CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208088Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 8, 2018
From	Suresh Kaul, MD, MPH
Subject	CDTL Review
NDA/BLA # and Supplement#	NDA 208088 (Resubmission)
Applicant	Lipocine Inc.
Date of Submission	August 8, 2017
PDUFA Goal Date	March 22, 2018
Proprietary Name	Tlando
Established or Proper Name	Testosterone undecanoate
Dosage Form(s)	Capsules
Applicant Proposed Indication(s)/Population(s)	Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone/Adult (18 years or older) males
Applicant Proposed Dosing Regimen(s)	225 mg twice daily (Fixed dose)
Recommendation on Regulatory Action	***Complete Response***
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended Dosing Regimen(s) (if applicable)	N/A

Executive Summary

Tlando capsule is an oral product containing testosterone undecanoate (TU) in a lipid formulation. Tlando is designed to enable absorption of TU via the intestinal lymphatic pathway to avoid the first-pass effect in the liver. TU is a straight chain fatty acid ester of testosterone, which is not alkylated at the 17-alpha position. TU is converted to testosterone by non-specific esterases present in the body. In the US, TU is approved as an injectable intramuscular formulation, but has not been approved for oral administration.

Lipocine submitted the original NDA for Tlando on August 28, 2015. The submission did not provide a single blood draw titration scheme which would result in titration decisions with 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 dosing recommendation for Tlando in clinical practice and in labeling and the drug could not be approved.

On June 28, 2016, DBRUP issued a Complete Response (CR) letter for the NDA.

The CR letter communicated the following deficiencies and the information needed to resolve the deficiencies:

"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**"**.

"ADDITIONAL COMMENTS as communicated in the CR Letter

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 postbaseline 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/Guid ances/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 hypothalamicpituitary-adrenal axis."

A post-action meeting was held with the Applicant on **October 6, 2016**. Key meeting discussion included the secondary endpoints (Cmax outliers) and their importance in demonstrating acceptable efficacy and safety, and the need to evaluate the proposed titration scheme and the design of the new trial. The applicant proposed to pursue a study with fixed dosage administered twice or three times a day with no titration involved.

The applicant resubmitted the NDA on **August 8, 2017** with two new phase 3 studies: Study LPCN 1021-16-002, a phase 3, open-label, multicenter, uncontrolled study evaluating the efficacy of Tlando in adult hypogonadal males. Subjects enrolled in the study received 225 mg of Tlando two times a day for 24 days. This study evaluated the dosing regimen for which the applicant is currently requesting approval. Study LPCN 1021-16-003 was a phase 3, open-label, multicenter, uncontrolled study evaluating the efficacy of Tlando in adult hypogonadal males. Similar to LPCN 1021-16-002, subjects received a fixed dose, but with a dosing regimen of 150 mg of Tlando three times a day. Other than the dosing regimen, the trial design, including the primary and secondary endpoints, inclusion and exclusion criteria, and dietary instructions were similar in both 002 and 003 studies.

In addition to a thorough review of these two phase 3 studies, the focus during this resubmission has been on three major areas: Assesment of Cmax outliers, blood pressure monitoring and ex-vivo conversion of Testosterone Undecanoate (TU) to Testosterone (T).

The application was presented at an Advisory Committee (AC) Meeting on **January 10th, 2018** to seek expert advice on these areas of review focus. Details of the AC discussion are included in Section 14 of this memo.

The applicant also submitted two position statements, one regarding the reliability of the serum testosterone data (dated March 2, 2018) and another regarding effects of oral testosterone on blood pressure (dated March 25, 2018.) These position statements are discussed in the division director memorandum and are not covered in this document.

1. Benefit-Risk Assessment

Recommendation
I recommend a Complete Response (CR) action for this NDA 208088 based on the benefit/risk assessment.

Benefit vs Risk
Tlando capsule is an oral product containing testosterone undecanoate (TU) in a lipid formulation. Tlando is designed to enable absorption of TU via the intestinal lymphatic pathway. It is converted to testosterone by non-specific esterases present in the body. Tlando is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone including congenital or acquired primary hypogonadism and congenital or acquired hypogonadotropic hypogonadism. Tlando's oral route of administration is expected to be more convenient for patients than the currently approved non-oral routes of administration. In addition, this product does not carry the risks of some of the approved products (e.g., transference of a topical gel to a child or female, pulmonary oil microembolism with injectable TU).

Also, with the fixed dosing regimen without titration as demonstrated in studies 002 and 003, the earlier concern of maintaining a reasonable agreement between titration decisions made in Phase 3 trial (001) based on Cavg and Cmax, and titration decisions made using the titration scheme based on a single blood draw is circumvented.

The efficacy goal for products indicated for testosterone replacement therapy is to maintain testosterone concentrations within the

eugonadal range and to avoid unacceptably high testosterone concentrations. Efficacy is established with primary and secondary endpoints based on the results of a pharmacokinetic assessment. The primary endpoint is the proportion of treated subjects who achieve a 24-hour time-averaged T concentration within the normal range. The Division's minimum acceptable percentage for this proportion is 75%, with a lower bound of 65% or greater for the associated 95%, 2-sided, confidence interval. Three secondary endpoints evaluate the proportion of treated subjects with testosterone Cmax (0-24h) values within predetermined limits and are designed to assess for unacceptably high testosterone concentrations (see details of predetermined limits in the efficacy section of this review).

The applicant submitted the results of one phase 3 trial (study-002) to support the efficacy of the 225 mg dose of Tlando administered BID without dose titration. Tlando met the primary endpoint of the trial but did not meet the three secondary Cmax endpoints. There are two major concerns with the findings. First, there are conflicting data as to the extent of ex-vivo conversion of TU to T after a blood sample is collected in the test tube. If there is clinically meaningful conversion to T in the tube, the measured T values will overestimate systemic T concentrations. This would call into question the reliability of the primary and secondary endpoint results. Second, if the T data are shown to be reliable, the product has not met the prespecified criteria for avoiding unacceptably high T concentrations.

The safety database for Tlando included 525 hypogonadal men who received the drug up to 382 days. The drug's effect on blood pressure (BP) remains unclear: Two trials (study-001 and study-002) did not show any clinically significant changes in cuff BP, while one trial (study-003) – which evaluated the same total daily dose proposed for marketing – showed a mean increase of 4 mmHg in cuff systolic BP (SBP). The concern over the BP results in study-003 was reinforced by the BP findings for another oral TU product also in development. A phase 3 study for that drug also showed a signal for an increase in cuff BP that was confirmed and clarified by ambulatory blood pressure monitoring (ABPM) in a subsequent phase 3 study. A clinically meaningful increase in BP is expected to increase the risk of major adverse cardiovascular events (e.g. myocardial infarction, stroke, and cardiovascular death) over time. Therefore, an ABPM study is needed to further characterize this risk for Tlando. Results from an ABPM assessment will impact the regulatory decision, including whether risk evaluation and mitigation strategies (REMS) would be needed to ensure the benefits of the drug outweigh its risks.

Despite reduced SHBG levels, estimated free T concentrations based on total T remained within normal ranges. DHT, a potent metabolite of T was elevated compared to the reference range provided in this submission. No association between increased DHT and lipids, SHBG or other clinical parameters could be established.

Tlando's effect on the hypothalamic pituitary adrenal axis remains unclear. Though, adrenal function was assessed in Cosyntropin stimulation sub-studies during study-002 and 003, the studies were insufficient to exclude a risk of adrenal insufficiency with chronic use . Further assessment of adrenal function over a longer duration is recommended to rule out the risk of adrenal dysfunction.

2. Background

Product Overview

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution. Testosterone is metabolized to dihydrotestosterone (DHT), which is also a potent androgen. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

The Endocrine Society defines hypogonadism in men as "a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency). Hypogonadism, resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas Secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (i.e., follicle stimulating hormone [FSH] and luteinizing hormone [LH])."

Regulatory Background Since the Original NDA Submission

Lipocine submitted the original NDA for Tlando on August 28, 2015. On June 28, 2016, DBRUP issued a Complete Response letter for the NDA. The CR letter stated the applicant had not provided a single blood draw titration scheme that results in titration decisions with 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 dosing recommendations for Tlando in labeling and the drug could not be approved.

- **October 6, 2016: Type A post-action meeting:** Key meeting discussion included the three Cmax secondary endpoints and their importance in demonstrating acceptable efficacy and safety, the need to evaluate the proposed titration scheme in a

new trial, and the design of the new trial.

The applicant resubmitted the NDA on August 8, 2017.

The resubmission review timeline was extended by three months on November 14, 2017, following submission of a major amendment.

3. CMC

Dr. Mark Seggel, PhD, CMC Technical lead, made the following determination in the comprehensive Office of Product Quality (OPQ) review dated Feb. 25, 2018.

Recommendations and Conclusion on Approvability
In its present form, Lipocine Inc.'s resubmission of their 505(b)(2) New Drug Application #208088, for Tlando (testosterone undecanoate) Capsules, 112.5 mg, is not ready for approval. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201. Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.
Interim dissolution test acceptance criteria have been established. Lipocine has agreed to provide additional dissolution profile data from production batches.

CDTL Comment
I concur with the recommendation made by CMC team lead Mark Seggel, PhD.

Dr. Seggel's review of February 25th, 2018 includes:
Drug Substance
Lipocine included a Letter of Authorization (LoA) to cross-reference (b) (4) Type II DMF (b) (4) without any other supporting information. However, there was no change to drug substance.

Drug product

From the drug product review perspective, this new drug application is recommended for **Approval** with a drug product expiration dating period of 24 months at 25C. (see OPQ IQA #1 dated May 31, 2016).

Biopharmaceutics

Dr. Hansong Chen concludes that from the Biopharmaceutics perspective, NDA 208088 for Tlando Capsules, 112.5 mg is adequate for **Approval with the commitment as follows:** Lipocine has agreed to implement the interim acceptance criteria and to generate the requested data post-approval.

Product Manufacturing Process and Product Quality Microbiology

The resubmission included one minor process change. The applicant proposes to use (b) (4) (b) (4). This change has no impact on manufacturing since the (b) (4) (b) (4)

Facilities

All drug substance and drug product manufacturing facilities were found to be operating in compliance with CGMPs.

Environmental Assessment

The claimed categorical exclusion from the Environmental Assessment requirements was previously found **Acceptable** (see OPQ IQA #1 dated May 31, 2016).

Labeling

In collaboration with DMEPA, labeling recommendations were previously conveyed to the applicant. Because the application will receive a Complete Response, labeling negotiations with the applicant have not been initiated. In its present form, the labeling does not comply with the requirements under 21 CFR 201. A full review of the package insert and container labels will be completed upon resubmission of the NDA.

CDTL Comment

I agree with Mark Seggel's overall recommendation. The resubmission did not have any major changes or specific deficiencies. However, Dr. Seggel wants to convey the following to the Applicant as an additional comment in the CR letter.
"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."

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team Drs. Laurie McLeod-Flynn, PhD, and Mukesh Summan, PhD, made the following conclusion and recommendation in their review dated February 16, 2018.
At this time, there is no impediment to Approval of this drug from a Pharmacology/Toxicology perspective.

No additional nonclinical studies were submitted with the 8th August 2017 resubmission. Reference is made to the Pharmacology/Toxicology review for NDA 208-088 by Laurie McLeod-Flynn, filed in DARRTS on 1st June 2016 which recommended approval of this product from a nonclinical perspective.

CDTL Comment
I agree with Dr. Flynn's current recommendation.

5. Clinical Pharmacology

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-3 has reviewed the information contained in the resubmission of NDA 208088, and recommends a Complete Response (CR) action from a Clinical Pharmacology perspective.

CDTL Comment
I agree with the recommendation made by Drs. Lee and Tran.

The Clinical Pharmacology team recommends the Applicant (1) provide additional information about the *ex vivo* testosterone undecanoate (TU) to testosterone (T) conversion to confirm the reliability of the phase 3 testosterone data and (2) identify a stopping criteria that can reproducibly and accurately identify patients not achieving time-averaged total T concentrations within the normal range. The stopping criteria should also avoid or minimize inaccurately discontinuing patients with T concentrations within the therapeutic range.

TU to T Conversion
The Clinical Pharmacology review team recommends that the Applicant conduct a definitive study assessing the potential 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 needs to account for 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 is 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.,30, 60, 90 and 120 minutes).

Dr. Lia Ming Lee in her review dated February 26th, 2018, further states that there appears to be evidence that suggests ex vivo TU to T conversion exists. However, there are conflicting data from the publications and new data from the Applicant which suggests that there is no conversion. The differences in the observed effects may be due in part to differences in the solvent used for TU spiking. Dr. Lee recommends the Applicant provide additional information to address the ex vivo conversion and confirm the reliability of the phase 3 testosterone data. For details about how to correct this deficiency, see Section 14.

CDTL Comment
I agree with Dr. Lee's recommendation.

Stopping Criteria
The Applicant's proposed dosing regimen is 225 mg TU twice daily with no dose titration. The phase 3 data from study 002 show that 80% of subjects achieved serum T Cavg concentration within the normal range. However, there were no criteria included in the Applicant's proposed label for identifying the 20% of patients who should discontinue the product in clinical practice because of T concentrations falling outside the normal range.

At the request of the review team, the Applicant provided the following discontinuation plan (stopping criteria) for their product:
To ensure an appropriate response to therapy, serum total testosterone concentrations should be checked periodically at 7 to 9 hours after the morning dose, beginning as soon as 3 to 4 weeks after beginning therapy. If the total testosterone concentration is consistently below 300 ng/dL, and symptoms have not improved following three months of therapy, an alternative treatment should be considered. If the total testosterone concentration consistently exceeds 1080 ng/dL, therapy with Tlando should be discontinued.

The proposed approach assumes that the T concentration between 7 to 9 hrs after the morning dose would be the same as the T concentration at t=8 hr (post-morning dose), but the Applicant did not provide any additional data or alternative approach (e.g., modeling and simulation) to support that assumption. The proposed stopping criteria also does not account for changes in T exposure in the elimination phase (as noted by the declining PK profile around t=8 hr) and PK variability. Overall, the proposed discontinuation algorithm appears to appropriately discontinue patients not achieving T Cavg within the normal range, but it may

result in a large percentage of patients being discontinued inaccurately, and the data for subjects with supratherapeutic T Cavg are very limited.

The clinical Pharmacology review team does not agree that the proposed stopping criteria using a single T concentration taken at t=8 hr can reproducibly and accurately identify patients having T Cavg outside the normal range and may exclude patients with T Cavg within the normal range. The team suggests that the Applicant should be requested to evaluate the adequacy and reproducibility of a stopping criteria by modeling and simulation approaches and/or using additional empirical data.

In addition, the review team also recommends that the Applicant address the following:

Potential cross-reactivity of TU to immunoassays used to assess total T concentrations in clinical practice:
Cross reactivity of TU, which is present in high amounts following oral TU therapy, with commercial T immunoassays may lead of overestimation of T concentrations. Dr. Lee in her review dated February 26, 2018 suggests that the Applicant should address, through literature or conducting studies, the potential for TU cross reactivity with T immunoassays in the next review cycle.

Drug-drug interactions:
The proposed product is a prodrug with significantly higher concentrations of TU compared to the active metabolite T. The Applicant has not provided any data addressing the potential interaction of TU with other drugs that are metabolized by cytochrome P450 enzymes. Dr. Lee, the Clinical Pharmacology reviewer recommends that the Applicant conduct studies to address the potential drug interaction for the prodrug TU.

CDTL Comment
I agree with the two main concerns discussed above by the Clinical Pharmacology review team. The applicant needs to resolve the issue of TU to T conversion by conducting a new ex-vivo study in subjects dosed with Tlando in order to demonstrate there is either no TU to T conversion or there is minimal conversion that would not affect the reliability of their PK data. Such a study needs to be conducted prior to conducting any other studies that are recommended in the CR letter.

I also agree with the suggestion provided by the Clinical Pharmacology review team to evaluate the adequacy and reproducibility of a stopping criteria by modeling and simulation approaches to address the 20% of subjects that could fall outside the eugonadal range.

Please note that a consult was made by the Division to CDRH, Drs. Marianela Parez-Tores and Courtney Lias, during this review cycle to seek their expert advice in order to resolve the issue of ex-vivo TU to T conversion. Folowing is their recommendation:

Dr. Torres in her review dated February 6, 2018 identified several deficiencies in the studies provided to support the sponsor's conclusion. These include some of the following: since samples collected in red-top tubes are required to stand for ~30 mins to allow clotting prior to centrifugation, it would not be possible to obtain a true baseline level of testosterone (at time zero) in serum samples, sample handling and storage conditions (including temperature and time) may impact the enzyme activity of the esterases that mediate the TU to T conversion (that was not fully characterized), stability of samples containing TU under different storage conditions is unknown and due to similarities in chemical structures of TU and T, if the drug is monitored using immunoassays (most commonly used T assays in clinical labs) the T values may be over-estimated and may not be adequate to monitor a patient.

Based on these concerns, CDRH concludes that the testosterone (T) concentration as measured in samples collected in serum (red top) may be overestimated due to TU to T ex vivo conversion. Data are not available to characterize this effect using samples from patients taking TU (rather than spiked samples).

Dr. Torres had the following observation and recommendations about the remaining concerns:

- Uncertainty remains regarding whether TU converts to T ex vivo, the studies presented showed conflicting data that is not conclusive. While it may not be possible to obtain a true baseline for serum samples that contain TU, it may be possible to use other anticoagulants that are validated for use with Testosterone assays, such as lithium heparin or K2EDTA.
- Data demonstrating the stability of TU and T in serum is not available to the review team. Information regarding suitable specimen collection and handling procedures is not available for serum specimens.
- Potential cross-reactivity of TU with commonly used T immunoassays should be evaluated if the T levels are used to monitor drug efficacy.

CDTL Comment

The suggestions and recommendation from CDRH experts will be conveyed to the Applicant as a deficiency with recommendations to address the deficiency in a CR letter. See Section 14 of this review.

6. Clinical Microbiology

The product exhibited no microbial growth over 6 mo accelerated and 12 mo long-term stability testing. Capsules are packed with desiccant in induction-sealed bottles and tested to contain NMT (b) (4) % w/w per (b) (4), microbiology reviewer. In addition, the raw materials are low bioburden.

CDTL Comment
No microbiology issues were identified.

7. Clinical/Statistical- Efficacy

The primary focus of the clinical review for the resubmission was data derived from new phase 3 trial LPCN 1021-16-002 for efficacy and LPCN 1021-13-001, (the pivotal phase 3 study from the original NDA submission) for safety. LPCN 1021-16-002 is a phase 3 study that provides safety, efficacy, and pharmacokinetic data relating to 225 mg of Tlando dosed twice per day (the proposed to-be-marketed dosing regimen) without titration for testosterone replacement therapy in men with primary and secondary hypogonadism.

Supportive safety data was derived from LPCN 1021-16-003, a new phase 3 study that evaluated 150 mg of Tlando dosed three times per day without titration, which did not meet its primary endpoint.

LPCN 1021-16-002 was a phase 3, open-label, multicenter, uncontrolled study evaluating the efficacy of Tlando in adult hypogonadal males. Subjects enrolled in the study received 225 mg of Tlando two times a day for 24 days. This study evaluated the dosing regimen for which the applicant is currently requesting approval.

The study was comprised of four scheduled visits: Visit 1 and 2 were for screening; Visit 3 was scheduled on Day 1 of the study for the start of dosing, and Visit 4 required confinement of subjects for intensive pharmacokinetic (PK) sampling. All study sites participating in the trial were located in the U.S. Inclusion and exclusion criteria were similar to 001 trial in the original submission. (For details see Dr. Kaufman, clinical reviewer's review, dated March 12, 2018).

The dose for the study was selected based on results from a double-blind, randomized, placebo-controlled, parallel-group, ascending dose, single and multiple dose study (Study M12-778) and analysis of the results from the original active controlled, safety and efficacy Phase 3 trial (LPCN 1021-13-001). Based on results from the M12-778 study the starting dose for this Phase 3 study was 225 mg Tlando administered BID, approximately every 12 hours with a standard meal. The observed Cavg0-24h for serum T was within the normal range of 300 to 1140 ng/dL in subjects dosed with 225 mg Tlando BID.

In study M12-778, 3 consecutive pre-dose serum T concentrations after BID Tlando administration were measured 2 times at around Days 7 and 14 to evaluate the time required to reach steady state. Based on the data, steady state was achieved before Day 14. Therefore, in the current Phase 3 study 002, 21 days was used as a minimum duration for a subject to remain on a dose before the next PK evaluation.

In addition to M12-778, data from prior Phase 3 study, LPCN 1021-13-001 was evaluated for subject Cavg and Cmax responder analysis at Week 3 and compared with Week 13. This study involved starting all subjects at a dose of 225 mg BID Tlando with intensive PK at Week 3. Based on the Cavg and Cmax values obtained at Week 3, subjects were up titrated to 300 mg BID or down titrated to 150 mg BID based on prespecified titration criteria. Further intensive PK sampling and dose titration was conducted at Week 7. Finally, efficacy was measured at Week 13. Based on the results obtained at Week 3 and Week 13, the subjects demonstrated similar responder analysis suggesting minimal impact of dose titration. Therefore, the new -002 study evaluated a fixed dose 225 mg BID with efficacy evaluation at Day 24 (following steady state).

All subjects received Tlando 225 mg TU (two capsules of 112.5 mg) taken twice daily (total daily dose of 450 mg taken as 225 mg TU in the morning and 225 mg TU in the evening), approximately 12 hours apart, approximately 30 minutes after morning and evening meals, with water. No dose adjustment was permitted.

Based on the findings of a food-fat effect study, LPCN 1021-14-001, the pharmacokinetics of Tlando were not sensitive to fat content. Therefore, specific fat dietary requirement was not utilized in this study. Subjects were advised to maintain a standard diet which provides a total daily caloric content of approximately 2400 calories (total per day) with no recommendations for specific fat content.

Study Endpoints

Primary Efficacy Endpoint: The primary efficacy endpoint and analysis for this study was the percentage of Tlando-treated subjects who had achieved a 24-hour average serum T concentration within the normal range of 300 to 1080 ng/dL at Visit 4 (Day 24 ± 4

days). For the primary efficacy endpoint of the study to be met, the target minimum acceptable responder percentage was 75%. A 95%, 2-sided, binomial confidence interval (CI) surrounding the point estimate must have had a lower bound of 65% or more to conclude that the Tlando treatment was efficacious.

Secondary Efficacy Endpoints: The secondary efficacy endpoints were defined as the percentage of subjects who exhibited maximum serum total T concentrations within predetermined limits upon completion of approximately 24 days of study treatment. The predetermined limits were:

1. T Cmax ≤ 1500 ng/dL (targeted to be ≥ 85%)
2. T Cmax between 1800 and 2500 ng/dL (targeted to be ≤ 5%)
3. T Cmax > 2500 ng/dL (targeted to be no subjects (0%)).

Patient Disposition

A total of 95 subjects were enrolled in the study. Overall, 94 (98.9%) subjects completed the study and one subject discontinued prior to completion of Visit 4 (PK visit). The subject who discontinued early was withdrawn from the study by the investigator due to a serious adverse event (gastric ulcer hemorrhage).

Efficacy Results

Primary Endpoint

Three datasets were analyzed for study LPCN 1021-16-002: the Safety Set (SS), the Full Analysis Set (FAS), and the Pharmacokinetic Set (PK Set). The PK Set included all subjects who received the drug, had no major protocol deviations that affected the PK analysis, and had sufficient and interpretable PK data for the evaluation of the PK endpoints. The PK Set included a total of 90 subjects.

The primary efficacy endpoint and analysis for this study was the percentage of Tlando-treated subjects who achieved a 24-hour average serum T concentration within the normal range (300-1180 ng/dL) upon completion of 24 days of treatment.

The primary endpoint analysis used the safety set (SS) with a last observation carried forward approach for missing PK data. Because the study included only one PK visit, the baseline value of serum T obtained prior to study enrollment was carried forward to impute missing Cavg values (BLOCF).

The results for the analysis of the primary endpoint for the SS population with BLOCF are summarized in Table 1.

Table 1: Proportion of Tlando-Treated Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range at Visit 4 (Day 24), Safety Set BLOCF (N=95)

Parameter	Target	Safety Set BLOCF N=95
Percentage subjects achieving T Cavg within normal range[1]	≥ 75%	80%
95% Confidence interval (lower, upper bound)	≥ 65% (Lower Bound)	72%, 88%

[1]Normal Range: 300 to 1080 ng/dL
BLOCF=Baseline observation carried forward
Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 51, Table 16.

The applicant also performed additional sensitivity analyses using the SS with a Model Based Multiple Imputation approach for missing data, and using the FAS and PK Sets. Results of the sensitivity analyses are displayed in Table 2.

Table 2: Model Based Imputation and Sensitivity Analysis of Primary Efficacy Endpoint: Proportion of Tlando-Treated Subjects Achieving Cavg within Normal Range at Visit 4

Subject population	Safety Set N=95	Safety Set N=95	Full Analysis Set N=94	PK Set N=90
Imputation Model	BLOCF	Model Based Imputation	None	None
% subjects achieving T Cavg within normal range[1]	80 %	81%	81%	81 %
95% Confidence interval	72%, 88%	72%, 88%	73%, 89%	73%, 89%

[1]

Normal Range: 300 to 1080 ng/dL
BLOCF=Baseline observation carried forward
Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 52, Table 17.

CDTL Comment

The primary endpoint for Tlando was met with prespecified analysis as well as the sensitivity analyses if the serum T data are shown to be reliable.

Secondary Endpoints

The prespecified analysis of the T Cmax secondary endpoints was based on Cmax(0-24h), the maximum serum T concentration that occurred during the 24-hour interval after the morning dose. Additional analyses were performed using Cmax(0-12h), the maximum serum T concentration during the 12-hour interval after the morning dose, and Cmax(12-24h), the maximum serum T concentration during the 12-hour interval after the evening dose. Results for the analysis of the secondary endpoint are summarized in Table 3.

Table 3: Proportion of Tlando-Treated Subjects Achieving Maximum Serum Total T Concentrations (Cmax) within Predetermined Limits at Day 24 Safety Set (N=95)

Measure	Target	Cmax (0-24h) N=95	Cmax (0-12h) N=95	Cmax (12-24h) N=95
Cmax < 1500 ng/dL, (%)	≥ 85%	74%	86%	83%
1800 ≤ Cmax ≤ 2500 ng/dL, (%)	≤ 5%	14%	7%	6%
Cmax > 2500 ng/dL (%)	0%	1%	0%	1%

Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 53, Tables 18 and 19.

Of the 25 subjects who had Cmax(0-24h) > 1500 ng/dL, 16% (4/25) had both post-morning and post-evening dose Cmax values that exceeded 1500 ng/dL. No subject had a Cmax value exceeding 1800 ng/dL occur after both daily doses.

The one subject, ((b) (6)) with Cmax > 2500 ng/dL was a 67-year-old male who had a Cmax value of 2730 ng/dL on Day 24, four hours after the evening dose and 16 hours after the morning dose. The subject had a medical history of cholecystectomy, which he did not recall at the time of enrollment but was discovered after he was enrolled into the trial when the Investigator assessed the subject's complete medical records. History of cholecystectomy is an exclusion criterion for the study (exclusion criterion 8). However, the Investigator, and medical monitor allowed the subject to remain in the trial.

CDTL Comment

Tlando did not meet the predetermined targets for any of the three secondary endpoints for Cmax(0-24h), the Cmax value for the prespecified time period (24 hours). A total of 26% of the subjects had Cmax(0-24h) ≥ 1500 ng/dL with 16% of these subjects having excursions after both the morning and evening doses of the drug. For the subject with the Cmax excursion above 2500 ng/dL, the effect of the subject's prior cholecystectomy on the elevated T level is unclear.

These T Cmax values may overestimate systemic T concentrations depending on the extent of ex vivo TU to T conversion. If these T Cmax data are shown to be reliable, the clinical significance of having such chronic, repeated excursions up to twice per day is unclear.

LPCN 1021-16-003

Study-003 was a second phase 3 study included in this resubmission. It was an open-label, multicenter, uncontrolled study evaluating the efficacy of Tlando in adult hypogonadal males. The dosing regimen in study-003 was a fixed dose of 150 mg of Tlando three times a day. Other than the dosing regimen, the trial design, including the primary and secondary endpoints, inclusion and exclusion criteria, and dietary instructions were similar to the design of study-002.

A total of 100 subjects were enrolled in the study. Their demographic and baseline characteristics were similar to those of the subjects included in LPCN 1021-16-002. The efficacy results are shown in Tables 4 and 5.

Table 4: Proportion of Tlando-Treated Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range at Visit 5 (Day 24), Safety Set BLOCF (N=100)

Parameter	Target	Safety Set BLOCF N=100
Percentage subjects achieving T Cavg within normal range[1]	≥ 75%	69%
95% Confidence interval (lower, upper bound)	≥ 65% (Lower Bound)	60%, 78%

[1]Normal Range: 300 to 1080 ng/dL
BLOCF=Baseline observation carried forward
Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-003, Table 15, p. 51.

Table 5: Proportion of Tlando-Treated Subjects Achieving Maximum Serum Total T Concentrations (Cmax) within Predetermined Limits at Visit 5 Safety Set (N=100)

Measure	Target	Cmax (0-24h) N=100
Cmax < 1500 ng/dL, (%)	≥ 85%	95%
1800 ≤ Cmax ≤ 2500 ng/dL, (%)	≤ 5%	1%
Cmax > 2500 ng/dL (%)	0%	0%

Source: NDA 208088 (seq 0026), Module 5.3.5.2 Table 17, p. 53.

CDTL Comment

The study failed to meet its primary endpoint, but met each of the criteria for the three Cmax secondary endpoints. The Applicant has acknowledged not meeting the primary efficacy endpoint in this study. Hence, this study has been submitted to further support their safety data base, but this dosing regimen is not proposed for marketing.

Statistical Review Team recommendations

Drs. Weiya Zhang and Mahboob Sobhan, from the statistical review team made the following recommendation
"From a statistical perspective, study 002 provided evidence demonstrating efficacy of a BID Tlando testosterone undecanoate oral capsule in the treatment of primary and secondary hypogonadism while Cmax did not reach the pre-specified criteria. Study 003 did not provide evidence in support of a TID Tlando testosterone undecanoate oral capsule for the indication."

No statistical issue was identified in the NDA review. The efficacy results were consistent with sensitivity analyses in Safety Set, Full Analysis Set, Pharmacokinetic Set, and model-based multiple imputation based on Safety Set.

CDTL Comment

It should be noted that study-002 did not meet any of the three secondary endpoints and as pointed out by the statistical review team, study-003 did not achieve the pre specified primary end point.

Efficacy Conclusion

It is presently unclear whether the Applicant has established efficacy for Tlando. Although Study 002 met the primary efficacy endpoint, the Applicant has not adequately addressed whether the T data are reliable and the study did not meet the three pre-specified Cmax secondary endpoints.

The Applicant first needs to definitively address the extent of ex vivo TU to T conversion. If the T data are shown to be unreliable, the Applicant will likely need to conduct a new Phase 3 trial. If the T data are reliable, a new trial may still be needed that also satisfies the secondary Cmax criteria unless the Applicant can provide adequate information to assure that the chronic Cmax excursions are not clinically relevant.

8. Safety

Overall Exposure

The safety database for Tlando included 525 hypogonadal men who received the drug from one to 382 days. The primary source of safety information is derived from LPCN 1021-13-001 a 52-week, randomized, active controlled trial. A total of 130 subjects received Tlando for at least 52 weeks during this study, 113 of whom were on a dose equal to or greater than the to-be-marketed dose (225 mg BID) at the end of the study.

Table 6 : Summary of Extent of Exposure for Phase 1 and 3 Studies (Single and Multiple Dose Periods) – Safety Population

Assessment	Original ISS Tlando N = 381	Updated ISS Tlando N = 525	Original ISS Andriol N = 34	Original ISS AndroGel 1.62% N = 104	Original ISS Placebo N = 18
Extent of Exposure (days)					
N	381	525	34	104	18
Mean (SD)	148.6 (163.46)	114.8 (149.71)	3.1 (3.24)	290.5 (123.16)	19.4 (7.01)
Median	33.0	26.0	1.0	364.0	15.0
Q1, Q3	15.0, 364.0	15.0, 274.0	1.0, 8.0	189.5, 366.0	15.0, 29.0
Min, Max	1, 382	1, 382	1, 8	1, 382	11, 29
Interval (weeks), n (%)					
[0,4]	170 (44.6)	296 (56.4)	34 (100)	7 (6.7)	12 (66.7)
(4,13]	54 (14.2)	72 (13.7)	0	8 (7.7)	6 (33.3)
(13,26]	14 (3.7)	14 (2.7)	0	9 (8.7)	0
(26,39]	11 (2.9)	11 (2.1)	0	7 (6.7)	0
>39	132 (34.6)	132 (25.1)	0	73 (70.2)	0

Studies: LPCN 1021-16-002, LPCN 1021-16-003, LPCN 1021-13-001, LPCN 1021-09-001, LPCN 1021-14-001, M12-778, M13-298, and S361.1.001
Source: NDA 208088 (seq 0026), Module 2.7.4, Table 8, p. 37.

Table 6 displays extent of exposure data for the supportive and pivotal safety studies combined. The extent of exposure for both the Original ISS for Tlando (safety data included in the original NDA) and the Updated ISS (includes new Tlando safety data from the LPCN 1021-16-002 and LPCN 1021-16-003 clinical studies combined with Original ISS data) are both provided. For treatments that were not administered in the LPCN 1021-16-002 and LPCN 1021-16-003 clinical studies (Andriol, Androgel, Placebo), the safety data from the Original ISS are presented. The most commonly used Tlando dose in these studies was the 225 mg BID dose (265 subjects),

which had a median exposure of 26 days (ranging from 1 to 382 days) with 26.0% of subjects receiving study drug for more than 39 weeks and 58.1% of subjects receiving study drug for ≤4 weeks.

CDTL Comment

Exposure to Tlando is adequate. The applicant met the goal of having at least 100 subjects exposed to Tlando for at least 52 weeks during LPCN 1021-13-001. Only key safety data from this trial pertinent to this review cycle are reviewed in this section. Refer to the reviews from the original review cycle for additional details. The applicant also submitted a paper that provided additional supportive safety data based on 1329 patients prescribed an oral TU formulation approved in the UK, but not in the US. (See Clinical reviewer's review from original submission).

Characteristics of Safety Population

The mean age for subjects receiving Tlando was 51.1 years and most subjects (89.7%) were less than 65 years old. Most subjects who received Tlando were White (84.2%) with Black or African American subjects accounting for 13.0% of the population. Slightly over half (52.6%) of the subjects who received Tlando were obese (i.e., BMI ≥ 30 kg/m^2). Table 7 presents demographic and baseline characteristics by treatment group for subjects in the supportive and pivotal safety studies combined.

Table 7: Summary of Demographics and Baseline Characteristics by Treatment Group for Supportive and Pivotal Safety Studies (Single and Multiple Dose Periods) – Safety Population

Characteristic	Original ISS Tlando N = 381	Updated ISS Tlando N = 525	Original ISS Andriol N = 34	Original ISS AndroGel 1.62% N = 104	Original ISS Placebo N = 18
Age (years), Mean (SD)	49.6 (10.81)	51.1 (10.59)	49.7 (9.63)	54.3 (9.44)	48.8 (7.66)
Age < 65 years, n (%)	353 (92.7)	471 (89.7)	34 (100)	92 (88.5)	17 (94.4)
Age ≥ 65 years, n (%)	28 (7.3)	54 (10.3)	0	12 (11.5)	1 (5.6)
Race, n (%)					
American Indian or Alaska Native	5 (1.3)	5 (1.0)	4 (11.8)	0	0
Asian	4 (1.0)	5 (1.0)	2 (5.9)	3 (2.9)	0
Black or African American	47 (12.3)	68 (13.0)	3 (8.8)	10 (9.6)	3 (16.7)
Multiple	0	2 (0.4)	0	0	0
White	322 (84.5)	442 (84.2)	25 (73.5)	91 (87.5)	15 (83.3)
Other	3 (0.8)	3 (0.6)	0	0	0
Weight (kg), Mean (SD)	91.83 (14.88)	95.27 (16.866)	82.61 (9.22)	99.30 (14.82)	80.61 (8.71)
Height (cm), Mean (SD)	175.45 (7.52)	176.23 (7.674)	174.01 (6.58)	178.74 (7.15)	171.61 (6.78)
Body Mass Index (kg/m2), Mean (SD)	29.72 (3.69)	30.57 (4.380)	27.24 (2.34)	31.02 (3.88)	27.31 (1.91)
< 30 kg/m², n (%)	205 (53.8)	249 (47.4)	29 (85.3)	37 (35.6)	16 (88.9)
≥ 30 kg/m², n (%)	176 (46.2)	276 (52.6)	5 (14.7)	67 (64.4)	2 (11.1)

Studies included: LPCN 1021-16-002, LPCN 1021-16-003, LPCN 1021-13-001, LPCN 1021-09-001, LPCN 1021-14-001, M12-778, M13-298, and S361.1.001
Source: NDA 208088 (seq 0026), Module 2.7.4, Table 20, pp. 53-54.

Safety Results

Deaths

No deaths occurred in any of the studies of Tlando.

Serious Adverse Events (SAE)

Studies-002 and-003

One subject experienced a SAE in Study-002. Subject (b) (6) experienced a SAE (gastric ulcer hemorrhage) and was discontinued from the study. This subject was admitted to the hospital with a bleeding gastric ulcer on Study Day 13. At that time, the subject's concomitant medications included aspirin 325 mg QD, which he had been taking for about 12 years, and meloxicam, which he had been taking for about 2.5 years. The investigator considered the SAE unrelated to the study drug. No SAE's occurred during study 003.

CDTL Comment

I agree with the Clinical Reviewer, Dr. Kaufman's assessment that this event is not related to the drug.

Discontinuations/Drop outs

Studies-002 and LPCN-003

One subject in study-002 was discontinued due to gastric ulcer hemorrhage. During Study-003, no subjects experienced a TEAE that led to study drug discontinuation.

Treatment Emergent Adverse Events and Adverse Reactions

Study-002

In general, the common (>2%) TEAEs reported in LPCN 1021-16-002 were similar to those reported in LPCN 1021-13-001 (See Clinical Review of original submission dated June 23, 2016 for details) with the exception of the TEAE "blood prolactin increased." Six (6.3%) subjects reported the TEAE "blood prolactin increased" in study-002 compared to none in study-001. Of the six subjects, three also were enrolled in study-003, and had a prolactin level within the normal range at the end of that study. One subject had a history of hyperprolactinemia. The two remaining subjects had end of study prolactin levels of 24.7 and 25.1 ng/mL. In addition, 45 subjects had end of study prolactin levels greater than the upper limit of the normal range (15.2 ng/mL), which were not reported as a TEAE. Seven of these 45 subjects had a baseline prolactin greater than the upper limit because the exclusion criteria (>17.7 ng/mL) was greater than the upper limit of the normal range.

Although no TEAEs of "blood prolactin increased" were reported in study-001, two subjects had slightly elevated prolactin levels at Week 52 (18.0 and 18.2 ng/mL). One of these subjects had an elevated prolactin level at Week 7 (22.4 ng/mL), normal levels at

Weeks 13, 26, and 39, and a slightly elevated level at Week 52 (18 ng/mL). Five additional subjects had elevated levels at Week 7. All had normal prolactin levels at their final study visits (Week 39 for one subject, Week 52 for the other four).
No TEAEs of "blood prolactin increased" were reported in study-003.

CDTL Comment
It is not clear what to make of these transient prolactin elevations in study 002. When the drug can be approved, consideration should be given to labeling these findings so that health care providers will be aware that the drug is associated with prolactin concentrations above the upper limit of the normal range.

Study-003
Nine (9.0%) subjects reported 10 TEAEs during study-003. The TEAE of "edema peripheral" was reported by 2 (2.0%) subjects. No other TEAEs were reported by more than one subject.

Laboratory Findings
Study-002
Hematocrit/Hemoglobin

Table 8: Hematocrit and Hemoglobin: Mean Baseline and Mean Change from Baseline LPCN 1021-16-002 – Safety Set (N+95)

		HCT Value (%)	HCT Value Change from Baseline (%)	Hgb Value (g/dL)	Hgb Value Change from Baseline (g/dL)
	N	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	95	45.0 (3.5)	--	14.62 (1.05)	--
Exit	90	45.8 (3.7)	0.9 (3.0)	14.63 (1.17)	0.02 (0.82)

HCT = hematocrit; Hgb = hemoglobin; SD = standard deviation
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 31, p. 68.

Table 9: Summary of Subject with HCT > 54% - Safety Set (LPCN 1021-16-002)

Subject Number (Study Disposition)	Age (yrs)	Visit (Day)	HCT Result	Dose/ Regimen	T Cavg/Cmax(0-24h) (ng/dL)	Adverse Event (Severity/Relationship/ Action Taken/ Resolution)
(b) (6) (Completed study)	55	Screening Visit 4 (25) Unscheduled	48% 57% 51%	225 mg BID	387/1150 (Visit 4)	No adverse events recorded due to lab value

CDTL Comment

One subject had shifted from a normal value at baseline to a high value at exit.

Study-003

Hematocrit/Hemoglobin

Table 10: Hematocrit and Hemoglobin: Mean Baseline and Mean Change from Baseline LPCN 1021-16-003 – Safety Set (N=100)

		HCT Value (%)	HCT Value Change from Baseline (%)	Hgb Value (g/dL)	Hgb Value Change from Baseline (g/dL)
	N	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	99	45.1 (3.38)	--	14.58 (1.05)	--
Exit	92	45.2 (3.65)	0.1 (2.39)	14.60 (1.12)	0.01 (0.65)

HCT = hematocrit; Hgb = hemoglobin; SD = standard deviation

Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 30, p. 69.

CDTL Comment

Two subjects shifted from a normal value of hematocrit at baseline to a high value at exit.

No subject shifted to a high hemoglobin value from baseline to study exit.

Prostate Specific Antigen (PSA)

Study 002 and 003

There was a slight increase in PSA values in the Tlando group, however no subjects were discontinued as a result of elevated PSA.

CDTL Comment

The labeling for currently approved testosterone products includes a recommendation to periodically monitor PSA.

Chemistry
Lipid Profile
Study 002
Mean HDL cholesterol decreased by 6.9 mg/dL from baseline to the exit visit on Day 25.
Mean LDL cholesterol decreased by 1.5 mg/dL from baseline to the exit visit on Day 25.
Mean Triglyceride concentrations decreased by 8.9 mg/dL from baseline to the exit visit on Day 25.
Mean Total cholestrol decreased by 10.6 mg/dL from baseline to the exit visit on Day 25.

Study 003
Mean HDL cholesterol decreased by 7.5 mg/dL from baseline to the exit visit.
Mean LDL cholesterol decreased by 4.0 mg/dL from baseline to the exit visit.
Mean Triglyceride concentrations increased by 41 mg/dL from baseline to the exit visit.
Mean Total cholestrol decreased by 6.4 mg/dL from baseline to the exit visit.

CDTL Comment
The labeling for currently approved testosterone products includes a recommendation to periodically monitor lipids. Most of the changes with Tlando appear favorable, except for the HDL-cholesterol reduction. Lowering of HDL-cholesterol is a well-known side effect of testosterone therapies.

Vital Signs
Study - 002
In this study, the mean and median blood pressure data showed no important SBP or DBP central tendency shifts (Table 11).

Table 11 : Mean Baseline and Mean Change from Baseline Values for Blood Pressure in Tlando-Treated Subjects (LPCN 1021-16-002)

		Systolic Blood Pressure (mmHg)		Systolic Change from Baseline (mmHg)			Diastolic Blood Pressure (mmHg)		Diastolic Change from Baseline (mmHg)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	95	130.2	14.3	-	-	95	80.4	10.1	-	-
Visit 4 (Day 24)	94	129.6	12.2	-0.5	13.5	94	79.6	8.5	-1.0	8.0
Exit (Day 25)	94	130.4	13.6	0.2	13.6	94	80.8	9.1	0.1	8.1

Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 14.3.5.

Study-003

In this study, mean systolic blood pressures were increased by approximately 4 mmHg at both Visit 5 (Day 23) and at exit (Day 25).

Table12: Mean Baseline and Mean Change from Baseline Values for Blood Pressure in Tlando-Treated Subjects (LPCN 1021-16-003)

		Systolic Blood Pressure (mmHg)		Systolic Change from Baseline (mmHg)			Diastolic Blood Pressure (mmHg)		Diastolic Change from Baseline (mmHg)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	100	129.0	12.8	-	-	100	81.3	8.7	-	-
Visit 5 (Day 23)	98	133.2	13.5	4.1	12.6	98	80.9	8.7	-0.3	7.7
Exit (Day 25)	98	133.3	13.2	4.3	12.0	98	81.2	8.8	0.0	7.8

Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 14.3.5.

Study-001

Blood Pressure and Heart Rate

In this study, for subjects who received Tlando, blood pressure measurements were taken at screening and at the following visits: Week 3, Week 7, Week 13, Week 26, Week 39, and Week 52. For subjects who received AndroGel 1.62%, vital signs were measured at screening and at the following visits: Week 2, Week 4, Week 7, Week 13, Week 26, Week 39, and Week 52.

In this study, there appears to be a consistent decrease in mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) over time relative to baseline in the Tlando arm. There was a mean increase in heart rate of 2-4 beats per minute for Androgel and 2-3 beats per minute for Tlando over the 52 weeks of the study.

Table13: Mean Baseline and Mean Change from Baseline Values for Systolic Blood Pressure in Tlando- and AndroGel-Treated Subjects Safety Set (LPCN 1021-13-001)

	Tlando					AndroGel 1.62%				
		Blood Pressure (mmHg)		Change from Baseline (mmHg)			Blood Pressure (mmHg)		Change from Baseline (mmHg)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	210	132.6	14.0	-	-	104	132.6	14.5	-	-
Week 7	182	131.4	14.3	-0.9	13.8	97	129.9	12.6	-3.1	13.5
Week 13	157	131.3	12.7	-0.8	12.6	92	130.7	12.5	-2.6	12.4
Week 26	144	130.7	13.3	-1.1	12.7	82	131.0	13.8	-2.0	14.4
Week 39	138	131.0	13.7	-0.5	13.9	76	132.8	13.9	-0.7	12.9
Week 52	130	131.2	14.7	-0.3	14.4	71	133.5	13.8	0.0	13.4
Early Term	49	130.2	11.2	-3.5	12.3	15	131.1	12.1	1.0	15.5

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 74, p. 132.

Table14: Mean Baseline and Mean Change from Baseline Values for Diastolic Blood Pressure in Tlando- and AndroGel-Treated Subjects Safety Set (LPCN 1021-13-001)

	Tlando					AndroGel 1.62%				
		Blood Pressure (mmHg)		Change from Baseline (mmHg)			Blood Pressure (mmHg)		Change from Baseline (mmHg)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	210	82.9	8.6	-	-	104	82.4	8.6	-	-
Week 7	182	79.7	8.9	-3.0	8.4	97	81.7	8.0	-0.9	7.7
Week 13	157	80.6	8.5	-2.5	7.5	92	82.6	9.4	0.0	9.4
Week 26	144	81.1	9.3	-1.9	8.2	82	82.1	9.0	-0.4	9.6
Week 39	138	82.1	8.3	-0.8	7.8	76	83.6	8.1	1.1	7.2
Week 52	130	81.4	9.2	-1.3	8.3	71	83.0	9.1	0.4	9.4
Early Term	49	81.3	7.9	-0.7	7.8	15	80.1	9.4	-1.6	8.6

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 73, p. 132.

These blood pressure data were evaluated in a consultative review by the Division of Cardiovascular and Renal Products (DCRP). Their conclusions and recommendations are as follows:

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

In study-002, there was an elevated pulse rate of approximately 4 beats per minute at the end of four weeks of dosing. In study-003, there was a 1 beat per minute increase in heart rate and a 4 mmHg increase in SBP after approximately four weeks of dosing.

The major contributor to defining the non-invasive hemodynamic effects of Tlando come from the 52-week study. However, the ability to generalize population central tendency data for vital signs from this study is limited by the non-duplicative testing in a trial that was not prospectively designed to definitively exclude a blood pressure effect and that had a large amount of missing data (premature withdrawal of 38% of the Tlando-treated subjects and the 32% of Androgel subjects over the 52 weeks of the study.) From the available data, it appears that there was an approximately 1-2 beats per minute increase in heart rate for both Tlando and

Androgel-treated subjects over the 52 weeks of therapy, without demonstrable increase in the central tendencies for SBP or DBP in either group. In contrast, "hypertension/blood pressure increased" was among the most common vital sign-related adverse events.

DCRP Recommendation

"Based on the available data, it appears that both Tlando and AndroGel raise heart rate, and study-003 demonstrates a mean 4 mmHg increase in SBP with Tlando. The 52-week study does not exonerate Tlando from blood pressure effects because its cuff blood pressure data acquisition was methodologically non-duplicative (single cuff pressures) in the setting of an open-label trial design with a 38% dropout rate in the experimental treatment arm. Therefore, a "no blood pressure effect" conclusion from that study is speculative and could be incorrect. The cardiology consultants recommend that the Applicant perform a well-designed ambulatory blood pressure monitoring (ABPM) study to further assess the effects of Tlando on blood pressure and heart rate."

CDTL Comment

I agree with DCRP regarding the need for an ambulatory blood pressure monitoring study (ABPM). Based on the signal with cuff blood pressures seen during study-003 and in the context of the finding of clinically meaningful increases in BP assessed with ABPM seen with another oral TU product, Tlando has a high probability of causing increases in blood pressure that could subsequently increase the risk for major cardiovascular adverse events, such as myocardial infarction, stroke and cardiovascular death. It is critical to resolve this concern pre-approval to inform the appropriate regulatory action, including whether risk mitigation beyond labeling, such as a REMS is needed to ensure the benefits of the drug outweigh its risks.

Levels of Testosterone Undecanoate (TU) and Dihydrotestosterone Undecanoate (DHTU)

An androgen receptor binding affinity study conducted by the applicant showed that the contribution of T, TU, and DHTU to the potential androgen receptor binding is 100.84%, compared to 100% for T alone. This supports the conclusion that TU and DHTU have low binding affinity for the androgen receptor. See Pharmacology/Toxicology review dated February 26, 2018.

DHT

In study 002, DHT was increased as compared to the reference range provided. A DHT outlier analysis was conducted using the reference interval established by (b) (4) Laboratories (10.6 to 71.9 ng/dL). Based on this reference interval, 78.9% of the subjects had DHT Cavg greater than the upper limit of normal (ULN) at Visit 4, with most of these subjects less than or equal to twice the ULN. However, in a verification assessment of the (b) (4) reference interval performed on a sample of 40 normal healthy males, 15% of the

normal sample values were greater than the ULN, which exceeded the criteria for verification by 5%. Therefore, the results of the outlier analysis may be overstated.

CDTL Comment
It is unclear if there is any risk associated with this increase in DHT.

Estradiol
The E2 reference interval for normal healthy males established by (b) (4) and verified by Study RHOD/RHOE is 10.0 to 42.0 pg/mL.

During the PK assessment at Day 24, serum E2 concentrations for the PK Set reached a peak concentration of 28.8 pg/mL at 8 hours after the morning dose, after which time the concentrations declined and fell below pre-dose levels after approximately 12 hours. The E2 concentration pattern after the evening dose was similar to the pattern observed after the morning dose, although mean serum E2 concentrations were higher for the evening dose, reaching a peak concentration of 40.5 pg/mL at 8 hours after the evening dose.

CDTL Comment
There was no significant increase seen in E2 levels.

Potential Effects on Adrenal Gland
Adrenal findings were noted during two nonclinical studies for TU. In the 26-week rat study, treatment with TU in eugonadal male rats resulted in a dose-dependent increase in both incidence and severity of diffuse adrenal cortical vacuolation. In the 90-day dog study, treatment with TU in eugonadal male dogs resulted in a dose-dependent increase in severity of cortical atrophy, that was characterized as atrophy of the zona fasciculata and zona reticularis.

To assess the clinical significance of the nonclinical adrenal findings, the applicant conducted Cosyntropin stimulation in a subset of subjects enrolled in studies -002 and -003.

The results of the Cosyntropin sub-study were consulted to and reviewed by an FDA endocrinologist. The consultant noted that the four-week treatment period in studies -002 and -003 is insufficient to definitively rule out a risk of adrenal insufficiency with chronic use of Tlando, and recommended further assessment of adrenal function over a longer study duration.

CDTL Comment

I agree with the consultant that the 24 day treatment period is insufficient to assess adrenal dysfunction in a drug that is expected to be taken chronically and therefore recommend conducting a study of longer duration to more definitively address this issue. This assessment could be conducted post-approval, with interim labeling informing prescribers that the long-term risk of adrenal insufficiency has not been evaluated. However, if additional pre-approval trial(s) are needed (e.g., if the Phase 3 testosterone data are unreliable), I recommend conducting further assessment of adrenal function in those pre-approval trial(s).

Summary of Safety

The safety database for Tlando included 525 hypogonadal men who received the drug from one to 382 days. The primary source of safety information is derived from LPCN 1021-13-001 a 52-week, randomized, active controlled trial. More than 100 subjects received Tlando for at least 52 weeks during this study and 68% of these subjects were on a dose equal to or greater than the to-be-marketed dose (225 mg BID) at the end of the study.

Increases in hematocrit and reductions in HDL-cholesterol are class effects of testosterones, are included in the labels of approved T products, and similarly would be labeled for Tlando. An increase in DHT levels was seen as compared to the reference range provided. DHT is a potent androgen. Class labeling for testosterone therapies to monitor for androgenic adverse effects (e.g., hematocrit, prostate, and lipids) will capture important androgenic effects that could be related to testosterone or DHT. However, it is unclear if there are any long-term risks associated with this increase in DHT. (b) (4) (b) (4) There was no increase in estradiol levels. The drug's effect on BP remains unclear: Two trials (study-001 and study-002) did not show clinically significant changes in cuff BP, while one trial (study-003) showed an increase of 4 mmHg in cuff SBP. However, the likelihood of a clinically meaningful increase in BP with Tlando seems probable when also taking into account the BP findings on ABPM with another oral TU testosterone in development. It is critical to resolve this concern pre-approval to inform the appropriate regulatory action, including whether risk mitigation beyond labeling, such as a REMS is needed to ensure the benefits of the drug outweigh its risks.

Tlando's effect on the hypothalamic pituitary adrenal axis also remains unclear. Though adrenal function was assessed in Cosyntropin stimulation sub-studies during LPCN 1021-16-002 and LPCN 1021-16-003, the studies' 24-day treatment periods were insufficient to assess whether Tlando, a drug that is expected to be taken chronically, causes adrenal dysfunction with long-term use. Further assessment of adrenal function over a longer duration is recommended to rule out the risk of adrenal dysfunction.

9. Advisory Committee Meeting

An Advisory Committee was convened for this NDA resubmission on January 10, 2018.
Following is a summary of questions and answers and discussion that the Advisory Committee provided:

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the safety of Tlando has been adequately characterized. If additional safety data are needed, discuss the type(s) of data that are needed and whether these data should be obtained pre-approval or whether these data can be obtained post-approval. Specifically cover:

    a. The effects of Tlando on cardiovascular risk factors, including blood pressure and lipids, together with effects on hematocrit, and the potential for Tlando to increase the risk of adverse cardiovascular outcomes in the population that will likely use the drug if it is approved. Specifically comment on whether ambulatory blood pressure monitoring is needed pre-approval.
    b. Supraphysiologic dihydrotestosterone (DHT) concentrations in some subjects.
    c. Subjects with maximal testosterone concentrations (C_{max}) exceeding the prespecified targets.
    d. The adrenal-related findings, including adrenocorticotropin (ACTH) stimulation results.

Committee Discussion: Several panel members recommended that a well-designed ambulatory blood pressure monitoring study be performed pre-approval. Based on comments made at the meeting, this recommendation took into account the mean 4 mmHg increase in systolic blood pressure seen with the three times daily dosing regimen that used the same total daily dose as the to-be-marketed regimen, the use of only cuff pressure measurements across all studies, and findings in the public domain showing a clinically meaningful increase in blood pressure with ambulatory blood pressure monitoring for another oral testosterone undecanoate product.

The lipid and hematocrit findings were largely noted to be a general feature of testosterone use and not a concern to most of the panel members.

The elevated dihydrotestosterone (DHT) concentrationss were judged to be a class effect and not known to be associated with any specific clinical risk. It was noted that European studies involving administration of DHT have not raised safety concerns.

There were differences of opinion regarding the clinical relevance of the testosterone Cmax findings. One comment was that the short duration of exposure to this maximal testosterone concentration should be less problematic. Another view was that having these peaks twice daily on a chronic basis could be of potential concern. Since there were no data that tied this exposure to adverse effects, the impact of the Cmax outliers was hard to judge for the panel members.

With regard to the adrenal findings, there was not a high level of concern although it was noted that technical problems with the testing made it difficult to interpret the findings (e.g., some subjects do not appear to have received Cosyntropin for their test).

See the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss whether the stopping criteria for use in clinical practice will appropriately identify patients who require discontinuation of Tlando.

   Committee Discussion: Some members raised concerns with the adequacy of the proposed stopping criteria, such as whether the criteria would appropriately capture patients with supratherapeutic testosterone Cavg. Some members also expressed concerns that health care providers would uptitrate the dose if the measured testosterone was low, even though the Applicant is seeking approval of only one dose, and that this could raise safety concerns. A recommendation was to use modeling and simulation approaches to refine the accuracy of the prediction.

   See the transcript for details of the committee discussion.

3. **DISCUSSION:** Discuss whether testosterone concentrations measured in serum tubes are reliable in patients treated with Tlando.

   Committee Discussion: Several committee members noted the conflicting data on the extent of ex vivo conversion of testosterone undecanoate to testosterone, and stated this is an important issue to resolve before the drug could be approved. Some committee members stated that if there is ex vivo conversion this should not be a safety concern because this conversion will overestimate testosterone concentrations. However, it was noted that ex vivo conversion could call into question the reliability of the data from the Phase 3 trial.
   See the transcript for details of the committee discussion

4. **VOTE:** Is the overall benefit/risk profile of Tlando acceptable to support approval as a testosterone replacement therapy?

   Provide a rationale for your vote.

   Yes: 6 No: 13 Abstain: 0

   Committee Discussion: Most committee members voted "No,"stating that the existing uncertainties should be resolved before approval. Recommendations included a pre-approval ambulatory blood pressure monitoring study and further assessment of the potential for ex vivo conversion of testosterone undecanoate to testosterone.

   Committee members who favored approval were willing to resolve the uncertainties after approval, citing an unmet need for an oral testosterone product.

10. Pediatrics

A pediatric waiver has been historically granted for this class of drugs because male hypogonadism is rare in the pediatric population. Recent discussions have begun to revisit this decision. We will inform the Applicant if there are changes to FDA's policy.

11. Other Relevant Regulatory Issues

Financial disclosures
The applicant has certified that the compensation of all clinical investigators was independent of the study outcome. They have also certified that no investigator had a proprietary interest in the product or equity interest in the sponsor of a covered study.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Denise Baugh, PhD, DMEPA reviewer has the following recommendation:

It does not appear that the submitted carton labeling is the final marketed version. For example, we note the 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) On the next review cycle the Applicant will need to submit the final 'intend-to-market' carton labeling and container labels for Agency review. We will communicate the following comments to the Applicant in the CR letter except for the comment about the Medication Guide, as one will likely be needed if Tlado is subsequently shown to elevate BP on ABPM.

Carton Labeling

1. Remove the Medication Guide (MG) statement from the principal display panel since the product will not have a MG.
2. Ensure the font size of the established name is at least one half the font size used to present the proprietary name in accordance with 21 CFR 201.10(g)(2).
3. Relocate the net quantity statement farther away from the strength statement on the principal display panel to minimize the risk of numerical confusion between the strength and the net quantity. Ensure that the net quantity remains on the principal display panel.

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

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection because OSIS recently inspected the site. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

12. Labeling

No labeling negotiation took place because of the Complete Response action.

13. Postmarketing Recommendations

No Postmarketing recommendations were made, other than perhaps further assessment for adrenal dysfunction. We will revisit this area when the drug can otherwise be approved.

14. Recommended Comments to the Applicant

The Complete Response letter should note the following four deficiencies:

1. Insufficient data to determine whether the testosterone concentrations are reliable because there is inadequate evidence to exclude clinically relevant *ex vivo* TU to T conversion in patients treated with Tlando.
    - The Applicant should provide information that definitively addresses the extent of ex vivo TU to T conversion. If the testosterone data are found to be unreliable, a new Phase 3 trial to establish efficacy would likely be needed.

2. Concerns that Tlando may lead to clinically meaningful increases in blood pressure that could increase the occurrence of major adverse cardiovascular events.
    - The Applicant should definitively assess the blood pressure effects of Tlando with a pre-approval ABPM trial to inform the appropriate regulatory action, including whether risk mitigation beyond labeling, such as a REMS is needed to ensure the drug's benefits outweigh its risks.

3. Failure to meet the three secondary endpoints for testosterone Cmax.
    - The Applicant may need a new trial that meets these secondary endpoints unless the Applicant can provide adequate data that show these excursions are not clinically relevant.

4. Inadequate proposal for determining whether a patient should discontinue the drug in clinical practice.
    - The Applicant should identify stopping criteria for use in clinical practive that can reproducibly and accurately identify those patients who do not achieve time-averaged T concentrations within the normal range.

The letter should also include recommendations that are not approvability issues, such as the need for further assessment of adrenal insufficiency and clarification of how the long-term data adequately meet ICH E1 guidelines.

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

/s/

SURESH KAUL
05/08/2018

HYLTON V JOFFE
05/08/2018
I concur with Dr. Kaul's recommendation that this application receive a Complete Response letter. This memorandum serves as the decisional memorandum on the application. Also see the division director memorandum to file.

Cross-Discipline Team Leader Memo

Date	June 23, 2016
From	Suresh Kaul, M.D., M.P.H
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	208088
Applicant	Lipocine Inc.
Date of Submission	August 28th, 2016
PDUFA Goal Date	June 28th, 2016
Proprietary Name / Established (USAN) names	Tolando Testosterone Undecanoate
Dosage forms / Regimen	(b) (4) (b) (4) 112.5 mg capsules 225 mg oral twice daily
Proposed Indication(s)	Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Recommended:	Complete Response (CR)

1. Background

Description of Product

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution. Dihydrotestosterone (DHT) is another androgen endogenously produced in the body. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

LPCN 1021 (testosterone undecanoate) capsules is an oral product containing (b) (4) (b) (4) 112.5 mg of testosterone undecanoate (TU) in a lipid formulation. LPCN 1021 is designed to enable absorption of TU via the intestinal lymphatic pathway. TU is a straight chain fatty acid ester of testosterone, which is not alkylated at the 17-alpha position. TU is converted to testosterone by non-specific esterases that are abundantly present in the body. In the U.S, TU is approved as an injectable formulation, but has not been approved for oral administration.

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

Regulatory History
Abbott Laboratories opened the original IND for LPCN 1021 (IND 106476) on April 2, 2010, and subsequently transferred ownership of the IND to the applicant (Lipocine) on May 14, 2012. During the development program for the proposed product, the applicant had four meetings with the Division of Bone, Reproductive and Urologic Products.

- **January 11, 2010 - Type C, guidance meeting (Pre-IND):** Key meeting discussion included proposed nonclinical program, opening study for the planned IND, clinical pharmacology development plan, planned pilot and definitive food effect studies, and required safety data for an NDA.

- **August 16, 2010: Type C guidance meeting:** Key meeting discussion included the applicant's Patient Reported Outcome (PRO) instrument.

- **November 15, 2012: Type C guidance meeting (EOP 2):** Key meeting discussion included appropriateness of the 505(b)(2) regulatory pathway for a LPCN 1021 NDA, adequacy of the conducted nonclinical program and the CMC plan to support a 505(b)(2) filing, and proposed phase 3 trial.

- **March 19, 2015: Type B pre-NDA meeting:** Key meeting discussion included status and overview of the definitive food effect study (LPCN 1020-14-001), adequacy of the nonclinical package for NDA filing, adequacy of the CMC package for NDA filing, adequacy of the efficacy and safety data from the ongoing phase 3 study for NDA filing, alcohol interaction study, and proposed approach for developing labeling instructions for dose titration.

2. Recommendation for Approvability

From a clinical perspective, I recommend that Tlando (testosterone undecanoate) capsules receive a Complete Response (CR) action. This recommendation is based on the applicant's failure to provide a titration scheme based on a single blood draw for use in clinical practice, which results in titration decisions that are reasonably consistent with the titration decisions that were made during the Phase 3 clinical study. Without an acceptable single blood draw titration scheme, it is not possible to make dosing recommendations in labeling. The Complete Response (CR) action would include a recommendation to conduct a new phase 3 trial with a titration scheme based on a single blood draw and demonstrate efficacy as a path forward.

3. CMC/Device

Recommendation and Conclusion on Approvability:
The chemistry, manufacturing and controls (CMC) reviewers concluded that sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product and that the drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. Although, there are no other outstanding CMC deficiencies, the Biopharmaceutics review team is requesting additional dissolution data using revised methodology to confirm the acceptance criterion.

However, because labeling (package insert, container/carton) discussions were not completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201, Mark Seggel, PhD, Acting Team Lead for quality review team made the following recommendation: "I concur with the OPQ review team recommendations that this 505(b)(2) NDA be approved pending finalization of the labeling, as required under 21 CFR 314.125(b)(8)."

CDTL Comment: *I agree with the determination made by the CMC review team.*

The CMC review team made the following review notifications:

Drug Substance: Overall, the drug substance is of suitable quality for use in Tlando (testosterone undecanoate) Capsules.

Drug Product: The regulatory specification necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product at release and on stability includes tests for capsule appearance, identity, assay ((b) (4)%), uniformity of dosage units (by capsule weight), (b) (4), microbial limits, and impurities. Based on the available stability data, an expiration dating period of 24-months when the drug product is stored at 25°C/60% RH has been granted.

Product Quality: Dr. Norman concluded that, "the microbial controls are adequate for this gelatin product."

Biopharmaceutics: Additional dissolution data using revised methodology to confirm the acceptance criterion is requested of the sponsor. Dr. Harith Mandula recommends approval.

Manufacturing Facilities: Dr. Juandria Williams, in OPQ's Office of Process and Facilities, has concluded that, "there appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 208088."

Environmental Analysis: While there clearly is some potential for hormonal activity from this product, which raised concern per recent draft FDA guidance on hormonally active drugs in the environment, there is little available data to establish that, at the expected level of exposure, there is the potential for serious harm to the environment from this action (21 CFR 25.21(a)). Thus, the request for a categorical exclusion from an environmental assessment (EA), supplemented by information submitted by the applicant to aid in determining whether extraordinary circumstances exist, is adequate. There is no information available indicating that additional environmental information is warranted in order to evaluate the claim of categorical exclusion. Furthermore, an adequate statement of no extraordinary circumstances was provided. The claim of categorical exclusion is accepted.

CDTLComment: *I agree with the overall assessment and conclusion made by Mark Seggel, PhD Chemistry Team Lead. Because, the current application, LPCN 1021 is recommended for a Complete Response (CR), the requested additional dissolution data will be added to the deficiency list in the CR and requested to be submitted during the next review cycle.*

4. Nonclinical Pharmacology/Toxicology

Recommendation:
The pharmacology/toxicology review team Drs. Laurie Mcleod Flynn, Lynnda Reid and Mukash Summan conducted a review of nonclinical pharmacology and toxicology. The review team concluded that there is no impediment to approval from a Pharmacology/Toxicology perspective and that it is appropriate that class labeling used for other testosterone replacement products also be used for this product.

CDTL Comment: *I concur with Pharmacology/Toxicology review team's recommendation.*

Following notifications were made by Dr. Mcleod-Flynn during her review:
Dr. Mcleod comments in her review that no determination of the subcellular distribution of TU was made, and it is possible that TU's subcellular distribution is different from that of testosterone which has very specific binding proteins in animals and humans. It is possible that, although AUC comparisons appear to show similar blood levels of TU and T (at the low doses) in rats and dogs compared to humans, that tissue levels are higher in animals than in humans or that intracellular compartmentalization or binding proteins are present among species. Moreover, no toxicological concerns were specifically attributed to systemic levels of TU and DHTU based on the nonclinical, repeat dose toxicological evaluation with a 13-fold higher concentration than would be expected to be seen in human.

Dr. Mcleod further comments that in the adrenal gland, there was an increase in the incidence and severity of diffuse cortical vacuolation in treated animals, characterized by small to large cytoplasmic vacuoles within cortical adrenocytes, primarily in the zona fasciculata and reticularis. There was an increase in the incidence and severity of thymic atrophy in treated animals compared with controls, characterized by a loss of lymphoid cells from both the cortex and medulla causing an overall decrease in the size of the gland. Clinically, no adverse effects on the adrenals or other glandular tissue or on reproductive tissues at physiological blood levels have been identified.

CDTL Comment: *Although, diffuse vacuolation was seen in the adrenal glands of rats, there were no corresponding clinical signs seen in humans during the phase 3 clinical trial.*

5. Clinical Pharmacology/Biopharmaceutics

Recommendation from Clinical Pharmacology Review Team LaiMing Lee, PhD; Myong-Jin Kim, PharmD; Luning (Ada) Zhuang, PhD; Jeffry Florian, PhD; and E. Dennis Bashaw, PharmD:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-3 (OCP/DCP-3) and Division of Pharmacometrics (OCP/DPM) has reviewed NDA 208088 for TU (b) (4) (b) (4) 112.5 mg oral capsules submitted to the Agency on August 28, 2015. The Phase 3 trial demonstrated efficacy based upon the evaluated sampling and titration plan. The intensive sampling scheme used in the Phase 3 trial is not practical for a clinical setting and cannot support labeling, nor has the proposed single point titration scheme been shown to be acceptable. Furthermore, none of the proposed single point titration schemes proposed by the sponsor provide a means of either

predicting or mitigating Cmax outliers that may occur following the evening dose. Given the lack of an adequate dose titration scheme that would be predictive of clinical response and would mitigate high T concentrations and potential safety issues, it is not possible to develop appropriate labeling at this time and a Complete Response action is recommended at this time.

CDTL Comment*: After reviewing different proposed single time point titration schemes, the Clinical Pharmacology and Clinical review team, still could not come up with an appropriate labeling instruction for the prescribers due to existing high numbers of outliers (as seen in Phase 3). All proposed titration schemes would result in either larger number of sub-therapeutic or supra-therapeutic subjects. Therefore, I concur with the recommendation from Clinical Pharmacology team. The action recommended is Complete Response (CR). The Sponsor would be advised to conduct a new phase 3 trial with a titration scheme based on a single blood draw and demonstrate efficacy as a path forward.*

The Clinical Pharmacology review included the following in their review:

Effect of food on the bioavailability of the drug:
TU is a lipophilic substance. Therefore, it is recommended that the LPCN 1021 capsules be taken with meals containing some lipids in order to increase absorption and bioavailability of testosterone. The Applicant evaluated the effect of fat content in an open-label, randomized, four-period, four-treatment, crossover, single dose study in hypogonadal males following administration of 225 mg oral TU (Study LPCN 1021-14-001). A total of up to 16 hypogonadal adult males received a 225 mg oral dose (2 x 112.5 mg capsules) of LPCN ~30 min after the meal had started and fasted for no less than 4 hrs after the drug administration.

Blood samples for determination of T, DHT, TU, and DHTU concentrations were collected pre-dose (within 45 min prior to dosing), and between 1 and 24 hours post-dose in each period. To assess the impact of food on T replacement therapy, the bioavailability of TU and T as a function of fat content are presented in this analysis.

Table 1: Fat and Caloric Description of the Meals:

Meal Description	Total Energy	Carbohydrate	Protein	Fat
	Calories	Quantity in grams (% Total Calories)		
Standard Fat	842.5	115.2 g (54.7%)	27.7 g (13.2%)	30.1 g (32.1%)
Low Fat	911.7	173 g (75.9%)	17.8 g (7.8%)	16.5 g (16.3%)
High Fat	930.7	82 g (35.2%)	30.3 g (13.0%)	53.5 g (51.7%)

Source: Clinical Pharmacology Review

According to the Food Effect Guidance (2002), a high-fat (~ 50 percent of total caloric content of the meal) and high-calorie (~ 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The high fat meal in the study was consistent with the recommendation from the FDA. The main objective of the study was to evaluate the effect of food content on the bioavailability of T in four treatment groups – fasting, low-fat, medium-fat, and high-fat.

The Clinical Pharmacology reviewer described the food effect as follows:

The bioavailability of TU and T is low in the absence of food and fat. Food significantly enhances the absorption of TU and thus its conversion to T; therefore, the product is proposed to be administered with food. The proposed label states that oral TU capsules should be taken with food without reference to a specific fat content. This recommendation is supported by Study LPCN 1021-14-001 and the Clinical Pharmacology review team.

CDTL Comment: *I concur with the determination made by the Clinical Pharmacologist.*

Analysis of the Proposed Titration Scheme:
Patients were divided into three groups based on changes to dosing at the Week 3 visit: (i) down-titrated due to high Cmax or Cavg (b) (4)); (ii) no-change in dose as Cavg was within the normal range with no Cmax outliers ((b) (4)); and iii) up-titrated in dose as Cavg was below the normal range ((b) (4)). All patients started with 225 mg BID and could select a meal with moderate fat content for consumption prior to dosing at the Week 3 visit. There were 61 patients having Cmax higher than 1500 ng/dL at the Week 3 visit, so the dose was reduced to 150 mg twice daily. Also, 105 patients had Cavg values within the normal range (300 to 1140 ng/dL) at the Week 3 visit, thus the dose was not changed. Only 25 patients had Cavg lower than normal range, so the dose was up-titrated to 300 mg BID.

Concordance by dosing subgroup between full profile (Cavg) and single time point (C3-6h) titrations using a titration threshold of 300 and 1140 ng/dL (in Phase 3) and (b) (4) ng/dL ((b) (4)) were taken into consideration.

The results verified the sponsor's concordance analysis that the thresholds of (b) (4) ng/dL can maximize the number of patients that would be titrated in a similar titration to the titration scheme in the Phase 3 trial. However, it is worth noting that no matter what single time point titration method is selected, there will be a portion of patients who will be titrated differently than what occurred in the Phase 3 trial.

CDTL Comment: *The clinical pharmacology review team concluded that greater than 30% discordance was identified between two titration schemes, and the percentage cannot be improved upon for some groups (e.g. down titration group).*

Following additional notifications were made during the review:

Renal Impairment: The Applicant's proposed product label states "(b) (4) (b) (4) ."

Hepatic Impairment: The Applicant's proposed product label states "(b) (4) (b) (4)"

Geriatric Use: The Applicant's proposed product label states "There have not been sufficient numbers of geriatric patients with (TLANDO) to determine whether efficacy or safety in those over 65 years of age differs from younger subjects. Of the (b) (4) patients enrolled in the (b) (4) (b) (4) utilizing (TLANDO), (b) (4) were over 65 years of age."

Pediatric Use: The Applicant's proposed product label states "The safety and effectiveness of (TLANDO) in pediatric patients less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses."

Drug-Drug Interactions: TU is absorbed into the lymphatic system and de-esterified to T, the active moiety, by non-specific esterases in the intestinal call and peripheral circulation. Therefore, the Sponsor did not conduct in vitro and in vivo studies to assess potential drug-drug interactions.

The following complete response (CR) deficiency was identified from the Clinical Pharmacology perspective:
The current proposed single point dose titration scheme does not provide sufficient assurance to mitigate high T concentrations (and their associated safety issues). As the Phase 3 titration scheme was based on a more sample rich sampling program the sponsor should provide additional modeling and simulation data to identify an appropriate timepoint for sampling and titration thresholds that would provide a higher degree of assurance and a new in vivo clinical trial to validate this methodology.

6. Clinical Microbiology

The microbiology reviewer conducted a product quality microbiology review of the submission and concluded that the microbiology control for the product is adequate according to current quality standards.

7. Clinical/Statistical - Efficacy

Overview of Clinical Program
The LPCN 1021 clinical development program included eight Phase 1 studies and one Phase 3 study. The Phase 3 clinical study, LPCN 1021-13-001, provides safety, efficacy, and pharmacokinetic data relating to the use of twice daily dosing of LPCN 1021 for testosterone replacement therapy in men with primary and secondary hypogonadism.

The primary focus of the clinical review was data derived from Study LPCN 1021-13-001.
Primary Efficacy Trial – LPCN 1021-13-001
Study LPCN 1021-13-001 was a phase 3, randomized, open-label, active-controlled, multicenter, parallel-group, efficacy and safety study in adult hypogonadal males. Subjects were randomly assigned in a 2:1 ratio to receive LPCN 1021 (oral testosterone undecanoate [TU]) or AndroGel 1.62% (testosterone topical gel, active control) for 52 weeks.

For a detailed review of inclusion and exclusion criteria see the Primary Reviewer's Review in DARRTS.

Efficacy Endpoints
Primary Endpoint
The primary efficacy endpoint was defined as the percentage of LPCN 1021 treated subjects who achieved a 24-hour average serum T concentration within the normal range of 300 to 1140 ng/dL upon completion of approximately 13 weeks of treatment. The target minimum acceptable percentage was 75%. A 95%, 2-sided, binomial confidence interval (CI) surrounding the point estimate had to have a lower bound of at least 65% to conclude efficacy.

Secondary Endpoints

The secondary efficacy endpoints were defined as the percentage of subjects who exhibited maximum serum total T concentrations within predetermined limits upon completion of approximately 13 weeks of study treatment. These limits for Cmax0-12h, Cmax12-24h, and Cmax0-24h were the following:

1. < 1500 ng/dL in ≥ 85% of all subjects
2. 1800 and 2500 ng/dL in ≤ 5% of subjects
3. ≤ 2500 ng/dL in all subjects treated

Additional endpoints included responses to the:

- International Prostate Symptom Score (I-PSS),
- Short Form-36v2 Health Survey Quality-of-Life Questionnaire (SF-36),
- Psychosexual Daily Questionnaire (PDQ)

CDTL Comment: *Both primary and secondary endpoints are acceptable as they are consistent with the class. However, additional end points were all exploratory.*

Review of Efficacy

The applicant conducted one phase 3 clinical study (Study LPCN 1021-13-001) to evaluate the efficacy of testosterone undecanoate capsules in maintaining serum testosterone levels within the normal range in hypogonadal men. The design and endpoints of the study are acceptable. The study demonstrated that the applicant's product, Tlando (testosterone undecanoate) capsules, has substantial evidence of efficacy for the treatment of primary and secondary hypogonadism. However, it is not possible to reliably translate these results into labeling for real-world use because of the titration issues discussed previously.

The applicant also conducted a phase 1 clinical pharmacology study (Study LPCN 1021-14-001) to evaluate the effect of food on Tlando. For details see the Clinical Pharmacology Review in DARRTS.

Indication

Tlando is intended for:

Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

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

Demographics

A total of 315 subjects were randomly assigned to treatment in the study. The study inclusion and exclusion criteria allowed for enrollment of subjects of 18 to 80 years of age and with a BMI less than 38 kg/m^2. The mean age at baseline was 53 years, with about 10% of the subjects older than 65 years of age. Mean weight and BMI of subjects at baseline were 97.8 kg and 30.9 kg/m^2, respectively. Most of the subjects enrolled were white (83.8%), followed by black or African American (13.3%), while subjects of other races comprised less than 3%. Baseline characteristics for the subjects randomly assigned to Tlando and AndroGel 1.62% were similar.

Table 2: Demographic and Baseline Characteristics (Randomly Assigned Subjects)

Parameter	LPCN 1021 N=210	AndroGel 1.62% N=105	Overall N=315
Gender			
Male	210 (100%)	105 (100%)	315 (100%)
Female	0	0	0
Race			
American Indian or Alaska Native	0	0	0
Asian	3 (1.4%)	3 (2.9%)	6 (1.9%)
Black or African American	32 (15.2%)	10 (9.5%)	42 (13.3%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	172 (81.9%)	92 (87.6%)	264 (83.8%)
Other	3 (1.4%)	0	3 (1.0%)
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			
Age[a]			
Mean (SD)	52.6 (10.24)	54.2 (9.39)	53.1 (9.98)
Minimum	26	28	26
Maximum	76	74	76
≤ 65	190 (90.5%)	96 (91.4%)	286 (90.8%)
> 65	20 (9.5%)	9 (8.6%)	29 (9.2%)
Weight (kg)			
Mean (SD)	97.09 (14.959)	99.20 (14.780)	97.79 (14.910)
Minimum	54.7	43.7	43.7
Maximum	151.0	126.1	151.0
BMI (kg/m²)[b]			

Mean (SD)	30.83 (3.877)	30.98 (3.877)	30.88 (3.871)
Minimum	20.8	15.6	15.6
Maximum	37.8	37.9	37.9
< 25, n (%)	12 (5.7)	5 (4.8)	17 (5.4)
≥ 25 and < 30, n (%)	80 (38.1)	33 (31.4)	113 (35.9)
< 30, n (%)	92 (43.8)	38 (36.2)	130 (41.3)
≥ 30, n (%)	118 (56.2)	67 (63.8)	185 (58.7)

[a]Age is calculated as the difference between date of birth and date of informed consent, in years.
[b]BMI = Body mass index, and it is calculated as weight (kg) / height (m)².
Source: NDA 208088 (seq 000), Module 5.3.5.1, Table 14.1.2.1, MO Review

CDTL Comment*: The demographic and baseline characteristics of subjects randomized in Study LPCN 1021-13-001 were similar in each treatment arm of the study and representative of the patient population that would be expected to be treated with Tlando. Medical history was obtained at screening and served as the basis for future clinical assessments. Body systems with the most frequent findings included endocrine/metabolic; musculoskeletal; genitourinary; cardiovascular; and head, eyes, ears, nose, and throat.*

In accordance with study entry criteria, all subjects had a medical history of hypogonadism. Of the 315 subjects randomly assigned to treatment in the study, 47.3% were naïve (never treated with androgen therapy). Both the treatment groups had a similar percentage of naïve patients (48.6% and 44.8% for Tlando and AndroGel 1.62%, respectively).

Mean baseline testosterone levels were 209 ng/dL for the Tlando group and 200 ng/dL for the AndroGel 1.62% group. At screening, overall mean SHBG, FSH, and LH levels were 30.35 nmol/L, 8.02 IU/L, and 5.42 IU/L, respectively, and were similar between the treatment groups.

Disposition of Subjects
A total of 315 subjects were randomly assigned to treatment in the study: 210 were assigned to the Tlando group and 105 were assigned to the AndroGel 1.62% group. One subject who was randomly assigned to AndroGel 1.62% did not receive treatment. Overall, 130 subjects (61.9%) in the Tlando and 71 subjects (67.6%) in the AndroGel 1.62% group completed the study.

The most common reasons for premature discontinuation were withdrawal of consent (13.8% and 8.6% of subjects in the Tlando and AndroGel 1.62% groups, respectively), "Other" reasons (8.6% and 7.6%, respectively), and lost to follow-up (6.2% and 11.4%, respectively). Subject disposition and reasons for premature study discontinuation are summarized in the following Table 3.

Table 3: Subject Disposition (All Enrolled Subjects)

Status	**LPCN 1021 n (%)**	**AndroGel 1.62% n (%)**	**Total n (%)**
Subjects who were randomly assigned to treatment	210	105	315

Subjects who received treatment (Safety Set)	210 (100)	104 (99.0)	314 (99.7)
Subjects who completed study	130 (61.9)	71 (67.6)	201 (63.8)
Subjects who discontinued early from study	80 (38.1)	34 (32.4)	114 (36.2)
Reasons for early discontinuation:			
Consent withdrawn	29 (13.8)	9 (8.6)	38 (12.1)
Lost to follow-up	13 (6.2)	12 (11.4)	25 (7.9)
Cmax > 1500 ng/dL after lowering assigned dose to LPCN 1021 150 mg BID	8 (3.8)	NA	8 (2.5)
HCT > 54%	2 (1.0)	1 (1.0)	3 (1.0)
PSA > 4 ng/mL or with change from baseline of > 1.4 ng/mL	1 (0.5)	1 (1.0)	2 (0.6)
Significant noncompliance with the protocol requirements	3 (1.4)	2 (1.9)	5 (1.6)
PI judgment[a]	3 (1.4)	0	3 (1.0)
Health risk to subject with continued participation (including adverse events)[b]	3 (1.4)	1 (1.0)	4 (1.3)
Other reasons	18 (8.6)	8 (7.6)	26 (8.3)

Source: MO Review

The most common reason for discontinuation in the category "other reasons" was that the subject had screened and/or been randomly assigned at another study site before enrolling at the current site, which occurred in 4 subjects in the LPCN 1021 group and 3 subjects in the AndroGel 1.62% group. When the duplication was discovered, the subject was discontinued from the study at both study sites.

Two subjects in the LPCN 1021 group and 3 subjects in the AndroGel 1.62% group experienced AEs that were recorded in the "other reasons" category. In addition, 1 subject who received LPCN 1021 had an "other reasons" of "withdrew on his own due to adverse event." Adverse events leading to study drug withdrawal in the 3 subjects receiving LPCN 1021 included abdominal pain and decreased libido (Subject (b) (6) feeling hot, flushing, agitation, and insomnia (Subject (b) (6) and dyspnea (Subject (b) (6) Adverse events leading to drug discontinuation in the 3 subjects receiving AndroGel 1.62% included musculoskeletal stiffness and joint stiffness (Subject (b) (6) headache (Subject (b) (6) and prostate cancer (Subject (b) (6)

In addition to the AEs included in the discontinuation category of "other reasons," 3 subjects in the LPCN 1021 group and 1 subject in the AndroGel 1.62% group experienced AEs that were included in the discontinuation category of "Continued study participation put the subject at health risk, including significant changes in medical history or reported or observed AEs, where continuation of the subject on the treatment could have put the subject at health risk." Adverse events leading to study drug withdrawal in the 3 subjects receiving LPCN 1021 included peripheral edema and weight increased (Subject (b) (6) abdominal discomfort (Subject (b) (6)

(b) (6) and staphylococcal bacteremia and osteomyelitis (Subject (b) (6) The AE leading to drug discontinuation in the subject receiving AndroGel 1.62% was anger (Subject (b) (6)

CDTL Comment*: The applicant believes that the higher rate of dropouts in the LPCN 1021 arm of the study was likely due to the design of the study rather than study drug-related issues. Before Week 13, the LPCN 1021 arm of the study required 3 overnight confinements with intensive blood samplings, which were not required in the AndroGel 1.62% arm of the study. When additional information was obtained from the sites regarding specific reasons subjects withdrew their consent, 12 subjects who withdrew consent cited confinement or schedule conflicts as their reason for withdrawal. In addition, 2 other subjects, who were withdrawn due to "other reasons," cited confinement or inability to complete overnight stays. Therefore, 14 subjects (6.7%) who received LPCN 1021 withdrew due to confinement or schedule conflicts. In comparison, 3 subjects (2.9%) who received AndroGel 1.62% cited schedule conflicts for withdrawing their consent. Also, 4.3% of LPCN 1021 subjects were withdrawn due to meeting protocol-specified Cmax or Cavg stopping criteria, which were not applicable to the AndroGel 1.62% arm of the study.*

CDTL Comment: *The applicant submitted discontinuation data based on whether the discontinuation occurred before or after the week 13 visit. Table 4 summarizes discontinuations before and after the week 13 visit.*

Table 4: Summary of Subject Discontinuation Before and After Completing Week 13 Visit Based on Applicant Classification

STATUS	Entire Study			
	LPCN 1021 n (%)		Androgel 1.62% n (%)	
Subjects Randomized	210		105	
Subjects who Received Treatment	210 (100)		104 (99.0)	
Total Subjects who Completed the Study	130 (61.9)		71 (67.6)	
Total Subjects who Discontinued Early from the Study	80 (38.1)		34 (32.4)	
	Before Completing Week 13 Visit		After Completing Week 13 Visit	
	LPCN 1021 n (%)	AndroGel 1.62% n (%)	LPCN 1021 n (%)	AndroGel 1.62% n (%)
Subjects who Discontinued Before Completing Week 13 Visit	53 (25.2)	12 (11.4)	-	-
Subjects who Discontinued After Completing Week 13 Visit	-	-	27 (12.9)	22 (21.0)
Reason for Early Discontinuation				
Consent Withdrawn				
Confinement or Schedule Conflict	11 (5.2)	1 (1.0)	3 (1.4)	2 (1.9)
Reason other than	4 (1.9)	1 (1.0)	6 (2.9)	1 (1.0)

Confinement or Schedule Conflict				
Protocol Deviation	4 (1.9)	2 (1.9)	3 (1.4)	1 (1.0)
Lost to Follow Up	8 (3.8)	1 (1.0)	6 (2.9)	11 (10.5)
Cmax or Cavg not Achieved; Met the Stopping Criteria	9 (4.3)	NA	NA	NA
Hematocrit >54%	1 (0.5)	0	2 (1.0)	1 (1.0)
Prostate Specific Antigen >4 ng/mL	1 (0.5)	1 (1.0)	0	0
Weight Gain	1 (0.5)	0	2 (1.0)	0
Adverse Event	6 (2.9)	1 (1.0)	1 (0.5)	4 (3.8)
Serious Adverse Event	2 (1.0)	0	1 (0.5)	0
Other, Lack of Efficacy	2 (1.0)	2 (1.9)	3 (1.4)	2 (1.9)
Other, Duplicate Subject[1]	4 (1.9)	3 (2.9)	0	0

[1]Subjects who enrolled at more than one site. In cases where this occurred, subjects were withdrawn at both study sites.
Source: NDA 208088 (seq 0012), Table 1 and 2

CDTL Comment*: The overall dropout rate during the entire study was similar between the Tlando and AndroGel 1.62% arms. However, during the initial 13 weeks of the study, when subjects in the Tlando, but not in the AndroGel 1.62% arm of the study had three overnight confinements with intensive blood samplings, the dropout rate for the Tlando arm was greater than that of the AndroGel 1.62% arm. During that time period, the dropout rate in the Tlando arm was driven by subjects who dropped out due to confinement/schedule conflict, subjects who met the stopping criteria for the study (these stopping criteria were not assessed for subjects in the AndroGel 1.62% arm), and subjects who were lost to follow up. The percentage of subjects dropping out for reasons other than these three were, in general, similar between both treatment arms.*

During the remainder of the study, the dropout rate for the AndroGel 1.62% arm was greater than the Tlando arm. This supports the applicant's explanation that dropouts from the Tlando arm of the study were likely due to the design of the study rather than study drug-related issues.

Efficacy Findings

Analysis of Primary Efficacy Endpoint

In Study LPCN 1021-13-001, the Efficacy Population Set (EPS) was designated as the primary analysis population for effectiveness prior to database lock. Additional analyses were done for the Full Analysis Set (FAS), Per Protocol Set (PPS), and the Pharmacokinetic (PK) Set.

The FAS included all subjects randomly assigned to treatment in the study who had at least 1 post-baseline efficacy variable response (T Cavg0-24h or T Cmax). Week 13 data were used for this analysis and the last observation carried forward (LOCF) approach was used for imputing missing efficacy data for subjects who discontinued early.

The PPS included all subjects who successfully completed the dose titration and treatment periods with sufficient data from the Week 13 final serum T concentration profile without major protocol deviations.

The EPS included all FAS subjects without major protocol deviations. These subjects comprised the same subjects as the PPS but also included subjects who had discontinued prematurely from the study and did not have Week 13 data, but had data for Week 3 and/or Week 7. Week 13 data were used for this analysis and the LOCF approach was used for imputing missing efficacy data for subjects who discontinued early.

The PK Set included all subjects who received LPCN 1021, had no major protocol deviations that affected the PK analysis, and had sufficient and interpretable PK data for the evaluation of the PK endpoints (i.e.,Cmax0-24h, Cmax0-12h, Cmax12-24h, Tmax, Cavg0-24h, and AUC0-24h of serum T) available from the Week 3, Week 7, and/or Week 13 profiles.

Protocol deviations were classified as 'major protocol deviations' based on the following criteria:

1. Subjects who were enrolled in the study but who did not meet all the entry criteria (subjects who did not meet all inclusion criteria and/or met any exclusion criterion).
2. Subjects with significant noncompliance to study drug administration. Significant noncompliance was defined as having taken more than 130% of anticipated dose units or less than 70% of anticipated dose units.
3. Subjects for whom dose titration procedures were not followed correctly leading to incorrect doses. For example, if a subject's PK profile indicated that the subject's dose should have been down-titrated at Week 8 because the Cmax0-24h at Week 7 exceeded 1500 ng/dL but the site did not down-titrate the subject's dose.
4. Subjects who did not follow the dosing regimen correctly. For example, subjects who took a starting dose of 112.5 mg BID instead of 225 mg BID.

Table5 summarizes the number of subjects included in each of the datasets that were analyzed.

Table 5: Datasets Analyzed in Study LPCN 1021-2013-001–Subjects Randomized to LPCN 1021

Dataset	**LPCN 1021 n (%)**
Subjects Randomly Assigned to Treatment	210
Safety Set	210 (100)
Full Analysis Set	193 (91.9)
Efficacy Population Set	151 (71.9)
Per-Protocol Set	130 (61.9)
Pharmacokinetic Set	130 (61.9)
Note: Percentages were calculated based on the total number of randomly assigned subjects in the LPCN 1021 group. Source: NDA 208088 (seq 0000), 2.7.3, Table 4, p.21, MO Review.	

Results

The efficacy analysis of LPCN 1021 involved an assessment of PK parameters at Week 13 after subjects had undergone dose titration. In order to include data for subjects who discontinued early from the study, the primary efficacy analysis was performed using available Week 13 data and missing data that were imputed using the LOCF method.

The primary efficacy endpoint for this study was the percentage of LPCN 1021-treated subjects who achieved a 24-hour average serum T concentration within the normal range (i.e., 300-1140

ng/dL) upon completion of 13 weeks of treatment. For the efficacy endpoint of the study to be met, the minimum acceptable percentage was 75%. A 95%, 2-sided, confidence interval surrounding the point estimate with a lower bound of 65% or more was required to conclude that the LPCN 1021 treatment was efficacious. The primary analysis dataset was the EPS.

Table 6: Proportion of LPCN 1021-Treated Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range at Week 13 – EPS and FAS

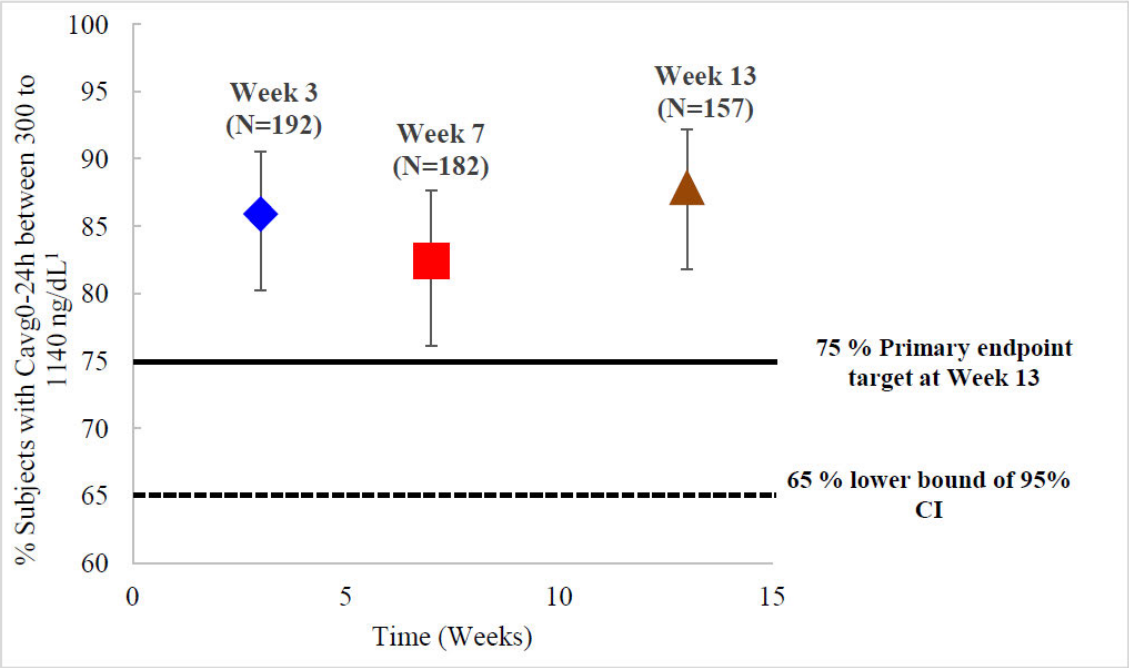
Parameter	Target	EPS N=151	FAS N=193
Percentage (No.) subjects achieving 24-hour average serum T concentration within normal range[1]	≥ 75%	87.4% (132/151)	87.0% (168/193)
95% Confidence interval	≥ 65% (Lower Bound)	81.70%, 92.73%	81.97%, 91.82%

EPS = Efficacy Population Set; FAS = Full Analysis Set; T = total testosterone
[1]Normal Range: 300 to 1140 ng/dL
Source: NDA 208088 (seq 0000), 2.7.3, Table 5 and 6, pp. 22-23, MO Review

The applicant performed additional sensitivity analyses for the PPS and PK datasets, which comprised the same set of 130 subjects, to evaluate the effect of imputing missing data in addition to protocol deviations. For these datasets, the percentage of subjects with a serum T Cavg0-24h within the normal range was 87.7% with a 95% confidence interval of 80.78% to 92.80%.

In addition to the analysis of the percentage of subjects achieving T Cavg0-24 within the normal range at Week 13, the applicant also conducted an exploratory analysis based of the percentage of subjects with T Cavg0-24 within the normal range at Week 3 and Week 7. At Week 3 and Week 7, 85.9% and 82.4%, respectively, had T Cavg0-24 within the normal range with the lower bound of the 95% confidence interval greater than 65%. Figure 1 shows the percentage of subjects meeting the criteria for the primary efficacy endpoint at Weeks 3, 7, and 13.

Figure 1: Percentage of Subjects Meeting the Efficacy Criteria and associated 95% CI lower bound for the Primary Efficacy Endpoint at Weeks 3, 7 and 13 – All Available Data



Source: NDA 208088 (seq 0000), 2.7.3, Figure 2, p. 28, MO Review.

CDTL Comment: *For the primary efficacy endpoint, the results of Study LPCN 1021-13-001 met the criteria for efficacy. This was demonstrated from the EPS dataset, the primary analysis dataset specified in the protocol, as well as the FAS, PPS, and PK datasets. In addition, the primary endpoint was met at Week 3 (prior to titration) and Week 7 (after the first titration), as well as Week 13 (after the second titration) when all available data at each of these time points were analyzed.*

SecondaryEfficacy

Analysis of Secondary Endpoints

Evaluation of the secondary endpoint was based on the T Cmax determined from the serum T PK evaluation and consisted of the percentage of treated subjects that had Cmax values within the predetermined limits upon completion of approximately 13 weeks of study treatment. The predetermined limits were:

1. T Cmax < 1500 ng/dL (targeted to be ≥ 85%)
2. T Cmax between 1800 and 2500 ng/dL (targeted to be ≤ 5%)
3. T Cmax > 2500 ng/dL (targeted to be 0%)

The Cmax values used for the analysis included Cmax0-24h, Cmax0-12h, and Cmax12-24h of serum T obtained after 13 weeks of treatment or with missing data imputed by the LOCF method. The protocol specified that the EPS dataset would be used for evaluation of the secondary endpoint.

LPCN 1021 was administered BID and was expected to have one T Cmax after each dose administration. Therefore, at Week 13 when full day PK values were obtained and dosing occurred every 12 hours, two T Cmax values were observed: the first after the morning dose (T Cmax0-12h) and the second after the evening dose (T Cmax12-24h).

Table 7: Proportion of LPCN 1021-Treated Subjects Achieving Maximum Serum Total Testosterone Concentrations within Predetermined Limits at Week 13 – Efficacy Population Set (N = 151)

Measure	Target	Cmax0-24h N=151	Cmax0-12h N = 151	Cmax12-24h N = 151
T Cmax < 1500 ng/dL, % (n)1	≥ 85%	82.8% (125/151)	89.4% (135/151)	89.4% (135/151)
1800 ≤ T Cmax ≤ 2500 ng/dL, % (n)	≤ 5%	4.6% (7/151)	2.6% (4/151)	2.0% (3/151)
T Cmax > 2500 ng/dL, % (n)	0%	2.0% (3/151)	2.0% (3/151)	0.7% (1/151)

Source: NDA 208088 (seq 0000), 2.7.3, Table 9, p. 29.MO Review.

The target for one of the secondary endpoints was that no subject should have a Cmax > 2500 ng/dL. However, three subjects (2.0%) in the EPS had a Cmax > 2500 ng/dL at Week 13: two subjects had T Cmax0-12h > 2500 ng/dL and one subject had both T Cmax0-12h and T Cmax12-24h > 2500 ng/dL. Information for these subjects is summarized in Table 8 and discussed in detail below.

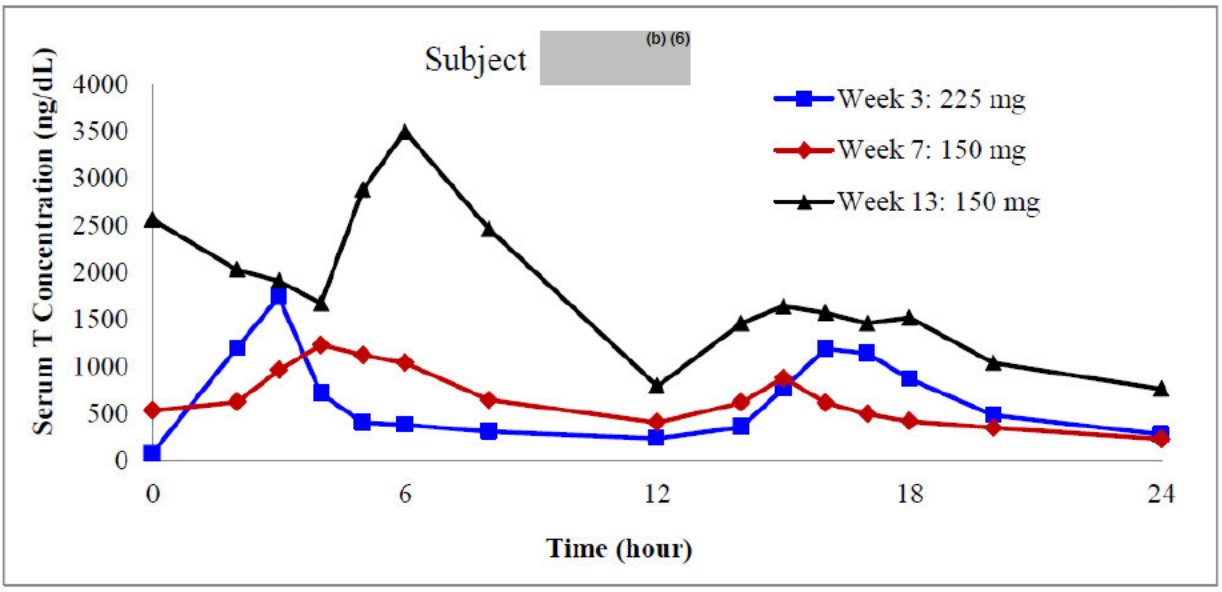
Table 8: Subjects with Cmax > 2500 ng/dL – EPS (N = 151)

Subject Number	Age (years)	Race / Ethnicity	BMI (kg/m2)	Dose at Cmax > 2500 ng/dL	Cmax (ng/dL)	Tmax (hr)	PK day
(b) (6)	35	White/ Hispanic or Latino	34.2	150 mg	3500	6.0	Week 13
	67	Black or African American/ Not Hispanic or Latino	28.9	300 mg	3390	2.0	Week 13
	53	White/ Not Hispanic or Latino	32.7	150 mg	2610	2.1	Week 13

Source: NDA 208088 (seq 0000), 2.7.3, Table 11, p. 30. MO Review.

Subject (b) (6) The subject is a 35 year-old male. A Cmax value of 3500 ng/dL was observed at Week 13 when the subject was on the 150 mg BID dose.

Figure 2: Total Serum Testosterone Concentration-Time Profile, Subject (b) (6)



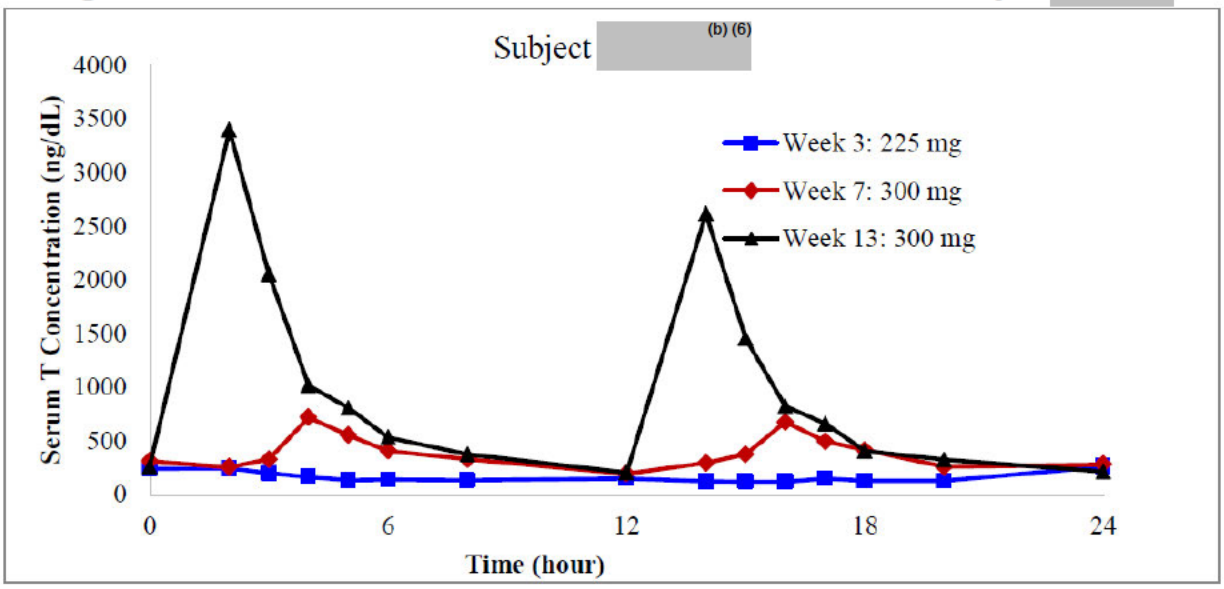
Source: NDA 208088 (seq 0000), 2.7.3, Figure 3, p. 33.

- The predose value at Week 13 was unusually high at 2560 ng/dL.
- Unusual serum testosterone levels at Week 13 compared to Week 3 and Week 7.
- Serum testosterone levels declined following the pre-dose measurement for Week 13 and then increased after 4 hours, which was not a typical observation of T levels in this study.
- Other pre-dose values at the 12 hour and 24 time points show levels of T in the normal range.
- Previous observed testosterone levels at a higher dose of 225 mg (Week 3 dose) and at the same dose of 150 mg (Week 7 dose same as Week 13 dose) were significantly lower.
- No dosing-related protocol deviations were noted for this subject
- No adverse events were reported for this subject through Week 13.

The applicant's assessment is that the observed Cmax >2500 ng/dL in this subject appears sporadic and transient and may have resulted from an unscheduled testosterone dose prior to the clinic visit.

Subject (b) (6) The subject is a 67 year old male. A Cmax value of 3390 ng/dL was observed at Week 13 when the subject was on the 300 mg BID TU dose.

Figure 3: Total Serum Testosterone Concentration-Time Profile, Subject (b) (6)



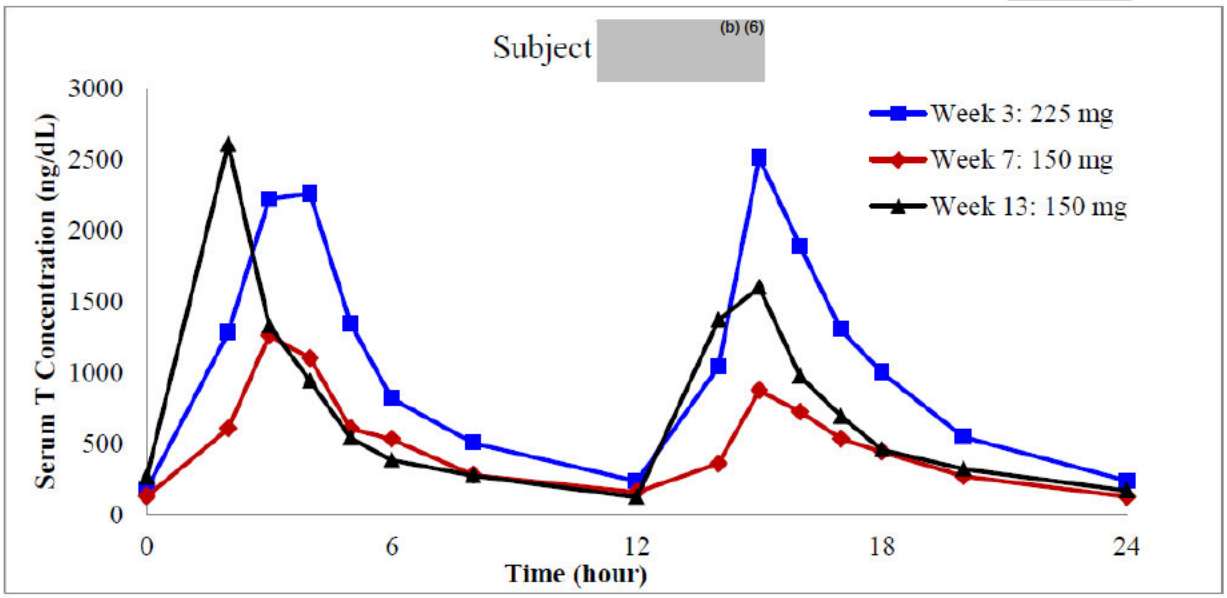
Source: NDA 208088 (seq 0000), 2.7.3, Figure 8, p. 38. MO Review.

- Based on the Week 3 Cavg of 157 ng/dL, the subject was uptitrated to 300 mg BID.
- At the 300 mg BID TU dose at Week 7, which was the same dose as Week 13, Cmax value was 715 ng/dL (low).
- At Week 13, testosterone concentration peaked 2 hours following both the morning and evening doses with testosterone concentrations of 3390 ng/dL at 2 hours and 2610 ng/dL at 14 hours (i.e., 2 hours following the evening dose).
- Previous testosterone concentrations observed at Week 3 and Week 7 are not consistent with Week 13 T levels.
- Testosterone concentrations at Week 3 and Week 7 were within or lower than the expected normal range suggesting that the Week 13 results were an outlier event.
- Testosterone concentrations did not exceed 2500 ng/dL at any other measured time points at Week 13.
- This subject completed the 52 week study with no adverse events reported throughout the study.

The applicant's assessment is that the Cmax excursion at Week 13 appears to be a sporadic event with a transient increase in Cmax with no meaningful clinical relevance.

Subject (b) (6) The subject is a 53 yr old male. A Cmax value of 2610 ng/dL was seen at Week 13 when on the 150 mg BID TU dose.

Figure 4: Total Serum Testosterone Concentration-Time Profile, Subject (b) (6)



Source: NDA 208088 (seq 0000), 2.7.3, Figure 9, p. 39. MO Review.

- At Week 3, Cmax was 2510 ng/dL and the dose was reduced to 150 mg BID at Week 4.
- At Week 7, Cmax was 1260 ng/dL and the dose remained at 150 mg BID.
- At Week 13, at same dose of 150 mg BID, Cmax was 2610 ng/dL and occurred at the 2 hour post dose time point; testosterone concentrations did not exceed 2500 ng/dL at any other time point.
- T concentrations were considerably lower at Week 7 than Week 13 even though the dose was 150 mg BID in both cases suggesting lack of dose dependency on the Cmax occurrence.
- At Week 13, Cmax values were higher following the morning dose (i.e., Cmax0-12h: 2610 ng/dL) than following the evening dose (i.e., Cmax12-24h: 1600 ng/dL)
- No dosing-related protocol deviations were noted for the subject.
- The subject did not report any adverse events through Week 13
- The subject reported an adverse event of dyspnea classified by the investigator to be mild in severity and related to study drug at Week 21, the subject chose to discontinue the study at Week 28 due to the adverse event.

The applicant's assessment is that this subject's Week 13 T level is unusual with no dose dependency and potentially could be due to improper dosing. The T level excursion appears to be transient and unrelated to the recommended dosing regimen with no meaningful clinical relevance.

CDTL Comment: *The secondary endpoint consisted of three components: T Cmax < 1500 ng/dL (targeted to be ≥ 85%), T Cmax between 1800 and 2500 ng/dL (targeted to be ≤ 5%), and T Cmax > 2500 ng/dL (targeted to be 0%).For the first component of the secondary endpoint (T Cmax < 1500 ng/dL), the drug met the target when the am (Cmax0-12h) or pm (Cmax12-24h) doses were assessed individually. When the entire 24 hour period was assessed (Cmax0-24h), the percentage of patients meeting the criteria was 82.8%, which is slightly less than the target.*

Given the twice daily dosing regimen of Tlando, it is not unexpected that during a 24 hour period there may be some subjects who have a Cmax < 1500 ng/dL for only the am or pm dose of the drug, but not for both of the doses.

For the second component of the secondary endpoint (T Cmax between 1800 and 2500 ng/dL), the drug met the target (≤ 5%) regardless of the time period assessed (Cmax0-12h, Cmax12-24h, and Cmax0-24h).

For the third component of the secondary endpoint (T Cmax > 2500 ng/dL), the drug failed to meet the target (0%). Three subjects (2%) in the EPS had a T Cmax > 2500 ng/dL at Week 13. Two subjects had T Cmax0-12h > 2500 ng/dL and one subject had both T Cmax0-12h and T Cmax12-24h > 2500 ng/dL.

Of the three subjects with T Cmax > 2500 ng/dL, one (Subject (b) (6) had the Cmax excursion at time point 0 (before the am dose of the drug). The T value declined following the pre-dose measurement and then increased after four hours. The applicant attributes the Cmax excursion seen in this subject to an unscheduled testosterone dose before his clinic visit. I believe that unscheduled dosing could result in the PK plot that was seen for this subject and is a reasonable explanation for the Cmax excursion.

For the other two subjects ((b) (6) and (b) (6) there was no apparent reason for the Cmax excursion.

Subject (b) (6) had a Cmax excursion during the Week 13 PK assessment: testosterone concentration peaked 2 hours following both the morning and evening doses with testosterone concentrations of 3390 ng/dL at 2 hours and 2610 ng/dL at 14 hours. The subject was up titrated to the 300 mg BID dose at Week 4 and had a Cmax of 715 ng/dL during the Week 7 PK assessment. The subject was on the 300 mg BID dose at Week 13. There was no apparent explanation for the Cmax excursion.

Subject (b) (6) had a Cmax excursion during the Week 13 PK assessment. The subject was down titrated to the 150 mg BID dose at Week 4 and was on that dose at Weeks 7 and 13. Cmax at the Week 7 assessment was 1260 ng/dL. There was no apparent explanation for the Cmax excursion.

Assessment of Cmax > 2500 ng/dL excursions using the Full Analysis Set identified 5 additional subjects who met this criterion. For detailed information see the MO's review in DARRTS.

CDTL Comment: *There were a total of eight subjects with Cmax excursion > 2500 ng/dL. Five subjects in the FAS study and three subjects in the EPS. For five of the subjects there were possible explanations for the excursions that the clinical review team believe are reasonable: two subjects ((b) (6) and (b) (6) had unusually high predose T values that may have been caused by unscheduled dosing; three subjects ((b) (6), and (b) (6) were titrated incorrectly or not titrated prior to the excursion. This may have led to the Cmax excursion in these subjects.*

For three of the subjects ((b) (6) and (b) (6) there was no apparent reason for the Cmax excursion > 2500 ng/dL. In general, these excursions were sporadic events with no apparent pattern to their occurrence. The excursions in two of the three subjects were preceded by PK assessments at the same dose for which the Cmax did not exceed 2500 ng/dL. In all three

subjects, the excursions were transient, occurred at the 2 hour PK timepoint, and were characterized by a rapid rise in T concentration that declined within 1-2 hours. Two of the subjects reported no adverse events during the study; one subject reported an adverse event of dyspnea at Week 21 of the study, which was classified as mild in severity and related to the study drug.

In the opinion of the clinical reviewer, there is a risk that some patients treated with Tlando will have sporadic Cmax excursions > 2500 ng/dL especially during the initial 1-2 hours of dosing. There were no factors identified that would predict which patients might be at risk for such excursions.

CDTL Comment: *I agree with the Clinical Reviewer's assessment.*

Other Endpoints
The applicant also evaluated the change from baseline to the end-of- study in the following patient reported instruments: International Prostate Symptom Score (I-PSS), Short Form-36 Health Survey Quality-of-Life Questionnaire (SF-36), and Psychosexual Daily Questionnaire (PDQ).

CDTL Comment: *Interpretation of the results from the patient reported instruments is limited. These instruments are not validated and there also was a lack of a placebo control. Therefore, in my opinion these are considered exploratory only.*

Subpopulations
The applicant performed subgroup analyses to evaluate the effect of BMI (obese vs non-obese) and prior androgen therapy (naïve vs non-naïve) on the primary endpoint of the study and on the pharmacokinetics of T (Cavg0-24h and Cmax0-24h).

CDTL Comment*: Based on the subgroup analysis of obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) subjects and subjects with prior androgen therapy, the drug is expected to be effective in both obese and non-obese patients and androgen naïve and non-naïve patients.*

Dose Titration During the Phase 3 Study
During the Phase 3 study, three dose levels of LPCN 1021 (150 mg, 225 mg and 300 mg TU) were administered twice daily to randomized subjects. All subjects started LPCN 1021 at the dose level of 225 mg TU BID and their dose was adjusted either up to 300 mg TU BID or down to 150 mg TU BID at Weeks 4 and 8 based on the pre-specified titration criteria from PK data (Cavg0-24 and Cmax) obtained at Weeks 3 and 7. The process of dose adjustments was to identify subjects that exhibit varying testosterone levels in response to administered dose and make adjustments to bring their Cavg into normal range and/or maintain Cmax < 1500 ng/dL.

At Week 13, which was the time of the efficacy analysis, 52% (82/157) of the subjects received the 225 mg BID starting dose and 41% (65/157) of the subjects required no titration. At Week 13, 89% (140/157) of the subjects required no more than one titration and about 10% of the subjects required two titrations. Thirty-two percent (50/157) of the subjects were down titrated, 16% (25/157) were up titrated, 7% (11/157) of the subjects who were initially down titrated were

followed by up titration, and 4% (6/157) of the subjects were up titrated followed by down titration at Week 13.

Figure5 shows the mean serum testosterone concentration-time profile of subjects at Week 3 stratified by titration requirement at Week 4. Figure6 shows the mean serum testosterone concentration-time profile of subjects at Week 13 stratified by final dose at Week 13.

Figure 5: Mean serum testosterone concentration-time profile of subjects at Week 3 stratified based on titration requirement at Week 4, All available data at Week 3 (N=192)

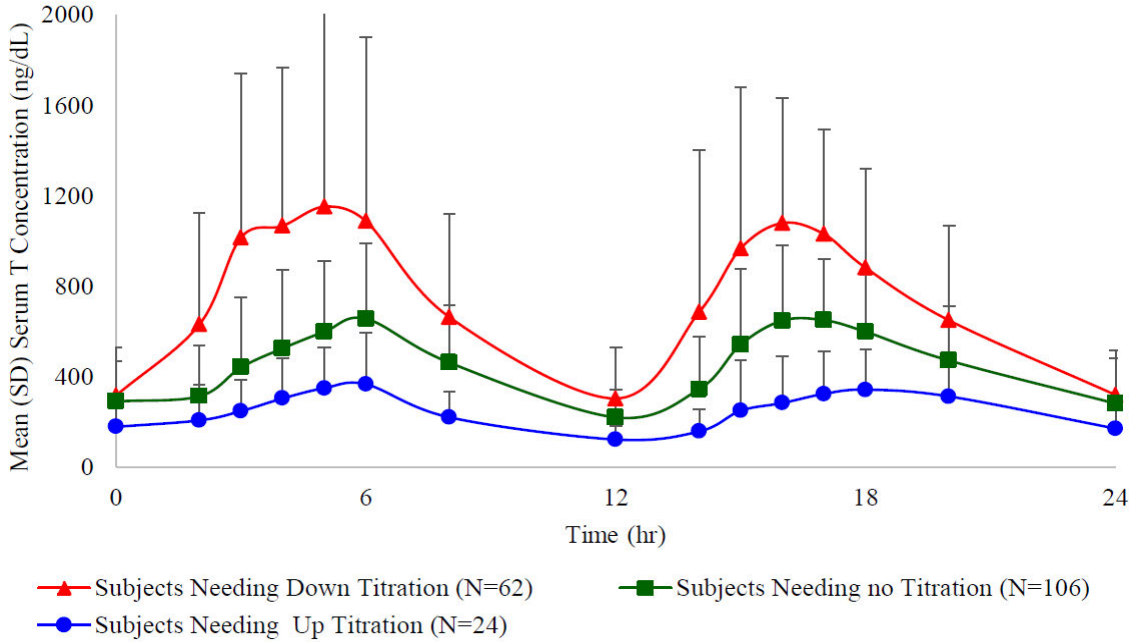
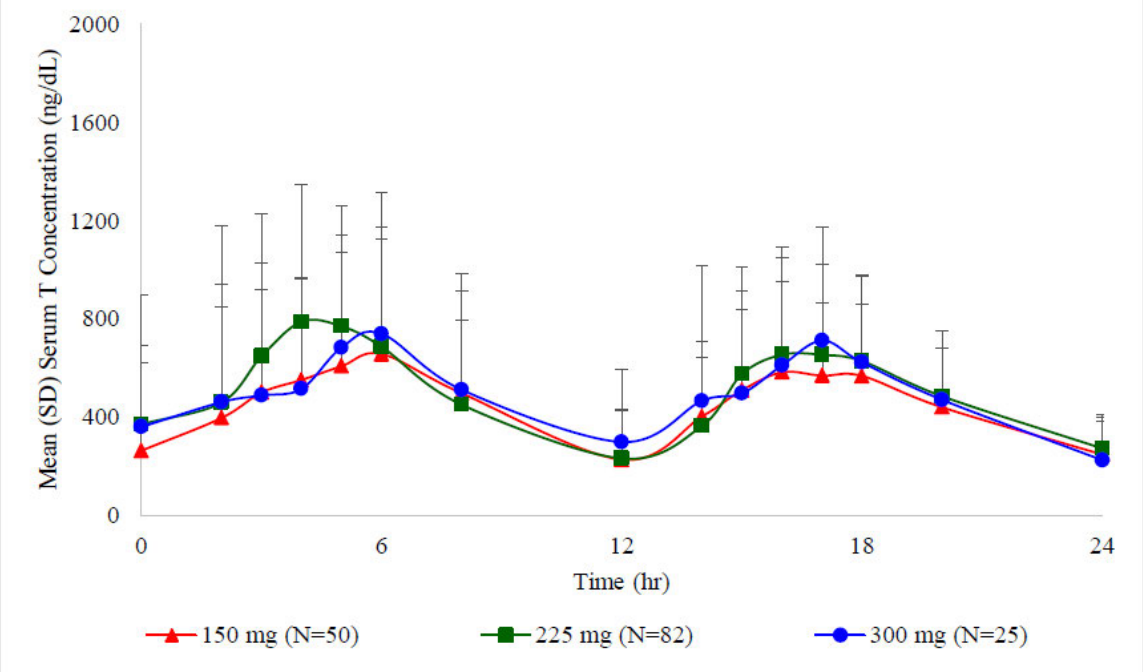


Figure 6: Mean serum testosterone concentration-time profile of subjects at Week 13 stratified based on final dose at Week 13, All available data at Week 13 (N=157)



Source: NDA 208088 (seq 0000), 2.7.3, Figure 21, p. 69, MO Review

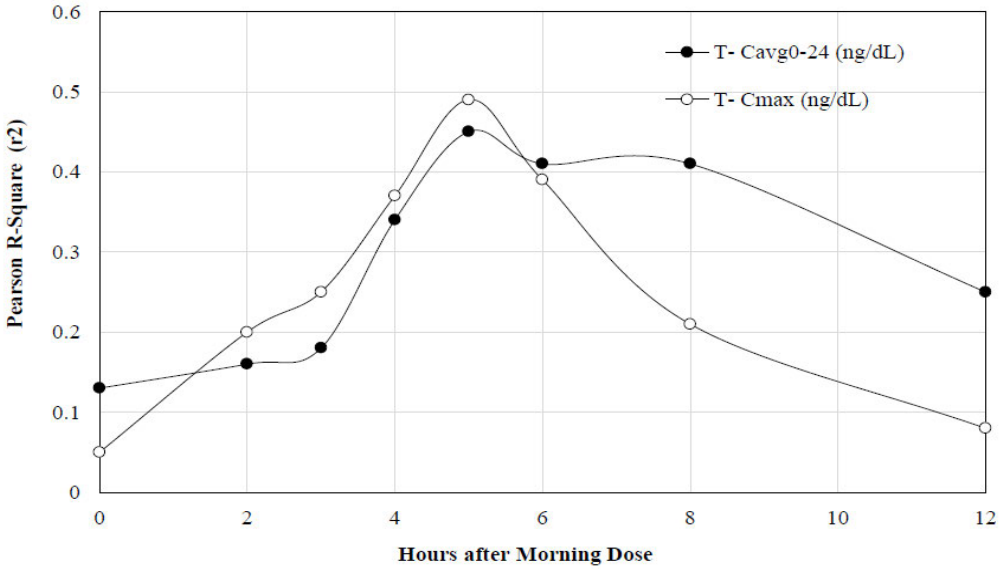
CDTL Comment*: The above two figures confirm that the convergence at Week 13 of the concentration-time profiles for the final doses suggest that the titrations at Week 4 and 8 were successful at bringing subjects' Cavg into the normal range.*

Analyses of Phase 3 Data Relevant to Single Blood Draw Titration Recommendation

Titration decisions in the Phase 3 study were based on Cavg0-24 and Cmax. The applicant conducted analyses of the Phase 3 data to develop a clinical practice titration recommendation, based on a single blood draw, which would lead to titration decisions that were similar to the titration decisions in the Phase 3 study.

The applicant evaluated the correlation between testosterone concentration at each time point from 0 through 12 hours post dose and Cavg0-24 and Cmax for the Week 3 and Week 7 data. This is shown in figure 7 below. Based on this analysis, the applicant concluded that the serum testosterone concentration 3 to 6 hours after the morning dose may be a good indicator for Cmax and Cavg0-24h.

Figure 7: Correlation between Serum Testosterone Concentration at Single Time Points and Cavg0-24h (ng/dL) and Cmax (ng/dL) at Week 3 and Week 7 (N = 373)



Source: NDA 208088 (seq 0000), 2.7.3, Figure 22, p. 71.

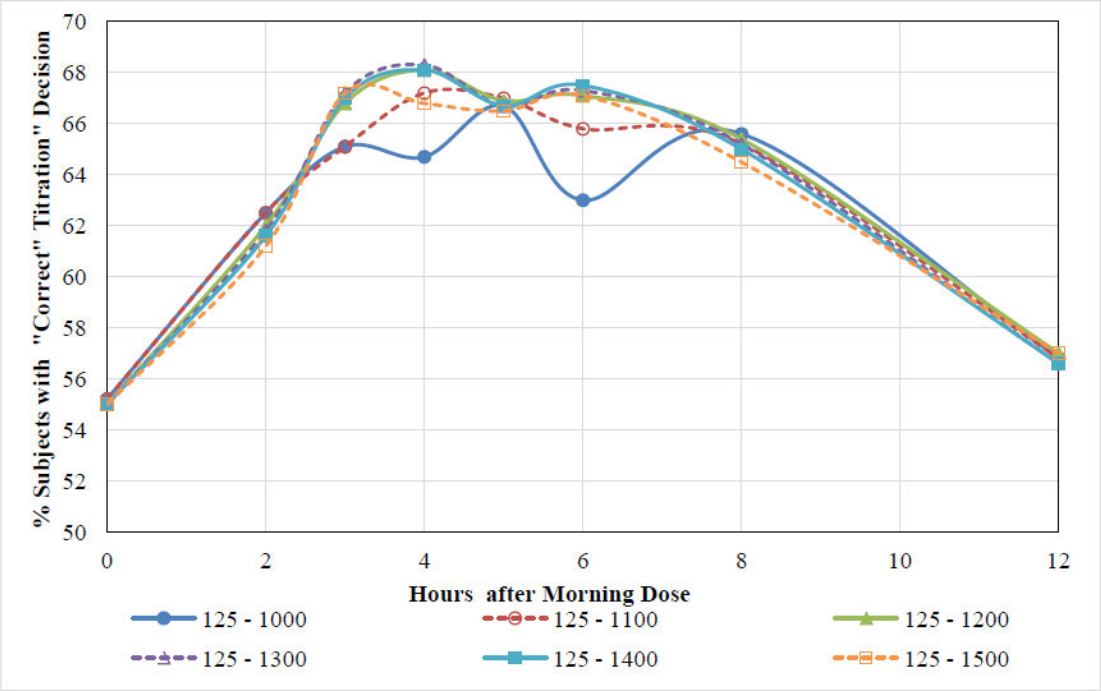
Titration decisions in the Phase 3 study were made using both Cmax and Cavg0-24 criteria. All upward titration decisions were based on Cavg0-24 (<300 ng/dL), while all downward titrations resulted from the Cmax criterion (> 1500 ng/dL). The correlation between Cmax and Cavg0-24 at Week 3 and Week 7 was calculated and found to be 0.72. Based on this analysis, the applicant concluded that Cavg0-24 provides a good representation of Cmax data when used for titration decisions.

CDTL Comment*: Given that all downward titrations were based on Cmax, the applicant's conclusion that Cavg0-24 can be used to represent Cmax, raises concerns.*

Data from Weeks 3, 7, and 13 of the Phase 3 study were used to determine the upper and lower bounds for single blood draw titration decisions that would most often lead to a "correct" titration decision. A "correct" titration decision was defined as being the same titration decision that would be made using the Phase 3 protocol-defined testosterone criteria based on T Cavg0-24 and Cmax. This analysis was performed by determining how frequently a titration decision based on C_t (e.g., C_{3h}, C_{4h}, C_{5h}, and C_{6h}) resulted in the "correct" titration decision.

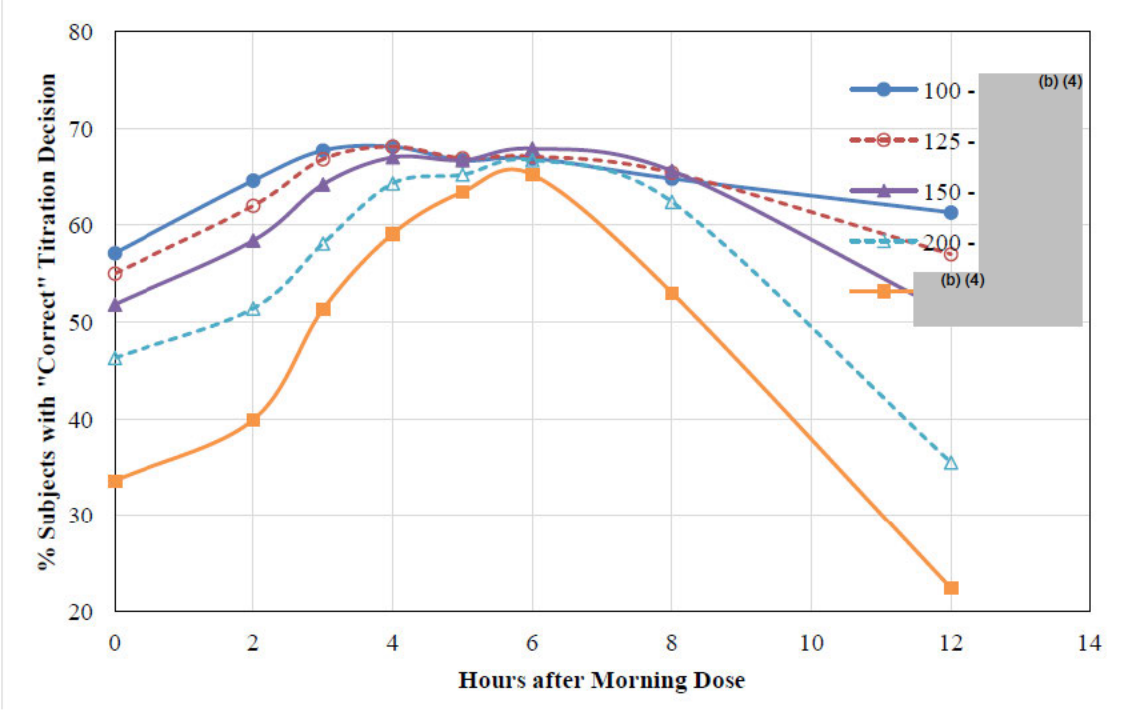
For this analysis, various testosterone concentrations were set as an upper bound (1000, 1100, 1200, 1300, 1400, and 1500 ng/dL) and a lower bound (100, 125, 150, 200, and 300 ng/dL) and evaluated to determine the combination of upper and lower boundaries at which a single blood draw titration decision outcome would most often match the "correct" titration decision. Figure **84**8 and Figure 9 show the percentage of subjects in which a single testosterone level led to the "correct" titration decision based on each set of upper and lower bounds.

Figure 84: Percentage of Subject Where a Single Testosterone Level Led to the "Correct" Titration Decision Using a Lower Bound of (b) (4) ng/dL and Various Upper Bounds Ranging from 1000 to 1500 ng/dL – Full Analysis Set (N = ~ 532)[1]



[1]Data from subjects with available data at Week 3(n=193), 7(n=182), and 13 (n=157) morning doses; therefore, each time point includes data from each of the 3 visits for these subjects.
Source: NDA 208088 (seq 0000), 2.7.3, Figure 24, p. 74.

Figure 9: Percentage of Subjects Where a Single Testosterone Level Led to the "Correct" Titration Decision Using Various Lower Bounds Ranging from 100 to [(b) (4)] ng/dL and an Upper Bound of [(b) (4)] ng/dL – Full Analysis Set (N = ~ 532)1



Data from subjects with available data at Week 3(n=193), 7(n=182), and 13 (n=157) morning doses; therefore, each time point includes data from each of the 3 visits for these subjects.
Source: NDA 208088 (seq 0000), 2.7.3, Figure 25, p. 75.

Titration decisions made on the basis of a single blood draw in the range of 3 to 6 hours after morning dose administration matched the Phase 3 titration criteria in 68% to 70% of subjects at each of these time points when the acceptable serum testosterone concentration value was set to a lower bound of [(b) (4)] ng/dL and an upper limit of [(b) (4)] ng/dL.

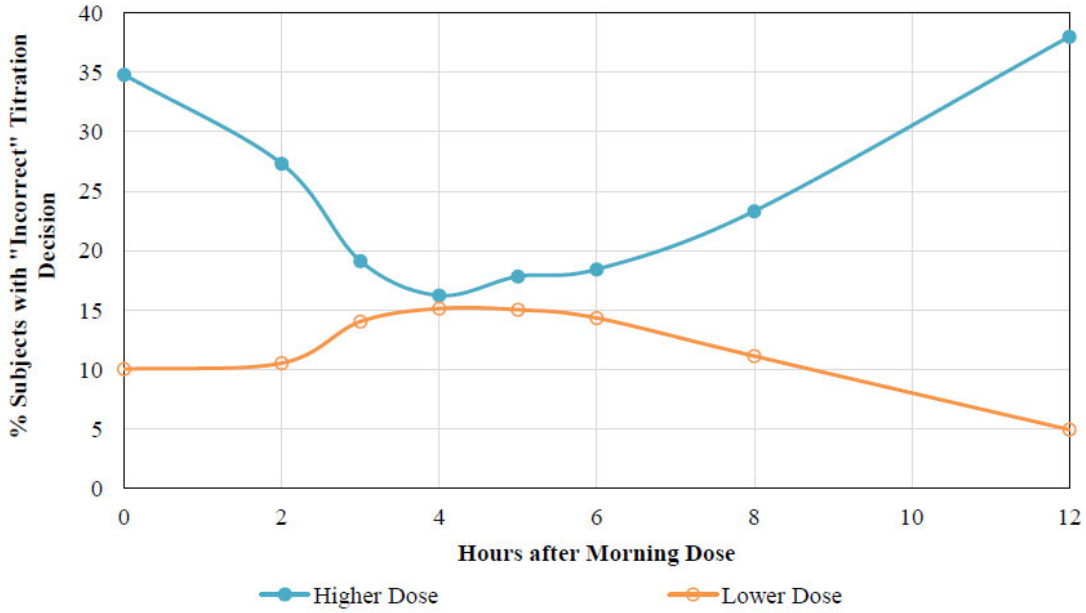
<u>Single Blood Draw (Clinical Practice) Titration Recommendation and Analysis of Agreement with Phase 3 Titrations</u>

Based on these results, the following titration criteria were proposed:

- [(b) (4)] hours after morning dose administration as the appropriate titration window
- [(b) (4)] ng/dL as the lower bound for recommending an upward titration
- [(b) (4)] ng/dL as the upper bound for recommending a downward titration

An analysis was performed to determine how frequently incorrect upward and incorrect downward titration decisions would be made using the proposed single blood draw titration algorithm. At the 3-, 4-, 5- and 6-hour time points, about 16 to 19% of subjects would have mistakenly been maintained at a higher dose and about 13 to 14% of subjects would have mistakenly been maintained at a lower dose using these upper and lower bounds. Figure10 shows the percent of subjects who would have been wrongly titrated up or down using the [(b) (4)] to [(b) (4)] ng/dL bounds.

Figure 10: Percentage of Subjects Where a Lower Bound of (b) (4) ng/dL and an Upper Bound of (b) (4) ng/dL Would Mistakenly Lead to a Higher or Lower Dose – Full Analysis Set (N = ~ 532)[1]



[1]Data from subjects with available data at Week 3(n=193), 7(n=182), and 13 (n=157) morning doses; therefore, each time point includes data from each of the 3 visits for these subjects. Source: NDA 208088 (seq 0000), 2.7.3, Figure 26, p. 76.

CDTL Comment*: In 29 to 33% of subjects, the single blood draw titration criteria proposed by the applicant would result in a titration decision that is not in agreement with the titration decision actually made in the Phase 3 study. This raises the concern that the results achieved in the Phase 3 study, in which titration was based on the PK parameters of Cavg and Cmax, may not be feasible in actual clinical use of the drug, where titration will be based on the T level of a single blood draw.*

In addition, the titration range proposed by the applicant ((b) (4) ng/dL) is considerably different from the generally accepted normal range used in clinical practice. This may result in additional titration errors during "real world" use of the drug.

Additional Titration Proposals

On May 20, 2016, the applicant submitted a new proposed titration scheme using the following criteria:

- (b) (4) hours after morning dose administration as the appropriate titration window
- (b) (4) ng/dL as the lower bound for recommending an upward titration
- (b) (4) ng/dL as the upper bound for recommending a downward titration

The 24-hour PK data from Weeks 3, 7, and 13 results in a total of 534 titration decisions, which were used in the applicant's analysis. Applying the Phase 3 titration scheme, 60.5% of subjects required no titration, 13.5 % of subjects required an upward dose titration, and 26.0% of subjects required a downward dose titration.

Table7 provides an assessment of the percentage of subjects that would have matched titration decisions by the single point titration schemes and the Phase 3 titration scheme.

Table 7: Titration Decision Concordance analysis: Single point titration decisions categorized by concordance with Phase 3 titration decision - All instances from Weeks 3, 7 and 13 (N=534, FAS dataset)

Bounds	**Lower bound of (b) (4) ng/dL Upper bound of (b) (4) ng/dL**	**Lower bound of (b) (4) ng/dL Upper bound of (b) (4) ng/dL**
Time Point	**Average of 3 to 6 hours**	**Average of 4 to 6 hours**
% Matched titration decisions (single point titration decision matched Phase 3 titration decision)		
% Matched titration decisions	67.2 %	62.6 %
Up Titration Match: Of the 13.5 % of subjects who were up titrated based on Phase 3 how many will match following single point titration		
% subjects that match*	14.9 %	52.8 %
Down Titration Match: Of the 26.0 % subjects who were down titrated based on Phase 3 how many will match following single point titration		
% subjects that match*	37.4 %	37.2 %
* % subjects that match derived from 100-% subjects that do not match. Source: NDA 208088 (seq 0019), 1.2, Table 1A, p. 3.		

The applicant believes that the proposed new single point titration with a lower bound of (b) (4) ng/dL of serum T, and the proposed new sampling time window of 4-6 hours maintains concordance in the majority of titration decision with Phase 3 and improves the non-concordance among the up titration decision outcomes in contrast to the previously submitted single point titration scheme.

CDTL Comment: *The (b) (4) ng/dL lower bound of the new proposed single blood draw titration criteria is more clinically relevant than the lower bound of the original criteria and resolves the issue of having titration bounds that are different from the generally accepted normal range. However, the new criteria do not reduce the number of "incorrect" titration decisions, in fact, the number of "incorrect" decisions increased with the new criteria. The Sponsor further continued to submit a few more proposals for single time point titration that were based on modeling of the data, however, no matter how the data was presented, it did not result in an acceptable agreement between the 24 hour Cavg derived data and single time point Cmax that could be labeled in order to provide proper and practical guidance to the prescriber. The purpose of concordance between the 24 hour PK data and a single time point is to have the best possible dosage adjustment based on one single morning blood draw.*

CDTL Summary comment: *The analyses of titration decisions made using the proposed single blood draw titration schemes did not show reasonable agreement with the titration decisions actually made during the Phase 3 study. Without a single blood draw titration scheme that is appropriate for clinical practice, it is not possible to make dosing recommendations for clinical use of the drug that can be labeled.*

Additional Efficacy Issues/Analyses

Free testosterone

During the Phase 3 study, mean free testosterone levels for LPCN 1021 and AndroGel 1.62% were calculated. For subjects treated with LPCN 1021, calculated mean free testosterone levels increased from 5.5 ng/dL at baseline to 12.9 ng/dL at week 13 and remained in the normal range at weeks 26, 39, and 52.

Dihydrotestosterone (DHT)

The mean baseline DHT concentrations for the Safety Set were 23.7 ng/dL (N=185) for the LPCN 1021 group and 22.7 ng/dL (N= 89) for the AndroGel 1.62% group. Measured DHT concentrations increased as T concentrations increased. The overall ratios of DHT/T at Weeks 3, 7, and 13 (N=130) showed arithmetic mean ratios that ranged between 0.16 and 0.26 over a 24-hour period. At Week 13, the mean serum DHT concentration pre-dose was 95.35 ng/dL. At 2 hours post dose, the mean DHT concentration decreased to 87.04 ng/dL and then increased to a peak concentration of 135.44 ng/dL at 6 hours post dose, after which DHT concentrations returned to below pre-dose levels (82.58 ng/dL and 85.56 ng/dL at 12 and 14 hours post dose, respectively). The DHT concentration profile after the evening dose was similar to the profile observed after the morning dose.

CDTL Comment*: The laboratory used by the applicant to measure DHT concentrations did not provide a reference (normal) range, therefore, whether DHT was maintained within the normal range during the Phase 3 study is unknown. In addition, PK assessments were done only on subjects in the LPCN 1021 treatment group but not on subjects treated with AndroGel 1.62%, so comparisons of Cavg between LPCN 1021 and AndroGel 1.62% during weeks 3, 7, and 13 are not possible. Though the applicant's analysis of DHT concentrations from the single 3 to 6 hour samples taken during weeks 26, 39, and 52 is reassuring, it does not provide a definitive answer to the question of whether LPCN 1021 maintains DHT within the normal range. I concur with the clinical reviewer.*

Estradiol

The arithmetic mean baseline E2 concentrations for the Safety Set (N=202) were 17.8 pg/mL for LPCN 1021. Cavg E2 concentrations increased to 29.3, 29.8, and 28.2 at weeks 3, 7, and 13, respectively. At Week 13, serum E2 concentrations reached a peak concentration of 31.51 pg/mL at 8 hours after dosing, after which time E2 concentrations declined and reached predose levels after approximately 12 hours. The E2 concentration profile after the evening dose was similar to the profile observed after the morning dose.

CDTL Comment*: For subjects treated with LPCN 1021, the mean overall Cavg0-24 for estradiol was within the normal range at week 13.*

Statistical Methodologies/Issues/Conclusion

Statistical Methodologies:

The Safety Set included all subjects who received at least 1 dose of study drug. The Full Analysis Set (FAS) included all subjects with at least 1 post-baseline efficacy variable response (Cavg0-24h or Cmax). The Efficacy Population Set (EPS) included all subjects in the FAS who

did not have a major protocol deviation. It is the efficacy analysis dataset. The Per-Protocol Set (PPS) included all subjects who completed the study without a major protocol deviation. The Pharmacokinetic (PK) Set included all subjects who received LPCN 1021, had no major protocol deviations that affected the PK analysis, and had sufficient and interpretable PK data for the evaluation of the PK endpoints.

Statistical Issue:
The statistical review team Weiya Zhang, Ph.D, and Mahboob Sobhan, Ph.D identified one minor statistical issue during the NDA review. It was specified in the SAP that asymptotic (rather than exact) confidence intervals were to be used in the efficacy analysis. However, the exact confidence interval was provided in the CSR. The difference was minimal and had no effect on the study results.

The efficacy results were consistent from sensitivity analyses in the Full Analysis Set, Per-Protocol Set, Safety Set, and model-based multiple imputation.

The statistical team further noted in their review that Study LPCN 1021-13-001 provides evidence demonstrating the efficacy of the twice daily LPCN 1021 (Testosterone Undecanoate) oral capsules for the treatment of adult male hypogonadism based on the proportion of men who achieved total serum testosterone levels within the normal range.

The primary efficacy endpoint of the study was the proportion of LPCN 1021-treated subjects who achieved a 24-hour average serum total testosterone (T) concentration (Cavg0-24h) within the normal range after approximately 13 weeks of treatment. The evidence was based on achieving total serum testosterone levels within the normal range after 13 weeks of treatment in at least 75% of men with the lower bound of the 95% confidence interval (CI) for the estimate of the proportion of men achieving the normal range no less than 65%.

LPCN 1021 increased the total serum testosterone level to within the normal range in 87.4% of men taking LPCN 1021 twice a day (95% CI of 81.1% to 97.2%) after 13 weeks of treatment in the Efficacy Population Set.

Approximately 83% of subjects had Cmax less than 1500 ng/dL after 13 weeks of treatment, which was less than the pre-specified acceptable criterion of at least 85%. In addition, there were 3 (2.0%) subjects whose Cmax0-24h was greater than 2500 mg/dL while it requires no subjects in this category.

Conclusions and Recommendations
The statistical review team Drs. Zhang and Sobhan concluded that from a statistical perspective, the study provided evidence in support of the efficacy of LPCN 1021 oral capsules in treatment of adult male hypogonadism.

CDTL Comment*: I concur with the conclusion from the statistical review team's point of view.*

8. Safety

Important Safety Issues associated with Testosterone Products
Labeled risks of testosterone administration in hypogonadal men include worsening of clinical symptoms of BPH, polycythemia, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity (with high doses of orally active 17-alpha-alkyl androgens such as methyltestosterone), and acne. Two major areas of concern in older men with aging-associated decline in serum testosterone are the effects of long-term testosterone administration on the risks of prostate cancer and progression of cardiovascular disease.

Transdermal testosterone preparations, which are applied to the skin, have been associated with secondary exposure of testosterone in women and children via direct skin-to-skin transfer. On September 18, 2009, the transdermal testosterone products that were being marketed at that time were required to include a Boxed Warning in product labeling and were required to have a risk evaluation and mitigation strategy (REMS) to address the serious risk of secondary transfer of testosterone to women and children. All transdermal testosterone products approved since that time have also been subject to the Boxed Warning and REMS requirements.

The injectable formulation of testosterone undecanoate has been associated with pulmonary oil microembolism (POME) reactions and anaphylaxis and its labeling includes a Boxed Warning for these reactions. In addition to labeling, distribution of the drug is subject to a risk evaluation and mitigation strategy (REMS) program that includes Elements to Assure Safe Use.

Safety Findings
The Safety Set included all subjects who were randomly assigned to treatment and received a dose of study drug. Subjects were analyzed according to the treatment received.

Exposure
A total of 315 subjects were randomly assigned to treatment and 314 subjects comprise the Safety Set for Study LPCN 1021-2013-001. Exposure to LPCN 1021 and AndroGel 1.62% ranged from 1 to 382 days. Median duration was the same for the 2 arms (364.0 days). Of the subjects randomized to LPCN 1021, 130 were exposed for 52 weeks.

CDTL Comment*: Exposure to LPCN 1021 appears to be adequate. The applicant met the goal of having at least 100 subjects exposed to LPCN 1021 for at least 52 weeks. The applicant also submitted a paper that provided additional supportive safety data based on 1329 patients prescribed an oral TU formulation approved in the UK, but not in the US.*

Dropouts and/or Discontinuations
During the Phase 3 study, 24 subjects (7.6%) experienced a TEAE that led to study drug discontinuation, including 19 subjects (9.0%) in the LPCN 1021 group and 5 subjects (4.8%) in the AndroGel 1.62% group. The only events that occurred in more than 1 subject were weight increased (3 subjects in the LPCN 1021 group), libido decreased (2 subjects in the LPCN 1021 group), and polycythemia (1 subject in each of the LPCN 1021 and AndroGel 1.62% groups). Eighteen of the 39 TEAEs that led to study drug discontinuation were considered by the investigator to be related to study drug: 15 events in 11 subjects in the LPCN 1021 group and 3 events in 3 subjects in the AndroGel 1.62% group.

Three subjects who received LPCN 1021 experienced SAEs that preceded study drug discontinuation: Subject (b) (6) (cervical vertebral fracture), Subject (b) (6) (staphylococcal bacteremia and osteomyelitis), and Subject (b) (6) (ataxia and balance disorder). None of the SAEs that preceded study drug discontinuation were considered related to the study drug by the investigator. None of the adverse events that preceded study drug discontinuation for subjects in the AndroGel 1.62% group were SAEs.

CDTL Comment*: The percentage of subjects who discontinued the Phase 3 study due to an adverse event is greater in the LPCN 1021 group than in the AndroGel 1.62% group. When the two additional subjects (subjects (b) (6) and (b) (6) who were added as a result of the sponsor's re-classification of discontinuations are included, a total of 26 subjects (8.3%) experienced a TEAE that led to study drug discontinuation: 20 subjects (9.5%) in the LPCN 1021 group and 6 subjects (5.8%) in the AndroGel 1.62% group. Events that occurred in more than 1 subject were weight increased (4 subjects in the LPCN 1021 group), libido decreased (2 subjects in the LPCN 1021 group), and polycythemia (1 subject in each of the LPCN 1021 and AndroGel 1.62% groups).*

Other than the AEs of weight increased and hematocrit > 54%, the AEs that resulted in discontinuation occurred in only one or two Tlando subjects. The discontinuations that resulted from the AE weight increased were all in the Tlando group and may have resulted due to the design of the study. Subjects in the Tlando group were required to eat a meal before taking the drug and instructed to include at least 25 – 30 grams of fat in that meal, while subjects in the AndroGel 1.62% group had no dietary recommendations during the study. This difference between the treatment groups may have contributed to the imbalance in subjects discontinuing due to weight increase.

Serious Adverse Events (SAE's)

Deaths:

No deaths occurred in any of the Phase 1 studies or the Phase 3 study of LPCN 1021.

Nonfatal Serious Adverse Events

During the Phase 3 study, a total of 19 treatment-emergent serious adverse events (SAE) were reported for 14 subjects (4.5%). For the LPCN 1021 group, 12 subjects (5.7%) experienced 15 treatment-emergent SAEs, and for the AndroGel 1.62% group, 2 subjects (1.9%) experienced 4 treatment-emergent SAEs. Overall, the treatment-emergent SAEs were most frequently categorized in the SOCs of infections and infestations (4 subjects, 1.3%) and musculoskeletal and connective tissue disorders (3 subjects, 1.0%). The only treatment-emergent SAE that was reported for more than 1 subject was sepsis, which was reported for 1 subject in both the LPCN 1021 and AndroGel 1.62% groups. For a detailed list of SAE's and subject narratives, see the Clinical Reviewer's review.

CDTL Comment*: In general the overall adverse events were comparable to other testosterone drug products in its class.*

Common Adverse Events
Common (> 2%) Treatment-Emergent Adverse Events (TEAE)
Except for the events of weight increase, acne, diarrhea, diabetes, PSA, hematocrit increase, and sinusitis, the incidence of common TEAEs for LPCN 1021 was similar or less than that of AndroGel 1.62%.

Significant Adverse Events
The applicant conducted a post hoc analysis of adverse events of special interest, which was not predefined in the study protocols. The adverse events of special interest for LPCN 1021 were determined based on known pharmacologic effects and adverse events for approved testosterone replacement therapies and include events related to the cardiovascular system, hepatic metabolism of steroids, effects on hematocrit, PSA, and other know androgenic effects.

CDTL Comment*: Except for the event of headache, all TEAEs of special interest occurred in less than 2.0% of LPCN 1021 subjects.*

Submission Specific Safety Concerns

Levels of Testosterone Undecanoate (TU) and Dihydrotestosterone Undecanoate (DHTU):
Testosterone undecanoate (TU) is a pro-drug that is metabolized to testosterone and DHTU. Levels of TU and DHTU were assessed by the applicant during the Phase 3 study.

TU and DHTU levels observed in the Phase 3 study were typically 20- and 10-fold higher than T levels, respectively. The applicant does not expect these increases to have a meaningful clinical impact and provided a rationale to support this expectation.

The conversions of TU to testosterone and of DHTU to DHT by esterases are rapid and the half-life for TU and DHTU is 1.2 hours and 1.6 hours, respectively (Study M12-778). Very minimal TU and DHTU tissue distribution was observed based on radioactive ADME rat study (S361.6.006). Based on an androgen receptor binding study, less than 1% relative affinity for TU and DHTU combined was observed when compared to testosterone. This low binding affinity would suggest that these compounds are not expected to have any meaningful clinical impact. Moreover, no toxicological concerns were specifically attributed to systemic levels of TU and DHTU based on the nonclinical, repeat dose toxicological evaluation with a 13-fold higher concentration than would be expected to be seen in humans.

CDTL Comment*: In the androgen receptor binding study, the IC50 was 6.1 nM for testosterone and greater than 10,000 nM for TU and DHTU. This supports the conclusion that TU and DHTU have low binding affinity for the androgen receptor. In addition, during the LPCN 1021 Phase 3 study, no significant change from baseline in androgen mediated lab parameters or adverse events were observed and the overall androgenic related adverse events were comparable to the active control which does not have any TU and DHTU levels.*

Laboratory:
Changes in HCT:

Five LPCN 1021 treated subjects had hematocrit values greater than 54%. However, there was only one subject whose Hct was recorded at 57% and was therefore terminated early from the study. The repeat Hct was 53.6%, 39 days after early termination. There were no clinical implications seen as a result of this transient increase in the Hct.

Changes in PSA:
Increases were also observed for PSA in both the Tlando and AndroGel 1.62% treatment arms. Elevated PSA values > 4 ng/mL were seen in 5 subjects: 3 subjects in the Tlando group and 2 subjects in the AndroGel 1.62% group. One subject in the Tlando group (Subject (b) (6) and 1 subject in the AndroGel 1.62% group (Subject (b) (6) discontinued because of the elevated PSA. PSA increases were transient and came down to normal ranges at recheck after 2-3 weeks.

CDTL Comment*: In my opinion this seems to be secondary to a transient inflammatory process.*

Changes in Lipids:
A decrease in HDL values was seen in subjects in both the Tlando and AndroGel 1.62% treatment groups. The decrease from baseline in subjects treated with Tlando was slightly greater than the decrease in subjects treated with AndroGel 1.62%. LDL levels showed an initial drop in both treatment groups. Mean triglycerides decreases from baseline were observed for the LPCN 1021 group during the course of the study, while mean increases were observed for the AndroGel 1.62% group through week 39. Mean total cholesterol decreased from baseline for both the LPCN 1021 and AndroGel 1.62% group.

C-reactive protein (CRP) was assessed at baseline and at weeks 7, 13, 26, 39, and 52 during the Phase 3 study and were found to be normal.

Sex hormone binding globulin (SHBG):
Serum sex hormone binding globulin (SHBG) concentration was measured at baseline, Week 7, Week 13, Week 26, Week 39 and Week 52 of the Phase 3 study. Mean SHBG levels showed a decrease at each post-baseline visit in subjects receiving LPCN 1021 while mean SHBG levels showed no significant decrease from baseline in subjects receiving AndroGel 1.62%. The effect of the reduction in SHBG on free testosterone levels was not significant.

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH): A decrease in LH and FSH was seen in both LPCN 1021 and Androgel 1.62% subjects which is expected with Testosterone treatment.

Electrocardiograms (ECGs)
At baseline the ECG assessments showed abnormal, but not clinically significant findings for 38.1% of subjects in the Tlando group and 53.8% of subjects in the AndroGel 1.62% group. No clinically significant findings were reported in either group.

Overall Safety assessment
It is my opinion that the safety results from Study LPCN 1111-15-001 do not raise any unique safety issues compared to approved testosterone therapies. However, there could be a potential safety risk associated with a titration scheme that results in higher numbers of outliers.

9. AdvisoryCommitteeMeeting

No advisory committee meeting was held during this review cycle.

10. Postmarket Experience

Tlando is not marketed in any country, therefore, no postmarketing data are available for this specific product. However, other oral testosterone undecanoate products have been approved and marketed in countries outside the US for many years.

11. Pediatrics

PeRC Recommendations:
The PeRC agreed with the division to grant a full waiver in pediatric patients.

12. Other Relevant Regulatory Issues

OfficeofPrescriptionDrugPromotion(OPDP)
OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DBRUP submit a new consult request during the subsequent review cycle.

Office of Study Integrity and Surveillance (OSIS)
OSIS made the following recommendation: We cannot assure the quality of the thawed samples detected in the phase 3 study. OCP and DBRUP reviewers should evaluate impact of these samples on the overall study outcomes. Apart from the thawed serum samples, we recommend that all other bioanalytical data from (b) (4) under this study should be accepted for further Agency review.

CDTL Comment*: Two of the four subjects with premature thawing of samples ((b) (6) and (b) (6) were in the AndroGel 1.62% treatment group, which was not evaluated for efficacy. The other two subjects ((b) (6) and (b) (6) were in the Tlando treatment group, but were not included in the Efficacy Population Set. Therefore, the thawed specimens should not have a material effect on the efficacy results of the study.*

FinancialDisclosure
The applicant has certified that the compensation of all clinical investigators was independent of the study outcome. They have also certified that no investigator had a proprietary interest in the product or equity interest in the sponsor of a covered study.

DMEPA/Tradename
DMEPA in their review of trade name wrote the following: We have completed our review of the proposed proprietary name, Tlando and have concluded that it is conditionally acceptable.

ControlledSubstancesStaff
The Applicant's proposed Section 9 Drug Abuse and Dependence of the label for NDA 208088 does not provide consumers with current information related to abuse/misuse of this drug, or provide updated safety data related to abuse, misuse, overdose, dependency and

withdrawal symptoms. Therefore, the Controlled Substance Staff (CSS) recommend labeling language to be included in section 9 of the label. However, since this application is receiving a Complete Response (CR) action for this review cycle, the label will be updated in the next review cycle.

13. Labeling

Labeling is deferred to the next review cycle.

14. Recommendations/Risk Benefit Assessment

Recommendation:
From a clinical perspective, I recommend that this NDA for Tlando (testosterone undecanoate) capsules receive a Complete Response (CR) action. This recommendation is based on the applicant's failure to provide a titration scheme based on a single blood draw for use in clinical practice, which results in titration decisions that are reasonably consistent with the titration decisions that were made during the Phase 3 clinical study. Without an acceptable single blood draw titration scheme, it is not possible to make dosing recommendations in labeling.

Risk Benefit Assessment
A comprehensive review of NDA 208088 was carried out. The NDA submission includes the results of one Phase 3 study, LPCN 1021-13-001, which provides safety, efficacy, and pharmacokinetic data relating to the use of twice daily dosing of Tlando for testosterone replacement therapy in men with primary and secondary hypogonadism.

During the Phase 3 study, three dose levels of Tlando (150 mg, 225 mg and 300 mg TU) were administered to subjects twice a day. All subjects started Tlando at the 225 mg TU BID dose level. Their dose could be adjusted either up to 300 mg TU BID or down to 150 mg TU BID at Weeks 4 and 8 based on pre-specified titration criteria from PK data obtained at Weeks 3 and 7. The purpose of dose titration was to identify subjects who exhibit varying testosterone levels in response to the administered dose and make adjustments to bring their Cavg into the normal range and/or maintain Cmax less than 1500 ng/dL.

Dose titration was based on the following Cavg0-24h criteria:

- If Cavg0-24h < 300 ng/dL, dose was titrated upward by 75 mg/dose;
- If Cavg0-24h > 1140 ng/dL, dose was titrated downward by 75 mg/dose.

In addition, the following criterion based on Cmax0-24h was also applied:

- If Cmax > 1500 ng/dL, dose was titrated downward by 75 mg/dose regardless of the Cavg0-24h

The primary efficacy endpoint for the study was the percentage of Tlando-treated subjects who achieved a 24-hour average serum T concentration within the normal range (i.e., 300-1140 ng/dL) upon completion of 13 weeks of treatment. For this endpoint to be met, the minimum acceptable percentage was 75% with a lower bound of the 95% confidence interval being 65% or more. Tlando met the primary efficacy endpoint of the study using the titration criteria based on Cavg0-24h and Cmax0-24h obtained from 24-hour PK data.

Since titration based on a 24-hour PK assessment of the patient is not feasible in "real world" (clinical practice), the applicant submitted (b) (4)

(b) (4)

Comparison of the titration decisions made (b) (4) scheme originally proposed in the NDA with the titration decisions actually made during the Phase 3 study showed that approximately 30% of the subjects had titration decisions that did not agree. The applicant's proposed (b) (4)

Therefore, the applicant has not demonstrated (b) (4)
(b) (4)

15. Regulatory Action

Complete Response (CR) action for this review cycle. The deficiencies described above should be corrected as a path forward and in-order to re-submit the application for review.

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/s/

SURESH KAUL
06/23/2016

HYLTON V JOFFE
06/23/2016
I concur with a Complete Response action. See the Division Director Summary Memorandum.