CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208088Orig1s000

SUMMARY REVIEW

Summary Review of NDA Resubmission

Application Number:	NDA 208088
Date of Submission:	January 28, 2022
PDUFA Date:	March 28, 2022
Review Completion Date:	March 24, 2022
Product:	Tlando (testosterone undecanoate) oral capsules
Indication:	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Applicant:	Antares Pharma, Inc.[1]

Executive Summary

On January 28, 2022, the Applicant submitted a class 1 resubmission in response to the December 8, 2020, tentative approval of NDA 208088. The final approval of Tlando was subject to the expiration of the period of exclusivity for Jatenzo which expires on March 27, 2022. The current submission is a request for final approval. In this resubmission, the Applicant confirmed that there were no Chemistry, Manufacturing and Control (CMC) changes made to Tlando since the date of tentative approval.

- The resubmission contains proposed labeling that includes only minor changes from the tentatively approved labeling. Labeling negotiations were completed and an agreement was reached on the content and the language in the Package Insert and Medication Guide.
- The submission also included a safety update report to the NDA on February 23, 2022. The report covered the period of time since the Applicant submitted the Safety Update Report for the fourth review cycle and included a literature search to identify new safety information/adverse events report for Testosterone, a database search of the FDA Adverse Events Reporting System (FAERS) for adverse event cases, a database search using EMBASE (Excerpta Medica database), safety data for a recently completed clinical study, LPCN 1144-18-002, (b) (4) (b) (4) (b) (4) and Safety data for an ongoing clinical study, LPCN 1144-20-002, (b) (4)

[1] The original NDA holder for Tlando was Lipocine, Inc. On October 21, 2021, Lipocine, Inc. transferred ownership of the NDA to Antares Pharma Inc.

NASH [redacted] (b) (4) The safety update raised no new safety concerns for Tlando.

Conclusion: The goal for products indicated for testosterone replacement therapy is to restore testosterone concentrations to the eugonadal range (average concentration [C_{avg}]) and to avoid unacceptably high maximal testosterone concentrations (C_{max}) based on prespecified thresholds. For approval, a product should meet both these goals. Tlando, NDA 208088 had met these goals during the previous review cycle. There are no current safety concerns. Label negotiations are finalized. Therefore, we conclude that there is substantial evidence of safety and effectiveness for Tlando as testosterone replacement therapy (TRT) in hypogonadal men.

Recommendation: From an overall perspective, Tlando (NDA 208088) is recommended for a full approval.

Background

First review cycle: The Applicant submitted the original NDA for Tlando on August 28, 2015. The submission did not provide a single blood-draw titration scheme for clinical practice that would result in a reasonable level of agreement with the titration decisions that were made during the phase 3 study. Without an acceptable single blood-draw titration scheme, it was not possible to make a dosing recommendation for Tlando in clinical practice and in labeling, which raised significant concerns for safety and efficacy, and the drug could not be approved. On June 28, 2016, the Division of Bone, Reproductive and Urologic Products (DBRUP) issued a Complete Response (CR) letter for the NDA. The Applicant was advised to use modeling and simulation data from the completed Phase 3 trial to select the titration scheme proposed for real-world use and to test this selected dose titration scheme in a new Phase 3 trial and show demonstrating acceptable efficacy and safety.

Second review cycle: The Applicant resubmitted the NDA for their second cycle review on August 8, 2017, with two new phase 3 studies. Study LPCN 1021-16-002 (referred to as Study 16-002) was a phase 3, open-label, multicenter, single-arm study that evaluated the efficacy of Tlando 225 mg twice daily (BID) without dose titration for 24 days in adult hypogonadal males. Study LPCN 1021-16-003 (referred to as Study 16-003) was a phase 3, open-label, multicenter, study evaluating the efficacy of Tlando 150 mg three times daily (TID) without dose titration in adult hypogonadal males.

On May 8, 2018, DBRUP issued a CR letter (the second time) for the NDA, noting the following deficiencies:

- Insufficient data to determine whether the testosterone concentrations are reliable because there is inadequate evidence to exclude clinically relevant ex vivo testosterone undecanoate (TU) to testosterone (T) conversion in patients treated with Tlando

- Concerns that Tlando may lead to clinically meaningful increases in blood pressure (BP) that could increase the occurrence of major adverse cardiovascular events
- Failure to meet the secondary endpoints for testosterone Cmax
- Inadequate proposal for determining whether a patient should discontinue the drug in clinical practice

The Applicant was asked to:

- Provide additional information that addresses the extent of ex vivo TU to T conversion with Tlando to confirm the reliability of the testosterone data.
- Conduct an ambulatory blood pressure monitoring (ABPM) trial to definitively assess whether the to-be-marketed dose of Tlando increase blood pressure in hypogonadal men.
- Once the Cmax data are shown to be reliable after resolving the ex vivo TU to T conversion, address why the prespecified criteria for avoiding unacceptably high testosterone concentrations should not apply to Tlando or why maximal testosterone excursions are not clinically relevant. The Applicant was advised that a new dosing regimen could be needed.
- Identify stopping criteria for use in clinical practice.

Third review cycle: The Applicant resubmitted the NDA for their third cycle review on May 9, 2019, with three new clinical studies. Study LPCN 1021-18-001 (hereafter "Study 18-001") was a phase 3, open-label, single-arm study to assess changes in blood pressure (BP) and pulse rate (PR) by ambulatory blood pressure monitoring (ABPM) after treatment with Tlando. Study LPCN 1021-18-003 (hereafter "Study 18-003") was an open-label, single-dose study that evaluated the influence of blood collection tubes and processing time on serum T concentration in the presence of TU in hypogonadal males. Study LPCN 1021-18-002, a phase 1, open-label, single-dose study that evaluated the influence of blood collection tubes and processing time on serum T concentration in the presence of TU in six healthy men, was submitted as a supportive safety study.

On November 8, 2019, DBRUP issued a CR letter (the third time) for the NDA, noting the following deficiency:

- Study 16-002, the phase 3 trial that evaluated the to-be-marketed 225 mg BID dose without titration met the primary efficacy endpoint, acceptably restoring average testosterone concentrations (Cavg) to the normal range. However, the trial did not meet the three secondary endpoints for maximal testosterone concentrations (Cmax), falling well-short of the prespecified targets for the proportion of subjects with testosterone Cmax of 1500 ng/dL or less (74% instead of the 85% target) and testosterone Cmax between 1800 and 2500 ng/dL (14% instead of the 5% target).

The Applicant was advised to generate acceptable clinical data with the dosing regimen to show that excessive testosterone Cmax excursions are not clinically relevant with chronic dosing, or to assess a new dosing regimen in a new phase

3 trial showing that the new dosing regimen meets the standard success criteria for the primary efficacy and secondary Cmax endpoints.

Fourth review cycle: The Applicant resubmitted the NDA for the fourth review cycle on February 28, 2020. The only new information that had not been previously reviewed in the prior three cycles was the reanalysis of testosterone Cmax data from, Study 16-002. The reanalysis included:

- T Cmax distribution analysis after adjustment of T Cmax thresholds based on Tlando pivotal study T assay Upper Limit of Normal (ULN) of 1080 ng/dL
- T Cmax values and distribution analysis post adjustment of T Cmax thresholds based on Tlando T assay ULN with individual patient T Cmax values adjustment by 3%, 5%, and 8% to account for ex vivo TU to T conversion
- Listings and relevant datasets for total excursion time (in minutes) in a 24-hour day for each patient with T Cmax greater than each of the secondary endpoint thresholds based on Tlando T assay ULN with each patient's T Cmax(0-24h) adjusted for ex vivo TU to T conversion by 0%, 3%, 5%, and 8%
- Cmax distribution analysis accounting for transient excursions (total excursion time of <60 minutes in 24-hour day period) with adjusted T Cmax thresholds with Tlando T assay ULN in the absence of any TU to T conversion, and post adjustment of individual patient T Cmax values by 3%, 5%, and 8% to account for ex vivo TU to T conversion

The review team conducted a thorough review of the resubmission and concluded that the NDA met both the primary and secondary (C_{max}) endpoints and could be approved. However, the application received a Tentative Approval (TA) on December 8, 2020, because of unexpired 3-year exclusivity granted to Jatenzo, another oral TU product approved for TRT.[2]

Current Submission (Fifth Review Cycle)

The current submission (SDN 82), received on January 28, 2022, is a class 1 resubmission that responds to the Division's Tentative Approval letter issued on December 8, 2020. The submission requests final approval for NDA 208088 and includes proposed labeling for the Package Insert, Medication Guide, and container labels.

Jatenzo Exclusivity

The issue that prevented full approval of Tlando during the previous review cycle was the unexpired 3-year exclusivity granted to Jatenzo. According to the

[2] See CDER Exclusivity Board Memo entered in DARRTS on December 8, 2020.

Orange Book[3], the only exclusivity listed for Jatenzo is New Product (Code NP) exclusivity. The expiration date listed for this exclusivity is March 27, 2022. Therefore, the exclusivity for Jatenzo will no longer block approval of NDA 208088 after March 27, 2022.

Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

Product Quality:
Please refer to the Memorandum to the Integrated Quality Assessment (IQA) #4 from Hamid Shafiei, PhD, dated March 22, 2022. Per this memorandum, in the IQA # 4 by the Application Technical Lead, Dr. Mark Seggel, dated August 24, 2020, this application was recommended for approval from the OPQ perspective. The current submission does not include any significant additional CMC information and the original recommendation of the approval of the application from the OPQ perspective remains unchanged. Therefore, from the Office of Pharmaceutical Quality (OPQ) perspective, NDA 208088 is recommended for approval.

Nonclinical Pharmacology/Toxicology:
The Applicant has not submitted any new nonclinical study reports, and none are needed. The Pharmacology/Toxicology review by Laurie McLeod-Flynn dated June 1, 2016 recommended approval. Per the review by Andrea Benedict, PhD, dated March 22, 2022, Pharmacology/Toxicology recommends approval of this application and had no proposed changes to Sections 8.1, 8.2, 12.1 or 13 of the prescription label compared to the previously agreed upon labeling at the time of tentative approval in December 2020.

Clinical Pharmacology:
The current submission includes no new clinical pharmacology data. Per the review by Li Wang, PhD, dated March 22, 2022, the Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology recommends approval of the NDA. There are no new labeling recommendations from the Office of Clinical Pharmacology in this review cycle. In the current NDA for Tlando, the Applicant did not provide any data addressing the drug-drug interaction potential of testosterone undecanoate, specifically with other drugs that are metabolized by cytochrome P450 enzymes or transported by transporters. At this time, it is still not clear what the potential drug interactions may be; therefore, the team does recommend the following PMR

- Conduct in vitro studies to assess the potential of testosterone undecanoate to inhibit cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). If the in vitro studies suggest a potential or a clinically relevant drug-drug interaction potential that cannot be discounted, a clinical drug interaction study(ies) may be

[3] Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=206089&Appl_type=N; accessed March 14, 2022.

required to assess the potential of TLANDO to inhibit CYP3A, P-gp, and BCRP.

Clinical Review:

Efficacy

The current submission does not include any additional efficacy information. For a full review of efficacy, see the multi-disciplinary review for the fourth review cycle dated December 3, 2020.[4]

Safety

The safety database for Tlando was reviewed during the first, second, and third review cycles. Refer to the November 8, 2019 multi-disciplinary review for the third review cycle for the most recent update to the safety database.[5]

During the previous review cycles, four safety issues of special interest were identified for Tlando:

- Blood pressure increase
- Increased hematocrit
- Increased serum prolactin (inconsistent finding)
- Potential effects on the hypothalamic-pituitary-adrenal axis

The following strategies are proposed to address these safety concerns:

- Blood pressure increases were quantified in an ambulatory blood pressure measurement (ABPM) trial (Study LPCN 1021-18-001) and will be addressed with labeling.
  For Tlando to be approved, its labeling will need to include:
  - A Boxed Warning regarding increase in BP
  - A Contraindication limiting the use of Tlando to men with hypogonadal conditions associated with structural or genetic etiologies
  - A Medication Guide informing patients of the serious side effects associated with Tlando, including increased BP

  In addition, to ensure that patients understand the risk of increased BP associated with Tlando, the Applicant will be required to conduct, as a postmarketing requirement (PMR), a study to assess patients' comprehension of the key risk messages about blood pressure increases and the associated increased risk of heart attacks and strokes contained in the Medication Guide. The PMR is described as follows:

  > An appropriately designed label comprehension study that assesses patients' understanding of key risk messages in the Medication Guide for testosterone replacement therapy. The primary objective of this study is to assess patient comprehension of materials related to increases in blood pressure that can

[4] Unireview entered in DARRTS December 3, 2020.
[5] Unireview entered in DARRTS November 8, 2019.

increase the risk of major adverse cardiovascular events with testosterone replacement therapy. Include men representative of those who use prescription testosterone therapy with a range of cardiac risk factors, a range of education levels, and various literacy levels. The study findings may result in revisions to the Medication Guide to optimize patients' understanding of important risks of testosterone replacement therapy.

- The issue of increased hematocrit will be addressed with labeling. During Study LPCN 1021-18-001, the study with longest duration (110 days) evaluating the to-be-marketed dose and dosing regimen (225 mg BID fixed dose), the mean increase in hematocrit was 3.2%. Because it is unclear whether hematocrit would further increase with longer use of Tlando, the polycythemia subsection of Warnings and Precautions for the Tlando labeling will include instructions to assess hematocrit every three months during the first year that patients are on the drug and periodically thereafter.

- The issue of increased serum prolactin will also be addressed in the Warnings and Precautions section of labeling. Because there is not sufficient data to definitively resolve the signal of increased serum prolactin seen in Study LPCN 1021-16-002, the labeling will include a Warnings/Precautions recommending that serum prolactin be periodically monitored.

- Potential effects on the hypothalamic-pituitary-adrenal axis: Although the Applicant included Cosyntropin stimulation substudies in Studies LPCN 1021-16-002 and LPCN 1021-16-003, the 24-day treatment period during these studies was insufficient to definitively exclude a risk of adrenal insufficiency with chronic dosing. No additional data regarding this issue is included in the current submission. Therefore, the Applicant will be required to conduct a longer duration Cosyntropin stimulation study as a postmarketing required study. The PMR is described as follows:

  An appropriately designed one-year trial to evaluate for the development of adrenal insufficiency with chronic oral testosterone undecanoate therapy. Assess adrenal function with Cosyntropin stimulation testing prior to starting testosterone undecanoate, and again after six months and one year on testosterone undecanoate. Test at earlier timepoints for subjects who demonstrate signs or symptoms consistent with adrenal insufficiency. Assess serum cortisol, adrenocorticotropic hormone, and corticosteroid binding globulin concentrations prior to Cosyntropin 0.25 mg injection and serum cortisol concentrations at 30 minutes and 60 minutes after the injection. Standardize the testing time to 8 AM and the route of Cosyntropin administration (intramuscular or intravenous). Perform

hormonal analytical assays in a central laboratory on batched serum samples.

The Applicant submitted a Safety Update Report to the NDA on February 23, 2022. The report covered the time since the Applicant submitted the Safety Update Report for the fourth review cycle and included the following information:

- A literature search to identify new safety information / adverse events report for Testosterone was conducted in PubMed for the terms "Testosterone, Adverse Events, Adult and Male" for the duration of 05/02/2020 to 02/16/2022
- A database search of the FDA Adverse Events Reporting System (FAERS) for adverse event cases for "testosterone undecanoate" for the years 2021 and 2022.
- A database search using EMBASE (Excerpta Medica dataBASE) performed using the expression 'testosterone undecanoate' covering the period from December 1, 2020, until January 31, 2022 (the cut-off date is January 31, 2022).
- Safety data for a recently completed clinical study, LPCN 1144-18-002, (b) (4) (b) (4) (b) (4) (b) (4)
- Safety data for an ongoing clinical study, LPCN 1144-20-002, (b) (4)(b) (4) (b) (4).

PubMed Search: The Applicant conducted a literature review to identify any new safety information related to the use of testosterone. The search was carried out using the PubMed database and the key words of "Testosterone, Adverse Events, Adult, and Male" for articles published from May 02, 2020, to February 16, 2022. None of the 17 papers retrieved from this search raised new safety concerns for Tlando.

FAERS Search: The Applicant conducted a search of the FAERS database for adverse event cases for "testosterone undecanoate" for the years 2021 and 2022. Over this period, 130 adverse event reports were submitted for testosterone undecanoate. Most of the reports were for the IM formulation of TU. Of the 32 reports submitted for oral TU, seven were classified as serious. None of the preferred terms reported in the serious reports had more than two reports (pulmonary embolism and testosterone increased). The other 25 reports were classified as non-serious. The FAERS search did not raise new safety concerns for Tlando.

EMBASE Search: The Applicant conducted a search using EMBASE for the expression 'testosterone undecanoate' covering the period from December 1, 2020, until January 31, 2022 (the cut-off date is January 31, 2022). A total of 79

articles were returned. Two of these articles specifically discussed Tlando.[6, 7] Both articles were funded by the previous owner of the Tlando NDA and described the studies conducted with Tlando. Neither the two Tlando articles nor the 77 other articles retrieved using EMBASE raised any new safety concerns for Tlando.

Completed and Ongoing Clinical Studies:

LPCN 1144-18-002

LPCN 1144-18-002 was a 36-week trial of male subjects with histologic evidence of NASH. The trial included both eugonadal and hypogonadal subjects who were randomized in a 1:1:1 ratio to the following three treatment groups:

- Treatment A (monotherapy, (b) (4)): Oral LPCN 1144[8], 225 mg TU capsule administered twice daily (BID).
- Treatment B (combination therapy, (b) (4)): Oral LPCN 1144 (225 mg TU) with d-alpha tocopherol (238 mg) capsule administered twice daily (BID).
- Treatment C (b) (4)): Oral matching placebo capsule administered twice daily (BID).

(b) (4)

[redacted]

[6] DelConte A et al. A new oral testosterone (Tlando) treatment regimen without dose titration requirement for male hypogonadism. Andrology 2022: Article in Press.

[7] Papangkorn K et al. Clinical experience with Tlando in hypogonadal men; Journal of Urology 2021 206:SUPPL 3 (e637)

(b) (4)

[redacted]

(b) (4)

LPCN 1144-20-002

LPCN 1144-20-002 is a phase 2, multicenter, single-arm, 36-week, open-label study evaluating the safety and tolerability of extended Oral Testosterone Undecanoate (TU monotherapy, LPCN 1144) in men with NASH who completed the LPCN 1144-18-002 study.

(b) (4)

The safety data from the completed and ongoing clinical studies do not raise new safety concerns for Tlando.

Overall, the safety data from the literature searches, databases searches and the completed and ongoing clinical studies do not raise new safety concerns for Tlando.

Labeling

The current submission includes proposed labeling (Package Insert and Medication Guide) for Tlando that is similar to the labeling that was agreed to at the time of the tentative approval on December 8, 2020.

All disciplines provided input to the label language and all recommended changes were incorporated in the final negotiated label. The agreed upon label includes the following key components:

- A Boxed Warning regarding increases in BP
- A Contraindication limiting the use of Tlando to men with hypogonadal conditions associated with structural or genetic etiologies
- A Medication Guide informing patients of the serious side effects associated with Tlando, including increased BP.

A final agreement was reached between the Division and the applicant on the content of the Package Insert and Medication Guide on March 22, 2022.

Postmarketing Required Studies
Four postmarketing studies or clinical trials will be required for NDA 208088: three under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA); and one under the Pediatric Research Equity Act (PREA).

505(o) PMRs:

- PMR #1: An appropriately designed label comprehension study that assesses patients' understanding of key risk messages in the Medication Guide for testosterone replacement therapy. The primary objective of this study is to assess patient comprehension of materials related to increases in blood pressure that can increase the risk of major adverse cardiovascular events with testosterone replacement therapy. Include men representative of those who use prescription testosterone therapy with a range of cardiac risk factors, a range of education levels, and various literacy levels. The study findings may result in revisions to the Medication Guide to optimize patients' understanding of important risks of testosterone replacement therapy.
- PMR #2: An appropriately designed one-year trial to evaluate for the development of adrenal insufficiency with chronic oral testosterone undecanoate therapy. Assess adrenal function with Cosyntropin stimulation testing prior to starting testosterone undecanoate, and again after six months and one year on testosterone undecanoate. Test at earlier timepoints for subjects who demonstrate signs or symptoms consistent with adrenal insufficiency. Assess serum cortisol, adrenocorticotropic hormone, and corticosteroid binding globulin concentrations prior to Cosyntropin 0.25 mg injection and serum cortisol concentrations at 30 minutes and 60 minutes after the injection. Standardize the testing time to 8 AM and the route of Cosyntropin administration (intramuscular or intravenous). Perform hormonal analytical assays in a central laboratory on batched serum samples.
- PMR #3: Conduct in vitro studies to assess the potential of TLANDO to inhibit cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). If the in vitro studies suggest a potential or a clinically relevant DDI, that cannot be discounted, a clinical drug interaction study(ies) may be required to assess the potential of TLANDO to inhibit CYP3A, P-gp, and BCRP.

PREA PMR:

- A trial of testosterone replacement therapy in pediatric males ages 12 years to less than 18 years of age for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism.

Recommended Regulatory Action

The Division recommends full approval of this application. There is sufficient data to support the overall efficacy and safety of Tlando oral capsules, 225 mg BID regimen. The principal benefit of Tlando is the convenience of oral dosing.

Designated Signatory Authority

I have reviewed the application and I agree with the determination that the benefit/risk of this product is acceptable. There are no outstanding issues that preclude approval. I recommend full approval of this application.

Martin Kaufman, D.P.M., M.B.A.
Clinical Reviewer, DUOG

Suresh Kaul, M.D., M.P.H.
Clinical Team Leader, DUOG

Catherine Sewell, M.D., M.P.H.
Deputy Director (Acting), DUOG

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTIN E KAUFMAN
03/24/2022 08:39:35 PM

SURESH KAUL
03/24/2022 09:35:29 PM

CATHERINE A SEWELL
03/24/2022 10:24:30 PM

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA #	208088
Applicant Name	Lipocine, Inc.
Date of Submission	August 28, 2015
PDUFA Goal Date	June 28, 2016
Proprietary Name / Established (USAN) Name	Tlando / testosterone undecanoate
Dosage Forms / Strength	(b) (4) (b) (4) 112.5 mg capsules
Proposed Indication	For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.
Action	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Martin Kaufman, D.P.M., M.B.A.
Statistical Review	Weiya Zhang, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Laurie McLeod-Flynn, Ph.D. and Mukesh Summan, Ph.D., D.A.B.T.
Office of Pharmaceutical Quality Review	Jeffrey Medwid, Ph.D., Donna Christner, Ph.D., Hamid Shafiei, Ph.D., Moo Jhong Rhee, Ph.D., Juandria Williams, Ph.D., Grace McNally, Haritha Mandula, Ph.D., Kelly Kitchens, Ph.D., James Norman, Ph.D., Yubing Tang, Ph.D., James Laurenson, M. Scott Furness, Mark Seggel, Ph.D.
Clinical Pharmacology Review (Includes Pharmacometrics)	LaiMing Lee, Ph.D., Myong-Jin Kim, Pharm.D., Luning (Ada) Zhuang, Ph.D., Jeffry Florian, Ph.D., and E. Dennis Bashaw, Pharm.D.
CDTL Review	Suresh Kaul, M.D., M.P.H.
Office of Surveillance and Epidemiology/DMEPA	Lolita White, Pharm.D., Walter Fava, R.Ph., M.S.Ed. and Danielle Harris, Pharm.D., B.C.P.S.
Office of Study Integrity and Surveillance	Xingfang Li, M.D., R.A.C., Michael Skelly, Ph.D., William Taylor, Ph.D., and Seongeun Cho, Ph.D.
Controlled Substance Staff	Joshua Hunt, Pharm.D. and Michael Klein, Ph.D.
OPDP	Trung-Hieu Brian Tran, Pharm.D., M.B.A.
Office of Medical Policy/Division of Medical Policy Programs	Twanda Scales, R.N., B.S.N., M.S.N/Ed., Marcia Williams, Ph.D., and LaShawn Griffiths, M.S.H.S.-P.H., B.S.N., R.N.

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
OPDP=Office of Prescription Drug Promotion

Signatory Authority Review

1. Introduction

Lipocine, Inc. submitted this 505(b)(2) New Drug Application (NDA) for oral testosterone undecanoate capsules (proposed trade name Tlando), seeking an indication for replacement therapy in adult men for conditions associated with a deficiency or absence of endogenous testosterone. The product is not approved in any country. This document serves as FDA's decisional memorandum on the application.

2. Background

Currently marketed testosterone products include topical formulations that are applied to the skin, a buccal system that is applied to the gums, an intranasal gel, formulations administered by intramuscular injection and subcutaneously implanted pellets. Methyltestosterone, which is the only FDA-approved orally administered testosterone therapy is rarely used because of concerns for hepatotoxicity. Therefore, if the Lipocine product is approved, it will likely dramatically change the landscape with regard to testosterone therapies, because the oral route of administration will be considerably easier to use than the more cumbersome routes of administration available with the commonly used marketed products.

Testosterone itself has poor oral bioavailability (4-7%) because of the first-pass hepatic effect. Lipocine has developed testosterone undecanoate, a prodrug ester of testosterone bound to undecanoic acid, that allows for oral dosing by targeting absorption via the intestinal lymphatics into the thoracic duct and then into the bloodstream, thereby reducing the first-pass effect. In the blood, testosterone undecanoate is widely metabolized to testosterone by circulating esterases. There is one FDA-approved testosterone undecanoate formulation, Aveed, which is administered by intramuscular injection. Another oral testosterone undecanoate formulation is marketed in some countries.

3. CMC/Device

Reviewers from the Office of Pharmaceutical Quality (OPQ) have concluded that there are sufficient data to ensure the identity, strength, quality, purity and potency of the drug product. See their review for details. All manufacturing facilities have acceptable Current Good Manufacturing Practice (CGMP) status. Labeling has been deferred because the Application will be receiving a Complete Response letter for other reasons (see Sections 7 and 13 of this memorandum). Besides labeling, there are no other outstanding OPQ deficiencies.

The drug substance is testosterone undecanoate, which is a prodrug of testosterone. The OPQ reviewers found the associated drug master file for the synthesis of testosterone undecanoate to be adequate, and impurities are controlled to an acceptable level.

The drug product is a testosterone undecanoate capsule available in [redacted] 112.5 mg testosterone undecanoate [redacted] The 112.5 mg dose is [redacted]

The proposed dosing is [redacted] 225 mg, [redacted] mg twice daily. These doses can be achieved as follows:

- [redacted]
- 225 mg = [redacted] (2 x 112.5 mg)
- [redacted]

The drug product includes the following excipients: glyceryl monolinoleate ([redacted] polyoxyl 40 hydrogenated castor oil [redacted]), ascorbyl palmitate ([redacted] and polyethylene glycol 8000 ([redacted] All excipients are compendial and commonly used in other approved oral products. Impurities (including a suspected [redacted] impurity) are controlled at acceptable limits. Manufacturing process controls are adequate. The OPQ reviewers have granted an expiration dating period of 24 months when the product is stored at 25°C/60% relative humidity.

For dissolution testing, the Biopharmaceutics reviewers have requested that the Applicant revise the Triton X-100 dissolution medium from [redacted]% to 1%. Most of the dissolution data for the drug product at release and on stability were obtained using the [redacted]% medium. Biopharmaceutics found the acceptance criterion adequate on an interim basis but initially requested a postmarketing commitment for Lipocine to submit additional dissolution data using 1% Triton X-100 within 11 months of approval of the application. Because the application will receive a Complete Response action for other reasons, we will request the additional dissolution profile data with the resubmission.

We requested an alcohol dose dumping study because of concerns that alcohol could alter bioavailability by solubilizing the drug. The Applicant chose to conduct an *in vitro* study, which showed dose-dumping with 20% and 40% alcohol. [redacted].

The OPQ reviewers agreed with the Applicant's request for categorical exclusion from an environmental assessment. They do not expect potential for serious harm to the environment based on the expected level of exposure to the product.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewers recommend approval of the NDA pending agreement on labeling. See the reviews by Laurie McLeod-Flynn, Ph.D., and Mukesh Summan, Ph.D., D.A.B.T., for details.

The Applicant is using the 505(b)(2) pathway to abbreviate its nonclinical pharmacology/ toxicology program and rely upon published literature to support some aspects, such as carcinogenicity and reproductive and developmental toxicology. The nonclinical pharmacology/toxicology portion of the NDA includes a 26-week rat toxicology study, 90-day dog toxicology study, *in vitro* genotoxicity studies, an *in vitro* human androgen receptor binding study, and rat and dog metabolism/elimination studies.

Testosterone undecanoate undergoes conversion to testosterone and dihydrotestosterone undecanoate (DHTU). In rats and dogs, testosterone undecanoate and DHTU were the major blood components; testosterone accounted for only about 1% of circulating drug in rats and 4% of circulating drug in dogs. Humans also have higher exposures to testosterone undecanoate and DHTU than to testosterone. However, the Applicant concluded that testosterone undecanoate and DHTU are not expected to have androgenic activity in humans because they did not effectively bind *in vitro* to the human androgen receptor, whereas testosterone did. Specifically, the half-maximal inhibitory concentrations (IC_{50}) for testosterone undecanoate and DHTU were greater than 10,000 nM (compared to 6.1 nM for testosterone) and they had no measurable inhibition constant (Ki).

Testosterone undecanoate was negative in the *in vitro* genotoxicity assays.

Table 1 shows how the exposures to testosterone undecanoate and testosterone in the 26-week rat and 90-day dog toxicity studies compare to the exposures seen in humans administered the maximum recommended dose.

Table 1. Exposures in two animal toxicology studies compared to exposures achieved with the maximum recommended dose in humans

26-Week Rat Toxicology Study	**Low Dose**	**Mid Dose**	**High Dose**
Testosterone Undecanoate	0.8x	6x	10x
Testosterone	0.6x	2x	6x
90-Day Dog Toxicology Study			
Testosterone Undecanoate	5x	16x	28x
Testosterone	5x	20x	29x

In both the 26-week rat and 90-day dog toxicology studies, findings were seen at all doses consistent with the known pharmacologic effect of testosterone. The Nonclinical Pharmacology/Toxicology reviewers did not identify any findings that would preclude approval. However, there was minimal to moderate diffuse adrenal gland cortical vacuolation in all treated males in the rat study, and moderate to marked adrenal cortical atrophy in all

treated males in the dog study. These changes were seen in the zona fasciculata (which produces glucocorticoids) and the zona reticularis (which produces androgens). There were no recovery groups; therefore, reversibility of these adrenal findings is unknown. Another oral testosterone undecanoate product under development by Clarus Therapeutics Inc. causes moderate to marked atrophy of the adrenal cortex in dogs with an accompanying reduction in serum cortisol (Lipocine did not measure serum cortisol in its rat or dog toxicology studies, or in humans). At our request, Clarus is testing whether their product can cause adrenal insufficiency in a subset of patients in their ongoing clinical trial. Lipocine will need to conduct a new phase 3 trial for other reasons (see Sections 7 and 13 of this memorandum) and too should assess whether their product has the potential to cause adrenal insufficiency in humans.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers recommend a Complete Response action because of deficiencies related to the titration scheme proposed for use in clinical practice. See their review for details. Note that this section of the memorandum does not include clinical pharmacology-related data from the pivotal phase 3 trial. Those data, including the basis for the Complete Response recommendation, are discussed in Section 7.

Notable findings from the clinical pharmacology review include:

- The pivotal food effect study and phase 3 trial used the to-be-marketed formulation.

- The Applicant did not conduct drug-drug interaction studies because testosterone undecanoate is metabolized by ubiquitous non-specific esterases.

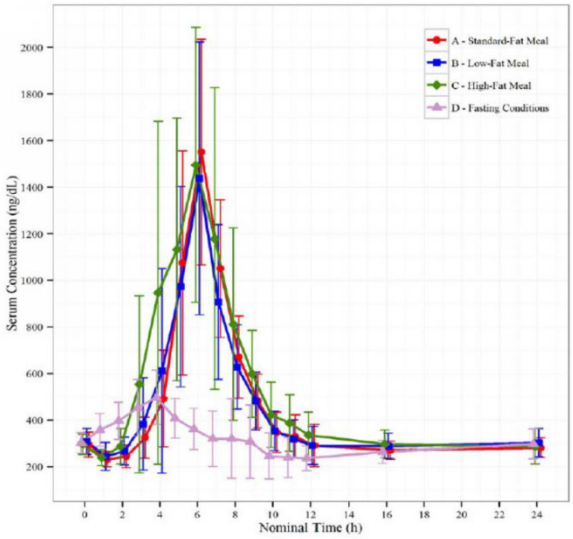
- The Applicant did not conduct dedicated phase 1 studies to evaluate the effect of intrinsic factors (e.g., organ impairment) on testosterone undecanoate and testosterone bioavailability. Because testosterone undecanoate is metabolized by ubiquitous esterases, renal or hepatic impairment is not expected to substantially alter concentrations.

- The Applicant selected the doses for the phase 3 trial based on Cavg and Cmax results from a phase 1 bioavailability study (S361.1.001) using single doses of 75, 150 and 225 mg testosterone undecanoate, and from a phase 2 multiple-dose study (M12-778) using doses of 75, 150, 225 and 300 mg twice daily. Based on these results – which are discussed in detail in Dr. Lee's review – the selected doses for phase 3 appear reasonable.

- The Applicant evaluated the food effect in an open-label, randomized, cross-over study in men who received 225 mg of the Lipocine product in the fasted state and about 30 minutes after the start of a meal with low-fat, moderate-fat, or high-fat content. As shown in Figure 1, the bioavailability of testosterone is low in the absence of food. As shown in the Figure, there is not a substantial difference in testosterone pharmacokinetic profiles between the two extremes of fat content (low-fat vs. high-fat meal). Specifically, for the low-fat to high-fat comparison, the testosterone geometric mean ratio was 0.83 for area under the

concentration-time curve $(AUC)_{0\text{-}12hr}$ and 0.96 for Cmax. Based on these results the Applicant is proposing that the product only be administered with food, without reference to specific fat content. The Clinical Pharmacology reviewers agree.

Figure 1. Mean (standard deviation) serum testosterone concentration-time profiles when the Lipocine product is taken in the fasted state or with meals.



6. Clinical Microbiology

The OPQ reviewers have concluded that the microbial controls are adequate. See the OPQ review for details.

7. Clinical/Statistical-Efficacy

This section briefly summarizes the design of the phase 3 trial, key efficacy results, and problems with the proposed titration scheme for real-world use. See the clinical review by Martin Kaufman, D.P.M., M.B.A., the clinical pharmacology review, the statistical review, and the Cross-Discipline Team Leader Memorandum by Suresh Kaul, M.D., M.P.H. for further details.

Study Design: The Applicant conducted one multicenter, randomized, open-label, phase 3 trial that randomized men with confirmed morning serum testosterone concentrations below 300 ng/dL to 52 weeks of treatment with either the Lipocine product (n=210) or AndroGel 1.62% (n=105). Most Lipocine-treated patients were 65 years of age or younger (91%), Caucasian (82%), and overweight or obese (94%).

All patients randomized to the Lipocine product started at 225 mg twice daily, with doses taken approximately 12 hours apart and with water about 30 minutes after breakfast and

dinner. Patients underwent 24-hour intensive pharmacokinetic sampling at Weeks 3 and 7. Based on the criteria outlined below, the Week 3 data were used to determine the need for dosage adjustment at Week 4, and the Week 7 data were used to determine the need for dosage adjustment at Week 8.

- No dosage change if $Cavg_{0\text{-}24hr}$ 300-1140 ng/dL and Cmax ≤1500 ng/dL
- Dose uptitrated by 75 mg twice daily if $Cavg_{0\text{-}24h}$ < 300 ng/dL
- Dose downtitrated by 75 mg twice daily if $Cavg_{0\text{-}24h}$ > 1140 ng/dL
- Dose downtitrated by 75 mg twice daily if Cmax >1500 ng/dL (regardless of $Cavg_{0\text{-}24h}$)

AndroGel 1.62% was dosed and titrated according to its FDA-approved labeling. The AndroGel arm was included for a comparative safety assessment. The trial was not designed to compare the efficacy of the Lipocine product to AndroGel 1.62%. Therefore, the AndroGel-treated patients did not undergo 24 hour pharmacokinetic assessments for Cavg and Cmax.

The primary efficacy endpoint was the percentage of Lipocine-treated patients who achieved testosterone $Cavg_{0\text{-}24h}$ within the reference range (300-1140 ng/dL) at Week 13. $Cavg_{0\text{-}24h}$ is a time-averaged calculation that divides total exposure (AUC, based on pharmacokinetic sampling over 24 hours) by 24. For success, at least 75% of the Lipocine-treated patients were to have $Cavg_{0\text{-}24h}$ within the reference range, and the lower bound of the corresponding two-sided 95% confidence interval was to be at least 65%.

Cmax is the maximal post-dose serum testosterone concentration. On the intensive pharmacokinetic sampling days, two Cmax values were recorded (one after the morning dose and the other after the evening dose). The following secondary endpoints based on testosterone Cmax at Week 13 were used to assess for unacceptably high exposures to the Lipocine product that could raise safety concerns.

- At least 85% of patients were to have Cmax <1500 ng/dL
- No more than 5% of patients were to have Cmax between 1800 and 2500 ng/dL
- No patients were to have Cmax >2500 ng/dL

The primary efficacy endpoint and Cmax secondary endpoints are standard criteria used in registration trials for testosterone replacement therapies to establish whether the product can reliably achieve serum testosterone concentrations within the normal range for young, healthy, eugonadal men.

The primary efficacy analysis and Cmax secondary analyses were based on patients who received at least one dose of study medication, had at least one post-baseline efficacy assessment ($Cavg_{0\text{-}24h}$ or Cmax), and had no major protocol violations. The last-observation-carried-forward approach was used for patients who were missing Week 13 data. Sensitivity analyses using different statistical populations and a model-based multiple imputation method were conducted to assess the potential impact of protocol deviations and missing data on the efficacy results (about 25% of the Lipocine-treated patients were missing efficacy data at Week 13).

Key Efficacy Results: Based on the primary efficacy analysis, 87% of the Lipocine-treated patients achieved $Cavg_{0\text{-}24h}$ within the reference range (Table 2). The corresponding lower bound of the two-sided 95% confidence interval was 81%. As discussed by Dr. Zhang, all sensitivity analyses yielded comparable results. In all analyses, the point estimate and lower bound of the corresponding 95% confidence interval clearly exceeded the prespecified thresholds for success.

Table 2. Primary efficacy results, including sensitivity analyses: Percentage of Lipocine-treated patients achieving testosterone $Cavg_{0\text{-}24h}$ within the reference range (Adapted from Tables 4, 5, 8 and 9 in Dr. Zhang's review)

Analysis Dataset	Response Rate	95% CI Lower Bound
Primary analysis	87%	81%
Efficacy population set (N=151)		
Sensitivity analyses		
Safety set (N=210)	80%	74%
Full analysis set (N=193)	87%	82%
Per protocol set (N=114)	87%	81%
Multiple imputation set (N=210)	87%	81%
Screening CLIA testosterone <241 ng/dL		
Efficacy population set (N=97)	87%	78%
Safety set (N=138)	78%	70%
Full analysis set (N=126)	86%	78%
Per protocol set (N=82)	87%	77%
Screening LC/MS testosterone <300 ng/dL		
Efficacy population set (N=102)	84%	76%
Full analysis set (N=132)	84%	77%

CI = confidence interval; CLIA = chemiluminescence immunoassay; LC/MS = liquid chromatography-mass spectrometry
Efficacy population set = patients with at least one post-baseline efficacy assessment and no major protocol violations. Missing data imputed using last-observation-carried-forward.
Safety set = patients who received at least one dose of study medication
Full analysis set = patients with at least one post-baseline efficacy assessment
Per protocol set = patients who completed the study without major protocol violations
Multiple imputation set used model-based multiple imputation on the safety set

Sensitivity Analyses Based on Screening Testosterone Assay: The Applicant used a testosterone chemiluminescence immunoassay to determine patient eligibility for the trial. Although this assay has a reference range of 241-827 ng/dL, the Applicant allowed enrollment into the trial if patients had confirmed serum testosterone concentrations below 300 ng/dL. A sensitivity analysis limited to patients with confirmed screening testosterone concentrations below 241 ng/dL still met the prespecified efficacy thresholds for success (Table 2).

The Applicant used a liquid chromatography-mass spectrometry assay for the Week 3, 7, and 13 intensive pharmacokinetic testosterone assessments. Ideally, the Applicant should have used this same assay to determine eligibility for patients entering the trial. The Applicant analyzed some screening samples using the liquid chromatography-mass spectrometry assay. A sensitivity analysis limited to those patients who had screening testosterone concentrations below 300 ng/dL with this assay still met the prespecified efficacy thresholds for success (Table 2).

Cmax Secondary Endpoints: Table 3 summarizes the results for the Cmax secondary endpoints. Drs. Kaufman and Kaul discuss these outliers in detail; key findings are summarized here.

Table 3. Cmax secondary efficacy endpoints at Week 13 (Adapted from Table 6 in Dr. Zhang's review)

$Cmax_{0-24h}$ (ng/dL)[1]	**Lipocine Group N=151 n (%)**	**Target**
<1500	125 (82.8%)	≥85%
≥1800 to ≤2500	7 (4.6%)	≤5%
>2500	3 (2.0%)	0%

Patients with at least one post-baseline efficacy assessment and no major protocol violations. Missing data imputed using last-observation-carried-forward.
[1]To meet the criteria for Cmax <1500 ng/dL, both the Cmax after the morning dose and Cmax after the evening dose would need to be <1500 ng/dL. Patients were classified as having Cmax ≥1800 to ≤2500 ng/dL or Cmax >2500 ng/dL if at least one of their Cmax values (either the morning Cmax or the evening Cmax or both) met these thresholds.

As shown in Table 3, only one of these three Cmax criteria (percentage of patients with Cmax ≥1800 to ≤2500 ng/dL) met the prespecified target.

For Cmax <1500 ng/dL, the Lipocine-treated patients fell slightly short of the 85% target. Four additional patients would have needed Cmax <1500 ng/dL to meet the target. Of note, four patients with Cmax >1500 ng/dL met the Cmax criteria for downtitration but prematurely discontinued from the trial before undergoing 24-hour pharmacokinetic assessments on the lowered dose. Therefore, these high Cmax values obtained before all titrations had been completed were imputed to Week 13 and counted. Had these patients undergone 24-hour pharmacokinetic assessments on the lowered dose, it is possible they may have met the Cmax criteria.

Three patients had Cmax >2500 ng/dL at Week 13 in the efficacy population set (the prespecified statistical population, defined as patients with at least one post-baseline efficacy assessment and no major protocol violations). However, there are a total of eight patients with Cmax >2500 ng/dL at Week 13 when considering all patients with at least one post-baseline

efficacy assessment, regardless of whether there was a major protocol violation. Dr. Kaufman has reviewed the data from these eight patients in detail. Three of these patients had titration problems (e.g., erroneous titration or no pharmacokinetic assessments after undergoing downtitration), one was appropriately discontinued at Week 7 because his serum testosterone was too high despite being downtitrated to the lowest Lipocine dose (and should accordingly also be discontinued in clinical practice), and two patients had high serum testosterone concentrations at time zero of pharmacokinetic sampling suggesting they had received unscheduled testosterone dose(s). There were two remaining patients with unexplained Cmax >2500 ng/dL, both of whom had Cmax <1500 ng/dL on the same Lipocine dose at the previous pharmacokinetic assessment day. These Cmax elevations were transient and not temporally associated with adverse events.

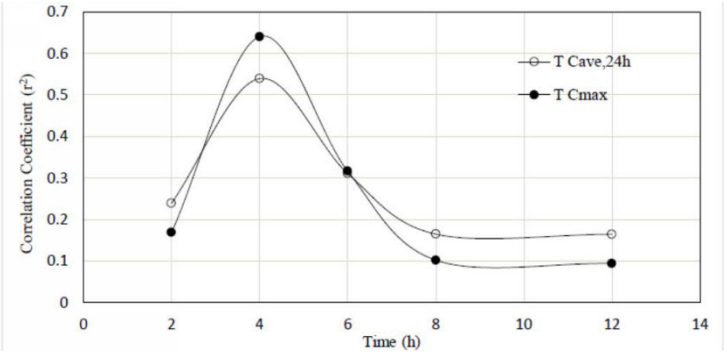
In summary, these Cmax outliers appear acceptable to support approval. However, this determination is moot because, as explained below, a new phase 3 trial is needed.

Titration Scheme: About 60% of the patients in the phase 3 trial had at least one dose titration prior to Week 13. As discussed above, the Applicant titrated patients in the phase 3 trial using testosterone Cavg and Cmax criteria based on 24-hour pharmacokinetic assessments. Such an approach is not feasible for clinical practice. Therefore, with the NDA submission, the Applicant proposed that all patients start at 225 mg twice daily (b) (4)

(b) (4)

The Applicant selected the 3-6 hour timeframe based on a correlation analysis between single point serum testosterone concentrations and $Cavg_{0\text{-}24h}$ and $Cmax_{0\text{-}24h}$. Figure 2 shows results of a correlation analysis based on the phase 2 data. Note, however, that the correlation coefficient (r^2) using these phase 2 data is at best 0.55-0.65 at 4 hours post-dose with a considerable decline to about 0.30 by 6 hours post-dose.

Figure 2. Correlation analysis between single time point serum testosterone concentrations and Cavg and Cmax following using the Lipocine phase 2 data.



The Pharmacometric reviewers found that a slightly different timepoint for sampling correlated better with Cavg and Cmax based on the Week 3 pharmacokinetic data from the phase 3 trial. Using these data, r^2 for the correlation with Cavg was greatest 5-8 hours post dose (0.63-0.68) and r^2 for the correlation with Cmax was greatest 4-6 hours post dose (0.61-0.74). However, using these different timepoints for titration did not improve the performance of the titration scheme proposed for clinical practice, as discussed further below.

During our review, we noted that a substantial proportion of patients who were titrated based on Cavg and Cmax at Weeks 3 and 7 in the phase 3 trial would not be similarly titrated using the Applicant's proposed single blood draw at 3-6 hours after the morning dose. At Week 3 in the phase 3 trial, 61 patients (32%) were downtitrated, 105 patients (55%) had no dose change and 25 patients (13%) were uptitrated. Of the 61 patients who were downtitrated at Week 3, only 41% would be downtitrated using the Applicant's proposed single point titration scheme. The remaining 59% of downtitrated patients at Week 3 would either have no change in dose (56%) or would be uptitrated (3%) based on the single point titration scheme. This is a safety concern because these patients on too high a testosterone dose would not have their testosterone undecanoate dose reduced using the single point titration scheme. Similarly, of the 25 patients who were uptitrated in the trial based on the Week 3 Cavg and Cmax criteria, 90% would have no change in dose using the Applicant's proposed single point titration scheme. This is an efficacy concern because most of these patients needing uptitration would not be uptitrated. Overall, the concordance between the titration decision made in the phase 3 trial at Week 3 and the titration decision based on the Applicant's proposed single point blood draw was only 65%. As discussed in the Pharmacometrics review, other tested thresholds for the single point titration at 3-6 hours (e.g., 300-1140 ng/dL – which were the Cavg bounds used in the phase 3 trial, 125-1140 ng/dL 150-1200 ng/dL, 200-1200 ng/dL, 250-1200 ng/dL, and 300-1200 ng/dL) resulted in similar or worse overall concordance compared to use of the 125-1200 ng/dL threshold.

Of note, the product is administered twice daily but the proposed single time point titration scheme is based on a serum testosterone measured only after the morning dose. It is not feasible in clinical practice to measure serum testosterone in the evening or night-time hours. The Pharmacometrics reviewers explored whether there could be high Cmax values occurring after the evening dose that led to downtitration in the trial but would be missed based on the Applicant's proposed single timepoint measured only after the morning dose. This analysis assessed the concordance between the Applicant's proposed single point titration scheme and titration decisions based on 12 hour Cavg and Cmax (i.e., Cavg and Cmax assessed over the course of 12 hours following the morning dose up until administration of the evening dose). However, this analysis did not result in a meaningful improvement in the concordance rates.

The discordance between the titration decisions made in the phase 3 trial and the titration scheme proposed for marketing is a major problem. The Pharmacometrics reviewers have concluded that the discordance rate cannot be meaningfully improved by selecting a different time interval or titration threshold for the single point titration scheme. Because about one-third of patients would be titrated in the real-world differently to how they were titrated in the trial, there are insufficient data to generalize the phase 3 trial results to real-world use and translate the phase 3 results into labeling.

We sent two information requests to the Applicant, seeking their views on this issue. The Applicant responded to these information requests and submitted a third, unsolicited response. These responses were not extensively reviewed by all members of the review team because of their proximity to the action goal date. However, a cursory assessment was made to determine whether at least one of these submissions should be considered a major amendment and lead to extension of the review clock. We decided against a major amendment because we did not identify the potential for the responses to allay our concerns such that an approval could be possible on this review cycle.

In the first response to our information request, the Applicant proposed a new titration scheme for clinical use – titration thresholds of 300-1200 ng/dL (instead of the initially proposed (b) (4) (b) (4) ng/dL) assessed 4-6 hours after the morning dose (instead of the initially proposed (b) (4) hours). However, using all available data from Weeks 3, 7, and 13, the newly proposed titration scheme is only 63% concordant with the titration decisions made in the phase 3 trial.

The Applicant also included analyses that attempted to address the clinical impact of the discordance between titration decisions in the trial and titration decisions based on the single point titration scheme. These new analyses used data from the phase 3 trial and, if needed, dose-response data derived from the phase 2 trial then recalculated the results for the primary efficacy endpoint and Cmax secondary endpoints. For example, in instances where the titration decision in the trial at Week 3 agreed with the single point titration scheme, the Applicant would use the Week 7 data in the new analysis. In instances where patients were titrated in the trial based on Week 3 data but would not be titrated based on the single point titration scheme, the Applicant carried forward the Week 3 Cavg and Cmax data (which were obtained prior to titration) and used those data at Week 7 in the new analysis. In instances where patients were not titrated in the trial based on the Week 3 data but would be titrated based on the single point titration scheme, the Applicant adjusted the Week 3 data using dose-response data derived from the phase 2 trial, then used these updated data in the new analysis. Based on these analyses, the Applicant concluded that the non-concordance is not likely to have a significant impact on the key efficacy results. However, these analyses based on a subset of data and modeling cannot provide adequate evidence of safety and effectiveness for the titration scheme proposed in clinical practice.

In the unsolicited submission, the Applicant proposed additional strategies for improving concordance between the phase 3 titration and single point titration schemes. The Applicant's first strategy proposed that patients be uptitrated only if two measurements on separate days both support uptitration. The Applicant stated that this strategy would improve overall concordance to 73%. The Applicant's second proposed strategy is to require two blood draws on separate days and to base the titration decision on the highest of the two values. The Applicant stated that this strategy would improve overall concordance to 72%. Of note, these concordance rates are still not optimal and the phase 3 trial was not designed to adequately assess the impact of confirmatory testing on appropriateness of titration. Therefore, these analyses also cannot provide adequate evidence of safety and effectiveness for the titration strategies proposed in clinical practice.

Key Testosterone Metabolites: The goal of testosterone replacement therapy is to restore testosterone and its key metabolites (dihydrotestosterone and estradiol) into the reference range. At Week 13, the mean $Cavg_{0-24h}$ for dihydrotestosterone was 112 ng/dL, the mean Cmax was 186 ng/dL, and the mean dihydrotestosterone/testosterone ratio was 0.26. At Week 13, the mean estradiol $Cavg_{0-24h}$ was 28.2 pg/mL, and the mean Cmax was 42.7 pg/mL. It is not possible to definitively determine whether dihydrotestosterone and estradiol concentrations were normalized with the Lipocine product because the assays did not have an accompanying reference range. In addition, it is not possible to accurately compare the dihydrotestosterone and estradiol concentrations obtained with the Lipocine product to those with AndroGel, because patients in the AndroGel group did not undergo 24-hour intensive pharmacokinetic sampling.

8. Safety

The Applicant met the target of at least 100 patients exposed to the Lipocine product for at least 52 weeks. A total of 130 Lipocine-treated patients (62%) and 71 AndroGel-treated patients (68%) completed the 52-week phase 3 trial. In this trial, 66 patients (31%) ended up on the 150 mg twice daily dose, 113 patients (54%) ended up on the 225 mg twice daily dose, and 31 patients (15%) ended up on the 300 mg twice daily dose.

Deaths: There were no reported deaths in any of the studies.

Serious Adverse Events: In the phase 3 trial, a total of 12 Lipocine-treated patients (6%) and two AndroGel-treated patients (2%) reported a serious adverse event. This imbalance between treatment arms is not driven by any particular serious adverse event. As discussed by Dr. Kaufman, each serious adverse event in the Lipocine arm was reported in only one patient, and none appear to be related to study medication or raise a particular concern.

Dropouts due to Adverse Events: In the phase 3 trial, a total of 20 Lipocine-treated patients (10%) and six AndroGel-treated patients (6%) discontinued due to an adverse event. Adverse events leading to discontinuation in more than one patient included increased body weight (four Lipocine-treated patients), hematocrit >54% (three Lipocine-treated patients and one AndroGel-treated patient), and decreased libido (two Lipocine-treated patients). As noted by Dr. Kaufman, the adverse events of increased weight may have been related to the study design (Lipocine-treated patients were required to eat a meal of at least 25-30 grams of fat before taking each dose of study medication). However, this is not entirely clear because the two treatment groups had comparable changes in mean body weight. Increased hematocrit is a well-known adverse effect of testosterone therapy and is discussed in further detail below. Other adverse events leading to dropout were isolated and either consistent with the known effects of testosterone therapy (e.g., increased prostate specific antigen) or unlikely to be related to study medication (e.g., staphylococcal bacteremia).

Common Adverse Events: The incidence of adverse events was comparable in the Lipocine and AndroGel treatment arms (32%). Notable adverse events that were reported at a higher incidence with Lipocine than with AndroGel were increased body weight (4.8% vs. 1.0%),

increased hematocrit (2.4% vs. 1.0%), diarrhea (2.9% vs. 1.0%), and diabetes mellitus (2.4% vs. 0%). Note that the objective body weight data and glucose data from the laboratory assessments were comparable between the two treatment groups.

Selected Laboratories:

Testosterone Undecanoate and DHTU: At Week 13, mean testosterone undecanoate exposures were about 20-fold higher than mean testosterone exposures (based on $Cavg_{0\text{-}24h}$), and mean maximal concentrations were about 40-fold higher than those seen with testosterone (based on $Cmax_{0\text{-}24h}$). For DHTU, mean exposures ($Cavg_{0\text{-}24h}$) and mean maximal concentrations ($Cmax_{0\text{-}24h}$) were about 10-fold higher than the corresponding mean testosterone concentrations. The Applicant puts forth several reasons for why these exposures are not expected to have clinical relevance. The rationale includes the short half-lives of dihydrotestosterone and DHTU (less than two hours), the lack of effective *in vitro* binding of dihydrotestosterone and DHTU to the human androgen receptor, no toxicologic concerns in rats and dogs with adequate safety margins, and similar androgenic effects compared to the AndroGel arm in the phase 3 trial. However, as noted by Dr. Kaufman, the available data cannot definitively exclude a clinical effect of testosterone undecanoate and DHTU. For example, even though they have short half-lives, there is still considerable exposure to testosterone undecanoate and DHTU over the course of 24 hours. In addition, some potential toxicologic effects (e.g., the adrenal effects) seen in rats and dogs could potentially be related to testosterone undecanoate or DHTU. Lastly, Dr. Kaufman notes some differences in androgenic effects between the Lipocine product and AndroGel (see below), which could potentially be related to metabolism of DHTU to DHT.

Hematocrit: In the phase 3 trial, mean hematocrit increased from 43% at baseline to 46% at Week 52 in the Lipocine group, and from 44% to 46% in the AndroGel group. Eight Lipocine-treated patients (3.8%) and one AndroGel-treated patient (1.0%) developed hematocrit greater than 54%. It is unknown whether differences in testosterone or dihydrotestosterone concentrations between the Lipocine arm and AndroGel arm may have contributed to these slightly different rates of hematocrit elevations, because the AndroGel arm did not undergo intensive 24-hour pharmacokinetic assessments. The labeling for currently approved testosterone products recommends periodic monitoring of hematocrit, which would also be incorporated into the Lipocine labeling.

Prostate-Specific Antigen: In the phase 3 trial, mean prostate-specific antigen increased from 0.7 ng/mL at baseline to 1.0 ng/mL at Week 52 in the Lipocine group, and from 0.6 ng/mL to 0.7 ng/mL in the AndroGel group. Prostate-specific antigen elevations to greater than 4 ng/mL occurred in three Lipocine-treated patients (1.4%) and two AndroGel-treated patients (1.9%). Dr. Kaufman notes that two of these Lipocine-treated patients had only a transient increase in prostate-specific antigen that was again below 4 ng/mL on repeat testing one week later, and that the third patient may have had an inflammatory process because the prostate-specific antigen increased rapidly to 12.2 ng/mL then decreased to 7.7 ng/mL three days later. There were no reports of prostate cancer among Lipocine-treated patients. The labeling for currently approved testosterone products recommends monitoring patients with benign prostate hypertrophy for worsening signs and symptoms, and to evaluate patients for prostate cancer

prior to initiating testosterone therapy and periodically during treatment. Similar language would also be incorporated into the Lipocine labeling.

Lipid Profiles: In the phase 3 trial, mean HDL cholesterol decreased from 49 mg/dL at baseline to 43 mg/dL at Week 52 in the Lipocine group, and from 46 mg/dL to 45 mg/dL in the AndroGel group. At Week 13, 57% of the Lipocine-treated patients and 37% of the AndroGel-treated patients had HDL cholesterol below 40 mg/dL. At Week 52, 37% of the Lipocine-treated patients and 32% of the AndroGel-treated patients had HDL cholesterol below 40 mg/dL. As noted by Dr. Kaufman, decreased serum HDL cholesterol is a risk factor for cardiovascular disease. Lipocine-treated patients had a reduction from baseline to Week 52 in mean serum total cholesterol and serum triglycerides, whereas serum LDL cholesterol remained essentially unchanged. The labeling for currently approved testosterone products recommends periodic monitoring of lipid parameters, which would also be incorporated into the Lipocine labeling.

Liver Tests: As mentioned previously, the only FDA-approved oral formulation of testosterone, methyltestosterone, can cause hepatotoxicity. There were no cases of Hy's Law among Lipocine-treated patients.

Sex Hormone Binding Globulin: In the phase 3 trial, mean sex hormone binding globulin (SHBG) decreased from 0.3 mg/dL at baseline to 0.2 mg/dL at Week 52 in the Lipocine group, and increased from 0.3 mg/dL to 0.4 mg/dL in the AndroGel group. The maximum decrease in SHBG among the Lipocine-treated patients occurred at Week 13 then concentrations plateaued for the remainder of the trial. Mean SHBG values remained in the lower portion of the reference range (0.2-0.7 mg/dL).

Vital Signs: In the phase 3 trial, mean body weight increased by 0.9 kg in the Lipocine group and 1.4 kg in the AndroGel group. These data do not support an overall adverse effect of Lipocine or study design features on body weight, in contrast to the reported sporadic adverse events of increased body weight.

In the phase 3 trial, mean systolic and diastolic blood pressure remained essentially unchanged over the 52 week treatment period, with no observed differences between the Lipocine and AndroGel treatment groups.

9. Advisory Committee Meeting

This NDA was not taken to advisory committee. The Application did not raise efficacy or safety issues needing external input.

10. Pediatrics

The Division in consultation with the Pediatric Review Committee (PeRC) agrees with the Applicant's request for a full waiver from conducting pediatric studies under the Pediatric

Research Equity Act (PREA). Hypogonadism is rare in children; therefore, studies of Lipocine in the pediatric population are highly impractical.

11. Other Relevant Regulatory Issues

Dr. Kaufman did not identify concerns related to financial disclosures of study investigators.

DMEPA found the proposed trade name, Tlando, acceptable. See their review for details. The trade name will be re-evaluated when the application can be approved.

The Office of Study Integrity and Surveillance (OSIS) inspected two clinical sites involved in the phase 3 trial and concluded that the data from those sites are acceptable for review. The inspectors did not identify objectionable conditions or issue an FDA-483 form at either site.

OSIS also inspected the bioanalytical method validations and sample analyses for testosterone, dihydrotestosterone, testosterone undecanoate, DHTU and estradiol for some of the serum samples analyzed in the phase 3 trial. The inspection identified thawing of four serum samples during shipping. Two of these samples were from AndroGel-treated patients, and the other two samples were from Lipocine-treated patients who were not included in the primary efficacy analysis. Therefore, these thawed samples have no impact on conclusions regarding the efficacy of the Lipocine product. These two samples from Lipocine-treated patients (representing less than 1% of the safety population in the phase 3 trial) also do not meaningfully impact safety conclusions.

There are no other unresolved regulatory issues.

12. Labeling

The Controlled Substance Staff recommends that Section 9 of the prescribing information include the updated language we have developed and will require in the near future for all testosterone products. However, labeling is being deferred because the Application cannot be approved on this review cycle. The only labeling comments we will communicate in the Complete Response letter pertain to the carton and container.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response, which is in agreement with the recommendation by the clinical pharmacology reviewers, medical officer, and Cross-Discipline Team Leader.

- Risk Benefit Assessment

The Phase 3 trial shows that the Lipocine product can reasonably replace serum testosterone concentrations to the normal range when the product is titrated using Cavg and Cmax criteria from intensive 24-hour pharmacokinetic sampling. This titration scheme is not feasible for real-world use. The Applicant proposed various titration schemes for use in the real-world based on a testosterone blood draw several hours after the morning dose. However, the concordance between the titration decision made in the phase 3 trial and the titration decision based on the Applicant's proposed single point blood draw is as low as 65%. This means that a substantial number of patients would not be downtitrated with real-world use when they were downtitrated in the trial and would not be uptitrated with real-world use when they were uptitrated in the trial. This raises efficacy and safety concerns, limits generalizability of the phase 3 efficacy and safety results to real-world use, and precludes the ability to develop appropriate dosing recommendations in labeling. To address this major deficiency, the Applicant will need to conduct a new phase 3 trial. They should first conduct modeling and simulations to optimize selection of a new single point titration scheme proposed for marketing and then test this titration scheme in the new phase 3 trial and show that the tested titration scheme leads to acceptable efficacy and safety.

There are some features of the existing phase 3 trial that should be improved upon in the new trial. First, the dropout rate was unusually high. The Applicant should work to minimize dropouts and loss-to-follow. The primary statistical population for efficacy should not exclude patients with protocol deviations. Also, the Applicant should use assays for the testosterone metabolites (dihydrotestosterone, estradiol) that have an accompanying reference range so that we can be assured that the Lipocine product restores these key metabolites to the normal range. Lastly, the Applicant should use the same, adequately validated serum testosterone assay for screening and for the 24-hour pharmacokinetic assessments.

There is a nonclinical signal for adverse adrenal effects in rats and dogs. A similar signal was seen in dogs with another oral testosterone undecanoate product that is currently testing for adrenal insufficiency in a subset of patients enrolled in its ongoing phase 3 trial. Lipocine should similarly assess for adrenal insufficiency (e.g., using cosyntropin stimulation testing) in a subset of patients in its new trial.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None at this time.

- Recommendation for other Postmarketing Requirements and Commitments

In 2015 we required a postmarketing safety trial for the class of testosterone therapies to evaluate the effect of these therapies on the incidence of major adverse cardiovascular events in men. This postmarketing requirement will also apply to Lipocine when the product can be approved unless the effect of testosterone therapy on major adverse cardiovascular events has been resolved. This will be revisited when the application can be approved.

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/s/

HYLTON V JOFFE
06/28/2016