated 95% CI limit of 78.0%. Results based on FAS and PP data sets were also similar having the estimates of the proportion > 75% (not shown).

3.3.4 Secondary Efficacy

Selected secondary efficacy results were also shown in Table 3.2.3. On Day 120 after taking AXIRON^{TM}, the proportion of subjects having sTT C_{max} between 1800ng/dL and 2500 ng/dL may be more than 5.0%. In addition, the proportion of subjects having C_{max} >2500ng/dL may be as high as 2.1%.

Table 3.2.3 Number and percent of subjects with Serum Total testosterone PK levels on Day 120 (N=138, Completers Population)		
PK Levels	n (%)	95% CI
C_{avg} (300-1050) ng/dL	116 (84.1)	(78.0, 90.2)
C_{max}:		
<1500 ng/dL	131 (94.9)	(91.3, 98.6)
≥1500 ng/dL	7 (5.1)	(1.4, 8.7)
>1800ng/dL and ≤ 2500 ng/dL	4 (2.9)	(0.1, 5.7)
>2500ng/dL	1 (0.7)	(0.0, 2.1)
C_{min} <300ng/dL	90 (65.2)	(57.3, 73.2)
Source: Reviewer's analysis		

The number and percent of subjects who achieved normal serum testosterone level on day 15 and day 60 are summarized in Table 3.2.4. The AXIRON™ appeared to be effective as early as Day 15. However, on Day 15, only 72.2% US completers had normal serum testosterone (Table 4.1).

Table 3.2.4 Number and percent of subjects within the normal Serum Total testosterone PK level on Day 15 and Day 60 (N=138, Completers Population)			
Evaluation Time	PK Level	n (%)	95% CI
Day 15	C_{avg} (300-1050) ng/dL	105 (76.1)	(69.0, 83.2)
Day 60	C_{avg} (300-1050) ng/dL	117 (84.8)	(78.8, 90.8)
Source: Reviewer's analysis			

3.3.5 Adjustment for Multiplicity

There was no multiplicity issue in the evaluation of primary efficacy analysis. The sponsor did not specify how to control the type I error rate for the secondary endpoints. For evaluation of efficacy on Day 60, a gate-keeping procedure was used, in which the efficacy on Day 120 was evaluated first.

3.3.6 Comments on the Efficacy Results

Our analysis confirms the efficacy of AXIRON™ in the treatment of hypogonadism on Day 120 as shown by the point estimate of 84.1% with the associated 95% CI of (77.95%, 90.17%) based on completer data set. In addition, AXIRON™ also showed efficacy as early as Day 60, with a rate of 84.8% and 95% CI of (78.79%, 90.78%).

3.4 Evaluation of Safety

The safety evaluation is referred to medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Region

The efficacy in US vs. non-US population was shown in the Table 4.1. On day 120, the AXIRON™ appeared to be more effective in the non-US subjects than US subjects with approximately 92% and 80.0% of the subjects having serum total testosterone in the normal range, respectively. No other subgroup analysis was identified clinically.

Table 4.1 Number and percent of subjects within the normal Serum Total testosterone PK level by time points and region: US vs. Non-US (N=138, Completers Population)

Evaluation Time	PK Level	US (N=90)		Non-US (N=48)	
		n (%)	(95% CI)	n (%)	(95% CI)
Day 15	C_{avg} (300-1050) ng/dL	65 (72.2)	(63.0,81.5)	40 (83.3)	(72.8, 93.9)
Day 60	C_{avg} (300-1050) ng/dL	77 (85.6)	(78.3, 92.8)	40 (83.3)	(72.8, 93.9)
Day 120	C_{avg} (300-1050) ng/dL	72 (80.0)	(71.7, 88.3)	44 (91.7)	(83.9, 99.5)
Source: Review's analysis					

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no statistical issues in the efficacy evaluation.

5.2 Conclusions and Recommendations

The data from study MTE08 supported the efficacy of AXIRON™ as testosterone replacement therapy for conditions associated with androgen deficiency on both Day 120 and Day 60. The proportion of subjects having total serum testosterone within normal range was 84.1% and 84.8% on Day 120 and Day 60, respectively.

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/s/

XIN FANG
11/01/2010

MAHBOOB SOBHAN
11/01/2010

STATISTICS FILING MEMORANDUM FOR A NDA

NDA:	22-504
Drug Name:	Axiron™ (2% testosterone solution)
Sponsor:	Acrux Pharma Pty Ltd
Indications:	Male Hypogonadism
Medical Officer:	Donald McNellis, M.D., HFD-580
Statistician:	Xin Fang, Ph.D., HFD-725
Project Manager:	Jeannie M Roule
Submission Date:	01/25/2010
45 day Meeting Date:	03/11/2010

A: Background

This memo pertains to filing review for Axiron NDA. The objective of this filing review is to determine whether this NDA is sufficiently complete for substantive statistical review. As part of the determination, we looked at the format and contents of the safety and efficacy data sets that will allow us to perform pertinent statistical analysis as per study protocol. The indication for male hypogonadism was pursued in the submission. In supporting the efficacy and safety review of Axiron™, Clinical data and reports were submitted from one Phase-III study entitled:

- **Study MET08/09:** "A Phase III open-label titration trial to evaluate the effectiveness and safety of different doses of a dermal application of Testosterone MD-Lotion® (cutaneous solution) in hypogonadal men

  &

  A Phase III open-label extension of the MTE08 trial (A Phase III open-label titration trial to evaluate the effectiveness and safety of different doses of a dermal application of Testosterone MD-Lotion® (cutaneous solution) in hypogonadal men) to evaluate skin-safety

Our statistical review will focus on the above study (MTE08/09).

B: Conclusion

After the preliminary review of the submission for the following items in the checklist, we found that the sponsor submitted both tabulation datasets, analysis datasets and associated documents for statistical review. From statistical perspective, this NDA is fileable.

STATISTICS FILING MEMORANDUM FOR A NDA

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			No ISS
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			√	Hypogonadism men
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

Xin Fang 03/05/2010

Reviewing Statistician Date

Mahboob Sobhan 03/05/2010

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for NDA_22504

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

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XIN FANG
03/11/2010

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03/11/2010