CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208088Orig1s000

OTHER ACTION LETTERS

NDA 208088

TENTATIVE APPROVAL

Lipocine Incorporated
Attention: Chidu Chidambaram
Vice President, Product Development
675 Arapeen Drive, Suite 202
Salt Lake City, UT 84108

Dear Mr. Chidambaram:

Please refer to your new drug application (NDA) dated and received, August 28, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) for Tlando (testosterone undecanoate) oral capsules.

We acknowledge receipt of your amendment dated February 28, 2020, which constituted a complete response to our November 8, 2019, action letter.

This NDA provides for the use of Tlando (testosterone undecanoate) for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the Prescribing Information, Medication Guide, and container labeling).

This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of your application under section 505(c)(3) of the FD&C Act [21 U.S.C. 355(c)(3)] may not be granted before the period has expired.

To obtain final approval of this application, submit an amendment two or six months prior to the: (1) expiration of the exclusivity protection or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as

appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

Please note that this drug product may not be marketed in the United States without final agency approval under section 505 of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the FD&C Act and 21 U.S.C. 331(d).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application receives full approval, you will need to address the PREA requirement because your application has a new dosing regimen.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FD&C Act authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FD&C Act will not be sufficient to identify unexpected serious risks of patients not accurately understanding the serious risk of increased blood pressure due to Tlando that can increase the risk of major adverse cardiovascular events and adrenal insufficiency with chronic Tlando use.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FD&C Act will not be sufficient to assess the aforementioned unexpected serious risk.

Therefore, based on appropriate scientific data, if your application is ultimately approved, FDA has determined that you will be required to conduct the following postmarketing studies:

- An appropriately designed label comprehension and knowledge study that assesses patient understanding of key risk messages in the Medication Guide for Tlando. The primary objective of this study is to assess patient comprehension and knowledge of materials related to increases in blood pressure that can increase the risk of major adverse cardiovascular events with Tlando. 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 patient understanding of important risks of Tlando.

- An appropriately designed one-year trial to evaluate development of adrenal insufficiency with chronic Tlando therapy. Assess adrenal function with Cosyntropin stimulation testing prior to starting Tlando, and again after six months and one year on Tlando. 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. (b) (4)

The timetables for these postmarketing requirements will be established at the time of full approval of your application.

If you have any questions, call Jeannie Roule, Regulatory Project Manager, at 301-796-3993.

Sincerely,

{See appended electronic signature page}

Christine Nguyen, M.D.
Director
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information

    - o Medication Guide
- Container Labeling

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

---

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/

CHRISTINE P NGUYEN
12/08/2020 02:02:16 PM

NDA 208088

COMPLETE RESPONSE

Lipocine Incorporated
Attention: Chidu Chidambaram
Vice President, Product Development
675 Arapeen Drive, Suite 202
Salt Lake City, UT 84108

Dear Mr. Chidambaram:

Please refer to your new drug application (NDA) dated and received August 28, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate (oral).

We acknowledge receipt of your amendment dated May 9, 2019, which constituted a complete response to our May 8, 2018, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Deficiency

Approvability of your NDA is dependent on providing evidence that the proposed dose and dosing regimen for your product will reliably restore testosterone concentrations to the eugonadal range and will avoid unacceptably high testosterone concentrations. LPCN 1021-16-002, the phase 3 trial that evaluated the to-be-marketed, 225 mg twice daily 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).

You state that the pre-specified criteria for testosterone Cmax should not apply to your product because the excursions were infrequent, of short duration and not clinically relevant. However, we note the following:

- You have now shown that there is limited *ex vivo* testosterone undecanoate (TU) to testosterone conversion under the conditions of your phase 3 trial. Therefore, your testosterone Cmax concentrations are reliable and reflect *in vivo* exposures.

- There are important limitations with your interday and intraday repeat Cmax outlier analyses. For example, your interday analyses in Study LPCN 1021-13-001 at Week 13 of the trial occurred after subjects had undergone two dose titrations in which one of the criteria for down titration was Cmax >1500 ng/dL. In addition, the data on repeated excursions are derived from limited longitudinal data – only one pharmacokinetic assessment day in 24-day Study LPCN 1021-16-002 and three such days in 52-week Study LPCN 1021-13-001. However, even with these limited data, repeated Cmax excursions occurred among a notable proportion of subjects who were Cmax outliers.

- A majority of subjects with Cmax >1500 ng/dL had a total excursion time lasting more than an hour over the 24-hour day.

- Your safety analysis comparing subjects who were Cmax outliers at Week 13 of Study LPCN 1021-13-001 to non-Cmax outliers at Week 13 with regard to subsequent changes from Week 13 to Week 52 in hematocrit, prostate specific antigen and other events of interest is not sufficient to address the potential for clinical relevance. This study tested other doses in addition to 225 mg twice daily and used Cmax as part of the criteria to determine dose titration prior to Week 13. Also, the last set of exposure data were obtained at Week 13 and there was no pharmacokinetic assessment at Week 52. Therefore, the exposure-response for safety at Week 52 is unknown.

- In Study LPCN 1021-18-001, the mean changes from baseline in hematocrit and hemoglobin after 110 days of treatment with the 225 mg twice daily fixed dose appear similar to what was seen after 52 weeks of treatment with the titrated dose in Study LPCN 1021-13-001. Due to cross-study comparisons, this finding is not definitive but raises questions about the role of the Cmax outlier excursions given that 225 mg twice daily and the titrated dose yield similar testosterone Cavg concentrations.

We conclude that you have not provided sufficient data to assure that the excessive increases in testosterone are not clinically relevant for your drug that will be used chronically, if approved.

Information Needed to Resolve the Deficiency

Generate acceptable clinical data with this dosing regimen to show that these excessive testosterone Cmax excursions are not clinically relevant with chronic dosing. Alternatively, assess a new dosing regimen in a new phase 3 trial and show that the dosing regimen acceptably meets the standard success criteria for not only the primary efficacy endpoint, but also for the secondary (Cmax) endpoints.

ADDITIONAL COMMENTS

We have the following recommendations that are not approvability issues:

1. Cosyntropin stimulation testing in your 24-day phase 3 trial did not definitively exclude a risk of adrenal insufficiency with chronic dosing. Further assessment of adrenal function over a longer duration is warranted.

2. Your product is administered orally as TU and achieves high systemic TU concentrations. Address the drug-drug interaction potential of TU as the perpetrator.

3. We note discrepant results on serum prolactin between Study LPCN 1021-16-002 and Study LPCN 1021-13-001. Assess serum prolactin in any new trials you conduct.

We also have the following comment:

> On October 2, 2019, Clarus Therapeutics submitted a citizen petition to FDA (Docket No. FDA-2019-P-4644) regarding FDA issuance of guidance on certain scientific standards for oral testosterone-ester prodrugs and FDA approval of such drugs. Our review of this citizen petition is ongoing, and this complete response letter should not be construed to grant, deny, or otherwise comment on this pending citizen petition.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

---

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on your proposed revisions, dated September 16, 2019.

PROPRIETARY NAME

Please refer to correspondence dated, August 2, 2019, which addresses the proposed proprietary name, TLANDO. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/

HYLTON V JOFFE
11/08/2019 02:31:02 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208088

COMPLETE RESPONSE

Lipocine Incorporated
Attention: Satish K. Nachaegari
Associate Director, Regulatory and Clinical Affairs
675 Arapeen Drive, Suite 202
Salt Lake City, UT 84108

Dear Mr. Nachaegari:

Please refer to your New Drug Application (NDA) dated and received August 28, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for testosterone undecanoate (oral).

We acknowledge receipt of your amendment dated August 8, 2017, which constituted a complete response to our June 28, 2016, action letter.

We also acknowledge receipt of your major amendment dated November 10, 2017, which extended the goal date by three months.

We also acknowledge receipt of the following submissions to your NDA: your February 28, 2018, letter regarding the January 10, 2018, advisory committee meeting; your March 2, 2018, position statement on the use of plain serum tubes; and your March 23, 2018, position statement on oral testosterone blood pressure effects.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Deficiencies

1. **Your trials measured serum testosterone concentrations in plain red top tubes and used those data to establish efficacy for your product. However, some of the available data[1] show clinically meaningful *ex vivo* conversion of testosterone undecanoate (TU) to testosterone (T) in these tubes. Due to the high concentrations of TU present in the blood of patients treated with your product, *ex vivo* conversion of a small fraction of TU to T could potentially lead to clinically meaningful increases in the measured T concentrations, yielding results that significantly**

(b) (4)

overestimate systemic T concentrations. You have not provided adequate evidence in your application (including your March 2, 2018, position statement) to exclude clinically meaningful *ex vivo* TU to T conversion with your sample collection and processing method (i.e., serum in plain red top tube at room temperature), despite our prior requests. Therefore, we have insufficient data to determine whether your efficacy and food effect findings, which are calculated using these T data, are reliable.

Information Needed to Resolve Deficiency #1

Provide additional information that definitively addresses the extent of *ex vivo* TU to T conversion with Tlando to confirm the reliability of your testosterone data. We recommend that you conduct a study assessing the potential for *ex vivo* TU to T conversion using samples collected from subjects dosed with oral TU to remove potential confounding effects of different spiking methods (i.e., differences in solvent). This assessment must account for the potential TU to T conversion from the time of blood withdrawal to time of sample analysis. For serum samples, it will be critical to account for any effect occurring in the first 30 minutes that are typically needed to allow for blood to clot. The duration of time the whole blood sample is allowed to sit before serum sample processing should cover the duration that may be expected in clinical practice (e.g., 15, 30, 60, 90 and 120 minutes). Prespecify in the protocol the maximum amount of T concentration overestimation from TU to T *ex vivo* conversion that would be acceptable for the matrix you propose for clinical use and to support the reliability of the efficacy data from your Phase 3 trial. Enroll enough subjects (e.g., 12 subjects), administer your drug product at the maximum recommended to-be-marketed dose, and achieve the same TU concentration as expected at steady state during clinical use. We strongly recommend that you resolve this deficiency before proceeding with additional trials (e.g., ambulatory blood pressure monitoring) because the results from this study could impact future development plans for your product. For example, if this study shows that your testosterone data are unreliable, you will need a new Phase 3 trial to establish efficacy. The results could also potentially impact the choice of dose that is studied in the new trial, which may prompt the need for additional safety data as well.

In addition, due to the similarities in the chemical structure of T and TU and because of the high concentration of TU relative to T in patient specimens, it is possible that T immunoassays commonly used in clinical practice would significantly cross-react with TU causing an overestimation of T concentrations regardless of sample type. If commercially available assays can be used for measuring T in patients treated with your product, provide data demonstrating the rate of TU cross-reactivity with T immunoassays commonly used in clinical practice.

We strongly recommend that you submit any protocols necessary to address this deficiency for review and await our comments before initiating the studies.

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.

3. **Approvability of your NDA is dependent on providing evidence that the proposed dose and dosing regimen for your product will reliably restore testosterone concentrations to the eugonadal range, and will avoid unacceptably high testosterone concentrations. LPCN 1021-16-002, the Phase 3 trial that evaluated the to-be-marketed dose, appears to meet the primary efficacy endpoint, although a final determination will be made after you have adequately addressed the *ex vivo* TU to T deficiency. However, the trial did not meet the three secondary endpoints for maximal testosterone concentrations (Cmax). Only 74% of the subjects had testosterone Cmax of 1500 ng/dL or less, compared to the protocol specified limit of at least 85%; 14% had testosterone Cmax between 1800 and 2500 ng/dL, compared to the protocol specified limit of 5% or less; and 1% had testosterone Cmax greater**

[2] https://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm585826.htm

than 2500 ng/dL, compared to the protocol specified limit of 0%. Therefore, assuming the testosterone data are shown to be reliable, the trial will not have met its prespecified criteria for avoiding unacceptably high testosterone concentrations.

Information Needed to Resolve Deficiency #3

If these Cmax data are shown to be reliable after you have resolved the *ex vivo* TU to T deficiency, thoroughly address why these criteria should no longer apply to your product when they were agreed-upon and prespecified in your protocol and have been consistently applied to all contemporary testosterone applications that have various pharmacokinetic profiles. As part of this justification, include adequate data that show these up to twice per day maximal testosterone excursions are not clinically relevant for your chronically administered product. At this time, we cannot exclude the possibility of needing to test a new dosing regimen and showing that it acceptably meets the standard success criteria for not only the primary efficacy endpoint, but also for these secondary Cmax endpoints.

4. **We have the following concerns with your proposal to use a sample at 7-9 hours after the morning dose to determine whether a patient should discontinue the drug:**
    - **You derived this proposal using testosterone data in your Phase 3 trial, and you have not adequately addressed whether those underlying data are reliable (see Deficiency #1).**
    - **Your proposal is based on an analysis of observed T concentrations at 8-hours post dose. However, you did not consider potential differences in T concentrations over the course of the 7-9 hour window.**
    - **There were few subjects with time-averaged T concentrations above the normal range in your trial to allow for a robust assessment of whether this proposal will appropriately identify patients who are supratherapeutic on your drug.**
    - **A significant number of subjects met your proposed discontinuation criteria despite having a time-averaged T concentration in the normal range.**

Information Needed to Resolve Deficiency #4

Identify stopping criteria for use in clinical practice that can reproducibly and accurately identify those patients who do not achieve time-averaged T concentrations within the normal range. The stopping criteria should also avoid or minimize the inappropriate discontinuation of patients who have T concentrations within the therapeutic range.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. Your 24-day Phase 3 trials provided insufficient data to definitively exclude a risk of adrenal insufficiency with chronic dosing. Further assessment of adrenal function over a longer duration is warranted.

2. Your product is administered orally as TU and achieves high systemic TU concentrations. Address the drug-drug interaction potential of TU as the perpetrator.

3. Submit the full study report for the *in vitro* study evaluating TU conversion to T. Only a brief description of the study design and results were submitted on December 27, 2017.

4. We note a signal for an increase in serum prolactin concentrations in subjects treated with your product. In the resubmission, provide further analyses based on the available serum prolactin concentrations, including mean changes, shift analyses from normal at baseline to above the upper limit of the reference range and outlier analyses (e.g., percentage of subjects developing serum prolactin concentrations above the upper limit of the reference range, above twice the upper limit of the reference range, and above three times the limit of the reference range).

5. We remind you of our information request regarding dissolution testing dated November 30, 2017, and your commitment dated December 8, 2017, to address the information request.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

- 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 carton labeling, the name “LPCN 1021” is presented in

(b) (4) Submit the final 'intend-to-market' carton labeling and container labels for review.

- Remove the Medication Guide (MG) statement from the principal display panel if your product will not have a MG.

- 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).

- 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.

- Change "See package for full prescribing information" to "See package insert for full prescribing information".

PROPRIETARY NAME

Please refer to correspondence dated, November 21, 2017, which addresses the proposed proprietary name, Tlando. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your resubmission. However, you may choose to include a REMS proposal with your resubmission if you believe a REMS is necessary for approval.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYLTON V JOFFE
05/08/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208088

COMPLETE RESPONSE

Lipocine Incorporated
Attention: Satish K. Nachaegari
Associate Director, Regulatory and Clinical Affairs
675 Arapeen Drive, Suite 202
Salt Lake City, UT 84108

Dear Mr. Nachaegari:

Please refer to your New Drug Application (NDA) dated and received August 28, 2015, and your amendments submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for testosterone undecanoate capsules.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

We acknowledge receipt of your amendments dated May 26, June 1, and June 21, 2016, which were not reviewed in detail for this action. Based on a cursory review, we determined that your proposals in these amendments cannot adequately assure the efficacy and safety of your real-world titration scheme. As explained below, you may begin by providing modeling and simulation data from your completed Phase 3 trial to identify an appropriate time point for sampling and titration thresholds, and then must show that the selected dose titration scheme that you propose for real-world use leads to acceptable efficacy and safety in a new Phase 3 trial.

Deficiencies

Approvability of your NDA is dependent upon deriving a dosing algorithm for the label that will provide health care providers and patients with a practical titration scheme, will ensure patients are effectively treated (within the eugonadal range), and will avoid unacceptably high serum testosterone concentrations.

You have proposed a titration scheme for clinical practice that is significantly different from the titration scheme used in the Phase 3 trial. The titration scheme used in your Phase 3 trial was based upon 24-hour testosterone Cavg with an additional criterion for down titration based upon testosterone Cmax outliers (defined as maximal serum testosterone concentrations greater than 1500 ng/dL) after the morning and evening doses. Up to about 35% of the titration decisions made in the Phase 3 trial based on your testosterone Cavg and Cmax criteria would not match the titration decisions made in clinical practice using your proposed real-world titration scheme. This raises efficacy and safety concerns with real-world use because a substantial number of patients

would not be downtitrated in clinical practice when they were downtitrated in the trial and would not be uptitrated in clinical practice when they were uptitrated in the trial. This finding substantially limits generalizability of the Phase 3 efficacy and safety results to real-world use. Your attempts to show that the impact of this issue on the key efficacy results is minimal (e.g., by using a subset of the Phase 3 data and modeling derived from the Phase 2 trial) cannot adequately assure the efficacy and safety of your proposed real-world titration scheme.

Information Needed to Resolve the Deficiencies

Use modeling and simulation data from the completed Phase 3 trial to select the titration scheme that you propose for real-world use. Test your selected dose titration scheme in a new Phase 3 trial and show that it leads to acceptable efficacy and safety.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, April 13, 2016, which addresses the proposed proprietary name, Tlando. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following additional comments and recommendations. You should adequately address these comments in your resubmission.

1. Generate and submit additional dissolution profile data (individual, average, standard deviation, profiles) using the following FDA-recommended dissolution method for release and stability testing of at least 6 production batches (n=12 tablets/batch):

Apparatus:	2 (Paddles) with helix sinkers
Paddle Speed:	100 rpm
Medium:	Tier I: 1% Triton-X in DI Water
	Tier II: Tier I + Enzyme (<75,000 units/L Pepsin)
Volume:	1000 mL
Temperature:	37°C ± 0.5°C

2. Submit draft carton and container labeling revised as follows:

   - 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) .

   - 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.

   - Your product will not be dispensed with a Medication Guide. Remove the Medication Guide statement from the carton labeling.

   - Change "[redacted] (b) (4)" to "See package insert for full prescribing information".

3. The goal of testosterone replacement therapy is to restore serum testosterone and its critical metabolites, dihydrotestosterone and estradiol, to the normal range. To definitively determine whether these metabolites are restored to the normal range, use a laboratory in your new Phase 3 trial that can provide a reference (normal) range for these metabolites based on the specific assays and processes used by the laboratory.

4. In your new Phase 3 trial, use the same testosterone assay for screening and for the post-baseline assessments. The testosterone concentration used to define hypogonadism in the inclusion criteria should be based on the lower limit of normal for the assay that is actually used during screening. The bioanalytical method validation and performance of your selected assay should be in compliance with the FDA's Bioanalytical Method Validation Guidance, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf.

5. Your existing Phase 3 trial had a high dropout rate. In your new Phase 3 trial, every effort should be made to have the patients remain in the trial and complete the protocol-specified visits and procedures.

6. In your new Phase 3 trial, the efficacy analysis should be based on all patients who take at least one dose of your drug product. We suggest a model-based imputation method to account for missing data. A sensitivity analysis can exclude patients with major protocol deviations, but this should not be the primary analysis population.

7. In the nonclinical toxicology studies, adrenal cortical vacuolation was noted in rats and adrenal cortical atrophy was noted in dogs. Although the clinical implications of these findings are not clear, they raise the possibility that your product or its metabolite(s) may cause adrenal insufficiency. In your new Phase 3 trial assess with Cosyntropin

stimulation testing whether your product has adverse effects on the hypothalamic-pituitary-adrenal axis.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYLTON V JOFFE
06/28/2016