CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208088Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 14, 2022
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 208088
Product Name and Strength:	Tlando (testosterone undecanoate) capsules, 112.5 mg
Applicant/Sponsor Name:	Antares Pharma, Inc.
OSE RCM #:	2020-487-2
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label received on March 11, 2022 for Tlando. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label for Tlando (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review memorandum. [a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kalonia, J. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAR 03. RCM No.: 2020-487-1.

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

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/s/

JUSTINE H KALONIA
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STEPHANIE L DEGRAW
03/14/2022 03:51:52 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	March 4, 2022
To:	Jeannie Roule, RPM Regulatory Project Manager **Division of Urology, Obstetrics, and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	TLANDO (testosterone undecanoate)
Dosage Form and Route:	capsules, for oral use, CIII
Application Type/Number:	NDA 208088
Applicant:	Antares Pharma, Inc.

1 INTRODUCTION

On January 28, 2022, Antares Pharma, Inc. submitted for the Agency's review a Class 1 resubmission for their product TLANDO (testosterone undecanoate) capsules, for oral use, CIII, NDA 208088. The Agency issued a tentative approval letter for TLANDO on December 8, 2020. Since the tentative approval, the ownership of TLANDO has been transferred from Lipocine Inc to Antares Pharma, Inc as of October 26, 2021. Currently, Antares Pharma, Inc. is seeking full approval for TLANDO (testosterone undecanoate) indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence or endogenous testosterone. On January 28, 2022, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TLANDO (testosterone undecanoate) capsules, for oral use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed MG for TLANDO (testosterone undecanoate).

2 MATERIAL REVIEWED

- Draft TLANDO (testosterone undecanoate) MG received on January 28, 2022, and received by DMPP on February 24, 2022.
- Draft TLANDO (testosterone undecanoate) Prescribing Information (PI) received on February 28, 2022, and received by DMPP on February 24, 2022.
- TLANDO (undecanoate**)** MG tentatively approved December 8, 2020.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 3, 2022
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 208088
Product Name and Strength:	Tlando (testosterone undecanoate) capsules, 112.5 mg
Applicant/Sponsor Name:	Antares Pharma, Inc.
OSE RCM #:	2020-487-1
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

On January 28, 2022, as part of a Class 1 Resubmission to request final approval for NDA 208088, the Applicant submitted revised container label, prescribing information (PI) and Medication Guide (MG) labeling for Tlando which includes revised Applicant information and NDC numbers. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised labeling for Tlando (Appendix A) to determine if it is acceptable from a medication error perspective.

2 REGULATORY HISTORY

NDA 208088 was originally submitted on August 8, 2015. Under that submission, DMEPA completed a label and labeling review and memo.[a,b] However, on June 28, 2016, the application received a complete response (CR) letter due to lack of an appropriate dosing titration scheme. Thus, on August 8, 2017, the Applicant submitted a Class 2 Resubmission in response to the CR letter. DMEPA again completed a label and labeling review.[c] Subsequently,

[a] Fava, W. Label and Labeling Review for testosterone undecanoate (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 15. RCM No.: 2015-2005.

[b] Fava, W. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 04. RCM No.: 2015-2005-1.

[c] Baugh, D. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 16. RCM No.: 2017-1641.

the application received a second CR letter on May 8, 2018 due to concerns regarding serum testosterone levels and potential clinically meaningful increase in blood pressure. DMEPA's recommendations for the container label were communicated to the Applicant at that time. Thus, on May 9, 2019, the Applicant submitted a Class 2 Resubmission in response to the CR letter. Under this submission, DMEPA completed a label and labeling review and memo[d,e] and our container recommendations were communicated to the Applicant. However, on November 8, 2019, the application received a third CR letter due to excessive testosterone Cmax excursions. On February 28, 2020, the Applicant submitted a Class 2 Resubmission in response to the CR letter. DMEPA completed a label and labeling review memo which provided some recommendations for the division for the PI and MG but noted that no additional recommendations for the container label were necessary at that time.[f]

On December 8, 2020, NDA 208088 received a tentative approval letter that stated, "final approval is subject to expiration of a period of patent protection and/or exclusivity for Jatenzo (testosterone undecanoate) oral capsule (NDA 206089)". Per the Orange Book, the exclusivity expiration date for Jatenzo is March 27, 2022. Also, we note that on October 26, 2021, the ownership of NDA 208088 was transferred from Lipocine Inc to Antares Pharma, Inc.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We re-evaluated the container label, PI, and MG to determine if our previous recommendations were implemented.

In addition to the changes noted by the Applicant, we note the following additional changes have been made to the container label, PI and MG labeling since our last review:[f]

- The following statements are no longer present on the container label:
  - "(b) (4)."
  - "(b) (4)."
    - We find this is consistent with the reference product, Jatenzo.
- The following statement has been added to the container label:
  - "Do NOT flush unused product."
- The storage temperature on the container label and in the PI have been revised from "(b) (4)" to "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)"
- The storage temperature in the medication guide has been revised from "(b) (4) (b) (4)" to "Store TLANDO at room temperature between 68°F to 77°F (20°C to 25°C)."

We find these changes acceptable from a medication error perspective.

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[d] Baugh, D. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 20. RCM No.: 2019-1011.

[e] Baugh, D. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 09. RCM No.: 2019-1011-1.

[f] Baugh, D. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 15. RCM No.: 2020-487.

Additionally, we note Antares highlighted the following changes on the container label with numbered red arrows:

Before Revisions by Antares	After Revisions by Antares
(b) (4)	

However, in the above images they did not identify that they changed the area to the right of the barcode, where the placeholder for components of the product identifier was located. We note that it now appears as a black rectangle with the GTIN outside of it, while the placeholder for the 2D data matrix barcode, Serial Number, Lot Number, and Expiration Date are now no longer present. Thus, we provide a comment to the Antares below to confirm that they will include the 2D data matrix barcode, Lot number, and expiration date in the bottom right corner of the label.

4 CONCLUSION

Our review of the PI and MG did not identify any medication error concerns. As such, we have no recommendations for the division at this time.

However, the revised container label is unacceptable from a medication error perspective because the following components of the product identifier are no longer present: 2D Data Matrix barcode, Serial Number, Lot Number, and Expiration Date. This information is required per the DSCSA, thus, we recommend Antares confirm the inclusion of this information on the label in Section 5 below.

5 RECOMMENDATIONS FOR ANTARES PHARMA, INC.

We recommend the following be implemented prior to final approval of this NDA:

Container Label

A. As currently proposed on the container label, we note that you have replaced the placeholder for components of the product identifier (i.e., 2D Data Matrix barcode, Serial Number, Lot Number, and Expiration Date) with a black rectangular box.

   In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA).[g] The Act requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to each package and

[g] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.

We recommend that you review the draft guidance. We request you add or confirm that there is a placeholder for the human-readable and machine-readable (2-D data matrix barcode) product identifier to the carton labeling. The DSCSA guidance on product identifiers recommends the format of the human-readable portion be located near the 2D data matrix barcode as follows:

- NDC: [insert NDC]
- Serial: [insert serial number]
- LOT: [insert lot number]
- EXP: [insert expiration date]

B. The format for the expiration date is not defined. Thus, we are unable to assess the expiration date format from a medication error perspective.
Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 28, 2022

- Prescribing Information and Medication Guide (image not shown): \\CDSESUB1\evsprod\nda208088\0080\m1\us\114-labeling\114a-draft-label\package-insert-mg-annotated.pdf

Container label

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/s/

JUSTINE H KALONIA
03/03/2022 12:15:21 PM

STEPHANIE L DEGRAW
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 2, 2022

To: Martin E. Kauffman, M.D.
Division of Urology, Obstetrics and Gynecology (DUOG)

Jeannie M. Roule, Regulatory Project Manager, DUOG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TLANDO (testosterone undecanoate) capsules, for oral use, CIII

NDA: 208088

In response to DUOG's consult request dated January 28, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide and carton/container labeling for the original NDA submission for TLANDO (testosterone undecanoate) capsules, for oral use, CIII (Tlando). Please note that this application received tentative approval during the first review and the current review is for the full approval of the application.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Jeannie Roule) on February 24, 2022, and are provided below at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on January 28, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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/s/

ELVY M VARGHESE
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 14, 2020
To:	Jeannie Roule Regulatory Project Manager **Division of Urology, Obstetrics, and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TLANDO (testosterone undecanoate)
Dosage Form and Route:	capsules, for oral use, CIII
Application Type/Number:	NDA 208088
Applicant:	Lipocine Inc.

1 INTRODUCTION

On February 28, 2020, Lipocine Inc. submitted for the Agency's review a Complete Response (class 2 resubmission) of their original New Drug Application (NDA) 208088 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmestic Act for testosterone undecanoate, capsules for oral use. The Agency issued a Complete Response (CR) Letter dated November 08, 2019 due to several clinical deficiencies. The proposed indication for TLANDO (testosterone undecanoate) capsules is testosterone replacement therapy in adults, 18 years or older, males for conditions associated with a deficiency of absence of endogenous testosterone - primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Urology, Obstetrics, and Gynecology (DUOG) on March 10, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TLANDO (testosterone undecanoate) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft TLANDO (testosterone undecanoate) MG received on February 28, 2020, and received by DMPP and OPDP on August 7, 2020.
- Draft TLANDO (testosterone undecanoate) Prescribing Information (PI) received on February 28, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 11, 2020.
- Approved JATENZO (testosterone undecanoate) comparator labeling dated March 27, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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SHARON W WILLIAMS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 4, 2020

To: Martin E. Kauffman, M.D.
Division of Urology, Obstetrics and Gynecology (DUOG)

Jeannie M. Roule, Regulatory Project Manager, DUOG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for for TLANDO (testosterone undecanoate) capsules, for oral use, CIII

NDA: 208088

In response to DUOG's consult request dated March 10, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide and carton/container labeling for the original NDA submission for TLANDO (testosterone undecanoate) capsules, for oral use, CIII (Tlando).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Jeannie Roule) on July 31, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Container Labeling: OPDP has reviewed the attached proposed carton/container labeling submitted by the Sponsor to the electronic document room on July 28, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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ELVY M VARGHESE
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MEMORANDUM

REVIEW OF LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 15, 2020
Requesting Office or Division:	Division of Urology, Obstetrics and Gynecology (DUOG)
Application Type and Number:	NDA 208088
Product Name and Strength:	Tlando (testosterone undecanoate) capsules, 112.5 mg
Applicant/Sponsor Name:	Lipocine Inc.
OSE RCM #:	2020-487
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant re-submitted their Tlando label and labeling on February 28, 2020 for NDA 208088 as a part of their Class-2 resubmission. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the label and labeling for Tlando (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

We re-evaluated the container label, medication guide (MG), and the prescribing information (PI) to determine if our previous recommendations were implemented.[abc]

The Applicant implemented all of our recommendations for the container label and we have no additional recommendations for the container label at this time.

However, we find that our previous recommendations for improvements to the prescribing information were not implemented and we repeat them in Section 3 below. Additionally, we

[a] Baugh D. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Feb 16. RCM No.: 2017-1641.

[b] Baugh D. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 20. RCM No.: 2019-1011.

[c] Baugh D. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Sep 09. RCM No.: 2019-1011-1.

identified one area for improvement in the Medication Guide and provide our recommendation below.

3 RECOMMENDATIONS FOR THE DIVISION OF UROLOGY, OBSTRETICS AND GYNECOLOGY

We ask that you consider the following recommendations prior to approval of this NDA:

A. Prescribing Information

1. Dosage and Administration (Highlights of Prescribing Information [HPI] and Section 2 of the Full Prescribing Information [FPI])
    a. The dosage and administration instructions do not indicate the route of administration, which may pose risk of wrong route of administration medication errors. The route of administration ('orally') should be included in the dosage and administration sections of the HPI and PI. For example, consider revising the statement '(b) (4) ' to read 'The recommended dose of TLANDO is 225 mg testosterone undecanoate taken orally twice daily with food'.
    b. Important administration statements (i.e., 'Swallow capsules whole. Do not chew, dissolve, or open capsule') are not included in the Dosage and Administration subsections of the HPI and the FPI. To decrease the risk of wrong technique medication errors during administration, consider adding the following statement to the dosage and administration sections of the PI: 'Swallow capsules whole. Do not chew, dissolve, or open capsules.'
2. How Supplied/Storage and Handling (Section 16 of the FPI)
    a. Section 16 ('How Supplied') is missing a description of the packaging configuration (i.e., bottle of 120 capsules) and important product identifier information (i.e., NDC number), which may contribute to confusion or risk of medication errors. Consider revising Section 16 to read: TLANDO (testosterone undecanoate) capsules are available in 112.5 mg. Capsules are packaged as 120 units in HDPE bottles with a foil liner and a child resistant cap (b) (4)

       112.5 mg capsules have a white opaque body and a grey opaque cap imprinted with "112" printed in black ink on the body with a (b) (4) colorless band.

3. Patient Counseling Information
    a. Section 17.3 (Patient Should be Advised of the Following Instructions for Use) is missing important administration instructions (i.e., 'Swallow

capsules whole. Do not chew, dissolve, or open capsule'). To ensure safe use of the product and to align with the container label, consider revising section 17.3 ([(b) (4)] to include the statement: 'Swallow capsules whole. Do not chew, dissolve, or open capsules.'

B. Medication Guide

1. The "How should I take TLANDO?" section of the Medication Guide is missing important administration instructions (i.e., 'Swallow capsules whole. Do not chew, dissolve, or open capsule'). To ensure safe use of the product and to align with the container label, consider revising section 17.3 [(b) (4)] [(b) (4)] to include the statement: 'Swallow capsules whole. Do not chew, dissolve, or open capsules.'

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 17, 2019

TO: Hylton Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)
Office of Drug Evaluation III
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of South Florida Medical Research, Aventura, FL and Granger Medical Clinic, Riverton, UT

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study LPCN 1021-18-003 (NDA 208088) conducted at South Florida Medical Research, Aventura, FL and Granger Medical Clinic, Riverton, UT.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI) for South Florida Medical Research, Aventura, FL and Granger Medical Clinic, Riverton, UT.

1.1. Recommendation

After reviewing the inspectional findings, I conclude the data from the audited study are reliable to support a regulatory decision. However, the actual elapsed time between sample collection and start of centrifugation for each blood collection tube at South Florida Medical Research is unknown.

2 Inspected Studies:

NDA 208088

Study Number: LPCN 1021-18-003
Study Title: "Study of Blood Collection Tubes Following Single Dose Administration of Oral Testosterone Undecanoate (TU, LPCN 1021)"

Clinical Site #1 (Site 207):
South Florida Medical Research
21150 Biscayne Blvd., Suite 300
Aventura, FL
Dates of study conduct: 11/14/2018 – 11/27/2018
Principal Investigator: Marc C. Gittelman, M.D., FACS

Clinical Site #2 (Site 218):
Granger Medical Clinic
12391 South 4000 West
Riverton, UT
Dates of study conduct: 11/08/2018 – 11/20/2018
Principal Investigator: Stephen B. Devenport, M.D.

South Florida Medical Research, Aventura, FL
ORA investigator Shirley S. Wen (BIMOE) inspected South Florida Medical Research, Aventura, FL from August 26-29, 2019.

Granger Medical Clinic, Riverton, UT
ORA investigator Jonathan R. Campos (BIMOW) inspected Granger Medical Clinic, Riverton, UT from September 3-6, 2019.

The inspections included a thorough examination of study records, subject records, informed consent process, institutional review board approvals, and blood sample processing times.

3 Inspectional Findings

South Florida Medical Research, Aventura, FL
At the conclusion of the inspection, investigator Wen did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, two items were discussed with South Florida Medical Research's management. The discussion items, site's response during the inspection and my evaluation follow.

Discussion item 1:
According to the protocol section 9.2.3. Blood Sampling, the blood samples needed to be centrifuged at approximately 1300 g at refrigerated conditions (2-8℃). In the visit source documentation, the study coordinator only recorded the duration time of sampling, holding time on ice and centrifugation and plasma harvesting. I was not able to verify the speed or temperature conditions during the centrifugation of the blood samples.

Site's Response:
The site management acknowledged that they would take these into their consideration and improve their activities.

OSIS Evaluation:
Documentation was not available to confirm the centrifugation speed. However, the sampling start and end times, centrifugation start and end times, and centrifugation temperature were documented.

For each sampling time point, it appears the specific blood collection start and stop times were not documented for each blood collection tube. For example, the start time of pre-dose samples was (b) (6) and the end time was (b) (6) for all sample collection tubes for one subject (**Attachment-1**). Thus, the actual elapsed time between the duration of sample collection and start of centrifugation for each blood collection tube is unknown. OSIS recommends that the review division evaluate the CRFs submitted to the NDA to further assess the impact of this finding.

Discussion item 2:
The test tubes for blood collection were provided by the sponsor and the remaining amount of test tubes were destroyed after the completion of the study. The site did not maintain the packing list. I was not able to confirm what types of test tubes were used for the study.

Site's Response:
The site management acknowledged that they would take these into their consideration and improve their activities.

OSIS Evaluation:
Documentation was not available to confirm the blood collection tubes used by the site. However, the sample collection sheet for one subject (**Attachment-1**) supports that samples were collected and processed in the appropriate tube types.

Granger Medical Clinic, Riverton, UT
At the conclusion of the inspection, investigator Compos did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

The ORA investigator expressed concerns with multiple instances of correction of errors (**Attachment-2**). However, the firm used good documentation practices and the corrections have no impact on the data integrity.

4 Conclusion:

After reviewing the inspectional findings, I conclude the data from clinical study LPCN 1021-18-003 are reliable to support a regulatory decision. However, the actual elapsed time between sample collection and start of centrifugation for each blood tube is unknown at South Florida Medical Research and the review division should evaluate the impact of this finding.

Srinivas R. Chennamaneni, Ph.D.
Staff Fellow

Final Classification:

NAI – South Florida Medical Research
Aventura, FL
FEI#: 3006092446

NAI – Granger Medical Clinic
Riverton, UT
FEI#: 3011701743

cc:
OTS/OSIS/Kassim/Arindam/Mitchell/
Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Au/Ayala/Biswas/Chennamaneni
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Draft: SRC 10/7/2019, 10/16/2019
Edit: GB 10/9/2019, 10/16/2019; SA 10/11/2019, 10/16/2019, 10/17/2019; CRB 10/17/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/ South Florida Medical Research, Aventura, FL, USA/FY19: 26-AUG-2019/Post-inspection Folder/EIR & EIR Review
/Granger Medical Clinic - Riverton, Riverton, UT, USA/FY19: 03-SEP-2019/Post-Inspection Folder/EIR & EIR Review

OSIS File #: BE 7072

FACTS: 11938164

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/s/

SRINIVAS RAO N CHENNAMANENI
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GOPA BISWAS
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CHARLES R BONAPACE
10/17/2019 06:36:20 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 16, 2019

To: Hylton V. Joffe, M.D., M.M.Sc, Director
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff (CSS)

From: Joshua Hunt, PharmD., Senior Regulatory Reviewer
Controlled Substance Staff (CSS)

Indication: testosterone replacement therapy
Dosages: oral capsules, 225mg (twice daily)
Drug substance: testosterone undecanoate (TLANDO)
Sponsor: Lipocine, Inc.

Materials Reviewed: NDA 208088 Complete Response (CR) resubmission from Sponsor

Review and Conclusions:

The Division of Bone, Reproductive and Urologic Products (DBRUP, or the Division) consulted CSS on May 10, 2019, regarding NDA 208088. Tlando contains testosterone undecanoate, a prodrug of testosterone which is a Schedule III controlled substance as defined under the Anabolic Steroids Control Act (effective 1991).

Due to outstanding clinical deficiencies, DBRUP plans to issue a Complete Response (CR) letter for this New Drug Application (NDA). This will represent the third CR action for this NDA. CSS defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the CR letter. We request that the Division consult CSS again if the NDA is re-submitted.

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/s/

JOSHUA S HUNT
10/17/2019 09:36:10 AM

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10/17/2019 01:19:04 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 16, 2019

To: Jeannie Roule, Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208088
OPDP labeling comments on TLANDO (testosterone undecanoate)

This memo is in response to DBRUP labeling consult request dated May 10,2019. Due to outstanding deficiencies, DBRUP plans to issue a Complete Response letter. Therefore, OPDP defers comments on the proposed labeling at this time and request that DBRUP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Jina Kwak at (301) 796-4809 or jina.kwak@fda.hhs.gov

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/s/

JINA KWAK
10/16/2019 03:02:48 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	October 16, 2019
To:	Hylton Joffe, MD Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	TLANDO (testosterone undecanoate)
Dosage Form and Route:	capsules, for oral use CIII
Application Type/Number:	208088
Applicant:	Lipocine Inc.

1 INTRODUCTION

On May 8, 2019, Lipocine Inc. resubmitted for the Agency's review a 505 (b)(2) NDA 208088 for LPCN 1021 (testosterone undecanoate) capsules. The applicant originally submitted this Application on August 28, 2015. The Agency issued a complete response letter on May 5, 2018 based on several clinical deficiences. Based on discsussions between the Applicant and DBRUP following the July 19, 2018 post-action meeting, the Applicant addressed all of the Division's comments and resubmitted the Application. TLANDO (testosterone undecanoate), capsules, for oral use CIII is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. On May 13, 2019, the Division of Bone, Reproductive and Urologic Products (DBRUP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TLANDO (testosterone undecanoate).

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for TLANDO (testosterone undecanoate).

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

AMANPREET K SARAI
10/16/2019 01:32:39 PM

MARCIA B WILLIAMS
10/16/2019 01:44:13 PM

LASHAWN M GRIFFITHS
10/16/2019 01:46:12 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 9, 2019
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 208088
Product Name and Strength:	Tlando (testosterone undecanoate) capsules, 112.5 mg
Applicant/Sponsor Name:	Lipocine Inc.
OSE RCM #:	2019-1011-1
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on September 3, 2019 for Tlando. The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised container label for Tlando (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Baugh D. Label and Labeling Review for Tlando (NDA 208088). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 20. RCM No.: 2019-1101.

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

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/s/

DENISE V BAUGH
09/09/2019 12:45:56 PM

BRIANA B RIDER
09/09/2019 08:20:14 PM

Interdisciplinary Review Team for Ambulatory Blood Pressure Monitoring (ABPM) Study Consultation Review

Submission	NDA 208088
Submission Number	051
Submission Date	5/9/2019
Date Consult Received	5/10/2019
Clinical Division	DBRUP

This review responds to your consult regarding the sponsor's ABPM evaluation. The IRT reviewed the following materials:

- LPCN 1021-18-001 study report (NDA 208088 / SDN 51; link);
- DCRP reviews for IND 106476 by Dr. Senatore dated 3/3/2018 and 7/13/2018 in DARRTS; and
- Complete Response letters issued by DBRUP dated 6/28/2016 and 5/8/2018.

1 SUMMARY OF FINDINGS

A dedicated ABPM study was conducted for LPCN 1021 (oral testosterone undecanoate, TU) to characterize the effects of chronic dosing LPCN 1021 on blood pressure (BP) in hypogonadal men. The study was an open-label, multicenter, single arm study evaluating the BP and heart rate (HR) change from baseline to 4-months post-treatment. The overall findings of the study show an increase in average 24-hour systolic BP (SBP, primary endpoint), diastolic BP (DBP) and HR. LPCN 1021 increased SBP by an average of 4.3 mmHg based on ABPM and by an average of 4.8 mmHg based on office cuff measurements (Table 1). The increase in BP was relatively constant throughout a day. LPCN 1021 also increased HR by an average of 2 bpm.

The exploratory subgroup analysis suggested that the effect of BP, particularly SBP, was larger in subjects with higher baseline cardiovascular (CV) risk, *e.g.*, subjects with multiple CV risk factors at baseline (Table *2*).

In summary, the results of the study demonstrated an increase in average BP and HR in hypogonadal men treated with LPCN 1021 and the mean effects were in general consistent with the results observed in another oral TU product suggesting a class BP effect.

Table 1: Mean and 95% CI for change from baseline in systolic BP, diastolic BP and HR on Visit 5 (FDA analysis, modified 24-h validity set)

Parameter	BP Method	Δ (mmHg)	95% CI (mmHg)
Systolic BP	ABPM 24-h average[a]	4.3	(2.1, 6.5)
	Cuff measurement[b]	4.8	(2.7, 6.9)
Diastolic BP	ABPM 24-h average[a]	1.4	(0.5, 2.3)
	Cuff measurement[b]	1.6	(0.3, 2.9)
HR (bpm)	ABPM 24-h average[a]	2.1	(1.0, 3.1)
	Cuff measurement[b]	2.0	(0.4, 3.6)

[a] ABPM analysis was conducted using modified 24-h validity set (n = 123)
[b] Vital sign measurements were recorded in triplicate 2 hours prior to start of the ABPM (safety analysis set, n =138)

Table 2: Sub-group analysis based on cardiovascular risk level at baseline for 24-h average SBP (FDA Analysis, modified 24-h validity set)

	Δ (95%CI) (mmHg)	
	Systolic BP 24-h average	**Diastolic BP 24-h average**
Overall (N = 123)	4.3 (2.1, 6.5)	1.4 (0.5, 2.3)
Baseline CV risk level[a]		
Low (20%); n=24	-1.5 (-6.5, 3.6)	-0.3 (-2.4, 1.8)
Moderate (39%); n=48	3.3 (-0.1, 6.7)	2.1 (0.6, 3.5)
High (41%); n=51	8.0 (4.4, 11.6)	1.5 (0.1, 2.9)

[a] Risk level was assigned using risk scores derived based on Framingham Heart Study. Low risk: risk point <9; Moderate risk: risk point 9-14; High risk: risk point ≥15

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

No additional post-approval studies are recommended.

2.2 PROPOSED LABEL

The sponsor included a boxed warning regarding the BP increases (the same language used in the JATENZO label) and described relevant information in sections 5 and 6. Below are proposed edits to the label submitted to SDN 51, eCTD 0050 (link) from the IRT.

Our proposed changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

Reviewer's comments: We recommend changing the average BP effect for ABPM. We do not agree with the sponsor's post-hoc ABPM data selection criteria which excluded 5 subjects from their primary analysis. Our analysis was based on mean 24-h average of SBP in subjects who had acceptable ABPM data based on the pre-specified validity criteria (n = 123).

We did not review the original efficacy trial (the 52-week trial) but do not think that the information about changes in antihypertensive medications is particularly useful.

(b) (4)

[redacted]

Reviewer's comments: We modified the ABPM results based on our analyses. We also recommend including the text regarding the results of baseline CV risk subgroup. We did not include the results of other individual subgroups (e.g. age, hypertension, diabetes etc.) because of coexistence of these subgroups in the study population (i.e., CV risk factors frequently occur in combination). For example, majority of subjects with diabetes also had hypertension at baseline. Reporting subgroup analysis based on baseline CV risk profile provides overall results by considering multiple CV risk factors at the same time.

We deleted the last sentence because the analysis was not particularly informative, and the results could be bias due to regression to the mean.

3 BACKGROUND

3.1 REGULATORY HISTORY

Lipocine, Inc developed an oral testosterone undecanoate formulation (TU, LPCN 1021, Tlando®) for the indication of replacement therapy in males with primary or secondary hypogonadism. The recommended dose of LPCN 1021 is 225 mg taken twice daily with food.

NDA 208088 was originally submitted in 2015 and received a complete response (CR) by DBRUP because of the concerns related to the proposed titration scheme. The applicant resubmitted NDA 208088 in August 2017 after conducting two new 24-days, single arm, phase 3 studies and subsequently received a CR in May 2018. Part of the CR included a requirement for an ambulatory blood pressure monitoring (ABPM) study to assess whether the to-be-marketed dose of LPCN 1021 increases blood pressure (BP) in hypogonadal men. The concern was that there may be a class BP effect of TU based on the newly available ABPM data from another orally administered TU (JATENZO) product[1]. Office visit blood pressure data measured in the LPCN 1021 program was insufficient to characterize the BP effect of chronic dosing of LPCN 1021.

In response to the requirement, the applicant proposed to conduct a dedicated ABPM study LPCN 1021-18-001. DCRP had previously reviewed the ABPM protocol dated 3/3/2018 and 7/13/2018 with the intention to ascertain alignment of the protocol with a previous ABPM study performed by Clarus Therapeutics supporting NDA 206089 for their oral TU produce (JATENZO). There were two main protocol changes according to the DCRP's comments: (1) the study duration was extended from 24 days to 4 months and (2) the study sample size was increased from N =75 to N =135 to rule out a 4 mmHg rise in SBP with 95% confidence interval.

Lipocine initiated the ABPM study LPCN 1021-18-001 on 9/5/2018 and submitted the results of the study (SDN 51 [eCTD seq 0050]) on 5/9/2019. DBRUP requested DCRP's inputs on the adequacy of the study and clinical significance of the results, and any recommendations for labeling and post-approval requirements.

3.2 REVIEW OBJECTIVES

The IRT review focused on the following issues:

- To evaluate the effect of LPCN 1021 on BP and HR after 4 months of treatment.
- To determine whether there are subgroups with increased risk for increase in BP and HR.

4 STUDY LPCN 1021-18-001

4.1 DESIGN

This was an open-label, multicenter, single arm study in hypogonadal male subjects. The study included a collection of 24-h ABPM recordings at baseline and at visit 5 (~4 months post-dose).

[1] https://www.fda.gov/advisory-committees/bone-reproductive-and-urologic-drugs-advisory-committee-formerly-reproductive-health-drugs-advisory/2018-meeting-materials-bone-reproductive-and-urologic-drugs-advisory-committee-formerly-advisory

4.2 POPULATION

The study enrolled male subjects between 18 and 80 years who were diagnosed to be primary or secondary hypogonadal.

The exclusion criteria relevant to the evaluation of ABPM include:

- Subjects with screening SBP or DBP above 160 mmHg or 100 mmHg, respectively; and
- Subjects who were not on stable dose of current medication (no changes in medication in the last 3 months).

4.3 ABPM RECORDINGS

Subjects were confined in the clinic for ABPM recordings at Visit 3 (baseline, Day -4) and at Visit 5 (~4 months post-dose, Day 107). For majority of subjects, ABPM recordings started in the morning at around 7 am following the administration of study drug. The ABPM recordings included collection of measurements every 15 min during daytime hours (7 am to 11 pm) and every 20 min during nighttime hours (11 pm to 7 am). A repeat ABPM measurement was performed if subjects did not have a valid ABPM recording determined by a central reader.

Vital sign measurements were also recorded about 2 hours prior to the start of each ABPM. Office BP and HR were measured in triplicate over a minimum of approximately 10 minutes after the subject had rested in a sitting position for at least 10 minutes.

4.4 ABPM DATA VALIDITY AND DATA SELECTION

For the 24-hour ABPM results to be qualified as valid, the data had to meet the following criteria:

- Minimum of 1 valid reading per hour, including during sleep; and
- Valid data for at least 22 out of 24 hours in the day.

In addition to the data validity criteria, 24-hour ABPM measurements were selected as stated below:

- If the first measurement starts at 7 AM on ABPM Day 1, select all measurements between 7 AM on ABPM Day 1 and 6:59 AM on ABPM Day 2.
- If the last measurement ends before 7 AM on ABPM Day 2 (e.g. 6:30 AM), all measurements in the 24-hour interval prior to the last measurement will be selected, e.g. 6 AM on ABPM Day 1 to 5:59 AM on ABPM Day 2.
- If the last measurement ends after 7 AM on ABPM Day 2, select all measurements between 7 AM on ABPM Day 1 and 6:59 AM on ABPM Day 2.

Reviewer's Comment: The ABPM validity criteria were rather stringent compared to the conventional criteria (e.g., at least 70% of all readings). However, the criteria were prespecified in the protocol and similar to those used in the ABPM study for JATENZO. DCRP had previously reviewed the protocol and accepted the criteria. For this reason, we are fine that the ABPM analysis was performed in this subset. However, we do not agree with the applicant's post-hoc data selection criteria, which were added in the second version of SAP, dated 1/23/2019. Particularly, for subjects who started an ABPM session after 7 am on Day 1, the

third criterion throws away any measurements collected after 6:59 am on Day 2. This ABPM data selection criteria are not justifiable considering that the protocol allows subjects to start the ABPM session in the evening at Visit 5. Those subjects would be excluded from the analysis because of the combination of this post-hoc data selection criteria and the validity criteria. In addition, the ABPM data for JATENZO has demonstrated a constant BP effect throughout a day which also does not support the applicant's data selection criteria. The review team is in favor of using all the collected ABPM data regardless start time of the ABPM session.

4.5 ANALYSIS DATASETS

- Full analysis set: all subjects enrolled into the study with ABPM data at Visit 3 and Visit 5.
- 24-hour validity set: subjects with a minimum of 1 valid ABPM reading per hour and valid data for at least 22 out of 24 hours in the day at Visit 3 and Visit 5.

4.6 PRIMARY ENDPOINT AND ANALYSIS

The sponsor proposed to use the change of the time weighted average 24-hour SBP as the primary endpoint. The time weighted average was area under curve (AUC) of BP values divided by time duration.

A linear regression model was used with baseline SBP as a covariate to analyze the primary endpoint in the Full analysis set. The change of 24-hour SBP from baseline to visit 5 is then predicted using the median of SBP at baseline.

Reviewer's Comment: The applicant used the time-weighted average 24-hour SBP (AUC/time) instead of the conventional ABPM primary endpoint— mean average 24-hour SBP. The choice of the primary endpoint was added in the second version of the SAP, which was not reviewed by DCRP but is aligned with the draft FDA guidance[2]. From our experience, the results are very similar between these two endpoints, which is also what was shown in the applicant's CSR. FDA analysis in section 5 was based on the conventional mean average to retain consistency in how we have analyzed ABPM data across programs. Of note, although the applicant stated that the primary analysis would be performed in the Full analysis set, it was actually done using the 24-hour validity set.

4.7 MAIN SECONDARY ENDPOINTS/ANALYSIS

- Change in time-weighted average daytime and nighttime SBP, time-weighted average 24-h, daytime and nighttime DBP
- Change in mean average 24-hour, daytime and nighttime SBP, DBP and HR
- Change in clinical BP and HR

[2] Draft guidance for Industry: Assessment of pressor effects of drugs (May 2018)

4.8 SELECTED SUBGROUP ANALYSIS

- Baseline CV risk level: CV risk scores were derived based on the scoring algorithm described in the Framingham Heart Study[3]. The sponsor then categorized the CV risk into three levels based on selected cut-off thresholds.
    - Low Risk: risk score < 11
    - Moderate Risk: 11≤ risk score <24
    - High Risk: risk score ≥ 24
- FDA requested subgroups:
    - Hypertension
    - Diabetes

Reviewer's Comment: We do not agree with the cut-off thresholds the sponsor used to categorize the CV risk level. The sponsor's rationale for the selected cuff-off thresholds was based on the example described in the draft pressure guidance (Figure 1 in the guidance). The purpose of that example was to illustrate that small sustained increases in BP have a larger impact on patients with higher baseline CV risk. The example should not be used as the basis to categorize an individual's CV risk. For example, the high-risk example in the guidance represents an individual with an extreme high CV risk (i.e. 10-year CV risk > 30%). We have requested the sponsor to submit the original CV risk score and re-categorized the baseline CV risk level based on the definitions used in the ACC/AHA guideline[4] as follows:

Low Risk: risk score < 9, roughly corresponding to 10-year CV risk < 7.5%

Moderate Risk: risk score 9-14, roughly corresponding to 10-year CV risk between 7.5 to 19.9%

High Risk: risk score >=15, roughly corresponding to 10-year CV risk ≥ 20%

5 REVIEWER'S ASSESSMENT

5.1 DEMOGRAPHICS

The study enrolled 144 hypogonadal men with 138 subjects receiving at least 1 dose of study drug (safety set).

Of the 138 subjects in the safety population, 126 subjects had ABPM recordings at baseline and post-treatment and 123 of them had acceptable ABPM data based on the pre-specified data validity criteria (FDA-modified 24-h validity set, see section 5.3). The demographics of the ABPM analysis population are shown in Table 3.

[3] D'Agostino RB et al., General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Circulation 2008; 117:743-753.

[4] Arnett et al, 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Circulation 2019

Table 3: Demographics of Subjects in the FDA-modified 24-h validity set (N = 123)

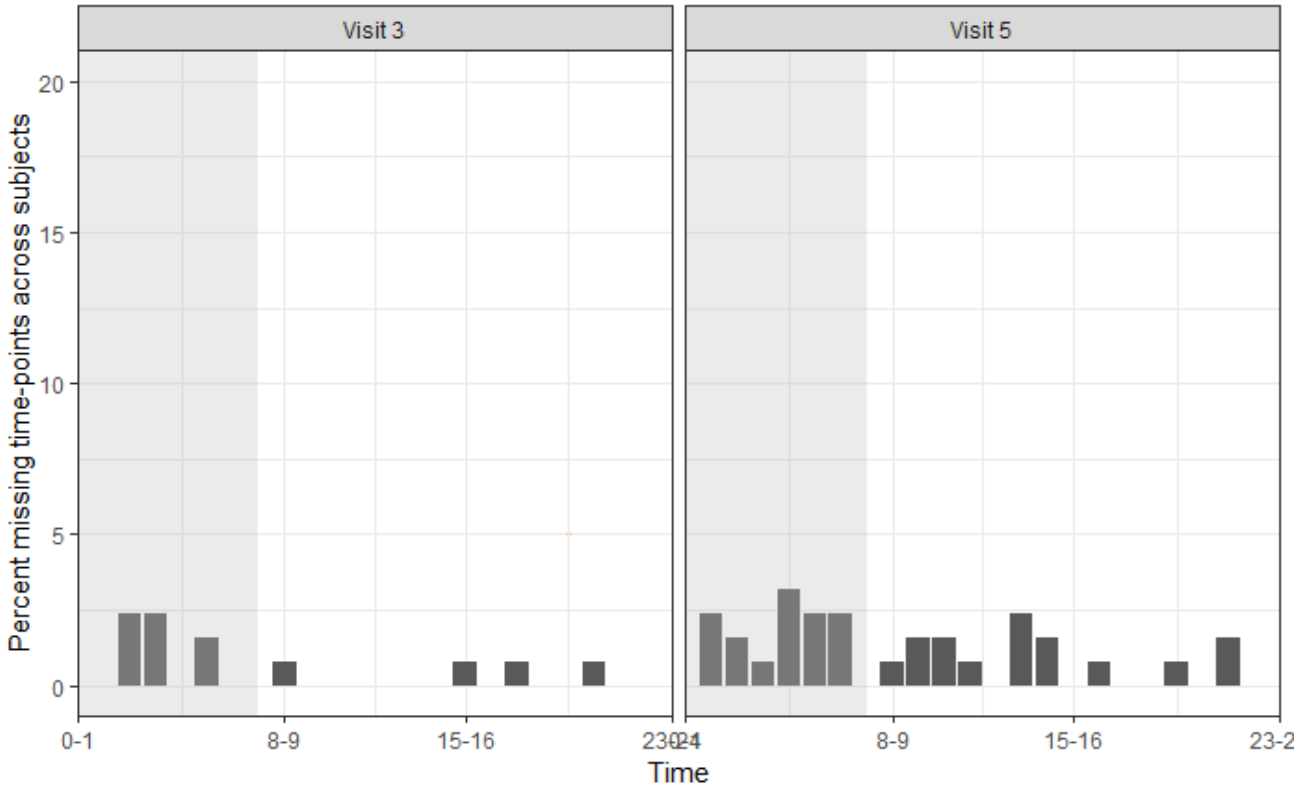
Subgroup	Testosterone Undecanoate (N = 123) n (%)
Age (years)	
Mean	54 ± 9.9
Age Group	
Age < 65	103 (83.7)
Age >=65	20 (16.3)
Race	
Asian	3 (2.4)
Black or African American	22 (17.9)
Other	1 (0.8)
White	97 (78.9)
Diabetes	
N	86 (69.9)
Y	37 (30.1)
Hypertension	
N	63 (51.2)
Y	60 (48.8)
Smoking Status	
Never	84 (68.3)
Current/Past	39 (31.7)
Baseline CV risk	
Low Risk	24 (19.5)
Moderate Risk	48 (39.0)
High Risk	51 (41.5)

Source: Reviewer's Analysis

5.2 DATA QUALITY

In the Full-analysis dataset (n = 126), the percent of missing data was generally less than 5% during the 24 hours on the baseline and post-dose visits (Figure 1), demonstrating good overall data quality.

Figure 1: Percent missing data by time for each visit (Visit 3= baseline; Visit 5 = after 4 months of treatment) for the Full-analysis dataset (N=126). Gray shaded areas represent night.

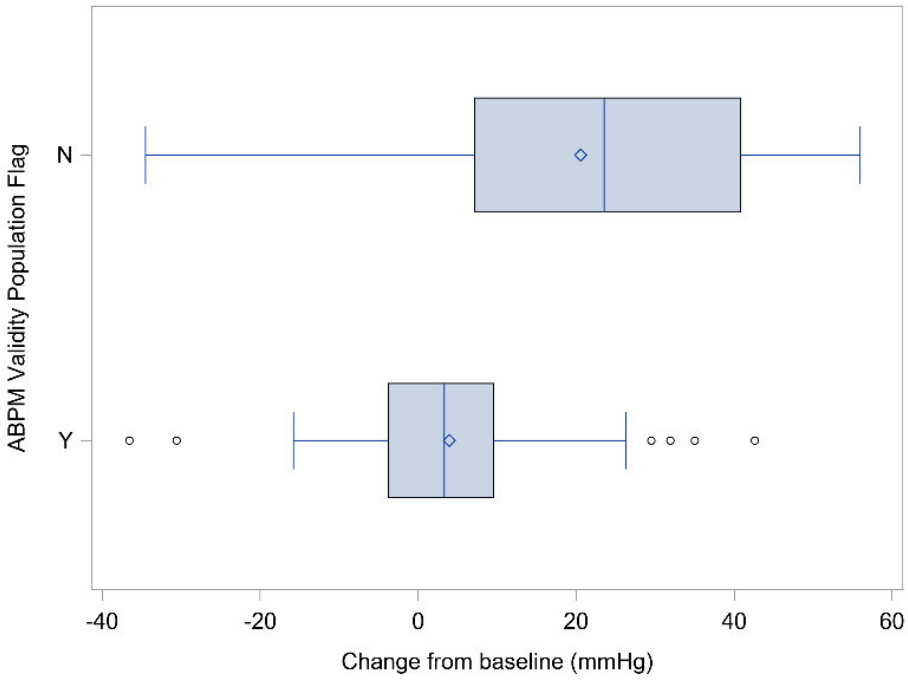


Source: Reviewer's analysis

5.3 CHOICE OF ANALYSIS SET

The applicant stated in the protocol that all ABPM analysis were performed in the Full analysis set (n = 126) but demonstrated their primary analysis using the 24-hour validity set (n =118) [5]. The mean BP change from baseline was notably higher among 8 subjects who were excluded from the Full analysis set (i.e., ABPM validity population = "N") vs. the mean change in the ABPM 24-h validity set (i.e., ABPM validity population = "Y") (Figure *2*).

Figure 2: Mean change from baseline by ABPM validity population



Source: Reviewer's analysis

Among 8 subjects who were excluded from the Full analysis set, 3 subjects were excluded based on the pre-specified 24-h validity criteria and 5 subjects were excluded because of the post-hoc ABPM data selection criteria (see section 4.4. for definition). As noted previously, we do not agree with the post-hoc ABPM data selection criteria and included the 5 excluded subjects in the analysis set.

- Therefore, FDA's ABPM assessment was performed in the modified 24-h validity set defined as: Modified 24-h validity set (n = 123): All subjects whose ABPM data at baseline and Visit 5 met pre-specified 24-h validity criteria regardless start time of the ABPM session.

Sensitivity analyses were also performed using the Full analysis set (n=126) and the sponsor's 24-h validity set (n=118).

[5] The sponsor listed an incorrect number (n =108) for 24-h validity set in Table 13 in CSR.

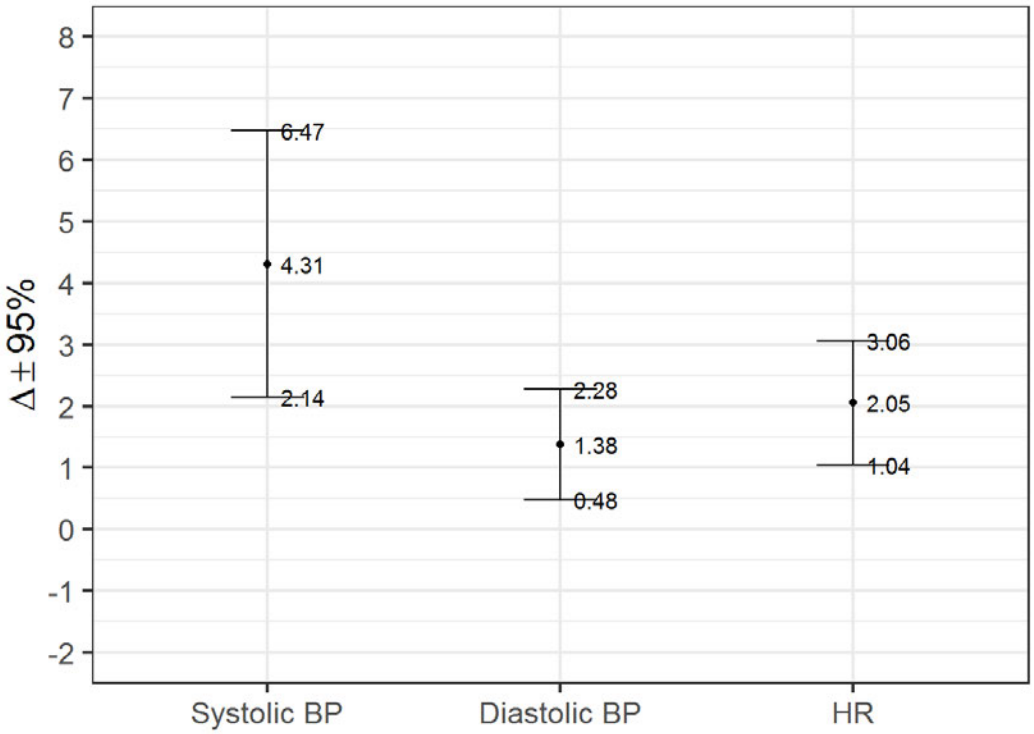
5.4 BLOOD PRESSURE ASSESSMENT

The reviewer analyzed the changes in systolic and diastolic BP and HR using a liner regression model with the corresponding baseline value as a covariate.

Changes from baseline in the mean SBP, DBP, and HR at Visit 5 were calculated and evaluated for the 24-hr (all readings within 24 hours after start of the ABPM), day time (all readings between 7 am to 11 pm) and night time (all readings between 11:01 pm to 6:59 am) for the modified 24-h validity set. The primary analysis shows that LPCN 1021 increased 24-h average SBP by an average of 4.3 mmHg. LPCN 1021 also increases DBP by an average of 1.4 mmHg and HR by an average of 2.1 bpm (*Figure 3*).

Our analysis shows intermediate effect on ambulatory SBP compared to the sensitivity analysis using Full analysis data set (n=126): ΔSBP= 4.88 (2.6, 7.1) mmHg and the sponsor's 24-h validity set (n=118) and ΔSBP= 3.96 (2.0, 5.9) mmHg.

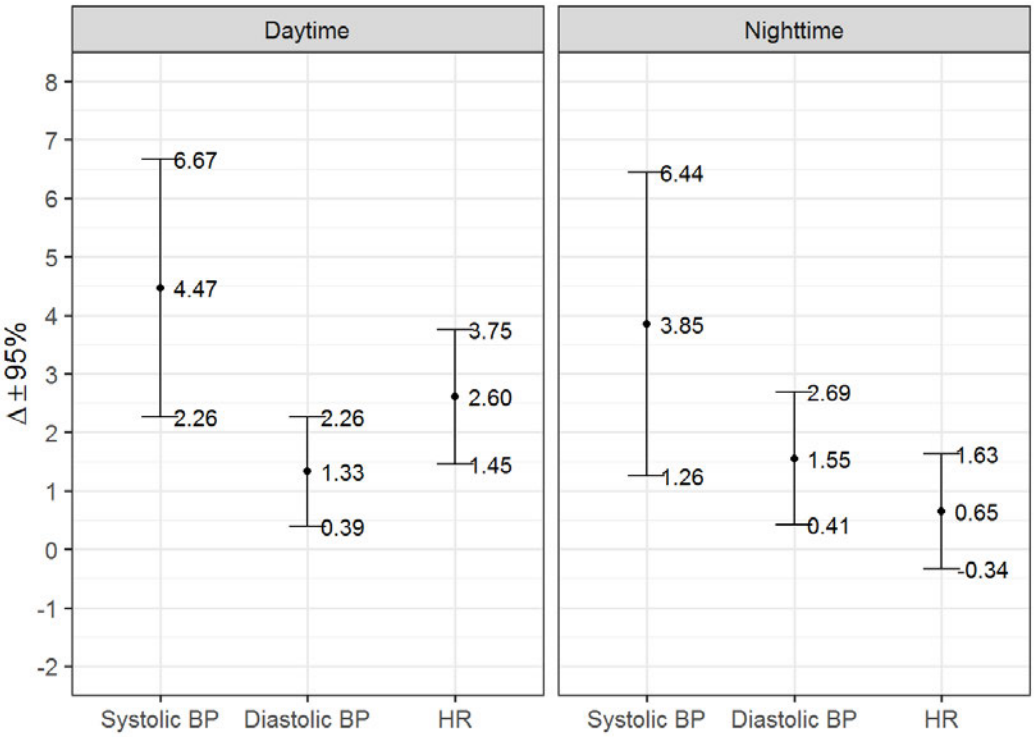
Figure 3: Change in Mean 24-h Average from Baseline at Visit 5 (FDA-modified 24-h validity set, n = 123)



Source: Reviewer's analysis

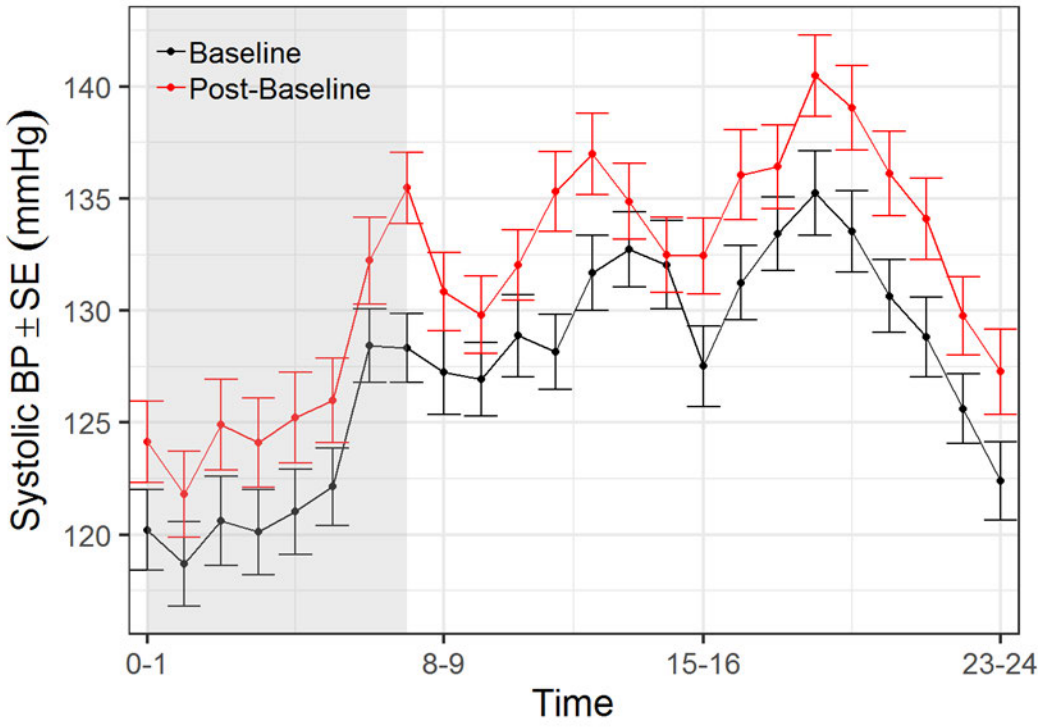
LPCN 1021 increased BP relatively constant throughout a day with increases in SBP by an average of 4.5 mmHg during daytime and 3.9 mmHg during nighttime (Figure 4). The heart rate effect appeared larger during daytime. The effect of LPCN 1021 on the hourly circadian SBP average is shown in Figure 5 which also illustrates a relatively constant upward shift throughout a day. This observation is consistent with what we observed from JATENZO.

Figure 4: Change in Day-time and Night-time average from Baseline at Visit 5 (FDA-modified 24-h validity set, n = 123)



Source: Reviewer's analysis

Figure 5: 24-hour Ambulatory SBP Profile for LPCN 1021 at Baseline and Post-baseline (FDA-modified 24-h validity set, n = 123)



Source: Reviewer's analysis

Table 4 shows subgroup analyses based on age, race, hypertension, diabetes and CV risk at baseline. It is noticed that SBP increases were greater in subjects with race other than white (i.e. 85% is black), subjects with diabetes (i.e., 78% had both diabetes and hypertension at baseline) and subjects with high CV risk at baseline. In particular, CV risk level was assigned based on multiple risk factors at baseline (e.g., age, race, diabetes, hypertension), showing a noticeable trend towards an increase in SBP with advancing CV risk.

Table 4: Subgroup analysis of Average 24-h SBP and DBP (FDA analysis, modified 24-h validity set)

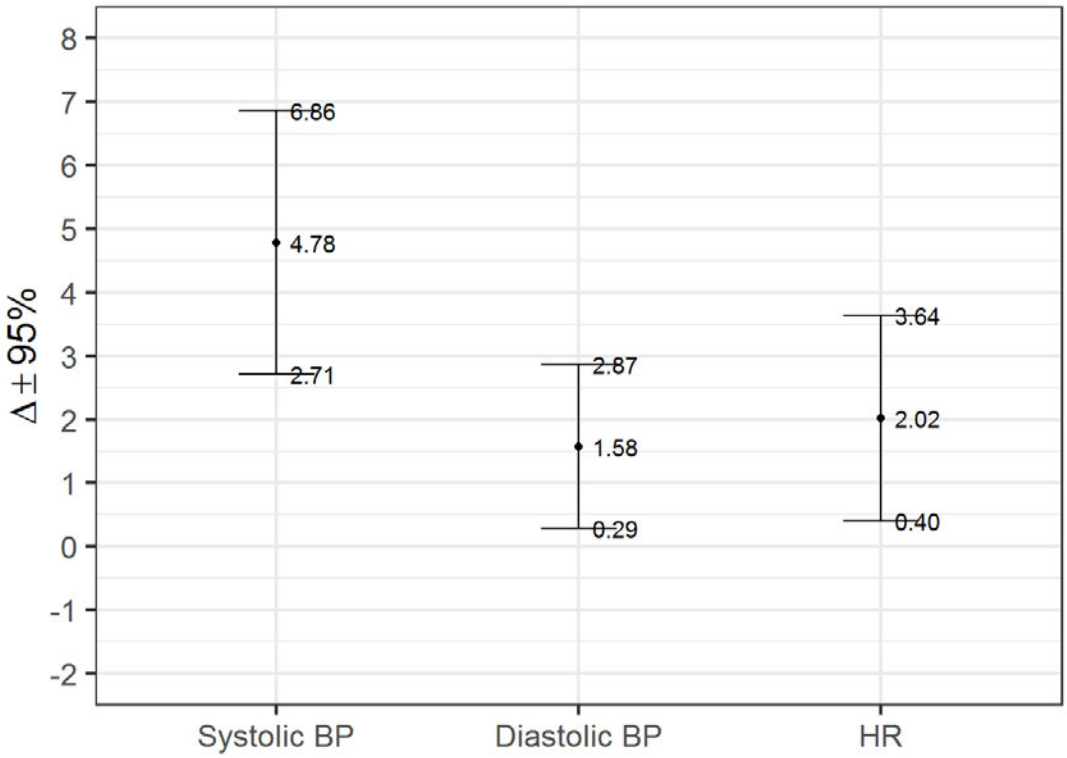
	Change from baseline at Visit 5 Least square mean difference (95% CI)	
	Average 24-h SBP	**Average 24-h DBP**
All population (N = 123)	4.3 (2.1, 6.5)	1.4 (0.5, 2.3)
Age		
≤ 55 years (n = 67)	3.2 (0.3, 6.2)	1.3 (0.1, 2.6)
>55 years (n = 56)	5.6 (2.4, 8.9)	1.4 (0.1, 2.8)
Race		
White (n = 97)	3.3 (0.9, 5.7)	0.9 (-0.1, 1.9)
Other (n = 26)[a]	8.2 (3.4, 12.9)	3.1 (1.1, 5.0)
Hypertension at baseline		
Yes (n =60)	5.6 (2.5, 8.7)	1.6 (0.3, 2.9)
No (n=63)	3.1 (0.1, 6.1)	1.1 (-0.1, 2.4)
Diabetes at baseline		
Yes (n = 37) [b]	9.3 (5.3, 13.3)	2.3 (0.7, 3.9)
No (n=86)	2.2 (-0.4, 4.7)	1.0 (-0.1, 2.1)
CV risk at baseline[c]		
Low risk (n=24)	-1.5 (-6.5,3.6)	-0.3 (-2.4, 1.8)
Moderate risk (n=48)	3.3 (-0.1, 6.7)	2.1 (0.6, 3.5)
High risk (n=51)	8.0 (4.4, 11.6)	1.5 (0.1, 2.9)

[a] 22 out of 26 are black
[b] 29 out of 37 subjects had both diabetes and hypertension at baseline
[c] Risk level was assigned using risk scores derived based on Framingham Heart Study. Low risk: risk point <9; Moderate risk: risk point 9-14; High risk: risk point ≥15
Source: Reviewer's analysis

Reviewer's Comment: *There are noticeable subgroup differences in BP changes based on individual CV risk factors and the baseline CV risk profile. These findings were a bit concerning suggesting a positive trend between BP increases, particularly SBP and baseline CV risk. Hence, the absolute CV risk associated with chronic use of LPCN 1021 can increase in much greater extent in patients with a higher baseline CV risk. We recommend describing the subgroup results in the label.*

Figure *6* shows the changes in BPs and HR based on the clinical vital sign data. These results are consistent with the findings based on ABPM.

Figure 6: Change in Clinical Vital Signs from Baseline at Visit 5 (safety set, n = 138)



[a] Vital signs were measured in triplicate prior to start of the ABPM

Source: Reviewer's analysis

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/s/

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07/16/2019 03:26:38 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: 29 June 2018

From: Fred Senatore, MD, PhD, FACC, Medical Officer
Division of Cardiovascular and Renal Products / CDER

Through: Martin Rose, MD, JD, Team Leader
Norman Stockbridge, MD, PhD, Division Director
Division of Cardiovascular and Renal Products / CDER

To: Jeannie Roule, RPM
Division of Reproductive and Urological Products / CDER

Subject: NDA 208088: Review Applicant's Action Plan to address deficiency #2 (ABPM).

This memo responds to your consult to us dated 14 Jun 2018 and received 21 Jun 2018 requesting our review of the Type A, Post-Action Briefing Package with specific focus on the Applicant's response to deficiency # 2 (lack of ABPM data) described in the CRL and the requisite action item to resolve the deficiency (perform an ABPM study). In the Briefing Package, the Applicant provides rebuttal arguments supporting their position that an ABPM study is not necessary and that their existing blood pressure database is sufficient for approval with a post-marketing commitment to perform an ABPM study.

DCRP received and reviewed the following: 1) your current consult to us, and 2) the Type-A meeting package (\\CDSESUB1\evsprod\NDA208088\208088.enx).

Summary Assessment

The Applicant argued that an ABPM study was not required for the following reasons: 1) There was no blood pressure effect in their 52-week study as well as other studies based on office sphygmomanometry; 2) Blood pressure observations in the JATENZO program was a dose effect rather than a class effect; 3) There is a 20 year historical safety record of oral testosterone; 4) In a post-hoc analysis, the Framingham Risk Score was not impacted using blood pressure data from their 52-week study; and 5) Reasons to perform an ABPM were not

applicable to TLANDO: a) if the nighttime/daytime BP profiles are different; b) if there is a “white coat” effect’ c) if there is a “masked effect”, d) if there were no BP data from multiple office visits (i.e., the ABPM study will simply repeat what is already known); and e) office sphygmomanometry is the standard both in clinical research and for drugs that are not designed to treat hypertension. The 52-week office visit blood pressure data were based on the standard mode of measurement thereby negating the need to perform an ABPM study.

The Applicant is currently performing an ABPM study (LPCN 1021-18-001) and proposes to complete this study as a post-approval commitment.

We reject the Applicant’s arguments and recommend that the Applicant continue the ABPM study already in progress and complete it to provide adequate information in the label.

Background

The Applicant originally submitted NDA 208088 for approval of oral testosterone undecanoate (TLANDO) on 28 Aug 2015. A CRL was issued to the Applicant on 28 Jun 2016. The NDA was amended and re-submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act on 08 Aug 2017.

In January 2018, the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) met to discuss the potential effect of TLANDO on blood pressure. Based on ABPM results from another oral testosterone product (JATENZO/Clarus), the Applicant was advised to perform an adequate pre-approval ABPM study.

In a position document dated 23 March 2018, the Applicant stated that blood pressure was already assessed by office sphygmomanometry throughout TLANDO clinical development, including 7 clinical studies conducted in hypogonadal men and 4 clinical studies conducted in postmenopausal women. Consequently, an ABPM study is not necessary. The Applicant highlighted the following 5 studies regarding TLANDO’s effect on systolic blood pressure:

- M12-778 (March 2011 to September 2011): a randomized double blind placebo-controlled dose escalating study to assess PK, safety, and tolerability. Doses were 75, 150, 225, and 300 mg PO BID for 14-28 days. Eighty-four hypogonadal men were enrolled.
    - Applicant Report: No increase in blood pressure from baseline or difference compared to placebo was observed for at least 15 days.
- LPCN 1021-14-001 (March 2015 to April 2015): an open-label, randomized, 4-period, 4-treatment crossover, single dose bioavailability and PK study to compare the rate and extent of absorption under various food and fat content conditions. A single dose of 225 mg PO was administered. Fourteen hypogonadal men were enrolled.
    - Applicant Report: No blood pressure increase with time over 24 hours was observed.

- LPCN 1021-13-001 (February 2014 to April 2015): a multi-center, randomized, open label, active-control, parallel group, efficacy and safety study to determine the proportion of subjects who achieved a 24-hour average serum testosterone concentration within the target range. TLANDO 225mg and titrated to 150 mg or 300 mg PO BID (as needed) was compared to the active control Androgel 1.62% topical (application frequency not specified in the briefing package) for 52 weeks of treatment. Two-hundred and ten (210) hypogonadal men were enrolled in the TLANDO arm and 105 hypogonadal men were enrolled in the Androgel arm.
    - Applicant Report: A decrease in blood pressure was observed throughout the duration of the study. The mean systolic blood pressure changes from baseline were: Week 3: -0.1 mmHg, Week 7: -0.9 mmHg, Week 13: -0.8 mmHg, Week 26: -1.1 mmHg, Week 39: -0.5 mmHg, Week 52: -0.3 mmHg indicating no long-term trend towards increased blood pressure in patients receiving TLANDO. At Week 3 (N=193/210) the dose was 225 mg BID for all patients (reviewer note: not clear if this dose remained the same throughout).
- LPCN 1021-16-002 (December 2016 to February 2017): a multi-center, open-label, one treatment study to validate a BID dosing regimen to achieve therapeutic concentrations. Doses were 225 mg PO BID for 24 days. Ninety-five hypogonadal men were enrolled.
    - Applicant Report: No increase in blood pressure was observed with TLANDO (mean systolic blood pressure change from baseline: Day 24: -0.5 mmHg, Day 25: +0.2 mmHg).
- LPCN 1021-16-003 (January 2017 to May 2017): a multi-center, open-label, one treatment study to validate a TID dosing regimen to achieve therapeutic concentrations. Doses were 150 mg PO TID for 24 days. One-hundred hypogonadal men were enrolled.
    - Applicant Report: An increase in systolic blood pressure but not diastolic blood pressure was observed (mean systolic blood pressure change from baseline: Day 24: +4.1 mmHg, Day 25: +4.3 mmHg). The Applicant stated that this study did not meet the primary efficacy endpoint and serum T levels were considerably lower than those observed with BID dosing. Moreover, blood pressure was recorded in the morning for the baseline measurements, but was otherwise recorded mid-day for the remaining measurements. In LPCN 1021-13-001 and LPCN 1021-16-002, clinic blood pressures were measured in the morning at baseline and subsequent scheduled visits suggesting that this study was unique and that the observed blood pressure effects were due to timing of measurement.

Another CRL was issued to the Applicant on 18 May 2018. Deficiency # 2 and the requirement to resolve deficiency # 2 as described in the CRL are stated here:

2. **Your drug may cause clinically meaningful increases in blood pressure. This concern is based on newly available ambulatory blood pressure monitoring (ABPM) data with another twice-daily, orally administered testosterone undecanoate product[2] and a signal of a clinically meaningful increase in cuff systolic blood pressure in one of the new Phase 3 trials (LPCN 1021-16-003) included in your resubmission. The information in your application (including your March 23, 2018, position statement on blood pressure) does not definitively resolve this concern. A clinically meaningful increase in blood pressure with your product would be a significant safety concern because this effect, if sustained with chronic therapy, can be reasonably expected to progressively increase the risk of major adverse cardiovascular events (e.g., stroke and myocardial infarction) over time. It is critical to resolve this concern pre-approval because the appropriate regulatory action will depend on the findings, including whether risk mitigation beyond labeling, such as a risk evaluation and mitigation strategy (REMS) could ensure the benefits of the drug outweigh its risks. Therefore, provide definitive evidence pre-approval as to whether your oral testosterone undecanoate formulation causes a clinically meaningful increase in blood pressure.**

Information Needed to Resolve Deficiency #2

Analyses of your existing cuff data, typically obtained once per clinic visit in trials not prospectively designed to definitively characterize the blood pressure effect of your chronically administered product, will not be sufficient to address this deficiency. Conduct an ABPM trial to definitively assess whether the to-be-marketed dose of your product increases blood pressure in hypogonadal men. This trial must be of sufficient duration to evaluate the effects of sustained drug exposure and must ensure that enough subjects have evaluable ABPM data at baseline and end of treatment to adequately characterize your drug's effect on blood pressure. This trial can either be conducted as a stand-alone trial or incorporated into another trial, for example, if a new Phase 3 trial is necessary because of unreliable testosterone data. We strongly recommend that you first resolve the deficiency related to *ex vivo* TU to T conversion before proceeding with this ABPM trial and that you await and adequately address our comments on the protocol before initiating the trial.

In response to deficiency # 2, the Applicant offered 5 rebuttal arguments to support their claim that an ABPM study was not necessary. They also proposed to complete an ongoing ABPM study (LPCN 1021-18-001) as a post-approval commitment. This study was initiated 30 April 2018.

We now review each of the Applicant's arguments and provide our assessment.

Applicant's Rebuttal to CRL Deficiency # 2

1. There was no blood pressure effect in the 52-week study as well as other studies.

Applicant's Argument: as per the position document described above.

DCRP Assessment: Blood pressure effects may be undetectable by office sphygmomanometry because of wide variability. Acquisition of data using this method once per clinic visit is unreliable for a regulatory assessment. An adequate determination of a blood pressure central tendency and spread of effect around the central tendency is best achieved by an ABPM study. Office blood pressure measurements by sphygmomanometry are no longer considered the standard for the diagnosis of hypertension and assessment of cardiovascular risk (https://www.ncbi.nlm.nih.gov/pubmed/26587588).

Please see our response to the Applicant's argument # 2 regarding "class effect" vs a "dose effect."

2. *The increase in blood pressure observed in the JATENZO product is not a class effect but rather a dose effect.*

Applicant's Argument: The JATENZO database showed that a mean dose of 241 mg BID corresponded to a mean clinic SBP increase from baseline of 0.5 mmHg (study 12011); a mean dose of 292 mg BID corresponded to a mean clinic SBP increase from baseline of 2.6 mmHg (study 9007); a mean dose of 325 mg BID corresponded with a mean SBP increase from baseline of 3.0 mmHg (study 15012). These data suggest a dose effect rather than a class effect. Furthermore, TLANDO study LPCN 1021-16-003 which evaluated 150 mg PO TID for 24 days showed a SBP increase of 5 mmHg (SD 11 mmHg). Comparing this to no change in SBP using 225 mg BID for 24 days in study LPCN 1021-16-002 supported the suggestion that blood pressure effects were dose related rather than an oral class related.

DCRP Assessment: JATENZO and TLANDO have the same active ingredient, testosterone undecanoate and are both given by the oral route. Unless proven otherwise, we would expect the two products to have similar effects on blood pressure. JATENZO was shown to increase blood pressure when it was assessed by ABPM which is a more reliable and reproducible method than standard cuff pressure. The blood pressure effects of TLANDO should be evaluated in the same way. If the Applicant wishes to evaluate a dosing distribution of the same total daily dose on blood pressure (i.e., 225 mg BID vs 150 mg TID) on blood pressure, an ABPM study should be conducted with measurements at Tmax for each dosing regimen.

3. *There is a long historical safety record (i.e. 20 years) with oral testosterone marketed outside the US.*

Applicant's Argument: An oral testosterone available outside the USA was evaluated in a cohort study assessing outcomes for almost 20 years and showed that hypertension rates in patients taking oral testosterone were favorable to the rates observed in the overall adult male population in the USA. The study showed the prevalence of hypertension changed from 17% to 20% with oral testosterone therapy (from the foreign epidemiological data), less than the prevalence of hypertension typically observed (29.4% of adult males in the USA) (*Centers for Disease Control and Prevention / National Center for Health Statistics, National Health and Nutrition Survey, Unites States, 2009-2010*).

DCRP Assessment: The Applicant has not provided specifics of the epidemiological study of the foreign data including the specific oral testosterone and its formulation, the patient characteristics and how they are applicable to the US population, how blood pressure was measured as well as the frequency of measurements and the magnitude of the blood pressure elevation. The Applicant's conclusion that TLANDO is safe based on foreign data showing that oral testosterone produced a 3% absolute increase in hypertension in non-US patients but remained below the prevalence of hypertension in the US is questionable.

4. There is no impact on the Framingham Risk Score

Applicant's Argument: A post-hoc analysis was performed using data from the 52-week study LPCN 1021-13-001 to calculate the change in Framingham score after one year of TLANDO treatment. The results showed TLANDO BID therapy over the 52-week study period had no impact on estimated global CV risk change from baseline (mean 0.3 standard deviation 4.5).

DCRP Assessment: The Framingham risk analysis was based on the Applicant's conclusion that there was no change in office cuff blood pressure measurements in the 52-week study. With all other risk factors kept constant, no change in risk is expected. Using the Framingham model, increases in SBP is worse in a high cardiovascular risk patient than in a low cardiovascular risk patient as illustrated in Figure 1. An increase in SBP of 4 mmHg in a patient at low cardiovascular risk will increase that risk by 0.6 events/1000 patient-years. In a patient with higher cardiovascular risk, an increase in SBP of 4 mmHg will increase that risk by 2.2 events/1000 patient-years. These numbers are small, but can have an impact when large numbers of patients take a drug that will increase the blood pressure. To properly assess the cardiovascular risk of TLANDO due to drug-related increases in blood pressure, an ABPM study needs to be performed to properly evaluate the central tendency and spread of effect around the central tendency as a prelude to risk assessment.

Figure 1: Framingham Risk Model and SBP Elevation of 4 mmHg

Risk Factor	Low CV Risk	High CV Risk
Age, y	55	65
Cholesterol, mg/dL	185	240
HDL, mg/dL	43	43
Non-treated SBP, mmHg	127 increased to 131 mmHg	127 increased to 131 mmHg
Smoker, yes (1) or no (0)	0	1
Diabetes, yes (1) or no (0)	0	1
Estimate of 10-y Risk, %	11.2 increased to 11.8	59.5 increased to 61.7
Absolute Risk Difference	0.6 events/1000 pt-yrs	2.2 events/1000 pt-yrs

5. None of the reasons to perform an ABPM study is applicable to TLANDO

Applicant's Argument:

- An ABPM study may be necessary if the nighttime BP profile is expected to show a different change from baseline as compared to the daytime profile: The ABPM data from JATENZO show that the nighttime change in average SBP from baseline was identical to the daytime change from baseline (mean change from baseline for SBP: daytime 5.0 mmHg, nighttime 4.9 mmHg), suggesting that there is no difference in effect on BP between daytime and nighttime. Therefore, an ABPM study is not necessary to evaluate oral testosterone's effect on daytime versus nighttime BP.

- AN ABPM study is typically used to rule out a "white coat effect": Some subjects have lower home/real world BP readings compared to measurements taken when they arrive at the clinic. A "white coat effect" would be expected when BP is measured during a single clinic visit, not over the course of multiple clinic visits. Given that TLANDO was evaluated in a 52-week study in which BP was measured over seven clinic visits, a "white coat" effect is not expected based on the TLANDO BP data. Therefore, an ABPM study is not necessary to evaluate oral testosterone's effect on BP unless multiple clinic visits showed an increase in BP.

- An ABPM study can be used to evaluate a "masked effect": Some subjects have higher home/real world BP readings compared with clinic measurements. If one observes an increase in BP over multiple visits to a clinic, then an ABPM study can show the actual increase is larger than that observed in the clinic. Multiple visits should allow the true BP value to be observed. There was no increase in BP over multiple visits in LPCN 1021-13-001. Therefore, there is no expected masked effect associated with TLANDO.

- The ABPM study will simply repeat what is already known: An ABPM study may change the size of a drug's BP effect, but it does not change the direction of this effect. Therefore, an ABPM study is not necessary unless multiple clinic visits show an increase in BP.

- Office BP measurements are the standard both in clinical research and for drugs that are not intended to treat hypertension. Applying this to TLANDO, an ABPM is not necessary.

DCRP Assessment: We disagree with the Applicant's argument. Please refer to our response under Applicant's argument # 1 and # 2.

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06/28/2018

MARTIN ROSE
06/28/2018

NORMAN L STOCKBRIDGE
06/28/2018

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 6, 2018

To: Hylton V. Joffe, M.D., M.M.Sc, Director
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: Dominic Chiapperino, Ph.D., Acting Director
Controlled Substance Staff (CSS)

From: Joshua Hunt, PharmD, Senior Regulatory Reviewer
Controlled Substance Staff (CSS)

Subjet: CSS review of NDA 208088 Complete Response (CR) resubmission from Sponsor
Drug substance: testosterone undecanoate (proposed name: Tlando)
Dosage/Route of administration: oral capsules, 225mg (twice daily)
Proposed Indication: For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Sponsor: Lipocine, Inc.
675 Arapeen Dr.
Salt Lake City, UT 84108

Materials reviewed:
1) Sponsor Labeling/Package Insert *Draft* October 31nd, 2017 (EDR section 1.14.1.3)

BACKGROUND

The Division of Bone, Reproductive and Urologic Products (DBRUP, or the Division) consulted CSS on August 10, 2017, regarding NDA 208088. This is a resubmission to a CR, which the Sponsor originally received back in June 2016. This 505(b)(2) application was re-submitted to the Agency on August 8, 2017. Subsequently, a public Advisory Committee (AC) Meeting was held by the Agency on January 10, 2018. A significant portion of the AC meeting discussions pertained to an increase in heart rate and blood pressure observed in certain Phase 3 treatment arms. Additional shifts in cholesterol (HDL and LDL) parameters, hematocrit increases, bioanalytical assay measurements, C_{max} outliers, pre-clinical adrenal insufficiency results, and

drug discontinuation criteria were part of the AC meeting agenda. The AC meeting vote was 13-6 against approval.

Joshua Hunt PharmD, CSS Senior Regulatory Reviewer, previously provided a consult review for this NDA, dated April 15, 2016, during the initial submission review cycle. CSS recommended the inclusion of abuse potential updates for Section 9 *Drug Abuse and Dependence* of the label based upon a concurrent Tracked Safety Issue (TSI) review. During the TSI, CSS provided DBRUP with a detailed memorandum outlining a justification for the necessity of updated Section 9 labeling language. In April 2016, CSS noted that DBRUP was actively drafting a "Safety Labeling Change Notification" letter to all applicants of currently approved testosterone drug products. In August 2016, a Safety Labeling Change (SLC) update requirement for Section 9 was sent to all sponsors of approved testosterone products. In their resubmission, the Sponsor of this NDA (Lipocine) did update Section 9 to reflect the labeling language already updated in the labeling of currently marketed testosterone products.

CONCLUSIONS:

TLANDO contains testosterone undecanoate, a prodrug of testosterone which is a Schedule III controlled substance as defined under the Anabolic Steroids Control Act (effective 1991)

RECOMMENDATIONS:

We have no additional recommendations for Lipocine, at this time. It is our (CSS) understanding that further labeling discussions have been canceled and this NDA holder will be receiving a second CR letter. We do request that the Division consult CSS again if the NDA is ever re-submitted. We are currently reviewing other testosterone applications and are considering additional class-wide labeling recommendations.

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/s/

JOSHUA S HUNT
03/06/2018

DOMINIC CHIAPPERINO
03/06/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 16, 2018

To: Jeannie Roule, Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208088
OPDP labeling comments on Testosterone Undecanoate

This memo is in response to DBRUP labeling consult request dated August 10, 2017. Due to outstanding deficiencies, DBRUP plans to issue a Complete Response letter. Therefore, OPDP defers comments on the proposed labeling at this time and request that DBRUP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Jina Kwak at (301) 796-4809 or jina.kwak@fda.hhs.gov

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/s/

JINA KWAK
02/16/2018

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 16, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products
Application Type and Number:	NDA 208088
Product Name and Strength:	Testosterone Undecanoate Capsules, 112.5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Lipocine, Inc.
FDA Received Date:	August 8, 2017
OSE RCM #:	2017-1641
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Bone, Reproductive, and Urologic Products (DBRUP) to review the container label, carton labeling, and prescribing information (PI) submitted August 8, 2017 for testosterone undecanoate (NDA 208088). Lipocine, Inc. submitted labels and labeling in their resubmission after Complete Response (CR)[a].

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Based on our review of the Prescribing Information (PI) labeling, carton labeling and container label, we determined that not all our previous recommendations to the Division and to the Applicant were implemented (See Appendix B). Specifically, the following recommendations remain outstanding:

A. Prescribing Information

1. The route of administration is not stated in the Dosage and Administration subsections of the Highlights of Prescribing Information (HPI) and the Full Prescribing Information (FPI).

2. Important administration statements (e.g. 'Swallow capsules whole. Do not chew, dissolve, or open capsule') are not included in the Dosage and Administration subsections of the HPI and the FPI.

[a] Complete response (CR) letter issued on June 28, 2016.

3. Section 16 (How Supplied/Storage and Handling) is missing critical product identifier information.

4. Section 17.3 (Patient Should be Advised of the Following Instructions for Use) is missing important administration instructions including: 'Swallow capsules whole. Do not chew, dissolve, or open capsule'

B. Container Label and Carton Labeling

1. The product will not have a medication guide (MG), however the carton labeling contains a MG statement.

2. The carton labeling submitted for Agency review does not appear to be the final version.

3. The net quantity is located near the strength statement and may cause confusion.

4. The presentation of the established name is not in accordance with 21 CFR 201.10(g)(2).

We provide recommendations regarding these areas below in Section 4.1 and 4.2 in order to help minimize the potential for medication errors with the use of this product.

We also note that since our previous reviews, (b) (4) We find this updated information is appropriately included in the prescribing information (PI) labeling, carton labeling and container labels.

4 CONCLUSION & RECOMMENDATIONS

We previously identified areas of the labels and labeling where additional important information should be added or information should be revised or removed in order to help ensure the safe use of the product. However, our review finds not all of our previous recommendations to the Division and to the Applicant were implemented. We provide recommendations below in Section 4.1 and 4.2 to address our concerns. We advise that these recommendations be implemented prior to approval of this application.

4.1 RECOMMENDATIONS FOR THE DIVISION

(b) (4)

A. Prescribing Information

Consider revising the Dosage and Administration section in both the Highlights and the Full Prescribing Information to include the following information to promote safe use of the product:

1. The route of administration, 'orally' should be included in the dosage and administration sections of the PI. (i.e. 'The recommended starting dose of {TRADENAME} is 225 mg testosterone undecanoate orally twice daily with food').

2. To decrease the risk of wrong technique medication errors during administration, consider adding the following statement to the dosage and administration sections of the PI: 'Swallow capsules whole. Do not chew, dissolve, or open capsules'.

3. Section 16 ('How Supplied') is missing important product identifier information (e.g. NDC number and quantity supplied) which may contribute to the risk of medication errors. Consider revising Section 16 (How Supplied) to read:

   {TRADENAME} (testosterone undecanoate) capsules are available as follows:
   112.5 mg capsules: white opaque body with grey opaque cap, imprinted with "112" in black. NDC (b) (4) bottle of 120 capsules

4. To ensure the safe use of the product and to align with Section 2 of the PI, the carton labeling and the container label, consider revising section 17.3 ('Patients Should be Advised of the Following Instructions for Use') to include the statement: 'Swallow capsules whole. Do not chew, dissolve, or open capsules'.

4.2 RECOMMENDATIONS FOR LIPOCINE INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comment

It does not appear the submitted carton labeling is the final marketed version. For example, we note your submission dated August 8, 2017 includes a container label with the conditionally approved proprietary name, TLANDO in blue capital letters on a white background. However, on the (b) (4), the name "LPCN 1021" is presented in (b) (4) Please submit the final 'intend-to-market' (b) (4) container labels for Agency review.

B. Carton Labeling

1. Remove the Medication Guide (MG) statement from the principal display panel since your product will not have an MG.

2. Ensure the font size of the established name is at least one half the font size used to present the proprietary name in accordance with 21 CFR 201.10(g)(2).

3. Relocate the net quantity statement farther away from the strength statement on the principal display panel to minimize the risk of numerical confusion between the strength and the net quantity. Ensure that the net quantity remains on the principal display panel

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for testosterone undecanoate received on August 8, 2017 from Lipocine Inc.

Table 2. Relevant Product Information for Testosterone Undecanoate Capsules	
Initial Approval Date	N/A
Active Ingredient	Testosterone undecanoate
Indication	Primary hypogonadism; hypgonadotropic hypogonadism
Route of Administration	oral
Dosage Form	capsules
Strength	112.5 mg
Dose and Frequency	225 mg (two 112.5 mg capsules) orally twice daily with food
How Supplied	HDPE child resistant bottles
Storage	25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 7, 2018, we searched DMEPA's previous reviews using the terms, 'testosterone undecanoate' and 'NDA 208088'. Our search identified two previous reviews[cd], and we determined that our recommendations were partially implemented or considered. See Sections 4 and 5 for our conclusions and recommendations.

[c] Fava, W. Label and Labeling Review for Testosterone Undecanoate (NDA 208088). Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US): 2016 March 15. 8 p. OSE RCM No.: 2015-2005.

[d] Fava W. Label, Labeling, and Packaging Review for Testosterone Undecanoate (NDA 208088). Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US): 2016 May 4. 5 p. OSE RCM No.: 2015-2005-1.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with post-market medication error data, we reviewed the following testosterone undecanoate capsules labels and labeling submitted by Lipocine Inc.

- Container label received on August 8, 2017
- Carton labeling received on August 8, 2017
- Prescribing Information (Image not shown) received on October 31, 2017

G.2 Label and Labeling Images

Container Label

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DENISE V BAUGH
02/16/2018

LOLITA G WHITE
02/16/2018

REVIEW MEMORANDUM

To: Jeannie Roule, MT
Project Manager
DBRUP/ODEII/OND/CDER

From: Marianela Perez-Torres, M.T., Ph.D.
Chemistry Branch Chief
DCTD/OIR/CDRH

Marianela Perez-torres -S
2018.02.06 16:42:57 -05'00'

Subject: **ICCR2017-02001 (CTS Document: ICC1800059)**
Lipocine Tlando (oral testosterone undecanoate); tubes used for measuring testosterone and assessment of TU to T ex vivo conversion

Date: February 6, 2018

CDRH Review Summary:

CDER requested CDRH's feedback regarding the sponsor's proposal that TU does not convert to T in specimens collected using red-top tubes and processed for serum. CDRH identified several deficiencies in the studies provided to support the sponsor's conclusion. These include some of the following: since samples collected in red-top tubes are required to stand for ~30 mins to allow clotting prior to centrifugation, it would not be possible to obtain a true baseline level of testosterone (at time zero) in serum samples, sample handling and storage conditions (including temperature and time) may impact the enzyme activity of the esterases that mediate the TU to T conversion (this was not fully characterized), stability of samples containing TU under different storage conditions is unknown and due to similarities in chemical structures of TU and T, if the drug is monitored using immunoassays (most commonly T assays in clinical labs) the T values may be over-estimated and would not be adequate to monitor patient. Based on these variables, CDRH cannot conclude that the testosterone (T) concentration as measured in samples collected in serum (red top) are not overestimated due to TU to T ex vivo conversion. Data are not available to characterize this effect using samples from patients taking TU (rather than spiked samples).

Following review of the clinical studies as provided by CDER to CDRH, CDRH's remaining concerns are as follows:

- Uncertainty remains regarding whether TU converts to T ex vivo, the studies presented showed conflicting data that is not conclusive. While it may not be possible to obtain a true baseline for serum samples that contain TU, it may be possible to use other

anticoagulants that are validated for use with Testosterone assays, such as lithium heparin or K2EDTA.

- Data demonstrating the stability of TU and T in in serum is not available to the review team. Information regarding suitable specimen collection and handling procedures is not available for serum specimens.

- Potential cross-reactivity of TU with commonly used T immunoassays should be evaluated if the T levels are used to monitor drug efficacy.

CDRH provided its comments to the draft presentations and FDA Backgrounder regarding the sponsor's data to ensure the safe and effective dosing of oral testosterone undecanoate (TU) via e-mail to CDER. CDRH also recommended requesting additional information to sponsor and drafted an IR letter, CDER was agreeable to send the letter but decided to wait on the outcome of the AC Meeting before deciding if it was adequate to send. These documents are included as attachments to this memo.

A. GENERAL INFORMATION:

CDRH Review Team:

- Marianela Perez-Torres, Ph.D., MT, Chemistry Branch Chief, DCTD
- Courtney Lias, Ph.D., Division Director, DCTD
- Eveline Arnold, Ph.D., Scientific Reviewer, DCTD

B. DOCUMENTS REVIEWED

CDRH reviewed the following documents, provided by CDER:

- NDA 208088: Evaluation of Potential Ex Vivo TU to T Conversion
- NDA 208088: Ex-vivo TU to T Conversion Evaluation During Sample Preparation
- Lipocine response (date November 27, 2017) to IR letter (date August 28, 2015)
- FDA - Lipocine Background Document – Clinical Pharmacology Issues
- FDA Clinical Pharmacology Slides for AC Meeting

C. REVIEW TIMELINE

During this consult request, CDRH attended the following meetings:

- December 11, 2017: Internal meeting with CDER
- December 18, 2017: AC Practice Session Lipocine (and Clarus)

- December 20, 2017: AC Practice Session Lipocine (and Clarus)
- December 21, 2017: AC Practice Session Lipocine (and Clarus)
- January 3, 2018: AC Practice Session Lipocine (and Clarus)
- January 10, 2018: NDA 208088, Lipocine: Advisory Committee Meeting for Oral TU product
- January 17, 2017: Status and Post-AC Meeting – Lipocine

D. REVIEW SUMMARY AND CONCLUSIONS:

Based on review of the information from the sponsor provided by CDER, as well as the panel discussion during the January 9, 2018 Advisory Committee Meeting, CDRH concludes additional information is needed form the sponsor to support the claim that samples collected in red-top tubes for measurement of testosterone are safe and effective for dosing of TU.

E. RECOMMENDATION

CDRH recommends this inter-center consult request be closed. All CDRH's comments are captured in attachments to this memo and emails will be uploaded to CDRH's CTS (Center Tracking System) reference section.

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/s/

JEANNIE M ROULE
02/13/2018

Memorandum of Endocrine Consultation

NDA	208088
eCTD	0027 (8/31/2017)
Drug	Testosterone undecanoate, oral
Sponsor	Lipocine, Inc.
Indication	Testosterone replacement in hypogonadal men
Requested by	Martin Kaufman, MD
Date of Request	October 5, 2017
Date Completed	December 18, 2017
Reviewer	Linda S. Jaffe, MD/DBRUP
Team Leader	Theresa Kehoe, MD/DBRUP
Materials Reviewed	Studies LPCN102-16-002 and LPCN102-16-003
	Individual data and narrative reports for subjects with abnormal test results submitted on 8/31/2017
	Nonclinical review submitted on 6/1/16
	References

Background

Lipocine, Inc. is developing oral testosterone undecanoate (TU) for testosterone replacement therapy in hypogonadal men. TU is a fatty acid ester of testosterone. TU is an inactive pro-drug which is hydrolyzed by esterases in vivo to yield testosterone and undecanoic acid. The relative binding affinity of TU for the androgen receptor is only 1% that of testosterone. TU taken orally is absorbed in the intestinal lymphatics such that a first pass hepatic effect is avoided.

Nonclinical studies have demonstrated adrenal cortical atrophy. The adrenal cortex is comprised of 3 zones: the zona glomerulosa, which produces aldosterone; the zona fasciculata, the largest zona and the site of glucocorticoid production; and the inner zona reticularis, the

site of adrenal androgen production. Glucocorticoid production is under regulation of the hypothalamus and pituitary gland, and adrenocorticotrophic hormone (ACTH). 26-week rat studies demonstrated an increase in the incidence and severity of diffuse adrenal cortical vacuolation in treated animals at all dose levels, characterized by small to large cytoplasmic vacuoles within cortical adrenocytes. These findings were seen primarily in the zona fasciculata and the zona reticularis. In a 90-day toxicology study in dogs, slight to moderate cortical atrophy of the adrenal glands was observed in all treated animals. Therefore, in accordance with a request from the agency, in December 2016, the cosyntropin stimulation protocol was added to evaluate to effects of LPCN 1021 on the hypothalamic-pituitary-adrenal (HPA) axis.

The current submission under review is in response to a Complete Response action dated August 28, 2015. The resubmission is dated August 8, 2017. Cosyntropin stimulation tests were performed in studies LPCN102-16-002 and LPCN102-16-003. Additional individual data and narrative reports for subjects with abnormal test results were submitted on 8/31/2017 in response to an IR.

We were asked to comment on the results of the Cosyntropin stimulation studies.

Protocol

Study LPCN1021-16-002, entitled Validation of Dosing Regimen of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men, was a Phase3 Multicenter study conducted in the U.S.

The primary efficacy endpoint and analysis for this study was the percentage of LPCN 1021 treated subjects who had achieved a 24-hour average serum testosterone (T) concentration within the normal range of 300 to 1080 ng/dL at Visit 4 (Study Day 24 ± 4 days).

A total of 95 hypogonadal men meeting inclusion criteria were enrolled into the study and assigned to receive 225 mg of LPCN 1021 two times per day for approximately 24 days (window of 20 to 28 days). Intensive PK sampling was done on Study day 23 after approximately 24 days of TU exposure.

Study LPCN 1021-16-003, entitled Dosing Flexibility Study of Oral Testosterone Undecanoate (TU LPCN 1021) in Hypogonadal Men is a multicenter study in the U.S. The primary efficacy endpoint and analysis for this study was the percentage of LPCN 1021 treated subjects who had achieved a 24-hour average serum T concentration within the normal range of 300 to 1080 ng/dL at Visit 5 (Day 24 ± 4 days). A total of 100 hypogonadal men meeting inclusion criteria were enrolled into the study and assigned to receive 150 mg of LPCN 1021 three times a day for about 24 days (window of 20 to 28 days). Intensive PK testing was performed on study Day 5 after approximately 24 days of TU exposure.

Both studies used the same Cosyntropin stimulation test protocol to evaluate for adrenal insufficiency.

Sites were referred to product label of Cosyntropin for exact dosage and administration instructions. In each study, the cosyntropin stimulation test was performed at screening visit 2 (Baseline) and End of Study (Day 24 +/- 4 days referred to as visit 4 in study LPCN 1021-16- 002 and visit 5 or exit in study LPCN 1021-16-003). At each time point, Cosyntropin 0.25 mg was administered intramuscularly (IM) or intravenously (IV). Cortisol measurements were obtained at 0 minutes (pre-injection) and 60 minutes post-injection.

The following criteria were considered a normal response:

- "Approximately" at least a doubling of the basal cortisol level
- Control plasma cortisol level should be > 5 mcg/100 ml
- Incremental cortisol increase should be $\geq$ 7 mcg/dL above basal levels
- Absolute cortisol value following stimulation >18 mcg/dL

Results

The sponsor pooled results and reported mean cortisol levels for subjects who had a baseline test and those that had an end of study test. Two subjects in the first study and 7 in the second who had baseline tests did not have an end of study test; therefore data at each time point are not matched.

Table 1. Mean cortisol values during cosyntropin tests

	Baseline			End of Study*		
Study	Time 0 (mcg/dL)	60 min (mcg/dL)	Δ	Time 0 (mcg/dL)	60 min (mcg/dL)	Δ
LPCN1021-16-002 N=39/37#	13.8	32.1	153.9%	14.4	30.0	143.6%

LPCN 1021-16-003 N=59/52#	13.0	31.6	160%	13.3	31.6	139.3

Modified from study LPCN102-16-002 Table 14.3.7.2 and study LPCN 1021-16-003 Table (Table 14.3.7.2).*24 +/- 4 days

#number of subjects participating at each time point baseline/end of study

Additionally, the sponsor submitted individual results for subjects in their response to an IR on August 31, 2017 which are discussed below.

Reviewer Comments

The sponsor relied on pooled data and mean change in cortisol level to assess the adrenal response to cosyntropin after 24+/-4 days of TU exposure. This analysis does not sufficiently address whether short-term TU exposure leads to suppression of the HPA axis. Instead, paired data should be analyzed and the proportion of subjects with a normal baseline test who develop an abnormal result with TU exposure should be determined. The generally accepted clinical criteria for assessment of the adrenal response to cosyntropin stimulation has changed from incremental increase of in cortisol of ≥7 mcg/dL to a cortisol level of ≥18 mcg/dL at any time point during the test, pre-injection (Time 0), or 30 or 60 minutes post injection (Bornstein S, et al. 2016).

Study LPCN1021-16-002

Applying the above criteria (cortisol level of ≥18 mcg/dL at any time point during the test), in study LPCN102-16-002, 36/37 subjects' results would be considered normal at both baseline and end of study. One subject who was flagged as having an abnormal baseline test and 2 subjects who were flagged as having abnormal end of study test results based on the outdated criteria of ≥7 mcg/dL increase have normal adrenal function based on the currently accepted criteria of ≥18 mcg/dL. The only abnormal result in this cohort, is the baseline test for subject (b) (6)

Subject (b) (6) had both an initial and post-stimulation cortisol level of 1.5 mcg/dL in his baseline test. This result is difficult to explain. This test was performed at 8:09 am. Cortisol secretion has a robust circadian rhythm with maximum levels in the early morning and nadir in the late afternoon/evening. This subject did go on to have a normal end of study test. The results suggest the subject may not have received cosyntropin at baseline or that the sample was mishandled.

Subject (b) (6) also had a problematic result on his end of study test in which his pre-injection cortisol level was 45 mcg/dL but the 60 min value declined markedly to 9.9 mcg/dL. There is no reasonable physiologic explanation for this result. These results raise concerns about sample handling, such as reversal of the sample times. Both of these subjects were tested at site 206.

Low morning cortisol levels can be concerning for adrenal insufficiency. Normal morning cortisol levels are generally considered to be above 10 mcg/dL. Levels below 3-5 mcg/dL are suggestive of adrenal insufficiency. Overall, excluding the 2 subjects discussed above, mean pre-stimulated cortisol levels were 14.4 mcg/dL and 14.2 mcg/dL, at baseline and EOS for this study cohort, respectively. However, several subjects were noted to have low pre-stimulated cortisol levels (<10 mcg/dL) either at EOS alone or at both study time points as noted in Table 2.

Table 2. Pre-stimulated Cortisol Values for Subjects with Low Morning End of Study Cortisol-Study LPCN1021-16-002

	Baseline		End of Study	
Subject	Cortisol (mcg/dL)	Time	Cortisol (mcg/dL)	Time
(b) (6)	17.5	7:25 am	5.8	7:45 am
	9.8	8:00 am	6.4	6:50 am
	5.2	7:35 am	3.6	6:21 am
	8.1	8:11 am	6.3	5:35 am

Source: LPCN1021-16-002 Safety Data Set Reviewer Analysis

Subject (b) (6) had a baseline pre-stimulated cortisol of 5.2 mcg/dL at 7:35 am and an end of study pre-stimulated cortisol level of 3.6 mcg/dL at 6:21 am; however, each time, this subject did go on to have a normal stimulation test. A similar pattern was noted in the other 3 subjects in Table 2 above. Subject (b) (6) was treated with methylprednisolone injection for osteoarthritis of his knees 8 days prior to his EOS test. This exposure could have contributed to the slight decline in his pre-stimulated cortisol level. A decline in pre-stimulated cortisol levels from baseline to EOS, however, was not uniform among subjects. Of the remaining 31 study subjects, 15 (48.4%) had an increase of more than 1 mcg/dL, 12 (38.7%) had a decrease of more than 1 mg/dL and 4 subjects (12.9%) had a change of no more than 1 mcg/dL.

Time of testing could have affected the pre-stimulated cortisol levels. The EOS tests were generally performed earlier (6-7 am) than the baseline test (8-9 am) for the majority of subjects. Although earlier testing is expected to be associated with higher AM cortisol levels, variability in individual endogenous circadian rhythms could explain individual differences in pre-stimulated cortisol levels. Differences in stress levels could also contribute. Alternatively, it is unknown whether TU causes a decline in corticosteroid-binding globulin (CBG) levels, the protein to which the majority of cortisol is bound in the circulation. In either of these scenarios, adrenal function would be considered normal. Whether a decline in endogenous morning cortisol levels with a normal stimulation test represents early suppression of the HPA axis with short term TU exposure is uncertain. Measuring simultaneous pre-stimulated ACTH, cortisol and CBG levels, as well as performing the stimulation test after a longer treatment course with TU might help to clarify these questions.

Study LPCN 1021-16-003

In study LPCN 1021-16-003, if the same criteria for normal response to cosyntropin stimulation are applied (cortisol ≥18 mcg/dL at any time point), then 7 of the 22 test results that were flagged as abnormal would be considered normal. Two additional subjects were discovered to have never received cosyntropin. One of these subjects had a Time 0 cortisol of 12.4 mcg/dL at baseline and 0.7 mcg/dL at end of study. His end of study unstimulated cortisol 60 minutes later was 5 mcg/dL. One subject ((b) (6) whose results were flagged as normal, had an abnormal baseline test with Time 0 cortisol 1.4 mcg/dL and 60 minute cortisol of 9.9 mcg/dL post stimulation. These results are consistent with adrenal insufficiency. However, his end of study results were normal. Review of the subject narrative report does not reveal any illnesses or medications that could explain transient adrenal insufficiency.

The most concerning finding in study LPCN 1021-16-003 is that the 5 subjects from Site 318 showed lack of stimulation both at baseline and at end of study. In this group, cortisol changes post-stimulation ranged from 0.9-1.2 mcg/dL. Three of these results in 2 patients ((b) (6) at both baseline and end of study, and subject (b) (6) at baseline) had at least 1 cortisol value ≥ 18 mcg/dL and therefore technically meet the criteria for normal adrenal function. Despite the technically normal results, the clustering of lack of cortisol response to cosyntropin is concerning for a problem with the test itself, such as the quality of the cosyntropin used or lack of proper cosyntropin administration. In their IR response submitted on Nov 3, 2017, the sponsor indicated that after discussions with staff and review of source documents, pharmacy records and invoices, they were unable to identify reasons for the unusual cosyntropin stimulation test results from site 318. An additional subject (b) (6) showed lack of stimulation at baseline but a normal end of study test. Subject (b) (6) had a decline in cortisol from 22.6 to 17.1 mcg/dL from Time 0 to 60 min, but again, results would be

considered normal using the most recent criteria. The standard test is performed with measurements at times 0, 30, and 60 minutes so a peak might have been missed at 30 minutes in this subject. Excluding subjects from site 318, mean pre-stimulated cortisol levels were 13.1 mcg/dL and 13.4 mcg/dL, at baseline and EOS, respectively. Eleven subjects were noted to have low pre-stimulated cortisol levels (<10 mcg/dL) either at EOS alone or at both time points as noted in Table 3.

Table 3. Pre-stimulated Cortisol Values for Subjects with Low Morning End of Study Cortisol-Study LPCN1021-16-003

	Baseline		End of Study	
Subject	Cortisol (mcg/dL)	Time	Cortisol (mcg/dL)	Time
(b) (6)	13	7:30 am	7.6	4:00 am
	13.7	8:29 am	9.9	6:10 am
	4.9	8:06 am	4.3	6:20 am
	4.5	9:21 am	4.7	5:50 am
	9.3	7:36 am	7.3	5:59 am
	24.6	8:49 am	8.9	8:00 am
	9.6	8:45 am	9.7	8:35 am
	11.8	7:57 am	6.6	6:05 am
	15.3	8:19 am	8.6	8:20 am
	20.9	7:45 am	8.4	4:58 am
	6.8	7:13 am	5.9	6:30 am

Source: LPCN1021-16-003 Safety Data Reviewer Analysis

All of these subjects had normal cosyntropin stimulation tests at baseline and EOS. None of the subjects had a history of glucocorticoid treatment. Several subjects had similarly low AM cortisol values both at baseline prior to TU treatment and EOS rather than a decline in AM cortisol from baseline to EOS, raising the possibility of endogenous low CBG levels at baseline. As in study LPCN1021-16-002 a decline in pre-stimulated cortisol levels from baseline to EOS

was not uniform. Of the remaining 44 subjects (excluding site 318), 16 (36.3%) had an increase of more than 1 mcg/dL, 20 (45.5%) had a decrease of more than 1 mg/dL and 8 subjects (18.2%) had a change of no more than 1 mcg/dL.

As discussed for study LPCN1021-16-002 above, whether differences in time when the study was performed with respect to subjects' endogenous circadian rhythms, changes in stress levels, a reduction in CBG with TU exposure or TU-induced adrenal insufficiency/HPA axis suppression can explain the low pre-stimulated cortisol values in these subjects is unclear and further evaluation is warranted.

Unique subjects were not studied in each of the two cosyntropin sub-studies. In their IR response dated August 31, 2017, the sponsor remarked that 2 of the subjects with abnormal results in study LPCN1021-16-002 also participated in LPCN1021-16-003 and had normal results. Overall, 77 subjects participated in the Cosyntropin sub-study in one or both studies: 18 participated in 002 only, 36 participated in LPCN1021-16-003 only, and 23 participated in both LPCN1021-16-002 and LPCN1021-16-003. In summary, all but one of abnormal cosyntropin test results in the two studies discussed above appear to be due to a lack of stimulation with no meaningful change in pre-injection vs. post injection cortisol levels. Lack of stimulation occurred in 1 subject at baseline in study LPCN1021-16-002 and five subjects at both baseline and end of study in LPCN1021-16-003. An additional 2 subjects in study LPCN1021-16-003 did not receive Cosyntropin according to the sponsor. One subject in study LPCN1021-16-003 had a truly abnormal baseline test and a normal end of study result.

Other important considerations are the duration of TU exposure and the mechanism by which TU might cause adrenal insufficiency. Primary adrenal insufficiency, as well as secondary/tertiary adrenal insufficiency is possible. If metabolites of TU cross-react with the glucocorticoid receptor at the level of the hypothalamus and or pituitary gland, secondary or tertiary adrenal insufficiency could result. While the cosyntropin test is considered an appropriate screening test for both primary and secondary adrenal insufficiency (Bornstein S at al. 2016, Grossman AB 2010), it is associated with supraphysiologic adrenal stimulation, and may result in false negative results early in the course of secondary/tertiary adrenal insufficiency. Four weeks of TU exposure may be insufficient to assess whether TU, a drug that is expected to be taken chronically, causes adrenal dysfunction. Overall, the data presented are insufficient to rule out a risk of adrenal insufficiency with chronic TU treatment. Technical factors such as the quality of the cosyntropin used, improper/lack of administration of cosyntropin and sample handling could also be potential explanations for the abnormal results. A more rigorous assessment of adrenal function of longer duration in subjects who are confirmed to have achieved adequate T levels on treatment should be performed.

Recommendations

- A more robust study should be performed to evaluate the possibility of adrenal insufficiency with long-term use of TU.
- Study personnel should be instructed on the dosing and administration of cosyntropin 0.25 mcg. The mode of administration (IV or IM) should be uniform in all subjects. Intravenous administration is recommended.
- The results of the current study can be used inform power calculations.
- Unique subjects should be included in each study.
- Cosyntropin 0.25 mg injection with cortisol testing pre-injection (Time 0), 30 and 60 minutes post-injection is an appropriate screening test.
- The minimum acceptable cut-off of cortisol level $\geq$18 mcg/dL should be used to evaluate results. The proportion of subjects who developed an abnormal response at study time points should be calculated. Inclusion of an active control group of subjects treated with a topical form of testosterone such as gel would strengthen the study.
- Testing times should be standardized to 8 AM and simultaneous pre-cosyntropin cortisol ACTH and CBG levels should be obtained each study time point (Par YK, et al 1999).
- Samples should be batched for the cortisol, ACTH and CBG assays.
- Serial tests should be performed at baseline and 6 month intervals, or sooner if clinically indicated, to determine if progressive adrenal insufficiency occurs with ongoing TU use.
- The cosyntropin study protocol should be submitted for review prior to initiation of the study.

References

Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101 (2):364.

Grosssman AB. Clinical review: The diagnosis and management of central hypoadrenalism. J Clin Endocrinol Metab 2010; 95: 4855.

Park YJ, Park KS, Kim JH, et al. Reproducibility of the cortisol response to stimulation with the low dose (1 microg) of ACTH. Clin Endocrinol (Oxf). 1999;51(2):153.

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/s/

LINDA S JAFFE
12/18/2017

THERESA E KEHOE
12/18/2017

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

DCRP Consult NDA 208088

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Date of Consult: 11/13/2017
Desired Completion Date: 9/27/2017
Date of Completion: 9/28/2017

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TO: Jeannie Roule, RPM, DBRUP
Scientific Reviewer, OIR/DCTD

PROCUCT NAME: Testosterone undecanoate (TU, oral, LPCN 1021)

PRODUCT CLASS: Androgen

SPONSOR: Lipocine

INVESTIGATIONAL INDICATION: Replacement therapy in adult men

BACKGROUND:

LPCN 1021 (testosterone undecanoate) capsules is an oral product containing testosterone undecanoate (TU) in a lipid formulation designed to enable absorption of TU via the intestinal lymphatic pathway. The LPCN 1021 clinical development program includes the following three phase 3 studies that evaluated the drug for testosterone replacement in men with primary and secondary hypogonadism:

- LPCN 1021-13-001, the pivotal study for NDA 208088 when it was submitted on August 28, 2015, is a 52 week, randomized, open-label, active-controlled efficacy and safety study in adult hypogonadal males with 210 subjects randomized to

LPCN 1021 and 105 randomized to AndroGel 1.62%. LPCN 1021 subjects started on a dose of 225 mg BID and could be titrated up (to 300 mg BID) or down (to 150 mg BID) based on total T concentration after 3 and 7 weeks of treatment. Subjects could have been naïve to testosterone treatment or may have been washed out from prior testosterone therapy. Primary efficacy was determined at week 13 with follow-up to week 52 for safety. The NDA received a CR action on June 28, 2016, due to an unacceptably high discordance between titration decisions made during the study (based on 24-hour Cavg) and the titration decisions that would be made using the titration scheme proposed for labeling (based on a single blood sample).

- LPCN 1021-16-002, an additional pivotal study submitted in the sponsor's August 8, 2016 resubmission, is a 25 day, open-label, single treatment study evaluating the efficacy and safety of LPCN 1021 in adult hypogonadal males that enrolled 95 subjects. Subjects may have been naive to T treatment or may enroll after stopping current treatment and completing an adequate washout period. The first 14 days of the study are a screening period. Drug is initiated at visit 3 with subjects receiving active therapy for approximately 15 days (window 14-18). Subjects are confined for PK assessments at Visit 4 on drug Day 14. Subjects ae then exited from the study on drug Day 16. All subjects received a 225 mg BID dose of LPCN 1021 without dose titration.

- LPCN 1021-16-003, a study submitted in the sponsor's August 8, 2016 resubmission, is a 25 day, open-label, single treatment study evaluating the efficacy and safety of LPCN 1021 in adult hypogonadal males that enrolled 100 subjects. Subjects may have been naive to T treatment or may enroll after stopping current treatment and completing an adequate washout period. The first 14 days of the study are a screening period. Drug is initiated at visit 3 with subjects receiving active therapy for approximately 24 days (window 20-28). Subjects are confined for PK assessments at Visit 4 on drug Day 23. Subjects ae then exited from the study on drug Day 25. All subjects received a 150 mg TID dose of LPCN 1021 without dose titration. The study did not meet the primary endpoint of the study.

In all three studies, vital signs including blood pressure measurements were taken once per visit in the morning. The exact time of the measurement is recorded in the eCRF and reported in the clinical database. The reported blood pressure values are the result of a single measurement.

There is an AC for this product scheduled 01/10/2018

DBRUP has the following questions for DCRP:

1. We request your opinion concerning the results from the cuff blood pressure assessments in studies LPCN 1021-13-001, LPCN 1021-16-002, and LPCN 1021-

16-003. Please note that a good percentage of subjects (43.5%) were on a stable un-titrated dose for 52 weeks in study 001.

2. Do you recommend any additional analyses of the cuff blood pressure assessments?

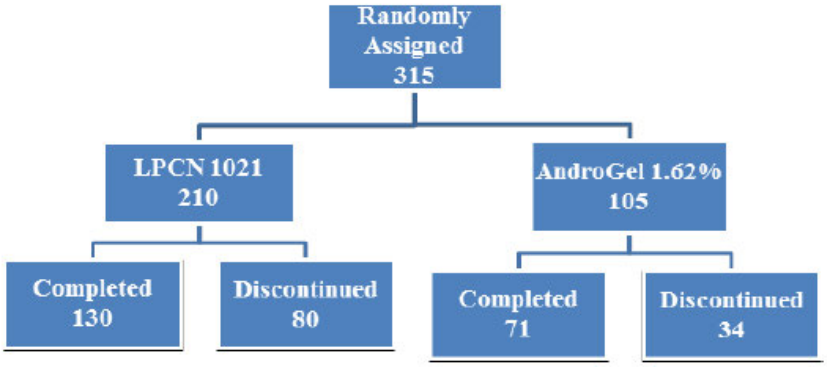
3. Are there any findings from the cuff blood pressure assessments that you believe require Ambulatory Blood Pressure Monitoring?

4. We request your recommendation for any additional studies, labeling and any enhanced reporting.

LPCN 1021-13-001: Vital signs were measured at each visit after the subject had been sitting at rest for at least 5 minutes. Blood pressures were measured at weeks 3, 7, 13, 26, 39, and 52.

Disposition of subjects

Figure 2. Subject Disposition (All Randomized Subjects)



Reviewer's comment: The premature dropout rate was high and there was a plethora of reasons for these early discontinuations, including hematocrits in excess of 54%. The reasons for early discontinuation are shown on the following table:

Table 13. Subject Disposition (All Enrolled Subjects)

Status	LPCN 1021 n (%)	AndroGel 1.62% n (%)	Total n (%)
Subjects who were randomly assigned to treatment	210	105	315
Subjects who received treatment (Safety Set)	210 (100)	104 (99.0)	314 (99.7)
Subjects who completed the study	130 (61.9)	71 (67.6)	201 (63.8)
Subjects who discontinued early from the study	80 (38.1)	34 (32.4)	114 (36.2)
Reasons for early discontinuation:			
Consent withdrawn	29 (13.8)	9 (8.6)	38 (12.1)
Lost to follow-up	13 (6.2)	12 (11.4)	25 (7.9)
Cmax > 1500 ng/dL after lowering assigned dose to LPCN 1021 150 mg BID	8 (3.8)	NA	8 (2.5)
HCT > 54%	2 (1.0)	1 (1.0)	3 (1.0)
PSA > 4 ng/mL or with CfB of > 1.4 ng/mL	1 (0.5)	1 (1.0)	2 (0.6)
Significant noncompliance with the protocol requirements	3 (1.4)	2 (1.9)	5 (1.6)
PI judgment[a]	3 (1.4)	0	3 (1.0)
Health risk to subject with continued participation (including adverse events)[b]	3 (1.4)	1 (1.0)	4 (1.3)
Other reasons	18 (8.6)	8 (7.6)	26 (8.3)
Duplicate subject	4 (1.9)	3 (2.9)	7 (2.2)
Adverse events	2 (1.0)	3 (2.9)	5 (1.6)
Unable to complete overnight	2 (1.0)	0	2 (0.6)
Abnormal ECG	1 (0.5)	0	1 (0.3)
Cavg0-24h < 300 ng/dL at Week 7	1 (0.5)	0	1 (0.3)
Discontinued by site in error	1 (0.5)	0	1 (0.3)
Entry criteria violation, enrolled with exclusionary Hgb	1 (0.5)	0	1 (0.3)
High levels of prolactin	1 (0.5)	0	1 (0.3)
Moved out of town	1 (0.5)	0	1 (0.3)
Subject did not want to take pills, wanted AndroGel 1.62%	1 (0.5)	0	1 (0.3)
Subject discontinued on his own due to adverse event	1 (0.5)	0	1 (0.3)
Undisclosed history of prostatectomy/prostate carcinoma discovered	1 (0.5)	0	1 (0.3)
Weight gain	1 (0.5)	0	1 (0.3)
Lack of efficacy	0	1 (1.0)	1 (0.3)
Stopping criteria Hgb > 16 g/dL	0	1 (1.0)	1 (0.3)

Blood pressure data presented by sponsor in the CSR

Table 74. Blood Pressure: Mean Baseline and Mean Change from Baseline Values for Systolic Blood Pressure in LPCN 1021-Treated Subjects (Safety Set)

	LPCN 1021					AndroGel 1.62%				
		Value (mm Hg)		Value Change from Baseline (mm Hg)			Value (mm Hg)		Value Change from Baseline mm Hg)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	210	132.6	13.99	--	--	104	132.6	14.50	--	--
Week 7	182	131.4	14.33	-0.9	13.79	97	129.9	12.56	-3.1	13.47
Week 13	157	131.3	12.65	-0.8	12.57	92	130.7	12.47	-2.6	12.37
Week 26	144	130.7	13.28	-1.1	12.74	82	131.0	13.82	-2.0	14.35
Week 39	138	131.0	13.71	-0.5	13.92	76	132.8	13.86	-0.7	12.87
Week 52	130	131.2	14.70	-0.3	14.36	71	133.5	13.76	0.0	13.43
Early Term	49	130.2	11.17	-3.5	12.25	15	131.1	12.06	1.0	15.46

Key: SD = standard deviation.
Note: The vital sign measurements at screening served as the baseline.
Source: Table 14.3.5.1.

Table 73. Blood Pressure: Mean Baseline and Mean Change from Baseline Values for Diastolic Blood Pressure in LPCN 1021-Treated Subjects (Safety Set)

	LPCN 1021					AndroGel 1.62%				
		Value (mm Hg)		Value Change from Baseline (mm Hg)			Value (mm Hg)		Value Change from Baseline mm Hg)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	210	82.9	8.58			104	82.4	8.61		
Week 7	182	79.7	8.93	-3.0	8.44	97	81.7	8.02	-0.9	7.67
Week 13	157	80.6	8.46	-2.5	7.47	92	82.6	9.37	0.0	9.42
Week 26	144	81.1	9.32	-1.9	8.17	82	82.1	8.95	-0.4	9.59
Week 39	138	82.1	8.27	-0.8	7.80	76	83.6	8.07	1.1	7.21
Week 52	130	81.4	9.18	-1.3	8.32	71	83.0	9.11	0.4	9.36
Early Term	49	81.3	7.85	-0.7	7.81	15	80.1	9.41	-1.6	8.58

Key: SD = standard deviation.
Note: The vital sign measurements at screening served as the baseline.
Source: Table 14.3.5.1.

Reviewers comment: There appears to be a consistent decrease in mean SBP and mean DBP over time relative to baseline in the LPCN 1021 arm, though 38% of LPCN 1021 subjects and 32% of Androgel subjects dropped out between baseline and week 52. Heart rate data is not displayed in text. End of text Table 14.3.5.1 demonstrates a mean and median increase in heart rate of 3-4 BPM for Androgel and 2-3 BPM for LPCN 1021 at weeks 2, 3, 4, 7, and 13, as shown below:

Test (unit)	Visit	Statistic	LPCN 1021 N = 210 Observed	LPCN 1021 N = 210 Change	Androgel 1.62% N = 104 Observed	Androgel 1.62% N = 104 Change	Overall N = 314 Observed	Overall N = 314 Change
Systolic Blood Pressure(mm-Hg)	Early Term	n	49	48	15	15	64	63
		Mean (SD)	130.2 (11.17)	-3.5 (12.25)	131.1 (12.06)	1.0 (15.46)	130.4 (11.29)	-2.4 (13.09
		Median	131.0	-3.5	130.0	0.0	130.5	-2.0
		Q1, Q3	123.0, 138.0	-12.0, 7.0	125.0, 141.0	-10.0, 13.0	123.0, 139.5	-12.0, 8.0
		Minimum	109	-32	102	-31	102	-32
		Maximum	154	18	148	26	154	26
Pulse Rate(BEATS/-MIN)	Baseline	n	210		104		314	
		Mean (SD)	70.7 (10.12)		69.1 (11.10)		70.2 (10.46)	
		Median	70.0		69.0		70.0	
		Q1, Q3	64.0, 76.0		61.5, 77.0		62.0, 77.0	
		Minimum	43		49		43	
		Maximum	98		96		98	
	Week 2	n			99	97	99	97
		Mean (SD)			72.9 (10.95)	3.7 (9.20)	72.9 (10.95)	3.7 (9.20)
		Median			73.0	3.0	73.0	3.0
		Q1, Q3			64.0, 81.0	-2.0, 8.0	64.0, 81.0	-2.0, 8.0
		Minimum			51	-15	51	-15
		Maximum			105	40	105	40
Pulse Rate(BEATS/-MIN)	Week 3	n	193	192			193	192
		Mean (SD)	72.2 (10.44)	1.8 (9.10)			72.2 (10.44)	1.8 (9.10)
		Median	71.0	2.0			71.0	2.0
		Q1, Q3	65.0, 80.0	-3.0, 7.0			65.0, 80.0	-3.0, 7.0
		Minimum	45	-31			45	-31
		Maximum	99	31			99	31
	Week 4	n			100	97	100	97
		Mean (SD)			73.0 (10.73)	4.1 (9.76)	73.0 (10.73)	4.1 (9.76)
		Median			72.5	3.0	72.5	3.0
		Q1, Q3			65.0, 78.0	0.0, 9.0	65.0, 78.0	0.0, 9.0
		Minimum			53	-20	53	-20
		Maximum			114	37	114	37
	Week 7	n	182	180	97	97	279	277
		Mean (SD)	72.7 (11.60)	2.0 (8.65)	72.3 (10.50)	3.4 (9.26)	72.5 (11.21)	2.5 (8.88)
		Median	72.5	2.0	72.0	3.0	72.0	3.0
		Q1, Q3	65.0, 80.0	-4.0, 8.0	65.0, 79.0	-1.0, 7.0	65.0, 79.0	-3.0, 8.0
		Minimum	44	-24	47	-26	44	-26
		Maximum	105	32	102	40	105	40
	Week 13	n	157	157	92	91	249	248
		Mean (SD)	73.0 (11.63)	2.6 (9.82)	73.3 (11.34)	4.7 (11.54)	73.1 (11.50)	3.3 (10.51)
		Median	74.0	2.0	74.0	3.0	74.0	3.0
		Q1, Q3	65.0, 80.0	-3.0, 8.0	65.0, 81.0	-4.0, 12.0	65.0, 80.0	-3.0, 9.0
		Minimum	47	-30	47	-19	47	-30
		Maximum	109	37	107	33	109	37

Adverse events

This study was randomized 2:1. The sponsor reports that, *"During the study, 27 subjects experienced 29 AEs that appeared to be related to vital sign measurements: 19 subjects (19 events) in the LPCN 1021 group and 8 subjects (10 events) in the AndroGel 1.62% group (Listing 16.2.7.1). Eleven of these vital sign-related AEs were considered by the investigator to be related to study drug (8 reported by subjects in the LPCN 1021 group and 3 reported by subjects in the AndroGel 1.62% group). The most common vital sign-related AEs were weight increased and hypertension (blood pressure increased)." During the study, 19 treatment-emergent SAEs were reported; none were considered related to study drug. Twelve subjects (5.7%) in the LPCN 1021 group experienced treatment-emergent SAEs compared with 2 subjects (1.9%) in the AndroGel 1.62% group. Of these subjects, 15 had narratives which included one reported term of chest pain (AndroGel), one reported term of non-cardiac chest pain (LPCN 1021), and one reported term of syncope (LPCN 1021). Overall, 24 subjects (7.6%) discontinued*

because of TEAEs. A total of 19 subjects (9.0%) in the LPCN 1021 group discontinued because of an AE compared with 5 subjects (4.8%) in the AndroGel 1.62% group. No deaths were reported during the course of the study.

Reviewer's comment: The sponsor should identify all subjects experiencing all HTN-related AEs and SAEs and provide all available information on these subjects/events. They should make clear how these events were identified (e.g. database scans with wide SMQs). Of note, there were 9 subjects who had narratives generated for HCT > 54%. On review of the SAE narratives that were made available, there were no important indicators of blood-pressure-based TESAEs.

LPCN 1021-16-002: Vital signs were measured at screening and at Day 24. Vital signs were measured after the subject had been sitting at rest for at least 5 minutes.

Blood pressure data presented by sponsor in the CSR

About vital signs, the CSR says only the following:

> Vital signs were measured at each visit after the subject had been sitting at rest for at least 5 minutes. Table 14.3.5 summarizes vital sign measurements including observed mean and mean change from baseline. Mean change from baseline values in vital sign measurements show no clinically meaningful changes for heart rate, temperature, or systolic/diastolic blood pressure. During the study, no subject experienced any treatment-related AEs related to vital sign measurements (Table 14.3.1.6). The vital sign measurement results are displayed by subject in Listing 16.2.9.

From the end of text tables, change from baseline data for vital signs is as follows:

			LPCN 1021 Dose 225 mg (BID) N=95	
Test (unit)	Visit	Statistics	Observed	Change from Baseline
Diastolic Blood Pressure (mmHg)	Baseline	n	95	
		Mean(SD)	80.4 (10.09)	
		Median	82.0	
		Q1, Q3	70.0, 88.0	
		Minimum	55	
		Maximum	104	
	Visit 4	n	94	94
		Mean(SD)	79.6 (8.49)	-1.0 (7.95)
		Median	80.0	-1.0
		Q1, Q3	73.0, 85.0	-5.0, 6.0
		Minimum	57	-21
		Maximum	100	16
	Exit	n	94	94
		Mean(SD)	80.8 (9.11)	0.1 (8.11)
		Median	80.0	0
		Q1, Q3	74.0, 87.0	-5.0, 6.0
		Minimum	61	-18
		Maximum	113	20
		p-value [a]	0.8790	

Systolic Blood Pressure (mmHg)	Baseline	n	95	
		Mean(SD)	130.2 (14.33)	
		Median	131.0	
		Q1, Q3	121.0, 139.0	
		Minimum	100	
		Maximum	173	
	Visit 4	n	94	94
		Mean(SD)	129.6 (12.15)	-0.5 (13.53)
		Median	130.0	-0.5
		Q1, Q3	121.0, 137.0	-9.0, 9.0
		Minimum	102	-48
		Maximum	163	49
	Exit	n	94	94
		Mean(SD)	130.4 (13.57)	0.2 (13.62)
		Median	128.0	1.0
		Q1, Q3	120.0, 139.0	-8.0, 7.0
		Minimum	104	-40
		Maximum	165	51
		p-value [a]	0.8859	
Pulse Rate (beats/min)	Baseline	n	95	
		Mean(SD)	71.3 (10.44)	
		Median	70.0	
		Q1, Q3	64.0, 78.0	
		Minimum	53	
		Maximum	100	
	Visit 4	n	94	94
		Mean(SD)	74.3 (9.54)	3.0 (7.78)
		Median	72.0	2.5
		Q1, Q3	68.0, 82.0	-1.0, 7.0
		Minimum	56	-17
		Maximum	100	24
	Exit	n	94	94
		Mean(SD)	75.6 (11.13)	4.3 (10.34)
		Median	73.5	3.0
		Q1, Q3	68.0, 83.0	-1.0, 12.0
		Minimum	53	-17
		Maximum	124	37
		p-value [a]	0.0001	

Reviewers' comment: On 225 mg BID, mean/median blood pressure data show no important SBP/DBP central tendency shifts. Heart rate is consistently elevated by approximately 3 – 4 BPM on visit 4 (drug day 14) and at exit (drug day 16).

Adverse Events

Overall, 6.3% of subjects (6/95) experienced 9 treatment-related TEAEs. No treatment-related TEAEs resulted in study discontinuation. There were no TEAEs reported related to blood pressure.

LPCN 1021-16-003:

Blood pressure data presented by sponsor in the CSR

About vital signs, the CSR says only the following:

> Vital signs were measured at each visit after the subject had been sitting at rest for at least 5 minutes. Table 14.3.5 summarizes vital sign measurements including observed mean and mean change from baseline. Mean change from baseline values in vital sign measurements show no clinically meaningful changes for heart rate, temperature, or systolic/diastolic blood pressure.

NDA 208088

From the end of text tables, change from baseline data for vital signs is as follows:

Test (unit)	Visit	Statistics	LPCN 1021 Dose 150 mg (TID) N=100 Observed	Change from Baseline
Diastolic Blood Pressure (mmHg)	Baseline	n	100	
		Mean(SD)	81.3 (8.69)	
		Median	82.0	
		Q1, Q3	75.0, 87.5	
		Minimum	63	
		Maximum	105	
	Visit 5	n	98	98
		Mean(SD)	80.9 (8.74)	-0.3 (7.68)
		Median	81.5	-1.0
		Q1, Q3	74.0, 86.0	-6.0, 4.0
		Minimum	60	-17
		Maximum	108	26
	Exit	n	98	98
		Mean(SD)	81.2 (8.79)	0.0 (7.75)
		Median	81.0	0
		Q1, Q3	75.0, 88.0	-5.0, 5.0
		Minimum	56	-20
		Maximum	109	22
Systolic Blood Pressure (mmHg)	Baseline	n	100	
		Mean(SD)	129.0 (12.79)	
		Median	130.0	
		Q1, Q3	120.0, 137.0	
		Minimum	98	
		Maximum	165	
	Visit 5	n	98	98
		Mean(SD)	133.2 (13.54)	4.1 (12.59)
		Median	133.0	4.0
		Q1, Q3	125.0, 138.0	-2.0, 10.0
		Minimum	109	-31
		Maximum	184	46
	Exit	n	98	98
		Mean(SD)	133.3 (13.22)	4.3 (12.00)
		Median	134.5	4.0
		Q1, Q3	124.0, 140.0	-3.0, 12.0
		Minimum	104	-29
		Maximum	181	32
Pulse Rate (beats/min)	Baseline	n	100	
		Mean(SD)	74.9 (10.12)	
		Median	73.5	
		Q1, Q3	68.0, 81.0	
		Minimum	53	
		Maximum	100	
	Visit 5	n	98	98
		Mean(SD)	75.8 (10.86)	0.9 (11.24)
		Median	77.0	0.5
		Q1, Q3	68.0, 84.0	-6.0, 7.0
		Minimum	54	-29
		Maximum	100	35
	Exit	n	98	98
		Mean(SD)	75.8 (10.78)	0.8 (10.12)
		Median	76.0	1.0
		Q1, Q3	68.0, 85.0	-5.0, 8.0
		Minimum	50	-26
		Maximum	100	26

Reviewers' comment: On 150 mg TID, mean/median systolic blood pressures are consistently up approximately 4 mmHg on Visit 5 and at exit. Heart rate is consistently elevated by approximately 1 BPM on visit 5 (drug day 23) and at exit (drug day 25).

Adverse Events

Overall, 9.0% (9/100) of subjects experienced at least 1 TEAE and 1% (1/100) experienced at least 1 TEAE that was considered related to study drug. There were no TEAEs reported related to blood pressure.

Assessment:

In all three of these open-label trials, only single morning cuff pressures were acquired. It is unclear that the same equipment and/or the same office staff were acquiring these data from visit to visit on each subject, raising the potential for wide variability in the vital sign readings that were recorded.

The two small PK studies 002 and 003 dosed 95 and 100 subjects respectively to either 225 mg BID or 150 mg TID of LPCN 1021, respectively. The former demonstrated an elevated pulse rate of approximately 4 BPM at the end of two weeks of dosing, whereas the latter demonstrated both a 1 BPM pulse rate increase and a 4 mmHg SBP increase after approximately three and one-half weeks of dosing. There were no TEAEs relevant to vital signs in either of these small studies.

The major contributor to defining the non-invasive hemodynamic effects of this drug come from the 52-week study 001. However, the ability to generalize population central tendency data for vital signs from study 001 is limited by the premature withdrawal of 38% of the LPCN 1021 subjects and the 32% of Androgel subjects over the 13 weeks of the efficacy assessment period. From the data we do have from study 001, it appears that there was an approximately 2-3 BPM increase in HR for LPCN 1021-treted subjects and an increase of 3-4 BPM in HR for Androgel-treated subjects over the first 13 weeks of therapy, without demonstrable increases in the central tendencies for SBP or DBP in either group over that time period. However, in the setting of a high premature dropout rate, it is noted that along with this lack of effect on the central tendencies of either SBP or DBP is the discordance from the adverse event analysis that the most common vital sign-related AEs were “weight increased” and “hypertension/blood pressure increased.”

Based on the available data, it appears that both LPCN 1021 and AndroGel raise heart rate, and study 003 demonstrates a 4 mmHg increase in SBP with LPCN 1021. Study 001 does not exonerate LPCN 1021 from blood pressure effects because its cuff BP data acquisition was methodologically non-duplicative (single morning cuff pressures) in the setting of an open-label trial design with a 38% dropout rate in the experimental treatment arm. Therefore, a “no BP effect” conclusion from 001 is speculative and could be incorrect. We recommend that the sponsor perform a well-designed, adequately sized, and appropriately controlled ABPM study so that cogent and relevant labeling can be written to inform prescribers about the effects of LPCN 2021on blood pressure and heart rate.

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/s/

PRESTON M DUNNMON
12/05/2017

SHARI L TARGUM
12/05/2017

STEPHEN M GRANT
12/06/2017

NORMAN L STOCKBRIDGE
12/06/2017

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/3/2017

TO: Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208088

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

SHILA S NKAH
11/03/2017

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 12, 2016

TO: Hylton V. Joffe, M.D., MMSc.
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)
Office of New Drugs (OND)

FROM: Xingfang Li, M.D., RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Inspections of the following clinical site: Meridien Research (site 108), Bradenton, FL, covering the following application:

NDA 208088, Testosterone undecanoate, sponsored by Lipocine Inc., USA

Recommendations:

We are aware that DBRUP issued a Complete Response letter for this application on June 28, 2016. If the study is resubmitted, this OSIS reviewer recommends that the data from the clinical portion of study LPCN 1021-13-001 conducted at **Meridien Research (site 108), Bradenton, FL,** should be accepted for further Agency review, with the exception of data from subject (b) (6)

EIR reviews for the bioanalytical site inspection and three other clinical site inspections have been finalized in DARRTS.

Study #: **LPCN 1021-13-001**
Study Title: "Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency or absence of endogenous testosterone – primary hypogonadism (congenital or

acquired) or secondary hypogonadism (congenital or acquired)"

Clinical Phase: 2/7/2014-4/30/2015

The audit included a thorough review of study records, including study protocol compliance, informed consent, institutional review board approvals, case report forms, and examination of facilities and test article accountability, as well as interviews and discussions with the firm's management and staff.

The inspection at **Meridien Research (site 108), Bradenton, FL,** was conducted by ORA Investigator Gene R. Gunn, from May 23 to June 2, 2016. Following the inspection, Form FDA-483 was issued (**Attachment 1**). OSIS reviewers received the firm's response via email on June 15, 2016 (**Attachment 2**). The Form FDA-483 observations and our evaluations follow:

OBSERVATION 1

(b) (4)

Firm's response to Form FDA 483: (b) (4)

(b) (4)

Firm's response to FDA Form 483: (b) (4)

(b) (4)

Firm's response to FDA Form 483: [redacted] (b) (4) (b) (4)

Conclusion:

This OSIS reviewer concludes that the data from the clinical portion of study LPCN 1021-13-001 conducted at **Meridien Research (site 108)**, with an exception of subject [redacted] (b) (6) should be accepted for further Agency review. However, we are aware of the Complete Response letter issued on June 28.

Final Classification:

VAI: **Meridien Research (site 108), Bradenton, FL (FEI: 3009992414)**

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Email cc:

OSIS/Kassim/Taylor/Haidar/Kadavil/Fenty-Stewart/Nkah/Miller
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OSIS/DGDBE/Cho/Choi/Skelly/Au/Li
CDER/OND/DBRUP/Joffe

ORA/Gene R Gunn

Draft: XFL 8/10/2016; 9/1/2016
Edits: MFS 8/12/2016; JC 8/12/2016; 9/6/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ Meridien Research (site 108), Bradenton, FL

OSIS file #BE7072; NDA 208088
FACTS: 11617921

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/s/

XINGFANG LI
09/06/2016

MICHAEL F SKELLY
09/06/2016

SEONGEUN CHO
09/06/2016

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 8, 2016

TO: Hylton V. Joffe, M.D. MMSc.
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)
Office of New Drugs (OND)

FROM: Xingfang Li, M.D., RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Inspection of the following clinical site: Baptist Health Center for Clinical Research, Little Rock, AR covering the following application:

NDA 208088, Testosterone undecanoate, sponsored by Lipocine Inc., USA

Recommendations:

This OSIS reviewer recommends that data from the clinical portion of study LPCN 1021-13-001 conducted at **Baptist Health Center for Clinical Research, Little Rock, AR** (site 139), should be accepted for further Agency review.

Inspection:

Study #: **LPCN 1021-13-001**
Study Title: "Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency or absence of endogenous testosterone – primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired)"
Clinical Phase: 2/7/2014-4/30/2015

The audit included a thorough review of study records, including study protocol compliance, informed consent, institutional review board approvals, case report forms, and examination of facilities and test article accountability, as well as interviews and discussions with the firm's management and staff.

The inspection at **Baptist Health Center for Clinical Research Little Rock, AR** was conducted by Johann M. Fitch from May 9 to May 13, 2016. Following the inspection, Form FDA-483 was issued (**Attachment 1**). OSIS received the firm's response to Form FDA-483 via email on June 3, 2016 (**Attachment 2**). The Form FDA-483 observations and our evaluations follow:

OBSERVATION 1

(b) (4)

OSIS reviewer's evaluation and conclusion:

(b) (4)

(b) (4) In this reviewer's opinion, there is no significant impact to patient safety or study outcomes.

Final Classifications:

VAI: Baptist Health Center for Clinical Research, Little Rock, AR
(**FEI: 3011684985**)

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Email cc:

OSIS/Kassim/Taylor/Haidar/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala
OSIS/DGDBE/Cho/Choi/Skelly/Au/Li
CDER/OND/DBRUP/Joffe
ORA/Johann M. Fitch

Draft: XFL 6/15/2016; 7/6/2016
Edits: MFS 6/16/2016; JC 7/8/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Baptist Health Center for Clinical Research, Little Rock, AR
OSIS file #BE7072; NDA 208088
FACTS: 11617921

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/s/

XINGFANG LI
07/11/2016

MICHAEL F SKELLY
07/11/2016

SEONGEUN CHO
07/11/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 9, 2016

To: Jeannie Roule
Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Trung-Hieu Brian Tran, Pharm D, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 208088**
Tlando (testosterone undecanoate) Capsules, for oral use

OPDP acknowledges receipt of your November 2, 2015, consult request regarding the Package Insert (PI) and Carton/Container Labeling for Tlando (testosterone undecanoate) Capsules, for oral use. Reference is made to the June 2, 2016, email from DBRUP which indicated that a Complete Response letter will be issued. For this reason, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DBRUP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Trung-Hieu Brian Tran, (240) 402-0281, or Trung-Hieu.Tran@fda.hhs.gov.

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/s/

TRUNG-HIEU B TRAN
06/09/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

REVIEW DEFERRAL MEMORANDUM

Date:	June 7, 2016
To:	Hylton Joffe, MD Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	testosterone undecanoate
Dosage Form and Route:	capsules for oral use CIII
Application Type/Number:	NDA 208088
Applicant:	Lipocine Inc.

1 INTRODUCTION

On August 28, 2015, Lipocine Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 208088 for testosterone undecanoate, capsules for oral use CIII. The proposed indication for testerone undecanoate is for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testerone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

On October 26, 2015 the Division of Bone, Reproductive and Urologic Products (DBRUP) requested the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for testosterone undecanoate, capsules for oral use CIII.

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for testosterone undecanoate, capsules for oral use CIII.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

TWANDA D SCALES
06/07/2016

MARCIA B WILLIAMS
06/07/2016

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 26, 2016

TO: Hylton V. Joffe, M.D., MMSc.
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)
Office of New Drugs (OND)

FROM: Xingfang Li, M.D., RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Inspections of the following clinical sites:

1. **Los Angeles BioMedical Research Institute at Harbor UCLA**, Torrance, CA
2. **UTSW Medical Center Urology Lewisville**, Lewisville, TX

covering the following application:

NDA 208088, Testosterone undecanoate, sponsored by Lipocine Inc., USA

Recommendations:

This OSIS reviewer recommends that data from the clinical portion of study LPCN 1021-13-001 conducted at **UTSW Medical Center Urology Lewisville** (formerly Teaxs Urology, site 154), at Lewisville, TX and **Los Angeles BioMedical Research Institute** at Harbor UCLA (site 105), Torrance, CA, should be accepted for further Agency review. However, this reviewer recommends that DBRUP and OCP reviewers evaluate the unexpected elevations of Lipoprotein-Associated Phospholipase (LAP-A2) found in some samples from patients enrolled in **UTSW Medical Center Urology Lewisville**, Lewisville, TX.

Please note that review of Establishment Inspection Reports (EIRs) for inspections at **Meridien Research** (site 108), Bradenton, FL, and **Baptist Health Center** (site 139), Little Rock, AR, is pending. The EIR review for the bioanalytical inspection at [redacted] (b) (4) is finalized in DARRTS.

Inspection:

Study #: **LPCN 1021-13-001**
Study Title: "Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency or absence of endogenous testosterone – primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired)"

Study Period: 2/7/2014-4/30/2015

The audit included a thorough review of study records, including study protocol compliance, informed consent, institutional review board approvals, case report forms, and examination of facilities and test article accountability, as well as interviews and discussions with the firm's management and staff.

The inspection at **UTSW Medical Center Urology Lewisville** (formerly Texas Urology, site 154), Lewisville, TX was conducted by Camille Brown from April 18 to April 26, 2016. Following the inspection, no objectionable condition was found and no Form FDA-483 was issued. However, the following item was discussed with the management at the inspection close-out, in order to clarify the record of communications on some clinical laboratory findings.

Elevated Lipoprotein-Associated Phospholipase (LAP-A2) levels within 7 out of 15 enrolled subjects randomized to Lipocine were observed at the following time points: Screening, Week 7, Week 13, week 26, Week 39, Week 52.

Dr. Goldberg consulted 2 cardiologists to determine whether these subjects should remain on study and if there was significant cardiovascular risk involved. Following consultation, Dr. Goldberg decided to continue these subjects on the study. AEs were recorded for elevated LAP-A2 values. No other AEs were noted in these subjects' records. EKG and other laboratory results were normal.

OSIS reviewers alerted the clinical pharmacology reviewer regarding the unexpected elevations in Lipoprotein-Associated Phospholipase (LAP-A2), and she alerted other clinical pharmacology and medical reviewers. This OSIS reviewer recommends that OCP and DBRUP reviewers evaluate the significance of the unexpected elevations in the level of LAP-A2.

The inspection at **Los Angeles BioMedical Research Institute at Harbor UCLA** was conducted by Diane C. Van Leeuwen from April 27 to April 29, 2016. Following the inspection, no objectionable condition was found and no Form FDA-483 was issued.

Final Classifications:

NAI: Harbor UCLA Medical Center (site 105), Torrance, CA (**FEI: 3010243454**)

NAI: UTSW Medical Center Urology (site 154), Lewisville, TX **(FEI: 3012133996)**

Email cc:

OSIS/Kassim/Taylor/Haidar/Kadavil/Fenty-Stewart/Nkah/Miller
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Li
CDER/OND/DBRUP/Joffe

ORA/Diane C Van Leeuwen
ORA/Camille Brown

Draft: XFL 5/20/2016; 5/27/2016
Edits: MFS 5/20/2016; JC 5/20/2016; 5/26/2016
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ Los Angeles BioMedical Research Institute at Harbor UCLA, Torrance, CA
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ UTSW Medical Center Urology Lewisville, Lewisville, TX

OSIS file #BE7072; NDA 208088
FACTS: 11617921

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

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/s/

XINGFANG LI
05/27/2016

SEONGEUN CHO
05/27/2016

MEMORANDUM

REVISED REVIEW OF LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 4, 2016
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	NDA 208088
Product Name and Strength:	Tlando (testosterone undecanoate) Capsules (b) (4) (b) (4) 112.5 mg
Submission Date:	August 28, 2015
Applicant/Sponsor Name:	Lipocine Inc.
OSE RCM #:	2015-2005-1
DMEPA Primary Reviewer:	Walter Fava, RPh., MSEd., Safety Evaluator
DMEPA Team Leader:	Danielle Harris, PharmD., BCPS

1 PURPOSE OF MEMO

This memo is prepared in response to new information provided by the Division of Bone, Reproductive, and Urologic Products (DBRUP) concerning the labels and labeling of testosterone undecanoate which has developed since the previous review.[1]

2 BACKGROUND

The Division of Bone, Reproductive, and Urologic Products (DBRUP) informed DMEPA on April 21, 2016 during a labeling meeting for NDA 208088, testosterone undecanoate, that the product will not require a medication guide. Other dosage forms within this therapeutic class are dispensed with a medication guide to warn about their potential for product transference, which is not an issue with this oral dosage form. This information makes it necessary for DMEPA

[1] Fava W. Label and Labeling Review for Testosterone undecanoate (NDA 208088). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 March 15. 8 p. OSE RCM No.: 2015-2005.

to amend our comments to the Applicant regarding the medication guide statement to the container label. Additionally, subsequent to that meeting, we were also informed by CMC that due to product stability issues, testosterone undecanoate capsules should be dispensed in the original container. Therefore, the product will need to include label and labeling statements to address that storage requirement. Our specific recommendations to address these issues are provided in section 3 and 4.

3 RECOMMENDATIONS FOR THE DIVISION

We recommend the following be implemented prior to approval of NDA 208088:

A. We request that DBRUP does not communicate our previous comment to the Applicant instructing them to revise the container label to include the statement, 'Dispense enclosed Medication Guide to each patient or Dispense accompanying Medication Guide to each patient'. We also recommend informing the Applicant to remove the (b) (4) submitted August 28, 2015. Our revised recommendations for the Applicant are provided in letter ready format in Section 4 below.

B. We defer to CMC to determine whether the product stability data requires revision to the labels and labeling to include a storage statement to address the need to dispense the product in the original container and, if so, to incorporate the statement into section 16 How Supplied/Storage and Handling. Other currently approved products that have similar storage issues use the statement, 'Keep container tightly closed. Protect from moisture and light. Do not repackage; dispense and store in original container'. Similarly, container label statements for currently approved labels use the statement, 'Dispense and store in original container'.

4 RECOMMENDATIONS FOR THE LIPOCINE INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. Ensure the font size of the established name is at least one half the font size used to present the proprietary name in accordance with 21 CFR 201.10(g)2).
2. Relocate the net quantity statement farther away from the strength statement on the principal display panel to minimize the risk of numerical confusion between the strength and the net quantity. Ensure that the net quantity statement remains on the principal display panel.

B. Carton Labeling

(b) (4)

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

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/s/

WALTER L FAVA
05/04/2016

DANIELLE M HARRIS
05/04/2016

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 26, 2016

TO: Hylton V. Joffe, M.D.
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)
Office of New Drugs (OND)

FROM: Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

William H. Taylor, Ph.D.
Deputy Director
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR for study submitted to NDA 208088, conducted at (b) (4)

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of study LPCN 1021-13-001 at (b) (4)

We recommend that OCP and DBRUP reviewers evaluate consequences of (b) (4) We recommend that all other bioanalytical data from (b) (4) in this study should be accepted for further Agency review.

Study Audited during this Inspection:

Study number: LPCN 1021-13-001 (NDA 208088)
Study Title: "Phase 3, Active-Controlled, Safety and Efficacy Trial of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men"
Sample Analysis: [redacted] (b) (4)

OSIS scientists [redacted] (b) (4) Ph.D. conducted the inspection of the bioanalytical portion of the study from [redacted] (b) (4). The audit covered the [redacted] (b) (4)

During the inspection [redacted] (b) (4) informed us that [redacted] (b) (4)

At the conclusion of the inspection, no Form FDA 483 was issued at [redacted] (b) (4)

Inspections at clinical sites for this study will be reviewed in a separate memorandum.

Discussion:

[redacted] (b) (4)

Recommendation:

[redacted] (b) (4)

Apart from the [redacted] (b) (4) we recommend that all other bioanalytical data from [redacted] (b) (4) under this study should be accepted for further Agency review. [redacted] (b) (4) (b) (4)

Michael F. Skelly, Ph.D.
DGDBE, OSIS

William H. Taylor, Ph.D.
OSIS

[1] Wang-C, Shiraishi-S, Leung-A, Baravarian-S, Hull-L, Goh-V, Lee-PWN, and Swerdloff-RS (2008) "Validation of a testosterone and dihydrotestosterone liquid chromatography tandem mass spectrometry assay" Steroids 73(13):1345-1352.

[2] Lachance-S, Dhingra-O, Bernstein-J, Gagnon-S, Savard-C, Pelletier-N, Boudreau-N, and Lévesque-A (2015) "Importance of measuring testosterone in enzyme-inhibited plasma for oral testosterone undecanoate androgen replacement therapy clinical trials." Future Science November 2015 Vol. 1 No. 4; http://www future-science.com/doi/full/10.4155/fso.15.55

Final Classification:

NAI: (b) (4) (Analytical)
FEI: (b) (4)

CC:
OTS/OSIS/Kassim/Taylor/Haidar/Fenty-Stewart/Nkah/Miller/Kadavil
OTS/OSIS/DNDBE/Bonapace/Dasgupta
OTS/OSIS/DGDBE/Cho/Skelly/Choi
Draft: MFS 4/22/2016
Edits: WHT 4/22/2016; JC 4/26/2016; MFS 4/26/2015

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Bioanalytical Sites/ (b) (4)
OSIS file: BE7072
FACTS: 1162324

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/s/

MICHAEL F SKELLY
04/26/2016

WILLIAM H TAYLOR
04/26/2016

SEONGEUN CHO
04/26/2016

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 15th, 2016

To: Hylton V. Joffe, M.D., Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

From: Joshua Hunt, PharmD, Senior Regulatory Reviewer
Controlled Substance Staff

Subject: **NDA 208088**
Name: LPCN 1021 (TESTOSTERONE UNDECANOATE (TU) ORAL**),** see discussion section for *proposed* proprietary name
Proposed Indication:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle stimulating hormone, luteinizing hormone) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Dosage: Oral Capsules, (b) (4) 112.5 mg
Company: Lipocine Inc.
675 Arapeen Dr Ste 202
Salt Lake City, UT 84108

Materials reviewed: EDR submission

Table of Contents

BACKGROUND:

The Division of Bone, Reproductive, and Urologic Products sent CSS a consult, dated October 26th 2015, requesting the review of 505(b)(2) NDA 208088 LPCN 1021 (testosterone undecanoate) capsules submitted by Lipocine Inc. CSS was not involved in the initial NDA filing meeting for this NDA.

LPCN 1021 (testosterone undecanoate) is an immediate release, solid oral dosage form for testosterone replacement therapy. (b) (4) the drug product is available as (b) (4) (b) (4) 112.5 mg capsules. LPCN 1021 (testosterone undecanoate) capsules is a formulation designed within a lipid vehicle. Currently, TU is only available as an injectable (brand name, Aveed®) product in the US. The formulation is designed to enable absorption of TU via the intestinal lymphatic pathway. Testosterone undecanoate is a straight chain fatty acid ester of testosterone, which is not alkylated at the 17-alpha position. TU is one of several 17β-esterified androgens which also includes testosterone enanthate and testosterone propionate, both of which must be given intramuscularly. TU is a "pro-drug" in that de-esterification of the undecanoate at C17 yields systemic T. It is understood that T and DHT are the primary active hormones derived from orally-administered TU.

The recent CSS review of another testosterone product (Aveed®), dated January 24, 2014, included labeling recommendations, related to abuse and misuse of testosterone. The recommendations were discussed with DBRUP and OSE on February 5, 2014. DBRUP determined that the misuse/abuse safety concern may apply to all testosterone products and should not be limited to Aveed®. Therefore, at that time, CSS's recommended labeling changes were not instituted. Tracked Safety Issue (TSI) 1351: *Testosterone Misuse and Abuse* was opened on April 4th, 2014 under a standard 12 month review timeline which included participants from DBRUP, DEPI, Drug Use, DPV, and CSS. The goal of the TSI was to evaluate the available evidence to accurately and appropriately inform Section 9 of labeling to assist healthcare providers in making prescribing decisions and in counseling patients. During the TSI review cycle, CSS provided DBRUP with a detailed memorandum outlining a justification for the necessity of updated Section 9 labeling language.

In response to this TSI, CSS noted that DBRUP is actively drafting a "SAFETY LABELING CHANGE NOTIFICATION" letter to all applicants of currently approved testosterone drug products. This letter is based on Section 505(o)(4) of the FDCA authorizing the Agency to require holders of approved drug and biological product applications to make safety related label changes based upon new safety information that becomes available after approval of the drug or biological product.

II. CONCLUSIONS

1. The Applicant's proposed **Section 9 Drug Abuse and Dependence** of the label for NDA 208088 does not provide consumers (physicians and patients) with current information related to abuse/misuse of this drug, or provide updated safety data related to abuse, misuse, overdose, dependency and withdrawal symptoms.

III. RECOMMENDATIONS

1. The recommended labeling language for NDA 208088 **Section 9 Drug Abuse and Dependence** is provided under **Labeling Issues**. *NOTE: This language is derived directly from the updated/proposed Section 9 language, as discussed and agreed upon in harmony at the most recent TSI meeting dated 06/24/2015.*

IV. LABELING ISSUES

(b) (4)

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(b) (4)

V. DISCUSSION:

The Applicant previously submitted the proposed proprietary name, (b) (4) on May 13, 2015. However, the Division of Medication Error Prevention and Analysis (DMEPA) found the name unacceptable due to the (b) (4) (b) (4). In response, the Applicant submitted a request for the review of the proposed proprietary name (b) (4) on December 16, 2015. (b) (4). The agency is now reviewing the latest name iteration received on March 1, 2016, proposed the proprietary name-**Tlando**.

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/s/

JOSHUA S HUNT
04/15/2016

MICHAEL KLEIN
04/15/2016

LABEL AND LABELING AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 15, 2016
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	NDA 208088
Product Name and Strength:	(Testosterone Undecanoate) Capsules (b) (4) (b) (4) 112.5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Lipocine Inc.
Submission Date:	August 28, 2015
OSE RCM #:	2015-2005
DMEPA Primary Reviewer:	Walter Fava, RPh., MSEd., Safety Evaluator
DMEPA Team Leader:	Danielle Harris, PharmD., BCPS

1 REASON FOR REVIEW

This review responds to a request from the Division of Bone, Reproductive, and Urologic Products (DBRUP) to review the container labels and carton and professional labeling for testosterone undecanoate (NDA 208088) for areas vulnerable to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the container labels and carton labeling noted that this product will have a medication guide which needs to be stated on the container label to comply with 21 CFR 208.24(d). Additionally we note that the established name shall be at least one half the font size of the proprietary name, which is yet to be approved, in accordance with 21 CFR 201.10 (g)(2). Furthermore, the net quantity statement is located in close proximity to the statement of strength, which may increase the risk of numerical confusion between the strength and net quantity.

Our review of the prescribing information identified the following areas of vulnerability from a medication error perspective:

- The Dosage and Administration section in both the Highlights and the Full Prescribing Information is missing information necessary to ensure the safe use of the product:
    - the route of administration, 'orally' is not stated
    - 'Swallow capsules whole. Do not chew, dissolve, or open capsules' is not stated

- The Dosage Forms and Strengths section of the Highlights does not state the "mg" after the numeric value (b) (4) in the statement "available (b) (4) 112.5 mg capsules."
- Section 3 'Dosage Forms and Strengths' of the Full Prescribing Information contains dosing information '(b) (4) (b) (4)', that should not be present in this section
- Section 16 How Supplied is missing critical information about the product including:
  - imprinting information
  - Package configuration and bottle size (net quantity)
  - NDC number
- Section 17 Patient Counseling Information, 'How should I use {TRADENAME}' does not include the statement: 'Swallow capsules whole. Do not chew, dissolve, or open capsules'.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labels and labeling for testosterone undecanoate may be improved to promote the safe and effective use of this product. We provide our specific recommendations in Section 4.1 and Section 4.2 and advise they are implemented prior to the approval of this NDA.

4.1 RECOMMENDATION FOR THE DIVISION

A. Consider revising the Dosage and Administration section in both the Highlights and the Full Prescribing Information to include the following information to promote safe use of the product:
   1. The route of administration, 'orally' (i.e. 'The recommended (b) (4) dose of {TRADENAME} is 225 mg testosterone undecanoate orally twice daily with food').
   2. 'Swallow capsules whole. Do not chew, dissolve, or open capsules'.

B. Consider revising the Dosage Forms and Strengths section of the Highlights to read, '{TRADENAME} is available as (b) (4) 112.5 mg capsules'.

C. Consider revising section 3 'Dosage Forms and Strengths' of the Full Prescribing Information by removing the dosing statement, '(b) (4) (b) (4)'.

D. Consider revising the section 16 How Supplied to read:

{TRADENAME} (testosterone undecanoate) capsules are available as follows:

(b) (4)

112.5 mg (b) (4)

'XXXX'. NDC (b) (4) bottle of 120 capsules

{TRADENAME} is supplied in HDPE bottles with a foil liner and child resistant cap.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP controlled room temperature].

(b) (4)

E. Consider revising section 17 Patient Counseling Information, 'How should I use {TRADENAME}' to include the statement: 'Swallow capsules whole. Do not chew, dissolve, or open capsules'.

4.2 RECOMMENDATIONS FOR THE LIPOCINE INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label
   1. Your product will be dispensed with a Medication Guide (MG). Each container or package shall therefore instruct the authorized dispenser to provide a MG to each patient and shall state how that MG is provided. Revise the principal display panel to include the statement, (b) (4) (b) (4) or 'Dispense accompanying Medication Guide to each patient' as per 21 CFR 208.24(d).
   2. Ensure the font size of the established name is at least one half the font size used to present the proprietary name in accordance with 21 CFR 201.10(g)2).
   3. Relocate the net quantity statement farther away from the strength statement on the principle display panel to minimize the risk of numerical confusion between the strength and the net quantity. Ensure that the net quantity statement remains on the principle display panel.

B. Carton Labeling

(b) (4).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for testosterone undecanoate that Lipocine submitted on August 28, 2015.

Table 2. Relevant Product Information for testosterone undecanoate	
Initial Approval Date	N/A
Active Ingredient	Testosterone undecanoate
Indication	Primary hypogonadism, hypogonadotropic hypogonadism,
Route of Administration	Oral
Dosage Form	Capsules
Strength	(b) (4) 112.5 mg
Dose and Frequency	(b) (4) or 225 mg po twice a day, (b) (4) (b) (4)
How Supplied/Container Closure	HDPE child resistant bottles of 120 capsules
Storage	25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP controlled room temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Results

Our search did not identify any previous reviews.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following testosterone undecanoate labels and labeling submitted by Lipocine on August 28, 2015.

- Container label
- Carton labeling
- Medication Guide (no image)
- Prescribing Information (no image)

G.2 Label and Labeling Images

(b) (4)

112.5 mg capsule container label

(b) (4)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

WALTER L FAVA
03/15/2016

DANIELLE M HARRIS
03/15/2016