CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208088Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supporting Doc #:	208088 (SDN 82/eCTD 0080)
Drug Name:	TLANDO (testosterone undecanoate oral capsule)
Indication(s):	Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency or absence of endogenous testosterone – primary or secondary hypogonadism (congenital or acquired)
Applicant:	Antares Pharma, Inc.
Date(s):	Received date: January 28, 2022
	PDUFA date: March 28, 2022
Review Priority:	Standard (Request for Final Approval)
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Weiya Zhang, Ph.D.
Secondary Reviewer:	Daphne Lin, Ph.D., Deputy Division Director
Medical Division:	Division of Urology, Obstetrics, and Gynecology
Clinical Team:	Martin Kaufman, M.D., Clinical Reviewer
	Suresh Kaul, M.D., Clinical Team Leader
Project Manager:	Jeannie Roule

Keywords: Clinical studies, NDA review

This document is to close the statistical reviewer's assignment of this NDA review.

Tlando (testosterone undecanoate capsules), NDA 208088, was tentatively approved on December 8, 2020. The tentative approval letter stated that the final approval of Tlando, NDA 208088 is subject to expiration of a period of patent protection and/or exclusivity of Jatenzo (testosterone undecanoate) oral capsules (NDA 206089). The Orange Book lists the exclusivity code as NP (New Product) for Jatenzo with an exclusivity expiration date of March 27, 2022. The applicant is submitting an amendment as a Request for Final Approval for Tlando, NDA 208088 in the current submission.

There were no new clinical efficacy data in the current submission. For statistical evaluation of effectiveness of Tlando testosterone undecanoate oral capsules as a replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, please refer to the statistical review dated June 1, 2016 for clinical study LPCN 1021-13-001 submitted in eCTD Sequence # 0000, and the statistical review dated February 22, 2018 for studies LPCN 1021-16-002 and LPCN 1021-16-003 submitted in eCTD Sequence # 0026.

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

/s/

WEIYA ZHANG
02/27/2022 09:19:33 AM

TSAE YUN D LIN
02/28/2022 08:37:18 AM

Clinical Pharmacology Review

NDA #:	208088
Link to EDR:	**\\cdsesub1\evsprod\NDA208088**
Submission Type:	Resubmission
Submission Date:	1/28/2022
Sponsor:	Antares Pharma, Inc.
Drug:	Tlando®
Review Date:	March 22, 2022
Review type:	Clinical Pharmacology Review Memorandum
Generic Name:	Testosterone Undecanoate (TU) Capsules
Dosage Form and Strength:	Capsule (112.5 mg)
Route of Administration:	Oral administration
Proposed Indication:	Tlando is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Associated IND:	106476
Reviewer:	Li Wang, Ph.D.
Team Leader:	Yanhui Lu, Ph.D.
OCP Final Signatory:	Doanh Tran, Ph.D.
OCP Division:	Division of Cardiometabolic and Endocrine Pharmacology
OND Division:	Division of Urology, Obstetrics, and Gynecology

1. EXECUTIVE SUMMARY

Tlando, Testosterone Undecanoate (TU) Capsules, NDA 208088, was tentatively approved on December 8, 2020. The ownership of this NDA was then transferred from Lipocine Inc. to Antares Pharma Inc. The tentative approval letter dated December 8, 2020 stated that final approval of this application was subject to expiration of a period of patent protection and/or exclusivity. In this submission, Antares Pharma Inc. submitted an amendment as a REQUEST FOR FINAL APPROVAL for Tlando. Antares Pharma Inc. also confirmed that there were no Chemistry, Manufacturing and Control (CMC) changes made to Tlando since the product was tentatively approved.

The current resubmission includes no new clinical pharmacology data. Labeling recommendation had been conveyed to the Applicant in the previous review cycle (refer to Office of Clinical Pharmacology Review dated February 26, 2018 in DARRTS for more information). There are no new labeling recommendations from the Office of Clinical Pharmacology in this review cycle. In this review cycle, the clinical pharmacology review team focused on the assessment of the need of a post-marketing requirement (PMR) to address the drug-drug interaction potential of TU.

2. RECOMMENDATON

From a Clinical Pharmacology perspective, NDA 208088 is approvable. The clinical pharmacology review team recommends the following PMR:

Conduct in vitro studies to assess the potential of testosterone undecanoate to inhibit cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). If the in vitro studies suggest a potential or a clinically relevant drug-drug interaction potential cannot be discounted, a clinical drug interaction study(ies) may be required to assess the potential of TLANDO to inhibit CYP3A, P-gp, and BCRP.

3. CLINICAL PHARMACOLOGY ASSESSMENT OF THE DRUG INTERACTION POTENTIAL OF TU

In 2019, Jatenzo was approved as the first oral TU product for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (NDA 206089). The following PMR was issued at the time of the NDA approval for Jatenzo:

Conduct in vitro studies to assess the potential of testosterone undecanoate to inhibit or induce drug metabolizing enzymes and transporters as outlined in the draft Guidance for Industry In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies available at:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf
If in vitro studies suggest a potential for interaction, additional in vivo studies may be required.

(b) (4)

In the current NDA for Tlando, the Applicant did not provide any data addressing the potential interaction of TU with other drugs that are metabolized by cytochrome P450 enzymes or transported by transporters (Refer to Office of Clinical Pharmacology Review dated February 26, 2018 in DARRTS). In the NDA 206089 (Jatenzo) submission, TU from Jatenzo is not expected to induce or inhibit CYP enzymes or inhibit transporters at the systemic level based on *in vitro* assessment. As the C_{max} of TU of Tlando at the dose of 225 mg administered twice daily (BID) (~0.1 µM) is much lower than that of Jatenzo at the dose of 396 mg BID (1-2 µM), Tlando is not expected to influence the activity of CYP enzymes or inhibit transporters at the systemic level. Given that the calculated I_{gut} value for a 225 mg dose of Tlando is 1970 µM, testing TU as an inhibitor of CYP3A4, P-gp, and BCRP at concentrations of up to 197 µM is required to demonstrate an I_{gut}/IC_{50} value of less than 10. It is still not clear whether the prodrug TU inhibits CYP3A in the intestine and apical intestinal transporters P-gp and BCRP or not

as the highest TU concentration used in the in vitro experiments was 10 µM for the inhibition of TU on CYP3A4 and 5 µM for the inhibition of P-gp and BCRP in the NDA 206089 (Jatenzo) PMR report. Therefore, the clinical pharmacology review team recommends that the Applicant conduct the following studies to address the potential drug interaction as a PMR:

Conduct in vitro studies to assess the potential of testosterone undecanoate to inhibit cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). If the in vitro studies suggest a potential or a clinically relevant DDI potential cannot be discounted, conduct a clinical drug interaction study(ies) to assess the potential of TLANDO to inhibit CYP3A, P-gp, and BCRP.

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

/s/

LI WANG
03/22/2022 09:30:18 AM

YANHUI LU
03/22/2022 11:13:30 AM

DOANH C TRAN
03/22/2022 11:40:43 AM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supporting Doc #:	208088 (eCTD Sequence #: 0066)
Drug Name:	TLANDO (Testosterone undecanoate oral capsule)
Indication(s):	Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency or absence of endogenous testosterone – primary or secondary hypogonadism (congenital or acquired)
Applicant:	Lipocine Inc.
Date(s):	Received date: February 28, 2020
	PDUFA date: August 28, 2020
Review Priority:	Standard (Resubmission)
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Weiya Zhang, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Urology, Obstetrics, and Gynecology
Clinical Team:	Martin Kaufman, M.D., Clinical Reviewer
	Suresh Kaul, M.D., Clinical Team Leader
Project Manager:	Jeannie Roule

Keywords: Clinical studies, NDA review

This document is to close the statistical reviewer's assignment of this NDA review.

There were not new clinical efficacy data submitted in this resubmission. For statistical evaluation of effectiveness of LPCN 1021 (testosterone undecanoate) oral capsules as a replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, please refer to the statistical reviews (dated 6/1/2016 and 2/2/2018) of the clinical studies LPCN 1021-13-001 submitted in eCTD Sequence # 0000, LPCN 1021-16-002 and LPCN 1021-16-003 submitted in eCTD Sequence # 0026.

The unireview of current submission was uploaded in DARRTS on 12/3/2020. The NDA was tentatively approved on 12/8/2020.

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

/s/

WEIYA ZHANG
12/10/2020 02:29:01 PM

MAHBOOB SOBHAN
12/10/2020 03:16:03 PM

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 208088
Supporting document/s:	SDN 82, eCTD 0080
Applicant's letter date:	1-28-2022
CDER stamp date:	1-28-2022
Product:	Testosterone Undecanoate (Proposed tradename TLANDO)
Indication:	Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency or absence of endogenous testosterone - primary or secondary hypogonadism (congenital or acquired)
Applicant:	Antares Pharma, Inc. 100 Princeton South Corporate Center, Suite 100, Ewing, NJ 08628 USA
Review Division:	Division of Urology, Obstetrics & Gynecology (DUOG)
Reviewer:	Andrea Benedict, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Acting Division Director:	Audrey Gassman, MD
Project Manager:	Jeannie Roule

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208088 are owned by Antares Pharma Inc or are data for which Antares Pharma Inc has obtained a written right of reference.

Any information or data necessary for approval of NDA 208088 that Antares Pharma Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208088.

1 Executive Summary

1.1 Introduction

Antares Pharma is requesting final approval of testosterone undecanoate (TU) capsules (proposed tradename TLANDO) with the indication of testosterone replacement therapy in adult males aged 18 and older, for conditions associated with a deficiency or absence of endogenous testosterone (primary or secondary hypogonadism (congenital or acquired)). This is a resubmission of their application that received tentative approval on 12-8-2020. At that time, final approval was subject to the expiration of a period of patent protection and/or exclusivity for another oral TU product, JATENZO (NDA 206089). The Orange Book notes that the exclusivity for JATENZO expires on March 27, 2022.

Of note, ownership of NDA 208088 was transferred from Lipocine Inc to Antares Pharma Inc on 10-26-2021.

1.2 Brief Discussion of Nonclinical Findings

The applicant has not submitted any nonclinical study reports, and none are necessary. Refer to the pharmacology/toxicology review by Laurie McLeod-Flynn, filed to DARRTS on 6-1-2016 which recommended approval of this product from a nonclinical perspective.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval of this application.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

There are no proposed changes to Sections 8.1, 8.2, 12.1 or 13 of the prescription label compared to the previously agreed upon labeling at the time of tentative approval in December 2020. There are minor wording differences between TLANDO and the testosterone class label of the approved product JATENZO. However, these do not impact any nonclinical data. TLANDO labeling models that of other testosterone class labels.

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

/s/

ANDREA BENEDICT
03/22/2022 12:14:23 PM

MUKESH SUMMAN
03/22/2022 12:16:36 PM

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number	NDA 208088
Priority or Standard	Priority
Submit Dates	August 28, 2015 (first review cycle) August 8, 2017 (second review cycle) May 9, 2019 (third review cycle) February 28, 2020 (current review cycle)
Received Dates	August 28, 2015 August 8, 2017 May 9, 2019 February 28, 2020
PDUFA Goal Date	August 28, 2020
Division/Office	Division of Urology, Obstetrics, and Gynecology Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Review Completion Date	December 3, 2020
Established/Proper Name	Testosterone undecanoate (oral)
(Proposed) Trade Name	Tlando
Pharmacologic Class	Androgen
Code name	N/A
Applicant	Lipocine Incorporated
Dosage form	Oral
Applicant proposed Dosing Regimen	225 mg testosterone undecanoate taken twice daily with food.
Applicant Proposed Indication/Population	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommendation on Regulatory Action	Tentative Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult males for conditions associated with a deficiency or absence of endogenous testosterone

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jeannie Roule/Samantha Bell
Nonclinical Reviewer	Laurie McLeod-Flynn
Nonclinical Team Leader	Kimberly Hatfield
Office of Clinical Pharmacology Reviewer	LaiMing Lee
Office of Clinical Pharmacology Team Leader	Yanhui Lu
Clinical Reviewer	Martin Kaufman
Clinical Team Leader	Suresh Kaul
Cross-Disciplinary Team Leader	Suresh Kaul
Office of Pharmaceutical Quality, Application Technical Lead	Mark Seggel
Office Director (or designated signatory authority)	Christine Nguyen

Additional Reviewers of Application

OPQ	Hong Cai, Wendy Wilson, James Norman, Yubing Tang, Haritha Mandula, Hansong Chen, Vidula Kolhatkar, James Laurenson, Marquita Burnett, Moo-Jhong Rhee
Statistical Reviewer	Weiya Zhang, Mahboob Sobhan, Daphne Lin
OPDP	Jina Kwak/Elvy Varghese
OSI	N/A
OSE/DMEPA	Denise Baugh/Briana Rider/Oyinlola Fashina/ Ameet Joshi/Danielle Harris
OSE/DRISK	Laura Zendel/Courtney Cunningham
OSE/DEPI	Wei Liu/Jie Li
OSE/DPV	Regina Lee/Lynda McCulley
OSE/DMPP	Kelly Jackson/Marcia Williams
CSS	Alicja Lerner/Sandra Saltz/Dominic Chiapperino and Silvia Calderon
Other	Aisha Johnson/Ann Marie Trentacosti/ Miranda Sinicrope

OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
DPV = Division of Pharmacovigilance
DMPP = Division of Medical Policy Programs
CSS = Controlled Substance Staff

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Laurie McLeod-Flynn, PhD	ORPURM/DPT	Sections:5	Select one: _X_ Authored ___ Approved
	Signature: Laurie L. Mcleod-flynn -S Digitally signed by Laurie L. Mcleod-flynn -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300106259, cn=Laurie L. Mcleod-flynn -S Date: 2020.08.12 10:24:39 -04'00'			
Nonclinical Team Leader	Kimberly Hatfield, PhD	ORPURM/DPT	Sections: 5	Select one: ___ Authored _X_ Approved
	Signature: Kimberly P. Hatfield -S Digitally signed by Kimberly P. Hatfield -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300387215, cn=Kimberly P. Hatfield -S Date: 2020.08.12 15:45:40 -04'00'			
Clinical Pharmacology Reviewer	Lai Ming Lee, Ph.D.	OCP/DCEP	Section: 6	Select one: _X_ Authored ___ Approved
	Signature: Lai M. Lee -S Digitally signed by Lai M Lee -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Lai M Lee -S 0 9 2342 19200300 100 1 1=1300366890 Date: 2020 08 06 16:57:08 04'00'			

Clinical Pharmacology Team Leader	Yanhui Lu, Ph.D.	OCP/DCEP	Section: 6	Select one: ___ Authored _X_ Approved
	Signature: Yanhui Lu -S Digitally signed by Yanhui Lu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yanhui Lu -S, 0.9.2342.19200300.100.1.1=2001501324 Date: 2020.08.06 19:02:43 -04'00'			
Clinical Pharmacology Deputy Director	Doanh Tran, Ph.D.	OCP/DCEP	Section: 6	Select one: ___ Authored _X_ Approved
	Signature: Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2020.08.07 08:45:25 -04'00'			
Office of Pharmaceutical Quality, Application Technical Lead	Mark Seggel	OPQ/ONDP/DNDPII/Br4	Section: 4.2	Select one: _X_ Authored _X_ Approved
	Signature: Mark R. Seggel -S Digitally signed by Mark R. Seggel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R. Seggel -S, 0.9.2342.19200300.100.1.1=1300071539 Date: 2020.08.12 11:43:35 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Martin Kaufman, D.P.M., M.B.A.	ORPURM/DUOG	Sections: 1, 2, 3, 7, 8, 12, 13, 14	Select one: __X__ Authored _____ Approved
	Signature: Martin E. Kaufman -S Digitally signed by Martin E. Kaufman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222976, cn=Martin E. Kaufman -S Date: 2020.08.17 14:45:35 -04'00'			

Glossary

ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, excretion
BLA	biologics license application
BID	twice daily
BP	blood pressure
CR	complete response
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
DBRUP	Division of Bone, Reproductive and Urologic Products
DMF	drug master file
FDA	Food and Drug Administration
NDA	new drug application
PK	pharmacokinetics
PMR	postmarketing requirement
SS	solvent + surfactant
T	testosterone
TU	testosterone undecanoate
ULN	upper limit of normal

1. Executive Summary

1.1. Product Introduction

Testosterone (T) is an endogenous androgen that is responsible for 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; and alterations in body musculature and fat distribution. Dihydrotestosterone (DHT) is another androgen endogenously produced in the body. T and DHT are necessary for the normal development of secondary sex characteristics.

The Tlando™ (proposed tradename) capsule is an oral product containing testosterone undecanoate (TU) in a lipid formulation for use as testosterone replacement therapy. Tlando is designed to enable oral 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 that is not alkylated at the 17-alpha position. TU is converted to testosterone by nonspecific esterases present in the body. In the United States, products containing TU are currently approved for testosterone replacement therapy include injectable intramuscular administration (Aveed) and for the oral route of administration (Jatenzo).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The goal for products indicated for testosterone replacement therapy is to restore testosterone concentrations to the eugonadal range (C_{avg}) and to avoid unacceptably high testosterone concentrations (C_{max}) based on prespecified thresholds. For approval, a product should meet both of these goals.

During the third review cycle, Study 16-002, the phase 3 trial that evaluated the to-be-marketed dose and dosing regimen, met the primary efficacy endpoint, acceptably restoring average testosterone concentrations (C_{avg}) to the normal range. However, the trial did not meet the secondary endpoints for maximal testosterone concentrations (C_{max}) thresholds based on the commonly used upper limit of normal (ULN) of T assay of 1000 ng/mL. The C_{max} findings fell short of the prespecified targets for proportion of subjects with testosterone C_{max} of 1500 ng/dL or less (1.5X ULN), 74% instead of the 85% target; C_{max} between 1800 and 2500 ng/dL (1.8-2.5X ULN), 14% instead of the 5% target; and C_{max} >2500 ng/dL (>2.5X ULN), 1% instead of 0%.

Addressing the C_{max} deficiency was the focus of this fourth review cycle. Using the C_{max} data from Study 16-002, the Applicant analyzed the prespecified C_{max} thresholds (≤1.5X ULN, 1.8-2.5X ULN, and >2.5X ULN) based on the actual ULN for the T assay used in this study (1080 ng/dL) instead of the ULN of 1000 ng/mL. These analyses showed that Tlando essentially

achieved the C_{max} thresholds. Study 16-002 demonstrated that Tlando met the prespecified primary endpoint (proportion of treated subjects with testosterone C_{avg} within the normal range) and essentially met the prespecified secondary endpoints (proportion of subjects with C_{max} within the predetermined limits). Therefore, we conclude that there is substantial evidence of effectiveness for Tlando as testosterone replacement therapy (TRT) in hypogonadal men.

This application, however, will receive Tentative Approval (TA) at this time because of pending expiration of exclusivity granted to Jatenzo, an oral TU product approved as a TRT. For details, refer to the Exclusivity Summary Memo signed on the date of the action.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tlando is an oral testosterone (T) replacement therapy containing testosterone undecanoate (TU) in a lipid formulation. If approved, Tlando will be the second oral TU product approved in the US, indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone, including congenital or acquired primary or secondary hypogonadism. A variety of other non-oral testosterone replacement therapies are also approved for this indication.

To demonstrate effectiveness, testosterone products are required to meet specific criteria related to serum T levels. The percentage of treated subjects with average T concentrations (Cavg) within the normal range should be 75% or greater with the lower bound of the 95% confidence interval of at least 65%. In addition, the T C_{max} should meet the following predetermined targets:

(1) ≥85% of subjects with T C_{max} ≤1.5 X ULN;
(2) ≤5% with T C_{max} between 1.8 and 2.5 X ULN; and
(3) 0% with T C_{max} greater than 2.5 X ULN.

The Applicant is seeking approval of Tlando oral capsule, 225mg twice-daily (BID) fixed dose without titration, based on the pivotal phase 3 Study 16-002. This study showed that Tlando successfully met the Cavg criteria. However, under the assumption of the commonly used T ULN of 1000 ng/dL, Tlando did not meet any of the three secondary T C_{max} endpoints. With the Agency's concurrence, the Applicant relied on actual ULN of the T assay in Study 16-002 (1080 ng/dL) to calculate the predetermined C_{max} limits, and re-analyzed the prespecified C_{max} targets based on these revised limits. These reanalyses demonstrated that Tlando essentially achieved the three predetermined C_{max} targets. Therefore, the findings on Cavg and C_{max} confirm that Tlando provides acceptable testosterone replacement in adult men with hypogonadism.

The safety database for Tlando includes a total of four phase 3 studies and six phase 1 studies. The safety profile of Tlando appears consistent with the known safety profile for other testosterone products. In particular, Tlando causes small increases in blood pressure (BP) similar in magnitude to that of Jatenzo (an oral TU product approved as testosterone replacement therapy); this safety finding can be adequately mitigated with labeling. There was a nonclinical safety signal of atrophy and diffuse vacuolization of the adrenal cortex. Although no clinical cases of adrenal hypofunction were identified in the safety database, the

Applicant will be required to conduct a post-marketing trial to evaluate the potential of adrenal insufficiency with chronic Tlando therapy.

Overall, the benefits of Tlando outweigh its risks to support a recommendation of approval. However, Tlando will receive a tentative approval because of pending expiration of exclusivity granted to Jatenzo. Refer to Exclusivity Memo signed on the date of the action in DARRTS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Male hypogonadism is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa as a result of disruption to one or more levels of the hypothalamic-pituitary-testicular axis.[1] • Signs and symptoms of androgen deficiency are generally nonspecific and include reduced sexual desire (libido), decreased spontaneous erections, loss of body (axillary and pubic) hair, loss of height, low bone mineral density and osteoporotic fracture, decreased energy, poor concentration and memory, reduced muscle mass and strength, and increased body fat. • A small subset of men diagnosed with hypogonadism have "classical" hypogonadism, which refers to hypogonadism caused by specific, well-recognized medical conditions, such as Klinefelter's syndrome, pituitary injury, or toxic damage to the testicles. The remainder are diagnosed with other conditions, such as age-related hypogonadism (middle-aged and elderly men	Male hypogonadism has important health implications. A minority of men diagnosed with hypogonadism have "classical" hypogonadism. The remainder have other conditions, such as age-related hypogonadism.

[1] Bhasin, S, Brito, JP, Cunningham, GR, Hayes, FJ, Hodis, HN, Matsumoto, AM, Snyder, PJ, Swerdloff, RS, Wu, FC, Yialamas, MA, 2018, Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline, J Clin Endorinol Metab, 103(5): 1715-1744.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	who have low testosterone compared to young, healthy men for no discernable reason other than older age).	
Current Treatment Options	• Testosterone is currently available in the United States as a buccal tablet, subcutaneous implant, transdermal patch, transdermal gel, transdermal solution, nasal gel, and parenteral injection. TU is approved as an intramuscular injection and an oral capsule. • These products are approved for testosterone replacement therapy in men with "classical" hypogonadism and have demonstrated effectiveness in maintaining testosterone concentrations within the eugonadal range while avoiding unacceptably high serum testosterone concentrations. • Testosterone is commonly used in men who do not have classical hypogonadism, such as those with age-related hypogonadism, although the effectiveness and safety of testosterone has not been established for these uses.	• There are many approved nonoral testosterone products available with different routes of administration. In March 2019, a TU capsule was approved for the oral route of administration. Approval of Tlando would provide another oral treatment option for male hypogonadism. • Testosterone replacement therapy is approved for men with classical hypogonadism. The safety and effectiveness of testosterone therapy for other hypogonadal conditions, such as age-related hypogonadism have not been established.
Benefit	• The primary efficacy Study 16-002 was submitted and reviewed during the second review cycle. The resubmission currently under review contains a reanalysis of the secondary C_{max} endpoints for this study. In this 24-day efficacy trial, 225 mg of Tlando BID without titration increased the time-averaged serum testosterone concentration (C_{avg}) into the normal range in 80% of subjects (95% CI: 72%, 88%). Tlando met the prespecified target for this primary efficacy endpoint (at least 75% of subjects achieving testosterone C_{avg} within the normal range with a lower bound of the corresponding 2-sided, 95% CI of >65%). • When the thresholds for the secondary (C_{max}) endpoints were based on the usual ULN (1000 ng/dL), 225 mg of Tlando BID	• The Cavg and C_{max} results from Study 16-002 are adequate for demonstration of effectiveness of Tlando as a testosterone replacement product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	failed to meet the C_{max} thresholds ensuring a TRT product would not cause unacceptably high C_{max} concentrations. However, the key concepts for these thresholds are based on multiples of the upper limit of normal (ULN) for the testosterone normal range (C_{max} ≤1.5X ULN; C_{max} between 1.8 and 2.5X ULN; and C_{max} >2.5X ULN). The ULN testosterone range for Study 16-002 was 1080 ng/dL. When the C_{max} thresholds are based on the actual ULN, and when ex vivo conversion of TU to T is accounted for, Tlando essentially met the prespecified C_{max} targets. • Eighty to eighty-four percent[2] of subjects had T C_{max} concentrations ≤1620 ng/dL (prespecified target ≥85% of subjects). The small difference between the percentage of subjects who achieved this endpoint and the prespecified percentage is not expected to impact the efficacy of the drug. • Five percent of subjects had T C_{max} between 1944 and 2700 ng/dL (prespecified target ≤5% of subjects). • Zero percent of subjects had T C_{max} >2700 ng/dL (prespecified target 0% of subjects).	
Risk and Risk Management	• Study LPCN 1021-18-001 was a 110-day ambulatory blood pressure monitoring (ABPM) trial that enrolled 144 hypogonadal men, treated with the 225 mg BID fixed dose of Tlando, and included ambulatory blood pressure monitoring at baseline and at the end of the trial. • The 110-day trial showed a numerically small, but clinically significant, increase in BP, consistent with what was seen with the approved oral TU product. This risk of small increase in BP	• Safety results from Study LPCN 1021-18-001 demonstrated a comparable safety profile to other TRT products. • The increase in BP with Tlando can be adequately mitigated with labeling to monitor BP with similar text to that of the currently approved oral TU product (Jatenzo).

[2] 80, 82, and 84% of subjects had T Cmax ≤ 1620 ng/mL depending on whether ex vivo TU to T conversion was 3, 5, or 8%.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	can be mitigated with labeling (a Boxed Warning, Contraindications, Warnings/Precautions, and Medication Guide) that is consistent with the other approved oral TU product. • Because this trial had the longest duration of any trial for the fixed 225 mg BID dose of Tlando, the long-term effect of the drug on hematocrit could not be determined. The risk that hematocrit could continue to increase after 110 days of treatment with Tlando can be mitigated with labeling (Warning/Precaution) that recommends monitoring of hematocrit. • There was a signal of adverse adrenal changes in animals. The Applicant has not assessed adrenal function with treatment beyond 24 days. The long-term risk can be further evaluated in the postmarketing setting when Tlando can be approved. • A signal for an increase in serum prolactin concentrations was seen during the 24-day study evaluating the fixed 225 mg BID dose, but not for the 52-week study evaluating the 225 mg BID dose with dose titration.	• Tlando's effect on hematocrit with the fixed 225 mg BID dose can be adequately mitigated with labeling that is consistent with the currently approved oral TU product. • A nonclinical signal for adrenal insufficiency was identified. Although no subjects developed adrenal insufficiency, a longer-term formal assessment with adrenocorticotropic hormone stimulation testing is needed to definitively assess this safety signal. This safety evaluation can be performed during the postmarketing period. • Although some elevations of serum prolactin were identified, none required additional clinical follow-up. This can be addressed with labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Original submission review (Section 6.1.6 – Other Endpoints) entered in DARRTS June 23, 2016
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

See the second cycle Clinical Review in the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) dated March 12, 2018.

2.2. Analysis of Current Treatment Options

See the third cycle Clinical Review in the FDA DARRTS dated November 8, 2019.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

For regulatory background of the first, second, and third review cycles of the NDA, see the third cycle Unireview in DARRTS (November 8, 2019).

First review cycle: The Applicant submitted the original NDA for Tlando on August 28, 2015. The submission did not provide a single blood-draw titration scheme that would result in a reasonable level of agreement with the titration decisions that were made during the phase 3 study. Without an acceptable single blood-draw titration scheme, it was not possible to make a dosing recommendation for Tlando in clinical practice and in labeling, and the drug could not be approved. On June 28, 2016, the Division of Bone, Reproductive and Urologic Products (DBRUP) issued a Complete Response (CR) letter for the NDA.

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

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

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

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

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

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

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

Post-action activities: After the November 8, 2019 CR action, the Applicant requested and was granted a meeting with DBRUP:

- January 16, 2020, Type A post action meeting: Key meeting discussion included ex vivo conversion and reliability of Tlando's serum data, the Applicant's proposal to modify the T C_{max} thresholds based on the ULN of the lab normal range, the clinical relevance of T $C_{max(0-24h)}$ excursions <1 hour, and the clinical relevance of T $C_{max(0-24h)}$ >1500 ng/dL. The Applicant agreed that there is some conversion of TU to T that ranges from 3% to 8%.

On January 21, 2020, the Applicant submitted a proposal to base the testosterone C_{max} thresholds on the actual testosterone upper limit of normal (ULN) of 1080 ng/dL.

On February 19, 2020, DBRUP sent an information request letter to the Applicant, which provided comments regarding the Applicant's proposal contained in the January 21, 2020 submission. The letter requested that the Applicant submit an NDA resubmission responding to

the November 8, 2019 CR. The letter stated that the resubmission should include the following from Study 16-002:

1. All the T C_{max} values for individual patients with (a) no adjustment and (b) after adjusting for 3%, 5%, and 8% T overestimation.
2. Listings, and accompanying datasets, of total excursion time in a 24-hour day for each patient with C_{max} greater than each of the secondary endpoint thresholds revised according to the ULN of 1080 ng/dL (i.e., <1620; between 1944 and 2700; >2700 ng/dL) with each patient's $C_{max(0-24h)}$ adjusted for ex vivo TU to T conversion of 0%, 3%, 5%, and 8%. Provide a separate listing and accompanying datasets for each of the four TU to T conversion estimates (0%, 3%, 5%, and 8%).

Fourth review cycle submission: The Applicant submitted the NDA for the fourth review cycle on February 28, 2020. The only new information that has not been previously reviewed in the prior 3 review cycles is the reanalysis of T C_{max} data from, Study 16-002. The reanalysis included:

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

3.2. Summary of Presubmission/Submission Regulatory Activity

See Section 3.1

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

4.1. Office of Scientific Investigations

No new clinical investigations were conducted during this review cycle. Refer to the multi-disciplinary review entered in DARRTS November 8, 2019 for site inspection details.

4.2. Product Quality

From the Office of Pharmaceutical Quality (OPQ) perspective, NDA 208088 is recommended for APPROVAL.

Tlando capsules contain 112.5 mg TU, a fatty acid ester of testosterone. The chemistry, manufacturing, and controls for TU are documented in Type II drug master file (DMF) (b) (4) The information provided in the DMF is adequate to support the use of the drug substance in the manufacture of the drug product.

The immediate-release drug product is prepared from a (b) (4) of TU and the following excipients: (b) (4) (glyceryl monolinoleate; (b) (4), polyoxyl 40 hydrogenated castor oil (b) (4), ascorbyl palmitate (b) (4) and polyethylene glycol 8000 (b) (4)

Overall, 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 at release and throughout the shelf-life. The drug substance and drug product manufacturing, packaging, and testing facilities have acceptable Current Good Manufacturing Practice status.

A 48-month expiration dating period for the drug product when stored at 25°C has been granted.

The request for a categorical exclusion from an environmental assessment, supplemented by information submitted by the Applicant to aid in determining whether extraordinary circumstances exist, is accepted.

For details, see Office of Pharmaceutical Quality Integrated Quality Assessments 1, 2, 3, and 4, dated June 2, 2016, February 26, 2018, October 11, 2019 and August 20, 2020, respectively.

4.3. Clinical Microbiology

No clinical microbiology supporting information was submitted or requested.

4.4. Devices and Companion Diagnostic Issues

The product does not include a device or companion diagnostic.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were submitted in the current NDA resubmission. All prior nonclinical studies have been reviewed and all nonclinical issues have been resolved. Nonclinical Pharmacology/Toxicology recommends approval. For details, refer to the June 1, 2016 nonclinical primary review in DARRTS by Dr. Laurie McLeod-Flynn and the June 6, 2016 nonclinical secondary review in DARRTS by Dr. Mukesh Summan.

5.2. Referenced NDAs, BLAs, DMFs

Not applicable

5.3. Pharmacology

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.4. ADME/PK

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5. Toxicology

5.5.1. General Toxicology

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5.2. Genetic Toxicology

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5.3. Carcinogenicity

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5.4. Reproductive and Developmental Toxicology

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

6. Clinical Pharmacology

6.1. Executive Summary

The pivotal phase 3 Study 16-002 evaluated the to-be-marketed oral TU product with a dose of 225 mg BID for approximately 24 days without dose adjustment or titration. The Applicant showed that it acceptably restored average testosterone concentrations (T C_{avg}) to the normal range. However, failure to meet the three C_{max} criteria to ensure that the dose and dosing regimen would not produce unacceptably high serum T concentrations a deficiency precluding approval in the second and third review cycles.

In this fourth review cycle, the Applicant provided sufficient support that the three secondary endpoints for T C_{max} were in the proximity of the C_{max} targets, following a modification in the T C_{max} thresholds calculated from the phase 3 study's T assay's actual ULN and after considering potential ex vivo TU to T conversion. The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology recommends approval.

6.2. Summary of Clinical Pharmacology Assessment

In the CR Letter dated November 9, 2019, the Division recommended that the Applicant provide evidence that the proposed dose and dosing regimen for the proposed product will reliably restore testosterone concentrations to the eugonadal range and will avoid unacceptably high testosterone concentrations.

In the post action meeting held on January 16, 2020 (see NDA 208088 Meeting Minutes, DARRTS February 14, 2020), the Applicant proposed to re-analyze the standard T C_{max} thresholds for Tlando based on their laboratory's serum T concentration upper limit of normal (ULN) value of 1080 ng/mL in lieu of the typically used ULN of 1000 ng/mL. Analysis of the T C_{max} thresholds based upon a particular laboratory's ULN is an approach that was previously applied by another applicant for an oral TU product and is accepted by FDA.

In the current resubmission, the Applicant proposed to adjust the T C_{max} thresholds (1.5X ULN, 1.8-2.5X ULN, >2.5X ULN) based upon the upper end of their laboratory eugonadal T range of 1080 ng/dL. With an ULN of 1080 ng/dL, the C_{max} thresholds and targets are:

- At least 85% of patients with T C_{max} $\leq$1620 ng/dL (≤1.5-fold ULN)
- No more than 5% of patients with T C_{max} between 1944 and 2700 ng/dL (1.8 to 2.5-fold ULN)
- 0% patients with T C_{max} >2700 ng/dL (>2.5-fold ULN)

In this review cycle, the Clinical Pharmacology team reviewed the Applicant's re-analysis of the secondary endpoints (i.e., proportion of patients within the target T C_{max} ranges) after

modification of the T C_{max} thresholds, and with and without individual T C_{max} adjustments to consider the potential of ex vivo TU to T conversion.

The prodrug TU is present systemically in high concentrations relative to the pharmacologically active metabolite T. In an effort to include TU excretion data in the product label, the Applicant submitted a publication by Horst et. al.* on August 26, 2020, that describes a limited mass balance study in 4 patients. ^{3}H-TU was administered to patients #1-3 by a stomach tube, which is not the intended route of administration. Only 1 of 4 patients (patient #4) received ^{3}H-TU by mouth; therefore, it is not possible to make a definitive conclusion of TU excretion properties. The Excretion section of the label for the proposed product will include class language for T excretion.

*Horst HJ, Holtje WJ, Dennis M, et. al. Lymphatic Absorption and Metabolism of Orally Administered Testosterone Undecanoate in Man. Klinische Wochen-schrift 54, 875-879 (1976).

6.2.1. Pharmacology and Clinical Pharmacokinetics

See Clinical Pharmacology review in DARRTS dated June 14, 2016, February 26, 2018, and November 7, 2019. See Unireview in DARRTS dated November 8, 2019.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed fixed dose is 225 mg BID with food. This regimen does not include a titration for dose adjustment.

Therapeutic Individualization

To ensure that patients are not subtherapeutic or supratherapeutic, the Clinical Pharmacology review team recommended that the Applicant include an approach to assess a patient's eligibility for continued use of the proposed product. The following recommendation will be included in the drug product label:

Monitoring for Continued Use or Discontinuation:

- Monitor serum testosterone (8 to 9 hours after the morning dose) 3 to 4 weeks after initiating Tlando and periodically thereafter. Based on serum testosterone measurements, determine if Tlando should be continued or discontinued:
  - Serum testosterone 300 to 1080 ng/dL: continue Tlando
  - Serum testosterone <300 ng/dL: discontinue Tlando
  - Serum testosterone >1080 ng/dL: discontinue Tlando.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

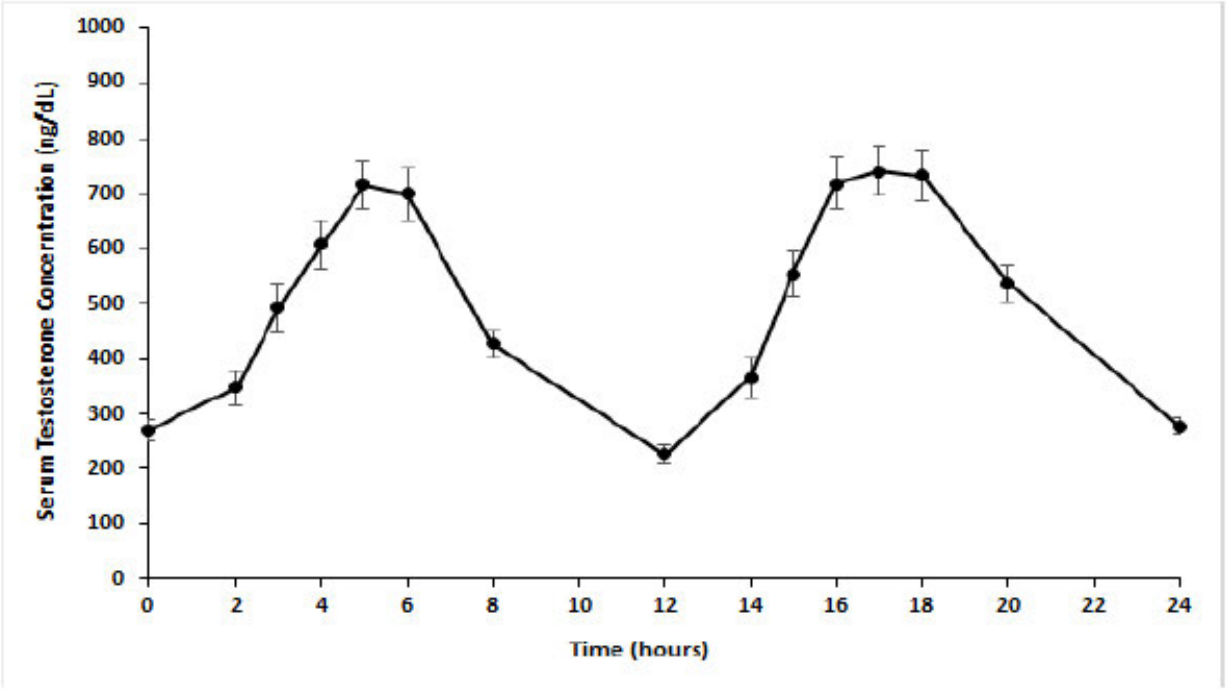
The pharmacokinetic (PK) characteristics for the proposed oral TU capsules was obtained from Study 16-002, the pivotal phase 3 study, which was reviewed in the previous cycle (Clinical Pharmacology review in DARRTS February 26, 2018). A brief summary is provided below.

Absorption

Testosterone

Median (min, max) time-to-peak serum T concentration was 5.0 (1.9, 11.9) hours after the morning dose, mean (SD) 24-h maximum concentration (C_{max}) was 1178 (484) ng/dL, and mean (SD) 24-h average concentration (C_{avg}) was 476 (174) ng/dL. The mean (SEM) steady state PK profile is shown in Figure 1.

Figure 1. Mean (±SEM) Pharmacokinetic Profile of Serum Testosterone on Day 24 After Twice-Daily Oral Administration of TU Oral Capsules 225 mg in Hypogonadal Men (N=90)

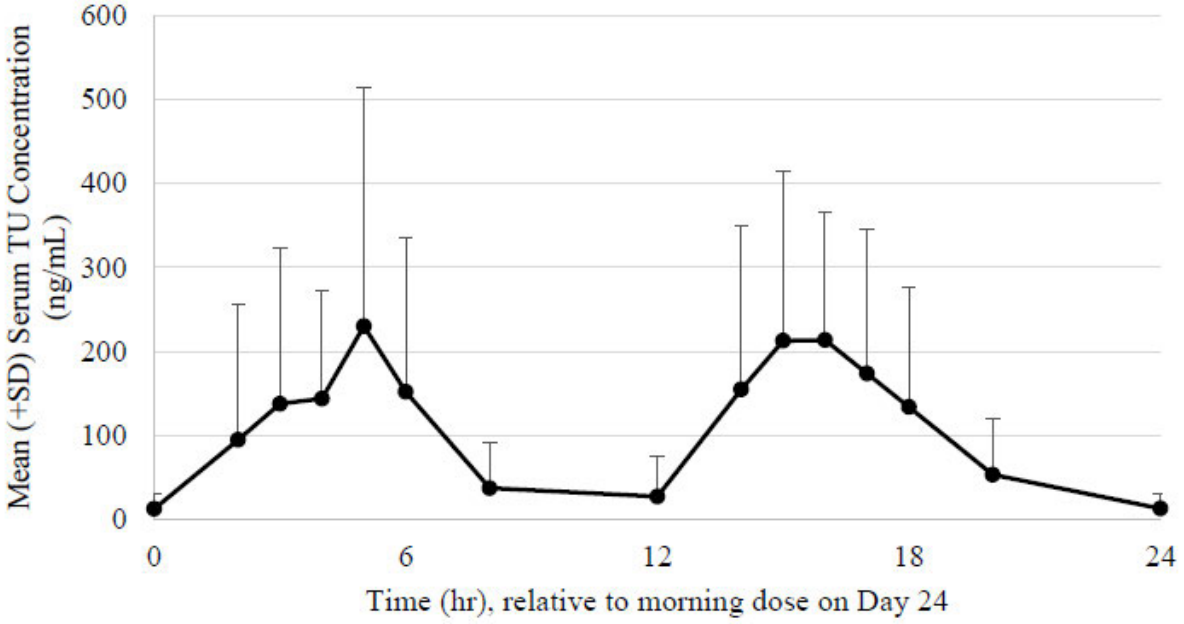


Source: Study LPCN 1021-16-002 Report Body, Figure 1 (updated report submitted August 26, 2020)
Abbreviations: T = testosterone; TU = testosterone undecanoate

Testosterone Undecanoate

Median (min, max) time-to-peak serum TU concentration was 4.9 (1.9, 11.9) hours after the morning dose, mean (SD) 24-h C_{max} was 46,974 (25,602) ng/dL, and mean (SD) 24-h C_{avg} was 11,106 (5036) ng/dL. The mean steady state PK profile is shown in Figure 2.

Figure 2. Mean (±SD) Pharmacokinetic Profile of Serum Testosterone Undecanoate on Day 24 After Twice-Daily Oral Administration of TU Oral Capsules 225 mg in Hypogonadal Men (N=90)



Source: Study LPCN 1021-16-002 Report Body, Figure 3
Abbreviations: TU = testosterone undecanoate

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The proposed dose and dosing regimen is 225 mg of TU [redacted] (b) (4) taken orally with food BID. The dosing scheme does not permit dose titration.

To support the dosing scheme, phase 3 pivotal Study 16-002 was conducted in hypogonadal men and oral TU capsules were taken 30 minutes after the morning and evening meals with water. PK assessment was conducted on Day 24 and no dose titration was incorporated in the study design. For approval of T products, the primary efficacy endpoint is ≥75% of patients achieving a 24-h C_{avg} between 300 and 1080 ng/dL (the laboratory's normal range). Study 16-002 met the predefined primary efficacy endpoint with 80% (76/95) of patients having a 24-h T C_{avg} between 300 to 1080 ng/dL.

Most drug products approved for T replacement include a recommendation for measurement of T concentrations after initiation of therapy that would be used to guide dose adjustment(s) or therapy discontinuation. For Tlando, there is no titration or dose adjustment, thus, the Applicant initially did not include a recommendation for a follow-up clinic visit for assessment of T concentrations. To ensure that patients are not subtherapeutic or supratherapeutic, the Clinical Pharmacology review team recommended that the Applicant include an approach to

assess a patient's eligibility for continued use (previously referred to as stopping criteria). See Section 6.2.2 regarding continued use or discontinuation of Tlando.

TU is a lipophilic molecule. Foods that contain lipids enhance the absorption of TU and improve the bioavailability of testosterone. Prior to the initiation of Study 16-002, the Applicant conducted Study LPCN 1021-14-001 to assess the effect of food and fat content (low, moderate, and high fat) on the bioavailability of TU and T in 13 to 14 hypogonadal men. Compared to fasting conditions, T C_{max} and $AUC_{0\text{-}12h}$ increased 3-fold and 2-fold, respectively, following a high-fat meal. There were no significant differences in the bioavailability of T due to fat content when the proposed product was administered with food containing low, moderate, or high fat.

See the prior Clinical Pharmacology reviews for more details on food effect and stopping criteria in DARRTS dated June 14, 2016.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. In eugonadal men, serum T concentrations typically range between 300 to 1000 ng/dL, although at times, the normal range for T concentration for specific labs may differ slightly from this typical range. Thee 24-h T C_{avg} for the primary efficacy endpoint has been set to coincide with the eugonadal range. T concentrations above the eugonadal range are considered an integral part of the safety assessment for all T and T ester products as supratherapeutic serum T concentrations may negatively impact BP, hematocrit, prostate health, and other safety parameters.

The key secondary endpoint criteria is that ≥85% of patients have a 24-h T C_{max} ≤1500 ng/dL, no more than 5% of patients have a 24-h T C_{max} between 1800 and 2500 ng/dL, and 0% patients have a 24-h T C_{max} exceeding 2500 ng/dL at the end of treatment. The T values of 1500, 1800, and 2500 ng/dL that define the three C_{max} secondary endpoints are based upon 1.5, 1.8, and 2.5 times the upper end of the typical eugonadal range (i.e., 1.5 x 1000 ng/dL =1500 ng/dL), respectively.

In a post action meeting submission on January 21, 2020 and in this NDA resubmission on February 28, 2020, the Applicant proposed to modify the T C_{max} thresholds based upon their laboratory upper limit of normal T concentration of 1080 ng/dL in lieu of the typical 1000 ng/mL. Bioanalytical Report for Projects RHOD and RHOE confirms that the T reference range of 300 to 1080 ng/dL was established using total T concentrations obtained from healthy male subjects 18 years and older at (b) (4) clinical research site. The T concentrations were assessed using (b) (4) liquid chromatography with tandem mass spectrometry assays.

In an Information Request to the Applicant dated February 19, 2020, the Clinical Pharmacology team stated that the modification of the T C_{max} thresholds based upon the Applicant's proposed upper eugonadal range of 1080 ng/dL appeared reasonable. However, the analysis of

proportion of patients within the target C_{max} ranges should be assessed after individual patient T C_{max} values are adjusted by 3%, 5%, and 8% to account for ex vivo TU to T conversion. The Clinical Pharmacology team also requested the Applicant provide the accompanying datasets. See NDA/BLA Multi-Disciplinary Review and Evaluation Section 6.3 Clinical Pharmacology Review regarding the ex vivo conversion of TU to T in serum tubes in DARRTS dated November 8, 2019.

In this review cycle, the Applicant submitted re-analyses of the secondary C_{max} endpoints (proportion of patients within the target T C_{max} ranges based on an ULN of 1080 ng/mL) after modification of the T C_{max} thresholds and with and without individual T C_{max} adjustments for the ex vivo conversion of TU to T.

The three T C_{max} thresholds were adjusted by a factor of 1.08 (1080/1000) to account for the Applicant's upper end of the laboratory range, compared to the commonly recognized upper end of 1000 ng/dL, as shown in Table 1.

Table 1. Original and Modified T C_{max} Thresholds

Original T C_{max} (ng/dL)*	Adjusted T C_{max} (ng/dL)**
≤1500	≤1620
1800 to 2500	1944 to 2700
>2500	>2700

Source: Study LPCN 1021-16-002 Report Body*; Summary of Clinical Efficacy – Appended 3rd Resubmission**
Abbreviations: T = testosterone

Per the phase 3 study protocol, blood samples were collected into serum tubes and were processed up to 60 min after blood draw. To account for up to 2 hours between blood draw and sampling processing, an ex vivo TU to T conversion rate of 3% to 8% is considered relevant to sample handling in the clinical setting. The re-analysis of the T C_{max} endpoints included individuals T C_{max} values adjusted for this ex vivo TU to T conversion range. The individual T C_{max} values with no adjustment and with an adjustment of 3%, 5%, and 8% were confirmed by reviewing the patient dataset, Study 16-002 Analysis Dataset ADPP1. For example, for patient # (b) (6) T C_{max} value as measured is 815 ng/dL. With 3%, 5%, and 8% ex vivo TU to T conversion rates, the T C_{max} values for the same patient should be 791, 776, and 755 ng/dL, respectively, and these values were confirmed in the dataset.

The proportion of patients within the modified T C_{max} thresholds is presented in Table 2. The column labeled 0% does not include ex vivo TU to T conversion adjustment to individual T C_{max} values. After adjusting individual T C_{max} values to account for T overestimation from ex vivo TU to T conversion, the proportion of patients within the modified T C_{max} thresholds are presented in columns labeled 3%, 5%, and 8%. The proportion of patients within the T C_{max} thresholds of between 1944 to 2700 ng/dL and >2700 ng/dL are 5.26% and 0%, respectively. These two secondary endpoints, which represents the highest and most concerning T C_{max} values, address significant safety concerns associated with TU therapy.

The proportion of patients with T C_{max} ≤1620 ng/dL was 80.00%, 82.11%, and 84.21% when the individual T C_{max} values are adjusted by 3%, 5%, and 8%, respectively. The 80 to 84.21% range represents an additional one to five patients with T C_{max} values that did not meet the lower T C_{max} target. The overall T C_{max} results are similar to typical thresholds and no clinically significant safety concerns were identified.

Table 2. Proportion of Patients With T C_{max} Values Within the Modified Target Thresholds (N=95)

T C_{max} (ng/dL) Thresholds	Target Proportion of Patients	Proportion of Patients With Adjusted T C_{max} Thresholds			
		0%	3%	5%	8%
≤1620	≥85%	78.95%	80.00%	82.11%	84.21%
1944 to 2700	≤5%	5.26%	5.26%	5.26%	5.26%
>2700	0%	1.05%	0%	0%	0%

Source: Clinical pharmacology reviewer's reanalysis of Applicant's data from Study LPCN 1021-16-002
Abbreviations: T = testosterone

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

For many testosterone products, including one currently approved oral TU product, patients are advised to have their serum T concentrations measured at steady state after initiating therapy to ensure proper dosing. Dose adjustment recommendations for these products are based upon dosing algorithms evaluated in their respective phase 3 program(s). The Applicant did not include a dose adjustment paradigm in their phase 3 Study 16-002.

In the May 8, 2018, CR letter, the Applicant was informed that they needed to identify a stopping criteria for use in clinical practice that can reproducibly and accurately identify those patients who do not achieve time-averaged T concentrations within the normal range. The stopping criteria should also avoid or minimize the inappropriate discontinuation of patients who have T concentrations within the therapeutic range.

In section 2.2 of the labeling, the Applicant proposed the following stopping criteria:

> To evaluate response to therapy, serum total testosterone concentrations should be checked at 8 to 9 hours after the morning dose periodically, beginning as soon as 3 to 4 weeks after beginning therapy. If the total testosterone concentration is consistently below 300 ng/dL, and (b) (4) If the total testosterone concentration consistently exceeds 1080 ng/dL (b) (4) TLANDO should be discontinued.

To support the proposed stopping criteria, the Applicant compared the T concentrations assessed at 6, 8, and 12 hours after the morning dose to the 24-h T C_{avg} from Study 16-002. Mean T concentration at 8 hours post-dose was 422 ng/dL and best correlated with 24-h C_{avg} of 476 ng/dL, compared to the other time points. The Clinical Pharmacology review team concurs with the 8 to 9 h window as it will accurately and reproducibly identify patients who do not

achieve the T C_{avg} within the eugonadal range. The title of the subsection will be modified to "Monitoring for Continued Use or Discontinuation" as noted above.

See NDA/BLA Multi-Disciplinary Review and Evaluation section 6.3 Clinical Pharmacology Review in DARRTS dated November 8, 2019.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. TU is a lipophilic drug substance. A food effect Study LPCN 1021-14-001 that included a single dose administration of 225 mg oral TU in hypogonadal men showed that bioavailability of TU and T was significantly enhanced in the presence of food. Compared to fasting conditions, T C_{max} and $AUC_{0\text{-}12h}$ increased 3-fold and 2-fold, respectively, following a high-fat meal. There were no significant differences in the bioavailability of T due to fat content. Based upon the food effect study results, the phase 3 Study 16-002 included administration of oral TU capsules with food. The proposed oral TU product should be administered with food. See Clinical Pharmacology review in DARRTS dated June 14, 2016 for more details on the food effect study results.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

No new clinical studies were submitted with the current resubmission. The clinical studies submitted for the previous review cycles are listed in the Tables of Clinical Studies of the reviews for the previous review cycles.

7.2. Review Strategy

No new efficacy studies were submitted in the current resubmission. The review strategy for the current review cycle primarily includes a reanalysis of the testosterone C_{max} data from Study 16-002. Refer to the multi-disciplinary review entered in DARRTS November 8, 2019, for the review strategy for the previous review cycle.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. Study 16-002: Testing of Fixed, Twice-Daily Dosing Regimen of Oral TU in Hypogonadal Men

See the Clinical Review for the second review cycle for the discussion of this trial.

8.1.2. Study Results

The effectiveness of the 225 mg BID dose of Tlando was reviewed during the second review cycle (see the Clinical Review for the Second Review Cycle entered in DARRTS March 12, 2018). The trial achieved the prespecified primary endpoint (Cavg) but did not achieve the key secondary endpoints related to C_{max} outliers. In addition, the clinical pharmacology review team indicated that the observed testosterone concentrations in Study 16-002 may have been overestimated as a result of ex vivo conversion of TU to T.

The Applicant conducted Study 18-003 to quantify the degree of ex vivo conversion of TU to T. The results of this study were submitted in the second resubmission (third review cycle) and were reviewed by the clinical pharmacology review team. They concluded that, although there is some ex vivo TU to T conversion, the amount of conversion is modest (3 to 8%) and did not affect the results for the primary and secondary endpoints in Study 16-002.

During the post action meeting after the third review cycle, the Applicant proposed to analyze the testosterone C_{max} thresholds for the secondary C_{max} endpoints using the ULN actually determined for Study 16-002, rather than the assumed ULN of 1000 ng/dL. The testosterone C_{max} thresholds are based on multiples of the ULN for the testosterone normal range (C_{max} $\leq$1.5X ULN; C_{max} between 1.8 and 2.5X ULN; and C_{max} >2.5X ULN). For Study 16-002, the Applicant conducted an interlaboratory reference interval verifications and assay cross-validation study (study RHOD) to determine the testosterone reference range (See clinical pharmacology review of study RHOD, Section 6.3.2). Based on the results of study RHOD, the ULN for the testosterone reference range was determined to be 1080 ng/dL. Table 3 presents the C_{max} thresholds as multiples of the ULN, with the ULN assumed to be 1000 ng/dL, and with the actual ULN of 1080 ng/dL in Study 16-002.

Table 3. Secondary Endpoint Thresholds With ULN Assumed To Be 1000 ng/dL and With the Actual ULN

Multiple of ULN	FDA Target	Assumed Threshold[1]	Actual Threshold[2]
C_{max} ≤1.5X ULN	≥85%	C_{max} ≤1500 ng/dL	C_{max} ≤1620 ng/dL
C_{max} between 1.8 and 2.5X ULN	≤5%	C_{max} between 1800 and 2500 ng/dL	C_{max} between 1944 and 2700 ng/dL
C_{max} >2.5X ULN	0%	C_{max} >2500 ng/dL	C_{max} >2700 ng/dL

Source: Clinical reviewer generated
[1] Based on the assumption that the ULN is 1000 ng/dL
[2] Based on the actual ULN (1080 ng/dL)
Abbreviations: ULN = upper limit of normal

Reanalysis of Testosterone C_{max} Outliers

Study 18-003 showed that there is 3 to 8% ex vivo conversion of TU to T in plain serum tubes, depending on the time interval between blood collection and specimen processing. This amount of ex vivo conversion did not affect the results for the primary endpoint: the criteria for the primary endpoint were still met even when the T C_{avg} results were adjusted for TU to T conversion. When the secondary endpoints were based on an assumed ULN of 1000 ng/dL, the small amount of ex vivo conversion also did not affect the results: the prespecified criteria for the secondary endpoints were still not met.

The Applicant submitted an analysis for the C_{max} secondary endpoints when the thresholds are based on the actual ULN of testosterone for the study and with ex vivo TU to T conversion of 3, 5, or 8%. When the thresholds for the secondary endpoints are based on the actual ULN (1080 ng/dL), the trial strictly met two of the three C_{max} criteria: No subjects had C_{max} greater than 2.5X ULN (>2700 ng/dL) and ≤5% had C_{max} between 1.8 and 2.5X ULN (1944 and 2700 ng/dL). This was true whether ex vivo conversion of TU to T was 3, 5, or 8%.

The trial did not strictly meet the third criterion of having ≥85% of subjects with C_{max} ≤1.5X ULN (1620 ng/dL). The percentage of subjects with C_{max} ≤1620 ng/dL was 76 (80%), 78 (82%), and 80 (84%) depending on whether ex vivo TU to T conversion was 3, 5, and 8%, respectively. Table 4 summarizes the analysis of T C_{max} outliers with thresholds based on the actual ULN (1080 ng/dL) for Study 16-002 and with adjustments for ex vivo TU to T conversion of 3, 5, and 8%.

Table 4. T C_{max} Outlier Analysis With Thresholds Based on the Actual ULN and Adjustments for Ex Vivo Conversion of TU to T of 3%, 5%, and 8% (N=95; Safety Set; Study 16-002)

T C_{max} Thresholds (ng/dL)	Target Proportion of Subjects	T C_{max} Outliers N (%)		
		Ex Vivo TU to T Conversion =3%	Ex Vivo TU to T Conversion =5%	Ex Vivo TU to T Conversion =8%
≤1620	≥85%	76 (80%)	78 (82%)	80 (84%)
Between 1944 and 2700	≤5%	5%	5%	5%
>2700	0%	0%	0%	0%

Source: NDA 208088 (seq 066), Module 2.7.3, Table 3 p 5.
Abbreviations: T = testosterone; TU = testosterone undecanoate; ULN = upper limit of normal

From the available data, it is not possible to precisely determine whether ex vivo conversion of TU to T was 3, 5, or 8%. However, the difference in the number of subjects exceeding the 1620

ng/dL threshold among the three possible ex vivo conversion amount is small: two additional subjects with TU to T conversion of 5% versus 8%, and two additional subjects with TU to T conversion of 3% versus 5%. In addition, for the four subjects whose C_{max} was $\leq$1620 with ex vivo conversion of 8% but not with ex vivo conversion of 3%, the amount by which their C_{max} exceeded 1620 ng/dL with ex vivo conversion of 3% ranged from 1 to 69 ng/dL. The difference between the FDA target ($\geq$85%) and the results achieved in Study 16-002, with ex vivo conversion of TU to T taken into account, is small. This difference is not expected to materially affect the efficacy of the drug.

In summary, when the results of Study 16-002 were adjusted for ex vivo TU to T conversion and the C_{max} thresholds were based on the actual ULN for the study, Tlando met the primary endpoint and two out of three of the C_{max} criteria for the secondary endpoints. The criterion that was not strictly met was missed by a small amount, which is not expected to affect the efficacy of the drug or be clinically meaningful.

8.1.3. Integrated Assessment of Effectiveness

Not applicable. The efficacy data for the dosing regimen proposed for marketing, 225 mg BID without dose titration, is derived solely from Study 16-002.

8.2. Review of Safety

The safety of Tlando was reviewed during the first, second, and third review cycles. Refer to the multi-disciplinary review entered in DARRTS on November 8, 2019, for the review of the most recent update to the safety database. Four safety issues of special interest are described below:

Blood Pressure Increases

In the second resubmission, the Applicant submitted the results of Study 18-001, an ABPM trial that showed that Tlando increases BP by a small, but clinically meaningful, magnitude in hypogonadal men. These findings were similar to those seen for the approved oral TU product. Refer to the multi-disciplinary review entered in DARRTS on November 8, 2019, for a discussion of the design (section 8.2.8) and results (section 8.2.5.1) of this study.

Based on the results for Study 18-001, for Tlando to be approved, its labeling will need to include:

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

In addition, to ensure that patients understand the risk of increased BP associated with Tlando, the Applicant will be required to conduct, as a postmarketing requirement (PMR), a study to

assess patients' comprehension of the key risk messages about blood pressure increases and the associated increased risk of heart attacks and strokes contained in the Medication Guide.

Increased Hematocrit

In Study 18-001, after 110 days of treatment with the 225 BID fixed dose, the mean increase in hematocrit was 3.2%. This increase was greater than the change seen in Study 16-002, the 24-day, fixed dose (225 mg BID) study, during which hematocrit increased by 0.9% after 24 days of treatment.

Because Study 18-001 is the study with longest duration evaluating the to-be-marketed dose and dosing regimen (225 mg BID fixed dose), it is unclear whether hematocrit would further increase with longer use of Tlando. To address this potential risk , the polycythemia subsection of Warnings and Precautions for the Tlando labeling will include instructions to assess hematocrit every three months during the first year that patients are on the drug and, if hematocrit becomes elevated, to stop the drug until hematocrit returns to an acceptable level.

Increased Serum Prolactin

The clinical review team noted a signal for an increase in serum prolactin concentrations in subjects treated with Tlando during Study 16-002. Refer to the multi-disciplinary review entered in DARRTS on November 8, 2019, for a complete discussion of this safety issue (section 8.2.5.2). The reason for the increased serum prolactin levels is not clear. Based on the 52-week data from study 13-001, it appears that 1-year of use of the drug does not meaningfully increase serum prolactin to a level where additional clinical evaluation was necessary. However, study 13-001 evaluated the 225 mg BID dose with dose titration, which is not the to-be-marketed dose/dosing regimen. Study 18-001, which use the 225 mg BID dose without titration, did not assess prolactin concentrations after the screening visit. No additional clinical data regarding this issue were submitted in the current submission.

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

Potential Effects on the Hypothalamic Pituitary Adrenal Axis

In the nonclinical toxicology studies, adrenal cortical vacuolation was noted in rats and adrenal cortical atrophy was noted in dogs. To assess the clinical implications of these findings, the Applicant included Cosyntropin stimulation substudies in Study 16-002 and Study 16-003. The Cosyntropin stimulation substudies were reviewed, in consultation with an FDA endocrinologist, during the second review cycle of the NDA. At that time, the clinical review team concluded that the 24-day treatment period was insufficient to definitively exclude a risk of adrenal insufficiency with chronic dosing and recommended further assessment of adrenal function over a longer duration to more definitively address this issue. For additional

information regarding the Cosyntropin stimulation substudies, please refer to the second cycle Clinical Review of the NDA.

In the current resubmission, the Applicant did not submit any additional data regarding this adrenal issue. The review team continues to believe that assessment of adrenal function over a longer period of time is warranted to definitively address this issue. Based on the available data and input from the Bone, Reproductive and Urologic Drugs Advisory Committee meeting on January 10, 2018 (see second cycle Clinical Review Section 9) we believe this assessment can be done postapproval. Therefore, the Applicant will be required to conduct a longer duration Cosyntropin stimulation study as a postmarketing required study.

8.2.1. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

Expectations on Safety in the Postmarket Setting

The safety of Tlando in the postmarket setting is expected to be similar to the safety of the currently approved oral TU product. The safety of the 225 mg BID fixed dose of Tlando was evaluated in two clinical trials: Study 16-002, a 24-day safety and efficacy trial, and Study 18-001, a 110-day ABPM trial.

The results for the C_{max} secondary endpoints for Tlando seen in Study 16-002 were similar to the results for the currently approved oral TU product.

Study 18-001, the 110-day ABPM trial, quantified increases in systolic and diastolic blood pressure for Tlando. These increases were similar to the increases for the currently approved oral TU product and will be mitigated in the same way with labeling.

Because the 110-day ABPM trial is the longest trial that evaluated the safety of the 225 mg BID fixed dose of Tlando, the long-term effects of the drug on hematocrit are unknown. To address this risk, labeling for Tlando will recommend monitoring hematocrit at regular intervals while patients are treated with the drug.

Similarly, because the duration of the cosyntropin substudy in Study 16-002 was not long enough to definitively exclude a risk of adrenal insufficiency with chronic dosing, the Applicant will be required to assess adrenal function over a longer duration as a PMR.

Finally, a signal for increased serum prolactin in Study 16-002 will be mitigated with labeling that recommends monitoring for serum prolactin and discontinuation of the drug if levels are increased.

Integrated Assessment of Safety

The safety database for Tlando included 654 hypogonadal men who received the drug from 1 to 382 days. The source of long-term safety data is derived from study 13-001, a 52-week, randomized, active-controlled trial, but this trial did not evaluate the to-be-marketed dose and dosing regimen. Safety data for the 225 mg BID dose without dose titration are derived from Study 16-002, a 24-day trial and Study 18-001, a 110-day ABPM trial. Supportive safety data are derived from Study 16-003, a 24-day trial that evaluated the 150 mg three times a day dose without dose titration and six phase 1 studies.

The current submission evaluates the Applicant's proposal to base the thresholds for the secondary endpoints on the actual ULN (1080 ng/dL) determined for Study 16-002. The submission included an analysis of the secondary endpoints with C_{max} thresholds based on the actual ULN and adjusted for 3, 5, and 8% ex vivo conversion of TU to T. The results showed that the subjects exceeding C_{max} outlier thresholds were acceptable.

The adrenal function was assessed in Cosyntropin stimulation substudies during Study 16-002 and Study 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. Therefore, further assessment of adrenal function over a longer duration is needed to rule out the risk of adrenal dysfunction, but as noted previously, this information can be obtained in the postmarketing setting.

A signal for an increase in serum prolactin concentration in subjects treated with Tlando was noted in Study 16-002, the 24-day fixed dose trial. Based on data from study 13-001, the 52-week study, it appears that serum prolactin levels are not meaningfully changed with longer treatment. However, study 13-001 evaluated the 225 mg BID dose with dose titration, whereas Study 16-002 evaluated that dose without titration. Therefore, we recommend that the labeling for Tlando include a recommendation to periodically monitor serum prolactin.

8.3. Statistical Issues

None.

8.4. Conclusions and Recommendations

In the prior review cycle dated November 8, 2019, the review team recommended a CR based on Tlando's inability to meet the secondary C_{max} endpoints. The deficiency in this CR letter stated:

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

> without titration met the primary efficacy endpoint, acceptably restoring average testosterone concentrations (C_{avg}) to the normal range. However, the trial did not meet the secondary endpoints for maximal testosterone concentrations (C_{max}), falling short of the prespecified targets for proportion of subjects with testosterone C_{max} of 1500 ng/dL or less (74% instead of the 85% target) and testosterone C_{max} between 1800 and 2500 ng/dL (14% instead of the 5% target).

In the current resubmission, the Applicant has successfully demonstrated that Tlando achieved the (C_{max}) secondary endpoints after modifying the ULN from the commonly used ULN threshold of 1000 ng/dL to the actual ULN threshold of 1080ng/dL. With the C_{max} thresholds based on the actual ULN and adjusted for 3, 5, and 8% ex vivo conversion of TU to T, the Applicant showed that the secondary endpoints have essentially been achieved (82%, 5% and 0%), and there are no excessive C_{max} excursions seen that are clinically relevant.

Additionally, as indicated in November 8, 2019 clinical review, small increases in BP with Tlando can be adequately mitigated with labeling. An inconsistent finding of prolactin increase can also be labeled. Lastly, a signal for adrenal insufficiency has not been identified so far in humans but longer-term formal assessment with adrenocorticotropic hormone stimulation testing is needed to assess this safety signal as a postmarketing study.

In summary, there is sufficient data to support the overall safety of Tlando oral capsules, 225 mg BID regimen. The principal benefit of Tlando is the convenience of oral dosing.

We recommend approval of this application. However, Tlando will receive a Tentative Approval because of pending expiration of exclusivity granted to Jatenzo, a currently approved oral TU product.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee was convened during the second review cycle of NDA 208088 on January 10, 2018. For a detailed summary of Advisory Committee discussion, see review in DARRTS dated May 8, 2019. The current review cycle did not raise issues requiring external expert input from another Advisory Committee meeting.

10. Pediatrics

Prior to 2018, the Agency had waived PREA requirements for testosterone replacement products because studies would be impossible or highly impractical (because primary/secondary hypogonadism rarely occur in pediatrics). Since 2018 and after discussion at the April 2019 Pediatric Advisory Committee meeting, the Agency determined that PREA requirements apply to these products because there are adolescent boys with

primary/secondary hypogonadism requiring testosterone replacement. Because the dosing amount per 24-hour period for Tlando is different from that of the approved oral testosterone product (Jatenzo), its dosing regimen is considered different from that of Jatenzo. As such, PREA requirement will apply to Tlando. When Tlando receives a final approval, it will be granted a full PREA waiver for all females, a partial waiver for males from 0 to less than (b) (4) years, and a deferral for males from (b) (4) years of age. (b) (4)

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling negotiations are complete. Key issues follow:

- Based on the results for study 18-001, the labeling for Tlando will include:
  - A Boxed Warning and Warnings/Precautions regarding blood pressure increases
  - A Contraindication limiting the use of Tlando to men with hypogonadal conditions associated with structural or genetic etiologies
  - A Medication Guide informing patients of the serious side effects associated with Tlando including increased blood pressure.

- Because the duration of the longest study evaluating the 225 mg BID fixed dose of Tlando was four months, the effect of that dose on hematocrit with longer use is unknown. The polycythemia subsection of Warnings and Precautions for the Tlando labeling will include instructions to assess hematocrit every three months during the first year of treatment and every six months thereafter, and to stop the drug if hematocrit becomes elevated.

- Because there is not sufficient data to definitively resolve the signal of increased serum prolactin seen in Study 16-002, the Warnings and Precautions section for the Tlando label will include a subsection regarding increases in prolactin. This subsection will include instructions to evaluate serum prolactin levels prior to initiating treatment with Tlando and 3 to 4 months after starting treatment. If serum prolactin remains elevated, discontinue Tlando.

12. Risk Evaluation and Mitigation Strategies

Risk Evaluation and Mitigation Strategies is not needed for this application.

13. Postmarketing Requirements and Commitment

Because Tlando was shown to increase BP and its labeling includes a Box Warning for BP increases, it is important that patients are informed of this finding and understand its ramifications. Therefore, the Applicant will be required to conduct a postmarketing study to assess patients' comprehension of the key risk messages related to BP increases and the associated increase risk of heart attacks and strokes contained in the Medication Guide.

In the nonclinical toxicology studies, adrenal cortical vacuolation was noted in rats and adrenal cortical atrophy was noted in dogs. Cosyntropin stimulation testing was included in the 24-day phase 3 trial, however, it did not definitively exclude a risk of adrenal insufficiency with chronic dosing. Therefore, we will require that the Applicant conduct a PMR to assess the risk of adrenal insufficiency with chronic dosing.

14. Office Director (or Designated Signatory Authority) Comments

None.

15. Appendices

15.1. Financial Disclosure

No new clinical studies were submitted during the current review cycle. Refer to the multi-disciplinary review for the third review cycle in FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) dated November 8, 2019, for the Financial Disclosure information.

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

/s/

SURESH KAUL
12/03/2020 01:37:04 PM

CHRISTINE P NGUYEN
12/03/2020 01:51:20 PM

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number(s)	208088
Priority or Standard	Standard
Submit Dates	August 28, 2015 (first review cycle) August 8, 2017 (second review cycle) May 9, 2019 (current review cycle)
Received Dates	August 28, 2015, August 8, 2017 and May 9, 2019
PDUFA Goal Date	November 9, 2019
Division/Office	Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III
Review Completion Date	November 8, 2019
Established/Proper Name	Testosterone undecanoate (oral)
(Proposed) Trade Name	Tlando
Pharmacologic Class	Androgen
Code name	N/A
Applicant	Lipocine Incorporated
Dosage form	Oral
Applicant proposed Dosing Regimen	225 mg testosterone undecanoate taken twice daily with food.
Applicant Proposed Indication(s)/Population(s)	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommended Dosing Regimen	N/A

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Management	Jeannie Roule, Jennifer Mercier
Nonclinical Reviewer	Laurie McLeod-Flynn
Nonclinical Pharmacology/Toxicology Team Leader	Mukesh Summan
Clinical Pharmacology Reviewer	LaiMing Lee
Clinical Pharmacology Team Leader	Yanhui Lu
Senior Clinical Analyst	Martin Kaufman
Clinical Team Leader	Suresh Kaul
Statistical Reviewer	Weiya Zhang
Statistical Team Leader	Mahboob Sobhan
Office of Pharmaceutical Quality, Application Technical Lead	Mark Seggel
Cross-Disciplinary Team Leader	Suresh Kaul
Office Director (or designated signatory authority)	Hylton Joffe

Additional Reviewers of Application

OPQ	Hamid Shafiei, Jeff Medwid, Donna Christner, James Norman, Yubing Tang, , Haritha Mandula, Hansong Chen, Vidula Kolhatkar, Juandria Williams, James Laurenson, Raanan Bloom, Marquita Burnett, Moo-Jhong Rhee
Microbiology	N/A
OPDP	Jina Kwak, Trung-Hieu Brian Tran
OSI	N/A
OSIS	Shila Nkah, Xingfang Li, Seongeun (Julia) Cho, Michael F. Skelly,William H. Taylor, Srinivas Rao Chennamaneni
OSE/DEPI	Wei Liu, Jie Li
OSE/DPV	Rachna Kapoor
OSE/DMEPA	Denise Baugh, Ebony Whaley, Briana Rider, Lolita White, Todd Bridges, Azeem Chaudhry, Danielle Harris, Mammah Borbor, Oyinlola Fashina, Walter Fava, Shawnetta Jackson, Pauline Cottrell, Corwin Howard
OSE/DRISK	Courtney Cunningham, Laura Zendel
OSE/DMPP	Aman Sarai, Marcia Williams, Twanda Scales, Marcia Williams, LaShawn Griffiths
CSS	Joshua Hunt, Dominic Chiapperino, Chad Reissig
OND/DCaRP	Fred Senatore, Preston Dunmonn, Shari L. Targum, Stephen Grant, Tzu-Yun McDowell,Chrisitne Garnett, Martin Rose, Norman Stockbridge
OND/PeRC	George Greeley

Other	Linda Jaffe, Theresa Kehoe, Anne Marie Trentacosti, Melinda McLawhorn

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Laurie McLeod-Flynn, Ph.D., D.A.B.T.	OND/DBRUP	Section: 5	Select one: __X_ Authored ___ Approved
	Signature: Laurie L. Mcleod-flynn -S Digitally signed by Laurie L. Mcleod-flynn -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300106259, cn=Laurie L. Mcleod-flynn -S Date: 2019.10.21 07:38:32 -04'00'			
Nonclinical Supervisor	Mukesh Summan, Ph.D.	OND/DBRUP	Section: 5	Select one: ___ Authored _X__ Approved
	Signature: Mukesh Summan -S Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9.2342.19200300.100.1.1=2000337340 Date: 2019.10.21 08:40:20 -04'00'			
Clinical Pharmacology Reviewer	Lai Ming Lee, Ph.D.	OCP/DCPIII	Section: 6	Select one: _X__ Authored ___ Approved
	Signature: Lai M. Lee -S Digitally signed by Lai M. Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lai M. Lee -S, 0.9.2342.19200300.100.1.1=1300366890 Date: 2019.10.25 09:52:05 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Yanhui Lu, Ph.D.	OCP/DCPIII	Section: 6	Select one: _X__ Authored _X_ Approved
	Signature: Yanhui Lu -S Digitally signed by Yanhui Lu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yanhui Lu -S, 0.9.2342.19200300.100.1.1=2001501324 Date: 2019.10.25 15:42:34 -04'00'			
Clinical Pharmacology Deputy Director	Doanh Tran, Ph.D.	OCP/DCPIII	Section: 6	Select one: ___ Authored _X__ Approved
	Signature: Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2019.10.25 15:51:19 -04'00'			

NDA 208088 Multi-disciplinary Review and Evaluation
Testosterone undecanoate (oral)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Senior, Clinical Analyst	Martin Kaufman, D.P.M., M.B.A	OND/DBRUP	Sections: 1, 2, 3, 7, and 8	**Select one:** _X__ Authored ___ Approved
	Signature: Martin E. Kaufman -S Digitally signed by Martin E. Kaufman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222976, cn=Martin E. Kaufman -S Date: 2019.10.23 14:55:59 -04'00'			
Statistical Reviewer	Weiya Zhang	OTS/Division of Biometrics III	Section: 8	**Select one:** _X__ Authored ___ Approved
	Signature: Weiya Zhang -S Digitally signed by Weiya Zhang -S Date: 2019.10.21 09:09:43 -04'00'			
Statistical Team Leader	Mahboob Sobhan	OTS/Division of Biometrics III	Section: 8	**Select one:** ___ Authored _X__ Approved
	Signature: Mahboob Sobhan -S Digitally signed by Mahboob Sobhan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mahboob Sobhan -S, 0.9.2342.19200300.100.1.1=1300084769 Date: 2019.10.21 10:14:40 -04'00'			
OPQ, Application Technical Lead	Mark Seggel, Ph.D.	OPQ/ONDP/DNDPII	Section: 4.2	**Select one:** _X__ Authored _X__ Approved
	Signature: Mark R. Seggel -S Digitally signed by Mark R Seggel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R Seggel -S, 0.9.2342.19200300.100.1.1=1300071539 Date: 2019.10.16 14:54:13 -04'00'			

Glossary

ABPM	ambulatory blood pressure monitoring
AE	adverse event
BID	twice daily
BLA	biologics license application
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CSR	clinical study report
CSS	Controlled Substance Staff
DARRTS	FDA Document Archiving, Reporting and Regulatory Tracking System
DBP	diastolic blood pressure
DBRUP	Division of Bone, Reproductive and Urologic Products
DMF	drug master file
eCTD	electronic common technical document
FAS	full analysis set
FDA	Food and Drug Administration
IND	Investigational New Drug
IRT	Interdisciplinary Review Team
ISS	Integrated Summary of Safety
K2E	di-potassium ethylenediaminetetraacetic acid
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSIS	Office of Study Integrity and Surveillance
PK	pharmacokinetic
PR	pulse rate
PSA	prostate-specific antigen
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SST	serum separation tubes
TEAE	treatment emergent adverse event
TID	three times a day
TU	testosterone undecanoate
ULN	upper limit of normal

1. Executive Summary

1.1. Product Introduction

Testosterone is an endogenous androgen that is responsible for 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; and 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.

The Tlando (the proposed tradename) 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 nonspecific esterases present in the body. In the United States, products containing TU are currently approved for injectable intramuscular administration (Aveed) and for the oral route of administration (Jatenzo).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The goal for products indicated for testosterone replacement therapy is to restore testosterone concentrations to the eugonadal range (Cavg) and to avoid unacceptably high testosterone concentrations (Cmax). For approval, a product should meet both of these goals. LPCN 1021-16-002 (hereafter “study 16-002”), the pivotal trial that evaluated the to-be-marketed dosing regimen of 225 mg twice daily without dose titration, met the prespecified primary endpoint (proportion of treated subjects with testosterone Cavg within the normal range) but did not meet the prespecified secondary endpoints (proportion of subjects with Cmax within the predetermined limits). Therefore, we conclude that Tlando does not reasonably restore serum testosterone concentrations to the normal range when dosed at 225 mg BID without dose titration.
For approval, the Applicant should either provide additional clinical data showing that the Cmax excursions with the 225 mg BID regimen are not clinically meaningful or conduct a new phase 3 trial with a dosing regimen that meets both the primary and the secondary efficacy endpoints.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Tlando capsule is an oral testosterone replacement therapy containing testosterone undecanoate (TU) in a lipid formulation. If approved, Tlando would be the second oral TU product indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone including congenital or acquired primary or secondary hypogonadism. A variety of other non-oral testosterone replacement therapies are also approved for this indication. The Applicant is seeking approval of a 225 mg twice daily dose without titration. While this dose acceptably increases average serum testosterone concentrations into the normal range, it leads to excessive increases in testosterone in an unacceptable number of patients, considerably exceeding the prespecified targets. The Applicant would need to provide additional clinical data with Tlando showing that these excessive increases are not clinically significant or could assess a new dosing regimen that more appropriately restores serum testosterone concentrations into the normal range. The other safety findings to date (e.g., small increases in blood pressure) can be adequately mitigated with labeling if/when Tlando can be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Male hypogonadism is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa as a result of disruption of one or more levels of the hypothalamic-pituitary-testicular axis.[1] • Signs and symptoms of androgen deficiency are generally non-specific and include reduced sexual desire (libido), decreased spontaneous erections, loss of body (axillary and pubic) hair, height loss, low bone mineral density and osteoporotic fracture; decreased energy; poor concentration and memory; reduced muscle mass and strength; and increased body fat.	Male hypogonadism has important health implications. A minority of men diagnosed with hypogonadism have "classical" hypogonadism. The remainder have other conditions such as age-related hypogonadism.

[1] Bhasin S Brito JP et al. Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endorinol Metab 103(5): 1715-1744, 2018.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• A small subset of men diagnosed with hypogonadism have "classical" hypogonadism, which refers to hypogonadism caused by specific, well-recognized medical conditions, such as Klinefelter's syndrome, pituitary injury or toxic damage to the testicles. The remainder are diagnosed with other conditions such as age-related hypogonadism (middle-aged and elderly men who have low testosterone compared to young, healthy men for no discernable reason other than older age).	
Current Treatment Options	• Testosterone is currently available in the United States as a buccal tablet, subcutaneous implant, transdermal patch, transdermal gel, transdermal solution, nasal gel, and parenteral injection. Testosterone undecanoate (TU) is approved as an intramuscular injection and an oral capsule. • These products are approved for testosterone replacement therapy in men with "classical" hypogonadism and have demonstrated effectiveness in maintaining testosterone concentrations within the eugonadal range while avoiding unacceptably high serum testosterone concentrations. • Testosterone is commonly used in men who do not have classical hypogonadism, such as those with age-related hypogonadism although the effectiveness and safety of testosterone has not been established for these uses.	There are many approved testosterone products available with different routes of administration. In March 2019, another TU capsule was approved for the oral route of administration. Approval of Tlando would provide another oral treatment option for male hypogonadism. Testosterone replacement therapy is approved for men with classical hypogonadism. The safety and effectiveness of testosterone therapy for other hypogonadal conditions, such as age-related hypogonadism have not been established.
Benefit	• In the 24-day efficacy trial, 225 mg of Tlando twice daily without titration (the proposed dosing regimen for marketing) increased the time-averaged serum testosterone concentration (Cavg) into the normal range in 80% of subjects (95% CI 72%, 88%). Tlando met the prespecified target for this primary efficacy endpoint (at least 75% of subjects achieving testosterone Cavg within the normal range with a lower bound of the corresponding 2-sided, 95% CI of >65%).	The dosing regimen proposed for marketing acceptably increases average serum testosterone concentrations into the normal range.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	The secondary endpoints in the 24-day trial assessed the extent to which Tlando 225 mg twice daily caused unacceptably high serum testosterone concentrations. The upper limit of the normal testosterone range was 1080 ng/dL. • 74% of subjects had maximal testosterone (T Cmax) concentrations <1500 ng/dL (prespecified target ≥85% of subjects) • 14% of subjects had T Cmax between 1800 and 2500 ng/dL (prespecified target ≤5% of subjects) • 1% of subjects had T Cmax >2500 ng/dL (prespecified target 0% of subjects) The long-term safety implications of these Cmax excursions well above the normal testosterone range and exceeding the prespecified targets could not be determined. However, these excursions raise concerns related to androgen excess, as suggested, for example, by the hemoglobin and hematocrit increases in the 110-day ambulatory blood pressure monitoring trial that also used this fixed dose regimen. The 110-day trial also showed a numerically small, but clinically significant, increase in blood pressure consistent with that seen with the approved oral TU product. When Tlando can be approved, this risk can be mitigated with labeling (a Boxed Warning and Medication Guide) like that for the other oral TU product. Based on an adrenal signal in animals, the Applicant has not excluded the potential for adrenal insufficiency with long-term use although there is no evidence of a major problem in the previously completed 52-week trial. The Applicant has sufficiently assessed this risk with use up to 24 days but has not performed ACTH stimulation testing with longer-term use. Like the approved oral TU product, the long-term risk can be further evaluated in the postmarketing setting when Tlando can be approved.	The long-term safety implications of the excessive number of subjects with Cmax excursions in the 24-day trial testing the 225 twice daily fixed dosing regimen could not be determined. Additional longer-term data for this regimen are needed. Alternatively the Applicant can assess another dosing regimen that more appropriately restores serum testosterone concentrations into the normal range by meeting both the standard primary and secondary endpoints for testosterone replacement therapies. The increase in blood pressure with Tlando can be adequately mitigated with labeling like that of the currently approved oral TU product. A signal for adrenal insufficiency has not been identified so far in humans but longer term formal assessment with ACTH stimulation testing is needed to definitively assess this safety signal. This is not needed pre-approval. There are discrepant findings on serum prolactin. This can be labeled. If a new phase 3 trial is conducted, serum prolactin should be monitored.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	An increase in serum prolactin concentration in subjects treated with Tlando was seen in the 24-day trial but not in a 52-week trial that tested a different dosing regimen. This finding can be labeled. If the Applicant conducts a new phase 3 trial, serum prolactin should be monitored.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Original submission review (Section 6.1.6 – Other Endpoints) entered in DARRTS June 23, 2016
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

See the second cycle Clinical Review in the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) dated March 12, 2018.

2.2. Analysis of Current Treatment Options

In the United States, many products are currently approved for replacement therapy in males with hypogonadism. Several formulations of testosterone and its esters are available, including a buccal tablet, subcutaneous implant, transdermal patch, transdermal gel, transdermal solution, nasal gel, subcutaneous injection, intermuscular injection, and oral capsule. Methyltestosterone, though prescribed infrequently because of its hepatic toxicity, is also available as an oral capsule.

TU was approved as an intramuscular injection in 2014 and as an oral capsule in 2019. Table 1 summarizes drug products approved for testosterone replacement.

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
Injection	Depo-testosterone (testosterone cypionate)	50-400 mg every 2-4 weeks		085635
	Testosterone cypionate	50-400 mg every 2-4 weeks		040530 040615 086030 090387 091244 201720 206368 207742 210362
	Testosterone enanthate	50-400 mg every 2-4 weeks		040575 085598 091120
Intramuscular	Aveed (testosterone undecanoate)	750 mg: second dose after 4 weeks, subsequent doses every 10 weeks	022219	
Subcutaneous	Xyosted (testosterone enanthate)	50-100 mg every 7 days	209863	
Oral	Testred (methyltestosterone)	10-50 mg daily		083976
	Android (methyltestosterone)	10-50 mg daily		087147
	Methyltestosterone	10-50 mg daily		080767 204851
	Jatenzo (testosterone undecanoate)	158-396 mg twice daily	206089	
Implant	Testopel (testosterone)	150-450 mg every 3 to 6 months		080911
Buccal	Striant (testosterone)	30 mg twice daily	021543	

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
Transdermal	Androderm (testosterone)	2-6 mg daily	020489	
	AndroGel (testosterone 1.62%)	20.25-81 mg daily	022309	
	Testosterone 1.62%	20.25-81 mg daily		204570 207373 208620 208560 204268
	AndroGel (testosterone 1%)	50-100 mg daily	021015	
	Testosterone gel 1%	50-100 mg daily		076737 076744 091073
	Testim (testosterone 1%)	50-100 mg daily	021454	
	Fortesta (testosterone)	10-70 mg daily	021463	
	Testosterone gel	10-70 mg daily		204571
	Vogelxo (testosterone gel)	50-100 mg daily	204399	
	Testosterone topical solution	30-120 mg daily		205328 209533 208061 204255
Nasal	Natesto (testosterone)	11 mg thrice daily	205488	

Source: Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), electronic version accessed August 13, 2019. Product labeling accessed at the DailyMed website and in DARRTS August 13, 2019.

Labeled risks of testosterone administration in hypogonadal men include worsening of clinical symptoms of benign prostatic hyperplasia, 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.

Transdermal testosterone preparations, which are applied to the skin, have been associated with secondary exposure of testosterone to children and women 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 to address the serious risk of secondary transfer of testosterone to women and children. All transdermal testosterone products approved since that time have also included the Boxed Warning in product labeling.

The injectable formulation of TU has been associated with pulmonary oil microembolism 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.

Even though there are many approved testosterone products available with different routes of administration, products with an oral route of administration may be more convenient for patients. It would avoid the need for periodic injections and, in patients for whom transference of topical testosterone to a child or female is a concern, an oral product would avoid this risk. There are currently two drug products approved for testosterone replacement therapy via the oral route of administration. Methyltestosterone capsules, a 17-alpha-alkyl androgen, is prescribed infrequently due to the risk of hepatotoxicity. More recently, Jatenzo capsules, a formulation of TU, was approved for oral administration.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lipocine submitted the original NDA for Tlando on August 28, 2015. The submission did not provide a single blood draw titration scheme that 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 a dosing recommendation for Tlando in clinical practice and in labeling, and the drug could not be approved. On June 28, 2016, the Division of Bone, Reproductive and Urologic Products (DBRUP) issued a Complete Response (CR) letter for the NDA.

Lipocine submitted the NDA for their second cycle review on August 8, 2017 with two new phase 3 studies: study 16-002, a phase 3, open-label, multicenter, single arm 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. Study LPCN 1021-16-003 (hereafter "study 16-003") was a phase 3, open-label, multicenter, uncontrolled study evaluating the efficacy of Tlando in adult hypogonadal males who received a fixed dose, but with a dosing regimen of 150 mg of Tlando three times a day (TID).

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

- Insufficient data to determine whether the testosterone concentrations are reliable because there is inadequate evidence to exclude clinically relevant ex vivo TU to T conversion in patients treated with Tlando.
- Concerns that Tlando may lead to clinically meaningful increases in blood pressure (BP) that could increase the occurrence of major adverse cardiovascular events.
- Failure to meet the secondary endpoints for testosterone Cmax.
- Inadequate proposal for determining whether a patient should discontinue the drug in clinical practice.

Lipocine submitted the NDA for their third cycle review on May 9, 2019.

3.2. Summary of Presubmission/Submission Regulatory Activity

For regulatory activity including the original submission and the first resubmission of the NDA on August 8, 2017, see the second cycle Clinical Review of the NDA in DARRTS.

The Applicant resubmitted NDA 208088 on August 8, 2017. After receiving a major amendment to the application on November 13, 2017, DBRUP extended the user fee goal date to May 8, 2018. After discussing the resubmission at an advisory committee meeting, DBRUP issued a CR letter for the NDA on May 8, 2018. The Applicant requested and was granted a meeting with DBRUP after the CR action.

- **July 19, 2018: Type A postaction meeting:** Key meeting discussion included the Applicant's action plan to address the issue of ex vivo TU to T conversion, study to address cross reactivity of commonly used testosterone immunoassays with TU, the Ambulatory Blood Pressure Monitoring study, the Applicant's action plan to address the issue of Cmax outliers (i.e., failure to meet the secondary endpoints), and the Applicant's action plan to address the issue of (b) (4) stopping criteria.

The Applicant resubmitted the NDA on May 9, 2019 for third cycle review.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

For prior inspection site details see the second cycle Clinical Review of NDA 208088 in DARRTS dated March 12, 2018, for Office of Study Integrity and Surveillance (OSIS) inspections conducted during the first and second review cycles.

During the current review cycle, OSIS conducted an inspection of the two clinical sites used in study 18-003, which assessed the extent of ex vivo TU to T conversion. Based on their inspection, OSIS concluded the data from the audited study are reliable to support a regulatory decision. See the Clinical Pharmacology section for details regarding the inspection findings.

4.2. Product Quality

From the Office of Product Quality (OPQ) perspective, the NDA is not ready for approval. Labeling discussions have not been completed, and in its present form the prescribing information does not comply with the requirements under 21 CFR 201.

Tlando capsules contain 112.5 mg TU. The chemistry, manufacturing, and controls for TU are documented in Type II drug master file (DMF) (b) (4) The information provided in the DMF is adequate to support the use of the drug substance in the manufacture of the drug product.

The drug product is prepared from a (b) (4) of TU and the following excipients: (b) (4) (glyceryl monolinoleate; (b) (4) polyoxyl 40 hydrogenated castor oil ((b) (4)), ascorbyl palmitate ((b) (4)), and polyethylene glycol 8000 (b) (4)

Overall, 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 Current Good Manufacturing Practice status.

A 48-month expiration dating period for the drug product when stored at 25°C has been granted.

The request for a categorical exclusion from an environmental assessment, supplemented by information submitted by the applicant to aid in determining whether extraordinary circumstances exist, is accepted.

See the OPQ Integrated Quality Assessment (IQA) #1, June 2, 2016, IQA #2, February 26, 2018, and IQA #3, October 11, 2019, for the detailed assessment of the chemistry, manufacturing and controls for the proposed drug.

4.3. Clinical Microbiology

No new information regarding product quality microbiology was reported in this resubmission. The reviewer concluded that microbiology control for this product is adequate according to current quality standards.

4.4. Devices and Companion Diagnostic Issues

The product does not include a device or companion diagnostic.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were submitted in the current NDA resubmission. All prior nonclinical issues have been resolved. Nonclincial Pharmacology/Toxicology recommends approval. For details, refer to the June 1, 2016 nonclinical review in DARRTS.

5.2. Referenced NDAs, BLAs, DMFs

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.3. Pharmacology

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.4. ADME/PK

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5. Toxicology

5.5.1. General Toxicology

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5.2. Genetic Toxicology

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5.3. Carcinogenicity

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5.4. Reproductive and Developmental Toxicology

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

5.5.5. Other Toxicology Studies

All nonclinical issues have been resolved. Refer to the June 1, 2016 Nonclinical review in DARRTS for details.

6. Clinical Pharmacology

6.1. Executive Summary

In the CR letter dated May 8, 2018, the Clinical Pharmacology issues that remained unresolved were the ex vivo conversion of TU to T in blood collection tubes that could potentially result in overestimation of systemic T concentration and identification of a stopping criteria for use in clinical practice. In the current resubmission, the Applicant included one new clinical study to address the transformation of TU to T by nonspecific esterases in freshly collected blood under typical sample handling conditions and an updated approach for stopping criteria. The results of the clinical study suggested that ex vivo conversion of TU to T did occur during processing of blood samples into serum in the blood collection tubes but the extent of the increase in T concentrations (3.2%) caused by the conversion should not affect the conclusions of the safety and efficacy of the proposed product obtained from the pivotal phase 3 trial and is thus not expected to have a clinically meaningful impact on a patient's T replacement therapy. The proposed stopping criteria of using a single time T concentration taken 8 to 9 hours after morning dose appears reasonable but detailed labeling recommendations will not be made in this review cycle because there is a remaining issue precluding approval.

In addition to the abovementioned Clinical Pharmacology issues, the Applicant failed to meet the Cmax criteria for safety in phase 3 study 16-002. There was no dose adjustment or titration in the study that included 225 mg oral TU given twice daily for 24 days. The three endpoints for Cmax were not met: 74% of patients had a T Cmax of 1500 ng/dL or less (prespecified target at least 85%); 14% of patients had T Cmax between 1800 and 2500 ng/dL (prespecified target less than 5%); and 1% had a T Cmax greater than 2500 ng/dL (prespecified target 0%). Failure to meet the Cmax criteria was raised at the end of the second review cycle. In the current resubmission, the Applicant proposed alternative approaches in the assessment of Cmax criteria such as analyzing the frequency and duration of Cmax excursions in the higher Cmax range. The Applicant attempted to show there was no clinical relevance of T Cmax using T concentrations at Week 13 and safety data at Week 52 from phase 3 study LPCN 1021-13-001 (hereafter "study 13-001"), a study that included multiple dose levels and a titration scheme (Refer to the Clinical section of this review for additional details). The Applicant did not provide adequate exposure — safety response analyses to support their assertion that the observed duration of time in the higher Cmax range did not lead to adverse reactions. Therefore, it is not possible to assess the safety of high T concentrations with chronic use of oral TU at 225 mg twice daily.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III recommends a CR because there is insufficient information to support the long-term safety of twice daily, chronic use of 225 mg oral TU.

6.2. Summary of Clinical Pharmacology Assessment

In the CR Letter dated May 8, 2018, the Division recommended that the Applicant conduct a clinical study to assess the potential for ex vivo TU to T conversion using samples collected from subjects dosed with oral TU. The assessment was to account for potential TU to T conversion from the time of blood draw to the time of sample analysis. In this review cycle, the applicant conducted study 18-003 to quantify the degree of ex vivo conversion of TU to T.

In this study, T concentrations in plasma samples prepared by collecting blood in potassium EDTA (K2E) tubes were considered Time Zero Controls because the blood samples were processed immediately after blood collection; thereby, conversion of TU to T by nonspecific esterases in the tubes prior to sample preparation and T concentration determination is likely to be negligible. Table 2 presents mean % difference of T concentrations in serum using different clotting times to prepare serum from blood samples collected in plain tubes (also referred to as serum separation tubes or SST) compared to that in plasma samples at 3 hours and 5 hours (anticipated Tmax of TU) following a single oral dose of TU 225 mg in hypogonadal men.

When 60 min (the maximum clotting time allowed in phase 3 trial for serum preparation) was used as the clotting time, the mean T concentration in serum at 5 hours post-dose was 3.2% higher than in K2E plasma. It appears that as the clotting time increased from 60 min to 120 min, the mean difference of T concentrations between serum and plasma increased. With a clotting time of 120 min (60 min beyond the specified duration of clotting time of up to 60 min in the phase 3 study protocol), the T concentration in serum was approximately 8.6% higher than in plasma at 3 hours post-dose and 7.3% higher at 5 hours post-dose (Table 2).

Table 2. Mean (SD) Percent Difference of T Concentrations in Serum Separation Tubes Following a Single Oral TU 225 mg in Hypogonadal Men (N=12), Compared to Plasma (K2E Tubes)

Clotting Time for Serum Preparation	3 hrs Post-Dose	5 hrs Post-Dose
30 min	-3.1 (10)	1.1 (8)
60 min	-0.3 (7)	**3.2 (9)**
90 min	1.6 (7)	5.6 (11)
120 min	8.6 (11)	**7.3 (12)**

Source: Applicant's data table

In this review cycle, the Clinical Pharmacology team also reviewed the Applicant's proposed stopping criteria to be used for identifying patients who would not achieve average total T concentration (Cavg) within the normal range in order to discontinue the treatment. To support the proposed single T measurement at 8 hours after the morning dose, the Applicant applied the single assessment approach to data from study 16-002 which had a 24-hr T Cavg of 476 ng/dL. Of the empirically available data, the mean T concentration at 8 hours post-dose (C8hr) is 422 ng/dL and best correlates with 24-hr Cavg, compared to the other time points. The correlation between Cavg and C8hr is not ideal (r^2=0.6), but the periodic monitoring of T concentrations as proposed by the Applicant will help identify patients that may need to discontinue the fixed-dose therapy because of T concentrations falling outside the therapeutic range. We concur with the Applicant that a T concentration determined between 8 and 9 hours after the morning dose can be used to identify significant outliers for discontinuation. Because

we are issuing a CR letter, labeling recommendations for discontinuation will not be made in this review cycle.

6.2.1. Pharmacology and Clinical Pharmacokinetics

See Clinical Pharmacology reviews in DARRTS dated June 14, 2016 and February 26, 2018.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose is 225 mg twice daily (BID). This regimen does not include a titration for dose adjustment.

Therapeutic Individualization

Not applicable.

Outstanding Issues

From a Clinical Pharmacology perspective, the Applicant adequately addressed the potential ex vivo TU to T conversion and proposed a clinically feasible discontinuation approach. The secondary Cmax outlier endpoints were not achieved based on the results from the phase 3 trial 16-002. This continues to be an outstanding safety issue. The Applicant proposed multiple approaches to address the safety concern caused by the excursion from the current Cmax criterion but none of the proposed approaches were deemed acceptable by the review team (Refer to Section 7 for more details).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

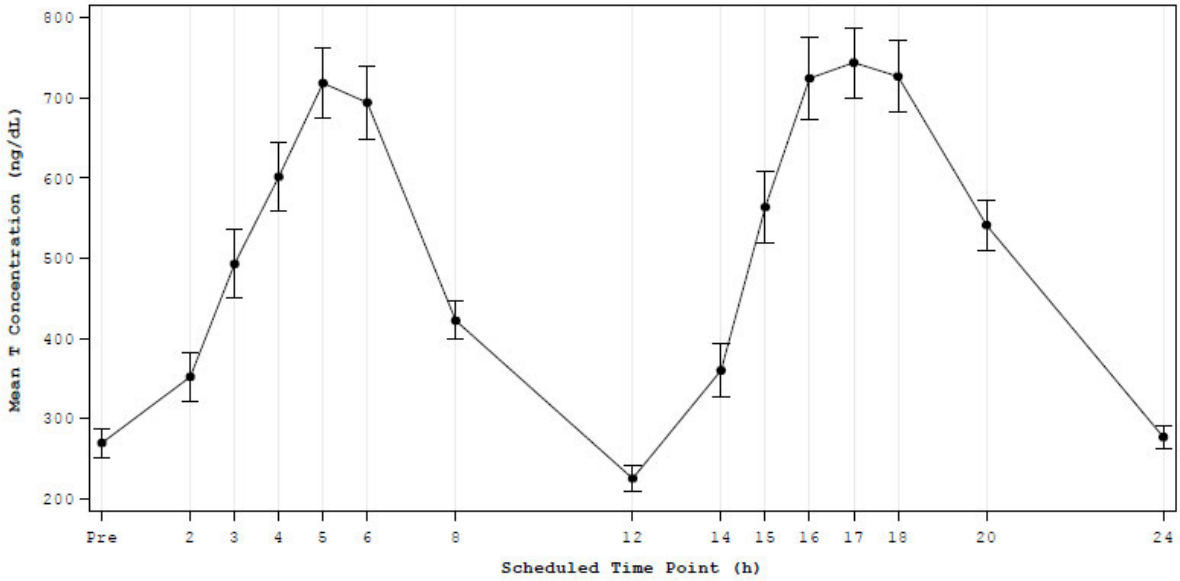
The pharmacokinetic (PK) characteristics for the proposed oral TU capsules was obtained from study 16-002, the pivotal phase 3 study, which was described and reviewed in the previous cycle (Clinical Pharmacology review in DARRTS February 26, 2018). A brief summary is provided below.

Absorption:

<u>Testosterone</u>

Median (min, max) time to peak serum T concentration (Tmax) was 5.0 (1.9, 11.9) hours after the morning dose, mean (SD) 24-hr maximum concentration (Cmax) was 1178 (484) ng/dL, and mean (SD) 24-hr average concentration (Cavg) was 476 (174) ng/dL. The mean steady state PK profile is shown in Figure 1.

Figure 1. Mean (±SD) Pharmacokinetic Profile of Serum Testosterone on Day 24 After Twice Daily Oral Administration of Testosterone Undecanoate Oral Capsules 225 mg in Hypogonadal Men (N=90, Study LPCN 1021-16-002).

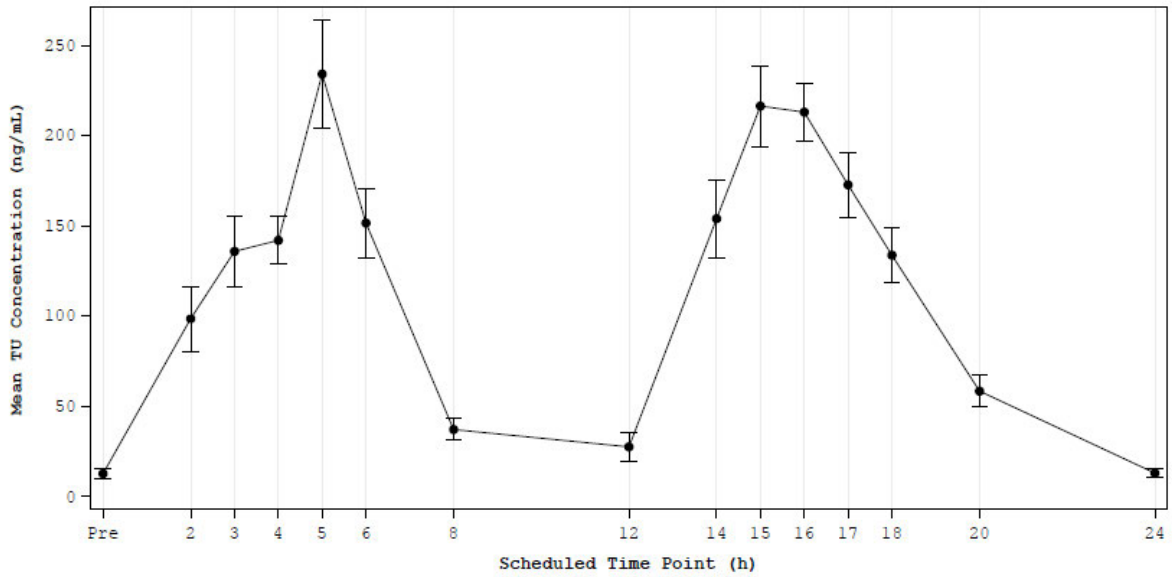


Source: LPCN 1021-16-002, Figure 14.2.2.1

Testosterone Undecanoate

Median (min, max) time to peak serum TU concentration (Tmax) was 4.9 (1.9, 11.9) hours after the morning dose, mean (SD) 24-hr Cmax was 46,974 (25,602) ng/dL, and mean (SD) 24-hr Cavg was 11,106 (5036) ng/dL.

Figure 2. Mean (±SD) Pharmacokinetic Profile of Serum Testosterone Undecanoate on Day 24 After Twice Daily Oral Administration of Testosterone Undecanoate Oral Capsules 225 mg in Hypogonadal Men (N=90)



Source: Study LPCN 1021-16-002 figure 14.2.2.2

This review focuses on the potential conversion of TU to T (study 18-003) and proposed stopping criteria.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The proposed dose and dosing regimen is 225 mg of TU ((b) (4) taken orally with food twice daily. To support the dosing regimen, phase 3 pivotal study 16-002 was conducted in hypogonadal men. PK assessment was conducted on Day 24 and no dose titration was incorporated in the study design. The study met the predefined primary efficacy endpoint of >75% of patients achieving a 24-hr Cavg between 300 and 1080 ng/dL. This study conducted in 95 patients, with twice daily administration of 225 mg oral TU resulted in 80% of patients achieving a 24-hr Cavg between 300 to 1080 ng/dL. The lower bound of the 95% confidence interval (CI) for the percentage of patients who had 24-hr Cavg between 300 to 1080 ng/dL was 72%, which is greater than the prespecified lower bound value of 65%. However, study 16-002 did not achieve the secondary Cmax endpoints. Refer to the Clinical section of this review for details.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No. The current secondary endpoint criteria for T or T ester products recommended by the Agency is that >85% of patients have a 24-hr T Cmax <1500 ng/dL, no more than 5% of patients have a 24-hr T Cmax between 1800 and 2500 ng/dL, and 0% patients have a 24-hr T Cmax exceeding 2500 ng/dL at the end of treatment (e.g., Week 12).

As noted previously, in the pivotal study 16-002 conducted in 95 hypogonadal men, the three endpoints for Cmax were not met: 74% of patients had a T Cmax of 1500 ng/dL or less (prespecified target at least 85%); 14% of patients had T Cmax between 1800 and 2500 ng/dL (prespecified target less than 5%); and 1% had a T Cmax greater than 2500 ng/dL (prespecified target 0%). The Applicant stated that in patients with high T Cmax, the duration of T concentration being above 1500 ng/dL was transient and that the percentage of patients with a Cmax between 1800 and 2500 ng/dL was closer to 5% using Cmax following a single dose interval (i.e., T Cmax 0-12 hr or T Cmax 12-24 hr), not over a 24-hr duration.

In the submissions dated May 13 2019 and September 25, 2019, the Applicant proposed varying approaches to analyze the excursion of T Cmax such as repeated interday and intraday excursions. The frequency of repeat intraday excursion were based upon the Week 3, 7, and 13 data of study 13-001 (a phase 3 study that included a titration scheme based, in part, on Cmax) and Day 24 of study 16-002 (a 24-day study with 24-hour PK assessment on only one day). Based on the existing data, we are unable to conclude that the Cmax outliers are not clinically relevant in patients who would use this drug chronically. Below we provide clinical pharmacology considerations on this issue. See the Clinical section for further details.

- The Applicant conducted an analysis of "Additive Consolidated Excursions" based upon the frequency of repeat intraday and interday Cmax excursions. This analysis requires that a subject have two T Cmax excursions within a 24-hr period; this method of counting only captures repeat occurrences of high Cmax and therefore lowers the frequency of T Cmax excursions. In addition, the frequency of repeat interday Cmax excursion was based on data from study 13-001. However, study 13-001 included a titration scheme which was based on meeting the criteria of either Cavg outside of the 300 to 1140 ng/dL range or T Cmax >1500 ng/dL; therefore, the frequency of Cmax excursions >1500 ng/dL at Week 13 (after two titration opportunities at Weeks 4 and/or 8) is expected to be lower than without titration or with titration but without the additional Cmax criterion. The Additive Consolidated Excursion analyses for a repeat Cmax excursion based upon study 13-001 is not representative of the currently proposed dosing regimen which does not include a titration scheme.
- The excursion of T Cmax per day (0 to 24 hours), not per dose, have been secondary endpoints that have been consistently applied to all approved T replacement therapy products, including those with multiple daily dosing. For example, the dosing regimen for testosterone nasal gel and the recently approved TU oral capsules are three times daily and two times daily, respectively. The T Cmax excursions for both approved products were based upon per day analyses, not per dose analyses. Therefore, the Applicant's alternative analysis approach using per dose T Cmax excursion is inconsistent with the current regulatory standards applied to T and T ester products and the Applicant has not provided adequate evidence to support the safety of the proposed product.
- In the submission dated September 25, 2019, the Applicant computed the excursion time for individual patients for those with a Cmax >1500 ng/dL in study 16-002 and study 13-001. The Applicant claims that excursion times are brief and infrequent (not occurring every day). As noted above, study 16-002 was a 24-day study with only one PK assessment day (Day 24) and study 13-001 included a two-tiered titration scheme that resulted in few Cmax outliers and only three PK assessment days. As a result of limited exposure data in study 16-002 and limited number of Cmax outliers in study 13-001, day-to-day (interday) and same day (intraday) excursions above the normal T range cannot be reliably assessed from the two studies. Using androgenic laboratory parameters (e.g., systolic blood pressure (SBP), high-density lipoprotein, hematocrit, prostate-specific antigen) at Week 52 from study 13-001, the Applicant claims that there were no clinical adverse events (AEs) from high T Cmax. However, the last set of exposure data were obtained at Week 13 and there was no PK assessment at Week 52. Therefore, the exposure-response for safety (based upon laboratory parameters) at Week 52 is unknown. The Applicant's conclusion that there are no significant differences in clinically relevant lab parameters in patients with Cmax >1500 ng/dL, compared to patients with Cmax <1500 ng/dL, is not supported by the available data.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

For many testosterone products, including one currently approved oral TU product, patients are advised to have their serum T concentrations measured at steady state after initiating therapy to ensure proper dosing. Dose adjustment recommendations for these products are based upon dosing algorithms evaluated in their respective phase 3 program(s). The Applicant did not include a dose adjustment paradigm in their pivotal phase 3 study 16-002. Although the primary efficacy endpoint was achieved, this regimen led to an unacceptable proportion of patients with T Cmax outliers and the Applicant has not provided adequate data to assure that those elevations are not clinically relevant. If the Applicant is unable to provide such data, a new trial will be needed, and that trial might use a dose titration algorithm.

Stopping Criteria

In the May 8, 2018, CR letter, the Applicant was informed that they needed to identify stopping criteria for use in clinical practice that can reproducibly and accurately identify those patients who do not achieve time-averaged T concentrations within the normal range. The stopping criteria should also avoid or minimize the inappropriate discontinuation of patients who have T concentrations within the therapeutic range.

In the current resubmission, the Applicant reanalyzed PK data from study 13-001 and study 16-002 to support stopping criteria that can reproducibly and accurately identify subjects who did not achieve normal range T concentrations during treatment, while avoiding or minimizing the inappropriate discontinuation of patients who have T concentrations within the normal range. These results are shown in Table 3 below. The percentage of patients who were correctly identified as having a T Cavg <300 ng/dL was the highest (83%) when the T concentration at 8 hours postmorning dose was used compared to other time points. All four subjects who had Cavg >1080 ng/dL were also correctly identified.

Table 3. Correlation of T Cavg and a Single T Concentration Measurement in Patients in Study LPCN 1021-16-002

Stopping Criteria Application		Patients correctly identified as having a T Cavg outside the normal range based on a single T measurement. after AM dose n (%)				
# of patients for discontinuation by Cavg criteria	Stopping Criteria	3 Hour	4 Hour	5 Hour	6 Hour	8 Hour
Cavg <300 ng/dL, N=24	T <300 ng/dL	17 (71%)	15 (63%)	10 (42%)	10 (42%)	20 (83%)
Cavg >1080 ng/dL, N=4	T >1080 ng/dL	1 (25%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Overall, N=28	Overall PAD patients	18 (64%)	19 (68%)	14 (50%)	14 (50%)	24 (86%)

Source: Study LPCN 1021-13-001 Table 14.2.11.1.1.sc

Applicant's Proposed Stopping Criteria

"To ensure an appropriate response to therapy, serum total testosterone concentrations should be checked periodically at 8 to 9 hours after the morning dose, 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 T should be discontinued."

Table 4. Serum Testosterone Pharmacokinetic Parameter and Concentrations at Day 24 Following Twice Daily Administration of Oral TU Capsule 225 mg With Food in Hypogonadal Men (FAS; N=94), Study LPCN 1021-16-002

PK Parameter	Mean (SD) (ng/dL)	Minimum	Maximum
Cavg (0-24hr)	476 (175)	171	918
C6hr	694 (441)	170	1950
C8hr	422 (230)	131	1110
C12hr	225 (150)	78	996

To support the proposed single T measurement at 8 hours after the morning dose, the Applicant applied the single assessment approach from study 16-002 with a 24-hr T Cavg of 476 ng/dL. Of the empirically available data, the mean T concentration at 8 hours post-dose is 422 ng/dL and best correlates with 24-hr Cavg, compared to the other time points (Table 4). Due to the outstanding uncertainty about the safety of the proposed product and the planned CR action, we are deferring labeling recommendations in this review cycle.

Are there clinically relevant food–drug or drug–drug interactions, and what is the appropriate management strategy?

Yes. TU is a lipophilic substance. A single dose study in hypogonadal males following administration of 225 mg oral TU (LPCN 1021-14-001) suggested that the bioavailability of TU and T was low and food significantly enhanced the absorption of TU and thus its conversion to T. Comparing high-fat food versus fasting conditions, the geometric mean ratio for TU for AUC0-12h was 12.6 and for Cmax was 11.0. Systemic exposure of T was similar when TU was administered with low-, medium-, and high-fat containing meals. For more details about the food effect study results, see the Clinical Pharmacology Review in DARRTS dated June 14, 2016.

Based on the food effect study results, oral TU capsules were administered with food without reference to a specific fat content in the pivotal phase 3 study 16-002. The Applicant's proposed labeling states to administer the product with food. Considering that data contained in the resubmission of this NDA do not support the safety of the product under the proposed dosing regimen (See Clinical Review) and there is a planned CR action, we are deferring labeling recommendations in this review cycle.

Is there evidence for ex vivo conversion of TU to T? If so, is it clinically relevant?

Yes. There is evidence for ex vivo conversion of TU to T but the conversion is not considered clinically relevant. The Applicant addressed the potential conversion of TU to T by nonspecific

esterases in the current NDA resubmission with study 18-003 entitled "Study of Blood Collection Tubes Following Single Dose Administration of Oral Testosterone Undecanoate (TU, LPCN 1021)".

This was an open-label, single dose study in twelve hypogonadal men ages 18 to 80 years with confirmed hypogonadism based upon two consecutive T blood samples obtained between 6 a.m. and 10 a.m. on two separate days. Subjects were given a single oral TU dose of 225 mg (2 x 112.5 mg capsules) TU with a meal. Blood samples were collected pre-dose and at 3 hours and 5 hours post-dose and processed in duplicates in three different tube types: plasma K2EDTA (K2E) tubes, serum separation tubes, and plasma sodium fluoride (NaF)/Na2EDTA tubes.

The objective was to assess the effect of blood collection tubes, processing time, and processing conditions on T concentrations in the presence of TU. The primary analysis was to compare the post-dose T concentrations in serum (SST) following room temperature (RT) clotting to those in plasma (K2E tubes) which was processed immediately after blood collections.

Based upon literature reports by LaChance et al., the potential for ex vivo conversion of TU to T is proportional to the TU concentration in the samples. In study 16-002 the mean (SD) average TU concentration following 24 days of twice daily administration of 225 mg oral TU capsules was 11,106 (5036) ng/dL. In the current study 18-003, mean (SD) serum TU concentration was 10,480 (17,066) ng/dL at 5 hours post-dose following a single dose of oral TU 225 mg. TU concentrations from samples collected 5 hours post-dose are similar to the average TU concentration in study 16-002 and appear to be representative of steady-state conditions of the pivotal phase 3 study. Therefore, any conclusions drawn about potential ex vivo TU to T conversion from the current study would be applicable to study 16-002 (Protocol for study 18-003 was reviewed under IND 106,476 DARRTS August 29, 2018).

Primary Analysis

T concentrations determined from plasma tubes (K2E) are considered Time Zero Controls because blood samples were processed immediately after blood collection; thereby, conversion of TU to T by nonspecific esterases in the tubes prior to sample preparation and T concentration determination is likely to be negligible. Per the phase 3 study protocols, blood samples were collected into serum tubes and were processed up to 60 min after blood draw. As shown in Table 2, based upon the anticipated maximum TU concentration (5 hours post-dose) and per-protocol processing time (up to 60 min), the mean difference in T concentration between SST and K2E tubes for the 5 hours post-dose samples with a clotting time of 60 min is 3.2%. If blood samples were processed within 120 min (60 min beyond the specified duration in the study protocol), the mean difference in T concentration between SST and K2E tubes is approximately 8%. These data indicate that there is ex vivo TU to T conversion.

The phase 3 Efficacy Endpoint is as follows:

- Percentage subjects achieving 24-hour serum T Cavg within normal range (300-1080 ng/dL): $\geq$75%, and
- 95% Confidence Interval: lower bound $\geq$65%

If we take into account the potential overestimation of either 3.2% or 8% noted above and apply it to the pivotal phase 3 study 16-002, the primary efficacy endpoint would still be met. For example, if a TU to T conversion of 8% is used to adjust the lower bound of the Cavg, then the adjusted lower bound of Cavg would be 324 ng/dL. Using this adjusted lower bound of 324 ng/dL, the proportion of patients that meet the 24-hr T Cavg would be 78%, and the lower bound of 95% CI would be 68% which still meets the predefined efficacy endpoint of exceeding 65% (Table 5).

Table 5. Effect of Ex Vivo TU to T Conversion on Primary Efficacy Endpoint: Proportion of Patients Achieving 24-hr T Cavg Within Normal Range in Phase 3 Study LPCN 1021-16-002 (SS BLOCF[a]; N=95; 225 mg BID; Day 24)

Parameter	Currently Reported	Adjusting T Threshold by 3%	Adjusting T Threshold by 8%
Lower bound of Cavg (ng/dL)	300	309	324
Number of (%) patients within predefined T Cavg	76/95 (80%)	75/95 (79%)	(74/95) 78%
95% CI (lower, upper bound)	72%, 88%	71%, 87%	68%, 86%

[a] Population: safety set, baseline last observation carried forward

In addition to above mentioned analysis of adjusting the lower bound of the T Cavg threshold, an additional analysis was conducted in which each patient's T Cavg was adjusted by 3.2% and 8% before assessing the percentage of patients falling within the normal range. When each patient's T Cavg was adjusted by 3.2% and 8%, the percentage of patients within the pre-defined T Cavg was 79% and 78%, respectively.

Clinical Meaningfulness

The mean 24-hr T concentration (24-hr Cavg) on Day 24 in study 16-002 was 476 ng/dL. The target T range was specified to be 300-1080 ng/dL. Based upon a T concentration difference of 3.2% between the SST and plasma K2E samples potentially caused by ex vivo TU to T conversion, the mean 24-hr T Cavg may be 461 ng/dL (3% less than 476 ng/dL). In the case of an extended processing time of 120 min (considered worst-case scenario), mean 24-hr T Cavg may be 438 ng/dL. Given that these values are still well within the reference range, a potential false increase in T concentration of 3.2% to 8% due to TU conversion is not likely to have a clinically meaningful impact. Note that even with adjusting for TU conversion of 3.2% to 8%, the criteria for the secondary endpoints were still not met.

OSIS Inspection of Clinical Sites

The Clinical Pharmacology review team requested the Office of Study Integrity and Surveillance (OSIS) to inspect the study conduct of the clinical sites where study 18-003 was conducted. The two sites included South Florida Medical Research (Site #207) and Granger Medical Clinic – Riverton (Site # 218), which enrolled four and eight patients, respectively. OSIS stated that there were no objectional conditions observed, no FORM FDA 483 was issued, and that the data from the audited study are reliable to support a regulatory decision (OSIS review in DARRTS October 17, 2019). There was, however, a lag time between the start of blood

collection and start of sample centrifugation at the South Florida site of up to 6 min in 4 of 12 subjects. The lag time of 5 to 6 min in 33% of the subjects would likely result in some conversion of TU to T, but it would not significantly alter our interpretation of clinical meaningfulness. The Clinical Pharmacology review team concurs with OSIS's conclusion that the data from study 18-003 are reliable.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant submitted three additional clinical studies to support the current resubmission dated May 9, 2019 (Table 6). See the second cycle Clinical Review of the NDA for the table of clinical studies submitted in the original submission and the first resubmission.

Table 6. Studies Submitted to Support the Current Resubmission

Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Bioavailability Studies					
LPCN 1021-18-002	To evaluate the influence of blood collection tubes and processing time on serum T concentrations in the presence of TU.	Open-label, single-dose study designed to evaluate the influence of blood collection tubes and processing time on serum T concentration in the presence of TU.	LPCN 1021-R 225 mg oral TU	6	Healthy males
LPCN 1021-18-003	To evaluate the influence of blood collection tubes and processing time on T concentrations after single dose administration of oral TU (LPCN 1021).	Open-label, single-dose study designed to evaluate the influence of blood collection tubes and processing time on T concentrations in the presence of TU.	LPCN 1021-R 225 mg oral TU	12	Hypogonadal males
Efficacy and Safety in Indication					
LPCN 1021-18-001	To assess average 24-hour, daytime (7:00 AM to 11:00 PM), and nighttime (11:00 PM to 7:00 AM) blood pressure (BP) and pulse rate (PR) by ambulatory blood pressure monitoring (ABPM) at baseline (Visit 3) and post-treatment (Visit 5).	Multicenter, open-label, single-arm study evaluating the change from baseline in ABPM measured BP.	LPCN 1021-R 225 mg TU two times daily	138	Hypogonadal males

7.2. Review Strategy

No new efficacy studies are submitted in the current resubmission. study 16-002, submitted in the first resubmission, provides safety, efficacy, and pharmacokinetic data for 225 mg of Tlando dosed twice per day without titration. Study 13-001, the pivotal phase 3 study submitted in the original NDA submission, provides safety data.

To evaluate whether Tlando causes a clinically meaningful increase in blood pressure, the Applicant submitted LPCN 1021-18-001 (hereafter “study 18-001”), which provides ambulatory blood pressure monitoring (ABPM) data at baseline and after treatment with Tlando.

In addition, to evaluate whether there was clinically meaningful ex vivo conversion of TU to T during sample collection and processing, the Applicant submitted study 18-002 and study LPCN 1021-18-003 (hereafter, “study 18-003”), which assessed the effect of blood collection tubes and processing time on T concentrations. These studies were reviewed to determine whether the data from previously submitted studies were reliable.

8. Statistical and Clinical and Evaluation

No new clinical efficacy data were submitted in this resubmission. For statistical evaluation of effectiveness of LPCN 1021 (TU) oral capsules as a replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, please refer to statistical reviews (DARRTS dates: June 1, 2016 and Feburary 22, 2018) of study 13-001 in electronic common technical document (eCTD) Sequence #: 0000 (submitted on August 26, 2015) and study 16-002 in eCTD Sequence #: 0026 (submitted on August 8, 2017).

For the replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, the efficacy evidence is based on achieving average serum testosterone levels (Cavg) within the normal range in at least 75% of men with the lower bound of the 95% confidence interval no less than 65%. The secondary evidence is based on at least 85% subjects with Cmax of serum testosterone levels less than 1500 ng/dL, 5% subjects with Cmax between 1800 to 2500 ng/dL, and no subject with Cmax greater than 2500 ng/dL.

As noted previously, study 13-001 did not use a titration scheme that could be translated into clinical practice. Below, we focus on study 16-002, which tested the dosing regimen proposed for marketing.

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. LPCN 1021-16-002: Testing of Fixed, Twice Daily Dosing Regimen of Oral Testosterone Undecanoate (TU) In Hypogonadal Men

See the Clinical Review for the second review cycle for the discussion of this trial.

8.1.2. Integrated Assessment of Effectiveness

The effectiveness of Tlando was reviewed during the previous review cycle (see the Clinical Review for the Second Review Cycle entered in DARRTS March 12, 2018). No new efficacy trials were submitted in the current resubmission of the NDA; therefore, study 16-002 provides the efficacy data for the dosing regimen proposed for marketing.

At the end of the previous review cycle, the clinical pharmacology review team raised concerns that testosterone concentrations in the pivotal study may have been overstated as a result of ex vivo conversion of TU to T. From a clinical perspective, this could affect the efficacy results of the completed trials, including study 16-002.

The Applicant conducted study 18-003 to quantify the degree of ex vivo conversion of TU to T. The results of this study were submitted in the current resubmission and were reviewed by the clinical pharmacology review team (see Section 6). They concluded that although there is some ex vivo TU to T conversion, the amount of conversion is modest and did not affect the results for the primary and secondary endpoints in study 16-002. The trial achieved the prespecified primary endpoint but did not achieve the prespecified secondary endpoints.

Therefore, we conclude that Tlando does not reasonably restore serum testosterone concentrations to the normal range with the proposed dosing regimen.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of Tlando was reviewed during the first and second review cycles. The primary source of safety data was study 13-001, a 52-week, randomized, active controlled trial that evaluated the 225 mg BID starting dose of Tlando with dose titration. Supportive sources of safety data were study 16-002, a 24-day trial that evaluated the 225-mg BID dose without dose titration; study 16-003, a 24-day trial that evaluated 150-mg TID without dose titration; and five phase 1 studies.

In the current submission, two new studies are also included in the safety database: study 18-001, a phase 3 ABPM trial; and study 18-003, a phase 1 single-dose trial that evaluated the influence of blood collection tubes and processing times on testosterone concentrations. The Integrated Summary of Safety (ISS) submitted in the current resubmission includes the safety data from study 18-001 and study 18-003 combined with the data from the ISS for the first resubmission (ISS2).

At the end of the second review cycle, three safety issues remained unresolved in addition to study 16-002 not meeting the secondary endpoints for T Cmax:

- There were insufficient data to determine Tlando's effect on blood pressure. This issue was based on a signal of a clinically meaningful increase in cuff systolic blood pressure in study 16-003.
- Concerns regarding Tlando's effect on serum prolactin concentrations. This issue was based on the prolactin concentration data in study 16-002. During the 24-day duration of this trial, mean prolactin concentration increased from 9.7 mg/mL at baseline to 16.7 ng/mL at the exit visit.
- There were insufficient data to definitively resolve concerns about whether Tlando poses a risk of adrenal insufficiency.

The Applicant submitted one new clinical trial, study 18-001, to address the blood pressure concern; a reanalysis of prolactin data from study 13-001 and study 16-002 to address the prolactin issue; and their rationale for why additional assessment of adrenal function may not be warranted to address the adrenal insufficiency issue. The three safety issues that were unresolved at the end of the second review cycle are discussed in detail in Section 8.2.5.

Testosterone Cmax Outliers:

The current resubmission also included the Applicant's rationale for why the pre-specified criteria for the secondary endpoints in study 16-002 should not apply to Tlando. The Applicant believes that the Cmax excursions (Cmax >1500 ng/dL) are infrequent and of short duration and, therefore, are not clinically relevant.

The Applicant submitted analyses of intraday and interday Cmax excursion repeat frequencies. The intraday analyses were conducted for study 16-002 and study 13-001. Based on the Applicant's calculations, the intraday Cmax excursion repeat frequencies are 4.3% and 2.5% for study 16-002 and study 13-001, respectively. The clinical review team does not agree with the Applicant's analyses. The analyses for both trials were not limited to subjects who were Cmax outliers (i.e., had Cmax >1500 ng/dL). Clearly, subjects who were not Cmax outliers could not have a repeat intraday excursion. Including all subjects, rather than just Cmax outliers, in the denominator of the analysis obscures the results. Additionally, the analysis for study 13-001 was done at Week 13 of the trial. At this time point, subjects had undergone two dose titrations in which one of the criteria for down titration was "Cmax >1500 ng/mL." The clinical review team conducted intraday analyses that were limited to Cmax outliers and, in the case of study 13-001, these analyses were conducted using the Week 3 data rather than Week 13. Week 3 was chosen because the Week 3 PK assessment occurred before the first dose titration and all subjects were being treated with the proposed to-be-marketed fixed dose (225 mg BID). Based on the clinical review team's analyses, the intraday Cmax excursion repeat frequencies among subjects who were Cmax outliers are 16% and 27% for study 16-002 and study 13-001, respectively.

The Applicant's interday Cmax excursion repeat frequency analysis could only be conducted for study 13-001 because study 16-002 only had one PK assessment. Based on the Applicant's calculations, the interday Cmax excursion repeat frequency is 12/287, or 4.2%. The clinical review team does not agree with the Applicant's analysis. The denominator in this analysis is inflated because it includes some subjects multiple times (e.g., if a subject was treated with the 225 mg dose at all three PK assessments, he would be counted three times in the denominator: for the Week 3/7, Week 3/13, and Week 7/13 analyses) and is not limited to Cmax outliers only. The clinical review team conducted an interday analysis that included subjects in the safety set, with two or more PK assessments at the 225-mg BID dose and at least one Cmax assessment >1500 ng/dL (i.e., were Cmax outliers). Based on the clinical review team's analysis, the interday Cmax excursion repeat frequency is 11/54=20% among subjects who were Cmax outliers. When considering the significance of this result, it should be noted that study 13-001 was a titration trial with a protocol-specified down titration (at Weeks 4 and 8) if the subject had Cmax >1500 ng/dL. Additionally, the protocol also specified that subjects with Cmax >1500 ng/dL at the 150-mg dose should be discontinued from the trial.

Based on the clinical review team analyses, it appears that 16% to 27% of subjects who were Cmax outliers in study 13-001 or study 16-002 had repeat occurrences (intraday or interday) of their Cmax excursion. These results are not consistent with the Applicant's claim that these excursions are sporadic. In addition, it is important to note that there were few PK assessment days — one in the 24-day Study LPCN 1021-13-002 and three in the 52-week study 13-001. Therefore, the frequency of outliers on non-PK assessment days is unknown.

The Applicant also provided data that they believe support the short duration of excursion times. The total excursion time (in 24 hours) ranged from 0.22 to 4.54 hours in study 16-002 and 0.14 to 9.37 hours for subjects on the 225 mg BID dose in study 13-001. The clinical

implications of these findings for a drug that will be administered chronically are not clear at this time.

To try and show that the Cmax outliers are not clinically relevant, the Applicant conducted a safety analysis comparing the 39 subjects who were Cmax outliers at Week 13 of study 13-001 to the 118 non-Cmax outliers at Week 13 with regard to subsequent changes from Week 13 to Week 52 in hematocrit, prostate specific antigen and other events of interest. The Applicant notes that there were no meaningful differences between these groups. However, this study tested doses other than 225 mg BID and used Cmax as part of the criteria to determine dose titration prior to Week 13. In addition, the extent of subsequent Cmax outliers in the two groups between Weeks 13 and 52 is unclear. Therefore, we agree with the Clinical Pharmacology team that this additional analysis is not adequate to provide assurance that Cmax outliers are not clinically relevant.

Lastly, the modest extent of ex vivo TU to T conversion does not meaningfully change the T Cmax outlier concentrations. Thus, the conclusion from our review of the first resubmission of the NDA remains unchanged: study 16-002 did not meet its prespecified secondary endpoints and consequently did not provide evidence that a dosing regimen of 225 mg BID without dose titration avoids unacceptably high serum testosterone concentrations.

8.2.2. Review of the Safety Database

Overall Exposure

The Integrated Summary of Safety for the current resubmission (ISS3) includes Tlando safety data from study 18-001 and study 18-003 combined with the data from the ISS for the first resubmission (ISS2). Of the 654 hypogonadal men in the safety population, 121 (19%) were from the new clinical trials study 18-001 and study 18-003 (109 from study 18-001 and 12 from study 18-003). In addition, there are eight rollover subjects who were not treated in previous studies but received treatment in study 18-001 and are counted in the safety population of ISS3.

For the 654 hypogonadal men who received Tlando in the supportive and pivotal safety studies included in ISS3 (single and multiple dose periods), Tlando was received for a median 51 days (range of 1 to 382 days) with 39% of the subjects receiving study drug for ≤4 weeks and 20% of subjects receiving study drug for more than 39 weeks. Table 7 summarizes the exposure for the studies included in ISS3.

Table 7. Summary of Extent of Exposure for Supportive and Pivotal Safety Studies (Single and Multiple Dose Periods) — Safety Population

Assessment	ISS2 Tlando N=525	ISS3 Tlando N=654	ISS1 Andriol 80 mg N=34	ISS1 Androgel 1.62% N=104	ISS1 Placebo N=18
Extent of Exposure (days)					
N	525	654	34	104	18
Mean (SD)	122 (148)[a]	117 (134)	3 (3)	291 (123)	19 (7)
Median	31[a]	51	1	364	15
Q1, Q3	15, 274	15, 134	1, 8	190, 366	15, 29
Min, Max	1, 382	1, 382	1, 8	1, 382	11, 29

Assessment	ISS2 Tlando N=525	ISS3 Tlando N=654	ISS1 Andriol 80 mg N=34	ISS1 Androgel 1.62% N=104	ISS1 Placebo N=18
Interval (weeks), n (%)					
[0,4]	238 (45)[a]	252 (39)	34 (100)	7 (7)	12 (67)
(4,13]	109 (21)[a]	114 (17)	0	8 (8)	6 (33)
(13,26]	34 (7)[a]	144 (22)	0	9 (9)	0
(26,39]	12 (2)[a]	12 (2)	0	7 (7)	0
>39	132 (25)	132 (20)	0	73 (70)	0
Total Dose (mg)					
N	520	649	3	101	18
Mean (SD)	49592 (61255)[a]	48986 (55290)	339 (407)	18016 (8687)	7850 (5551)
Median	14981[a]	22913	80	18760	6525
Q1, Q3	6525, 98550[a]	6525, 63000	80, 960	12458, 23571	4350, 12825
Min, Max	0, 217050[a]	0, 217050	80, 960	875, 39317	1500, 17100

[a]The values have changed from the original submission of ISS2. The mean (SD) value in ISS2 column changed for extent of exposure (days) from 117 (148) to 122 (148) and median changed from 29 to 31. The interval in weeks (0 to 4 weeks) value in ISS2 changed from 249 (47) to 238 (45). 4 to 13 weeks from 119 (23) to 109 (21). 13 to 26 weeks from 14 (3) to 34 (7). 26 to 39 weeks from 11 (2) to 12 (2). Total dose values also changed for ISS2 column. Reason: there are 3 subjects from 16-002, 8 subjects from 16-003 and 10 subjects from 16-002/003 who rolled over to 18-001 study which changed the ISS2 values for extent of exposure (days), interval (weeks) and total dose. Among the above-mentioned subjects, there are eight subjects who are screen failures in 16-002 and 16-003 and rolled over to 18-001 study where they exposed to study drug. For example, subject LPCN 1021-16-002-(b) (6) in 16-002 study has extent of exposure (days)=24, interval (weeks)=0 to 4 weeks, total dose=10575 and the subject rolled over to 18-001 study and has extent of exposure (days)=151, interval (weeks)=13 to 26 weeks, total dose=64575. The subject LPCN 1021-16-002-(b) (6) is screen failure in 16-002 study where the subject is not exposed to study drug, rolled over to 18-001 study and exposed to study drug.
[ ] = inclusive; ( ) = exclusive
ISS1: Includes only data from studies included in the original ISS.
ISS2: Includes data from studies LPCN 1021-16-002 and LPCN 1021-16-003 integrated with studies included in the original ISS.
ISS3: Includes data from new studies LPCN 1021-18-001 and LPCN 1021-18-003 integrated with studies in ISS2.
Source: NDA 208088 (seq 0050), Module 2.7.4, Table 8, p. 45–46.

Adequacy of the safety database:

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 study 13-001. The demographics and baseline characteristics are similar between the original ISS and the updated ISS and are representative of the patient population likely to use Tlando. However, it is noted that only two studies, study 16-002 and study 18-001, evaluated the 225 mg BID with a fixed dosing regimen. The maximum duration of treatment with this dosing regimen was approximately 110 days; however, there are additional long-term supportive safety data from subjects who were titrated in study 13-001 to doses above 225 mg BID.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

See Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

Categorization of Adverse Events

Different Medical Dictionary for Regulatory Activities (MedDRA) versions were used in the coding of AE terms in the clinical trials. Study 13-001 (pivotal safety study) study events were coded using MedDRA 16.1, LPCN 1021-14-001, LPCN 1021-16-002, study 16-003, study 18-001, and study 18-003 study events were coded using MedDRA 17.1 whereas earlier clinical studies

used even earlier versions. In the ISS, the integrated AEs from all supportive and pivotal safety studies were up-coded to MedDRA 17.1. Therefore, for pivotal safety data presented alone, adverse events are reported using MedDRA 16.1, and where supportive and pivotal safety data are integrated, adverse events are reported using MedDRA 17.1.

Routine Clinical Tests

Routine clinical testing of subjects was conducted throughout the phase 3 studies and appears to be adequate.

8.2.4. Safety Results

Deaths

No deaths occurred in any study of Tlando.

Serious Adverse Events

LPCN 1021-13-001, LPCN 1021-16-002, LPCN 1021-16-003 and Phase 1 Studies[2]

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

LPCN 1021-18-001 (ABPM study)

Two subjects experienced a serious adverse event (SAE) in study 18-001.

Subject (b) (6) a 42-year-old white male, experienced the SAE of schizoaffective disorder bipolar type on Study Day 23. His medical history included bipolar disorder (since (b) (6)), schizoaffective disorders (since (b) (6)), and depression (since (b) (6)), and his concomitant medications included citalopram, valproate semisodium, and sildenafil. The subject was admitted to the hospital and was noted to be verbally aggressive, uncooperative, resistant, guarded, and exhibiting poor hygiene and eye contact. Upon admission, the subject tested positive for cocaine (reported as a nonserious adverse event) on a urine drug screen. While hospitalized, the study medication was interrupted. Treatment of the event included aripiprazole, citalopram, and divalproex sodium.

On Study Day 27, the subject was stable for hospital discharge and the event was considered resolved; the subject was discharged from the hospital on psychotropic medications as designated by the inpatient psychiatric team. That same date, the study medication was restarted.

On Study Day 41, the subject was withdrawn from the study as a result of testing positive for cocaine (reason for termination from study was classified as “lost to follow-up”).

[2] LPCN 1021-18-003 was a phase 1, one-dose study that enrolled 12 subjects. No adverse events were reported during the study. Therefore, the summary of adverse events reported in phase 1 studies in the current resubmission is the same as those reported in the first resubmission.

Based on the subject's history of psychiatric disorders and use of cocaine prior to onset, it does not appear that this event was related to the study drug.

Subject (b) (6) a 65-year-old white male with a medical history that included arthritis (since (b) (6)), experienced the SAE of arthritis on Study Day 80. The subject was admitted to the hospital for scheduled right hip replacement as a result of continued right hip arthritis with associated right lower extremity pain.

On Study Day 81, the event was considered resolved and the subject was discharged from the hospital in stable condition. The study drug was interrupted because of the event and was restarted on Study Day 82. The subject continued in the study.

Based on the subject's history of arthritis, it does not appear that the event was related to the study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

LPCN 1021-13-001, LPCN 1021-16-002, LPCN 1021-16-003 and Phase 1 Studies[3]

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

LPCN 1021-18-001

Three (2.1%) subjects experienced a treatment emergent adverse event (TEAE) that led to study drug discontinuation.

Subject (b) (6) experienced an AE of dizziness on Study Day 2. The event was considered resolved on Study Day 8. The subject discontinued from the study because of the event of dizziness and the investigator assessed the AE as related to study drug.

Subject (b) (6) a 63-year-old white male with a history that included hypertension (since (b) (6)), experienced an AE of hypertension on Study Day 109. On Study Day 114, the event was considered resolved. The subject discontinued from the study because of the event, which the investigator assessed as related to the study drug.

Subject (b) (6) a 59-year-old Black male with a history that included obesity (since (b) (6)), experienced an AE of weight increased on Study Day 28. On Study Day 52, the event of weight increased was considered resolved. On Study Day 42, the subject experienced an AE of insomnia. On Study Day 63, the event of insomnia was considered resolved. The subject discontinued from the study because of the events of weight increase and insomnia. The investigator assessed the AEs of weight increase and insomnia as not related to the study drug.

Two additional subjects had TEAEs that coincided with, but were not the cause of, study termination. Subject (b) (6) experienced the TEAE of controlled substance cocaine use; the reason for discontinuation determined by the investigator was "lost to follow-up" (this subject

[3] LPCN 1021-18-003 was a phase 1, one-dose study that enrolled 12 subjects. No adverse events were reported during the study. Therefore, the summary of adverse events reported in phase 1 studies in the current resubmission is the same as those reported in the first resubmission.

is discussed under Serious Adverse Events). Subject (b) (6) experienced a TEAE of "hypertension" at the time of study completion. Due to the TEAE, the investigator withdrew the study drug but marked the subject's status as study completed.

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 Applicant determined the adverse events of special interest for Tlando based on known pharmacologic effects and adverse events for approved testosterone replacement therapies. The adverse events of special interest include events related to the cardiovascular system, hepatic metabolism of steroids, effects on hematocrit, PSA, and other know androgenic effects. Treatment emergent adverse events of special interest for the integrated phase 1 and phase 3 studies are summarized in Table 8. Studies LPCN 1021-18-001, LPCN 1021-18-003, 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 are included in the integrated analysis.

Table 8. Treatment-Emergent Adverse Events of Special Interest for Testosterone Replacement Therapy — Safety Population

Applicant-Defined Groups MedDRA Preferred Term[a]	ISS2 Tlando N=525	ISS3 Tlando N=654	Original ISS Andriol 80 mg N=34	Original ISS AndroGel 1.62% N=104	Original ISS Placebo N=18
Cardiac and Cerebrovascular Disorders					
Atrial Fibrillation	1 (0.2)	1 (0.2)	0	2 (1.9)	0
Blood Pressure Increased	3 (0.6)	3 (0.5)	0	2 (1.9)	0
Blood Creatine Phosphokinase Increased	1 (0.2)	2 (0.3)	0	0	0
Bradycardia	0	0	0	1 (1.0)	0
Bundle Branch Block Bilateral	0	0	0	1 (1.0)	0
Cardiac Flutter	1 (0.2)	1 (0.2)	0	0	0
Electrocardiogram Abnormal	1 (0.2)	1 (0.2)	0	1 (1.0)	0
Electrocardiogram Change	1 (0.2)	1 (0.2)	0	0	0
Electrocardiogram T Wave Inversion	1 (0.2)	1 (0.2)	0	0	0
Enzyme Level Increased[b]	3 (0.6)	3 (0.5)	0	0	0
Heart Rate Increased	2 (0.4)	2 (0.3)	1 (2.9)	0	0
Hypertension	7 (1.3)	13 (2.0)	0	5 (4.8)	0
Left Atrial Dilatation	0	0	0	1 (1.0)	0
Mitral Valve Incompetence	1 (0.2)	1 (0.2)	0	0	0
Palpitations	2 (0.4)	2 (0.3)	1 (2.9)	0	0
Sinus Tachycardia	0	0	0	1 (1.0)	0
Tachycardia	2 (0.4)	2 (0.3)	0	1 (1.0)	0
Tricuspid Valve Incompetence	1 (0.2)	1 (0.2)	0	0	0
Ventricular Extrasystoles	0	0	0	1 (1.0)	0
Ventricular Hypertrophy	1 (0.2)	1 (0.2)	0	0	0

Applicant-Defined Groups MedDRA Preferred Term[a]	ISS2 Tlando N=525	ISS3 Tlando N=654	Original ISS Andriol 80 mg N=34	Original ISS AndroGel 1.62% N=104	Original ISS Placebo N=18
Blood and Lymphatic System					
Anaemia	3 (0.6)	3 (0.5)	0	0	0
Blood Cholesterol Increased	0	0	1 (2.9)	0	0
Blood Triglycerides Increased	3 (0.6)	4 (0.6)	0	2 (1.9)	0
Haematocrit Increased	4 (0.8)	8 (1.2)	0	0	0
Haemoglobin Increased	1 (0.2)	1 (0.2)	0	0	0
High Density Lipoprotein Decreased	1 (0.2)	1 (0.2)	0	0	0
Hypercholesterolaemia	2 (0.4)	2 (0.3)	0	0	0
Hyperlipidaemia	1 (0.2)	2 (0.3)	0	2 (1.9)	0
Lipids Increased	2 (0.4)	2 (0.3)	0	0	0
Polycythaemia	1 (0.2)	3 (0.5)	0	1 (1.0)	0
Red Blood Cell Count Increased	1 (0.2)	1 (0.2)	0	0	0
Hepatic System					
Alanine Aminotransferase Increased	1 (0.2)	1 (0.2)	0	0	0
Blood Bilirubin Increased	0	0	0	1 (1.0)	0
Hepatic Enzyme Increased	0	0	0	1 (1.0)	0
Renal and Reproductive System					
Dysuria	0	0	0	1 (1.0)	0
Enuresis	0	0	0	1 (1.0)	0
Nocturia	0	0	0	2 (1.9)	0
Prostate Cancer	0	0	0	1 (1.0)	0
Prostatic Specific Antigen Increased	5 (1.0)	5 (0.8)	0	0	0
Prostatitis	1 (0.2)	1 (0.2)	0	1 (1.0)	0
Prostatomegaly	2 (0.4)	2 (0.3)	0	0	0
Testicular Atrophy	0	0	0	1 (1.0)	0
Testicular Disorder	0	0	0	1 (1.0)	0
Urinary Retention	1 (0.2)	1 (0.2)	0	0	0
Nervous System					
Dizziness	4 (0.8)	6 (0.9)	0	2 (1.9)	1 (5.6)
Headache	21 (4.0)	22 (3.4)	1 (2.9)	5 (4.8)	2 (11.1)
Sleep Apnoea Syndrome	3 (0.6)	3 (0.5)	0	1 (1.0)	0
Tension Headache	1 (0.2)	1 (0.2)	0	0	0
Transient Ischaemic Attack	1 (0.2)	1 (0.2)	0	0	0
Psychiatric System					
Abnormal Dreams	1 (0.2)	1 (0.2)	0	0	0
Agitation	1 (0.2)	1 (0.2)	0	0	0
Anger	0	0	0	1 (1.0)	0
Anxiety	3 (0.6)	3 (0.5)	1 (2.9)	1 (1.0)	0
Depression	0	0	0	1 (1.0)	0
Insomnia	5 (1.0)	6 (0.9)	0	1 (1.0)	0
Irritability	2 (0.4)	2 (0.3)	0	2 (1.9)	0
Libido Decreased	3 (0.6)	3 (0.5)	0	0	0
Major Depression	0	0	0	1 (1.0)	0
Middle Insomnia	0	0	0	1 (1.0)	0
Mood Altered	1 (0.2)	1 (0.2)	0	0	0
Panic Attack	1 (0.2)	1 (0.2)	0	0	0
Restlessness	1 (0.2)	1 (0.2)	0	0	0

Applicant-Defined Groups MedDRA Preferred Term[a]	ISS2 Tlando N=525	ISS3 Tlando N=654	Original ISS Andriol 80 mg N=34	Original ISS AndroGel 1.62% N=104	Original ISS Placebo N=18
Other Potential Androgen Effects					
Acne	7 (1.3)	7 (1.1)	0	3 (2.9)	0
Alopecia	0	0	0	1 (1.0)	0
Gynaecomastia	0	2 (0.3)	0	1 (1.0)	0
Hirsutism	1 (0.2)	1 (0.2)	0	0	0
Oedema	1 (0.2)	1 (0.2)	0	0	0
Oedema Peripheral	5 (1.0)	6 (0.9)	0	1 (1.0)	0

Note: Studies included: LPCN 1021-18-001, LPCN 1021-18-003, 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.
Note: No AEs were reported in LPCN 1021-18-003.
Note: ISS2 includes data from studies LPCN 1021-16-002 and LPCN 1021-16-003 integrated with studies included in the original ISS.
Note: ISS3 includes data from new studies LPCN 1021-18-001 and LPCN 1021-18-003 integrated with studies in ISS2.
[a]MedDRA version 17.1.
[b]Lipoprotein-associated phospholipase (LAP-A2).
Source: NDA 208088 (seq 0050), Module 2.7.4, Table 34, p. 85–87.

Except for the events of hypertension and headache, all TEAEs of special interest occurred in less than 2.0% of Tlando subjects. The incidence of headache for Tlando-treated subjects was less than that of AndroGel 1.62% subjects. The effect of Tlando on blood pressure is discussed in Section 8.2.5.1.

Treatment Emergent Adverse Events and Adverse Reactions

An adverse event was considered treatment emergent if the event began or worsened in severity after initiation of the study drug. Subjects reporting more than one adverse event for a given MedDRA preferred term were counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a system organ class (SOC) were counted only once for that SOC.

As a result of differences in the length of the studies, dose, and dosing regimen, the results for each of the phase 3 studies are presented separately. Integrated results for the phase 1 studies are also presented.

LPCN 1021-13-001, LPCN 1021-16-002, LPCN 1021-16-003 and Phase 1 Studies[4]

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

[4] LPCN 1021-18-003 was a phase 1, one-dose study that enrolled 12 subjects. No adverse events were reported during the study. Therefore, the summary of adverse events reported in phase 1 studies in the current resubmission is the same as those reported in the first resubmission.

LPCN 1021-18-001

Table 9. Common (>2%) Treatment Emergent Adverse Events (TEAE) Occurring During LPCN 1021-18-001 (Safety Set)

	Tlando (225 mg BID) N=138	
System Organ Class Preferred Term	**Subjects n (%)**	**Events n**
Any TEAE	33 (23.9)	57
Infections and infestations		
Upper respiratory tract infection	5 (3.6)	5
Vascular disorders		
Hypertension	6 (4.3)	7
Investigations		
Haematocrit increased	4 (2.9)	4

Source: Reviewer analysis of NDA 208088 (seq 0050), 5.3.5.2, Table 14.3.1.2, p. 372–375 and dataset ADAE.

Laboratory Findings

LPCN 1021-13-001, LPCN 1021-16-002, and LPCN 1021-16-003

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

LPCN 1021-18-001

During study 18-001, samples for the clinical laboratory tests were collected at screening and the end of study (Visit 6).

Hematology

Mean (SD) increase from baseline to Visit 6 for hematocrit was 3.2% (3.6%). Hematocrit values at study exit ranged from 34% to 59%. Six (4.6%) subjects with hematocrit values in the normal range (35% to 54%)[5] at baseline had values >54% at Visit 6. The highest hematocrit value at exit was 59%.

Mean (SD) increase from baseline to Visit 6 for hemoglobin was 0.9 (1.05) g/dL. Thirty (23.1%) subjects with hemoglobin values in the normal range (11.5 g/dL to 16.5 g/dL)[6] at baseline had values >16.5 g/dL at Visit 6. Table 10 summarizes the changes in hematocrit and hemoglobin from baseline.

Table 10. Hematocrit and Hemoglobin: Mean Baseline and Mean Change From Baseline LPCN 1021-18-001 — Safety Set (N=138)

Visit	N	HCT Value (%) Mean (SD)	HCT Value Change from Baseline (%) Mean (SD)	Hgb Value (g/dL) Mean (SD)	Hgb Value Change from Baseline (g/dL) Mean (SD)
Baseline	138	44 (3)	--	14.6 (1.1)	--
Exit	129	47 (5)	3.2 (3.6)	15.4 (1.5)	0.9 (1.05)

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

[5] Normal value based on protocol defined exclusion criterion for hematocrit.
[6] Normal value based on protocol defined exclusion criterion for hemoglobin.

Source: NDA 208088 (seq 0050), 5.3.5.2, CSR LPCN 1021-18-001 Tables 53 and 54, p. 139–140.

The mean changes from baseline for both hematocrit and hemoglobin in study 18-001 are greater than the changes seen in study 16-002, the 24-day, fixed dose (225 mg BID) study. During study 16-002, hematocrit increased by 0.9 and hemoglobin increased by 0.02 g/dL after 24 days of treatment.

If the results from study 18-001 are compared to those of study 13-001, the 52-week study in which doses were titrated based on Cavg and Cmax, the mean change from baseline for hematocrit and hemoglobin after 110 days of treatment with the fixed dose in study 18-001 is similar to what it was after 365 days of treatment with the titrated dose in study 13-001.

Due to limitations of these data and cross study comparisons, the meaning of this finding is not completely clear. However, it raises concerns regarding the effect of the fixed dose (225 mg BID) on hematocrit and hemoglobin, and it is unclear whether these increases could be related to Cmax outlier excursions.

Clinical Chemistry

Change from baseline to study exit for high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol are summarized in Table 11, Table 12, Table 13, and Table 14. The reduction in HDL cholesterol is a well-known side effect of testosterone therapy. The small increase in LDL cholesterol is not likely to be clinically meaningful.

Table 11. Mean Baseline and Change From Baseline Values of HDL in LPCN 1021-18-001, Safety Set (N=138)

Visit	N	HDL Value (mg/dL) Mean (SD)	Change from Baseline (mg/dL) Mean (SD)
Baseline	138	42 (12)	--
Exit	130	36 (11)	-7 (8)

Key: HDL = high-density lipoprotein; SD = standard deviation.
Source: NDA 208088 (seq 0050), 5.3.5.2, CSR LPCN 1021-18-001 Table 56, p. 141.

Table 12. Mean Baseline and Change From Baseline Values of LDL in LPCN 1021-18-001, Safety Set (N=138)

Visit	N	LDL Value (mg/dL) Mean (SD)	Change from Baseline (mg/dL) Mean (SD)
Baseline	128	113 (34)	--
Exit	122/118[a]	118 (36)	4 (27)

Key: LDL = low-density lipoprotein; SD = standard deviation.
Source: NDA 208088 (seq 0050), 5.3.5.2, CSR LPCN 1021-18-001 Table 57, p. 141–142.
[a]122 subjects with an LDL value at exit, 118 of whom had a baseline value for calculating change from baseline.

Table 13. Mean Baseline and Change From Baseline Values of Triglycerides in LPCN 1021-18-001, Safety Set (N=138)

Visit	N	Triglycerides Value (mg/dL) Mean (SD)	Change from Baseline (mg/dL) Mean (SD)
Baseline	138	191 (122)	--
Exit	130	189 (179)	0 (133)

Key: SD = standard deviation.
Source: NDA 208088 (seq 0050), 5.3.5.2, CSR LPCN 1021-18-001 Table 58, p. 142.

Table 14. Mean Baseline and Change From Baseline Values of Total Cholesterol in LPCN 1021-18-001, Safety Set (N=138)

Visit	N	Total Cholesterol Value (mg/dL) Mean (SD)	Change from Baseline (mg/dL) Mean (SD)
Baseline	138	193 (45)	--
Exit	130	187 (42)	-6 (33)

Key: SD = standard deviation.
Source: NDA 208088 (seq 0050), 5.3.5.2, CSR LPCN 1021-18-001 Table 59, p. 143.

Vital Signs

LPCN 1021-13-001, LPCN 1021-16-002, and LPCN 1021-16-003

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

LPCN 1021-18-001

Study 18-001 was an open-label, multicenter, single arm study. The primary objective of the study was to assess average 24-hour, daytime (7 a.m. to 11 p.m.), and nighttime (11 p.m. to 7 a.m.) BP and pulse rate (PR) by ambulatory blood pressure monitoring. For a complete discussion of BP and PR during the study, refer to the Division of Cardiovascular and Renal Products Interdisciplinary Review Team (IRT) for ABPM consultative review in DARRTS (July 16, 2019).

Electrocardiograms

LPCN 1021-13-001, LPCN 1021-16-002, and LPCN 1021-16-003

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

LPCN 1021-18-001

Electrocardiograms were performed only at screening.

QT

LPCN 1021-13-001, LPCN 1021-16-002, and LPCN 1021-16-003

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

LPCN 1021-18-001

Subjects with history of long QT syndrome were excluded from the study.

Immunogenicity

No studies of immunogenicity were done to support this application.

8.2.5. Analysis of Submission-Specific Safety Issues

At the end of the second review cycle, in addition to Cmax outliers, three safety issues remained unresolved: (1) insufficient data to determine Tlando's effect on blood pressure; (2)

concerns regarding Tlando's effect on serum prolactin concentrations; and (3) insufficient data to definitively resolve concerns about whether Tlando poses a risk of adrenal insufficiency. Each of these submission-specific safety issues is discussed in detail below.

8.2.5.1. Blood Pressure Increases

During the second review cycle of the NDA, the clinical review team became concerned that Tlando might cause clinically meaningful increases in blood pressure. This concern was based on a signal of a clinically meaningful increase in cuff systolic blood pressure in study 16-003, the 24-day study that tested a fixed 150 mg TID dose of Tlando. Cuff blood pressure data from previously submitted Tlando studies were not sufficient to resolve this concern. In addition, an increase in blood pressure was detected on ABPM with another oral TU product. Therefore, an ABPM trial to definitively assess whether Tlando increases blood pressure was required.

In the current resubmission, the Applicant submitted the results of study 18-001, an ABPM trial to assess whether Tlando increases BP in hypogonadal men. Please refer to section 8.2.8 for additional details regarding the design of this study.

The results of study 18-001 were reviewed in consultation with the Division of Cardiovascular and Renal Products Interdisciplinary Review Team for ambulatory blood pressure monitoring. The IRT concluded that the results of the trial demonstrated an increase in average BP and heart rate in hypogonadal men treated with Tlando and that the mean effects were generally consistent with the results observed with another oral TU product suggesting a class blood pressure effect.

The IRT found that Tlando increased systolic blood pressure (SBP) by an average of 4.3 mmHg based on ABPM and by an average of 4.8 mmHg based on office cuff measurements. The increase in blood pressure was relatively constant throughout the day. The drug also increased heart rate by an average of 2 bpm. In addition, an exploratory subgroup analysis suggested that the effect of BP, particularly SBP, was larger in subjects with higher baseline cardiovascular risk, e.g., subjects with multiple cardiovascular risk factors at baseline. The findings of the IRT review are summarized in Table 15 and Table 16. For additional details, see the IRT's consultative review in DARRTS (July 16, 2019).

The IRT did not recommend conducting any additional post-approval studies regarding Tlando's effect on blood pressure. The results of study 18-001 will be included in the product's labeling (see section 11.1) if the drug is approved.

Table 15. Mean and 95% CI for Change from Baseline in Systolic BP, Diastolic BP and HR on Visit 5 (FDA Analysis, Modified 24-h Validity Set)

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

[a]ABPM analysis was conducted using modified 24-h validity set (n=123)
[b]Vital sign measurements were recorded in triplicate 2 hours prior to start of the ABPM (safety analysis set, n=138)
Source: IRT Consultative Review: NDA 208088, entered in DARRTS July 16, 2019, Table 1, p.2.

Table 16. Subgroup Analysis Based on Cardiovascular Risk Level at Baseline for 24-h Average SBP (FDA Analysis, Modified 24-h Validity Set)

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

[a]Risk level was assigned using risk scores derived based on Framingham Heart Study. Low risk: risk point <9; Moderate risk: risk point 9-14; High risk: risk point ≥15.
Source: IRT Consultative Review: NDA 208088, entered in DARRTS July 16, 2019, Table 2, p.2.

8.2.5.2. Increased Serum Prolactin

The clinical review team noted a signal for an increase in serum prolactin concentrations in subjects treated with Tlando during study 16-002, the 24-day, single arm trial that evaluated a fixed 225 mg BID dose of Tlando. In this trial, serum prolactin concentration was assessed at screening (baseline) and at the end of the trial. The mean prolactin concentration increased from 9.7 mg/mL at baseline to 16.7 ng/mL at the exit visit. The mean change from baseline was 7.0 ng/mL. At baseline, no subject had a serum prolactin concentration greater than two times the upper limit of normal (ULN); at exit, three subjects had a value that was greater than two times the ULN and one subject had a value that was greater than three times the ULN. No subject had a value that was greater than four times the ULN at exit. Analysis of shift data showed that 44 (47%) subjects shifted from normal at baseline to high at exit. Serum prolactin data for study 16-002 are summarized in Table 17 and Table 18.

Table 17. Observed, Change from Baseline, and Outlier Analysis Serum Prolactin Concentration LPCN 1021-16-002 (Safety Set)

Parameter	**Baseline n=95**	**Exit (n=93)**	**Change from Baseline (n=93)**
Mean (SD) ng/mL	9.7 (3.6)	16.7 (7.6)	7.0 (6.7)
Median ng/mL	9.2	15.8	5.5
Minimum ng/mL	1.0	2.9	-5.1
Maximum ng/mL	17.5	48.7	37.7
>2 × ULN n (%)	0	3 (3.2)	-
>3 × ULN n (%)	0	1 (1.1)	-
>4 × ULN n (%)	0	0	-
>5 × ULN n (%)	0	0	-

Normal Reference Range: 4.042 ng/mL-15.228 ng/mL
Source: Reviewer created table from Tables 14.3.4.2 and 14.3.4.8; CSR LPCN 1021-16-002 (Section 14).

Table 18. Summary of Prolactin Shift Data — LPCN 1021-16-002 (Safety Set)

		Baseline		
Visit	**Risk Level**	**Low n (%)**	**Normal n (%)**	**High n (%)**
Exit n=93	Low	2 (2.2%)	0	0
	Normal	1 (1.1%)	38 (40.9%)	1 (1.1%)
	High	0	44 (47.3%)	7 (7.5%)

Normal Reference Range: 4.042 ng/mL-15.228 ng/mL
Source: Table 14.3.4.7; CSR LPCN 1021-16-002 (Section 14).

To further explore the signal for increased serum prolactin concentration, the serum prolactin data from study 13-001 was also analyzed. This trial was a randomized, 52-week, active control (AndroGel 1.62%) trial that evaluated the 225 BID dose with dose titration. A total of 315 hypogonadal males were randomized in the trial: 210 to the Tlando treatment group and 105 to the AndroGel 1.62% treatment group. Serum prolactin concentration was assessed at screening (baseline), and Weeks 7, 13, 26, 39, and 52. In the Tlando treatment group, the mean serum prolactin concentration increased from 6.5 ng/mL at baseline to 7.4 ng/mL at Week 52. The mean change from baseline at Week 52 was 1.5 ng/mL. At baseline, one subject had a serum prolactin concentration greater than two times the upper limit of normal; at Week 52, no subjects had a value greater than two times the ULN. Analysis of shift data showed that two (1.5%) subjects shifted from normal at baseline to high at Week 52.

Results for the AndroGel 1.62% treatment group were similar to those for the Tlando group: mean serum prolactin concentration increased from 6.3 to 7.4 ng/mL over the 52 weeks of the study with a mean change from baseline of 1.1 ng/mL. At Week 52, no subjects had a serum prolactin value greater than two times the ULN, and one (1.4%) subject shifted from normal at baseline to high at Week 52. Serum prolactin data for study 13-001 are summarized in Table 19 and Table 20.

The reason for the increased serum prolactin levels seen in study 16-002 is not entirely clear. Since prolactin was not assessed at the Week 3 visit in study 13-001, comparisons between the two studies at that timepoint are not possible. Based on the 52-week data from study 13-001, it appears that 1-year of use does not meaningfully increase serum prolactin.

However, it should be noted that study 13-001 evaluated the 225 mg BID dose with dose titration, while study 16-002 evaluated the same dose without titration. Based on the finding for hematocrit and hemoglobin in study 18-001, it is not clear that the long-term safety data for the titrated dose can be extrapolated to the fixed dose. Study 18-001 did not assess prolactin concentrations after the screening visit and thus added no useful data regarding Tlando's effect on prolactin. Therefore, prolactin data for the 225 mg BID dose, without an opportunity for dose titration, is limited to study 16-002 — the 24-day trial.

Table 19. Observed, Change from Baseline, and Outlier Analysis Serum Prolactin Concentration LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
Visit	n	Mean (SD) ng/mL	Median ng/mL	Min ng/mL	Max ng/mL	n	Mean (SD) ng/mL	Median ng/mL	Min ng/mL	Max ng/mL
Baseline	207	6.5 (3.7)	5.7	0.2	41.1*	104	6.3 (2.7)	5.5	2.0	19.0
Week 7	119	8.3 (4.1)	7.5	1.5	24.9	95	7.8 (3.6)	6.6	4.0	24.3
CFB	118	1.9 (3.8)	1.7	-9.5	19.1	95	1.5 (3.0)	1.3	-8.8	13.8
Week 13	152	8.4 (4.2)	7.5	1.1	27.8	89	8.6 (5.4)	7.5	2.6	36.2*
CFB	149	2.3 (3.8)	1.8	-7.8	22.0	89	2.1 (4.8)	1.3	-11.2	29.3
Week 26	144	7.9 (3.8)	7.2	0.6	25.5	82	8.3 (4.4)	7.3	2.8	23.6
CFB	141	1.7 (3.2)	1.5	-5.0	19.7	82	1.9 (3.1)	1.1	-3.0	12.2
Week 39	137	7.4 (4.2)	6.8	1.1	36.0*	76	7.5 (3.3)	6.8	2.7	19.8
CFB	134	1.4 (3.4)	1.0	-5.4	21.4	76	1.1 (2.4)	0.8	-6.6	9.6
Week 52	128	7.4 (3.5)	6.7	0.6	18.2	69	7.4 (3.6)	6.2	3.1	18.8
CFB	125	1.5 (2.7)	1.3	-7.5	12.0	69	1.1 (2.3)	0. 6	-4.6	8.1
Early Term	50	8.2 (4.2)	7.6	2.4	21.1	14	7.2 (2.1)	7.0	4.2	10.2
CFB	50	1.4 (4.1)	1.0	-9.5	12.3	14	0.9 (1.7)	1.2	-3.2	3.2
End of Study	178	7.6 (3.7)	6.8	0.6	21.1	83	7.3 (3.3)	6.4	3.1	18.8
CFB	175	1.5 (3.2)	1.2	-9.5	12.3	83	1.1 (2.2)	0.8	-4.6	8.1

*One subject had a prolactin serum concentration greater than 2 times the ULN at this timepoint.
CFB = Change from Baseline
Normal Reference Range: 2.1 ng/mL-17.7 ng/mL.
Source: Reviewer created table from Tables 14.3.4.2.1g and 14.3.4.2.1L; CSR LPCN 1021-13-001 (Section 14).

Table 20. Summary of Prolactin Shift Data — LPCN 1021-13-001 (Safety Set)

		Baseline Assessment									
		Tlando					AndroGel 1.62%				
Visit	Assessment	N	Low n (%)	Normal n (%)	High n (%)	Not Done n (%)	N	Low n (%)	Normal n (%)	High n (%)	Not Done n (%)
Week 7	Low	177	1 (0.6)	0	0	0	95	0	0	0	0
	Normal		0	111 (62.7)	0	1 (0.6)		1 (1.1)	90 (94.7)	0	0
	High		0	6 (2.8)	0	0		0	3 (3.2)	1 (1.1)	0
	Not Done		3 (1.7)	53 (29.9)	0	2 (1.1)		0	0	0	0
Week 13	Low	157	3 (1.9)	0	0	0	90	0	0	0	0
	Normal		0	139 (88.5)	0	3 (1.9)		1 (1.1)	82 (91.1)	0	0
	High		0	7 (4.5)	0	0		0	5 (5.6)	1 (1.1)	0
	Not Done		1 (0.6)	4 (2.5)	0	0		0	1 (1.1)	0	0
Week 26	Low	144	3 (2.1)	1 (0.7)	0	0	82	0	0	0	0
	Normal		1 (0.7)	132 (91.7)	0	3 (2.1)		1 (1.2)	78 (95.1)	0	0
	High		0	4 (2.8)	0	0		0	2 (2.4)	1 (1.2)	0
	Not Done		0	0	0	0		0	0	0	0
Week 39	Low	137	4 (2.9)	0	0	0	76	0	0	0	0
	Normal		0	127 (92.7)	0	3 (2.2)		1 (1.3)	73 (96.1)	1 (1.3)	0
	High		0	3 (2.2)	0	0		0	1 (1.3)	0	0
	Not Done		0	0	0	0		0	0	0	0
Week 52	Low	130	4 (3.1)	2 (1.5)	0	0	70	0	0	0	0
	Normal		0	117 (90.0)	0	3 (2.3)		1 (1.4)	66 (94.3)	0	0
	High		0	2 (1.5)	0	0		0	1 (1.4)	1 (1.4)	0
	Not Done		0	2 (1.5)	0	0		0	1 (1.4)	0	0

		Baseline Assessment									
		Tlando					AndroGel 1.62%				
Visit	Assessment	N	Low n (%)	Normal n (%)	High n (%)	Not Done n (%)	N	Low n (%)	Normal n (%)	High n (%)	Not Done n (%)
Early Term	Low	50	0	0	0	0	14	0	0	0	0
	Normal		1 (2.0)	47 (94.0)	0	0		0	14 (100.0)	0	0
	High		0	2 (4.0)	0	0		0	0	0	0
	Not Done		0	0	0	0		0	0	0	0

Normal Reference Range: 2.1 ng/mL-17.7 ng/mL.
Source: Table 14.3.6.2.19a; CSR LPCN 1021-13-001 (Section 14) with reviewer correction of Week 7 data.

8.2.5.3. Potential Effects on the Hypothalamic Pituitary Adrenal Axis

In the nonclinical toxicology studies, adrenal cortical vacuolation was noted in rats and adrenal cortical atrophy was noted in dogs. To assess the clinical implications of these findings, the Applicant included Cosyntropin stimulation substudies in study 16-002 and study 16-003. The Cosyntropin stimulation substudies were reviewed, in consultation with an FDA endocrinologist, during the second review cycle of the NDA. At that time, the clinical review team concluded that the 24-day treatment period was insufficient to definitively exclude a risk of adrenal insufficiency with chronic dosing and recommended further assessment of adrenal function over a longer duration to more definitively address this issue. For additional information regarding the Cosyntropin stimulation sub-studies, please refer to the second cycle Clinical Review of the NDA.

In the current submission, the Applicant did not submit any additional data regarding this issue. The Applicant believes that assessment of adrenal function may not be warranted over a longer duration because cortisol levels in study 16-002 and study 16-003 were not significantly different at the end of the study compared to baseline and also, subjects in study 13-001 did not exhibit the signs and symptoms of adrenal insufficiency.

The clinical review team continues to believe that assessment of adrenal function over a longer period of time may be warranted to definitively address this issue. However, based on the currently available data and input from the Bone, Reproductive and Urologic Drugs Advisory Committee meeting on January 10, 2018 (see second cycle Clinical Review Section 9), we believe that a longer duration Cosyntropin stimulation study could be conducted as a postmarketing required study.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

No Clinical Outcome Assessment analyses Informing safety and/or tolerability were submitted in the resubmission.

8.2.7. Safety Analyses by Demographic Subgroups

Age

Of the 654 hypogonadal men who received Tlando, 72 (11.0%) were 65 years or older. Table 21 and Table 22 display TEAEs by SOC for subjects less than 65 years of age and at least 65 years of age, respectively, by treatment group.

Table 21. TEAEs by System Organ Class for Subjects <65 Years across Pooled Tlando Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	ISS2 Tlando N=471	ISS3 Tlando N=582	Andriol 80 mg N=34	AndroGel 1.62% N=92	Placebo N=17
Any TEAE	196 (41.6)	222 (38.1)	12 (35.3)	59 (64.1)	8 (47.1)
Blood and Lymphatic System Disorders	6 (1.3)	8 (1.4)	0	2 (2.2)	0
Cardiac Disorders	7 (1.5)	7 (1.2)	1 (2.9)	5 (5.4)	0
Congenital, Familial and Genetic Disorders	1 (0.2)	1 (0.2)	0	0	0
Ear and Labyrinth Disorders	1 (0.2)	1 (0.2)	0	1 (1.1)	0
Endocrine Disorders	0	0	0	1 (1.1)	0
Eye Disorders	5 (1.1)	5 (0.9)	0	2 (2.2)	0
Gastrointestinal Disorders	42 (8.9)	42 (7.2)	2 (5.9)	9 (9.8)	8 (47.1)
General Disorders and Administration Site Conditions	24 (5.1)	25 (4.3)	1 (2.9)	11 (12.0)	1 (5.9)
Hepatobiliary Disorders	0	1 (0.2)	0	0	0
Immune System Disorders	1 (0.2)	1 (0.2)	0	1 (1.1)	0
Infections and Infestations	49 (10.4)	56 (9.6)	3 (8.8)	19 (20.7)	0
Injury, Poisoning and Procedural Complications	22 (4.7)	23 (4.0)	2 (5.9)	9 (9.8)	0
Investigations	42 (8.9)	48 (8.2)	3 (8.8)	11 (12.0)	0
Metabolism and Nutrition Disorders	13 (2.8)	19 (3.3)	0	7 (7.6)	0
Musculoskeletal and Connective Tissue Disorders	31 (6.6)	31 (5.3)	1 (2.9)	12 (13.0)	1 (5.9)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.2)	1 (0.2)	0	1 (1.1)	0
Nervous System Disorders	31 (6.6)	33 (5.7)	2 (5.9)	8 (8.7)	3 (17.6)
Psychiatric Disorders	15 (3.2)	17 (2.9)	1 (2.9)	7 (7.6)	0
Renal and Urinary Disorders	6 (1.3)	7 (1.2)	0	7 (7.6)	0
Reproductive System and Breast Disorders	4 (0.8)	6 (1.0)	0	6 (6.5)	0
Respiratory, Thoracic and Mediastinal Disorders	16 (3.4)	18 (3.1)	0	7 (7.6)	0
Skin and Subcutaneous Tissue Disorders	30 (6.4)	31 (5.3)	1 (2.9)	8 (8.7)	2 (11.8)
Surgical and Medical Procedures	1 (0.2)	1 (0.2)	0	1 (1.1)	0

System Organ Class, n (%)	ISS2 Tlando N=471	ISS3 Tlando N=582	Andriol 80 mg N=34	AndroGel 1.62% N=92	Placebo N=17
Vascular Disorders	9 (1.9)	14 (2.4)	1 (2.9)	6 (6.5)	0

Studies included: LPCN 1021-18-001, LPCN 1021-18-003, 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.
Note: No AEs were reported in LPCN-18-003
Note: If a subject experiences more than one adverse event in a category, the subject is counted only once in the subject count (n, %) for that category
Source: NDA 208088 (seq 0050), 2.7.4, Table 74, p. 164.

Table 22. TEAEs by System Organ Class for Subjects >65 Years Across Pooled Tlando Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	ISS2 Tlando N=54	ISS3 Tlando N=72	Andriol 80 mg N=0	AndroGel 1.62% N=12	Placebo N=1
Any TEAE	25 (46.3)	31 (43.1)	0	9 (75.0)	1 (100)
Blood and Lymphatic System Disorders	2 (3.7)	3 (4.2)	0	0	0
Cardiac Disorders	0	1 (1.4)	0	1 (8.3)	0
Ear and Labyrinth Disorders	0	0	0	1 (8.3)	0
Gastrointestinal Disorders	4 (7.4)	4 (5.6)	0	2 (16.7)	0
General Disorders and Administration Site Conditions	2 (3.7)	2 (2.8)	0	1 (8.3)	1 (100)
Immune System Disorders	0	0	0	1 (8.3)	0
Infections and Infestations	4 (7.4)	6 (8.3)	0	3 (25.0)	0
Injury, Poisoning and Procedural Complications	2 (3.7)	2 (2.8)	0	2 (16.7)	0
Investigations	8 (14.8)	9 (12.5)	0	1 (8.3)	0
Metabolism and Nutrition Disorders	0	1 (1.4)	0	2 (16.7)	0
Musculoskeletal and Connective Tissue Disorders	3 (5.6)	4 (5.6)	0	0	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	0	1 (8.3)	0
Nervous System Disorders	7 (13.0)	8 (11.1)	0	0	0
Psychiatric Disorders	0	0	0	1 (8.3)	0
Renal and Urinary Disorders	3 (5.6)	3 (4.2)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	3 (5.6)	3 (4.2)	0	2 (16.7)	0
Skin and Subcutaneous Tissue Disorders	1 (1.9)	1 (1.4)	0	0	0
Surgical and Medical Procedures	1 (1.9)	1 (1.4)	0	0	0
Vascular Disorders	2 (3.7)	4 (5.6)	0	0	0

Studies included: LPCN 1021-18-001, LPCN 1021-18-003, 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.
Note: No AEs were reported in LPCN-18-003
Note: If a subject experiences more than one adverse event in a category, the subject is counted only once in the subject count (n, %) for that category
Source: NDA 208088 (seq 0050), 2.7.4, Table 75, p. 165.

Of subjects who were treated with Tlando, 38.1% of younger subjects experienced at least one TEAE compared with 43.1% of older subjects. A higher percentage of older subjects experienced at least one TEAE with AndroGel 1.62% compared with younger subjects (75.0% versus 64.1%, respectively) although the smaller sample sizes with AndroGel limit conclusions. For older subjects who received Tlando, adverse events occurred most frequently in the SOCs of investigations (12.5% of older subjects versus 8.2% of younger subjects), nervous system

disorders (11.1% versus 5.7%, respectively), infections and infestations (8.3% versus 9.6%, respectively), gastrointestinal disorders (5.6% versus 7.2%), musculoskeletal and connective tissue disorders (5.6% versus 5.3%, respectively), and vascular disorders (5.6% versus 2.4%, respectively).

Body Mass Index

Of the 654 hypogonadal men who received Tlando in a Tlando study, 369 (56.4%) had a body mass index (BMI) of 30 kg/m^2 or greater — the criteria for obesity. Table 23 and Table 24 display TEAEs by SOC for subjects with BMI less than 30 kg/m^2 (non-obese) and at least 30 kg/m^2 (obese), respectively, by treatment.

Table 23. Treatment Emergent Adverse Events for Subjects with Body Mass Index <30 kg/m^2 Across Pooled Tlando Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	ISS2 Tlando N=205	ISS3 Tlando N=285	Andriol 80 mg N=29	AndroGel 1.62% N=37	Placebo N=16
Any TEAE	102 (41.0)	110 (38.6)	12 (41.4)	26 (70.3)	8 (50.0)
Blood and Lymphatic System Disorders	2 (0.8)	3 (1.1)	0	1 (2.7)	0
Cardiac Disorders	5 (2.0)	6 (2.1)	1 (3.4)	0	0
Congenital, Familial and Genetic Disorders	1 (0.4)	1 (0.4)	0	0	0
Ear and Labyrinth Disorders	0	0	0	1 (2.7)	0
Eye Disorders	3 (1.2)	3 (1.1)	0	0	0
Gastrointestinal Disorders	22 (8.8)	22 (7.7)	2 (6.9)	4 (10.8)	7 (43.8)
General Disorders and Administration Site Conditions	9 (3.6)	9 (3.2)	1 (3.4)	3 (8.1)	2 (12.5)
Immune System Disorders	1 (0.4)	1 (0.4)	0	0	0
Infections and Infestations	23 (9.2)	25 (8.8)	3 (10.3)	9 (24.3)	0
Injury, Poisoning and Procedural Complications	12 (4.8)	13 (4.6)	2 (6.9)	6 (16.2)	0
Investigations	21 (8.4)	21 (7.4)	3 (10.3)	6 (16.2)	0
Metabolism and Nutrition Disorders	4 (1.6)	5 (1.8)	0	3 (8.1)	0
Musculoskeletal and Connective Tissue Disorders	15 (6.0)	15 (5.3)	1 (3.4)	6 (16.2)	1 (6.3)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	0	1 (2.7)	0
Nervous System Disorders	20 (8.0)	22 (7.7)	2 (6.9)	4 (10.8)	3 (18.8)
Psychiatric Disorders	7 (2.8)	7 (2.5)	1 (3.4)	2 (5.4)	0
Renal and Urinary Disorders	2 (0.8)	2 (0.7)	0	2 (5.4)	0
Reproductive System and Breast Disorders	2 (0.8)	2 (0.7)	0	4 (10.8)	0
Respiratory, Thoracic and Mediastinal Disorders	7 (2.8)	7 (2.5)	0	3 (8.1)	0
Skin and Subcutaneous Tissue Disorders	14 (5.6)	15 (5.3)	1 (3.4)	3 (8.1)	2 (12.5)
Surgical and Medical Procedures	1 (0.4)	1 (0.4)	0	0	0
Vascular Disorders	4 (1.6)	7 (2.5)	1 (3.4)	2 (5.4)	0

Studies included: LPCN 1021-18-001, LPCN 1021-18-003, 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.
Note: No AEs were reported in LPCN-18-003
Note: If a subject experiences more than one adverse event in a category, the subject is counted only once in the subject count (n, %) for that category
Source: NDA 208088 (seq 0050), 2.7.4, Table 78, p. 171.

Table 24. Treatment Emergent Adverse Events by System Organ Class for Subjects with Body Mass Index ≥30 kg/m^2 Across Pooled Tlando Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	ISS2 Tlando N=276	ISS3 Tlando N=369	Andriol 80 mg N=5	AndroGel 1.62% N=67	Placebo N=2
Any TEAE	119 (43.1)	143 (38.8)	0	42 (62.7)	1 (50.0)
Blood and Lymphatic System Disorders	6 (2.2)	8 (2.2)	0	1 (1.5)	0
Cardiac Disorders	2 (0.7)	2 (0.5)	0	6 (9.0)	0
Ear and Labyrinth Disorders	1 (0.4)	1 (0.3)	0 1 (1.5)	0	
Endocrine Disorders	0	0	0	1 (1.5)	0
Eye Disorders	2 (0.7)	2 (0.5)	0	2 (3.0)	0
Gastrointestinal Disorders	24 (8.7)	24 (6.5)	0	7 (10.4)	1 (50.0)
General Disorders and Administration Site Conditions	17 (6.2)	18 (4.9)	0	9 (13.4)	0
Hepatobiliary Disorders	0	1 (0.3)	0	0	0
Immune System Disorders	0	0	0	2 (3.0)	0
Infections and Infestations	30 (10.9)	37 (10.0)	0	13 (19.4)	0
Injury, Poisoning and Procedural Complications	12 (4.3)	12 (3.3)	0	5 (7.5)	0
Investigations	29 (10.5)	36 (9.8)	0	6 (9.0)	0
Metabolism and Nutrition Disorders	9 (3.3)	15 (4.1)	0	6 (9.0)	0
Musculoskeletal and Connective Tissue Disorders	19 (6.9)	20 (5.4)	0	6 (9.0)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.4)	1 (0.3)	0	1 (1.5)	0
Nervous System Disorders	18 (6.5)	19 (5.1)	0	4 (6.0)	0
Psychiatric Disorders	8 (2.9)	10 (2.7)	0	6 (9.0)	0
Renal and Urinary Disorders	7 (2.5)	8 (2.2)	0	5 (7.5)	0
Reproductive System and Breast Disorders	2 (0.7)	4 (1.1)	0	2 (3.0)	0
Respiratory, Thoracic and Mediastinal Disorders	12 (4.3)	14 (3.8)	0	6 (9.0)	0
Skin and Subcutaneous Tissue Disorders	17 (6.2)	17 (4.6)	0	5 (7.5)	0
Surgical and Medical Procedures	1 (0.4)	1 (0.3)	0	1 (1.5)	0
Vascular Disorders	7 (2.5)	11 (3.0)	0	4 (6.0)	0

Studies included: LPCN 1021-18-001, LPCN 1021-18-003, 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.
Note: No AEs were reported in LPCN-18-003.
Note: If a subject experiences more than one adverse event in a category, the subject is counted only once in the subject count (n, %) for that category
Source: NDA 208088 (seq 0050), 2.7.4, Table 79, p. 172.

Of subjects who were treated with Tlando, 38.6% of non-obese subjects experienced at least one TEAE compared with 38.8% of obese subjects. In contrast, a higher percentage of non-obese subjects experienced at least one TEAE with AndroGel 1.62% compared with obese subjects (70.3% versus 62.7%, respectively) although the smaller sample sizes with AndroGel limit conclusions. For obese subjects who received Tlando, adverse events occurred most frequently in the SOCs of infections and infestations (10.0% of obese subjects versus 8.8% of non-obese subjects), investigations (9.8% versus 7.4%, respectively), gastrointestinal disorders (6.5% versus 7.7%, respectively), musculoskeletal and connective tissue disorders (5.4% versus 5.3%, respectively), and nervous system disorders (5.1% versus 7.7%, respectively).

8.2.8. Specific Safety Studies/Clinical Trials

LPCN 1021-18-001

Study 18-001 was an open-label, multicenter, single arm study evaluating the BP changes from baseline (Visit 3) to post-treatment (Visit 5) assessed by ABPM in Tlando-treated adult hypogonadal male subjects.

The total duration of the study was approximately 110 days, not including the screening period, and was comprised of six scheduled visits:

- Visits 1 and 2 for screening
- Visit 3 (Day -4) to assess subject's baseline BP and PR via ABPM
- Visit 4 (Day 1 of treatment) to enroll subjects and to provide subjects with study medication for the start of dosing
- Visit 5 (Day 106-107) to assess subject's post-treatment BP and PR via ABPM
- Visit 6 (Day 110) to perform exit visit procedures

There were two confinement visits (Visits 3 and 5) during the study of approximately 30 hours each prior to the start of the dosing and at the end of the study.

ABPM was performed in the clinic during the confinement visits (Visits 3 and 5). The ABPM device recorded BP and PR every 15 minutes during daytime hours (7 a.m. to 11 p.m.) and every 20 minutes during nighttime hours (11 p.m. to 7 a.m.). At the end of the 24-hour measurements, sites uploaded the data to a central site. A central reader qualified the data as valid or not. Data were considered valid if it met the following criteria: (1) minimum of 1 valid reading per hour, including during sleep and (2) valid data for at least 22 out of 24 hours in the day. If data were not valid at Visit 3 or Visit 5, a repeat measurement may have been allowed at the discretion of study medical monitor.

Key Inclusion Criteria

1. Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism prior to age 65.
2. Subjects diagnosed to be primary (congenital or acquired) or secondary hypogonadal (congenital or acquired).
3. Serum total T below lab normal range (300 ng/dL) based on two consecutive blood samples obtained between 6 a.m. and 10 a.m., on two separate days at approximately the same time of day, following an appropriate washout of current androgen replacement therapy, if required.
4. Naïve to androgen replacement or had discontinued current treatment and completed adequate washout of prior androgen therapy. Washout was completed prior to collection of baseline serum T samples to determine study eligibility.

Key Exclusion Criteria

1. Clinically significant abnormal laboratory value, in the opinion of the investigator, in serum

chemistry, hematology, or urinalysis including but not limited to:

a. Hemoglobin <11.5 g/dL or >16.5 g/dL
b. Hematocrit <35% or >54%
c. Serum transaminases >2.5 times upper limit of normal
d. Serum bilirubin >2.0 mg/dL
e. Creatinine >2.0 mg/dL
f. PSA >4 ng/mL
g. Prolactin >17.7 ng/mL

2. Subjects with screening systolic BP or diastolic BP above 160 mmHg or 100 mmHg, respectively
3. Subjects with symptoms of moderate to severe benign prostatic hyperplasia. History of gastric surgery, cholecystectomy, vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH, or absorption.
4. Known tolerability issues with ABPM devices
5. Subjects who were not on stable dose of current medication (no changes in medication in the last 3 months)
6. History of untreated obstructive sleep apnea or not compliant with sleep apnea treatment

Treatments Administered

The treatment phase of the study consisted of approximately 107 days starting at Visit 4 and ending at Visit 5. The morning of study Visit 4 (Day 1 of treatment), eligible subjects returned to the clinic. Sites dispensed study drug and instructed subjects to take Tlando 225 mg twice daily, with a meal (approximately 30 minutes following meal), for approximately 107 days.

Data Sets Analyzed

Safety set (SS): The safety set included all subjects who received a dose of study drug. All safety analyses were conducted in the SS.

Full analysis set (FAS): The FAS consisted of all subjects enrolled into the study with valid ABPM data at Visit 3 and Visit 5.

24-hour validity set: The 24-hour validity set consisted of all subjects enrolled in the study with a minimum of 1 valid ABPM reading per hour, including during sleep, and valid data for at least 22 out of 24 hours in the day.

Primary Endpoint

Change from Visit 3 to Visit 5 of the weighted average 24-hour SBP. The primary analysis was done using the FAS.

Key Secondary Endpoints

1. Change in weighted average daytime and nighttime SBP, weighted average daytime diastolic blood pressure (DBP), weighted average nighttime DBP, and weighted average 24-hour DBP assessed by ABPM from Visit 3 to Visit 5.
2. Change in mean average daytime and nighttime SBP, mean average 24-hour SBP, mean

average daytime DBP, mean average nighttime DBP, and mean average 24-hour DBP assessed by ABPM from Visit 3 to Visit 5.
3. Change in average daytime, nighttime, and 24-hour PR assessed by ABPM from Visit 3 to Visit 5.
4. Change in morning systolic and diastolic BP and PR measured in triplicate at the clinic ("Clinic BP and PR") from Visit 3 to Visit 5.

Statistical Analysis Plan

A statistical analysis plan describing the data handling rules and analyses was developed and finalized on September 15, 2018. Subsequently, an amendment to the statistical analysis plan was made (January 23, 2019). The amendment included the following changes:

- The primary endpoint of the study was changed from change in average daytime systolic blood pressure to change in average 24-hour systolic blood pressure based on the recent FDA public workshop on ambulatory blood pressure monitoring studies ("Evaluating the Pressor Effects of Drugs and Ambulatory Blood Pressure Monitoring Studies"). The public workshop noted that the primary endpoint for ABPM studies should be the change in 24-hour average blood pressure.
- Added change in daytime systolic blood pressure to the secondary endpoints, and revised secondary endpoints for consistency.
- Added details for blood pressure analysis.
- Added details for subgroup analysis.
- Changed the development phase from phase 1 to phase 3. The FDA's Division of Bone, Reproductive and Urologic Products noted that although Protocol LPCN 1021-18-001 listed the development phase of the study as phase 1, the study design is not consistent with the definition of a phase 1 study in 21 CFR Part 312.21. The Division requested that Lipocine change the designated development phase to be consistent with the CFR. Based on the CFR study descriptions, the development phase for Protocol LPCN 1021-18-001 was changed to phase 3.
- Updated to reflect other changes made to Protocol LPCN 1021-18-001.
- Minor editorial changes for consistency.

Study Results

See Section 8.2.5.1 Blood Pressure Increases.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

LPCN 1021-13-001, LPCN 1021-16-002, and LPCN 1021-16-003

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

LPCN 1021-18-001

No neoplasms were reported in study 18-001.

Human Reproduction and Pregnancy

No studies on pregnancy or lactation were conducted as part of the clinical research program for Tlando. Exposure of a female fetus to androgens may result in varying degrees of virilization.

Pediatrics and Assessment of Effects on Growth

Tlando was not studied in males less than 18 years of age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of overdose with Tlando were reported in the clinical studies of Tlando, and no new data regarding overdose were generated for Tlando for this submission. No formal abuse potential studies or studies to evaluate withdrawal or rebound were conducted or required as part of the clinical development program for Tlando.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

See the Clinical Review for the Second Review Cycle in DARRTS (March 12, 2018).

Expectations on Safety in the Postmarket Setting

Tlando's postmarket safety expectations cannot be determined because the safety profile of the proposed to-be-marketed dosing regimen (225 mg BID without dose titration) has not been fully characterized. Only two trials were submitted that evaluated this dosing regimen: study 16-002, a 24-day safety and efficacy trial; and study 18-001, a 110-day ABPM trial.

Study 16-002 had a number of subjects with testosterone Cmax excursions greater than 1500 ng/mL and did not meet its prespecified secondary endpoints. The safety implications of these Cmax excursions could not be determined because of the short duration of the trial. Study 18-001 also raised concerns about the effect of the fixed 225 mg BID dose on hematocrit and hemoglobin concentrations. Therefore, the available data are not sufficient to fully characterize the long-term safety profile of the 225 mg BID dose without titration and Tlando's postmarket safety expectations cannot be determined from the available data.

8.2.11. Integrated Assessment of Safety

The safety database for Tlando included 654 hypogonadal men who received the drug from 1 to 382 days. The primary source of safety data is derived from study 13-001, a 52-week, randomized, active controlled trial. Supportive sources of safety data include study 16-002, a 24-day trial that evaluated the 225 mg BID dose without dose titration; study 16-003, a 24-day trial that evaluated the 150 mg TID dose without dose titration; and study 18-001, a 110-day ABPM trial in which subjects were dosed with the 225 mg BID dose without dose titration; and five phase 1 studies. Study 16-002 and study 18-001 are the only phase 3 trials in which all subjects were dosed with the 225 mg BID dose without dose titration.

Study 16-002 did not meet its prespecified secondary endpoints as a result of an excessive number of subjects with testosterone Cmax excursions greater than 1500, 1800, and 2500 ng/mL. The safety implications of these Cmax excursions well above the normal testosterone range could not be determined because of the short duration of the trial and the lack of a comparator group. In addition, it is unclear whether these Cmax excursions are related to the similar mean change from baseline for hematocrit and hemoglobin after 110 days of treatment with the fixed dose in study 18-001 compared to 365 days of treatment with the titrated dose in study 13-001. Additional data for the 225 mg BID fixed dosing regimen is needed to better evaluate the safety implications of these findings. Alternatively, the Applicant could evaluate another dosing regimen that meets both the primary and secondary endpoints.

As discussed in the clinical review of the first resubmission of the NDA, Tlando's effect on the hypothalamic pituitary adrenal axis remains unclear. Though adrenal function was assessed in Cosyntropin stimulation substudies during study 16-002 and study 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. This concern was not addressed in the current submission. Therefore, further assessment of adrenal function over a longer duration is needed to rule out the risk of adrenal dysfunction, but as noted previously, this information can be obtained in the postmarketing setting if needed.

A signal for an increase in serum prolactin concentration in subjects treated with Tlando was noted in study 16-002 — the 24-day fixed dose trial. Based on data from study 13-001, the 52-week study, it appears that serum prolactin levels are not meaningfully changed with longer treatment. However, study 13-001 evaluated the 225 mg BID dose with dose titration, whereas study 16-002 evaluated that dose without titration. Based on the finding for hematocrit and hemoglobin in study 18-001, it is not clear that the long-term safety data for the titrated dose can be extrapolated to the fixed dose. If the Applicant was to conduct a new phase 3 trial we recommend monitoring of serum prolactin in that trial.

8.3. Statistical Issues

None

8.4. Conclusions and Recommendations

The Applicant has failed to meet the standard Cmax secondary endpoints for study 16-002. For a drug that is to be chronically administered, the long-term safety implications from the excessive number of subjects with Cmax excursions in study 16-002 could not be determined because of the short duration of this trial and the short duration of study 18-001. It is also unclear whether the hematocrit and hemoglobin changes in study 18-001 could be related to excessive testosterone replacement in some subjects. Therefore, additional data for the 225 mg BID fixed dosing regimen for longer duration is needed to better evaluate the safety implications of these findings or alternatively the Applicant can test a new dosing regimen that meets both the primary and secondary endpoints.

In summary, there is insufficient data to support the overall safety of Tlando capsules, 225 mg twice daily regimen. As a result of the uncertainty about the long-term safety of the proposed drug product, we recommend a Complete Response.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee was convened during the second review cycle of NDA 208088 on January 10, 2018. For a detailed summary of Advisory Committee discussion, see review in DARRTS dated May 8, 2019. The current review cycle did not raise issues requiring external expert input from another Advisory Committee meeting.

10. Pediatrics

The Applicant requested (b) (4) When Tlando can be approved, it will likely be exempt from PREA because there is already an approved oral TU product and Tlando does not contain a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

No labeling discussions took place because of the CR action.

12. Risk Evaluation and Mitigation Strategies

At this time we do not anticipate a need for a REMS but defer the final decision until Tlando can be approved.

13. Postmarketing Requirements and Commitment

Not applicable at this time because we are issuing a CR letter.

14. Appendices

14.1. Financial Disclosure

Refer to the second cycle review in DARRTS dated March 12, 2018, for studies submitted prior to the current review cycle.

Covered Clinical Study (Name and/or Number): LPCN 1021-18-001, LPCN 1021-18-002, LPCN 1021-18-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 72		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

/s/

MARTIN E KAUFMAN
11/08/2019 01:14:37 PM

MARTIN E KAUFMAN on behalf of SURESH KAUL
11/08/2019 01:16:32 PM

HYLTON V JOFFE
11/08/2019 02:26:26 PM

Office of Clinical Pharmacology Review
Individual Study Review

NDA Number	208088 SDN051
Link to EDR	\\CDSESUB1\evsprod\NDA208088\208088.enx
Submission Date	May 9, 2019
Submission Type	Resubmission (standard review)
Brand Name	Tlando®
Generic Name	Testosterone undecanoate
Dosage Form and Strength	Oral capsule; 225 mg twice daily
Route of Administration	Oral
Proposed Indication	Treatment of hypogonadism
Applicant	Lipocine Inc.
Associated IND	106,476
OCP Review Team	LaiMing Lee, PhD; Yanhui Lu, PhD
OCP Final Signatory	Doanh Tran, PhD

Study LPCN 1021-18-003

Title: Study of Blood Collection Tubes Following Single Dose Administration of Oral Testosterone Undecanoate (TU, LPCN 1021).

Method: This was an open-label, single dose, single day study in twelve hypogonadal men age 41 to 68 years with confirmed hypogonadism based upon two consecutive blood samples obtained between 6 am and 10 am on two separate days. Subjects were given a single oral testosterone undecanoate (TU) dose of 225 mg (2 x 112.5 mg capsules) with a meal. Blood samples were collected in three different tube types pre-dose and at 3 and 5 hrs post-dose.

Objectives: To assess the effect of blood collection tubes, processing time, and processing condition on testosterone (T) concentrations in the presence of TU.

Study Period: November 8 to November 27, 2018.

Treatment Products: LPCN 1021 (oral TU capsules), each capsule containing 112.5 mg TU, batch no. 3315J13A.

Major Inclusion Criteria:

1. Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism prior to age 65
2. Serum total T below 300 ng/dL based on two blood samples obtained between 6 and 10 AM on two separate occasions at least 48 hours apart. Previously documented results could be used in place of one or both of the screening T measurements if the assay occurred within one year of Visit 1, and the subject had not been on androgen replacement therapy during that time.
3. Naive to androgen replacement or discontinued current treatment and completed adequate washout of prior androgen therapy. Washout was completed prior to collection of baseline serum T samples to determine study eligibility

Key Exclusion Criteria:

1. Donation or loss of 550 mL or more blood volume (including plasmapheresis) or receipt of a transfusion of any blood product within 3 months prior to the start of treatment.

Pharmacokinetic Blood Sampling:

Venous blood samples were collected for the determination of T and TU concentrations while patients were confined in the clinic for up to 10 hrs at Day 1 (Visit 3).

A pre-dose sample was collected within 45 min prior to oral TU dosing. Blood samples were collected 3 and 5 hrs post-dose into plasma EDTA anticoagulant (K2E), serum silica clot (SST), and plasma sodium fluoride/EDTA anticoagulant (NaFE) tubes for pre-analytical processing. Plasma collected in the K2E tubes #1 and #2 (duplicates) serve as time-zero control for the assessment of pre-analytical TU to T conversion.

Schedule of Assessments (study report table 1):

Visit	Screening[1]		Dosing and Sampling					Exit
Day (Relative to start of dosing)	Visit 1	Visit 2	-2 hours	-0.5 hours	0 hours	3 hours	5 hours	
Time on the Day								
Informed consent	X							
Inclusion/exclusion	X		X					
Height, weight, body mass index (BMI)[2]	X							
Medical history[3]	X							
Physical examination**	X							
Vital signs			X					
Clinical laboratory test sample collection (PSA)**		X						
Screening T measurement*	X	X						

Visit	Screening[1]		Dosing and Sampling					Exit
Day (Relative to start of dosing)	Visit 1	Visit 2	-2 hours	-0.5 hours	0 hours	3 hours	5 hours	
Time on the Day								
Adverse event reporting			X					
Prior and concomitant medication[4]	X		X					
Confinement begins			X					
Study enrollment			X					
Meal provided				X				
Study drug administered					X			
Pre-dose blood sampling				X				
Post-dose blood sampling						X	X	
Study exit interview								X

* Previously documented T results below 300 ng/dL could be used to in place of one or both of the screening T measurements, if the T assay occurred within one year of Visit 1, and the subject had not been on androgen replacement therapy during that time.
** Previously documented PSA results below 4 ng/mL and, physical exam could be used if the assessments occurred within one year of Visit 1.

[1] Screening: All or part of the procedures could be conducted on the day of dosing provided site had adequate time to complete the pre- study assessments

[2] Height and BMI at screening only

[3] Medical history for the past 3 years at screening, anything changed basis at subsequent visits

[4] Full medication history at screening and anything changed basis at subsequent visits

Blood Collection Tubes and Processing Conditions:

1. Plasma EDTA Tubes (K2E): two 6 mL Vacutainer tubes containing K_2EDTA anticoagulant (lavender top/BD tube 367863)
   - K2E tubes 1 and 2 were inverted 8 to 10 times and centrifuged immediately for 10 min (at ~1300 g and 2 to 8°C). Plasma was separated into cryovials and stored at -20°C individually.
   - This sample serves as a control (zero time point)

2. Serum Separation Tubes (SST): five 4 mL Vacutainer tubes containing silica clot activator (gold top/DB tube 367977)
   - Five SST tubes (Tubes 1, 2, 3, 4, 5) were inverted 6 times. Each tube sat at room temperature (RT) for up to 120 min for clotting, then centrifuged for 10 min (at ~1300 g). Serum was separated into cryovials and stored at -20°C individually.

a. Tubes 1 and 2: at RT for 30 min (the manufacturer's recommended clotting time)
b. Tube 3: at RT for 60 min (extended clotting time)
c. Tube 4: at RT for 90 min (extended clotting time)
d. Tube 5: at RT for 120 min (extended clotting time)

- These samples assess the effect of extended processing times on TU to T conversion

3. Plasma Sodium Fluoride (NaF)/Na_2EDTA (NaFE): twelve 2 mL Vacutainer tubes containing esterase inhibitor and anticoagulant Na_2EDTA (grey top/BD tube 367587).
   - Six NaFE tubes (ice condition) were inverted 8 to 10 times. Tubes NaFE #1 to 6 sat on ice for up to 90 min, then centrifuged for 10 min (at ~1300 g and 2 to 8°C). Plasma was separated into cryovials and stored at -20°C individually.
     a. Tubes 1 and 2: on ice for 15 min
     b. Tubes 3 and 4: on ice for 30 min
     c. Tubes 5 and 6: on ice for 90 min
   - Six NaFE tubes (RT condition) were inverted gently (8 to 10 times). Tubes NaFE #7 to 12 sat at RT for up to 90 min, then centrifuged for 10 min (at ~1300 g). Plasma was separated into cryovials and stored at -20°C individually.
     a. Tubes 7 and 8: at RT for 15 min
     b. Tubes 9 and 10: at RT for 30 min
     c. Tubes 11 and 12: at RT for 90 min
   - These samples assess the effect of esterase inhibitors and temperature on TU to T conversion

Processed serum and plasma samples were sent to [redacted] (b) (4) for determination of pre-dose and post-dose T concentrations, and post-dose TU concentrations.

Primary Analysis:
Comparison of the post-dose T concentrations from SST tubes #1 through 5 following RT clotting with post-dose T concentrations from plasma K2E tubes #1 and 2 processed immediately.

Additional Analysis:
Pre-dose and post-dose T concentrations were determined for each subject and blood collection tube with descriptive statistics:
plasma: K2E processed immediately;
serum: SST 30, 60, 90, and 120 min clotting time at RT;
plasma: NaFE 15, 30, and 90 min on ice; and NaFE 15, 30, and 90 min at RT

In addition, the post-dose to pre-dose T concentration ratios were calculated for each subject and each blood collection tube. Additional analysis may be performed on the post-dose to pre-dose T concentration ratios.

To assess the effect of deviating from the manufacturer's recommended clotting time, post-dose T concentrations for the SST extended clotting time samples (60, 90, and 120 min) were compared to the K2E time-zero plasma samples.

Reviewer's Comment:

The Applicant proposed for their statistical analysis to use a two one-sided test procedure and to calculate the 90% confidence interval (CI) for the ratio of the ln-transformed geometric means of the T concentrations for the serum and plasma samples. In addition, the Applicant proposed to conclude a lack of meaningful difference with the upper bound of the CI less than or equal to 125% of the serum/plasma average ratio. At the post-CR meeting held between the Applicant and the Agency on July 19, 2018, the Clinical Pharmacology review team did not concur with the Applicant's proposed criterion for determining clinical meaningful difference. Despite the objection, the Applicant used the standards for bioequivalence determination (geometric means of point estimate and 90% confidence interval limits fall within 80% and 125%) to assess whether varying conditions impacted ex vivo TU to T conversion. In this review, clinical meaningful differences are assessed in the context of how the TU to T conversion would affect the values of 24-hr T Cavg and the primary efficacy criteria (proportion of patients with a 24-hr T Cavg falling within the normal range), and the secondary (safety) endpoint of the pivotal Phase 3 safety and efficacy trial LPCN 1021-16-002.

Results:

Table 1. Mean (SD) Percent Difference of T concentration in serum (SST) 3 and 5 hrs post-dose of a single oral TU 225 mg in hypogonadal men (N=12), compared to plasma (K2E) (data from sponsor's table).

Clotting time	3 hrs post-dose	5 hrs post-dose
30 min	-3.09 (10)	1.1 (8)
60 min	-0.3 (7)	3.2 (9)
90 min	1.6 (7)	5.6 (11)
120 min	8.6 (11)	7.3 (12)

Reviewer's Comments - T concentrations in Serum (SST) vs Plasma (K2E):

Maximum Concentration of TU

Based upon literature reports by LaChance et al.[1], the potential for ex vivo conversion of TU to T is proportional to the TU concentration in the samples. In Study LPCN 1021-16-002 the mean (SD) average TU concentration following 24 days of twice daily administration of 225 mg oral TU capsules was 11,106 (5036) ng/dL. In the current Study LPCN 1021-18-003, mean (SD) serum TU concentration was 10,480 (17,066) ng/dL at 5 hrs post-dose following a single dose of oral TU 225 mg. TU concentrations from samples collected 5 hrs post-dose were similar to the average TU concentrations in Study LPCN 1021-16-002 and appeared to be representative of steady-state conditions of the pivotal phase 3 study. Therefore, any conclusions drawn about potential ex vivo TU to T conversion from the current study

would be applicable to Study LPCN 1021-16-002 (Protocol for Study LPCN 1021-18-003 was reviewed under IND 106,476 DARRTS August 29, 2018).

[1] Lachance S, Dhingra O, Bernstein J, et al. Importance of measuring testosterone in enzyme-inhibited plasma for oral testosterone undecanoate androgen replacement therapy clinical trial. Future Sci OA 2015; 1(4).

Processing Condition of Samples

According to the Phase 3 study LPCN 1021-16-002 laboratory manual, serum was prepared from blood samples that could clot at room temperature for at least 30 min. Within 60 min of blood collection, the serum tube would be centrifuged for 10-15 min at 650 to 1450 g. Prepared serum was aliquoted into two tubes and frozen within 30 min at -15° to -25°C before shipment to (b) (4) for analysis. Therefore, similar sample processing conditions of the pivotal Phase 3 study were included in the current study for evaluation.

Primary Analysis

T concentrations determined from plasma tubes (K2E) are considered Time Zero Controls because blood samples were processed immediately after blood collection; thereby, conversion of TU to T by non-specific esterases in the tubes prior to sample preparation and T concentration determination is likely to be negligible. Per the phase 3 study protocols, blood samples were collected into serum tubes and were processed up to 60 min after blood draw. As shown in Table 1 above, based upon the anticipated maximum TU concentration (5 hrs post-dose) and per-protocol processing time (up to 60 min), the difference in T concentration between SST and K2E tubes for the 5 hrs post-dose sample with a clotting time of 60 min is 3.2%. If blood samples were processed within 120 min (60 min beyond the specified duration in the study protocol), the difference in T concentration between SST and K2E tubes is approximately 8%. These data indicate that there is ex vivo TU to T conversion.

The Phase 3 efficacy endpoint is as follows:

- Percentage subjects achieving 24-hour serum T Cavg within normal range (300-1080 ng/dL): $\geq$ 75%, and
- 95% Confidence Interval: lower bound $\geq$ 65%

If we take into account the potential over-estimation of either 3.2% or 8% noted above and apply it to the pivotal phase 3 study LPCN 1021-16-002, the primary efficacy endpoint would still be met. For example, if a TU to T conversion of 8% is used to adjust the lower bound of the Cavg, then the adjusted lower bound of Cavg would be 324 ng/dL. Using this adjusted lower bound of 324 ng/dL, the proportion of patients that meet the 24-hr T Cavg would be 77.9%, and the lower bound of 95% CI would be 68.2% which still meets the predefined efficacy endpoint of exceeding 65% (Table 2).

Table 2. Effect of Ex Vivo TU to T Conversion on Primary Efficacy Endpoint: Proportion of Patients Achieving 24-hr T Cavg Within Normal Range in Phase 3 Study LPCN 1021-16-002 (SS BLOCF*; N=95; 225 mg BID; Day 24).

	Currently Reported	Adjusting T Threshold by 3%	Adjusting T Threshold by 8%
Lower bound of Cavg (ng/dL)	300	309	324
No (%) patients within pre-defined T Cavg	76/95 (80.0%)	75/95 (78.9%)	(74/95) 77.9%
95% CI (lower, upper bound)	72%, 88%	71%, 87%	68%, 86%

*population: safety set block last observation carried forward

Clinical Meaningfulness

The mean 24-hr T concentration (24-hr Cavg) on Day 24 in Study LPCN 1021-16-002 was 476 ng/dL. The target T range was specified to be 300-1080 ng/dL. Based upon a T concentration difference of 3.2% between the serum SST and plasma K2E samples potentially due to ex vivo TU to T conversion, the mean 24-hr T Cavg may be 461 ng/dL (3% less than 476 ng/dL). In the case of an extended processing time of 120 min (considered worst-case scenario), mean 24-hr T Cavg may be 438 ng/dL. Based on feedback at the Bone, Reproductive, and Urologic Drugs Advisory Committee meeting on January 10, 2018, a potential false increase in T concentration of 3.2% to 8% due to TU conversion is not likely to have a clinically meaningful impact on how a physician treats a patient with T replacement therapy. Additionally, even with adjusting for TU conversion of 3.2% to 8%, the criteria for the secondary endpoints were still not met (refer to Multi-Disciplinary Unireview in DARRTS for this submission).

Effect of Blood Collection Tubes and Processing Conditions (Time and Temperature) on Ex Vivo TU to T Conversion

Table 3. Testosterone Concentrations in Various Test Tubes in Samples Collected Pre-Dose, 3 hrs and 5 hrs Following Single Oral Administration of Oral TU 225 mg in 12 Hypogonadal Men (data from study report tables 9, 10, 12).

	Mean (SD) Testosterone Concentration (ng/dL)		
	Pre-dose	3 hrs post-dose	5 hrs post-dose
K2E at RT (plasma)			
Tube 1 (time zero control)	237 (74)	467 (342)	539 (292)
Tube 2 (time zero control)	240 (82)	451 (309)	545 (310)
SST at RT (serum)			

Tube 1 (30 min)	440* (663)	426 (258)	553 (334)
Tube 2 (30 min)	239 (79)	427 (260)	556 (334)
Tube 3 (60 min)	232 (70)	442 (276)	567 (339)
Tube 4 (90 min)	236 (77)	458 (300)	580 (346)
Tube 5 (120 min)	238 (75)	487 (324)	589 (344)
NaFE on ice (plasma)			
Tube 1 (15 min)	200 (62)	326 (184)	436 (249)
Tube 2 (15 min)	204 (66)	340 (193)	451 (269)
Tube 3 (30 min)	206 (60)	332 (191)	433 (238)
Tube 4 (30 min)	200 (63)	330 (178)	450 (263)
Tube 5 (90 min)	197 (64)	345 (216)	455 (260)
Tube 6 (90 min)	206 (63)	342 (201)	447 (256)
NaFE at RT (plasma)			
Tube 7 (15 min)	205 (73)	343 (199)	471 (319)
Tube 8 (15 min)	200 (68)	350 (209)	460 (301)
Tube 9 (30 min)	198 (63)	351 (208)	462 (312)
Tube 10 (30 min)	199 (63)	354 (208)	452 (291)
Tube 11 (90 min)	202 (72)	395 (251)	491 (333)
Tube 12 (90 min)	198 (60)	402 (265)	488 (319)

*pre-dose T concentration in subject (b) (6) was 2530 ng/dL

Table 4. Mean (SD) Percent Difference of T concentration in plasma (NaFE) at Room Temperature 3 and 5 hrs post-dose of a single oral TU 225 mg in hypogonadal men (N=12), compared to plasma (K2E) 3 hrs and 5 hrs post-dose (data from sponsor's table).

	3 hrs post-dose	5 hrs post-dose
15 min	-20.0 (14)	-15.5 (15)
30 min	-19.2 (11)	-16.9 (14)
90 min	-11.2 (7)	- 11.6 (14)

Table 5. Mean (SD) Percent Difference of T concentration in plasma (NaFE) on Ice 3 and 5 hrs post-dose of a single oral TU 225 mg in hypogonadal men (N=12), compared to plasma (K2E) 3 hrs and 5 hrs post-dose (data from sponsor's table).

	3 hrs post-dose	5 hrs post-dose
15 min	-21.8 (14)	-18.0 (9)
30 min	-22.1 (14)	-18.1 (9)
90 min	-20.4 (12)	- 16.8 (9)

Reviewer's Comments - T concentrations in Plasma (NaFE vs K2E):

- With the exception of one patient (# (b) (6)), the mean pre-dose T concentrations were approximately 200 ng/dL which is within the expected range of T concentrations in hypogonadal subjects. The mean T concentrations was approximately 100 ng/dL higher in the samples drawn 5 hrs post-dose, compared to samples drawn 3 hrs post-dose. These data are congruent with known pharmacokinetic characteristics of oral TU capsules obtained from other clinical studies (e.g. median maximum T concentration occurring 5 hrs post-morning dose).
- Potassium fluoride (KF) and sodium fluoride (NaF) have been used as esterase inhibitors to minimize the conversion of TU to T by non-specific esterases in blood during the sample processing period. EDTA is an anticoagulant that is commonly found with NaF (tubes containing NaF and EDTA are referred to as NaFE) in collection tubes used to prepare plasma. The purpose of NaF or any other esterase inhibitor was to minimize the degradation of TU to T in the tubes during the processing period.
- In this study, the Applicant assessed the effect of using NaF as an esterase inhibitor to prevent the ex vivo conversion of TU to T with blood samples collected 3 hrs and 5 hrs post TU dosing and permitted to clot at room temperature or on ice. However, the study did not include a time zero control of NaFE tubes.
- For NaFE blood samples collected 5 hrs post-dose and left at room temperature for 30 min before processing, mean T concentrations was approximately 17% lower, compared to plasma (K2E) control samples. See Tables 3 and 4.
- For NaFE blood samples collected 5 hrs post-dose and placed on ice for 30 min before processing, mean T concentrations was approximately 18% lower, compared to plasma (K2E) control samples. See Tables 3 and 5.
- The evaluation of T concentrations in SST versus in K2E was considered as the primary analysis to determine the extent of ex vivo TU to T conversion for the pharmacokinetic samples collected in the pivotal Phase 3 study. With the clotting time of 60 min, the maximum clotting time used for sample processing in the pivotal Phase 3 study, the ex vivo conversion of TU to T was 3.2% at 5 hrs post-dose and was determined to be not clinically meaningful as described above.

OSIS Inspection of Clinical Sites

The Clinical Pharmacology review team requested the Office of Study Integrity and Surveillance (OSIS) to inspect the study conduct of the clinical sites where Study LPCN 1021-18-003 was conducted. The two sites included South Florida Medical Research (Site #207) and Granger Medical Clinic – Riverton (Site # 218), which enrolled 4 and 8 patients, respectively. OSIS stated that there were no objectional conditions observed, no FORM FDA 483 was issued and that the data from the audited study are reliable to support a regulatory decision (OSIS review in DARRTS dated October 17, 2019). There was, however, a lag time between the start of blood collection and the start of sample centrifugation at the South Florida site of up to 6 min in 4 of 12 subjects. The lag time of 5 to 6 min in 33% of the subjects would likely result in the conversion of TU to T, but it would not significantly alter our interpretation of clinical meaningfulness. The Clinical Pharmacology review team concurs with OSIS's conclusion that the data from LPCN 1021-18-003 is reliable.

From the Case Report Forms (CRFs), the lag time from each of the 12 subjects in the K2E tubes (Tubes #1) 5 hrs post-dose are identified in the following table. Due to the procedure utilized by the South Florida site, the lag time between the start of sample collection and the start of centrifugation was up to 6 min. For the Granger site, the lag time was 1 min or less.

Clinical Site	Patient #	Sampling Start Time	Centrifuge Start Time	Lag Time (min)
South Florida Medical Research (Site #207)	(b) (6)	15:52	15:58	6
		15:35	15:40	5
		15:55	16:00	5
		15:30	15:35	5
Granger Medical Clinic Riverton (Site # 218)		10:53	10:53	0
		10:52	10:52	0
		10:53	10:54	1
		10:45	10:45	0
		10:53	10:53	0
		10:55	10:55	0
		10:47	10:47	0
		10:47	10:47	0

Bioanalytical

Concentrations of testosterone undecanoate and testosterone in serum were determined in using a validated LC-MS/MS method. Serum and plasma samples (K2E) were sent to (b) (4) laboratories ((b) (4) for determination of T and TU concentrations. The (b) (4) Analytical Report RLJE, RLJF, RLAS2, and RLAT2; issued April 5, 2019.

Table 6. Overview of Bioanalytical Method for Measurement of Testosterone Undecanoate and Testosterone Concentrations in Serum for Study LPCN 1021-18-003

Study #	LPCN 1021-18-003	
Analytes	Testosterone Undecanoate	Testosterone
Method #	Project RHJE	Project RLJE
Methodology	LC-MS/MS	LC-MS/MS
Biological matrix	Serum	Serum
Calibration curve range	200 to 100,000 ng/dL	10 to 5,000 ng/dL
Internal standard	Testosterone undecanoate-d_3	Testosterone-d_3
Validation report #	LCMSC 521.1	LCMSC 260.10
Inter-run accuracy for each QC	LLOQ (197 ng/dL): -1.50% bias LQC (512 ng/dL): 2.46% bias MQC (38,880 ng/dL): -3.06% bias HQC (72,600 ng/dL): -3.22% bias	LLOQ (25 ng/dL): 3.12% bias LQC (273 ng/dL): -2.07% bias MQC (882 ng/dL): 2.48% bias HQC (3910 ng/dL): -2.35% bias
Inter-run precision for each QC	LLOQ (197 ng/dL): 4.71% CV LQC (512 ng/dL): 15.2% CV* MQC (38,880 ng/dL): 4.20% CV HQC (72,600 ng/dL): 4.10% CV	LLOQ (25 ng/dL): 6.70% CV LQC (273 ng/dL): 7.03% CV MQC (882 ng/dL): 6.41% CV HQC (3910 ng/dL): 5.98% CV
Long-term stability	750 days at -20°C	399 days at -20°C
Freeze-thaw stability	5 cycles at -20C	5 cycles at -20°C

* For TU, the inter-run precision for the low QC sample (LQC) was 15.2%; thereby not meeting the 15% acceptable limit for acceptable inter-run precision. However, the deviation from the acceptance criteria was small and the inter-run precision at LLOQ was acceptable (much lower than the 20% acceptance limit).

Table 7. Overview of Bioanalytical Method for Measurement of Testosterone Undecanoate and Testosterone Concentrations in Plasma (K2E) for Study LPCN 1021-18-003

Study #	LPCN 1021-18-003	
Analytes	Testosterone Undecanoate	Testosterone
Method #	Project RHJE	Project RLJE
Methodology	LC-MS/MS	LC-MS/MS
Biological matrix	Plasma	Plasma

Calibration curve range	200 to 100,000 ng/dL	10 to 5,000 ng/dL
Internal standard	Testosterone undecanoate-d_3	Testosterone-d_3
Validation report #	4088972	4088410
Inter-run accuracy for each QC	LLOQ (199 ng/dL): -0.39% bias LQC (498 ng/dL): -0.33% bias MQC (40,400 ng/dL): 0.93% bias HQC (75,800 ng/dL): 1.11% bias	LLOQ (10 ng/dL): 0.49% bias LQC (30.4 ng/dL): 0.38% bias MQC (2640 ng/dL): 3.04% bias HQC (3810 ng/dL): 1.31% bias
Inter-run precision for each QC	LLOQ (199 ng/dL): 2.73% CV LQC (498 ng/dL): 4.25% CV MQC (40,400 ng/dL): 2.35% CV HQC (75,800 ng/dL): 1.58% CV	LLOQ (25 ng/dL): 11.6% CV LQC (30.4 ng/dL): 6.05% CV MQC (2640 ng/dL): 4.14% CV HQC (3810 ng/dL): 4.40% CV
Long-term stability	750 days at -20°C	399 days at -20°C
Freeze-thaw stability	5 cycles at -20C	5 cycles at -20°C

Overall, the assay for TU and T demonstrated selectivity, accuracy, precision, and recovery. They are acceptable from a Clinical Pharmacology perspective.

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

/s/

LAI M LEE
10/25/2019 11:12:41 AM

YANHUI LU
10/25/2019 11:20:07 AM

DOANH C TRAN
11/07/2019 09:18:04 AM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supporting Doc #:	208088 (eCTD Sequence #: 0050)
Drug Name:	TLANDO (Testosterone undecanoate oral capsule)
Indication(s):	Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency or absence of endogenous testosterone – primary or secondary hypogonadism (congenital or acquired)
Applicant:	Lipocine Inc.
Date(s):	Received date: May 9, 2019
	PDUFA date: November 9, 2019
Review Priority:	Standard (Resubmission)
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Weiya Zhang, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Martin Kaufman, M.D., Clinical Reviewer
	Suresh Kaul, M.D., Clinical Team Leader
Project Manager:	Jeannie Roule

Keywords: Clinical studies, NDA review

No new clinical efficacy data were submitted in this resubmission. For statistical evaluation of effectiveness of LPCN 1021 (testosterone undecanoate) oral capsules as a replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, please refer to statistical reviews of clinical studies LPCN 1021-13-001 in eCTD Sequence #: 0000 (submitted on 8/26/2015) and LPCN 1021-16-002 in eCTD Sequence #: 0026 (submitted on 8/8/2017).

For the replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, the efficacy evidence is based on achieving average serum testosterone levels (C_{avg}) within the normal range in at least 75% of men with the lower bound of the 95% confidence interval no less than 65%. The secondary evidence is based on at least 85% subjects with C_{max} of serum testosterone levels less than 1500 ng/dL, 5% subjects with C_{max} between 1800 to 2500 ng/dL, and no subject with C_{max} greater than 2500 ng/dL.

Both Studies LPCN 1021-13-001 and LPCN 1021-16-002 demonstrated that at least 75% of men achieved C_{avg} within the normal range with the lower bound of the 95% confidence interval no less than 65%. But neither study met the secondary evidence of C_{max} criteria defined above.

Overall, both studies did not provide adequate evidence to support the efficacy of LPCN1021 for the indication of a replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

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

/s/

WEIYA ZHANG
10/16/2019 12:14:50 PM

MAHBOOB SOBHAN
10/16/2019 12:37:16 PM

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208088
Priority or Standard	Standard
Submit Date(s)	August 8, 2017
Received Date(s)	August 8, 2017
PDUFA Goal Date	February 8, 2018
Division/Office	DBRUP/ODE 3
Reviewer Name(s)	Martin Kaufman, DPM, MBA
Review Completion Date	March 11, 2018
Established/Proper Name	Testosterone undecanoate
(Proposed) Trade Name	Tlando
Applicant	Lipocine Inc.
Dosage Form(s)	Capsules
Applicant Proposed Dosing Regimen(s)	225 mg BID (without dose titration)
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
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

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; and 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.

Tlando (testosterone undecanoate) capsules 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. 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 formulation, but has not been approved for oral administration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In my opinion, the Applicant did not provide substantial evidence of effectiveness for the dosing regimen (225 mg BID without dose titration) proposed for marketing. LPCN 1021-16-002, the pivotal trial that evaluated the to-be-marketed dosing regimen of 225 mg BID without dose titration, met the primary endpoint (proportion of treated subjects with Cavg within the normal range). This provides substantial evidence that Tlando meets the goal of maintaining testosterone concentrations within the eugonadal range. However, the study did not meet the secondary endpoint (proportion of subjects with Cmax above the predetermined limits). Therefore, the study did not provide substantial evidence that a dosing regimen of 225 mg BID without dose titration avoids unacceptably high serum testosterone concentrations.

To provide substantial evidence of effectiveness, the Applicant should conduct a Phase 3 trial with a dosing regimen that meets both the primary and the secondary efficacy endpoints.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Tlando (testosterone undecanoate) capsules 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. Based on a thorough review of the clinical data submitted in the resubmission of the NDA, I conclude that the modest benefits of Tlando do not outweigh the uncharacterized risk of systolic blood pressure elevation and the uncharacterized risk of long term adrenal effects. Therefore, I recommend that Tlando receive a Complete Response for this review cycle.

Hypogonadism is a serious medical condition. Testosterone replacement therapy is recommended for the treatment of men with classical androgen deficiency syndromes and patients with low testosterone levels resulting from chronic illness. Though most testosterone use occurs in older men with low testosterone levels, the safety and efficacy of testosterone therapy in this patient population has not been demonstrated.

There are many approved testosterone products available in the U.S. with routes of administration other than the oral route. Tlando's oral route of administration would be more convenient for patients and would avoid the need for periodic injections. In addition, in patients for whom topical gels pose a risk of transference of testosterone to a child or female, an oral product avoids this risk.

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. The substantial evidence that a drug product meets these goals is derived from a Phase 3 study 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 average 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 95%, 2-sided, confidence interval. The secondary endpoint is the proportion of treated subjects with testosterone Cmax(0-24h) values within predetermined limits. The Division's predetermined criteria for these limits are:

1. T Cmax $\leq$ 1500 ng/dL: $\geq$ 85%
2. T Cmax between 1800 and 2500 ng/dL: $\leq$ 5%

3. T Cmax > 2500 ng/dL: 0%

The Applicant submitted the results of one Phase 3 trial (LPCN 1021-16-002) to support the efficacy of the 225 mg dose of Tlando administered BID without dose titration. A total of 95 hypogonadal male subjects were enrolled in this 24-day, open label, one arm trial. The primary and secondary endpoints were the ones described above. The percentage of subjects achieving testosterone Cavg within the normal range during the trial was 80% (95% CI: 72%, 88%), which was greater than the minimal acceptable percentage required by the Division. Therefore, Tlando met the primary endpoint of the trial and provided substantial evidence that it maintains testosterone concentrations within the eugonadal range.

Though it met the primary endpoint, Tlando did not meet the secondary endpoint of the trial. In the trial, only 74% of the subjects had testosterone Cmax of 1500 ng/dL or less, compared to the protocol specified limit of 85% or less; 14% had testosterone Cmax between 1800 and 2500 ng/dL, compared to the protocol specified limit of 5% or less; and 1% had testosterone Cmax greater than 2500 ng/dL, compared to the protocol specified limit of 0%. Therefore, Tlando did not meet the secondary endpoint and the trial did not provide substantial evidence that the product avoids unacceptably high testosterone concentrations.

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. Though the safety database is considered adequate, there are still some gaps in Tlando's safety profile. The drug's effect on SBP remains unclear: Two trials (LPCN 1021-13-001 and LPCN 1021-16-002) failed to show clinically significant changes in cuff SBP, while one trial (LPCN 1021-16-003) showed an increase of 4 mmHg in cuff SBP. The concern over the SBP results in LPCN 1021-16-003 was reinforced by the SBP findings for another oral TU testosterone also in development. A Phase 3 study for that drug showed an increase in cuff SBP that was confirmed by ABPM in a subsequent Phase 3 study. An increase in SBP is especially important in older men, the patient population most likely to use Tlando, because they are more likely to have other preexisting cardiovascular risk factors. An ABPM study is needed to further characterize this risk.

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. Further assessment of adrenal function over a

longer duration is recommended to rule out the risk of adrenal dysfunction.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Male hypogonadism is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic pituitary-testicular axis.[1] Testosterone replacement therapy is indicated to treat the androgen deficiency component of hypogonadism. • Signs and symptoms of androgen deficiency include reduced sexual desire (libido) and activity, decreased spontaneous erections, loss of body (axillary and pubic) hair, reduced shaving; height loss, low trauma fracture, low bone mineral density; decreased energy, motivation, initiative, and self-confidence; poor concentration and memory; reduced muscle bulk and strength; increased body fat, body mass index; and diminished physical or work performance. • The prevalence of symptomatic androgen deficiency in men 30 to 79 years of age is 5.6% and increases substantially with age.[2] There is also a high prevalence of low testosterone levels in HIV-infected	Hypogonadism is a serious medical condition. Testosterone replacement therapy is recommended for men with classical androgen deficiency syndromes (e.g. Klinefelter's syndrome, Kallmann's syndrome, pituitary tumors) to maintain secondary sex characteristics, sense of well-being, and bone mineral density, and improve sexual function Testosterone therapy is also recommended for patients with chronic illness and low testosterone levels (e.g. HIV-infected men with weight loss) and in men receiving high doses of glucocorticoids. The safety and efficacy of testosterone

[1] Bhasin S Cunningham GR et al. Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. J Clin Endorinol Metab 95: 2536-2559, 2010.
[2] Araujo AB Esche GR et al. Prevalence of Symptomatic Androgen Deficiency in Men. J Clin Endocrinol Metab 92: 4241-4247, 2007.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	men and in men treated with glucocorticoids.	therapy in older men with low testosterone levels has not been demonstrated.
Current Treatment Options	• Testosterone is currently available in the United States as a buccal tablet, subcutaneous implant, transdermal patch, transdermal gel, transdermal solution, nasal gel, and parenteral injection. Testosterone undecanoate is approved only as an intramuscular injection in the US. • These products are approved for testosterone replacement therapy and have demonstrated effectiveness in maintaining testosterone concentrations within the eugonadal range while avoiding unacceptably high serum testosterone concentrations.	Even though there are many approved testosterone products available with different routes of administration, a product with an oral route of administration would be more convenient for patients and would avoid the need for periodic injections. In patients for whom transference of testosterone to a child or female is a concern, an oral product would avoid this risk.
Benefit	• LPCN 1021-16-002 is the pivotal trial supporting the to-be-marketed dosing regimen of Tlando. The trial evaluated the 225 mg dose taken BID without dose titration for 24 days in 95 hypogonadal men. The trial was open-label with a single treatment arm. • The primary efficacy endpoint for the trial was the percentage of Tlando-treated subjects who achieved a 24-hour Cavg serum T concentration within the normal range after 24 days of treatment. The minimum acceptable percentage for demonstrating efficacy was 75% with a lower bound of a 95%, 2-sided, binomial CI of $\geq$ 65%. The percentage of subjects achieving T Cavg within the normal range during LPCN 1021-16-002 was 80% (95% CI 72%, 88%).	The Applicant did not provide substantial evidence of effectiveness for the dosing regimen (225 mg BID without dose titration) proposed for marketing. LPCN 1021-16-002, the pivotal trial that evaluated this dosing regimen met the primary endpoint (proportion of treated subjects with Cavg within the normal range). This provides substantial evidence that Tlando meets the goal of maintaining testosterone concentrations within the eugonadal range.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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 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%) During LPCN 1021-16-002, 74%, 14%, and 1% of the subjects, respectively, met the above predetermined limits. • These primary and secondary endpoints have been used in the pivotal trials for most testosterone products approved for replacement therapy during the past 10 years. • The goal of an effective product indicated for testosterone replacement therapy is to maintain testosterone concentrations within the eugonadal range and to avoid unacceptably high serum testosterone concentrations. Meeting the predetermined limits for the primary and secondary endpoints provides the substantial evidence that a product meets these goals.	However, the study did not meet the secondary endpoint (proportion of subjects with Cmax within the predetermined limits). Therefore, the study did not provide substantial evidence that a dosing regimen of 225 mg BID without dose titration avoids unacceptably high serum testosterone concentrations.
Risk and Risk Management	• A total of 525 hypogonadal men received Tlando for 1 to 382 days in five Phase 1 and three Phase 3 trials. The three Phase 3 trials included: LPCN 1021-13-001, a 52-week trial that evaluated the 225 mg BID dose with dose titration; LPCN 1021-16-002, a 24-day trial that evaluated the 225 mg BID dose without dose titration; and LPCN 1021-16-003, a 24-day trial that evaluated the 150 mg TID dose without dose titration. In the 52-week trial, more than 100 subjects were received Tlando for at least 52 weeks and 68% of	There are still gaps in Tlando's safety profile. The drug's effect on SBP remains unclear: Two trials (LPCN 1021-13-001 and LPCN 1021-16-002) failed to show clinically significant changes in cuff SBP, while a subsequent trial (LPCN 1021-16-003) showed a 4 mmHg increase. An ABPM study is recommended to further characterize this risk.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	these subjects were on a dose equal to or greater than the to-be-marketed dose (225 mg BID). The safety database was consistent with the Division's recommendations during product development. • The safety database is consistent with the population of men expected to use Tlando. The mean age was 51.1 years with most subjects (90%) less than 65 years old. Over half (52.6%) of the subjects were obese (i.e., BMI ≥ 30 kg/m^2). • Safety concern 1: Uncharacterized potential risk of increased systolic blood pressure (SBP). This safety concern is unexpected and is based on the 4 mmHg increase in cuff SBP seen in LPCN 1021-16-003 and recently reported results from a Phase 3 study for another oral TU product. In that study, the oral TU product was shown to increase systolic blood pressure (SBP) by an average of approximately 5 mmHg by ambulatory blood pressure monitoring (ABPM). • Safety concern 2: The potential effects of Tlando on the hypothalamic pituitary adrenal axis have not been fully characterized. This risk was identified in two nonclinical studies. The clinical significance of the nonclinical adrenal findings was assessed in Cosyntropin stimulation sub-studies in LPCN 1021-16-002 and LPCN 1021-16-003. However, the studies' 24-day treatment periods were insufficient to assess whether Tlando, a drug that is expected to be taken chronically, causes adrenal dysfunction. Further assessment of adrenal function over a longer study duration is recommended to rule out a risk of adrenal dysfunction.	The long-term effect of Tlando on the hypothalamic pituitary adrenal axis remains unknown. Though the results of the Cosyntropin stimulation sub-study were reassuring, the study's duration was only 24 days, which was not sufficient to rule out an adrenal effect in a drug that will be taken chronically.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Original submission review (Section 6.1.6 – Other Endpoints)
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

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.

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) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic pituitary-testicular axis."[3] Male hypogonadism, a clinical syndrome 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]).

The 2010 Endocrine Society guidelines recommend replacement therapy for symptomatic men with classical androgen deficiency to induce and maintain secondary sex characteristics and to improve bone mineral density, sexual function, sense of well-being, and muscle mass and strength. Replacement therapy is also recommended for patients with chronic illness and low testosterone levels (e.g. HIV-infected men with weight loss) and in men receiving high doses of glucocorticoids.

The safety and efficacy of testosterone replacement in older men with low testosterone levels has not been demonstrated.

2.2. Analysis of Current Treatment Options

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

[3] Bhasin S Cunningham GR et al. Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. J Clin Endorinol Metab 95: 2536-2559, 2010.

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.

Transdermal testosterone preparations, which are applied to the skin, have been associated with secondary exposure of testosterone to children and women 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 adhere to 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 REMS program that includes Elements to Assure Safe Use.

Even though there are many approved testosterone products available with different routes of administration, a product with an oral route of administration would be more convenient for patients and would avoid the need for periodic injections. In patients for whom transference of testosterone to a child or female is a concern, an oral product would avoid this risk.

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
Parenteral	Depo-testosterone/ testosterone cypionate	50–400 mg every 2 – 4 weeks		085635
	testosterone cypionate	50–400 mg every 2 – 4 weeks		090387 091244 040652 040530 040615 086030 201720 207742
	Delatestryl/testosterone enanthate	50–400 mg every 2 – 4 weeks	009165	
	testosterone enanthate	50–400 mg every 2 – 4 weeks		091120 040647 040575 085598

	Aveed/testosterone undecanoate	750 mg: second dose after 4 weeks, subsequent doses every 10 weeks	022219	
Oral	Testred/methyltestosterone	10-50 mg daily		083976
	Android/methyltestosterone	10-50 mg daily		087147
	methyltestosterone	10-50 mg daily		080767 204851
	Androxy/fluoxymesterone	5-20 mg daily		088342
Implant	Testopel/testosterone	150-450 mg every 3 to 6 months		080911
Transbuccal	Striant/testosterone	30 mg twice daily	021543	
Transdermal Patch	Androderm/testosterone	2-6 mg daily	020489*	
Transdermal Gel	AndroGel/testosterone 1.62%	20.25-81 mg daily	022309	
	testosterone 1.62%	20.25-81 mg daily		204268 205781
	AndroGel/testosterone 1%	50-100 mg daily	021015	
	testosterone gel 1%	50-100 mg daily		076737 076744
	testosterone gel 1%	50-100 mg daily	202763*	
	Testim/testosterone 1%	50-100 mg daily	021454	
	testosterone gel 1%	50-100 mg daily		091073
	Fortesta/testosterone	10-70 mg daily	021463	
	testosterone gel	10-70 mg daily		204571
	testosterone gel (Teva)	50-100 mg daily	202763	
	testosterone gel (Perrigo)	50-100 mg daily	203098	
	Vogelxo/testosterone gel	50-100 mg daily	204399	
Transdermal Solution	Axiron/testosterone	30-120 mg daily	022504*	
	testosterone topical solution	30-120 mg daily		205328 209533 208061 204255
Nasal Gel	Natesto/testosterone	11 mg thrice daily	205488	

*Discontinued
Source: Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), electronic version accessed March 9, 2018. Product labeling accessed at the DailyMed website and the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) March 9, 2018.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Testosterone was initially approved in the United States in 1953. Since that time, many different formulations with various routes of administration have been approved and marketed. Testosterone is currently marketed in the United States as a buccal tablet,

subcutaneous implant, transdermal patch, transdermal gel, transdermal solution, nasal gel, and injectable.

Oral administration of testosterone generally results in low bioavailability due to extensive first-pass metabolism. Methyl testosterone, a 17-alpha-alkyl androgen, is an androgenic preparation given by the oral route that is indicated for testosterone replacement therapy. However, because it is associated with serious hepatic adverse effects, its clinical use is limited.

Testosterone undecanoate is approved in the U.S. only as an intramuscular injection. Although Tlando has not been approved in any other countries, other oral TU products have been approved outside of the U.S. for many years.

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 provide 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.

The Applicant resubmitted the NDA on August 8, 2017.

3.2. Summary of Presubmission/Submission Regulatory Activity

Abbott Laboratories opened the original IND for Tlando (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 (DBRUP) prior to submitting the original NDA.

- **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 Tlando 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.

Lipocine submitted the original NDA for Tlando on August 28, 2015. On June 28, 2016, DBRUP issued a Complete Response (CR) letter for the NDA. The Applicant had an addition meeting with DBRUP after the CR action.

- **October 6, 2016: Type A post-action meeting:** Key meeting discussion included the secondary endpoint (Cmax outliers) and its 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.

3.3. Foreign Regulatory Actions and Marketing History

Tlando is not currently approved in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) conducted inspections of the bioanalytical laboratory used in the Phase 3 study (LPCN 1021-13-001) and two of the clinical sites that participated in that study.

Based on their inspections, OSIS had the following recommendations:

(b) (4) (Bioanalytical laboratory)

- OCP and DBRUP reviewers should evaluate consequences of premature thawing of some serum samples (Subjects (b) (6)) during shipping.

- All other bioanalytical data from the bioanalytical laboratory in this study should be accepted for further Agency review.

Reviewer 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.

Los Angeles BioMedical Research Institute at Harbor UCLA, Torrance, CA (Site 105)

- Data from the clinical portion of study LPCN 1021-13-001 conducted at this site should be accepted for further Agency review.

UTSW Medical Center Urology Lewisville, Lewisville, TX (Site 154)

- Data from the clinical portion of study LPCN 1021-13-001 conducted at this site should be accepted for further Agency review. However, DBRUP and OCP reviewers should evaluate the unexpected elevations of Lipoprotein-Associated Phospholipase (LAP-A2) found in some samples from patients enrolled at this site.

Reviewer comment: Lipoprotein-Associated Phospholipase (LAP-A2) was assessed during the Phase 3 study. Mean LAP-A2 values were similar for the Tlando and AndroGel 1.62% treatment arms throughout the study. Sporadic elevations above the upper limit of the normal range (235 ng/mL) were reported in both treatment groups. In the Tlando treatment group 36% of the subjects had at least one LAP-A2 value greater than 235 ng/mL compared to 44% in the AndroGel 1.62% group. The percentage of subjects with at least one LAP-A2 elevation who were enrolled at site 154 was greater than the percentage for the study in general. The reason for this is not clear.

For the new Phase 3 studies submitted in the re-submission (LPCN 1021-16-002, and LPCN 1021-16-003) OSIS recommended accepting the data without an on-site inspection because the bioanalytical laboratory ([(b) (4)] had been recently inspected with a No Action Indicated (NAI) outcome.

4.2. Product Quality

The OPQ review team conducted a review of product quality. The reviewers had the following recommendations and conclusions:

> 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.

4.3. Clinical Microbiology

The microbiology reviewer conducted a product quality microbiology review of the application and concluded that the microbiology control, as amended, for the product is adequate according to current quality standards

4.4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team conducted a review of preclinical pharmacology and toxicology and concluded that there is no impediment to approval from a pharmacology/toxicology perspective.

4.5. Clinical Pharmacology

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology-3 reviewed the information contained in the resubmission of NDA 208088 and recommends a Complete Response action from a Clinical Pharmacology perspective. The Clinical Pharmacology team recommends the Applicant (1) provide addition information about the *ex vivo* testosterone undecanoate (TU) to testosterone (T) conversion to confirm the reliability of the Phase 3 data and (2) identify a stopping criteria that can reproducibly and accurately identify patients not achieving average total T concentration within the normal range. The stopping criteria should also avoid or minimize inaccurately discontinuing patients with T concentrations within the therapeutic range.

To address the potential ex vivo TU to T conversion, the Clinical Pharmacology team recommends the Applicant conduct a study assessing the potential for ex vivo TU to T conversion using samples collected from subjects dosed with oral TU to remove potential confounding effects of different spiking methods (i.e., differences in solvent). This assessment 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).

In addition, prior to the next NDA resubmission, the Clinical Pharmacology team recommends the Applicant address (1) the potential cross-reactivity of TU to immunoassays used to assess total T concentrations in clinical practice and (2) the potential drug-drug interaction of TU, as the perpetrator. For completeness, they also recommend the Applicant submit the full study report for the new in vitro study evaluating TU conversion to T (referred to as study #2 in this review); the Applicant submitted a brief description of the study design and results on December 27, 2017.

Reviewer comment: Ex-vivo conversion of TU to T could affect the results reported for the Phase 3 trials. My assessment of the trial results assumes no or minimal ex-vivo conversion. However, based on the conclusions of the Clinical Pharmacology review team, *there is some uncertainty that this assumption is correct.*

4.6. Devices and Companion Diagnostic Issues

This application did not include a device or companion diagnostic.

4.7. Consumer Study Reviews

This application did not include any consumer studies.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Studies Submitted to Support the Application

Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Bioavailability Studies					
LPCN 1021-05-001	(1) Assess BA/PK of T following oral administration of LPCN1021 TU capsule formulations; (2) Compare BA/PK of T following LPCN1021 TU capsules to Andriol.	BA/PK of four oral TU capsule formulations	LPCN 1021-01 LPCN 1021-02 LPCN 1021-05 LPCN 1021-06 Andriol	LPCN 24 Andriol: 24	Post-menopausal women
LPCN 1021-09-001	Determine BA/PK of T after single, multiple dosing oral TU capsules. Assess dose proportionality. Evaluate the PK of two LPCN formulations.	Randomized, open-label, single and multiple dose pilot BA/PK study of two oral TU capsule formulations	LPCN 1021-07 LPCN 1021-08 Andriol	36	Hypogonadal males
S361.1.002	Determine the bioavailability and PK of TU, T, DHT, and DHTU after single dose administration under fasted, no-fat, low-fat, normal-fat, and high-fat conditions	Open-label, single dose, pilot food effect study	LPCN 1021-07 LPCN 1021-10	20	Post-menopausal women
LPCN 1021-14-001	Compare rate and extent of absorption of T, DHT, TU, and DHTU following administration of a single oral dose of LPCN as 2 x 112.5 mg capsules under various food and fat content conditions.	Open-label, randomized, four-period, four-treatment, crossover, single-dose BA/PK	LPCN 1021 Registration Lot	14	Hypogonadal males

Comparative Bioavailability Studies					
S361.1.001	Determine BA/PK of T, TU, E2, DHT, DHTU after 75 mg, 150 mg, 225 mg single doses of oral TU capsules	Open-label, single dose BA/ PK	LPCN 1021-07 LPCN 1021-10	24	Hypogonadal males
M13-298	Assess the relative BA of four LPCN formulations after a single dose and 14 days of BID dosing	Single and multiple dose relative BA	LPCN 1021-11 LPCN 1021-12 LPCN 1021-13 LPCN 1021-14 225 mg oral TU BID	32	Hypogonadal males
M12-868	Determine BA of TU capsules from two different lots after single-dose admin.	Open-label, crossover	LPCN 1021-07 75 mg oral TU	12	Post-menopausal women
1111-15-001	Study the bioavailability and PK of LPCN 1111 and LPCN 1021 tablets and capsules	Open-label, randomized, cross-over, single-dose, four-treatment, four-period BA/PK	LPCN 1021 Registration Lot 225 mg TU LPCN 1111 550 mg, testosterone tridecanoate, capsule LPCN 1111 550 mg, testosterone tridecanoate, tablet	10	Post-menopausal women
Pharmacokinetic Study					

M12-778	Assess safety and tolerability of escalating multiple oral doses	Randomized double-blind, pbo-controlled dose escalating	LPCN 1021-07 75, 150, 225 300 mg BID Placebo	84	Hypogonadal males
Efficacy and Safety in Indication					
LPCN 1021-13-001	(1) Determine proportion of LPCN treated subjects who achieved T Cavg0-24h within normal range after ~13 weeks of study treatment. (2)Determine % LPCN treated subjects with Cmax:<1500 ng/dL; 1800-2500 ng/dL; and > 2500 ng/dL after ~ 13 weeks Assess CFB in safety parameters for LPCN and active control, groups. Evaluate CFB in the I-PSS, SF-36 QOL questionnaire, and PDQ for LPCN and control groups.	Multicenter, randomized, open-label, active-control, parallel-group,	LPCN 1021 To-be-Marketed Formulation 225 mg TU titrated to 150 mg or 300 mg oral TU BID, as needed Active Control: AndroGel 1.62%, topical	LPCN 1021: 210 AndroGel 1.62%: 105	Hypogonadal males
LPCN1021-16-002	Primary: To validate a dosing regimen of LPCN 1021 to achieve therapeutic concentrations of T in Hypogonadal Men. Secondary: To assess the safety and tolerability of LPCN 1021.	Multicenter, open-label	LPCN 1021 Registration Lot 225 mg TU, BID	95	Hypogonadal males

LPCN1021-16-003	Primary: To validate an alternate dosing regimen of LPCN 1021 to achieve therapeutic concentrations of T in Hypogonadal Men. Secondary: To assess the safety and tolerability of LPCN 1021.	Multicenter, open-label	LPCN 1021 Registration Lot 150 mg TU, TID	100	Hypogonadal males

Source: NDA 208088 (seq 0026), Module 5.2, Table 5.2 p 1-5.

5.2. Review Strategy

The primary focus of the clinical review for the resubmission was data derived from LPCN 1021-16-002 for efficacy and LPCN 1021-13-001, the pivotal Phase 3 study for the original NDA submission, for safety. LPCN 1021-16-002 is a new Phase 3 study that provides safety, efficacy, and pharmacokinetic data relating to 225 mg of Tlando dosed twice per day 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, which did not meet its primary endpoint; and from the five Phase 1 studies conducted in hypogonadal males (Studies LPCN 1021-09-001, S361.1.001, M12-778, M13-298, and LPCN 1021-14-001) submitted in the original NDA.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. LPCN 1021-16-002: Validation of Dosing Regimen of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men

6.1.1. Study Design

Overview and Objective

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

Trial Design

Basic study design: 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.

Visit 1 & 2: Subjects underwent a screening period to complete the pre-study examinations and to confirm their hypogonadal status. Serum total T below 300 ng/dL based on two consecutive blood samples obtained between 6 and 10 AM, on two separate days at approximately the same time of day, following an appropriate washout of current androgen replacement therapy were used for screening T levels.

Visit 3: A total of 95 hypogonadal men meeting all of the inclusion criteria and none of the exclusion criteria were enrolled in the study and assigned to receive 225 mg of Tlando two times a day for about 24 days (window of 20 to 28 days).

Visit 4: On Day 23, subjects were confined lasting for about 38 hours. Subjects entered the clinic in the afternoon of Day 23 (approximately 14 hours prior to anticipated dosing of the Day 24 morning dose) and remained confined until the 24-hour blood draw on Day 25 was completed. Subjects exited the study on Day 25.

On Day 23, subjects were provided with an evening meal and study drug was administered in the clinic (at approximately 12 hours prior to anticipated dosing on Day 24 morning). Following the administration of the morning dose with a meal on Day 24, intensive PK sampling was carried out. Blood samples were collected at 0 (pre-dose), 2, 3, 4, 5, 6, 8, 12 (prior to evening dose), 14, 15, 16, 17, 18, 20 and 24 hours relative to morning dose.

Trial location: All study sites participating in the trial were located in the U.S.

Key inclusion/exclusion criteria:
The key inclusion criteria were:

- Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism prior to age 65.
- Subjects should be diagnosed to be primary (congenital or acquired) or secondary hypogonadal (congenital or acquired).
- Serum total T below 300 ng/dL based on 2 consecutive blood samples obtained between 6 and 10 AM, on two separate days at approximately the same time of day (between 6 and 10 AM), following an appropriate washout of current androgen replacement therapy.
- Naïve to androgen replacement or has discontinued current treatment and completed adequate washout of prior androgen therapy. Washout must be completed prior to collection of baseline serum T samples to determine study eligibility.

The key exclusion criteria were:

- Clinically significant findings in the pre-study examinations including abnormal breast examination requiring follow-up.
- Abnormal prostate digital rectal examination (DRE) with palpable nodule(s).
- Subjects with symptoms of moderate to severe benign prostatic hyperplasia.
- Clinically significant abnormal laboratory value, in the opinion of the investigator, in serum chemistry, hematology, or urinalysis including but not limited to:
    - Baseline hemoglobin < 11.5 g/dL or > 16.5 g/dL
    - Hematocrit < 35% or > 54%
    - Serum transaminases > 2.5 times upper limit of normal
    - Serum bilirubin > 2.0 mg/dL

  - Creatinine > 2.0 mg/dL
  - PSA > 2 ng/mL
  - Prolactin > 17.7 ng/mL
- History of gastric surgery, cholecystectomy, vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH or absorption.
- History of or current or suspected prostate or breast cancer.
- History of untreated and severe obstructive sleep apnea.

Dose selection: 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 an active controlled, safety and efficacy trial (LPCN 1021-13-001).

M12-778 study was conducted with Tlando and matching placebo in 84 subjects who were divided into 5 groups. In two groups (Groups 3 and 5), subjects were administered 225 mg twice daily Tlando for 15 and 28 days, respectively, in a total of 25 subjects of whom, 24 subjects completed the study. Intensive blood sampling to determine serum pharmacokinetics of T, DHT, TU, DHTU and estradiol were carried out on various days including the last day of dosing (Day 15 for Group 3, Day 28 for Group 5). Based on the serum T Cavg and Cmax endpoints for the study, 225 mg reliably restored the Cavg into the normal range with an acceptable Cmax range.

Based on results from the M12-778 study the dose for this Phase 3 study was 225 mg Tlando administered BID, approximately every 12 hours with a standard meal. The observed Cavg for serum T was within the normal range of 300 to 1140 ng/dL in subjects dosed with 225 mg Tlando BID.

Additionally, in this study, 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 this Phase 3 study, 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 preset 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, this study evaluated a fixed dose 225 mg BID as the recommended dose and dosing regimen with efficacy evaluation at Day 24 (following steady state).

Study treatments: 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.

Dietary restrictions/instructions: Previous studies with Tlando have required subjects to follow a diet with 800 to 1400 calories per meal with 20% to 35% fat content. 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, a 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. Consistent with these recommendations, during confinement periods, subjects were provided with meals that met the caloric requirements by the study site. Study drug was administered in the morning and evening, approximately 30 minutes after breakfast and dinner.

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 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%)).

Statistical Analysis Plan

A review of the statistical analysis plan is provided in the statistical review. No statistical issues were identified.

Protocol Amendments

There were two noteworthy protocol amendments.

> Administrative change #1-November 2, 2016: Screening of subjects should include an electrocardiogram at the screening visit to identify, and subsequently exclude, subjects with long QT syndrome.
>
> Protocol clarification #2-December 19, 2016: Protocol LPCN 1021-16-002 specifies that the Cosyntropin stimulation test will be performed on the first 50 subjects to undergo screening Visit 2. However, the intent of the Sponsor is to perform the Cosyntropin test on 50 subjects during Visit 2, regardless of the order of the subjects undergoing Visit 2.

Neither change is expected to affect the efficacy results of the study. The change to the Cosyntropin-stimulation sub-study is not expected to have a material effect on study results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements.

The protocol, the subject information and informed consent form (ICF), and other relevant study documentation were approved by the Institutional Review Board (IRB) for each study center before initiation of the study.

Financial Disclosure

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 (see Appendix 13.2).

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).

Protocol Violations/Deviations

Evaluation of the protocol deviations to classify them as Major or Minor was conducted by the Applicant. The following general guidelines were followed when classifying protocol deviations as major:

- Subjects who were enrolled but who did not meet all inclusion criteria or met any exclusion criteria.
- Subjects who were significantly noncompliant with study drug administration (took more than 120% of anticipated dose units or less than 80% of anticipated dose units).
- Subjects with significant deviations from following protocol recommended dose or dosing regimen. A significant deviation is defined as when a subject did not take 225 mg two times a day for at least 20 days preceding Visit 4. However, this did not include subjects who had minor deviations of a missed dose.

A total of 4 subjects were reported to have major protocol deviations during the study. Two subjects were enrolled but did not meet all inclusion criteria or met one or more of the exclusion criteria and two subjects were significantly noncompliant with study drug administration.

Table of Demographic Characteristics

Table 3: Demographic and Baseline Characteristics, Safety Set (N=95)

Demographic Parameters	Value
Age (years), Mean (SD)	56.0 (8.9)
≤ 65 Years, n (%)	79 (83.2)
> 65 Years, n (%)	16 (16.8)
Sex, n (%)	
Male	95 (100)
Race, n (%)	
Asian	1 (1.1)
Black or African American	15 (15.8)
White	77 (81.1)
Multiple	2 (2.1)
Ethnicity, n (%)	
Hispanic or Latino	25 (26.3)
Not Hispanic or Latino	70 (73.7)
Body Mass Index (kg/m²), Mean (SD)	32.8 (5.5)
< 25 kg/m², n (%)	3 (3.2)
≥ 25 to < 30 kg/m², n (%)	26 (27.4)
≥ 30 kg/m², n (%)	66 (69.5)
Weight (kg), Mean (SD)	103.6 (18.7)

Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 48, Table 12.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Medical history was obtained at screening and served as the basis for future clinical assessments. The most frequent medical conditions reported included hypertension (49.5%), erectile dysfunction (48.4%), libido decreased (32.6%), back pain (24.2%), obesity (24.2%), and type 2 diabetes mellitus (23.2%).

The most frequent concomitant and prior medications reported included metformin (23.2%), acetylsalicylic acid (21.1%), and lisinopril (15.8%).

Subjects who were naïve to testosterone treatment or who had stopped their current treatment and completed a protocol-specified washout period were permitted to enroll in the study. Prior androgen therapy was reported by 68.4% of subjects.

The mean (SD) baseline testosterone level was 202 (74) ng/dL.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Drug reconciliation was performed to document drug dispensed and drug returned to the study site. Subjects with compliance more than 120% or less than 80% at Day 24 were classified as having major protocol deviations. Overall mean compliance for subjects receiving Tlando was 99.7%.

Efficacy Results – Primary Endpoint

Datasets Analyzed: 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 SS included all subjects who were randomized and received a dose of the study drug. It was the primary analysis population for effectiveness and comprised all 95 of the subjects enrolled in the trial.

The FAS was composed of all subjects with at least one post baseline efficacy variable response (Cavg or Cmax) and included 94 of the 95 enrolled subjects.

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. 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 120% of anticipated dose units or less than 80% of anticipated dose units.
3. Subjects who significantly deviated from follow protocol recommended dose or dosing regimen. The significant deviation is defined as when a subject did not take 225 mg two times a day for at least 20 days preceding Visit 4. However, this does not include subjects who had minor deviations of a missed dose.

Results: 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. For the efficacy endpoint of the study to be met, the minimum acceptable percentage was 75%. A 95%, 2-sided, binomial CI surrounding the point estimate must have had a lower bound of 65% or more to conclude that the treatment was efficacious.

The primary endpoint analysis used the 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 4.

Table 4: 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 5**.

Table 5: 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.

Reviewer comment: Tlando met the primary efficacy endpoint of the study for the prespecified analysis as well as the sensitivity analyses.

Data Quality and Integrity

The Applicant indicated that this study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6) and applicable regulatory requirements including the archiving of essential documents.

No data quality issues were identified.

Efficacy Results – Secondary and other relevant endpoints

Secondary Endpoint
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 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 0%)

The prespecified analysis of the secondary endpoint 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 6**.

Table 6: 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) $\underline{\geq}$ 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.

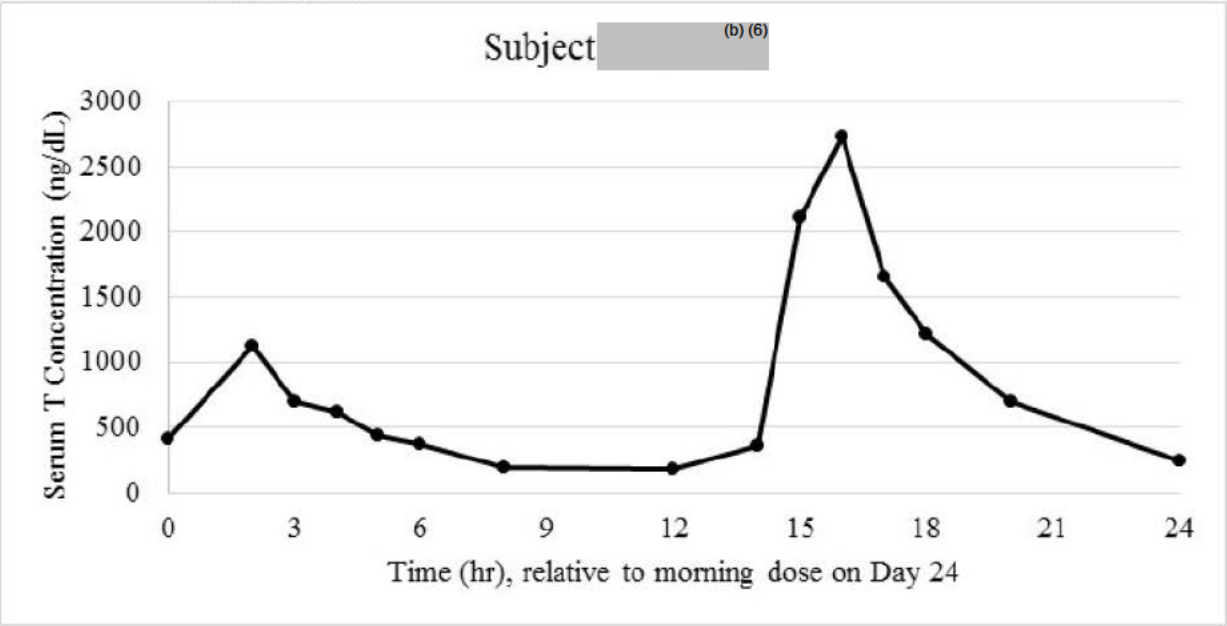
The subject ((b) (6) with Cmax > 2500 ng/dL was a 67-year-old male who had a Cmax value of 2730 ng/dL on Day 24 four hours after the evening dose (16 hours after the morning dose). The subject's medical/surgical history included: hypertension, hemorrhoids, decreased sexual desire, lack of energy, midline ventral hernia, mild benign prostate hyperplasia, myopia, and vasectomy. Concomitant medications included ramipril.

The subject also had a medical history of cholecystectomy, which he did not recall at the time of enrollment but which 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 Applicant, investigator, and medical monitor allowed the subject to remain in the trial.

Figure 1 shows the total serum testosterone concentration-time profile for subject (b) (6)

Figure 1: Total Serum Testosterone Concentration-Time Profile

Subject (b) (6)



Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 (Section 14 Narratives) p. 4, Figure 1.

Reviewer comment: Tlando did not meet the predetermined limits for any of the three components of the secondary endpoint for Cmax(0-24h), the prespecified Cmax time period (24 hours) and, therefore, did not meet the secondary efficacy endpoint.

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.

Other Relevant Assessments

Free Testosterone

Free testosterone values were calculated using the method described by Vermeulen et.al.[4] The calculated mean (SD) free testosterone Cavg(0-24h) was 13 (4.4) ng/dL following 24 days of treatment with Tlando 225 mg BID compared to 4.7 (1.8) ng/dL at baseline. The calculated free T levels following 24 days of treatment were within the normal values of free T, 9 to 30 ng/dL, reported by the Applicant.

Testosterone Metabolites: Dihydrotestosterone (DHT) and Estradiol E2

During LPCN 1021-16-002 (the 225 mg twice daily study), pharmacokinetic assessments for dihydrotestosterone (DHT) and estradiol (E2), the major metabolites of testosterone, were

[4] Vermeulen A Verdonck L et al. A Critical Evaluation of Simple Methods for the Estimation of Free Testosterone in Serum. J Clin Endocrinol Metab 1999 84(10): 3666-3672.

performed on Study Day 24. Serum samples were analyzed for total testosterone, DHT and E2 at (b) (4) Bioanalytical Laboratory by using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

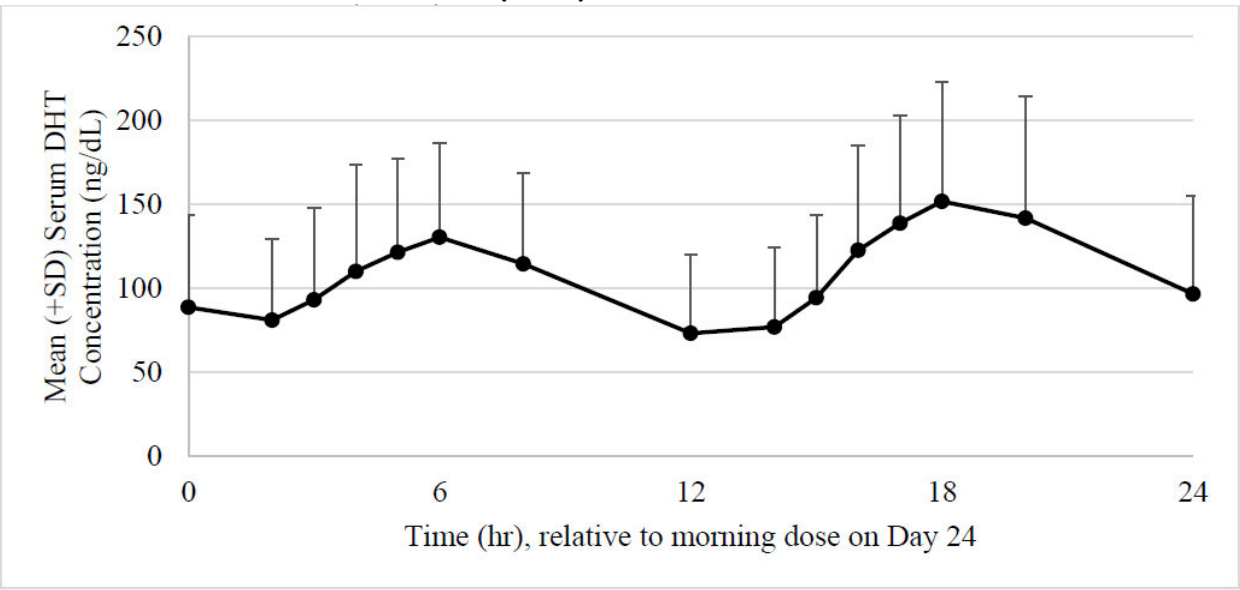
Because (b) (4) is a bioanalytical laboratory and had not established reference intervals for testosterone, DHT, and E2 in normal males, Study RHOD/RHOE was conducted to assess the relative 'analytical system' comparability between (b) (4) LC/MS/MS-based bioanalytical methods for the analysis of total testosterone, DHT, and E2 in human serum, and those of a clinical reference laboratory ((b) (4) Laboratory), which utilized the same analytical technology, to ensure that the testosterone, DHT, and E2 reference intervals established at (b) (4) could be adopted to specimens analyzed at (b) (4) The study objectives were: (1) to conduct limited verifications of the reference intervals, previously established for total testosterone, DHT, and E2 in human serum of normal healthy males by a clinical reference laboratory ((b) (4) Laboratory), by analyzing an appropriate set of subject population samples using (b) (4) LC/MS/MS assays, and (2) to carry out inter-laboratory cross-validations of the respective (b) (4) and clinical reference laboratory LC/MS/MS analytical methods.

Comparison of the results for the serum sample unknowns obtained by (b) (4) and (b) (4) Laboratories indicated very close and fully acceptable agreement for total T, DHT, and E2. The Limited Inter-laboratory Reference Interval Verifications analysis showed that (b) (4) testosterone and E2 results for a 40-sample set of normal subjects were consistent with the reference intervals established for those analytes by (b) (4) However, the DHT results did not verify the (b) (4) reference interval, as greater than 15% (6 out of 40) of the normal sample values exceeded the upper reference limit.

DHT: The DHT reference interval for normal healthy males established by (b) (4) is 10.6 to 71.9 ng/dL. This reference interval was not verified by Study RHOD/RHOE.

During the PK assessment at Day 24, mean pre-dose serum DHT concentrations were 88.4 ng/dL. At 2 hours post-dose, mean DHT concentrations dropped to 80.4 ng/dL and then reached a peak concentration of 129.5 ng/dL at 6 hours post-dose after which time DHT concentrations returned to below pre-dose levels (72.1 ng/dL and 75.8 ng/dL at 12 and 14 hours post dose, respectively). The DHT concentration pattern after the evening dose was similar to the pattern observed after the morning dose with mean serum DHT concentrations reaching peak concentrations of 149.6 ng/dL at 6 hours after the evening dose (18-hour time point from pre-dose). **Figure 2** displays the DHT concentration verses time curve for the PK Set during the 24-hour PK assessment at Day 24.

Figure 2: Mean (± SD) Dihydrotestosterone Concentration vs. Time Curve at Visit 4 PK Set (N=90) LPCN 1021-16-002



Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 56, Figure 2.

PK parameters for DHT on Day 24 are summarized in **Table 7**.

Table 7: Pharmacokinetic Parameters for Serum Dihydrotestosterone after Tlando Dosing at Visit 4 PK Set (N=90) LPCN 1021-16-002

	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/dL	Mean (SD)	108 (46)	--	--
Cmax, ng/dL	Mean (SD)	179 (72)	152 (64)	168 (74)
Tmax, h	Median (min, max)	16.9 (2.0, 24.0)	5.9 (1.9, 11.9)	5.9 (2.0, 12.0)

Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 56, Table 21.

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. DHT outliers are summarized in **Table 8**.

Table 8: Proportion of Subjects with DHT Cavg and Cmax in the Normal Range, and at Various Levels Above the ULN
PK Set (N=90) LPCN 1021-16-002

Parameter	N	n (%) of Subjects Above			
		ULN	2 times ULN	3 times ULN	5 times ULN
Cavg (ng/dL)	90	71 (78.9)	17 (18.9)	2 (2.2)	0
Cmax (ng/dL)	90	87 (96.7)	60 (66.7)	26 (28.9)	2 (2.2)

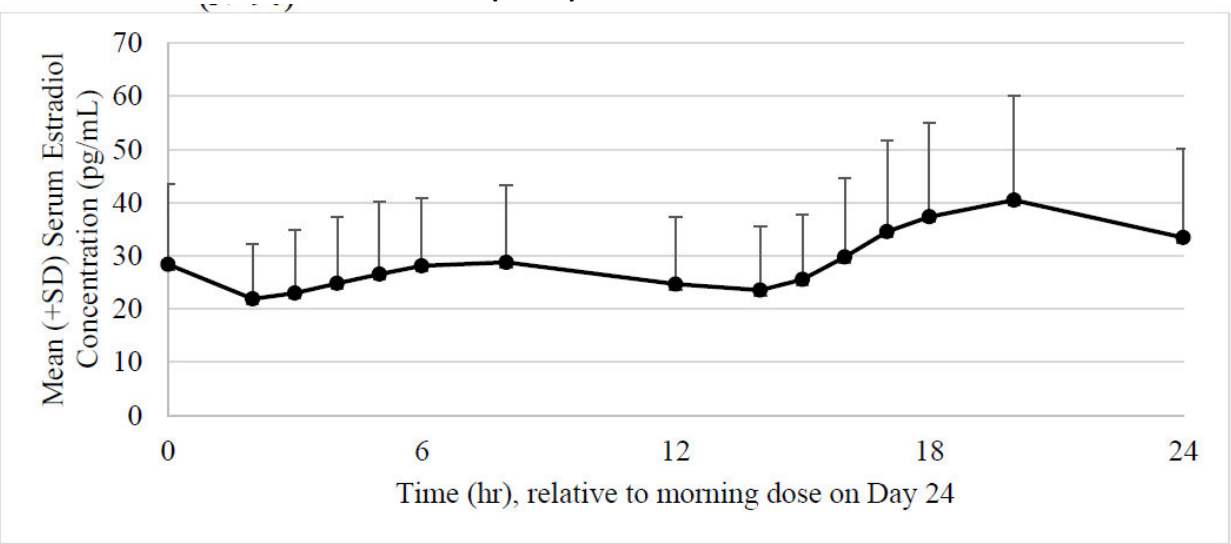
Source: NDA 208088 (seq 0035), 1.2, Table 2, p. 2.

Reviewer comment: In my opinion, there is a risk that patients treated with Tlando 225 mg BID without titration will have DHT concentrations that exceed the normal range. The extent of that risk is unclear because the reference range used by the Applicant failed a verification assessment with samples from normal healthy males.

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. **Figure 3** displays the E2 concentration verses time curve for the PK Set during the 24-hour PK assessment at Day 24.

Figure 3: Mean (± SD) Estradiol Concentration vs. Time Curve at Visit 4
PK Set (N=90) LPCN 1021-16-002



Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 59, Figure 5.

PK parameters for E2 on Day 24 are summarized in **Table 9**.

Table 9: Pharmacokinetic Parameters for Estradiol after Tlando Dosing at Visit 4
PK Set (N=90) LPCN 1021-16-002

	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/dL	Mean (SD)	29 (13)	--	--
Cmax, ng/dL	Mean (SD)	44 (20)	34 (16)	43 (20)
Tmax, h	Median (min, max)	18.0 (4.0, 24.7)	6.0 (2.0, 12.0)	7.9 (0, 12.7)

Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 59, Table 24.

E2 outliers are summarized in **Table 10**.

Table 10: Proportion of Subjects with Estradiol Cavg and Cmax in the Normal Range, and at Various Levels Above the ULN
PK Set (N=90) LPCN 1021-16-002

Parameter	N	n (%) of Subjects Above			
		ULN	2 times ULN	3 times ULN	5 times ULN
Cavg (pg/mL)	90	14 (15.6)	0 (0)	0 (0)	0 (0)
Cmax (pg/mL)	90	41 (45.6)	3 (3.3)	0 (0)	0 (0)

Source: NDA 208088 (seq 0035), 1.2, Table 5, p. 3.

Reviewer comment: For E2, the mean Cavg was within the normal range and the mean Cmax was slightly greater than the upper limit. About 16% of subjects exceeded the ULN, none of these subjects had a value that was greater than 2 times the upper limit.

Dose/Dose Response

Dose response was not assessed in this trial.

Durability of Response

Durability of response was not assessed in this trial.

Persistence of Effect

Persistence of effect was not assessed in this trial.

Additional Analyses Conducted on the Individual Trial

Body Mass Index: Subgroup analyses of primary efficacy endpoint and pharmacokinetics of serum T were conducted for low and high BMI (BMI < 30 kg/m2 and ≥ 30 kg/m2). For the FAS, 93% of non-obese subjects and 75% of obese subjects achieved T Cavg0-24 between 300 to 1080 ng/dL with corresponding lower bound 95% confidence intervals of 84% and 65%,

respectively. Therefore, the percentage of subjects with T Cavg0-24 between 300 and 1080 met the pre-specified targets of ≥ 75% in both BMI groups including the corresponding 95% CI being ≥ 65%. **Table 11** presents the proportion of subjects achieving T Cavg0-24 within the normal range based on BMI.

Table 11: Proportion of Subjects with T Cavg (0-24) within Normal Range at Visit 4 in Non-Obese (BMI < 30 kg/m2) and Obese Subjects (BMI ≥ 30 kg/m2) FAS (N = 94)

Parameter	BMI < 30 kg/m^2 (N=29)	BMI ≥ 30 kg/m^2 (N=65)
% subjects achieving 24-hour average serum T concentration within normal range	93%	75%
95% Confidence interval	84 %, 100 %	65 %, 86 %

Source: NDA 208088 (seq 0026), Module 5.3.5.2, CSR LPCN1021-16-002 p. 61, Table 25.

Reviewer comment: Based on the subgroup analysis of obese (BMI ≥ 30 kg/m$^{2)}$ and non-obese (BMI < 30 kg/m^2) subjects, the drug is expected to be less effective in obese patients compared to non-obese patients.

6.2. LPCN 1021-16-003: Dosing Flexibility Study of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men

Study LPCN 1021-16-003 was a Phase 3, open-label, multicenter, uncontrolled study evaluating the efficacy and safety of Tlando in adult hypogonadal males. Similar to LPCN 1021-16-002, subjects received 450 mg of Tlando per day. However, the dosing regimen in LPCN 1021-16-003 was a fixed dose of 150 mg of Tlando three times a day, after a meal. Other than the dosing regimen, the trial design, including the primary and secondary endpoints, inclusion and exclusion criteria, and dietary instructions was similar to the design of LPCN 1021-16-002.

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 study failed to meet its primary endpoint, but met each of the criteria for the secondary endpoint. The efficacy results are displayed in **Table 12** and **Table 13**.

Table 12: 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 13: 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, CSR LPCN1021-16-003, Table 17, p. 53.

6.3. LPCN 1021-13-001: Active-Controlled, Safety and Efficacy Trial of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men

LPCN 1021-13-001 was a 52-week active control (AndroGel 1.62%) randomized trial. The efficacy for Tlando treated subjects was assessed after 13 weeks of treatment. All subjects started at the same dose of 225 mg (2 capsules of 112.5 mg) taken BID approximately 12 hours apart (total daily dose of 450 mg) and approximately 30 minutes after morning and evening meals with water. Dose titration could occur at Weeks 4 and 8. The dose could be increased to 300 mg BID or decreased to 150 mg BID based on predetermined Cavg and Cmax values obtained during the PK assessments at Weeks 3 and 4. The efficacy results for the study are displayed in **Table 14** and **Table 15**.

Table 14: Proportion of Tlando-Treated Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range at Week 13 Efficacy Population Set (N=151)

Parameter	Target	Efficacy Population Set N=151
Percentage subjects achieving T Cavg within normal range[1]	≥ 75%	87%
95% Confidence interval (lower, upper bound)	≥ 65% (Lower Bound)	82%, 93%

[1]Normal Range: 300 to 1040 ng/dL
Source: NDA 208088 (seq 0000), Module 5.3.5.1, CSR LPCN1021-13-001, Table 22, p. 77.

Table 15: Proportion of Tlando-Treated Subjects Achieving Maximum Serum Total T Concentrations (Cmax) within Predetermined Limits at Week 13 Efficacy Population Set (N=151)

Measure	Target	Cmax (0-24h) N=100
Cmax < 1500 ng/dL, (%)	≥ 85%	83%
1800 ≤ Cmax ≤ 2500 ng/dL, (%)	≤ 5%	5%
Cmax > 2500 ng/dL (%)	0%	2%

Source: NDA 208088 (seq 0000), Module 5.3.5.1, CSR LPCN1021-13-001, Table 24, p. 79.

A complete description of this trial is provided in the review of the original NDA submission.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary endpoint for all three Phase 3 studies (LPCN 1021-13-001, LPCN 1021-16-002 and LPCN 1021-16-003) was the proportion of Tlando-treated subjects who achieve a 24-hour average serum T concentration within the normal range upon completion of treatment. The minimum acceptable percentage is 75%. A 95%, 2-sided, binomial confidence interval surrounding the point estimate must have a lower bound of $\geq$ 65%.

Both LPCN 1021-13-001 (225 mg BID with titration up to 300 mg BID or down to 150 mg BID at weeks 4 and 8) and LPCN 1021-16-002 (225 mg BID without titration) achieved the primary endpoint. LPCN 1021-16-003 (150 mg TID without titration) failed to achieve the primary endpoint. The results for the primary endpoint are summarized in **Table 16**.

Table 16: Proportion of Tlando-Treated Subjects Achieving 24-hour Cavg Serum Testosterone Concentration within Normal Range[1] on Efficacy Day

Study	Limit	LPCN 1021-13-001	LPCN 1021-16-002	LPCN 1021-16-003
Dosing Regimen	--	225 mg BID with titration[2]	225 mg BID no titration	150 mg TID no titration
Subject population	--	EPS N=151	Safety set N=95	Safety set N=100
% subjects achieving T Cavg within the normal range	$\geq$ 75 %	87%	80%	69%
95% Confidence interval (lower, upper bound %)	$\geq$ 65% (Lower Bound)	82%, 93%	72%, 88%	60%, 78%

EPS = Efficacy Population Set (subjects with at least 1 postbaseline efficacy variable response who did not have a major protocol deviation)
[1]Normal Range: 300 to 1140 ng/dL (LPCN 1021-13-001); 300 to 1080 ng/dL (LPCN 1021-16-002 and LPCN 1021-16-003)
[2]Subjects could be titrated up or down 75 mg at weeks 4 and 8.

Reviewer comment: For the 225 mg BID dose, dose titration(s) increased the percentage of subjects achieving serum T Cavg within the normal range compared to dosing without titration (87% vs 80%). The 150 mg TID dose did not achieve the minimum percentage of subjects in the normal range necessary to consider that dose and regimen effective.

7.1.2. Secondary and Other Endpoints

The secondary endpoint for the three Phase 3 studies was based on the proportion of subjects with T Cmax(0-24h) values within various predetermined limits.

The predetermined limits are:

1. T Cmax ≤ 1500 ng/dL: ≥ 85%
2. T Cmax between 1800 and 2500 ng/dL: ≤ 5%
3. T Cmax > 2500 ng/dL: 0%

Neither LPCN 1021-13-001 nor LPCN 1021-16-002 met all three of the components established for the secondary endpoint. LPCN 1021-13-001 (225 mg BID with dose titration) met one of the components (1800 ≤ Cmax ≤ 2500 ng/dL), while LPCN 1021-16-002 (225 mg BID without dose titration) met none of the components. Only LPCN 1021-16-003 met all three of the components, however, that trial did not meet the primary endpoint. The results for the secondary endpoint are summarized in **Table 17**.

Table 17: Proportion of Tlando-Treated Subjects Achieving Serum Total T Cmax within Predetermined Limits on Efficacy Day

Study	Limit	LPCN 1021-13-001	LPCN 1021-16-002	LPCN 1021-16-003
Dosing Regimen	--	225 mg BID with titration[1]	225 mg BID no titration	150 mg TID no titration
Subject population	--	EPS Set N=151	Safety set N=95	Safety set N=100
Cmax < 1500 ng/dL, (%)	≥ 85	83%	74%	95%
1800 ≤ Cmax ≤ 2500 ng/dL (%)	≤ 5%	5%	14%	1%
Cmax > 2500 ng/dL (%)	0%	2%	1%	0%

EPS = Efficacy Population Set (subjects with at least 1 postbaseline efficacy variable response who did not have a major protocol deviation)
[1]Subjects could be titrated up or down 75 mg at weeks 4 and 8.

*Reviewer comment: Additional data for the 225 mg BID dose without titration were available from the Week 3 PK assessment in LPCN 1021-13-001. During this study, the first opportunity for dose titration occurred at Week 4 (based on the results of the Week 3 PK assessment), therefore, all subjects were being dosed with a fixed dose of 225 mg BID of Tlando during the first 3 weeks of the study. The results of a post-hoc analysis of the secondary endpoint using data from the Week 3 PK assessment are summarized in **Table 18**.*

Table 18: Proportion of Tlando-Treated Subjects Achieving Serum Total T Cmax within Predetermined Limits at Week 3 PK Assessment Prior to First Titration[1] (LPCN 1021-13-001)

Study	***Limit***	***LPCN 1021-13-001 (Week 3)***
Dosing Regimen	--	*225 mg BID fixed dose prior to first titration*
Subject population	--	*EPS Set N=151*
Cmax < 1500 ng/dL, (%)	*≥ 85*	*68%*
1800 ≤ Cmax ≤ 2500 ng/dL (%)	*≤ 5%*	*12%*
Cmax > 2500 ng/dL (%)	*0%*	*5%*

EPS = Efficacy Population Set (subjects with at least 1 postbaseline efficacy variable response who did not have a major protocol deviation)
[1]All subjects were dosed with 225 mg BID of the drug during the first 3 weeks of the study.
Reviewer analysis: Dataset ADPP LPCN 1021-13-001

These results are consistent with the results from LPCN 1021-16-002 – Tlando did not meet the prespecified limits for any of the components of the secondary endpoint when dosed at 225 mg BID without titration.

7.1.3. Subpopulations

Study results could not be pooled because of differences in study design, doses, and dosing regimen. Refer to Section 6.1.2 Additional Analyses Conducted on the Individual Trial for the subpopulation analysis in LPCN 1021-16-002.

7.1.4. Dose and Dose-Response

The Applicant conducted Study M12-778 to assess the safety, tolerability, and PK of escalating doses of Tlando. The study evaluated multiple oral dose administration of 75 mg LCPN 1021 capsules at the 75 mg, 225 mg, and 300 mg dose levels for 15 days and at the 225 mg and 300 mg dose levels for 29 days under fed conditions. Average T concentrations (Cavg) in the eugonadal range within a dosing interval were consistently achieved with the 225 mg dose level with mean Cmax exceeding 1000 ng/dL only during Day 1 and Day 8 in both the 15- and 29-day dosing regimens. Dose escalation to the 300 mg dose resulted in increased serum T levels. The 75 mg dose level resulted in T concentrations that were deemed to be sub-therapeutic.

Steady state appeared to be reached after approximately 14 days of BID dosing.

The 225 mg BID dose was evaluated in LPCN 1021-13-001 and LPCN 1021-16-002. In LPCN 1021-13-001 the dose could be titrated up or down by 75 mg at Weeks 4 or 8. In LPCN 1021-16-002 the dose was fixed for the entire trial. Both studies met the primary, but not the secondary, efficacy endpoint.

A 150 mg TID fixed dose was evaluated in LPCN 1021-16-003. This study did not meet the

primary efficacy endpoint.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Based on the results of Study M12-778, the time to onset of treatment effect (steady state) was reached after about 14 days of BID dosing. Duration and durability of efficacy effects were not evaluated. Efficacy was not evaluated after Week 13 in LPCN 1021-13-001 and Day 24 in LPCN 1021-16-002 and LPCN 1021-16-003.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

During LPCN 1021-13-001 the dose of Tlando could be titrated a Week 4 and Week 8 based on predetermined values of Cavg(0-24h) and Cmax(0-24h) observed during the PK assessments performed at Weeks 3 and 4. Since titration based on a 24-hour PK assessment of the patient is not feasible in the postmarket setting, the Applicant submitted a titration scheme based on a single blood draw that it proposed to use for the dosing recommendations in labeling.

The single blood draw titration scheme should maintain reasonable agreement between titration decisions made in the Phase 3 trial (based on Cavg and Cmax) and titration decisions made using the titration scheme based on a single blood draw. In approximately 35% of the subjects in LPCN 1021-13-001 the titration decisions that would be based on a single blood draw did not agree with the titration decisions made during the Phase 3 study. This resulted in a Complete Response action for the original NDA submission.

Both LPCN 1021-16-002 and LPCN 1021-16-003 circumvent this issue by using a fixed dosing regimen without titration.

7.2.2. Other Relevant Benefits

Tlando's oral route of administration would be more convenient for patients and would avoid the need for periodic injections. In addition, in patients for whom topical gels pose a risk of transference of testosterone to a child or female, an oral product avoids this risk.

7.3. Integrated Assessment of Effectiveness

The goal of an effective testosterone product indicated for replacement therapy is to maintain testosterone concentrations within the eugonadal range and avoid unacceptably high serum testosterone concentrations. The substantial evidence that a drug product meets these goals is derived from a Phase 3 study with primary and secondary endpoints based on a pharmacokinetic assessment. The primary endpoint is the proportion of treated subjects who achieve a 24-hour average T concentration within the normal range. The Division's minimum

acceptable percentage for this proportion is 75%, with a lower bound of ≥ 65% for the 95%, 2-sided, confidence interval. The secondary endpoint is the proportion of treated subjects with T Cmax(0-24h) values within various predetermined limits. The Division's predetermined limits are:

1. T Cmax ≤ 1500 ng/dL: ≥ 85%
2. T Cmax between 1800 and 2500 ng/dL: ≤ 5%
3. T Cmax > 2500 ng/dL: 0%

In LPCN 1021-16-002, the pivotal trial that evaluated the to-be-marketed dosing regimen of 225 mg BID without dose titration, Tlando met the primary endpoint. This provides substantial evidence that the drug meets the goal of maintaining testosterone concentrations within the eugonadal range. However, the drug did not meet the secondary endpoint. Therefore, the study did not provide substantial evidence that a dosing regimen of 225 mg BID without dose titration avoids unacceptably high serum testosterone concentrations.

8. Review of Safety

8.1. Safety Review Approach

The primary source of safety data is LPCN 1021-13-001 a 52-week, randomized, active controlled trial that evaluated the 225 mg BID dose of Tlando with dose titration. 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. Supportive sources of safety data were LPCN 1021-16-002, a 24-day trial that evaluated the 225 mg BID dose without dose titration; and LPCN 1021-16-003, a 24-day trial that evaluated the 150 mg TID dose without dose titration; and five Phase 1 studies.

During the development program for another oral TU drug product, increases in cuff systolic blood pressure were demonstrated during a Phase 3 study. This finding was confirmed in an ABPM study conducted as part of another Phase 3 study for the same drug. Based on these findings, increased systolic blood pressure is considered a potential safety issue for oral TU drugs and particular attention was paid to the blood pressure data during the review of Tlando.

Adrenal findings were noted during two nonclinical studies conducted by the Applicant. To assess the clinical significance of the nonclinical adrenal findings, the Applicant included a Cosyntropin stimulation sub-study in LPCN 1021-16-002 and LPCN 1021-16-003. The results of the sub-studies are presented in Section 8.5.2 Potential Effects on the Hypothalamic Pituitary Adrenal Axis.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Phase 1 and Phase 3 Studies
Duration (days) and amount (mg) of exposure were summarized for each treatment/dose group. The denominators for calculating the percentages were based on the number of patients with exposure data for each treatment/dose group.

For the 525 hypogonadal men who received Tlando in the supportive and pivotal safety studies (single and multiple dose periods), Tlando was received for a median 26 days (range of 1 to 382 days) with 56.4% of the subjects receiving study drug for ≤4 weeks and 25.1% of subjects receiving study drug for more than 39 weeks. **Table 19** summarizes the extent of exposure for the Phase 1 and Phase 3 studies.

Table 19: 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
Total Dose (mg)					
N	3781	520	34	101	18
Mean (SD)	59793.65 (68108.89)	47506.30 (61485.768)	338.82 (407.00)	18015.52 (8687.05)	7850.00 (5551.37)
Median	17100.00	12825.00	80.00	18759.60	6525.00
Q1, Q3	2475.00, 118125.00	6525.00, 98550.00	80.00, 960.00	12457.80, 23571.00	4350.00, 12825.00
Min, Max	0.0, 217050.0	0.0, 217050.0	80.0, 960.0	874.8, 39317.4	1500.0, 17100.0

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 20 displays extent of exposure data for the supportive and pivotal safety studies combined with multiple dose periods by Tlando dose level. 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.

Table 20: Summary of Extent of Exposure by Dose Level for Supportive and Pivotal Safety Studies (Multiple Tlando Dose Period) – Safety Population

Assessment	Original ISS 75 mg BID N = 16	Original ISS 100 mg BID N = 19	Original ISS 150 mg BID N = 82	Updated ISS 150 mg TID N=100	Original ISS 225 mg BID N = 170	Updated ISS 225 mg BID N=265	Updated ISS 450 mg Daily Dose N=314	Original ISS 300 mg BID N = 40
Days of Exposure, n	16	19	82	100	170	265	314	40
Mean (SD)	15.0 (0.00)	7.9 (0.23)	217.4 (157.39)	26.2 (2.85)	171.7 (166.45)	119.0 (150.78)	108.8 (140.44)	226.2 (155.15)
Median	15.0	8.0	320.5	26.0	73.5	26.0	30.5	363.5
Q1, Q3	15.0, 15.0	8.0, 8.0	52.0, 365.0	24.0, 28.0	15.0, 365.0	21.0, 359.0	23.0, 96.0	52.5, 366.0
Min, Max	15, 15	7, 8	14, 374	21, 35	1, 382	1, 382	1, 382	29, 373
Interval (weeks), n (%)								
[0,4]	16 (100)	19 (100)	16 (19.5)	81 (81.0)	65 (38.2)	154 (58.1)	144 (45.9)	0
(4,13]	0	0	16 (19.5)	19 (19.0)	23 (13.5)	29 (10.9)	88 (28.0)	15 (37.5)
(13,26]	0	0	4 (4.9)	0	8 (4.7)	8 (3.0)	8 (2.5)	2 (5.0)
(26,39]	0	0	4 (4.9)	0	5 (2.9)	5 (1.9)	5 (1.6)	2 (5.0)
>39	0	0	42 (51.2)	0	69 (40.6)	69 (26.0)	69 (22.0)	21 (52.5)
Total Dose (mg)								
n	16	19	82	98	168	262	310	39
Mean (SD)	2175.00 (0.00)	1194.74 (22.94)	66103.35 (46826.25)	11082.40 (1693.697)	73841.52 (69786.47)	51223.57 (63517.359)	46795.65 (59279.604)	120340 38 (84310.23)
Median	2175.00	1200.00	87900.00	10800.00	35100.00	11475.00	12937.50	126075.00
Q1, Q3	2175.00, 2175.00	1200.00, 1200.00	21300.00, 113025.00	10200.00, 11850.00	6525.00, 153450.00	9450.00, 127125.00	9900.00, 61425.00	17100.00, 205837.50
Min, Max	2175.0, 2175.0	1100.0, 1200.0	3900.0, 130050.0	6600.0, 19350.0	0.0, 176400.0	0.0, 176400.0	0.0, 176400.0	4500.0, 217050.0

Studies included: LPCN 1021-16-002, LPCN 1021-16-003, LPCN 1021-13-001, LPCN 1021-09-001, M12-778, and M13-298
Extent of exposure (days) was calculated as the sum of the difference between the last dose date and the first dose date plus one day for each period.
[ ] = inclusive; ( ) = exclusive.
Denominators for percentages are based on the number of subjects in the analysis population with exposure to each treatment.
Original ISS: Includes only data from studies included in the Original ISS.
Updated ISS: Includes data from new studies (LPCN 1021-16-002/003) integrated with studies included in the Original ISS.
Source: NDA 208088 (seq 0026), Module 2.7.4, Table 10, p. 39.

Study LPCN 1021-13-001 (52-week randomized controlled study)

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 Tlando 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 Tlando, 130 were exposed for 52 weeks. **Table 21** summarizes the extent of exposure for Study LPCN 1021-2013-001.

Table 21: Summary of Extent of Exposure
Study LPCN 1021-13-001 – Safety Population

Assessment	Tlando N = 210	AndroGel 1.62% N = 104[1]
Extent of Exposure (days)		
n	210	104
Mean (SD)	260.0 (144.01)	290.5 (123.16)
Median	364.0	364.0
Q1, Q3	88.0, 366.0	189.5, 366.0
Min, Max	1, 382	1, 382
Interval (weeks), n (%)		
[0,4]	17 (8.1)	7 (6.7)
(4,13]	36 (17.1)	8 (7.7)
(13,26]	14 (6.7)	9 (8.7)
(26,39]	11 (5.2)	7 (6.7)
>39	132 (62.9)	73 (70.2)
Total Dose (mg)		
N[2]	207	101
Mean (SD)	105678.99 (61612.71)	18015.52 (8687.05)
Median	113887.50	18759.60
Q1, Q3	40950.00, 156712.50	12457.80, 23571.00
Min, Max	0.0, 217050.0	874.8, 39317.4

[1]One subject was randomized to AndroGel 1.62% but did not receive treatment.
[2]Three subjects each in Tlando and AndroGel treatment arms did not have their final dose data available at 52 Weeks / early termination and therefore their total exposure was not estimated.
Extent of exposure (days) calculated as sum of the difference between the last dose date and the first dose date plus one day for each period.
[ ] = inclusive; ( ) = exclusive.
Denominators for percentages are based on the number of subjects in the analysis population with exposure to each treatment.
Source: NDA 208088 (seq 0026), Module 2.7.4, Table 5, p. 34.

Slightly more than half of subjects in the safety set (113 of 210, 53.8%) were on the final dose of 225 mg and had a median exposure of 364.0 days. For subjects with a final Tlando dose of 225 mg, 69 (61.1%) received the dose for more than 39 weeks and the median total dose received was 144,000.00 mg. For subjects with a final dose of 150 mg Tlando, the median number of days of exposure was 363.0 days, the median dose was 102,000.00 mg, and 42 (63.6%) subjects received the dose for more than 39 weeks. For subjects with a final dose of 300 mg Tlando, the median number of days of exposure was 365.0 days, the median dose was 197,475.00 mg, and 21 (67.7%) subjects received the dose for more than 39 weeks. **Table 22** displays extent of exposure data for Study LPCN 1021-13-001 by final Tlando dose level.

Table 22: Summary of Extent of Exposure by Final Dose Level for Study LPCN 1021-13-001 (Multiple Tlando Dose Period) – Safety Population

Assessment	150 mg N = 66	225 mg N = 113	300 mg N = 31
Extent of Exposure (days)			
n	66	113	31
Mean (SD)	266.5 (135.41)	249.9 (153.07)	283.5 (127.41)
Median	363.0	364.0	365.0
Q1, Q3	93.0, 365.0	77.0, 366.0	182.0, 367.0
Min, Max	36, 374	1, 382	49, 373
Interval (weeks), n (%)			
[0,4]	0	17 (15.0)	0
(4,13]	16 (24.2)	14 (12.4)	6 (19.4)
(13,26]	4 (6.1)	8 (7.1)	2 (6.5)
(26,39]	4 (6.1)	5 (4.4)	2 (6.5)
>39	42 (63.6)	69 (61.1)	21 (67.7)
Total Dose (mg)			
n	66	111	30
Mean (SD)	81080.68 (39561.44)	107971.62 (62658.69)	151312.50 (70809.80)
Median	102000.00	144000.00	197475.00
Q1, Q3	36150.00, 113587.50	38137.50, 160312.50	85875.00, 207300.00
Min, Max	9450.0, 130050.0	0.0, 176400.0	4500.0, 217050.0

Extent of exposure (days) calculated as sum of the difference between the last dose date and the first dose date plus one day for each period.
[ ] = inclusive; ( ) = exclusive.
Denominators for percentages are based on the number of subjects in the analysis population with exposure to each treatment.
Source: NDA 208088 (seq 0026), Module 2.7.4, Table 6, p. 35.

8.2.2. Relevant characteristics of the safety population:

The demographic and baseline characteristics 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 provided in this section.

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/m²). **Table 23** presents demographic and baseline characteristics by treatment group for subjects in the supportive and pivotal safety studies combined.

Table 23: 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.

8.2.3. Adequacy of the safety database:

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. The demographics and baseline characteristics are similar between the Original ISS and the Updated ISS and are representative of the patient population likely to use Tlando.

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 Section 8.9.1 – Safety Concerns Identified Through Postmarketing Experience).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

In the Cosyntropin stimulation sub-study (LPCN 1021-16-002 and LPCN 1021-16-003), the Applicant relied on pooled data and mean change in cortisol level to assess the adrenal

response to Cosyntropin after TU exposure. This analysis did not sufficiently address whether short-term TU exposure leads to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. The data required reanalysis to determine the proportion of subjects with a normal baseline test who develop an abnormal result after TU exposure. In addition, the Applicant did not use the generally accepted clinical criteria for assessment of the adrenal response to Cosyntropin stimulation. Reanalysis using the currently accepted criteria was necessary to evaluate these data.

8.3.2. Categorization of Adverse Events

Different MedDRA versions were used in the coding of AE terms in the clinical trials. LPCN 1021-13-001 study events were coded using MedDRA 16.1, LPCN 1021-14-001, LPCN 1021-16-002, and LPCN 1021-16-003 study events were coded using MedDRA 17.1 while earlier Phase 1 studies used even earlier versions. In the ISS, all AEs reported in supportive and pivotal safety studies were up-coded to MedDRA 17.1. Therefore, for pivotal safety data presented alone, adverse events are reported using MedDRA 16.1 and where supportive and pivotal safety data are integrated, adverse events are reported using MedDRA 17.1. Seven AEs that occurred during the LPCN 1021-13-001 study were affected by differences in MedDRA coding and are summarized in **Table 24**.

Table 24: Adverse Events Affected by Different MedDRA Versions for LPCN 1021-13-001 Study Coding

AE Verbatim	MedDRA 16.1 Preferred Term	MedDRA 16.1 System Organ Class	MedDRA 17.1 Preferred Term	MedDRA 17.1 System Organ Class
Balantitis	Balanitis	Reproductive System And Breast Disorders	Balanoposthitis	Reproductive System And Breast Disorders
Epididymitis	Epididymitis	Reproductive System And Breast Disorders	Epididymitis	Infections And Infestations
Irritability	Irritability	General Disorders And Administration Site Conditions	Irritability	Psychiatric Disorders
Seasonal Allergic Rhinitis	Rhinitis Seasonal	Respiratory, Thoracic And Mediastinal Disorders	Seasonal Allergy	Immune System Disorders
Therapeutic Response Unexpected	Therapeutic Response Unexpected	General Disorders And Administration Site Conditions	Therapeutic Response Changed	General Disorders And Administration Site Conditions
Soft Stools	Diarrhoea	Gastrointestinal Disorders	Faeces Soft	Gastrointestinal Disorders
Skin Abrasion	Excoriation	Injury, Poisoning And Procedural Complications	Skin Abrasion	Injury, Poisoning And Procedural Complications

Source: NDA 208088 (seq 0026), Module 2.7.4, Table 25, p. 62.

8.3.3. Routine Clinical Tests

Routine clinical testing of subjects was conducted throughout the Phase 3 studies and appears to be adequate.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in any of the Phase 1 or Phase 3 studies of Tlando.

8.4.2. Serious Adverse Events

Study LPCN 1021-13-001

During LPCN 1021-13-001, a total of 19 treatment-emergent serious adverse events (SAE) were reported for 14 subjects (4.5%). For the Tlando 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 Tlando and AndroGel 1.62% groups. **Table 25** summarizes the treatment-emergent SAEs during Study LPCN 1021-13-001.

Table 25: Summary of Treatment-emergent Serious Adverse Events in Study LPCN 1021-13-001 Study (Safety Set)

System Organ Class Preferred Term	Tlando (N = 210) n (%)	AndroGel 1.62% (N = 104) n (%)	Overall (N = 314) n (%)
Any treatment-emergent SAE	12 (5.7)	2 (1.9)	14 (4.5)
Infections and infestations	3 (1.4)	1 (1.0)	4 (1.3)
Sepsis	1 (0.5)	1 (1.0)	2 (0.6)
Cholecystitis infective	0	1 (1.0)	1 (0.3)
Osteomyelitis	1 (0.5)	0	1 (0.3)
Pneumonia	0	1 (1.0)	1 (0.3)
Pneumonia streptococcal	1 (0.5)	0	1 (0.3)
Staphylococcal bacteraemia	1 (0.5)	0	1 (0.3)
Musculoskeletal and connective tissue disorders	3 (1.4)	0	3 (1.0)
Arthritis	1 (0.5)	0	1 (0.3)
Osteonecrosis	1 (0.5)	0	1 (0.3)
Spinal osteoarthritis	1 (0.5)	0	1 (0.3)
Gastrointestinal disorders	2 (1.0)	0	2 (0.6)
Abdominal pain	1 (0.5)	0	1 (0.3)
Gastrooesophageal reflux disease	1 (0.5)	0	1 (0.3)
General disorders and administration site conditions	1 (0.5)	1 (1.0)	2 (0.6)
Chest pain	0	1 (1.0)	1 (0.3)
Non-cardiac chest pain	1 (0.5)	0	1 (0.3)
Injury, poisoning and procedural complications	2 (1.0)	0	2 (0.6)
Cervical vertebral fracture	1 (0.5)	0	1 (0.3)
Face injury	1 (0.5)	0	1 (0.3)
Nervous system disorders	2 (1.0)	0	2 (0.6)
Ataxia	1 (0.5)	0	1 (0.3)
Balance disorder	1 (0.5)	0	1 (0.3)
Syncope	1 (0.5)	0	1 (0.3)

Adverse event classification using MedDRA 16.1.
Source: NDA 208088 (seq 0000), 5.3.5.1, Table 58, p. 116.

Table 26 lists the SAEs that occurred during Study LPCN 1021-13-001 by subject. None of the SAEs were considered by the investigator to be related to the study drug. Subject (b) (6) experienced four SAEs prior to receiving the first dose of study drug.

Table 26: Serious Adverse Events during the Study LPCN 1021-13-001 – Safety Set

Subject Number	Study Drug Dose	MedDRA Preferred Term	Study Day SAE Onset	SAE Duration (days)	Relationship to Study Drug/ Severity
Tlando					
(b) (6)	225 mg	Face injury	362	2	NR/Moderate
	150 mg	Abdominal pain	286	4	NR/Severe
	225 mg	Osteonecrosis	147	3	NR/Severe
	225 mg	Sepsis	218	3	NR/Severe
	150 mg	Cervical vertebral fracture	359	11	NR/Severe
		Spinal osteoarthritis	386	5	NR/Severe
	225 mg	Staphylococcal bacteraemia	49	6	NR/Moderate
		Osteomyelitis	49	51	NR/Moderate
	300 mg	Noncardiac chest pain	134	2	NR/Moderate
	225 mg	Pneumonia streptococcal	54	12	NR/Severe
	225 mg	Arthritis	45	5	NR/Severe
	225 mg	Syncope	231	2	NR/Mild
	150 mg	GERD	139	3	NR/Severe
	225 mg	Balance disorder	79	2	NR/Moderate
		Ataxia	79	2	NR/Moderate
AndroGel 1.62%					
(b) (6)	81 mg	Chest pain	165	2	NR/Severe
	NA	Rib fracture	-24	53	NR/Moderate
		Pneumothorax	-24	53	NR/Moderate
		Lumbar vertebral fracture	-24	53	NR/Moderate
		Splenic rupture	-24	53	NR/Moderate
	81 mg	Cholecystitis infective	45	8	NR/Severe
		Pneumonia	45	8	NR/Severe
		Sepsis	45	8	NR/Severe

NR = not related; GERD = Gastroesophageal reflux disease
[a]Subject (b) (6) provided written informed consent, but experienced SAEs prior to receiving the first dose of study drug and later was randomized to AndroGel 1.62%
Source: Source: NDA 208088 (seq 0026), 2.7.4, Table 30, p. 70.

Reviewer comment: Each of the serious adverse events reported during Study LPCN 1021-13-001 was reviewed. I agree that these events do not appear to be related to the study drug.

Studies LPCN 1021-16-002 and LPCN 1021-16-003

One subject experience a SAE in Study LPCN 1021-16-002. Subject (b) (6) experienced a SAE (gastric ulcer hemorrhage) and was discontinued from the study. This subject was admitted to the hospital and 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.

Reviewer comment: Based on the subject's concomitant treatment with two NSAIDs (aspirin and meloxicam) I agree that the event does not appear to be related to the study drug.

No SAEs occurred during Study LPCN 1021-16-003.

Phase 1 Studies
No serious adverse events (SAE) occurred during the Phase 1 studies in the target population.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study LPCN 1021-13-001
During Study LPCN 1021-13-001, 24 subjects (7.6%) experienced a treatment emergent adverse event (TEAE) that led to study drug discontinuation, including 19 subjects (9.0%) in the Tlando 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 Tlando group), libido decreased (2 subjects in the Tlando group), and polycythemia (1 subject in both the Tlando 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 Tlando group and 3 events in 3 subjects in the AndroGel 1.62% group.

Three subjects who received Tlando 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.

As described in the review of the original NDA submission (Section 6.1.3 Subject Disposition), the Applicant conducted an investigation for subjects who discontinued the study prematurely with a reason of withdrew consent. Information obtained after the study had ended revealed that the specific reasons for the withdrawn consent included weight gain for Subject (b) (6) who had received Tlando and worsening insomnia for Subject (b) (6) who had received AndroGel 1.62%. In addition, adverse events that had an action taken as study drug discontinued were not always considered the reason for study discontinuation in terms of disposition. For example, Subject (b) (6) was prematurely withdrawn from the study for the reason of meeting the Cmax or Cavg stopping criteria. Subjects (b) (6) and (b) (6) were withdrawn by the investigator due to a reason of consent withdrawn (subsequently classified by the Applicant as a confinement or schedule conflict). The additional information obtained by the Applicant from the study sites after completion of the study revealed that Subject (b) (6) (b) (6)s reason for withdrawing from the study was that the previous PK visit had taken too much time and he couldn't take two days off work anymore. Subject (b) (6)s reason for withdrawing was that he withdrew his consent due to his work schedule. Because these

subjects had been experiencing adverse events during their discontinuation, the action taken for these adverse events was study drug discontinued.

Table 27 lists subjects, including the subjects re-classified by the Applicant, who experienced an adverse event immediately preceding drug discontinuation.

Table 27: Adverse Events Leading to Study Discontinuation
Study LPCN 1021-13-001 - Safety Set

Subject Number	Study Drug Dose	MedDRA Preferred Term	Relationship to Study Drug/ Severity	Discontinuation Reason (Sponsor Classification)
Tlando				
(b) (6)	225 mg	Libido Decreased	NR/Mild	Confinement or schedule conflict
	225 mg	Weight Increased	NR/Mild	Weight gain
	225 mg	Polycythaemia	Related/Mild	Hematocrit >54%
	NA	ECG Abnormal	Related/Moderate	Adverse event
	225 mg	Weight Increased	NR/Mild	Weight gain
	300 mg	NA[1]	NA[1]	Weight gain
	225 mg 225 mg	Abdominal Pain Libido Decreased	NR/Moderate Related/Moderate	Adverse event
	150 mg	Acne	Related/Mild	Cmax or Cavg not achieved; met stopping criteria
	225 mg 225 mg	Oedema Peripheral Weight Increased	Related/Mild Related/Moderate	Adverse event
	150 mg 150 mg 150 mg	Spinal Cord Oedema Cervical Vertebral Fracture Muscle Spasms	NR/Moderate NR/Severe NR/Mild	Serious adverse event
	225 mg	Abdominal Discomfort	Related/Moderate	Adverse event
	225 mg 225 mg	Staphylococcal Bacteraemia Osteomyelitis	NR/Moderate NR/Moderate	Serious adverse event
	225 mg 225 mg 225 mg	Diarrhoea Fatigue Irritability	NR/Mild NR/Mild NR/Mild	Confinement or schedule conflict
	225 mg 225 mg 225 mg 225 mg	Feeling Hot Flushing Agitation Insomnia	Related/Moderate Related/Moderate Related/Moderate Related/Mild	Adverse event
	150 mg	RBC Count Increased	NR/Mild	Hematocrit >54%
	150 mg	PSA Increased	Related/Moderate	PSA > 4 ng/mL
	NA NA	Ataxia Balance Disorder	NR/Moderate NR/Moderate	Serious adverse event
	150 mg	APTT Prolonged	Related/Moderate	Adverse event
	150 mg	Dyspnoea	Related/Mild	Adverse event
	150 mg	Haematocrit Increased	Related/Mild	Hematocrit >54%

Subject Number	Study Drug Dose	MedDRA Preferred Term	Relationship to Study Drug/ Severity	Discontinuation Reason (Sponsor Classification)
AndroGel 1.62%				
(b) (6)	60.75 mg	Polycythaemia	Related/Mild	Hematocrit > 54%
	40.5 mg	Anger	Related/Moderate	Adverse event
	81 mg 81 mg	Joint Stiffness Musculoskeletal Stiffness	NR/Mild NR/Mild	Adverse event
	81 mg	Headache	Related/Mild	Adverse event
	40.5 mg	Insomnia[2]	NR/Mild	Adverse event
	81 mg	Prostate Cancer	NR/Moderate	Adverse event

NR = not related; APTT = Activated Partial Thromboplastin Time
[1]Information obtained from the site after the study had ended indicated that the subject withdrew due to an increase in weight gain. An adverse event of weight gain had not been recorded for this subject in the eCRF.
[2]Information obtained from the site after the study had ended indicated that the subject withdrew from the study due to worsening insomnia. The adverse event of insomnia for this subject had an action taken of "dose not changed" in the eCRF.
Source: NDA 208088 (seq 0026), 2.7.4, Table 31, pp. 71-72.

Reviewer comment: The percentage of subjects who discontinued Study LPCN 1021-13-001 due to an adverse event is greater in the Tlando 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 Applicant'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 Tlando 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 Tlando group), hematocrit > 54% (3 subjects in the Tlando group and 1 subject in the AndroGel 1.62% group), and libido decreased (2 subjects in the Tlando group).

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 been the result of the study design. 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.

The discontinuations that resulted from hematocrit > 54% are discussed in detail in Section 8.4.6 Laboratory Findings.

<u>Studies LPCN 1021-16-002 and LPCN 1021-16-003</u>
One subject (Subject (b) (6) in LPCN 1021-16-002 was discontinued due to gastric ulcer hemorrhage. This subject is discussed in Section 8.4.2 Serious Adverse Events. During Study LPCN 1021-16-003, no subjects experienced a TEAE that led to study drug discontinuation.

Phase 1 Studies

During the Phase 1 studies in the target population, one Tlando treated subject withdrew from a study (Study LPCN 1021-09-001) prematurely due to an upper respiratory tract infection. The adverse event was considered by the investigator to be mild in severity and not related to study treatment.

8.4.4. 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 Tlando 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. Treatment emergent adverse events of special interest for the integrated Phase 1 and Phase 3 studies are summarized in **Table 28**.

Table 28: Treatment-Emergent Adverse Events of Special Interest for Testosterone Replacement Therapy – Safety Population

Sponsor Defined Groups MedDRA Preferred Term[1]	Original ISS Tlando N = 381	Updated ISS Tlando N = 525	Original ISS Andriol 80 mg N = 34	Original ISS AndroGel 1.62% N = 104	Original ISS Placebo N = 18
Cardiac and Cerebrovascular Disorders					
Atrial Fibrillation	1 (0.3)	1 (0.2)	0	2 (1.9)	0
Blood Pressure Increased	3 (0.8)	3 (0.6)	0	2 (1.9)	0
Blood Creatine Phosphokinase Increased	1 (0.3)	1 (0.2)	0	0	0
Bradycardia	0	0	0	1 (1.0)	0
Bundle Branch Block Bilateral	0	0	0	1 (1.0)	0
Cardiac Flutter	1 (0.3)	1 (0.2)	0	0	0
Electrocardiogram Abnormal	1 (0.3)	1 (0.2)	0	1 (1.0)	0
Electrocardiogram Change	1 (0.3)	1 (0.2)	0	0	0
Electrocardiogram T Wave Inversion	1 (0.3)	1 (0.2)	0	0	0
Enzyme Level Increased	3 (0.8)	3 (0.6)	0	0	0
Heart Rate Increased	2 (0.5)	2 (0.4)	1 (2.9)	0	0
Hypertension	6 (1.6)	7 (1.3)	0	5 (4.8)	0
Left Atrial Dilatation	0	0	0	1 (1.0)	0
Mitral Valve Incompetence	1 (0.3)	1 (0.2)	0	0	0
Palpitations	2 (0.5)	2 (0.4)	1 (2.9)	0	0
Sinus Tachycardia	0	0	0	1 (1.0)	0
Tachycardia	2 (0.5)	2 (0.4)	0	1 (1.0)	0
Tricuspid Valve Incompetence	1 (0.3)	1 (0.2)	0	0	0
Ventricular Extrasystoles	0	0	0	1 (1.0)	0

Sponsor Defined Groups MedDRA Preferred Term[1]	Original ISS Tlando N = 381	Updated ISS Tlando N = 525	Original ISS Andriol 80 mg N = 34	Original ISS AndroGel 1.62% N = 104	Original ISS Placebo N = 18
Ventricular Hypertrophy	1 (0.3)	1 (0.2)	0	0	0
Blood and Lymphatic System					
Anaemia	2 (0.5)	3 (0.6)	0	0	0
Blood Cholesterol Increased	0	0	1 (2.9)	0	0
Blood Triglycerides Increased	3 (0.8)	3 (0.6)	0	2 (1.9)	0
Haematocrit Increased	4 (1.0)	4 (0.8)	0	0	0
Haemoglobin Increased	1 (0.3)	1 (0.2)	0	0	0
High Density Lipoprotein Decreased	1 (0.3)	1 (0.2)	0	0	0
Hypercholesterolaemia	2 (0.5)	2 (0.4)	0	0	0
Hyperlipidaemia	1 (0.3)	1 (0.2)	0	2 (1.9)	0
Lipids Increased	2 (0.5)	2 (0.4)	0	0	0
Polycythaemia	1 (0.3)	1 (0.2)	0	1 (1.0)	0
Red Blood Cell Count Increased	1 (0.3)	1 (0.2)	0	0	0
Hepatic System					
Alanine Aminotransferase Increased	1 (0.3)	1 (0.2)	0	0	0
Blood Bilirubin Increased	0	0	0	1 (1.0)	0
Hepatic Enzyme Increased	0	0	0	1 (1.0)	0
Renal and Reproductive System					
Dysuria	0	0	0	1 (1.0)	0
Enuresis	0	0	0	1 (1.0)	0
Nocturia	0	0	0	2 (1.9)	0
Prostate Cancer	0	0	0	1 (1.0)	0
Prostatic Specific Antigen Increased	4 (1.0)	5 (1.0)	0	0	0
Prostatitis	1 (0.3)	1 (0.2)	0	1 (1.0)	0
Prostatomegaly	2 (0.5)	2 (0.4)	0	0	0
Testicular Atrophy	0	0	0	1 (1.0)	0
Testicular Disorder	0	0	0	1 (1.0)	0
Urinary Retention	1 (0.3)	1 (0.2)	0	0	0
Nervous System					
Dizziness	4 (1.0)	4 (0.8)	0	2 (1.9)	1 (5.6)
Headache	19 (5.0)	21 (4.0)	1 (2.9)	5 (4.8)	2 (11.1)
Sleep Apnoea Syndrome	3 (0.8)	3 (0.6)	0	1 (1.0)	0
Tension Headache	1 (0.3)	1 (0.2)	0	0	0
Transient Ischaemic Attack	1 (0.3)	1 (0.2)	0	0	0
Psychiatric System					
Abnormal Dreams	1 (0.3)	1 (0.2)	0	0	0
Agitation	1 (0.3)	1 (0.2)	0	0	0
Anger	0	0	0	1 (1.0)	0
Anxiety	3 (0.8)	3 (0.6)	1 (2.9)	1 (1.0)	0
Depression	0	0	0	1 (1.0)	0

Sponsor Defined Groups MedDRA Preferred Term[1]	Original ISS Tlando N = 381	Updated ISS Tlando N = 525	Original ISS Andriol 80 mg N = 34	Original ISS AndroGel 1.62% N = 104	Original ISS Placebo N = 18
Insomnia	5 (1.3)	5 (1.0)	0	1 (1.0)	0
Irritability	2 (0.5)	2 (0.4)	0	2 (1.9)	0
Libido Decreased	3 (0.8)	3 (0.6)	0	0	0
Major Depression	0	0	0	1 (1.0)	0
Middle Insomnia	0	0	0	1 (1.0)	0
Mood Altered	1 (0.3)	1 (0.2)	0	0	0
Panic Attack	1 (0.3)	1 (0.2)	0	0	0
Restlessness	1 (0.3)	1 (0.2)	0	0	0
Other Potential Androgen Effects					
Acne	7 (1.8)	7 (1.3)	0	3 (2.9)	0
Alopecia	0	0	0	1 (1.0)	0
Gynaecomastia	0	0	0	1 (1.0)	0
Hirsutism	1 (0.3)	1 (0.2)	0	0	0
Oedema	1 (0.3)	1 (0.2)	0	0	0
Oedema Peripheral	3 (0.8)	5 (1.0)	0	1 (1.0)	0

[1]MedDRA version 17.1
Source: NDA 208088 (seq 0026), 2.7.4, Table 34, p. 75-76.

Reviewer comment: Except for the event of headache, all TEAEs of special interest occurred in less than 2.0% of Tlando subjects. The incidence of headache was similar for Tlando and AndroGel 1.62% treated subjects.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

An adverse event was considered treatment emergent if the event began or worsened in severity after initiation of randomized study drug. SAEs were collected from the time the subject provided written informed consent. Subjects reporting more than one adverse event for a given MedDRA preferred term were counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a system organ class (SOC) were counted only once for that SOC.

Due to differences in the length of the studies, dose, and dosing regimen the results for each of the Phase 3 studies is presented separately in this section. Integrated results for the Phase 1 studies are also presented.

Study LPCN 1021-13-001

Table 29: Common (>2%) Treatment-Emergent Adverse Events (TEAE) Occurring During LPCN 1021-13-001 (Safety Set)

System Organ Class Preferred Term	Tlando N=210		AndroGel 1.62% N=104		Overall N=314	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE occurring in ≥ 2% of subjects	68 (32.4%)	88	33 (31.7%)	48	101 (32.2%)	136
Infections and Infestations	25 (11.9%)	29	14 (13.5%)	16	39 (12.4%)	44
Upper Respiratory Tract Infection	11 (5.2%)	12	6 (5.8%)	6	17 (5.4%)	18
Nasopharyngitis	8 (3.8%)	8	5 (4.8%)	5	13 (4.1%)	13
Bronchitis	4 (1.9%)	4	3 (2.9%)	3	7 (2.2%)	7
Sinusitis	5 (2.4%)	5	1 (1.0%)	2	6 (1.9%)	7
Investigations	14 (6.7%)	15	2 (1.9%)	2	16 (5.1%)	17
Weight Increased	10 (4.8%)	10	1 (1.0%)	1	11 (3.5%)	11
HCT Increased	5 (2.4%)	5	1 (1.0%)	1	6 (1.9%)	6
Nervous System Disorders	10 (4.8%)	10	5 (4.8%)	6	15 (4.8%)	16
Headache	10 (4.8%)	10	5 (4.8%)	6	15 (4.8%)	16
Musculoskeletal and Connective Tissue Disorders	9 (4.3%)	11	6 (5.8%)	7	15 (4.8%)	18
Back Pain	6 (2.9%)	6	3 (2.9%)	3	9 (2.9%)	9
Arthralgia	3 (1.4%)	5	4 (3.8%)	4	7 (2.2%)	9
General Disorders and Administration Site Conditions	5 (2.4%)	5	7 (6.7%)	8	12 (3.8%)	13
Fatigue	5 (2.4%)	5	7 (6.7%)	8	12 (3.8%)	13
Vascular Disorders	6 (2.9%)	6	5 (4.8%)	5	11 (3.5%)	11
Hypertension	6 (2.9%)	6	5 (4.8%)	5	11 (3.5%)	11
Skin and Subcutaneous Tissue Disorders	7 (3.3%)	7	3 (2.9%)	3	10 (3.2%)	10
Acne	7 (3.3%)	7	3 (2.9%)	3	10 (3.2%)	10
Gastrointestinal Disorders	6 (2.9%)	6	1 (1.0%)	1	7 (2.2%)	7
Diarrhea	6 (2.9%)	6	1 (1.0%)	1	7 (2.2%)	7
Metabolism and Nutrition Disorders	5 (2.4%)	5	0 (0.0%)	0	5 (1.6%)	5
Diabetes mellitus	5 (2.4%)	5	0 (0.0%)	0	5 (1.6%)	5

Source: Reviewer analysis of NDA 208088 (seq 0000), 5.3.5.1, Table 14.3.1.3.2, p. 550-551 and dataset ADAE.

Reviewer comment: Except for the events of weight increase, acne, diarrhea, diabetes, hematocrit increase, and sinusitis, the incidence of common TEAEs for Tlando was similar or less than that of AndroGel 1.62%.

Of the 10 cases of weight increase reported in Tlando subjects, four were assessed by the investigator as mild in severity and considered not related to the study drug; two were assessed

as mild and related to the study drug; and four were assessed as moderate in severity and related to the study drug. Three of the 10 subjects who reported the AE of weight increase discontinued the study due the AE. Though the cause of the imbalance in the number of subjects reporting weight increase in not entirely clear, I believe it may have resulted from differences in the dietary recommendations that were given to the two treatment groups. Subjects in the Tlando group were required to eat a meal before each dose of the drug and instructed to include at least 25 – 30 grams of fat in the meal, while subjects in the AndroGel 1.62% group had no dietary restrictions or recommendations. For Tlando subjects who had lower fat diets before the study, the minimum fat recommendation may have caused them to increase the fat (and caloric) content of their meals.

Of the seven cases of acne reported in Tlando treated subjects, six were assess by the investigator as mild and one was assess as moderate in severity. One subject discontinued the study due to the AE. All but one of the cases was considered related to the study drug.

Of the six cases of diarrhea reported in the Tlando group, one was considered related to the study drug and was assessed as mild in severity. The other five cases were not considered related to the study drug. In one of these cases, the subject discontinued from the study due to the AE. The AE was assessed as mild in that case.

Of the five cases of diabetes reported in Tlando treated subjects, one was considered related to the study drug and was assessed as mild in severity. The other four cases were not considered related to the drug. All subjects reporting this AE completed the study.

Five Tlando treated subjects had hematocrit values greater than 54%. These subjects are reviewed in detail in Section 8.4.6 Laboratory Findings.

None of the cases of sinusitis reported in Tlando subjects was considered related to the study drug. All subjects with this AE completed the study.

Studies LPCN 1021-16-002

Common (>2%) Treatment-Emergent Adverse Events (TEAE) Occurring During LPCN 1021-16-002 (Safety Set)

System Organ Class Preferred Term	Tlando (225 mg BID) N=95	
	Subjects n (%)	Events n
Any TEAE	20 (21.1)	33
Investigations		
Blood prolactin increased	6 (6.3)	6
Weight Increased	2 (2.1)	2
Nervous System Disorders		
Headache	2 (2.1)	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	2 (2.1)	2

Source: Reviewer analysis of NDA 208088 (seq 0026), 5.3.5.2, Table 14.3.1.2, p. 118-120 and dataset ADAE.

In general, the common (>2%) TEAEs reported in LPCN 1021-16-002 were similar to those reported in LPCN 1021-13-001 with the exception of the TEAE "blood prolactin increased." Six (6.3%) subjects reported the TEAE "blood prolactin increased" in LPCN 1021-16-002 compared to none in LPCN 1021-13-001. Of the six subjects, three also enrolled in LPCN 1021-16-003 and had a prolactin level within the normal range after 24 days of treatment in that study. One had a history of hyperprolactinemia. The remaining two subjects had end of study prolactin levels of 24.7 and 25.1 ng/mL.

In addition to the six subjects who reported the TEAE of "blood prolactin increased," 45 subjects had end of study prolactin levels that were greater than the upper limit of the normal range (15.228 ng/mL), which were not reported as a TEAE. Seven of these subjects had a baseline value that was greater than the upper limit because the exclusion criterion for prolactin level (>17.7 ng/mL) was greater than the upper limit of the normal range.

Although no TEAEs of "blood prolactin increased" were reported in LPCN 1021-13-001, two Tlando-treated subjects had slightly elevated prolactin levels at Week 52 (18.0 and 18.2 ng/mL). One of these subjects ((b) (6) 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). The other subject ((b) (6) had elevated levels at Weeks 26 (18.7 ng/mL) and 52 (18.2 ng/mL), and normal levels at Weeks 13 and 39 (this subject's prolactin was not assessed at Week 7). Five subjects in addition to Subject (b) (6) also had elevated prolactin levels at Week 7. All five had normal prolactin levels at their final study visits (Week 39 for one subject, Week 52 for the other four).

In the AndroGel treatment group, two subjects had slightly elevated prolactin levels at Week 52 (18.3 and 18.8 ng/mL). One of these subjects ((b) (6) had elevated prolactin levels at Weeks 7, 13, 26, 39, and 52 (range 18.3 to 34.1 ng/mL). The other subject ((b) (6) had elevated levels at Weeks 7, 13, 26, and 52 (range 18.8 to 23.6 ng/mL), but a normal level at Week 39 (16.3 ng/mL). Two subjects in addition to Subjects (b) (6) and (b) (6) also had elevated prolactin levels at Week 7. One had a normal prolactin level at his final study visit (Week 52), the other was lost to follow-up and had prolactin assessed only at Week 7.

No TEAEs of "blood prolactin increased" were reported in LPCN 1021-16-003. However, eight subjects had end of study prolactin levels that were greater than the upper limit of normal (15.228 ng/mL). Three of these subjects had a baseline value that was greater than the upper limit because the exclusion criterion for prolactin level (17.7 ng/mL) was greater than the upper limit of normal.

Reviewer comment: The increased number of subjects with elevated prolactin levels after 24 days of exposure to Tlando in LPCN 1021-16-002 was not consistent with the results seen in LPCN 1021-13-001 or LPCN 1021-16-003. The cause of this increase is unclear. Based on the results in LPCN 1021-13-001 (the 52-week trial with active comparator), Tlando's effect on prolactin levels appears to be similar to the effect seen with AndroGel.

LPCN 1021-16-003
Nine (9.0%) subjects reported 10 TEAEs during LPCN 1021-16-003. The TEAE of "edema peripheral" was reported by 2 (2.0%) subjects. No other TEAEs were reported by more than one subject.

Phase 1 Studies
In the Phase 1 studies, three common (≥ 2%) AEs were reported by Tlando subjects: headache (5.3%), dry skin (4.1%), and constipation (3.5%). The incidence of headache in the Phase 1 studies was similar to the incidence in the Phase 3 study (5.3% vs 4.8%, respectively). The incidence of dry skin and constipation was greater in the Phase 1 studies (dry skin 4.1% vs 0; constipation 3.5% vs 0.5%).

Reviewer comment: The AE of dry skin was the only common AE that was reported in the Phase 1 studies but not in LPCN 1021-13-001.

8.4.6. Laboratory Findings

LPCN 1021-13-001
During LPCN 1021-13-001, a central laboratory performed screening and safety laboratory tests. After enrollment in the study, any laboratory test value outside the reference range that the investigator considered to be clinically significant was repeated to verify the out-of-range value and was followed to a satisfactory clinical resolution. A laboratory test value that required

a subject to be discontinued from the study or required a subject to receive treatment was recorded as an adverse event.

During the study, blood and urine samples for the clinical laboratory tests were collected for subjects in both treatment arms at screening and at the following visits: Week 7, Week 13, Week 26, Week 39, and Week 52. Samples for clinical laboratory tests were collected in the morning before meals and study drug administration. The test results from screening served as the baseline for future assessments.

Hematology
Increases were observed for hematocrit (HCT) in both the Tlando and AndroGel 1.62% treatment arms. **Table 30** summarizes the changes in HCT from baseline.

Table 30: Hematocrit: Mean Baseline and Mean Change from Baseline Values of Hematocrit in Tlando- and AndroGel 1.62%-Treated Subjects - LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
		HCT Value (%)		HCT Value Change from Baseline (%)			HCT Value (%)		HCT Value Change from Baseline (%)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	206	43.48	3.20	--	--	103	44.03	3.36	--	--
Week 7	177	44.47	3.73	1.13	3.03	96	44.99	3.26	0.90	2.72
Week 13	155	45.21	3.90	1.76	3.19	91	45.83	3.85	1.85	3.45
Week 26	144	45.86	3.62	2.46	3.10	81	46.67	3.78	2.63	3.15
Week 39	137	46.28	3.97	2.82	3.27	76	46.25	3.73	2.28	3.39
Week 52	128	46.10	3.83	2.90	3.45	67	46.25	3.47	2.16	3.39
Early Term	50	45.40	4.44	1.60	3.13	14	46.36	3.57	1.81	2.12

Source: Source: NDA 208088 (seq 0000), 5.3.5.1, Table 60, p. 122.

During the study, nine subjects had a HCT that was greater than 54%: eight in the Tlando group and one in the AndroGel 1.62% group. The data for those subjects are summarized in **Table 31**.

Table 31: Summary of Subjects with Elevated > 54%Hematocrit (HCT) in LPCN 1021-13-001 – Safety Population

Subject Number (Study Disposition)	Age (years)	Visit	HCT Result	Total Dose Taken	Adverse Event (Severity/Relationship/ Action Taken/ Resolution)
Tlando					
(b) (6) (Hematocrit >54%)	55	Screening Week 7 Week 13 ET	46.0% 49.7% 54.6% 52.9%	43088 mg	Polycythemia (Mild/Related/Drug withdrawn/ Not resolved)
(b) (6) (Completed study)	51	Screening Week 7 Week 13 Unscheduled Week 26 Week 39 Week 52	46.9% 51.3% 55.3% 50.8% 51.1% 48.8% 52.1%	130050 mg	No adverse events recorded due to lab value.
(b) (6) (Completed study)	57	Screening Week 7 Unscheduled Week 13 Week 26 Week 39 Week 52	47.4% 54.4% 48.9% 48% 53.5% 53.3% 53.1%	167850 mg	No adverse events recorded due to lab value.
(b) (6) (Adverse event, decreased libido)	54	Screening ET	45.3% 54.2%	24300 mg	No adverse events recorded due to lab value.
(b) (6) (Completed study)	53	Screening Week 7 Week 13 Week 26 Week 39 Week 52	45% 43.8% Not Done 50.5% 52.3% 54.5%	153900 mg	No adverse events recorded due to lab value.
(b) (6) (Hematocrit >54%)	68	Screening Unscheduled Week 7 Week 13 Unscheduled Week 26 Week 39 Unscheduled ET	49.5% 46.1% 53.1% 55% 54.9% 52.5% 55% 57.1% 53.6%	91275 mg	Red blood cell count increased (Mild/ Not related/Drug withdrawn/ Resolved)
(b) (6) (ET due to protocol violation)	57	Screening Week 7 Week 13 Unsch ET	47.4% 49.5% 54.1% 54.8% 51%	32175 mg	Hematocrit increased (Mild/Related/Dose not changed/ Resolved)

(b) (6) (ET due to hematocrit >54%)	54	Screening Week 7 ET	47.1% 54.3% 53.5%	24300 mg	Hematocrit increase (Mild/Related/Withdrawn/ Not resolved)
AndroGel 1.62%					
(b) (6) (ET due to hematocrit >54%)	57	Screening Week 7 Week 13 Week 26 Week 39 ET	43.6% 45.7% 49.1% 50% 55.8% 51.3%	909 g	Polycythemia (Mild/Related/Drug Withdrawn/ Resolved)

Source: NDA 208088 (seq 0000), 2.7.4, Table 48, p. 85-86.

Reviewer comment: During the course of the study, mean HCT values were similar in both treatment groups. The mean percentage change from baseline to week 52 was 2.90% for Tlando subjects and 2.16% for AndroGel 1.62% subjects. However, a greater number of subjects in the Tlando group had a HCT value that was greater than 54%. Of the nine subjects with a HCT value greater than 54%, eight were in the Tlando group and one was in the AndroGel 1.62% group.

Of the eight subjects in the Tlando group with a HCT value greater than 54%, two subjects ((b) (6) (b) (6) and (b) (6) had HCT values that were less than 54% during a re-assessment done one week after the original assessment. Both subjects continued in the study and neither had a HCT value greater than 54% during the remainder of the study.

One subject ((b) (6) discontinued from the study due to an unrelated AE (decreased libido) and had a HCT value of 54.2% at the early termination visit. It should be noted that the subject was exposed to the study drug for 32 days and that the early termination assessment was done 28 days after the last exposure to the drug.

Of the remaining five subjects, only one had a HCT value that exceeded 55%. Subject (b) (6) had the highest HCT value (57.1%) reported in Tlando treated subjects. The subject was discontinued from the study due to the increase in HCT. At the early termination visit, which occurred 39 days after the date of last exposure to the drug, the HCT was 53.6%. This subject also reported one SAE during the study. On Study Day 139, the subject experienced worsening of GERD with esophagitis, which required hospitalization. The event was not considered related to the study drug by the investigator. During the event, the study drug was interrupted for three days. No additional AEs were reported for this subject.

Increases were also observed for hemoglobin in both the Tlando and AndroGel 1.62% treatment groups. **Table 32** summarizes the changes in hemoglobin from baseline.

Table 32: Hemoglobin: Mean Baseline and Mean Change from Baseline Values of Hemoglobin in Tlando- and AndroGel 1.62%-Treated Subjects – LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
		Hgb Value (g/L)		Hgb Value Change from Baseline (g/L)			Hgb Value (g/L)		Hgb Value Change from Baseline (g/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	206	143.9	10.94	--	--	103	146.1	11.03	--	--
Week 7	177	143.7	12.28	0.3	9.06	96	146.7	10.42	0.4	8.34
Week 13	155	144.9	12.82	1.1	10.15	91	148.3	12.47	2.3	10.53
Week 26	144	147.1	12.37	3.5	9.47	81	151.3	11.35	5.4	9.72
Week 39	137	149.1	13.42	5.3	10.33	76	150.6	12.30	4.7	10.60
Week 52	128	152.1	13.04	9.1	10.59	67	152.8	11.74	6.9	11.23
Early Term	50	146.6	14.02	2.3	9.19	14	151.0	12.37	2.3	8.54

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 61, p. 122.

Reviewer comment: During the study, mean hemoglobin values were similar in both treatment groups. The mean hemoglobin at week 52 was 152.1 g/L for Tlando subjects and 152.8 g/L for AndroGel 1.62% subjects. The mean change from baseline to week 52 was 9.1 g/L for Tlando subjects and 6.9 g/L for AndroGel 1.62% subjects.

Prostate-specific Antigen (PSA)
Increases were observed for PSA in both the Tlando and AndroGel 1.62% treatment arms. **Table 33** summarizes the changes in PSA from baseline.

Table 33: PSA: Mean Baseline and Mean Change from Baseline Values of PSA in Tlando- and AndroGel 1.62%-Treated Subjects – LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
	N	PSA Value (µg/L)		PSA Value Change from Baseline (µg/L)		N	PSA Value (µg/L)		PSA Value Change from Baseline (µg/L)	
		Mean	SD	Mean	SD		Mean	SD	Mean	SD
Baseline	208	0.70	0.47	--	--	104	0.62	0.40	--	--
Week 7	182	0.86	0.69	0.16	0.51	96	0.66	0.46	0.06	0.30
Week 13	156	0.82	0.58	0.12	0.37	91	0.67	0.53	0.08	0.35
Week 26	144	0.93	0.72	0.22	0.45	82	0.71	0.40	0.14	0.31
Week 39	137	0.89	0.57	0.18	0.36	76	0.68	0.41	0.11	0.33
Week 52	129	0.98	0.66	0.24	0.43	69	0.70	0.36	0.15	0.24
Early Term	50	1.08	1.73	0.35	1.69	14	0.89	0.57	0.06	0.21

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 67, p. 126.

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. The Tlando treated subjects with PSA values > 4 ng/ml are discussed below.

Reviewer comment: In general, mean PSA increased in both the Tlando and AndroGel 1.62% treatment groups, however, the increase in the Tlando group was greater than the increase in the AndroGel 1.62% group (0.24 ng/mL versus 0.15 ng/mL at week 52). Three subjects in the Tlando group had PSA > 4 ng/mL compared to two in the AndroGel 1.62% group. In two of the three subjects in the Tlando group, the increase in PSA was transient and the PSA level was < 4 ng/mL when it was re-checked one week after the increase. In the third subject, there was a rapid increase to 12.2 ng/mL that decreased to 7.8 ng/mL three days later. Based on the information provided, it is more likely that this increase was the result of a transient inflammatory process than of the study drug.

The labeling for currently approved testosterone products includes a recommendation to periodically monitor PSA. The labeling for Tlando should also include this recommendation.

Clinical Chemistry
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 greater than the decrease in subjects treated with AndroGel 1.62%. Mean HDL values and changes from baseline are summarized in **Table 34**.

Table 34: Mean Baseline and Mean Change from Baseline Values of HDL in Tlando- and AndroGel 1.62%-Treated Subjects – LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
		HDL Value (mg/dL)		HDL Value Change from Baseline (mg/dL)			HDL Value (mg/dL)		HDL Value Change from Baseline (mg/dL)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	48.5	12.7	--	--	104	46.5	10.6	--	--
Week 7	182	39.3	9.9	-9.5	8.0	96	44.1	10.0	-2.9	7.0
Week 13	157	39.9	9.5	-8.6	7.6	91	43.9	9.5	-2.9	6.9
Week 26	144	41.6	9.8	-7.2	8.6	82	43.3	10.3	-3.1	7.6
Week 39	137	41.7	9.9	-7.4	8.0	76	44.7	10.5	-2.1	8.5
Week 52	128	43.3	10.3	-5.7	7.9	68	44.8	9.8	-2.1	8.7
Early Term	50	43.6	11.4	-5	9.3	14	38.4	9.1	-3.1	6.6

Source: NDA 208088 (seq 0035), 5.3.5.1, LPCN 1021-13-001, Table 14.3.4.2.1d, pp. 7-9.

Mean LDL levels showed an initial drop in both treatment groups. In the Tlando group, levels returned to baseline by week 26 and then remained relatively stable through the end of the study. In the AndroGel 1.62% group, the initial drop was maintained through the end of the study. Mean LDL values and changes from baseline are summarized in **Table 35**.

Table 35: Mean Baseline and Mean Change from Baseline Values of LDL in Tlando- and AndroGel 1.62%-Treated Subjects – LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
		LDL Value (mg/dL)		LDL Value Change from Baseline (mg/dL)			LDL Value (mg/dL)		LDL Value Change from Baseline (mg/dL)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	194	113.6	30.9	--	--	97	109.9	36.4	--	--
Week 7	175	108.5	35.5	-6.6	23.7	90	100.7	29.3	-9.7	27.2
Week 13	150	109.5	36.2	-4	22.9	81	99.6	32.6	-10.5	21.3
Week 26	140	113.3	37.2	0.5	25.3	77	99.7	28.0	-10.2	23.4
Week 39	134	112.6	36.8	0.2	29.7	70	105.7	31.4	-2.1	27.9
Week 52	124	112.7	37.4	-0.2	26.3	64	102.8	35.8	-8.2	28.4
Early Term	49	113.9	32.3	-6.7	22.5	13	96.2	23.9	-7.2	14.9

Source: NDA 208088 (seq 0035), 5.3.5.1, LPCN 1021-13-001, Table 14.3.4.2.1d, pp. 10-12.

Mean triglycerides decreases from baseline were observed for the Tlando group during the course of the study, while mean increases were observed for the AndroGel 1.62% group through week 39. Mean triglyceride values and changes from baseline are summarized in **Table 36**.

Table 36: Triglycerides: Mean Baseline and Mean Change from Baseline Values of Triglycerides in Tlando- and AndroGel 1.62%-Treated Subjects LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
		TG Value (mg/dL)		TG Value Change from Baseline (mg/dL)			TG Value (mg/dL)		TG Value Change from Baseline (mg/dL)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	192	142.5	--	--	104	186.4	113.9	--	--
Week 7	182	179.9	113.7	-10.6	112.8	96	196.5	112.4	10.9	79.7
Week 13	157	171.2	96.4	-12.8	105.5	91	208.2	141.2	18.5	99.0
Week 26	144	170.4	130.1	-15.6	153.6	82	221.3	237.0	29.1	213.0
Week 39	137	162.5	98.4	-16.1	84.2	76	199.6	149.4	10.3	100.0
Week 52	128	158.8	103.8	-18.6	93.9	68	178.8	131.0	-6.6	95.1
Early Term	50	214.9	144.5	-9.4	116.6	14	281.5	272.5	92.4	211.6

Source: NDA 208088 (seq 0035), 5.3.5.1, LPCN 1021-13-001, Table 14.3.4.2.1d, pp. 13-15.

Mean total cholesterol decreased from baseline for both the Tlando and AndroGel 1.62% group. Mean total cholesterol values and changes from baseline are summarized in **Table 37**.

Table 37: Total Cholesterol: Mean Baseline and Mean Change from Baseline Values of Total Cholesterol in Tlando- and AndroGel 1.62%-Treated Subjects – LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
		TC Value (mg/dL)		TC Value Change from Baseline (mg/dL)			TC Value (mg/dL)		TC Value Change from Baseline (mg/dL)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	197.6	37.4	--	--	104	192	43.2	--	--
Week 7	182	182.7	41.0	-16.6	28.0	96	183.4	37.1	-9.4	29.6
Week 13	157	182.8	40.8	-13.6	27.6	91	182.7	43.4	-10.9	28.7
Week 26	144	186.7	41.7	-9.8	29.0	82	184.6	41.0	-9.1	33.2
Week 39	137	185.1	40.2	-10.5	34.8	76	189.8	44.3	-2.9	35.5
Week 52	129	185.4	41.3	-9.3	33.2	69	181.7	43.3	-10.9	34.1
Early Term	50	199.2	42.7	-9.3	27.5	14	185.3	34.9	5.2	33.4

Source: NDA 208088 (seq 0035), 5.3.5.1, LPCN 1021-13-001, Table 14.3.4.2.1d, pp. 16-18.

Reviewer comment: HDL levels decreased in both treatment groups, however, the decrease was greater in the Tlando group. After 52 weeks of treatment, mean HDL levels decreased from 48.5 to 43.3 mg/dL in Tlando treated subjects and from 46.4 to 44.8 mg/dL in AndroGel 1.62% treated subjects. Decreased HDL is considered a risk factor for cardiovascular disease. Levels of other lipids assessed during the study (triglycerides, total cholesterol, and LDL) decreased or remained unchanged during treatment with Tlando.

The labeling for currently approved testosterone products includes a recommendation to periodically monitor lipids. The labeling for Tlando should also include this recommendation.

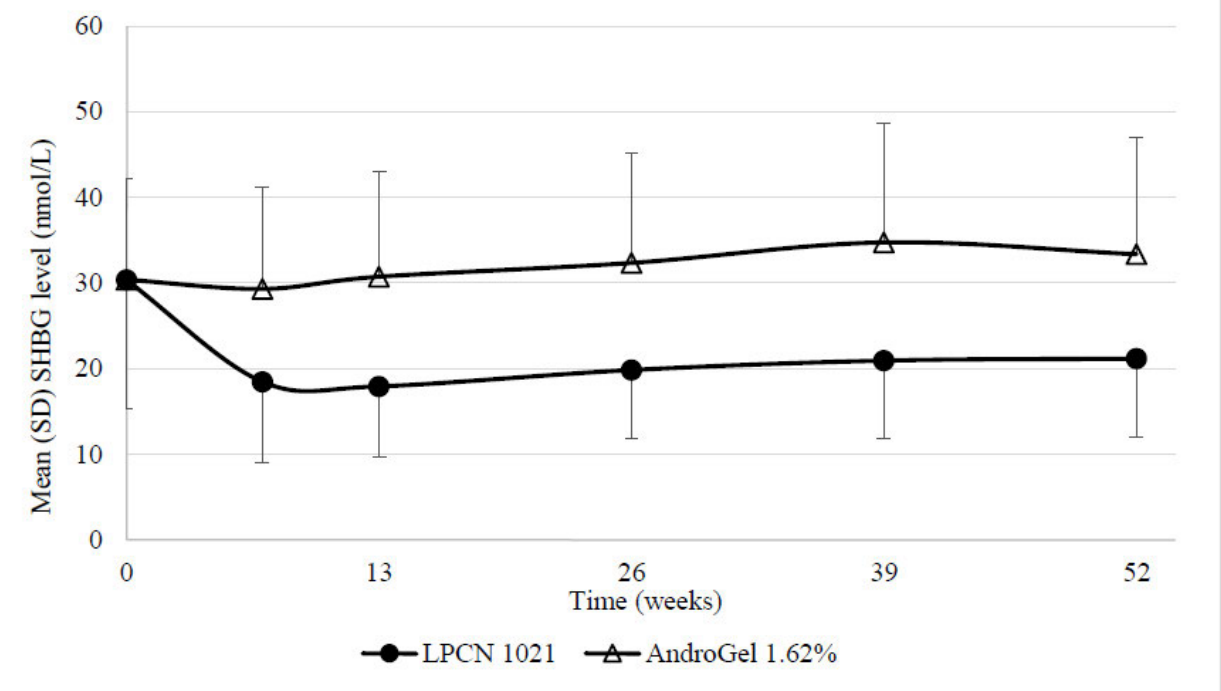
Sex hormone binding globulin (SHBG)
Serum sex hormone binding globulin (SHBG) concentration was measured at baseline, Week 7, Week 13, Week 26, Week 39 and Week 52 of the Phase 3 study. Mean SHBG levels showed a decrease at each post-baseline visit in subjects receiving Tlando while mean SHBG levels showed no significant decrease from baseline in subjects receiving AndroGel 1.62%. Mean SHBG results for subjects treated with Tlando and AndroGel 1.62% are shown in **Table 38** and **Figure 4**.

Table 38: Sex Hormone Binding Globulin (SHBG) Levels (nmol/L) and Change from Baseline through Week 52 during LPCN 1021-13-001 – Safety Set

	Tlando					AndroGel 1.62%				
		SHBG Level (nmol/L)		SHBG Change from Baseline (nmol/L)			SHBG Level (nmol/L)		SHBG Change from Baseline (nmol/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	204	30.34	15.01	--	--	99	30.35	11.79	--	--
Week 7	115	18.44	9.40	-11.49	7.82	93	29.27	11.87	-0.69	6.56
Week 13	145	17.90	8.18	-11.75	7.16	86	30.70	12.29	0.03	5.55
Week 26	140	19.81	7.93	-9.74	8.71	81	32.31	12.86	1.77	6.60
Week 39	136	20.91	9.09	-8.75	10.15	76	34.71	13.97	3.89	8.15
Week 52	126	21.14	9.20	-8.91	9.74	67	33.33	13.65	2.39	7.91
Early Term	48	24.97	11.67	-5.40	9.61	13	29.36	12.27	0.43	6.66

Source: NDA 208088 (seq 0000), 2.7.4, Table 63, p. 107.

Figure 4: Change (+/- SD) in SHBG (nmol/L) Values over Time during LPCN 1021-13-001 – Safety Set (N = 314)



Source: NDA 208088 (seq 0000), 2.7.4, Figure 4, p. 106.

The largest decrease in SHBG during treatment with Tlando was observed at Week 13 (change from baseline of -11.75 nmol/L), after which SHBG levels increased slightly and remained relatively stable. The mean SHBG values of Tlando treated subjects remained within the normal range (17.3 to 65.8 nmol/L) reported by the Applicant.

Reviewer comment: The effect of the reduction in SHBG on free testosterone levels is discussed in Section 6.1.2 - Study Results.

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)
LH and FSH decreased in both the Tlando and AndroGel 1.62% treatment groups. Decreases in the Tlando group were greater than decreases in the AndroGel 1.62% group. **Table 39** and **Table 40** show mean values and changes from baseline for LH and FSH, respectively, during LPCN 1021-13-001.

Table 39: Mean Baseline and Mean Change from Baseline Values of LH in Tlando- and AndroGel 1.62%-Treated Subjects During LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
		LH Value (IU/L)		LH Value Change from Baseline (IU/L)			LH Value (IU/L)		LH Value Change from Baseline (IU/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	5.75	7.34	--	--	104	4.75	4.40	--	--
Week 7	119	1.43	4.30	-4.05	5.75	95	1.74	2.97	-2.80	2.53
Week 13	152	1.61	3.90	-3.98	5.35	89	1.54	2.64	-3.11	2.14
Week 26	144	1.77	3.38	-4.07	6.42	82	1.20	1.79	-3.30	2.54
Week 39	137	2.12	4.05	-3.77	6.67	76	1.82	2.35	-2.77	2.60
Week 52	128	2.35	4.48	-3.75	7.23	69	1.59	2.42	-2.95	2.61
Early Term	50	3.41	4.02	-1.50	4.87	14	1.78	1.50	-2.62	2.55

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 69, p. 127.

Table 40: Mean Baseline and Mean Change from Baseline Values of FSH in Tlando- and AndroGel 1.62%-Treated Subjects During LPCN 1021-13-001 (Safety Set)

	Tlando					AndroGel 1.62%				
		FSH Value (IU/L)		FSH Value Change from Baseline (IU/L)			FSH Value (IU/L)		FSH Value Change from Baseline (IU/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	8.43	10.30	--	--	104	7.20	7.61	--	--
Week 7	119	2.29	5.02	-5.50	8.06	95	3.26	5.47	-3.93	5.29
Week 13	152	2.88	7.70	-5.15	6.66	89	3.02	5.65	-4.26	4.47
Week 26	144	3.37	6.94	-5.08	8.21	82	2.44	3.90	-4.21	4.59
Week 39	136	3.76	8.02	-4.86	8.01	76	3.51	5.01	-3.31	4.86
Week 52	128	3.97	9.25	-4.93	9.50	69	3.08	4.44	-3.92	5.13
Early Term	50	5.15	7.55	-2.68	9.29	14	3.35	3.12	-3.77	5.40

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 70, p. 128.

Reviewer comment: A decrease in LH and FSH is expected during treatment with testosterone.

<u>LPCN 1021-16-002</u>
During LPCN 1021-16-002, samples for the clinical laboratory tests were collected at screening and the end of study (Visit 4).

Hematology
Mean (SD) increase from baseline to Visit 4 for hematocrit was 0.9 (3.00). Hematocrit values at study exit ranged from 33 to 57. To minimize incidences of excessive HCT increases, the study had a discontinuation criterion for subjects whose HCT exceeded 54%. No subjects were discontinued for having met this criterion. One subject had shifted from a normal value at baseline to a high value at exit.

Mean (SD) change from baseline to Visit 4 for hemoglobin was 0.02 (0.82) g/dL. Hemoglobin values at study exit ranged from 10.7 to 17.1. No subject shifted to a high hemoglobin value from baseline to study exit. **Table 41** summarizes the changes in hematocrit and hemoglobin from baseline and **Table 42** summarized the data for the subject whose HCT exceeded 54% at the exit visit.

Table 41: 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 42: 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

Prostate-specific Antigen (PSA)
Increases were observed for PSA during LPCN 1021-16-002. Results are summarized in **Table 43**.

Table 43: PSA: Mean Baseline and Mean Change from Baseline Values of PSA in LPCN 1021-16-002, Safety Set (N=95)

		PSA Value (µg/L)	Value Change from Baseline (µg/L)
	N	Mean (SD)	Mean (SD)
Baseline	95	0.80 (0.44)	--
Exit	90	1.00 (0.67)	0.20 (0.44)

Key: PSA = prostate-specific antigen; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 36, p. 70.

In addition to the changes in PSA values over time, the study had a stopping criterion in which subjects with a PSA value increase from baseline of more than 1.4 ng/mL, or who had absolute values above 4 ng/mL, were to be discontinued from the study. No subjects discontinued the study due to elevated PSA values.

Clinical Chemistry
Change from baseline to study exit for HDL, LDL, triglycerides, and total cholesterol are summarized in **Table 44**, **Table 45**, **Table 46**, and **Table 47**.

Table 44: HDL: Mean Baseline and Mean Change from Baseline Values of HDL in LPCN 1021-16-002, Safety Set (N=95)

		HDL Value (mg/dL)	Change from Baseline (mg/dL)
	N	Mean (SD)	Mean (SD)
Baseline	95	40.4 (10.26)	--
Exit	93	33.5 (9.45)	-6.9 (7.30)

Key: HDL = high-density lipoprotein; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 32, p. 68.

Table 45: LDL: Mean Baseline and Mean Change from Baseline Values of LDL in LPCN 1021-16-002, Safety Set (N=95)

		LDL Value (mg/dL)	Change from Baseline (mg/dL)
	N	Mean (SD)	Mean (SD)
Baseline	95	115.4 (32.97)	--
Exit	93	113.8 (39.03)	-1.5 (26.17)

LDL = low-density lipoprotein; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2 CSR LPCN 1021-16-002, Table 33, p. 68.

Table 46: Triglycerides: Mean Baseline and Mean Change from Baseline Values of Triglycerides in LPCN 1021-16-002, Safety Set (N=95)

		Triglyceride Value (mg/dL)	Change from Baseline (mg/dL)
	N	Mean (SD)	Mean (SD)
Baseline	95	183.3 (119.01)	--
Exit	93	176.2 (108.95)	-8.9 (85.44)

Key: SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 34, p. 69.

Table 47: Total Cholesterol: Mean Baseline and Mean Change from Baseline Values of Total Cholesterol in LPCN 1021-16-002, Safety Set (N=95)

		Total Cholesterol Value (mg/dL)	Change from Baseline (mg/dL)
	N	Mean (SD)	Mean (SD)
Baseline	95	192.0 (42.42)	--
Exit	93	181.8 (45.51)	-10.6 (33.11)

SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 35, p. 69.

Sex hormone binding globulin (SHBG)
Serum sex hormone binding globulin (SHBG) concentration was measured at baseline and the end of study visit (Day 24). There was a decrease from the mean value at baseline to Day 24. Results are summarized in **Table 48**.

Table 48: SHBG: Mean Baseline and Mean Change from Baseline Values of SHBG in LPCN 1021-16-002, Safety Set (N=95)

		SHBG Value (nmol/L)	Change from Baseline (nmol/L)
	N	Mean (SD)	Mean (SD)
Baseline	95	29.53 (11.59)	--
Exit	93	18.72 (9.50)	-10.81 (7.52)

SHBG= sex hormone binding globulin; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 37, p. 70.

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)
LH and FSH decreased during the study. Results are summarized in **Table 49** and **Table 50**.

Table 49: LH: Mean Baseline and Mean Change from Baseline Values of LH in LPCN 1021-16-002, Safety Set (N=95)

		LH Value (nmol/L)	Change from Baseline (nmol/L)
	N	Mean (SD)	Mean (SD)
Baseline	93	6.17 (5.56)	--
Exit	62	2.17 (3.34)	-4.74 (4.92)

LH= luteinizing sex hormone; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 38, p. 70.

Table 50: FSH: Mean Baseline and Mean Change from Baseline Values of FSH in LPCN 1021-16-002, Safety Set (N=95)

		FSH Value (mIU/mL)	Change from Baseline (mIU/mL)
	N	Mean (SD)	Mean (SD)
Baseline	95	7.06 (6.30)	--
Exit	92	2.23 (3.56)	-4.91 (4.88)

LH= luteinizing sex hormone; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 39, p. 71.

LPCN 1021-16-003

During LPCN 1021-16-002, samples for the clinical laboratory tests were collected at screening and the end of study (Visit 5).

Hematology

Mean (SD) increase from baseline to Visit 5 for hematocrit was 0.1 (2.39). Hematocrit values at study exit ranged from 33 to 54. To minimize incidences of excessive HCT increases, the study had a discontinuation criterion for subjects whose HCT exceeded 54%. No subjects were discontinued for having met this criterion. Two subjects shifted from a normal value at baseline to a high value at exit.

There were no clinically significant changes in hemoglobin values from baseline to study exit. Mean (SD) change from baseline to Visit 5 was 0.01 (0.65). Hemoglobin values at study exit ranged from 10.7 to 17.4. No subject had shifted to a high hemoglobin value from baseline to study exit. **Table 51** summarizes the changes in hematocrit and hemoglobin from baseline.

Table 51: 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.

Prostate-specific Antigen (PSA)
Increases were observed for PSA during LPCN 1021-16-003. Results are summarized in **Table 52**.

Table 52 PSA: Mean Baseline and Mean Change from Baseline Values of PSA in LPCN 1021-16-003, Safety Set (N=100)

		PSA Value (µg/L)	Value Change from Baseline (µg/L)
	N	Mean (SD)	Mean (SD)
Baseline	100	0.81 (0.41)	--
Exit	96	0.91 (0.49)	0.10 (0.29)

Key: PSA = prostate-specific antigen; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 35, p. 71.

In addition to the changes in PSA values over time, the study had a stopping criterion in which subjects with a PSA value increase from baseline of more than 1.4 ng/mL, or who had absolute values above 4 ng/mL, were to be discontinued from the study. No subjects discontinued the study due to elevated PSA values.

Clinical Chemistry
Change from baseline to study exit for HDL, LDL, triglycerides, and total cholesterol are summarized in **Table 53**, **Table 54**, **Table 55**, and **Table 56**.

Table 53: HDL: Mean Baseline and Mean Change from Baseline Values of HDL in LPCN 1021-16-003, Safety Set (N=100)

		HDL Value (mg/dL)	Change from Baseline (mg/dL)
	N	Mean (SD)	Mean (SD)
Baseline	100	40.2 (9.84)	--
Exit	96	32.6 (9.22)	-7.5 (7.14)

Key: HDL = high-density lipoprotein; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 31, p. 70.

Table 54: LDL: Mean Baseline and Mean Change from Baseline Values of LDL in LPCN 1021-16-003, Safety Set (N=100)

		LDL Value (mg/dL)	Change from Baseline (mg/dL)
	N	Mean (SD)	Mean (SD)
Baseline	100	113.2 (39.34)	--
Exit	96	108.7 (43.12)	-4.0 (27.66)

LDL = low-density lipoprotein; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2 CSR LPCN 1021-16-003, Table 32, p. 70.

Table 55: Triglycerides: Mean Baseline and Mean Change from Baseline Values of Triglycerides in LPCN 1021-16-003, Safety Set (N=100)

		Triglyceride Value (mg/dL)	Change from Baseline (mg/dL)
	N	Mean (SD)	Mean (SD)
Baseline	100	189.6 (104.72)	--
Exit	96	231.7 (116.48)	41.2 (102.81)

SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 33, p. 70.

Reviewer comment: Unlike LPCN 1021-13-001 (225 mg Tlando BID with titration) and LPCN 1021-16-002 (225 mg Tlando BID without titration), during LPCN 1021-16-003 (150 mg Tlando TID without titration) triglycerides increased.

Table 56: Total Cholesterol: Mean Baseline and Mean Change from Baseline Values of Total Cholesterol in LPCN 1021-16-003, Safety Set (N=100)

		Total Cholesterol Value (mg/dL)	Change from Baseline (mg/dL)
	N	Mean (SD)	Mean (SD)
Baseline	100	191.2 (45.86)	--
Exit	96	181.8 (50.68)	-6.4 (33.71)

SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 34, p. 71.

Sex hormone binding globulin (SHBG)
Serum sex hormone binding globulin (SHBG) concentration was measured at baseline and the end of study visit. Results are summarized in **Table 57**.

Table 57: SHBG: Mean Baseline and Mean Change from Baseline Values of SHBG in LPCN 1021-16-003, Safety Set (N=100)

		SHBG Value (nmol/L)	Change from Baseline (nmol/L)
	N	Mean (SD)	Mean (SD)
Baseline	100	24.86 (9.30)	--
Exit	96	15.38 (7.33)	-9.33 (6.55)

SHBG= sex hormone binding globulin; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 36, p. 72.

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)
LH and FSH decreased during the study. Results are summarized in **Table 58** and **Table 59**.

Table 58: LH: Mean Baseline and Mean Change from Baseline Values of LH in LPCN 1021-16-003, Safety Set (N=100)

		LH Value (nmol/L)	Change from Baseline (nmol/L)
	N	Mean (SD)	Mean (SD)
Baseline	100	5.62 (4.69)	--
Exit	61	2.28 (4.93)	-3.91 (2.92)

LH= luteinizing sex hormone; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 37, p. 72.

Table 59: FSH: Mean Baseline and Mean Change from Baseline Values of FSH in LPCN 1021-16-003, Safety Set (N=100)

		FSH Value (mIU/mL)	Change from Baseline (mIU/mL)
	N	Mean (SD)	Mean (SD)
Baseline	100	6.37 (5.35)	--
Exit	95	1.87 (4.16)	-4.35 (3.53)

LH= luteinizing sex hormone; SD = standard deviation.
Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-003 Table 38, p. 72.

8.4.7. Vital Signs

In LPCN 1021-13-001 (the 52-week study), LPCN 1021-16-002 (the new study testing 225 mg BID), and LPCN 1021-16-003 (the new study testing 150 mg three times daily), vital signs were measured at each visit after the subject had been sitting at rest for at least 5 minutes. For each of the three studies, the mean changes in temperature and weight from baseline to the end of study were not clinically significant for subjects treated with Tlando.

During the development program for another oral TU testosterone replacement product, an increase in cuff systolic blood pressure was demonstrated during a Phase 3 study. This finding was confirmed in a subsequent Phase 3 study for the same drug in which blood pressure and heart rate were assessed using ambulatory blood pressure monitoring (ABPM). Based on these findings, the Vital Signs review will focus on blood pressure and heart rate.

LPCN 1021-13-001

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 the 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 (**Table**

60 and **Table 61**). 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.

Table 60: 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.

Table 61: 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.

LPCN 1021-16-002

In this study, the mean and median blood pressure data showed no important SBP or DBP central tendency shifts (**Table 62**). Heart rate was consistently elevated by approximately 3-4 beats per minute on Visit 4 (Day 24) and at the exit visit (Day 25).

Table 62: 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.

LPCN 1021-16-003

In this study, mean systolic blood pressures were increased by approximately 4 mmHg at both Visit 5 (Day 23) and at exit (Day 25) (**Table 63**). Heart rate was elevated by approximately one beat per minute at both Visit 5 and at exit.

Table 63: 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.

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

- In all three of these open-label studies, only single morning 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 LPCN 1021-16-002, there was an elevated pulse rate of approximately 4 beats per minute at the end of four weeks of dosing. In LPCN 1021-16-003, 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 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 increases 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.

• Based on the available data, it appears that both Tlando and AndroGel raise heart rate, and LPCN 1021-16-003 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 morning cuff pressures) in the setting of an open-label trial design with a 38% dropout rate in the experimental treatment arm. Therefore, a "no blood pressure effect" conclusion from that study is speculative and could be incorrect. The cardiology consultants recommend that the Applicant perform a well-designed, adequately sized, and appropriately controlled ambulatory blood pressure monitoring study to further assess the effects of Tlando on blood pressure and heart rate.

Reviewer comment: I agree with DCRP regarding the need for an ambulatory blood pressure monitoring study. Based on the signal with cuff blood pressures seen during LPCN 1021-16-003 and in the context of the finding of increased SBP assessed with ABPM seen in a similar oral TU product, I believe that the Applicant should conduct an ABPM study to further assess the effects of Tlando on blood pressure and heart rate. This study should be conducted pre-approved.

8.4.8. Electrocardiograms (ECGs)

LPCN 1021-13-001

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 at baseline. Shifts from normal to abnormal, not clinically significant occurred at Week 7 for 15.4% and 10.3% of the Tlando and AndroGel 1.62% subjects, respectively; at Week 13 for 17.2% and 11.8% of the subjects, respectively; at Week 26 for 13.1% and 11.0% of subjects, respectively; at Week 39 for 16.7% and 14.5% of subjects, respectively; at Week 52 for 23.8% and 11.4% of subjects respectively; and at Early Termination for 5.9% and 0% of subjects, respectively.

Three subjects who received Tlando and two subjects who received AndroGel 1.62% had shifts from normal or abnormal (not clinically significant), at baseline to abnormal (clinically significant) during the study.

Reviewer comment: During the Phase 3 study, the number of subjects with shifts from normal or abnormal (not clinically significant) to abnormal (clinically significant) was similar for the Tlando and AndroGel 1.62% treatment groups. One subject treated with Tlando was discontinued from the study due to an AE of ECG abnormal. This subject had a history of systolic ejection murmur II/IV (since (b) (6)) and hypertension (since (b) (6)). His screening ECG was abnormal (not clinically significant).

LPCN 1021-16-002 and LPCN 1021-16-003
ECGs were performed only at screening.

8.4.9. QT

Subjects with long QT syndrome were excluded from LPCN 1021-13-001, LPCN 1021-16-002, and LPCN 1021-16-003.

8.4.10. Immunogenicity

No studies of immunogenicity were done to support this application.

8.5. Analysis of Submission-Specific Safety Issues

Two submission-specific safety issues were identified for this application. Testosterone undecanoate (TU), unlike testosterone, is a pro-drug that is metabolized to testosterone and dihydrotestosterone undecanoate (DHTU). Therefore, assessment of TU and DHTU levels is a submission specific safety issue for this oral TU products. In addition, due to adrenal findings that were noted during two nonclinical studies for TU, assessment of Tlando's effect on the hypothalamic pituitary adrenal axis is also a submission-specific issue.

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

Testosterone undecanoate (TU) is a pro-drug that is metabolized to testosterone and DHTU. In Study LPCN 1021-16-002, the Phase 3 study with a fixed dose of 225 mg BID, levels of TU and DHTU were assessed at Day 24.

At Day 24, the mean serum TU concentration at pre-dose was 12.94 ng/mL and then reached a peak concentration of 470 ng/mL. at 4-5 hours post-dose after which time mean TU concentrations returned to pre-dose levels (27.52 ng/mL at hour 12 and 13.30 ng/mL at hour 24). The TU concentration pattern after the evening dose was similar to the pattern observed

after the morning dose except that peak concentration was reached at 4 hours after the evening dose, 1 hour earlier than for the morning dose. PK parameters for serum TU by time period (morning and evening) are displayed in **Table 64**.

Table 64: Serum PK Parameters of Serum TU after Tlando Dosing at Visit 4 – PK Set (N = 90)

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/mL	Mean (SD)	111 (50)	--	--
Cmax, ng/mL	Mean (SD)	470 (256)	359 (282)	364 (195)
Tmax, h	Median (Min, Max)	14.0 (2.0, 20.7)	4.9 (1.9, 11.9)	4.0 (1.9, 12.0)

Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 22, p. 57.

Day 24 mean serum DHTU concentration at pre-dose was 11.64 ng/mL and then reached a peak concentration of 80.48 ng/mL at 5 hours post-dose after which time mean DHTU concentration returned to pre-dose levels (15.74 ng/mL) at 12 hours post-dose. The DHTU concentration pattern after the evening dose was similar to the pattern observed after the morning dose though DHTU levels were higher and occurred sooner after the evening dose (mean serum DHTU concentrations reached peak concentration of 100.12 ng/mL at 4 hours after the evening dose). PK parameters for serum DHTU by time period (morning and evening) are displayed in **Table 65**.

Table 65: Serum PK Parameters of Serum DHTU after Tlando Dosing at Visit 4 – PK Set (N = 90)

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/mL	Mean (SD)	47 (22)	--	--
Cmax, ng/mL	Mean (SD)	155 (76)	116 (70)	140 (75)
Tmax, h	Median (Min, Max)	15.7 (3.0, 20.0)	5.0 (1.9, 11.9)	4.6 (2.0, 12.0)

Source: NDA 208088 (seq 0026), 5.3.5.2, CSR LPCN 1021-16-002 Table 23, p. 58.

Reviewer comment: 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. Please refer to the pharmacology/toxicology review of the original NDA submission for a detailed review of the nonclinical studies.

8.5.2. Potential Effects on the Hypothalamic Pituitary Adrenal Axis

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 included a Cosyntropin stimulation sub-study in LPCN 1021-16-002 and LPCN 1021-16-003. The Cosyntropin stimulation test was administered as a 0.25 mg dose via intramuscular or intravenous injection per the Cosyntropin product label. Cosyntropin was administered at the screening visit (Visit 2). Subjects who had the Cosyntropin stimulation test at screening and were subsequently enrolled and completed the study had the test repeated at the end of study (EOS) visit. Cortisol was measured at 0 minutes and 60 minutes following Cosyntropin administration. The Applicant relied on pooled data and mean change in cortisol level to assess the adrenal response to Cosyntropin after 24 +/- 4 days of TU exposure.

This analysis does not sufficiently address whether short-term TU exposure leads to suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Instead, paired data should be analyzed and the proportion of subjects with a normal baseline test who develop an abnormal result with TU exposure should be determined. The generally accepted clinical criteria for assessment of the adrenal response to Cosyntropin stimulation has changed from incremental increase in cortisol of >7 mcg/dL to a cortisol level of >18 mcg/dL at any time point during the test, pre-injection (Time 0), or 30 or 60 minutes post injection.

During Studies LPCN 1021-16-002 and LPCN 1021-16-003, 77 subjects participated in the Cosyntropin sub-study in one or both studies: 18 participated in LPCN 1021-16-002 only, 36 participated in LPCN 1021-16-003 only, and 23 participated in both studies.

A total of 68 subjects had an end of study (EOS) cortisol assessment. A subject's Cosyntropin stimulation test was considered normal if his cortisol level was greater than or equal to 18 mcg/dL pre-stimulation or at 60 minutes post-stimulation. Six of the 68 subjects (9%) with an EOS cortisol assessment had an abnormal Cosyntropin stimulation test. All of these subjects participated in the sub-study during Study LPCN 1021-16-003.

Of these six subjects, five also had an abnormal Cosyntropin test during screening (Visit 2), prior to exposure to Tlando. For two of these subjects (LPCN 1021-16-002-(b) (6) 16-003-(b) (6) (b) (6) and LPCN 1021-16-002-(b) (6) 16-003-(b) (6) the Applicant confirmed that Cosyntropin was not administered to the subjects. One of these subjects (LPCN 1021-16-002-(b) (6) 16-003-(b) (6) had an EOS cortisol level of 0.7 mcg/dL at 0 minutes, suggestive of adrenal insufficiency, that increased to 5.0 mcg/dL at 60 minutes without stimulation. The subject's screening cortisol levels at Visit 2 were 12.4 and 15.5 mcg/dL at 0 and 60 minutes (without stimulation), respectively.

The other three subjects were all from study site 318 and had a minimal response to Cosyntropin stimulation at the EOS assessment as well as the screening assessment. This was the case for all the subjects (n=6) who participated in the sub-study at Site 318: the change in post-stimulation cortisol levels ranged from -0.9 to 1.2 mcg/dL at screening and from -0.5 to 0.7

mcg/dL at the EOS visit. The Applicant could not explain this unexpected finding at this study site.

The remaining subject with abnormal Cosyntropin stimulation test results had an abnormal result at the EOS visit, but not at screening. This subject (LPCN 1021-16-003-(b) (6) was also from study site 318. His EOS post-stimulation cortisol level was 11 mcg/dL compared to 11.5 mcg/dL pre-stimulation. At screening, his cortisol level increased from 22.1 mcg/dL to 22.3 mcg/dL. This lack of effect after Cosyntropin administration was similar to what was seen for the other subjects at study site 318.

Cortisol levels for subjects with an abnormal Cosyntropin stimulation test at the EOS visit are summarized in **Table 66**.

Table 66: Cosyntropin Stimulation Test Results - Subjects with Abnormal Results at End of Study

USUBJID	LPCN 1021-16-002				LPCN 1021-16-003			
	Screening Visit 2		EOS Visit 4		Screening Visit 2		EOS Visit 5	
	0 Min	60 Min	0 Min	60 Min	0 Min	60 Min	0 Min	60 Min
LPCN 1021-16-002-(b) (6) 16-003-(b) (6)	--	--	--	--	12.4	15.5	0.7	5
LPCN 1021-16-002-(b) (6) 16-003-(b) (6)	--	--	--	--	7.2	7.7	13.1	8.7
LPCN 1021-16-003(b) (6)	--	--	--	--	12.8	11.9	13	13.1
LPCN 1021-16-003	--	--	--	--	11.6	11.4	12.5	12.1
LPCN 1021-16-003	--	--	--	--	7.6	7.8	14.9	14.8
LPCN 1021-16-003	--	--	--	--	22.1	22.3	11.5	11

EOS = End-of study
Source: Reviewer's analysis.

The results of the Cosyntropin sub-study were consultatively reviewed by an FDA endocrinologist. In addition, to the findings above, the consultant noted that the four-week treatment period may be insufficient to assess whether Tlando, a drug that is expected to be taken chronically, causes adrenal dysfunction. The consultant concluded that the data are insufficient to rule out a risk of adrenal insufficiency, and recommended further assessment of adrenal function over a longer study duration.

Reviewer comment: Only one subject had a normal Cosyntropin stimulation result at screening and an abnormal result at the end of study, after 24 days of exposure to Tlando. This subject participated in the study at a site where all the subjects in the Cosyntropin sub-study had a minimal response to stimulation, which may have resulted from technical problems conducting the test. 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 recommend conducting a study of longer duration to more definitively address this issue.

8.6. Safety Analyses by Demographic Subgroups

Age

Of the 525 hypogonadal men who received Tlando in a supportive or pivotal safety study, 54 (10.3%) were 65 years or older. **Table 67** and **Table 68** display TEAEs by SOC for subjects less than 65 years of age and at least 65 years of age, respectively, for supportive and pivotal safety studies by treatment group.

Table 67: TEAEs by System Organ Class for Subjects < 65 Years for Supportive and Pivotal Safety Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	Original ISS Tlando N = 353	Updated ISS Tlando N = 471	Andriol 80 mg N = 34	AndroGel 1.62% N = 92	Placebo N = 17
Any TEAE	174 (49.3)	196 (41.6)	12 (35.3)	59 (64.1)	8 (47.1)
Infections and Infestations	43 (12.2)	49 (10.4)	3 (8.8)	19 (20.7)	0
Gastrointestinal Disorders	40 (11.3)	42 (8.9)	2 (5.9)	9 (9.8)	8 (47.1)
Investigations	37 (10.5)	42 (8.9)	3 (8.8)	11 (12.0)	0
Musculoskeletal and Connective Tissue Disorders	30 (8.5)	31 (6.6)	1 (2.9)	12 (13.0)	1 (5.9)
Nervous System Disorders	29 (8.2)	31 (6.6)	2 (5.9)	8 (8.7)	3 (17.6)
Skin and Subcutaneous Tissue Disorders	28 (7.9)	30 (6.4)	1 (2.9)	8 (8.7)	2 (11.8)
General Disorders and Administration Site Conditions	21 (5.9)	24 (5.1)	1 (2.9)	11 (12.0)	1 (5.9)
Injury, Poisoning and Procedural Complications	19 (5.4)	22 (4.7)	2 (5.9)	9 (9.8)	0
Respiratory, Thoracic and Mediastinal Disorders	16 (4.5)	16 (3.4)	0	7 (7.6)	0
Psychiatric Disorders	15 (4.2)	15 (3.2)	1 (2.9)	7 (7.6)	0
Metabolism and Nutrition Disorders	13 (3.7)	13 (2.8)	0	7 (7.6)	0
Vascular Disorders	8 (2.3)	9 (1.9)	1 (2.9)	6 (6.5)	0
Cardiac Disorders	7 (2.0)	7 (1.5)	1 (2.9)	5 (5.4)	0
Blood and Lymphatic System Disorders	6 (1.7)	6 (1.3)	0	2 (2.2)	0
Eye Disorders	5 (1.4)	5 (1.1)	0	2 (2.2)	0
Renal and Urinary Disorders	5 (1.4)	6 (1.3)	0	7 (7.6)	0
Reproductive System and Breast Disorders	4 (1.1)	4 (0.8)	0	6 (6.5)	0
Congenital, Familial and Genetic Disorders	1 (0.3)	1 (0.2)	0	0	0
Ear and Labyrinth Disorders	1 (0.3)	1 (0.2)	0	1 (1.1)	0
Immune System Disorders	1 (0.3)	1 (0.2)	0	1 (1.1)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.3)	1 (0.2)	0	1 (1.1)	0
Surgical and Medical Procedures	1 (0.3)	1 (0.2)	0	1 (1.1)	0
Endocrine Disorders	0	0	0	1 (1.1)	0

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), 2.7.4, Table 73, p. 135.

Table 68: TEAEs by System Organ Class for Subjects ≥ 65 Years for Supportive and Pivotal Safety Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	Original ISS Tlando N = 28	Updated ISS Tlando N = 54	Andriol 80 mg N = 0	AndroGel 1.62% N = 12	Placebo N = 1
Any TEAE	16 (57.1)	25 (46.3)	0	9 (75.0)	1 (100)
Investigations	5 (17.9)	8 (14.8)	0	1 (8.3)	0
Nervous System Disorders	5 (17.9)	7 (13.0)	0	0	0
Gastrointestinal Disorders	3 (10.7)	4 (7.4)	0	2 (16.7)	0
Infections and Infestations	2 (7.1)	4 (7.4)	0	3 (25.0)	0
Musculoskeletal and Connective Tissue Disorders	2 (7.1)	3 (5.6)	0	0	0
Renal and Urinary Disorders	2 (7.1)	3 (5.6)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	2 (7.1)	3 (5.6)	0	2 (16.7)	0
Injury, Poisoning and Procedural Complications	2 (7.1)	2 (3.7)	0	2 (16.7)	0
Blood and Lymphatic System Disorders	1 (3.6)	2 (3.7)	0	0	0
General Disorders and Administration Site Conditions	1 (3.6)	2 (3.7)	0	1 (8.3)	1 (100)
Vascular Disorders	1 (3.6)	2 (3.7)	0	0	0
Skin and Subcutaneous Tissue Disorders	1 (3.6)	1 (1.9)	0	0	0
Surgical and Medical Procedures	1 (3.6)	1 (1.9)	0	0	0
Cardiac Disorders	0	0	0	1 (8.3)	0
Ear and Labyrinth Disorders	0	0	0	1 (8.3)	0
Immune System Disorders	0	0	0	1 (8.3)	0
Metabolism and Nutrition Disorders	0	0	0	2 (16.7)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	0	1 (8.3)	0
Psychiatric Disorders	0	0	0	1 (8.3)	0

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), 2.7.4, Table 74, p. 136.

Of subjects who were treated with Tlando, 41.6% of younger subjects experienced at least one TEAE compared with 46.3% of older subjects. A higher percentage of older subjects experienced at least one TEAE with AndroGel 1.62% compared with younger subjects (75.0% vs 64.1%, respectively). For older subjects who received Tlando, adverse events occurred most frequently in the SOCs of investigations (14.8% of older subjects vs 8.9% of younger subjects), nervous system disorders (13.0% vs 6.6%, respectively), gastrointestinal disorders (7.4% vs 8.9%), infections and infestations (7.4% vs 10.4%, respectively), and musculoskeletal and connective tissue disorders (5.6% vs 6.6%, respectively).

*Reviewer comment: A greater percentage of older Tlando treated subjects reported at least one TEAE compared with younger subjects (*46.3% *% vs. 41.6%). For subjects who received Tlando, except for the Renal and Urinary Disorders SOC and the Respiratory, Thoracic and Mediastinal*

Disorders SOC, the SOCs to which TEAEs were most frequently (>5%) reported were similar for older and younger subjects. A greater percentage of older subjects reported TEAEs to the Renal and Urinary Disorders SOC (5.6% vs. 1.3%) and the Respiratory, Thoracic and Mediastinal Disorders SOC (5.6% vs. 3.4%).

Body Mass Index

Of the 525 hypogonadal men who received Tlando in a supportive or pivotal safety study, 276 (52.6%) had a BMI of 30 kg/m^2 or greater, which meets the criteria of obesity. **Table 69** and **Table 70** display TEAEs by SOC for subjects with BMI less than 30 kg/m^2 (non-obese) and at least 30 kg/m^2 (obese), respectively, for supportive and pivotal safety studies by treatment.

Table 69: Treatment Emergent Adverse Events by System Organ Class for Subjects with Body Mass Index < 30 kg/m^2 for Supportive and Pivotal Safety Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	Original ISS Tlando N = 205	Updated ISS Tlando N = 249	Andriol 80 mg N = 29	AndroGel 1.62% N = 37	Placebo N = 16
Any TEAE	91 (44.4)	102 (41.0)	12 (41.4)	26 (70.3)	8 (50.0)
Infections and Infestations	20 (9.8)	23 (9.2)	3 (10.3)	9 (24.3)	0
Gastrointestinal Disorders	22 (10.7)	22 (8.8)	2 (6.9)	4 (10.8)	7 (43.8)
Investigations	18 (8.8)	21 (8.4)	3 (10.3)	6 (16.2)	0
Nervous System Disorders	19 (9.3)	20 (8.0)	2 (6.9)	4 (10.8)	3 (18.8)
Musculoskeletal and Connective Tissue Disorders	14 (6.8)	15 (6.0)	1 (3.4)	6 (16.2)	1 (6.3)
Skin and Subcutaneous Tissue Disorders	14 (6.8)	14 (5.6)	1 (3.4)	3 (8.1)	2 (12.5)
Injury, Poisoning and Procedural Complications	11 (5.4)	12 (4.8)	2 (6.9)	6 (16.2)	0
General Disorders and Administration Site Conditions	8 (3.9)	9 (3.6)	1 (3.4)	3 (8.1)	2 (12.5)
Respiratory, Thoracic and Mediastinal Disorders	7 (3.4)	7 (2.8)	0	3 (8.1)	0
Psychiatric Disorders	7 (3.4)	7 (2.8)	1 (3.4)	2 (5.4)	0
Cardiac Disorders	5 (2.4)	5 (2.0)	1 (3.4)	0	0
Metabolism and Nutrition Disorders	4 (2.0)	4 (1.6)	0	3 (8.1)	0
Vascular Disorders	3 (1.5)	4 (1.6)	1 (3.4)	2 (5.4)	0
Eye Disorders	3 (1.5)	3 (1.2)	0	0	0
Blood and Lymphatic System Disorders	2 (1.0)	2 (0.8)	0	1 (2.7)	0
Renal and Urinary Disorders	2 (1.0)	2 (0.8)	0	2 (5.4)	0
Reproductive System and Breast Disorders	2 (1.0)	2 (0.8)	0	4 (10.8)	0
Congenital, Familial and Genetic Disorders	1 (0.5)	1 (0.4)	0	0	0
Immune System Disorders	1 (0.5)	1 (0.4)	0	0	0
Surgical and Medical Procedures	1 (0.5)	1 (0.4)	0	0	0
Ear and Labyrinth Disorders	0	0	0	1 (2.7)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	0	1 (2.7)	0

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), 2.7.4, Table 77, p. 140.

Table 70: Treatment Emergent Adverse Events by System Organ Class for Subjects with Body Mass Index ≥ 30 kg/m^2 for Supportive and Pivotal Safety Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	Original ISS Tlando N = 176	Updated ISS Tlando N = 276	Andriol 80 mg N = 5	AndroGel 1.62% N = 67	Placebo N = 2
Any TEAE	99 (56.3)	119 (43.1)	0	42 (62.7)	1 (50.0)
Infections and Infestations	26 (14.8)	30 (10.9)	0	13 (19.4)	0
Investigations	24 (13.6)	29 (10.5)	0	6 (9.0)	0
Gastrointestinal Disorders	21 (11.9)	24 (8.7)	0	7 (10.4)	1 (50.0)
Musculoskeletal and Connective Tissue Disorders	18 (10.2)	19 (6.9)	0	6 (9.0)	0
Nervous System Disorders	15 (8.5)	18 (6.5)	0	4 (6.0)	0
Skin and Subcutaneous Tissue Disorders	15 (8.5)	17 (6.2)	0	5 (7.5)	0
General Disorders and Administration Site Conditions	14 (8.0)	17 (6.2)	0	9 (13.4)	0
Respiratory, Thoracic and Mediastinal Disorders	11 (6.3)	12 (4.3)	0	6 (9.0)	0
Injury, Poisoning and Procedural Complications	10 (5.7)	12 (4.3)	0	5 (7.5)	0
Metabolism and Nutrition Disorders	9 (5.1)	9 (3.3)	0	6 (9.0)	0
Psychiatric Disorders	8 (4.5)	8 (2.9)	0	6 (9.0)	0
Vascular Disorders	6 (3.4)	7 (2.5)	0	4 (6.0)	0
Renal and Urinary Disorders	5 (2.8)	7 (2.5)	0	5 (7.5)	0
Blood and Lymphatic System Disorders	5 (2.8)	6 (2.2)	0	1 (1.5)	0
Reproductive System and Breast Disorders	2 (1.1)	2 (0.7)	0	2 (3.0)	0
Cardiac Disorders	2 (1.1)	2 (0.7)	0	6 (9.0)	0
Eye Disorders	2 (1.1)	2 (0.7)	0	2 (3.0)	0
Ear and Labyrinth Disorders	1 (0.6)	1 (0.4)	0 1 (1.5)	0	
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.6)	1 (0.4)	0	1 (1.5)	0
Surgical and Medical Procedures	1 (0.6)	1 (0.4)	0	1 (1.5)	0
Endocrine Disorders	0	0	0	1 (1.5)	0
Immune System Disorders	0	0	0	2 (3.0)	0

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), 2.7.4, Table 78, p. 141.

Of subjects who were treated with Tlando, 41.0% of non-obese subjects experienced at least one TEAE compared with 43.1% of obese subjects. In contrast, a higher percentage of non-obese subjects experienced at least one TEAE with AndroGel 1.62% compared with obese subjects (70.3% vs 62.7%, respectively). For obese subjects who received Tlando, adverse events occurred most frequently in the SOCs of infections and infestations (10.9% of obese

subjects vs 9.2% of non-obese subjects), investigations (10.5% vs 8.4%, respectively), gastrointestinal disorders (8.7% vs 8.8%, respectively), musculoskeletal and connective tissue disorders (6.9% vs 6.0%, respectively), nervous system disorders (6.5% vs 8.0%, respectively), skin and subcutaneous tissue disorders (6.2% vs 5.6%, respectively), and general disorders and administration site conditions (6.2% vs 3.6%).

Reviewer comment: A slightly greater percentage of obese Tlando treated subjects reported at least one TEAE compared with non-obese subjects (43.1% vs 41.0%). For subjects who received Tlando, except for the General Disorders and Administration Site Conditions SOC, the SOCs to which TEAEs were most frequently (>5%) reported were similar for obese and non-obese subjects. A greater percentage of obese subjects reported TEAEs to the General Disorders and Administration Site Conditions SOC (6.2% vs 3.6%).

8.7. Specific Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted to this NDA.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Two subjects reported malignant neoplasms during the 52-week Phase 3 study (LPCN 1021-13-001): one in the Tlando treatment group (thyroid neoplasm-malignant) and one in the AndroGel 1.62% treatment group.

Subject (b) (6) is a 41 year old white male randomized to the Tlando treatment group. The subject reported the adverse event of thyroid neoplasm-malignant on study day 272. The event was assessed as not related to the study drug by the investigator.

Subject (b) (6) is a 66 year old white male randomized to the AndroGel 1.62% treatment group. The subject reported the adverse event of prostate cancer on study day 62. The event was assessed as not related to the study drug by the investigator.

No neoplasms were reported in LPCN 1021-16-002 and LPCN 1021-16-003.

8.8.2. Human Reproduction and Pregnancy

No studies on pregnancy or lactation were conducted as part of the clinical research program for Tlando. Exposure of a female fetus to androgens may result in varying degrees of virilization.

8.8.3. Pediatrics and Assessment of Effects on Growth

Tlando was not studied in males less than 18 years of age.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of overdose with Tlando were reported in the Phase 1 or Phase 3 clinical studies of Tlando, and no new data regarding overdose were generated for Tlando for this submission. No formal abuse potential studies or studies to evaluate withdrawal or rebound were conducted as part of the clinical research program for Tlando.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through 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 U.S. for many years.

The Applicant submitted a paper titled, "*The risk of adverse outcomes in association with use of testosterone products: a cohort study using the UK-based general practice research database*."[5] The paper describes a cohort study of men in the UK based General Practice Research Database who were users of oral testosterone undecanoate and injectable forms of testosterone. The study cohort included 5841 men who received at least one study testosterone preparation (injectable: n = 4190; oral: n = 1329; both oral and injectable n = 322). The paper reported the following results: adjusted relative risks for oral compared with injectable testosterone were 0.8 (95% CI 0.6, 1.2) for hypertension; 0.13 (0.05, 0.35) for polycythemia; 1.1 (0.7, 1.7) for prostate cancer; 1.5 (1.1, 2.2) for BPH; and 1.1 (0.8, 1.4) for prostatism. The authors concluded that the risks of prostate cancer and prostatism were similar in users of the two preparations, but risks were higher for hypertension and polycythemia in the injectable compared with the oral testosterone users. The risk of BPH was slightly higher in the oral users, but the difference was small and could have been due to bias.

Reviewer comment: The formulation and dose of oral testosterone undecanoate capsules marketed in the UK are different from Tlando. Therefore, the results of the paper submitted by the Applicant have limited applicability to the product under review. However, the results provide support for the long-term safety of oral testosterone undecanoate in general.

8.9.2. Expectations on Safety in the Postmarket Setting

Tlando's postmarket safety expectations cannot be determined because the drug's effect on SBP is unclear and the risk that the drug could adversely affect SBP remains uncharacterized. In addition, the drug's effect on the hypothalamic pituitary adrenal axis also remains unclear. Though adrenal function was assessed in LPCN 1021-16-002 and LPCN 1021-16-003, the

[5]Jick SS Hagberg KW. The risk of adverse outcomes in association with use of testosterone products: a cohort study using the UK-based general practice research database. Br J Clin Pharmacol 2012 75(1): 260-270.

studies' 24-day treatment periods were insufficient to assess whether Tlando, a drug that is expected to be taken chronically, causes adrenal dysfunction.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues from other disciplines were identified.

8.10. Integrated Assessment 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. Though the safety database is considered adequate, there are still some gaps in Tlando's safety profile. The drug's effect on SBP remains unclear: Two trials (LPCN 1021-13-001 and LPCN 1021-16-002) did not show clinically significant changes in cuff SBP, while one trial (LPCN 1021-16-003) showed an increase of 4 mmHg in cuff SBP. The concern over the SBP results in LPCN 1021-16-003 was reinforced by the SBP findings for another oral TU testosterone that is also in development. A Phase 3 study for that drug showed an increase in cuff SBP that was confirmed by ABPM in a subsequent Phase 3 study. An increase in SBP is especially important in older men, the patient population most likely to use Tlando, because they are more likely to have other preexisting cardiovascular risk factors. An ABPM study is needed to further characterize this risk.

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. Further assessment of adrenal function over a longer duration is recommended to rule out the risk of adrenal dysfunction.

9. Advisory Committee Meeting and Other External Consultations

The Bone, Reproductive and Urologic Drugs Advisory Committee met on January 10, 2018 to discuss NDA 208088. The committee provided input to the following discussion and voting questions.

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).

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.*

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.*

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. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling is deferred to the next review cycle.

10.2. Nonprescription Drug Labeling

Not applicable, Tlando is proposed as a prescription drug.

11. Risk Evaluation and Mitigation Strategies (REMS)

Recommendations for postmarket risk evaluation and mitigation strategies (REMS) are deferred to the next review cycle.

12. Postmarketing Requirements and Commitments

Recommendations for clinical postmarket requirements and commitments are deferred to the next review cycle.

13. Appendices

13.1. References

The Applicant conducted a literature review to evaluate safety regarding the DHT levels observed in clinical trials. Five double-blind, placebo-controlled trials in which males were treated with a DHT gel are summarized in **Table 71**.

Table 71: Summary of Randomized Placebo-controlled Studies on Transdermal DHT-gel from the Literature

Duration Dosing (Month)	Subjects	DHT Gel Dose	Serum level in the DHT group**			Safety	Reference
			DHT (ng/dL)	T (ng/dL)	DHT/T ratio		
1	Healthy male 35-55 yrs N=l2D N=l5P	70mg /day	7x Base: 35	Decreased Base: 440	NA	No change in clinical labs. No difference in intra-prostate DHT, PSA, PV and androgen- related gene expression. Supraphysiologic increases in serum DHT did not significantly alter intraprostatic levels of DHT, testosterone, or prostate epithelial cell androgen-regulated gene expression in healthy men.	Page et al: *J Clin Endocrinol Metab* 96: 430-437, 2011.
3	Healthy male >60 yrs; N=l8D N=l9P	70 mg qd	490-534 Base: 41	144-210 Base: 432	2.4-3.7 Base: 0.09	Dihydrotestosterone treatment had no adverse effects on prostate (unchanged prostate volumes and prostate-specific antigen) and cardiovascular (no adverse change in vascular reactivity or lipids) safety markers. Increased Hct/Hb (in normal range.	Ly et al: *J Clin Endocrinol Metab* 86: 4078-4088, 2001.
6	Healthy male 50-70 yrs; N=60D N=60P	125-250 mg /day	238 Base: 44	170 Base: 464	1.4 Base: 0.09	No adverse effects on prostate; no changes on lipids. Hemoglobin concentrations increased from 146.0 +/- 8.2 to 154.8 +/- 11.4 g/liter, and hematocrit from 43.5 +/- 2.5% to 45.8 +/- 3.4% (P < 0.001). Prostate weight and prostate-specific antigen levels did not change during the treatment. No major adverse events were observed.	Kunelius et al: *J Clin Endocrinol Metab* 87: 1467- 1472, 2002.
6	Hypogonadal male, 55-80 yrs; N=43D N=44D N=41P	35mg /day 70mg /day	244-300 Base: NA	106-124 Base: 226-231	2.3-2.4 Base: NA	2 deaths (unrelated), n=l 5 SAEs (2 related: prostate cancer and one increased PSA); no effects on prostate volume but increase PSA (3.4% on DHT-gel vs. 0% on placebo); increased Hct/Hb, polycythemia; no effects on BP	A Phase 2 trial from *Ascend Therapeutics, Inc. Clintrial.gov: NCT00490022*
24	Healthy male without prostate disease >50 yrs; N=55D N=58P	70mg /day	730 Base: 64	69 Base: 490	10.5 Base: 0.1	Slightly increased PSA and prostate volume; no changes on lipids; Dihydrotestosterone increased hemoglobin levels (7% [CI, 5% to 9%]), serum creatinine levels (9% [CI, 5% to 11%]), and lean mass (2.4% [CI, 1.6% to 3.1%) but decreased fat mass (5.2% [CI, 2.6% to 7.7%]) (P <0.001 for all). Protocol-specific discontinuations due to DHT were asymptomatic increased hematocrit (n = 8), which resolved after stopping treatment, and increased prostate-specific antigen levels (n = 3; none with prostate cancer) in the DHT group. No serious adverse effects due to DHT occurred	Idan et al: *Ann Intern Med* 153:621-632, 2010.

D=DHT Gel; P=Placebo; Base=baseline; NA=not available
**Serum DHT and T were stable over the course of treatment;
Source: NDA 208088 (seq 0000), 2.7 3, Table 21, p. 53.

Reviewer comment: Except for the Idan study, the reviewed studies were six months or less in duration. Two of the studies had less than 20 treated subjects and all but one were conducted in healthy men.

During the 24 month study by Idan et al., two subjects in the DHT treatment group reported serious adverse events of concern: one subject reported the event of pulmonary embolism, another reported the event of deep venous thrombosis. There were no reports of pulmonary embolism or deep venous thrombosis in the placebo group.

This reviewer did not find these studies to be supportive of the safety of long-term exposure to elevated levels of DHT.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): S361.1.001, M13-298, M12-868, M12-778, LPCN 1021-05-001, LPCN 1021-09-001, LPCN 1021-13-001, LPCN 1021-13-001, LPCN 1021-14-001, LPCN 1021-16-002, LPCN 1021-16-003, LPCN 1111-15-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 508		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

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

/s/

MARTIN E KAUFMAN
03/12/2018

SURESH KAUL
03/12/2018

Office of Clinical Pharmacology Review

NDA Number	208088 SDN027
Link to EDR	\\CDSESUB1\evsprod\NDA208088\208088.enx
Submission Date	August 8, 2017
Submission Type	Resubmission (standard review)
Brand Name	Tlando®
Generic Name	Testosterone undecanoate
Dosage Form and Strength	Oral capsule; 225 mg twice daily
Route of Administration	Oral
Proposed Indication	Treatment of hypogonadism
Applicant	Lipocine Inc.
Associated IND	106,476
OCP Review Team	LaiMing Lee, PhD; Doanh Tran, PhD
OCP Final Signatory	Gilbert Burckart, PharmD

Contents

1. EXECUTIVE SUMMARY

1.1 Recommendations

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

To address the potential ex vivo TU to T conversion, we recommend the Applicant conduct a study assessing the potential for ex vivo TU to T conversion using samples collected from subjects dosed with oral TU to remove potential confounding effects of different spiking methods (i.e., differences in solvent). This assessment needs to account 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).

In addition, prior to the next NDA resubmission, we recommend the Applicant address (1) the potential cross-reactivity of TU to immunoassays used to assess total T concentrations in clinical practice and (2) the potential drug-drug interaction of TU, as the perpetrator. For completeness, we also recommend the Applicant submit the full study report for the new in vitro study evaluating TU conversion to T (referred to as study #2 in this review); the Applicant submitted a brief description of the study design and results on December 27, 2017.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Evidence of effectiveness was demonstrated by the Phase 3 study LPCN 1021-16-002. However, this finding is pending resolution of bioanalytical concerns regarding potential ex vivo conversion of TU to T.
General dosing instructions	The recommended dose is 225 mg (2 capsules of 112.5 mg) twice daily (BID) with food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	None

Labeling	The review team has no labeling recommendations at this time. Labeling will be considered during the next review cycle.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the phase 3 study LPCN-1021-16-002.
Other (bioanalytical)	The potential for ex vivo conversion of TU to T in blood samples collected from patients is a concern.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Testosterone is a steroid hormone produced mainly by the Leydig cells in the male testes. T is responsible for the development and maintenance of male reproductive tissues and male secondary characteristics. The Applicant developed TU oral capsules for the treatment of hypogonadism.

Absorption:

Testosterone

Median (min, max) time to peak serum T concentration (Tmax) was 5.0 (1.9, 11.9) hrs after the morning dose, mean (SD) 24-hr maximum concentration (Cmax) was 1178 (484) pg/dL, and mean (SD) 24-hr average concentration (Cavg) was 476 (174) ng/dL.

Figure 2.1-1. Mean (+SD) Pharmacokinetic Profile of Serum Testosterone on Day 24 After Twice Daily Oral Administration of Testosterone Undecanoate Oral Capsules 225 mg in Hypogonadal Men (N=90), Study LPCN 1021-16-002.

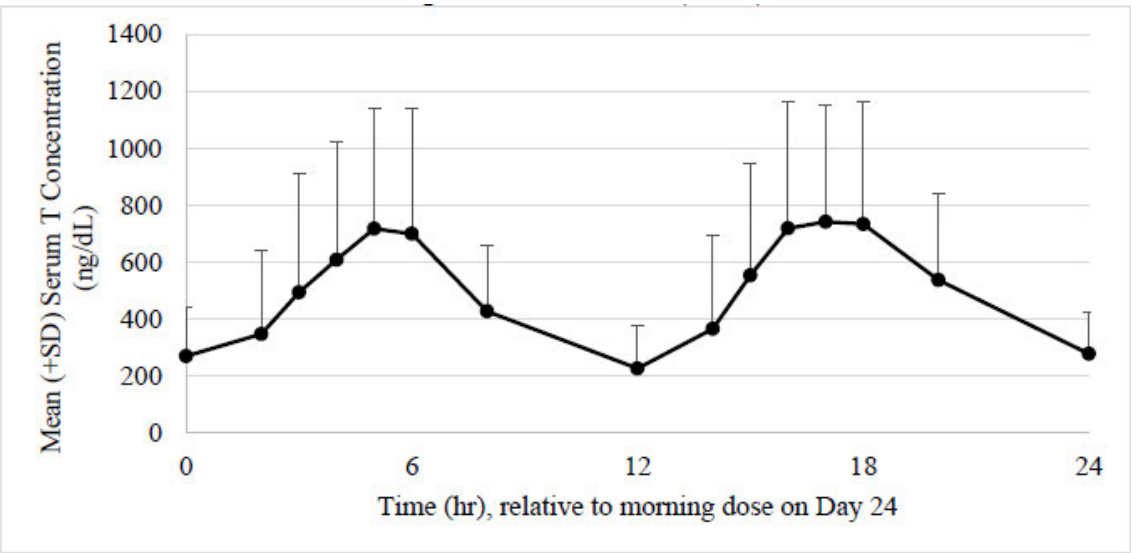


Table 2.1-1. Pharmacokinetic Parameters for Serum Testosterone Following Twice Daily Administration of Oral TU Capsule 225 mg With Food in Hypogonadal Men (N=90), Study LPCN 1021-16-002.

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
T Cavg0-24h, ng/dL	Mean (SD)	476 (174)		
T Cmax, ng/dL	Mean (SD)	1178 (484)	979 (479)	989 (475)
Tmax, h	Median (Min, Max)	14.8 (2.0, 24.0)	5.00 (1.9, 11.9)	4.80 (2.0, 12.0)

Testosterone Undecanoate

Median (min, max) time to peak serum TU concentration (Tmax) was 4.9 (1.9, 11.9) hrs after the morning dose, mean (SD) 24-hr Cmax was 11,106 (5036) pg/dL, and mean (SD) 24-hr Cavg was 46,974 (25,602) ng/dL.

Figure 2.1-2. Mean (±SD) Pharmacokinetic Profile of Serum Testosterone Undecanoate on Day 24 After Twice Daily Oral Administration of Testosterone Undecanoate Oral Capsules 225 mg in Hypogonadal Men (n=90).

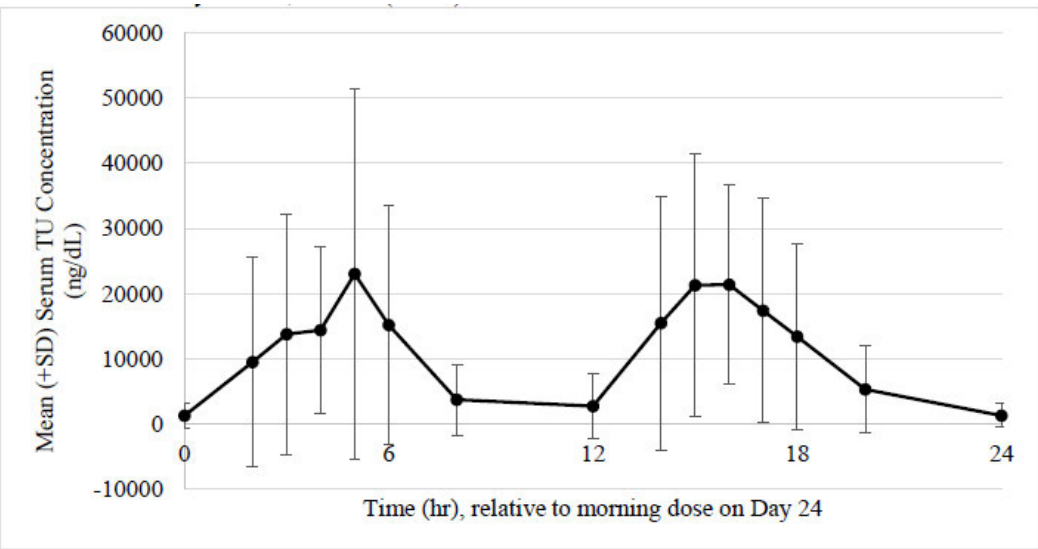


Table 2.1-2. Pharmacokinetic Parameters for Serum Testosterone Undecanoate Following Twice Daily Administration of Oral TU Capsule 225 mg With Food in Hypogonadal Men (N=90), Study LPCN 1021-16-002.

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/dL	Mean (SD)	11106 (5036)		
Cmax, ng/dL	Mean (SD)	46974 (25602)	35948 (28233)	36363 (19523)
Tmax, h	Median (Min, Max)	14.0 (2.0, 20.7)	4.9 (1.9, 11.9)	4.0 (1.9, 12.0)

Distribution: In humans, circulating T, like most steroids, is likely to be distributed to many, if not essentially all, tissues of the body. T is approximately 98% bound to plasma proteins including SHBG (~65 to 80%) and albumin (~20 to 30%) or as free T (0.5% to 2%).

Metabolism: The de-esterification of TU to produce T and 5α-reduction of TU to produce dihydrotestosterone undecanoate (DHTU) takes place in the intestinal wall as well as in the peripheral circulation. Both TU and DHTU are hydrolyzed in the intestinal wall and in the general circulation to yield testosterone and dihydrotestosterone (DHT). T is converted to estradiol by enzyme aromatase. DHT and estradiol are biologically active metabolites. DHT concentrations increased with T concentrations during oral TU treatment.

Excretion: Once T is formed from TU, there is considerable variation in the half-life of T as reported in the literature, ranging from 10 to 100 minute. T is metabolized to various 17-keto steroids through two different pathways.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

For the treatment of hypogonadism, the proposed dose is 225 mg of TU ((b) (4) taken orally with food twice daily (BID).

2.2.2 Therapeutic individualization

No dose adjustments are recommended for this proposed product. For the majority of topical testosterone products, patients are advised to have their serum T concentrations measured approximately 14 days after initiating therapy to ensure proper dosing. Dose adjustment recommendations for those products are based upon dosing algorithms evaluated in their respective phase 3 program(s). For this proposed product, the Applicant did not include a dose adjustment paradigm in their pivotal phase 3 study LPCN 1021-16-002. Instead, the Applicant is proposing a stopping or discontinuation criteria based upon post-hoc analysis (see section 3.3.3 for more details).

2.3 Outstanding Issues

- Potential for ex vivo conversion of TU to T (see section 3.3.1)
- Stopping criteria – identifying patients who require discontinuation of Tlando (see section 3.3.3)
- Cross reactivity of TU with immunoassays (see section 3.3.1)
- Drug-drug interaction of TU, as a perpetrator (see section 3.3.4)

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-3 has no labeling recommendations currently. Labeling will be considered during the next review cycle.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Testosterone undecanoate (also referred to as LPCN 1021 and Tlando™) is a fatty acid ester of T, an oral steroid prodrug. Through non-specific esterase activity, the ester portion of TU is cleaved to form T, the active moiety.

The Clinical Pharmacology review of the original NDA submission included the following clinical studies for oral TU:

- Phase 3 study LPCN 1021-13-001 (pivotal safety and supportive efficacy of 225 mg BID with dose titration)
- Phase 1 study S361.1.002 (pilot food effect study in postmenopausal women)
- Phase 1 study LPCN 1021-14-001 (food/fat content effect study)
- Phase 2 study M12-778 (dose finding study)

The current NDA resubmission included the following clinical studies and information:

- Pivotal Phase 3 study LPCN 1021-16-002 (efficacy of fixed dose 225 mg BID)
- Phase 3 study LPCN 1021-16-003 (efficacy of fixed dose 150 mg three times daily (TID)) – not reviewed by the Clinical Pharmacology Team
- Preliminary in vitro TU stability
- Literature regarding TU stability

Phase 3 study LPCN 1021-13-001 (included 225 mg TU BID with dose titration) was submitted and reviewed by the Clinical team in the original NDA review cycle. In this current resubmission, the Clinical review team will use the 52-week safety data from Phase 3 study LPN 1021-13-001 for pivotal safety and supportive efficacy for the proposed fixed dose 225 mg BID.

This NDA resubmission includes phase 3 studies LPCN 1021-16-002 and LPCN 1021-16-003, which administered TU 225 mg BID with food and 150 mg TID with food, respectively. Guidance regarding blood collection times to most accurately capture Cmax and calculation of Cmax outliers were provided to the Applicant following both protocol reviews.

In addition, the Clinical Pharmacology review team requested the Applicant address potential ex vivo conversion of TU to T as part of the protocol review (Advice/Information Request dated June 6, 2017 under IND 106,476) and following NDA resubmission (Information Request dated October 5, 2017 under NDA 208088).

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Testosterone is a steroid hormone produced mainly by the Leydig cells in the male testes. Testosterone is responsible for the development and maintenance of male reproductive tissues and male secondary characteristics.
Active Moieties	Testosterone undecanoate (inactive prodrug), testosterone (active metabolite)
General Information	
Maximum Tolerated Dose	The highest dose evaluated was 300 mg BID in the phase 3 study LPCN 1021-13-001 (original NDA submission). Maximum tolerated dose was not established in this development program.
Dose Proportionality	The proposed dosing regimen is 225 mg BID with food. Each 225-mg dose was given as two 112.5 mg capsules in the phase 3 studies LPCN 1021-16-002 and LPCN 1021-13-001, and is also the proposed dosing instruction.

Bioanalysis	Liquid chromatography- mass spectrometry/mass spectrometry (LC-MS/MS) methods were used to measure serum and plasma concentrations of testosterone undecanoate and testosterone. The bioanalytical methods were adequately validated.
Drug Interaction	Testosterone undecanoate is de-esterified to T by non-specific esterases. No drug interaction studies were conducted with oral testosterone undecanoate capsules. Class labeling would apply to this product. Because the concentration of the prodrug TU is high relative to the active metabolite T (~16-fold after adjusting for molecular weight differences), the Applicant will be requested to address its potential drug interaction with cytochrome P450 enzymes.
Absorption (Dose: 225 mg BID)	
Tmax (median (range))	For testosterone: 5.0 (1.9-11.9) hrs For testosterone undecanoate: 4.9 (1.9-11.9) hrs
Systemic Exposure (mean (SD))	Serum testosterone 24-hr Cavg: 476 (174) ng/dL Serum testosterone 24-hr Cmax: 1178 (484) pg/dL Serum testosterone undecanoate 24-hr Cavg: 11,106 (5036) pg/dL Serum testosterone undecanoate 24-hr Cmax: 46,974 (25,602) ng/dL
Distribution	
Protein Binding	Testosterone is highly bound to sex hormone binding globulin (SHBG) and albumin.
Elimination	
Metabolism	Testosterone undecanoate is de-esterified to T by non-specific esterases.
Excretion	Once T is formed from TU, there is considerable variation in the half-life of T as reported in the literature, ranging from 10 to 100 minutes.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The current basis of approval for T products, including oral TU, are pharmacokinetic endpoints. There are no approved clinical endpoints based upon signs and symptoms of T treatment. This section includes statistical analysis for the assessment of efficacy followed by a pending concern regarding data reliability, namely ex vivo TU to T conversion, and a concern regarding potential cross reactivity of TU with commercial T immunoassay.

Efficacy results:

Phase 3 study LPCN 1021-16-002 provided the pivotal evidence to support efficacy for the use of TU to treat hypogonadism in men with twice daily administration of oral capsules 225 mg with food. The primary efficacy endpoint is the percentage of patients with 24-hr T Cavg within the therapeutic range of 300 to 1080 ng/dL. To meet the efficacy endpoint, the minimum acceptable percentage is 75% with a lower bound of the 95% confidence interval (CI) be 65% or more.

The study met the predefined efficacy endpoint with ≥ 75% of patients achieving a 24-hr Cavg between 300 and 1080 ng/dL. In this study with 95 patients, twice daily administration of 225 mg oral TU resulted in 80% of patients achieving a 24-hr Cavg between 300 to 1080 ng/dL. The lower bound of the 90% CI was 72%, which is greater than predefined minimum 65%. Table 3.3.1-1 summarizes the statistical results from the pivotal study for 95 patients who were treated with oral TU 225 mg BID with food (without regard to fat content) for approximately 24 days.

Table 3.3.1-1. Proportion of TU-treated Patients Achieving 24-hr Average Serum Testosterone Concentrations Within Normal Range on Day 24 (N=95) in study LPCN 1021-16-002 (Applicant's table 16).

Parameter	Target	Safety Set BLOCF N=95
Percentage subjects achieving 24-hour average serum T concentration within normal range[1]	≥ 75%	80%
95% Confidence interval (lower, upper bound %)[2]	≥ 65% (Lower Bound)	72%, 88%

Key: T = total testosterone
[1]Normal Range: 300 to 1080 ng/dL
[2]A 95%, 2-sided, binomial confidence interval surrounding the point estimate was calculated.
Source: Table 14.2.4.4

Phase 3 study LPCN 1021-13-001 provided supportive evidence for efficacy of the fixed dose 225 mg BID. The Applicant conducted a post hoc analysis of subjects taking the fixed dose of 225 mg BID at Week 3 before titration. The results showed the percentage of TU-treated patients who had achieved a 24-hr average serum T concentration within the normal range of 300 to 1140 ng/dL at Week 3 was 86% with a lower bound of the 95% confidence interval of 81%.

Concerns regarding potential for ex vivo TU to T conversion:

Published literature and available data suggests that TU can convert to T ex vivo (e.g., in test tubes in whole blood in the presence of non-specific esterases). If TU is converted to T during the sample preparation period (i.e., time between blood draw from a patient and the collection of serum or plasma), the reported T concentration can be an over-reporting of the patient's T concentration and the reported efficacy results may be inaccurate.

This section of the review includes findings and conclusions from in vitro studies obtained from two publications (Wang et al. and Lachance et al.) and the Applicant. The publications and one of the Applicant's studies (referred to as study #1) showed that testosterone esters, including testosterone enanthate (TE) and TU, are converted to T in an amount that is clinically relevant. In contrast, one set of data from the Applicant (referred to as study #2) showed that TU was not converted to T.

Study from Wang et al.

In 2008, Wang and co-authors assessed the effects of TE and TU on measured T and DHT. The authors dissolved TE and TU in ethanol and phosphate buffer solution (PBS) before adding to whole blood in either plain (without an enzyme inhibitor) or fluoride (an esterase inhibitor) collection tubes. After the addition of TE or TU solution, the blood sat in the tubes at room temperature (RT) for 30 min before centrifugation at 4°C for 20 min. The resulting serum was assayed for T and DHT by LC-MS/MS.

Results showed that in plain tubes, hydrolysis of TE to T increased serum T by 73 and 740 ng/dL at TE concentrations of 10,000 and 100,000 ng/dL, respectively, and use of tubes containing fluoride, an esterase inhibitor, abolished most of the ex vivo TE to T conversion. However, their data showed that T did not increase when TU was added to whole blood using plain tubes, suggesting there was no ex vivo TU to T conversion.

While the authors concluded that addition of TE to blood collected in plain tubes caused a dose related increase serum T levels due to the action of non-specific esterases in the red cells. The reason for the observed apparent lack of conversion from TU, a molecule similar to TE, to T is not known.

Study from Lachance et al.

In 2015, Lachance and co-authors assessed the potential degradation of TU in blood under conditions similar to typical clinical practice. The in vitro studies included TU dissolved in methanol or ethanol/PBS, spiked in whole blood, aliquots set at room temperature for at least 30 min before processing to plasma or serum, collected in tubes with and without esterase inhibitor additive, and measured T concentrations by LC-MS/MS. T concentrations were used to determine TU to T conversion rate. Lachance and co-authors also attempted to address Wang's conclusion that TU-T conversion does not exist.

The following tables show the TU conversion rates and amount T following incubation of TU under different experimental conditions.

Table 3.3.1-2. Serum Testosterone Concentrations Harvested from Whole Blood Spiked with Various Amounts of Testosterone Undecanoate (Lachance's table 1).

Table 1. Conversion of testosterone undecanoate into testosterone according to the testosterone undecanoate concentrations and the incubation time.

TU Concentration Fortified (ng/dl)	Duration of incubation (min)	Concentration testosterone measured (ng/dl)	% difference vs TU = 0 (%)	% difference 30 vs 60 min (%)
0	0	23.75	–	–
1500	30	36.76	54.8	24.6
	60	45.81	92.9	
10,000	30	152.66	542.8	65.8
	60	253.18	966.0	
30,000	30	306.02	1188.5	73.9
	60	532.19	2140.8	
70,000	30	732.49	2984.2	72.4
	60	1262.81	5217.1	

TU: Testosterone undecanoate.

~130 ng/dL

~230 ng/dL

The data showed that serum T concentrations were higher with greater duration of incubation and with higher initial TU concentration. Compared to samples with no TU added (endogenous T only), T concentration increased ~130 and ~230 ng/dL when we consider the sample processing conditions most similar to that in the phase 3 study LPCN 1021-16-002 (TU concentration at 11,106 ng/dL and sample sitting at RT for 20-60 min before processing).

Table 3.3.1-3. Testosterone Concentrations in Serum or Plasma Harvested from Whole Blood Spiked with Testosterone Undecanoate Under Various Experimental Conditions (Lachance's table 4).

Table 4. Testosterone and phosphate buffer saline concentrations in serum or plasma harvested from blood spiked with testosterone undecanoate working solution prepared in phosphate buffer saline or methanol; spiking level 60,000 ng/dl.

Experiments	Endogenous level in serum	Endogenous level in plasma	30 min serum RT	60 min serum RT	Plasma 10 min 4°C	Plasma 30 min 4°C	Plasma 60 min 4°C
Mean testosterone concentration (ng/dl)							
Whole blood spiked with TU in PBS	255.4	221.7	295.4	349.0	236.0	232.9	231.1
Whole blood spiked with TU in methanol	255.4	221.7	854.8	1255.4	322.5	339.9	320.5
Mean TU concentration (ng/dl)							
Whole blood spiked with TU in PBS	N/A	N/A	3991.0	5892.3	74408.7	54088.0	26618.7
Whole blood spiked with TU in methanol	N/A	N/A	97110.3	96132.3	97235.0	95628.0	93816.3

PBS: Phosphate buffer saline; RT: Room temperature; TU: Testosterone undecanoate.

40 ng/dL

~600 ng/dL

- Endogenous T concentrations in serum (blood collected in plain tubes with no esterase inhibitor) and plasma (blood collected in $NaF/K_2C_2O_4$ tubes with esterase inhibitor) are slightly different (255.4 vs. 221.7 ng/dL).
- Compared to endogenous T concentration, T increased 40 ng/dL when TU was dissolved in ethanol/PBS and the blood sample sat at RT for 30 min before processing.
- Compared to endogenous T concentration, T increased ~600 ng/dL when TU was dissolved in methanol and the blood sample sat at RT for 30 min before processing.
- Difference may be due to the solvent used to dissolve TU prior to spiking in whole blood.
- When TU dissolved in ethanol/buffer (PBS), the investigator noted a precipitate formation suggesting that TU was no longer in the solution, thus, lowering the effective TU concentration.
- The investigators noted that TU concentrations were variable and generally lower when the stock was prepared in PBS/ethanol versus in methanol.
- TU dissolved in methanol resulted in TU concentrations that were generally higher and similar in both serum and plasma.

Applicant's Study #1

One in vitro study used measured T concentrations in plasma to estimate TU conversion rate (referred to as Study #1 in this review). Whole blood was freshly drawn from three donors and sub-aliquoted. One of the sub-aliquots was left unfortified, while the other aliquots were fortified with TU and DHTU at 100,000 and 50,000 ng/dL, respectively. The samples were incubated at room temperature for 30 min, as would be specified to allow clot formation when preparing serum samples. Plasma was then harvested from the unfortified sample and one of the fortified samples for each individual by centrifugation for 10 minutes at 2 to 8°C. Sets of the remaining tubes were placed either on ice or at room temperature, and plasma was harvested after an additional 60 and 120 min. The in vitro studies assessed TU stability under various sample handling conditions with reported TU conversion rates found in the table below.

Table 3.3.1-4. Percentage of TU conversion in three different blood samples following different sampling preparation procedures (Applicant's table).

Analyte Evaluated	Total Exposure	Estimated % Conversion				
		40 Minutes (Initial)	100 Minutes (+60 on ice)	160 Minutes (+120 on ice)	100 Minutes (+60 at RT)	160 Minutes (+120 at RT)
TU (based on appearance of T)	Donor 1	1.84	2.43	2.71	2.88	4.97
	Donor 2	1.84	2.52	2.64	3.95	5.78
	Donor 3	0.85	0.99	1.23	1.83	3.19

Based upon the above reported rate of ex vivo TU to T conversion and the observed TU concentrations from phase 3 study LPCN 1021-16-002, there may be a significant difference in the currently reported T concentrations and the actual T concentrations (without ex vivo TU conversion). For example, if using the mean Cavg for TU of 11,100 ng/dL and a 3.95% ex vivo conversion of TU to T, this can result in an

overestimation of serum T Cavg concentration of 276 ng/dL. This represents a worst-case scenario likely to be encountered during the PK assessment period in a phase 3 study, and suggests that the currently reported T concentrations and statistical efficacy results from study LPCN 1021-16-002 may not be reliable.

Applicant's Study #2

Whole blood from 4 donors was collected in 4 mL plain Vacutainer tubes. Immediately after drawing the blood, the working TU standard (200 mcL) was injected through the stopper using a syringe, and the tube was thoroughly mixed by inverting several times. Whole Blood expected TU concentration was calculated as Spiking Solution Concentration X * (0.2 mL/4 mL). No method validation report was submitted with the new in vitro data; therefore, confirmation of the assay reproducibility, accuracy, and reliability cannot be confirmed. Summary of results is shown in Table 3.3.1-5.

Table 3.3.1-5. TU Spiked Volumes, Expected TU Concentrations, and Measured TU and T in Individual Donors (Prepared from Applicant's In Vitro Study, table 1, December 4 & 27, 2017)

Expected TU Concentration (ng/dL)	Mean (range) Measured TU Concentration (ng/dL)	Mean (%CV) (n=3) of Serum T Concentration (ng/dL)			
		Donor 1	Donor 2	Donor 3	Donor 4
0	0 (0)	646 (3.5 %)	482 (9.4%)	431 (4.7%)	257 (4.4%)
500	130 (104-152)	666 (2.8%)	481 (2.4%)	446 (6.0%)	261 (5.7%)
5,000	1135 (846-1568)	607 (8.7%)	483 (5.4%)	446 (5.8%)	266 (3.8%)
16,650	2549 (1829-2987)	652 (2.6%)	469 (7.6%)	451 (6.6%)	282 (9.2%)
42,500	3492 (2521-4116)	661 (2.5%)	512 (3.4%)	465 (4.5%)	276 (7.6%)

Based upon the new in vitro data in Study #2, it appears that ex vivo conversion of TU to T during the sample handling period is not expected to occur. However, this reviewer notes the following concerns with the preliminary data:

- Measured TU concentration in the spiked samples was significantly lower than expected TU concentration (e.g., the highest spike TU concentration was expected to be 42,500 ng/dL, but the mean (range) measured TU concentration was 3492 (2521-4116) ng/dL). The discrepancy in the expected and measured concentration suggests that there may be an issue with assay recovery. The full report was not submitted to the NDA; therefore, a thorough review of the results from study #2 is not possible at the time of this review cycle.

- Mean TU concentrations in spiked samples were significantly lower than TU Cavg from phase 3 study LPCN 1021-16-002 (3,492 vs. 11,106 ng/dL) (but we acknowledge that it was still relatively high compared to T Cavg observed in phase 3 study LPCN 1021-16-002).

Overall, 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 suggest 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. This reviewer recommends the Applicant provide addition information to address the ex vivo conversion and confirm the reliability of the phase 3 data. This reviewer recommends the Applicant conduct a study assessing the potential for ex vivo TU to T conversion using samples collected from subjects dosed with oral TU to remove potential confounding effects of different spiking methods (i.e., differences in solvent). This assessment needs to account 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).

See Section 4.2.2 Ex Vivo TU to T Conversion for additional details.

Concerns regarding potential cross reactivity of TU with commercial T immunoassay:

Immunoassays are used in clinical laboratories for on-site measurement of plasma or serum hormones such as T. While convenient, immunoassay measurements can be prone to interference from compounds with structure similarity to the steroid hormone of interest. TU is an undecanoate ester of T and can potentially cross react with immunoassays designed to measure T. Cross reactivity of TU, which is present in high amounts following oral TU therapy, with commercial T immunoassays may produce false positive and result in an interference with T measurements and/or over reporting of T concentrations. The Applicant should address, through literature or conducting studies, the potential for TU cross reactivity with T immunoassays in the next review cycle.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen was assessed in phase 3 study LPCN 1021-16-002 and partially in phase 3 study LPCN 1021-13-001. Cmax, a key safety criteria noted below, are based upon thresholds set for topical products that provide relatively consistent and sustained systemic delivery of T. Therefore, excessive fluctuations in T exposure for topical T products are considered a safety concern as it may be related to adverse cardiovascular events, hematocrit changes, lipid changes, etc. The same Cmax criteria is currently applied to oral T products; however, the exposure profiles for these products differ significantly to the topical products. It is also currently unclear how duration and/or frequency outside the normal range impacts the safety profile of oral products. However, there are concerns with high

Cmax observed with the proposed product (see discussion below). Defer to Clinical Review on the final safety assessment.

Testosterone Cmax:

The key safety endpoints in the Phase 3 study were defined as the percentage of subjects who exhibited maximum serum total T concentrations (Cmax) within predetermined limits upon completion of approximately 24 days of study treatment. The predetermined limits for T Cmax were:

- T Cmax ≤ 1500 ng/dL: target of ≥ 85%
- T Cmax between 1800 and 2500 ng/dL: target of ≤ 5%
- T Cmax > 2500 ng/dL: target of no subjects (0%)

Testosterone Cmax (0-24 hr) is based on maximum serum concentration of T that occurred in the 24-hr interval on Day 24 (post morning and evening doses). On the other hand, T Cmax (without notation of 0-24) is the result of T Cmax (0-12 hr) values that were observed over two 12-hr periods covering the separate morning and evening doses administered on Day 24. The results are shown in Tables 3.3.1-2 and 3.3.1-3.

Table 3.3.1-2. Proportion of TU-treated Patients Achieving Maximum T Concentration Within Predetermined Limits on Day 24 (N=95) (Applicant's Table 18).

Measure	Target	T-Cmax	T Cmax (0-24)
Number of Subjects		95	95
Number of Cmax observations		190	95
T Cmax < 1500 ng/dL, %	≥ 85%	85 %	74%
1800 ≤ T Cmax ≤ 2500 ng/dL, %	≤ 5%	7 %	14%
T Cmax > 2500 ng/dL (n)	No subject	One subject* (single measurement)	One subject*

Table 3.3.1-3. Proportion of TU-treated Patients Achieving Maximum T Concentration Within Predetermined Limits on Day 24 Following the Morning (0-12) and Evening (12-24) Dose Separately (N=95) (Applicant's Table 19).

Measure	Target	Cmax (0-12) N = 95	Cmax (12-24) N = 95
T Cmax < 1500 ng/dL, % (n)	≥ 85%	86 %	83 %
1800 ≤ T Cmax ≤ 2500 ng/dL, % (n)	≤ 5%	7 %	6 %
T Cmax > 2500 ng/dL, % (n)	No subject	None	One subject

In Study LPCN 1021-16-002, none of the three Cmax criteria was met. For example, only 74% of patients had a T Cmax of < 1500 ng/dL as opposed to the present criteria of ≥85%. Approximately 6% of patients had a Cmax between 1800 and 2500 ng/dL, compared to the criteria set at ≤5%. The Cmax excursions of this magnitude for the two lower Cmax criteria are generally not considered a safety concern.

On the other hand, of the predefined T Cmax limits, those exceeding 2500 ng/dL is a significant safety concern. In this study, there was 1 of 95 (1.1%) patient with a 24-hr T Cmax greater than 2500 ng/dL, which suggests a limited concern. However, the Clinical team noted from phase 3 study LPCN 1021-13-001 (submitted under the original NDA) a higher percentage (8 of 151 (5.3%)) of patients had a T Cmax exceeding 2500 ng/dL after 3 weeks of oral TU treatment at 225 mg BID. Refer to the Clinical review for more details.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, a management strategy is needed. Specifically, a reproducible and robust discontinuation approach for patients not having a T concentration within the normal range is needed.

The Applicant's proposed dosing regimen is 225 mg TU twice daily with no dose titration. The phase 3 data from study LPCN 1021-16-002 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 because of T concentrations 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 Applicant provided the following rationale:

> The stopping criteria utilize the normal range for testosterone of 300 to 1080 ng/dL established in Study LPCN 1021-16-002 as the lower and upper testosterone concentration bounds. The post morning dose blood draw between 7 and 9 hours sampling time was selected based on an analysis of the PK data from Study LPCN 1021-16-002. This analysis showed that applying these criteria at this timepoint would result in a recommendation to discontinue therapy in most subjects who had a Cavg0-24 below the normal range at the efficacy assessment of the study (14 out of 18 subjects with Cavg0-24 < 300 ng/dL). There were no subjects with Cavg0-24 above the normal range in the study.
>
> These criteria were subsequently tested in an analysis using the Week 3 PK data from Study LPCN 1021-13-001. The analysis showed that applying these criteria to the Week 3 PK profile data would result in a recommendation to discontinue therapy in most of the subjects with a Cavg0-24 below the normal range (20 out of 24 subjects with Cavg0-24 < 300 ng/dL), and all the

subjects with a Cavg0-24 above the normal range at Week 3 (4 out of 4 subjects with Cavg0-24 > 1080 ng/dL). The analyses from both studies are summarized in table below.

[redacted]	Criteria: 300 – 1080 ng/dL Between 7 and 9 Hrs Post AM Dosing*	
	LPCN 1021-16-002 Efficacy assessment (225 mg twice daily)	LPCN 1021-13-001 Week 3 PK data (225 mg twice daily)
Total N	94	193
Total number of subjects with Cavg0-24< 300 ng/dL	18	24
Subjects with Cavg0-24 < 300 ng/dL who are identified using proposed criteria	14	20
Total number of subjects with Cavg0-24> 1080 ng/dL	0	4
Subjects with Cavg0-24 > 1080 ng/dL who are identified using proposed criteria	-	4

* Results based on 8 hours post AM dosing data.

The Applicant's proposed stopping criteria is based upon T concentrations determined at t=8 hr post morning dose. Based upon this assessment of using T concentration from a single time point, the Applicant showed the following:

- For Study LPCN 1021-16-002: 14 of 18 (78%) patients identified with Cavg <300 ng/dL would be correctly discontinued. There were no patients with Cavg >1080 ng/dL.
- For Study LPCN 1021-13-001: 20 of 24 (83%) patients identified with Cavg <300 ng/dL and all 4 of 4 patients with Cavg >1080 ng/dL would be correctly discontinued.

Approximately 4.3% (4 of 94) and 2.1% (4 of 193) of patients from studies LPCN 1021-16-002 and LPCN 1021-13-001, respectively, had a T Cavg less than 300 ng/dL but they were not identified using the proposed stopping criteria.

Of concern is the inappropriate discontinuation of ~30% (23 of 76) patients from study LPCN 1021-16-002 who met the proposed discontinuation criteria (T concentration at t=8 hr less than 300 ng/dL) despite having a T Cavg within the normal range.

In addition, 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.

This reviewer 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 Applicant should be requested to evaluate the adequacy and reproducibility of such a stopping criteria by modeling and simulation approaches and/or using additional empirical data.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food effect:

The Applicant evaluated the effect of food and fat content on the bioavailability of a single oral dose of Tlando. This was an open-label, randomized, four-period, four-treatment, crossover study in hypogonadal males. Subjects were served low-fat (~15% fat), moderate-fat (20-35% fat), and high-fat (~50% fat) meals consisting of 800-1000 calories, or fasted overnight for at least 10 hrs. For treatment with meal subjects received a 225-mg oral dose (2 x 112.5 mg capsules) of Tlando approximately 30 min after the meal had started and fasted for no less than 4 hrs after drug administration. Water 240 mL was given with drug administration. For fasted treatment period subjects received the same dose with 240 mL water.

Figure 3.3.4-1 shows the mean serum T concentration time profiles. Tables 3.3.4-1 and 3.3.4-2 show the statistical analysis of various meal types without and with baseline subtraction, respectively. The results showed that there is a significant increase in serum T Cmax and AUC when taken with food compared to fasting conditions. There were some differences in AUC among the 3 meals with different fat content but the magnitude was relatively small. The Phase 3 study was conducted under fed condition but irrespective of the fat content. Overall, the range of fat content in food does not appear to have a significant effect on T bioavailability as the presence of fat in food to even a modest extent increases the bioavailability versus fasting

Figure 3.3.4-1: Mean (SD) Serum Testosterone Concentration-Time Profiles Following Various Fat Content Meals (Treatments A, B and C (N=13)) and Fasting Conditions (Treatment D (N=14)) (Applicant's analysis).

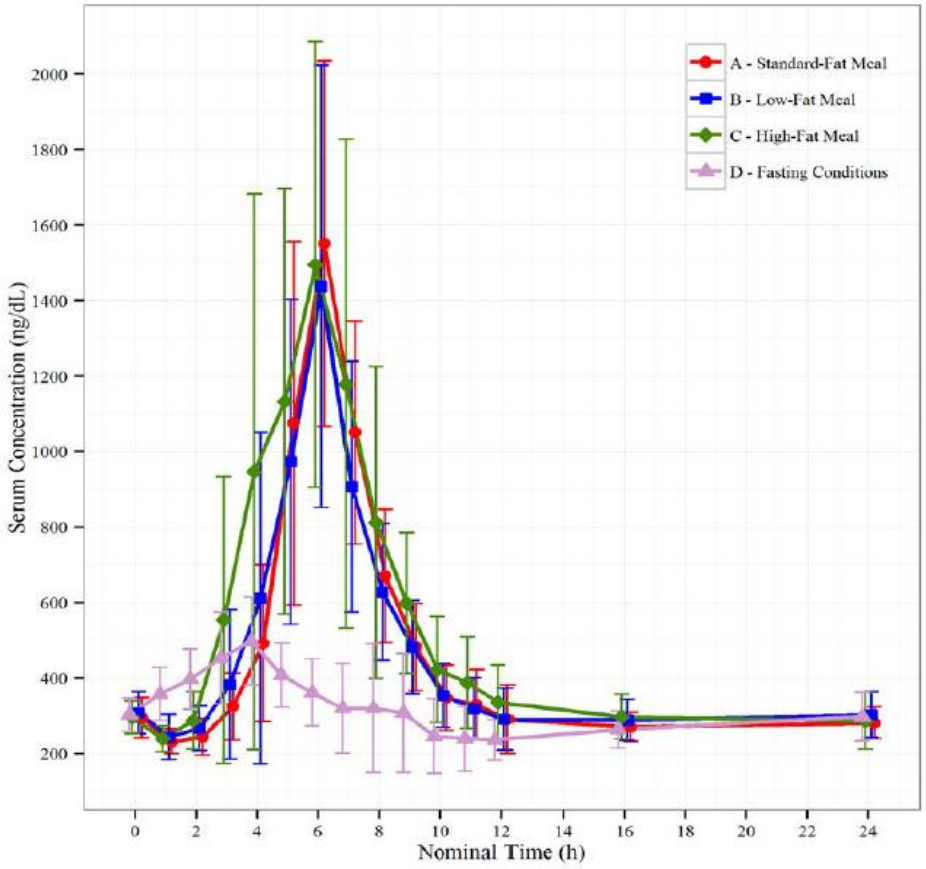


Table 3.3.4-1. Statistical Analysis of Testosterone Pharmacokinetic Parameters after Various Meal Intake.

PK Parameter	Treatment Comparisons	Geometric LSM Ratio
AUC0-t	high fat vs. fasting	161%
	high fat vs. mod fat	114%
	high fat vs. low fat	115%
AUC0-12hr	high fat vs. fasting	198%
	high fat vs. mod fat	117%
	high fat vs. low fat	120%
Cmax (0-t)	high fat vs. fasting	286%
	high fat vs. mod fat	103%
	high fat vs. low fat	103%

LSM=least square means

Table 3.3.4-2. Statistical Analysis of Baseline-Adjusted Testosterone PK Parameters after Various Meal Intake.

PK Parameter	Treatment Comparisons	Geometric LSM Ratio
AUC0-t	high fat vs. fasting	508%
	high fat vs. mod fat	124%
	high fat vs. low fat	141%
Cmax (0-t)	high fat vs. fasting	478%
	high fat vs. mod fat	100%
	high fat vs. low fat	103%

LSM=least square means

Drug-drug interactions:

Testosterone is an endogenous substance. Testosterone replacement therapy attempts to achieve T concentration within the normal range. Therefore, assessment of drug interaction potential of T is not needed. However, the proposed product is a prodrug that has shown significantly higher concentration of the prodrug 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. This reviewer recommends that the Applicant conduct studies to address the potential drug interaction for the prodrug TU.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Concentrations of testosterone undecanoate and testosterone in serum were determined in using a validated LC-MS/MS method.

Table 4.1-1. Overview of Bioanalytical Method for Studies LPCN 1021-16-002

Study #	LPCN 1021-16-002	
Analytes	Testosterone Undecanoate	Testosterone
Method #	Project RHLG	Project RHLE
Methodology	LC-MS/MS	LC-MS/MS
Biological matrix	Serum	Serum
Calibration curve range	200 to 100,000 ng/dL	10 to 5,000 ng/dL
Internal standard	Testosterone undecanoate-d_3	Testosterone-d_3
Validation report #	LCMSC 521.1	LCMSC 521.1/LCMSC 260.10
Inter-run accuracy for each QC	LLOQ (197 pg/dL): -1.50% bias LQC (512 pg/dL): 2.46% bias MQC (38,880 pg/dL): -3.06% bias HQC (72,600 ng/dL): -3.22% bias	LLOQ (25 pg/dL): 3.12% bias LQC (273 pg/dL): -2.07% bias MQC (882 pg/dL): 2.48% bias HQC (3910 pg/dL): -2.35% bias
Inter-run precision for each QC	LLOQ (197 pg/dL): 4.71% CV LQC (512 pg/dL): 15.2% CV* MQC (38,880 pg/dL): 4.20% CV HQC (72,600 ng/dL): 4.10% CV	LLOQ (25 pg/dL): 6.70% CV LQC (273 pg/dL): 7.03% CV MQC (882 pg/dL): 6.41% CV HQC (3910 pg/dL): 5.98% CV
Long-term stability	750 days at -20°C	97 days at -20°C
Freeze-thaw stability	5 cycles at -20C	5 cycles at -20°C

* For TU, the inter-run precision for the low QC sample (LQC) was 15.2%; thereby not meeting the 15% acceptable limit for acceptable inter-run precision. However, the deviation from the acceptance criteria was small and the inter-run precision at LLOQ was acceptable (much lower than the 20% acceptance limit).

Overall, the assay for TU and T demonstrated selectivity, accuracy, precision, and recovery. They are acceptable from a Clinical Pharmacology perspective.

4.2 Individual Study Reports

4.2.1 Study LPCN 1021-16-002

Title: Validation of Dosing Regimen of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men.

Method: This was a multi-center, U.S. study in hypogonadal men with a mean age of 56 yrs. About 80% were White and 15% were Black or African American. All subjects received a fixed dose of 225 mg oral TU capsules (2x 112.5 mg TU) with water approximately 12 hours apart, 30 minutes after the morning and evening meals. Treatment duration was approximately 24 days (ranging from 20 to 28 days). No dose adjustments were included in this study. This was an efficacy study with pharmacokinetic endpoints.

Objectives: The primary objective was to assess the percentage of patients treated with oral testosterone undecanoate (TU) who achieved a 24-hr average serum T concentration (24-hr Cavg) within the range of 300 to 1080 ng/dL.

Study Period: January 12, 2017 to April 6, 2017

Treatment Products: LPCN 1021 (oral TU capsules), each capsule containing 112.5 mg TU mg, batch no. 3315J13A

Major Inclusion Criteria:

1. Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism prior to age 65
2. Subjects should be diagnosed to be primary (congenital or acquired) or secondary hypogonadal (congenital or acquired)
3. Serum total T below 300 ng/dL based on 2 consecutive blood samples obtained between 6 and 10 am, on two separate days at approximately the same time of day (between 6 and 10 am), following an appropriate washout of current androgen replacement therapy
4. Naive to androgen replacement or discontinued current treatment and completed adequate washout of prior androgen therapy. Washout was completed prior to collection of baseline serum T samples to determine study eligibility
5. Judged to be in good general health as determined by the investigator at screening

Major Exclusion Criteria:

1. History of significant sensitivity or allergy to androgens, or product excipients
2. Clinically significant findings in the pre-study examinations including abnormal breast examination requiring follow-up
3. Abnormal prostate digital rectal examination (DRE) with palpable nodule(s)
4. Subjects with symptoms of moderate to severe benign prostatic hyperplasia
5. Clinically significant abnormal laboratory value, in the opinion of the investigator, in serum chemistry, hematology, or urinalysis including but not limited to:

a. Baseline hemoglobin < 11.5 g/dL or > 16.5 g/dL
b. Hematocrit < 35% or > 54%
c. Serum transaminases > 2.5 times upper limit of normal
d. Serum bilirubin > 2.0 mg/dL
e. Creatinine > 2.0 mg/dL
f. PSA > 2 ng/mL
g. Prolactin > 17.7 ng/mL

6. History of stroke or myocardial infarction within the past 5 years
7. Use of known inhibitors (e.g., ketoconazole) or inducers (e.g., dexamethasone, phenytoin, rifampin, carbamazepine) of cytochrome P450 3A within 30 days prior to study drug administration and through the end of the study
8. Subject who is not willing to use adequate contraception for the duration of the study

Pharmacokinetic Blood Sampling:
Blood samples were collected for the determination of TU, T, E2, DHT, and DHTU concentrations while patients were confined in the clinic at Day 24. Samples were collected within 30 min before the morning dose (0 hr), and within 10 min of 2, 3, 4, 5, 6, 8, 12 (before evening dose), 14, 15, 16, 17, 18, 20, and 24 hrs after the morning dose.

Bioanalytical Methods:
The Office of Clinical Pharmacology requested the Office of Study Integrity and Surveillance (OSIS), Division of New Drug Bioequivalence Evaluation (DNDBE) to inspect the bioanalytical site (b) (4) (b) (4) OSIS recommended to accept the data without an on-site inspection. OSIS stated that (b) (4) was recently inspected with No Action Indicated (NAI). Refer to memo in DARRTS November 3, 2017.

Long-term storage stability in serum was 750 days at -20°C and 97 days at -20°C for Tu and T, respectively. The first day of study was Jan 12, 2017 and the last day samples were analyzed was April 28, 2017; therefore, the longest duration serum samples were stored at -20C before analysis is ~3 months 16 days. Considering that there was at least 20 days of dosing before blood draw, the demonstrated storage stability covered the duration between blood draw and sample assay.

Refer to Bioanalytical Method Validation in section 4.1 and to the Ex Vivo TU to T Conversion in section 4.2.2.

Results:

The following pharmacokinetic parameters were calculated by standard non-compartmental methods for TU, T, DHT, DHTU, and E2:

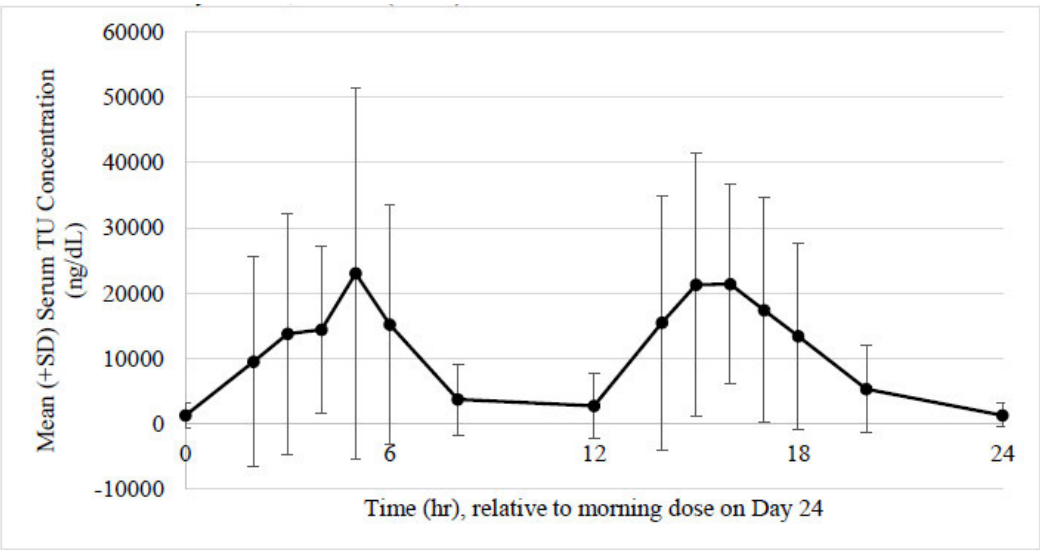
- AUC0-24: area under the concentration-time curve from T=0 to 24 hrs
- Cavg0-24: average concentration from 0 to 24 hrs obtained by dividing AUC0-24/24
- Cmax: maximum concentration following administration of LPCN 1021 prior to next dose

- 24-hr Cmax: maximum concentration occurring in a 24-hr interval

The Applicant conducted additional analysis that included estimating the duration for which a subject's serum T concentration levels exceed 1500 ng/dL, 1800 ng/dL and 2500 ng/dL and the ratio of AUC of DHT/T and E2/T was calculated. The TU and T concentrations are reported as baseline-uncorrected values in the tables and figures below unless otherwise noted.

1) Testosterone Undecanoate Pharmacokinetics

Figure 4.2.1-1. Mean (±SD) Serum Testosterone Undecanoate Concentration vs Time Profile at Visit 4 (~Day 24) Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's figure 3).



Source: Lipocine's updated Dec 27, 2017

Table 4.2.2-1. Pharmacokinetic Parameters of Serum TU at Visit 4 (~Day 24) at Different Dosing Periods Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's updated table 22).

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/dL	Mean (SD)	11106 (5036)		
Cmax, ng/dL	Mean (SD)	46974 (25602)	35948 (28233)	36363 (19523)
Tmax, h	Median (Min, Max)	14.0 (2.0, 20.7)	4.9 (1.9, 11.9)	4.0 (1.9, 12.0)

2) Testosterone Pharmacokinetics

Figure 4.2.1-2. Mean (±SD) Serum Testosterone Concentration vs Time Profile at Visit 4 (~Day 24) Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's figure 1).

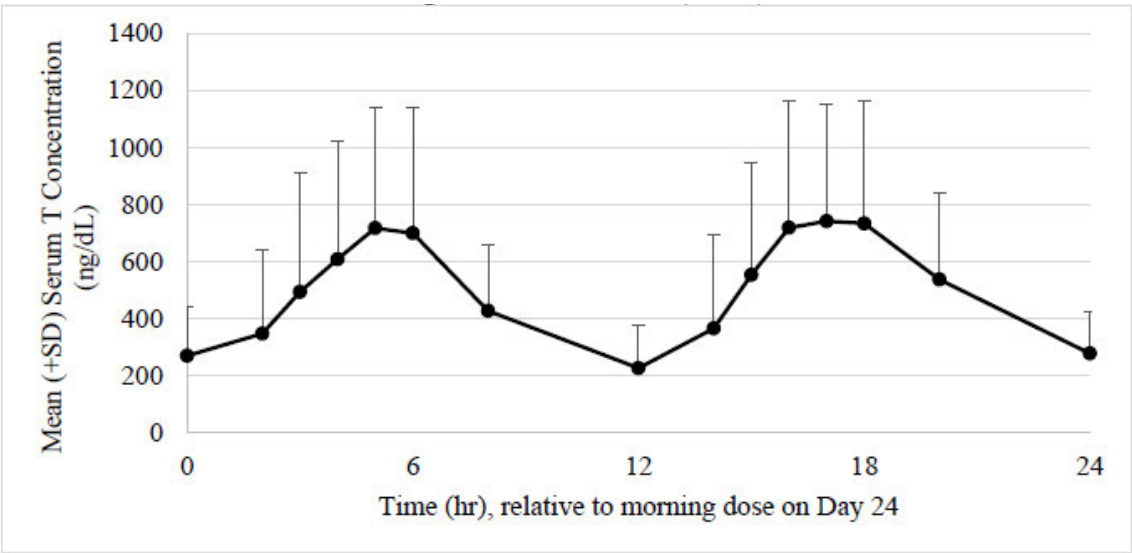


Table 4.2.1-2. Pharmacokinetic Parameters of Serum T at Visit 4 (~Day 24) at Different Dosing Periods Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's table 20).

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
T Cavg0-24h, ng/dL	Mean (SD)	476 (174)		
T Cmax, ng/dL	Mean (SD)	1178 (484)	979 (479)	989 (475)
Tmax, h	Median (Min, Max)	14.8 (2.0, 24.0)	5.00 (1.9, 11.9)	4.80 (2.0, 12.0)

3) Dihydrotestosterone Pharmacokinetics

Figure 4.2.1-3. Mean (±SD) Serum Dihydrotestosterone Concentration vs Time Profile at Visit 4 (~Day 24) Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's figure 2).

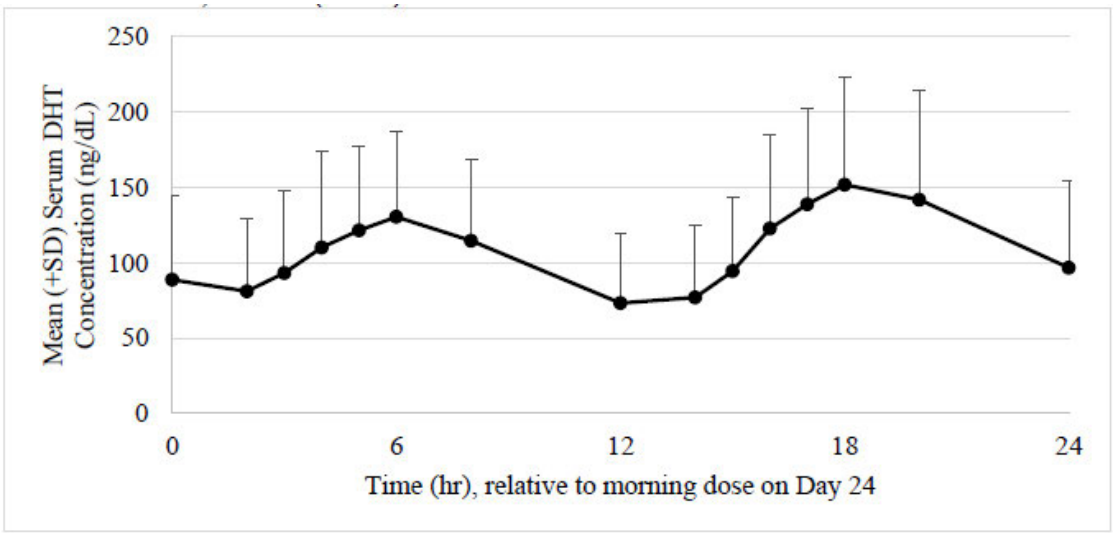


Table 4.2.1-3. Pharmacokinetic Parameters of Serum Dihydrotestosterone at Different Dosing Periods Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's table 21).

	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/dL	Mean (SD)	108 (46)		
Cmax, ng/dL	Mean (SD)	179 (72)	152 (64)	168 (74)
Tmax, h	Median (min, max)	16.9 (2.0, 24.0)	5.9 (1.9, 11.9)	5.9 (2.0, 12.0)

4) Dihydrotestosterone Undecanoate Pharmacokinetics

Figure 4.2.1-4. Mean (±SD) Serum Dihydrotestosterone Undecanoate Concentration vs Time Profile at Visit 4 (~Day 24) Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's figure 4).

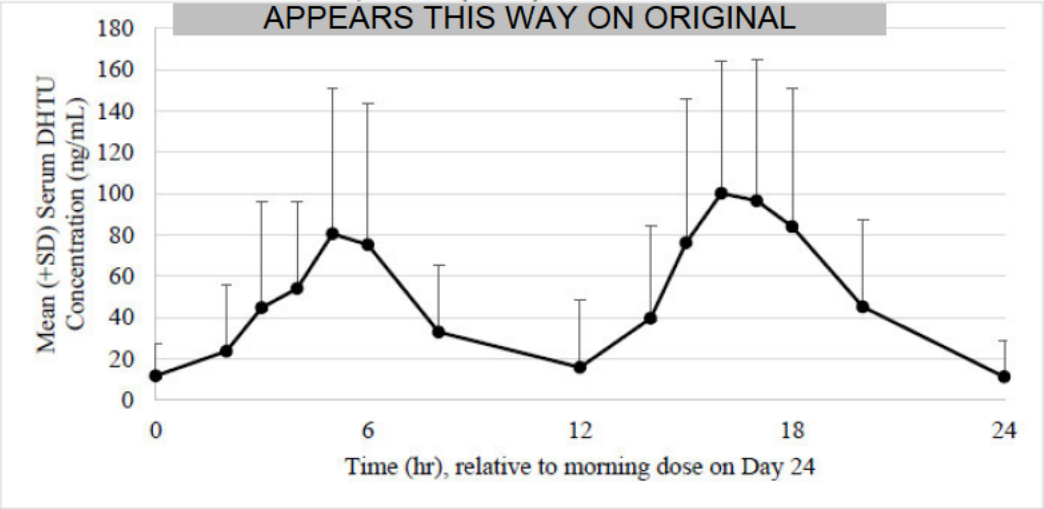


Table 4.2.1-4. Pharmacokinetic Parameters of Serum Dihydrotestosterone Undecanoate at Different Dosing Periods Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's table 23).

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/mL	Mean (SD)	47 (22)		
Cmax, ng/mL	Mean (SD)	155 (76)	116 (70)	140 (75)
Tmax, h	Median (Min, Max)	15.7 (3.0, 20.0)	5.0 (1.9, 11.9)	4.6 (2.0, 12.0)

5) Estradiol Pharmacokinetics

Figure 4.2.1-5. Mean (±SD) Serum Estradiol Concentration vs Time Profile at Visit 4 (~Day 24) Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's figure 5).

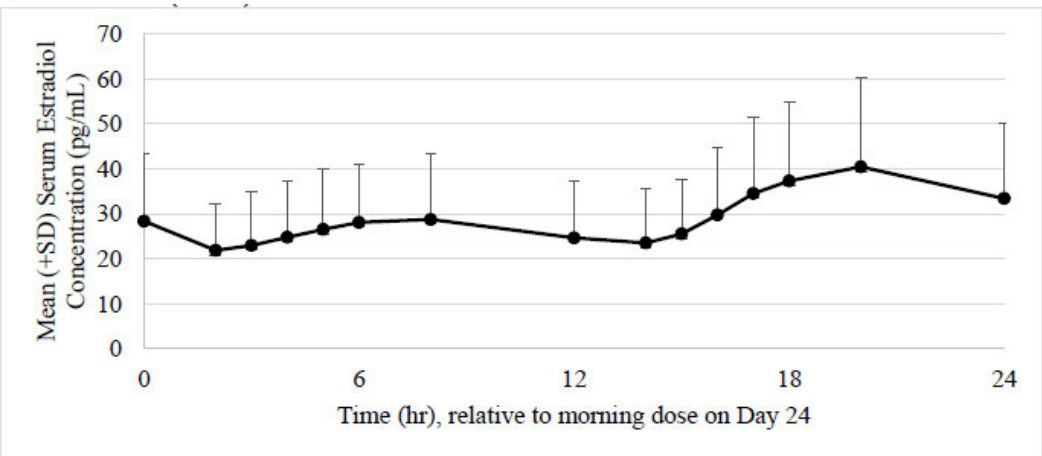


Table 4.2.1-5. Pharmacokinetic Parameters of Serum Estradiol at Different Dosing Periods Following Twice Daily Oral TU Administration 225 mg (N=90) (Applicant's table 24).

	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/dL	Mean (SD)	29 (13)		
Cmax, ng/dL	Mean (SD)	44 (20)	34 (16)	43 (20)
Tmax, h	Median (min, max)	18.0 (4.0, 24.7)	6.0 (2.0, 12.0)	7.9 (0, 12.7)

Endpoints:

Primary endpoint (efficacy):

The primary efficacy endpoint was the percentage of TU-treated patients who had achieved a 24-hr average serum T concentration within the normal range of 300 to 1080 ng/dL at Visit 4 (Day 24 ± 4 days). The target minimum responder percentage was 75% with the lower bound of the 95% confidence interval (CI) surrounding the point estimate be 65% or more.

Table 4.2.1-6. Proportion of TU-treated Patients Achieving 24-hr Average Serum Testosterone Concentrations Within Normal Range on Day 24 (N=95) (Applicant's table 16).

Parameter	Target	Safety Set BLOCF N=95
Percentage subjects achieving 24-hour average serum T concentration within normal range[1]	≥ 75%	80%
95% Confidence interval (lower, upper bound %)[2]	≥ 65% (Lower Bound)	72%, 88%

Key: T = total testosterone
[1]Normal Range: 300 to 1080 ng/dL
[2]A 95%, 2-sided, binomial confidence interval surrounding the point estimate was calculated.
Source: Table 14.2.4.4

Secondary endpoint (safety):

The secondary endpoints were defined as the percentage of subjects who exhibited maximum serum total T concentrations (Cmax) within predetermined limits upon completion of approximately 24 days of study treatment.

The predetermined limits for T Cmax were:

- T Cmax ≤ 1500 ng/dL: target of ≥ 85%
- T Cmax between 1800 and 2500 ng/dL: target of ≤ 5%
- T Cmax > 2500 ng/dL: target of no subjects (0%)

T Cmax (0-24 hr) is based on maximum serum concentration of T that occurred in the 24-hr interval on Day 24 (post morning and evening doses). On the other hand, T Cmax (without notation of 0-24) is the result of T Cmax (0-12 hr) values that were observed over two 12-hr periods covering the separate morning and evening doses administered on Day 24.

Table 4.2.1-7. Proportion of TU-treated Patients Achieving Maximum T Concentration Within Predetermined Limits on Day 24 (N=95) (Applicant's Table 18).

APPEARS THIS WAY ON ORIGINAL

Measure	Target	T-Cmax	T Cmax (0-24)
Number of Subjects		95	95
Number of Cmax observations		190	95
T Cmax < 1500 ng/dL, %	≥ 85%	85 %	74%
1800 ≤ T Cmax ≤ 2500 ng/dL, %	≤ 5%	7 %	14%
T Cmax > 2500 ng/dL (n)	No subject	One subject* (single measurement)	One subject*

Table 4.2.1-8. Proportion of TU-treated Patients Achieving Maximum T Concentration Within Predetermined Limits on Day 24 Following the Morning (0-12) and Evening (12-24) Dose Separately (N=95) (Applicant's Table 19).

APPEARS THIS WAY ON ORIGINAL

Measure	Target	Cmax (0-12) N = 95	Cmax (12-24) N = 95
T Cmax < 1500 ng/dL, % (n)	≥ 85%	86 %	83 %
1800 ≤ T Cmax ≤ 2500 ng/dL, % (n)	≤ 5%	7 %	6 %
T Cmax > 2500 ng/dL, % (n)	No subject	None	One subject

Reviewer's Comment:

- Of the predefined T Cmax limits, those exceeding 2500 ng/dL is a safety concern. In this study, there was 1 of 95 patients with a 24-hr T Cmax greater than 2500 ng/dL.
- However, the Clinical team noted from phase 3 study LPCN 1021-13-001 (submitted under the original NDA) that there were 5.3% (8 of 151) of patients had a T Cmax exceeding 2500 ng/dL after 3 weeks of oral TU treatment at 225 mg BID.

Stopping Criteria:

The Applicant's proposed dosing regimen is 225 mg TU twice daily with no titration. The data show that 80% of subjects achieved serum T Cavg concentration within the normal range. However, there are no

criteria included in the Applicant's proposed label for identifying the 20% of patients who should discontinue the product because of testosterone concentrations outside the normal range.

The Applicant acknowledged that a small percentage of subjects taking any testosterone replacement therapy may not achieve testosterone concentrations in the target therapeutic range.

The FDA requested that the Applicant provide a detailed discontinuation plan (stopping criteria) for their product. The Applicant proposed the following labeling recommendation:

(b) (4)

The Applicant provided the following rationale:

The stopping criteria utilize the normal range for testosterone of 300 to 1080 ng/dL established in Study LPCN 1021-16-002 as the lower and upper testosterone concentration bounds. The post morning dose blood draw between 7 and 9 hours sampling time was selected based on an analysis of the PK data from Study LPCN 1021-16-002. This analysis showed that applying these criteria at this timepoint would result in a recommendation to discontinue therapy in most subjects who had a Cavg0-24 below the normal range at the efficacy assessment of the study (14 out of 18 subjects with Cavg0-24 < 300 ng/dL). There were no subjects with Cavg0-24 above the normal range in the study.

These criteria were subsequently tested in an analysis using the Week 3 PK data from Study LPCN 1021-13-001. The analysis showed that applying these criteria to the Week 3 PK profile data would result in a recommendation to discontinue therapy in most of the subjects with a Cavg0-24 below the normal range (20 out of 24 subjects with Cavg0-24 < 300 ng/dL), and all the subjects with a Cavg0-24 above the normal range at Week 3 (4 out of 4 subjects with Cavg0-24 > 1080 ng/dL). The analyses from both studies are summarized in Table below.

APPEARS THIS WAY ON ORIGINAL

	Criteria: 300 – 1080 ng/dL Between 7 and 9 Hrs Post AM Dosing*	
	LPCN 1021-16-002 Efficacy assessment (225 mg twice daily)	LPCN 1021-13-001 Week 3 PK data (225 mg twice daily)
Total N	94	193
Total number of subjects with Cavg0-24< 300 ng/dL	18	24
Subjects with Cavg0-24 < 300 ng/dL who are identified using proposed criteria	14	20
Total number of subjects with Cavg0-24> 1080 ng/dL	0	4
Subjects with Cavg0-24 > 1080 ng/dL who are identified using proposed criteria	-	4

* Results based on 8 hours post AM dosing data.

The Applicant's proposed stopping criteria assumes that the T concentration between 7 to 9 hrs after the morning dose would be the same as the mean T concentration at t=8 hr (post-morning dose), but did not provide any additional data or alternative approach (e.g., modeling and simulation) to support that assumption. Additionally, the proposed stopping criteria also does not account for the changes in T exposure in the elimination phase (as noted by the declining PK profile around t=8 hr and PK variability. The Applicant believes that these stopping criteria, in conjunction with Endocrine Society Guidelines for testosterone therapy, are sufficient for the safe and effective use of oral TU.

For Study LPCN 1021-13-001: 20 of 24 (83%) patients identified with Cavg <300 ng/dL and all 4 of 4 patients with Cavg >1080 ng/dL would be correctly discontinued.

For Study LPCN 1021-16-002: 14 of 18 (78%) patients identified with Cavg <300 ng/dL would be correctly discontinued. There were no patients with Cavg >1080 ng/dL

Applying these same criteria (i.e., testosterone concentration being less than 300 ng/dL or more than 1080 ng/dL) to a T concentration at 8 hrs post-dose in the 76 subjects in LPCN 1021-16-002 who had Cavg within the normal range would result in 23 subjects (30%) meeting the discontinuation criteria. This suggests that while the proposed criteria may lead to appropriate discontinuation of patients not achieving Cavg within the normal range, but it may also result in a large percentage of patients being discontinued inappropriately.

Reviewer's Comments:

- The protocol for study LPCN 1021-16-002 was review by the Clinical Pharmacology team under IND 106,476 with the following notable comments conveyed to the Applicant in the Special Protocol Assessment No Agreement Letter dated November 28, 2016:
    - Assessment of 24 hr Cmax excursions following both morning and evening doses for secondary endpoint assessment
    - Intensive blood sampling time points following morning and evening doses to capture Cmax
    - Treatment duration longer than 14 days to ensure steady state is reached
    - No restriction on fat content with meals
- In a subsequent amendment, the Applicant incorporated protocol changes in their phase 3 study that addressed the outstanding Clinical Pharmacology issues outlined above.
- The primary efficacy endpoint (percentage of patients with Cavg within the predefined therapeutic range) and the secondary endpoints (percentage of Cmax excursions) are consistent with approval criteria for currently approved testosterone products.
- For the efficacy endpoint, the Applicant met the predefined endpoint with $\geq$ 75% of patients achieving a 24-hr Cavg. In this study with 95 patients, twice daily administration of 225 mg oral TU

resulted in 80% of patients achieving a 24-hr Cavg between 300 to 1080 ng/dL. The lower bound of the 90% CI was 72%, which is greater than predefined minimum 65%.

- For the secondary endpoint, the Applicant did not demonstrate that $\geq$ 85% of patients had a 24-hr Cmax less than 1500 ng/dL. Based upon their results, 74% of patients did not exhibit a Cmax greater than 1500 ng/dL. Based upon the Cmax (0-12hr) and Cmax (12-24hr) results, the deviations outside of the target range occurred at about the same rate after the morning and evening dose. The deviation from the prespecified values were not associated with notable clinical symptoms, per the Clinical review team.
- The 24-day study included a fixed dose of 225 mg BID. No dose titration was included in the phase 3 study. Based upon the efficacy endpoint, ~20% patients did not have a 24-hr T concentration within the therapeutic range either over 1080 ng/dL or under 300 ng/dL.
- In the resubmission, the Applicant did not include a mechanism to identify these patients who may be supra-therapeutic or under-dosed. At the request of the review team, the Applicant proposed a stopping criteria based upon a single time point take several weeks after initiating oral TU therapy. The Applicant's proposed stopping criteria to use C8hr to correlate to 24-hr Cavg is a cursory attempt at deriving an optimal approach to identifying patients who may be sub or supra-therapeutic. The adequacy and reproducibility of such a stopping criteria should be refined by modeling and simulation and/or additional empirical data.
- Intensive blood sampling for pharmacokinetics assessment was recommended to capture T Cmax. The blood sampling scheme was not refined to identify a time point(s) that would best correlate to the 24-hr Cavg. This reviewer recommends the Applicant identify a stopping criteria that can be reproduced and accurately identify the ~20% of patients not achieving Cavg within the normal range. Additionally, the stopping criteria should minimize or avoid inaccurately discontinuing patients with T concentrations within the therapeutic range.

4.2.2 Ex Vivo TU to T Conversion

Published literature and available data suggests that TU can convert to T ex vivo (e.g., in test tubes in whole blood in the presence of non-specific esterases). If TU is converted to T during the sample preparation period (i.e., time between blood draw from a patient and the collection of serum or plasma), the reported T concentration can be an over-reporting of the patient's T concentration.

This section of the review includes findings and conclusions from in vitro studies obtained from two publications and the Applicant. The publications and one of the Applicant's studies (referred to as study #1) showed that testosterone esters, including testosterone enanthate (TE) and TU, are converted to T in an amount that is clinically relevant. In contrast, one set of data from the Applicant (referred to as study #2) showed that TU was not converted to T.

Published Literature by Wang et.al.[1]

In 2008, Wang and co-authors assessed the effects of TE and TU on measured T and DHT. The authors dissolved TE and TU in ethanol and phosphate buffer solution (PBS) before adding to whole blood in either plain (without an enzyme inhibitor) or fluoride (an esterase inhibitor) collection tubes. After the addition of TE or TU solution, the blood sat in the tubes at room temperature for 30 min before centrifugation at 4°C for 20 min. The resulting serum was assayed for T and DHT by LC-MS/MS.

The following data and conclusions were reported by the authors:

Table 4.2.2-1 Interference of T esters during blood collection and processing on serum T and DHT measurements (Wang publication, table 2).

T esters added (nmol/L)	Measured T (nmol/L)	Measured DHT (nmol/L)
TE 0	8.98	0.69
TE 25	9.01	0.63
TE 75	9.33	0.66
TE 250	11.5	0.63
TE 749	11.84	0.61
TE 2496	**34.65**	0.66
TU 0	8.91	0.64
TU 22	9.27	0.71
TU 66	8.85	0.7
TU 219	8.86	0.71
TU 657	8.66	0.66
TU 2190	9.6	0.7
TU 0 + TE 0	9.12	0.73
TU 22 + TE 25	9.3	0.71
TU 66 + TE 75	9.06	0.69
TU 219 + TE 250	11.89	0.7
TU 657 + TE 749	11.44	0.71
TU 2190 + TE 2496	**40.83**	0.81
TU 0 + TE 0 (fluoride)	7.46	0.71
TU 2190 + TE 2496 (fluoride)	**11.79**	0.81

- In plain tubes, hydrolysis of TE to T increased serum T by 73 and 740 ng/dL (2.5 and 25.7 nmol/L) at TE concentrations of 10,000 and 100,000 ng/dL (250 and 2496 nmol/L), respectively.
- Ex vivo TE to T conversion mostly abolished by using fluoride tubes
- T did not increase when TU was added to whole blood using plain tubes

The authors concluded that addition of TE to blood collected in plain tubes caused a dose related increase serum T levels due to the action of non-specific esterases in the red cells. The reason for the observed apparent lack of conversion from TU, a molecule similar to TE, to T is not known.

[1] Wang C, Shiraishi S, Leung A, et al. Validation of a testosterone and dihydrotestosterone liquid chromatography tandem mass spectroscopy assay: Interference and comparison with established methods. Steroid 2008 Dec 12; 73(13): 1345-1352

Published Literature by Lachance et.al.[2]

In 2015, Lachance and co-authors assessed the potential degradation of TU in blood under conditions similar to typical clinical practice. The in vitro studies included TU dissolved in methanol or ethanol/PBS, spiked in whole blood, aliquots set at room temperature for at least 30 min before processing to plasma or serum; in tubes with and without esterase inhibitor additive, and measured T concentrations by LC-MS/MS. T concentrations were used to determine TU to T conversion rate. Lachance and co-authors attempted to address Wang's conclusion that TU-T conversion does not exist.

The following data and conclusions were reported by the authors:

Table 1. Conversion of testosterone undecanoate into testosterone according to the testosterone undecanoate concentrations and the incubation time.

TU Concentration Fortified (ng/dl)	Duration of incubation (min)	Concentration testosterone measured (ng/dl)	% difference vs TU = 0 (%)	% difference 30 vs 60 min (%)
0	0	23.75	–	–
1500	30	36.76	54.8	24.6
	60	45.81	92.9	
10,000	30	152.66	542.8	65.8
	60	253.18	966.0	
30,000	30	306.02	1188.5	73.9
	60	532.19	2140.8	
70,000	30	732.49	2984.2	72.4
	60	1262.81	5217.1	

TU: Testosterone undecanoate.

- Serum T concentrations increased over time and was more significant with higher TU concentration.

Table 1. Conversion of testosterone undecanoate into testosterone according to the testosterone undecanoate concentrations and the incubation time.

TU Concentration Fortified (ng/dl)	Duration of incubation (min)	Concentration testosterone measured (ng/dl)	% difference vs TU = 0 (%)	% difference 30 vs 60 min (%)
0	0	23.75	–	–
1500	30	36.76	54.8	24.6
	60	45.81	92.9	
10,000	30	152.66	542.8	65.8
	60	253.18	966.0	
30,000	30	306.02	1188.5	73.9
	60	532.19	2140.8	
70,000	30	732.49	2984.2	72.4
	60	1262.81	5217.1	

TU: Testosterone undecanoate.

~130 ng/dL

~230 ng/dL

- T concentration increased ~130 and ~230 ng/dL when we consider the sample processing conditions most similar to that in the phase 3 study LPCN 1021-16-002 (TU concentration at 11,106 ng/dL and sample sitting at RT for 20-60 min before processing).

Table 4. Testosterone and phosphate buffer saline concentrations in serum or plasma harvested from blood spiked with testosterone undecanoate working solution prepared in phosphate buffer saline or methanol; spiking level 60,000 ng/dl.

Experiments	Endogenous level in serum	Endogenous level in plasma	30 min serum RT	60 min serum RT	Plasma 10 min 4°C	Plasma 30 min 4°C	Plasma 60 min 4°C
Mean testosterone concentration (ng/dl)							
Whole blood spiked with TU in PBS	255.4	221.7	295.4	349.0	236.0	232.9	231.1
Whole blood spiked with TU in methanol	255.4	221.7	854.8	1255.4	322.5	339.9	320.5
Mean TU concentration (ng/dl)							
Whole blood spiked with TU in PBS	N/A	N/A	3991.0	5892.3	74408.7	54088.0	26618.7
Whole blood spiked with TU in methanol	N/A	N/A	97110.3	96132.3	97235.0	95628.0	93816.3

PBS: Phosphate buffer saline; RT: Room temperature; TU: Testosterone undecanoate.

40 ng/dL

~600 ng/dL

- Endogenous T concentrations in serum (blood collected in plain tubes with no esterase inhibitor) and plasma (blood collected in NaF/$K_2C_2O_4$ tubes with esterase inhibitor) are slightly different.
- Compared to endogenous T concentration, T increased 40 ng/dL when TU was dissolved in ethanol/PBS and the blood sample sat at RT for 30 min before processing.
- Compared to endogenous T concentration, T increased ~600 ng/dL when TU was dissolved in methanol and the blood sample sat at RT for 30 min before processing.
- Difference may be due to the solvent used to dissolve TU prior to spiking in whole blood.
- When TU dissolved in ethanol/buffer (PBS), the investigator noted a precipitate formation suggesting that TU was no longer in the solution, thus, lowering the effective TU concentration.

- The investigators noted that TU concentrations were variable and generally lower when the stock was prepared in PBS/ethanol versus in methanol.
- TU dissolved in methanol resulted in TU concentrations that were generally higher and similar in both serum and plasma.

[2] Lachance S, Dhingra O, Bernstein J, et al. Importance of measuring testosterone in enzyme-inhibited plasma for oral testosterone undecanoate androgen replacement therapy clinical trial. Future Sci OA 2015; 1(4)

Lipocine's Data

The Applicant was requested to evaluate that their sample collection method consider the potential ex vivo conversion of TU to T and take steps to ensure that no TU is converted to T (in Advice/Information Request letter dated June 6, 2017 under IND 106,476 and in Information Request letter dated October 5, 2017 under NDA 208088). On November 9, 2019, the Applicant responded to the two requests and referred the review team to the bioanalytical report S361.1.001.B3 (Clinical study S361.1.001) and method validation reports S361.B.001 "*Validation report: The determination of testosterone undecanoate and dihydrotestosterone undecanoate in human serum with HPLC with MS/MS detection by* (b) (4)" and LCMSC 521.1, Project RBJF2 "*Quantitation of testosterone undecanoate and 5α-dihydrotestosterone undecanoate in human serum via HPLC with MS/MS detection.*"

As part of their method validation, the Applicant assessed the stability of TU and DHTU in whole blood. Their ex vivo TU stability assessment was carried out in sodium heparin anticoagulant test tubes. Two of three studies measured TU concentrations to estimate TU conversion rate. These two studies are not discussed further here because the change in TU concentration is small and measuring TU directly is not sensitive to detect the presence and magnitude of TU to T conversion.

One in vitro study measured T concentrations in plasma to estimate TU conversion rate (referred to as Study #1 in this review). Whole blood was freshly drawn from three donors and sub-aliquoted. One of the sub-aliquots was left unfortified, while the other aliquots were fortified with TU and DHTU at 100,000 and 50,000 ng/dL, respectively. The samples were incubated at room temperature for 30 min, as would be specified to allow clot formation when preparing serum samples. Plasma was then harvested from the unfortified sample and one of the fortified samples for each individual by centrifugation for 10 minutes at 2 to 8°C. Sets of the remaining tubes were placed either on ice or at room temperature, and plasma was harvested after an additional 60 and 120 min. The in vitro studies assessed TU stability under various sampling handling conditions.

Table 4.2.2-2. Percentage of TU conversion in three different blood samples following different sampling preparation procedures (Applicant's table).

Analyte Evaluated	Total Exposure	Estimated % Conversion				
		40 Minutes (Initial)	100 Minutes (+60 on ice)	160 Minutes (+120 on ice)	100 Minutes (+60 at RT)	160 Minutes (+120 at RT)
TU (based on appearance of T)	Donor 1	1.84	2.43	2.71	2.88	4.97
	Donor 2	1.84	2.52	2.64	3.95	5.78
	Donor 3	0.85	0.99	1.23	1.83	3.19

Based on the phase 3 study LPCN 1021-16-002 protocol, whole blood was collected in tubes without an enzyme inhibitor, allowed to clot for 20 to 60 min at room temperature, centrifuged for 10 to 15 min to harvest serum, and the resulting serum stored at -20°C or shipped on dry ice for analyte assessments. TU conversion rates based upon samples evaluated after 30 min room temperature incubation (labeled as "40 minutes" in the table above) represents samples that would be processed immediately after blood collection. TU conversion rates based upon samples evaluated after 90 minutes at room temperature (labeled as "100 Minutes" in the table above) represents a worst-case sample processing conditions in the phase 3 study.

TU conversion was 1.51% based upon the mean of 3 donors at 40 Minutes where the blood samples incubated at room temperature for 30 min to mimic clotting, spun for 10 min, and frozen at -20°C for analysis. This represents the "best case scenario" where the least amount of ex vivo conversion would be expected because the blood samples would be processed immediately after blood sampling.

TU conversion was 3.95% based upon a single donor at 100 Minutes where the blood samples would have incubated at room temperature for 90 min (60 min + 30 min to mimic clotting time), spun for 10 min, and frozen at -20°C for analysis. This scenario represents a worst-case scenario likely to be encountered during the PK assessment period in the phase 3 study.

The following are TU pharmacokinetic profile and parameters from the Phase 3 study LPCN 1021-16-002 following twice oral daily administration of TU capsules 225 mg in hypogonadal men.

Figure 4.2.2-1. Mean (±SD) Testosterone Undecanoate Concentration vs Time on Day 24 Following Oral Testosterone Undecanoate (225 mg twice daily) Administration in Hypogonadal men (N=90) (Applicant's updated figure 3).

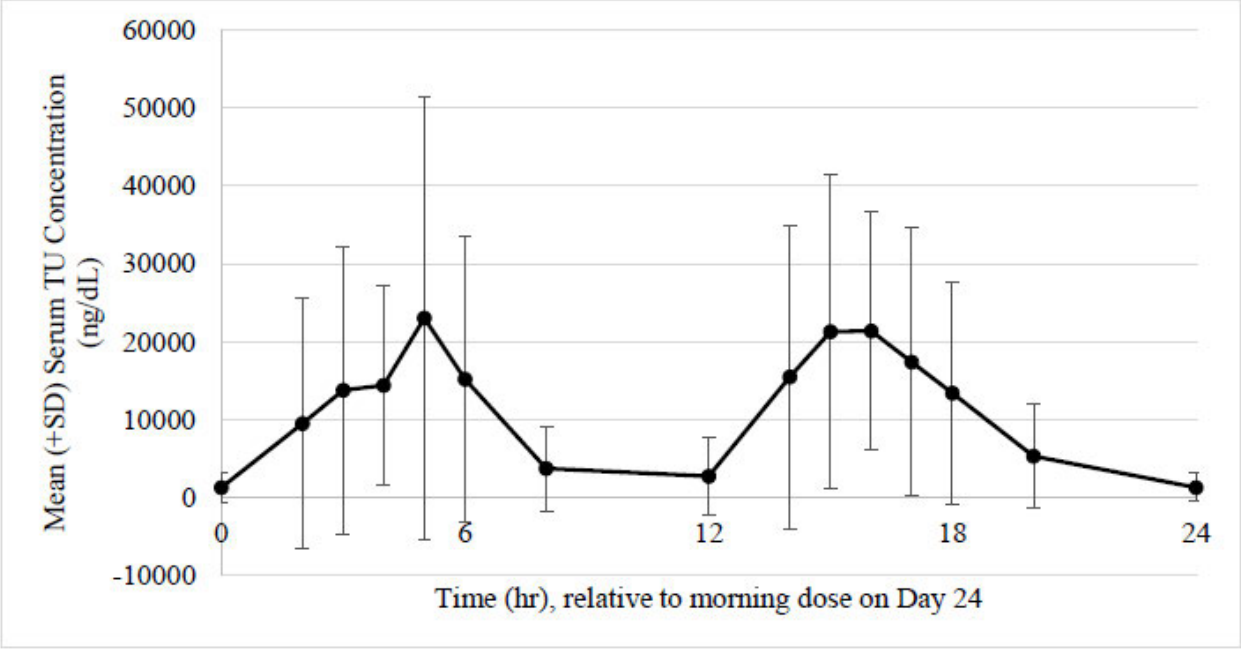


Table 4.2.2-3. TU Pharmacokinetics on Day 24 Following Oral Testosterone Undecanoate (225 mg twice daily) Administration in Hypogonadal men (N=90) (Applicant's updated table 22)

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg0-24h, ng/dL	Mean (SD)	11106 (5036)		
Cmax, ng/dL	Mean (SD)	46974 (25602)	35948 (28233)	36363 (19523)
Tmax, h	Median (Min, Max)	14.0 (2.0, 20.7)	4.9 (1.9, 11.9)	4.0 (1.9, 12.0)

Table 4.2.2-4. Potential Difference in Serum Testosterone Concentration in Patients due to Ex Vivo Conversion of Testosterone Undecanoate.

	TU concentration (ng/dL)	%TU converted to T	**Resulting T concentration (ng/dL)**
Mean Cavg	11100	3.95	**276**
Mean Cmax	47000	3.95	**1170**
Mean Cavg	11100	1.51	**106**
Mean Cmax	47000	1.51	**447**

Based upon the reported rate of TU to T conversion and the observed TU concentrations from phase 3 study LPCN 1021-16-002, there may be a significant difference in the currently reported T concentrations and the actual T concentrations (without ex vivo TU conversion). For example, if using the mean Cavg for TU of 11100 ng/dL and a 3.95% ex vivo conversion of TU to T, this can result in an

overestimation of serum T Cavg concentration of 276 ng/dL. This suggests that the currently reported T concentrations from study LPCN 1021-16-002 may not be reliable.

Following a teleconference with the Applicant regarding our assessment of their in vitro data, the Applicant conducted an additional in vitro study (referred to as Study #2 in this review). On December 9 and 27, 2017, the Applicant provided the following preliminary report of the method and data.

Whole blood was collected in 4 mL plain Vacutainer tubes and assumed to be filled. Immediately after drawing the blood, the working TU standard (200 mcL) was injected through the stopper using a syringe, and the tube was thoroughly mixed by inverting several times. Whole Blood expected TU concentration was calculated as Spiking Solution Concentration X * (0.2 mL/4 mL).

Table 4.2.2-5. TU Spiked Volumes, Expected TU Concentrations, and Measured TU and T in Individual Donors (Applicant's In Vitro Study, table 1, December 27, 2017)

	New Data			Provided earlier	
Donor	**Spiking Solution Conc.**	**Projected Whole Blood TU Conc.***	**Measured TU Level in Serum**	**Measured TU Level in Serum**	**Measured T Level in Serum Mean (%CV)**
Units	**ng/mL**	**ng/mL**	**ng/mL**	**ng/dL**	**ng/dL**
Donor 1	0	0	0	0	646 (3.5%)
	100	5	1.04	104	666 (2.8%)
	1,000	50	15.68	1568	607 (8.7%)
	3,333	166.5	18.29	1829	652 (2.6%)
	8,500	425	25.21	2521	661 (2.5%)
Donor 2	0	0	0	0	482 (9.4%)
	100	5	1.52	152	481(2.4%)
	1,000	50	10.29	1029	483 (5.4%)
	3,333	166.5	29.87	2987	469 (7.6%)
	8,500	425	40.75	4075	512 (3.4%)
Donor 3	0	0	0	0	431 (4.7%)
	100	5	1.20	120	446 (6.0%)
	1,000	50	8.46	846	446 (5.8%)
	3,333	166.5	25.31	2531	451 (6.6%)
	8,500	425	32.57	3257	465 (4.5%)
Donor 4	0	0	0	0	257 (4.4%)
	100	5	1.45	145	261 (5.7%)
	1,000	50	10.96	1096	266 (3.8%)
	3,333	166.5	28.47	2847	282 (9.2%)
	8,500	425	41.16	4116	276 (7.6%)

* This value in whole blood is projected based on the volume of spiking solution and blood. Projected Serum TU concentration were not estimated due to unknown values of RBC partitioning, clot matrix effects and hematocrit levels in the donors.

Table 4.2.2-6. TU Spiked Volumes, Expected TU Concentrations, and Measured TU and T in Individual Donors (Prepared from Applicant's in vitro Study, table 1, December 4 & 27, 2017)

Expected TU Concentration (ng/dL)	Mean (range) Measured TU Concentration (ng/dL)	Mean (%CV) (n=3) of Serum T Concentration (ng/dL)			
		Donor 1	Donor 2	Donor 3	Donor 4
0	0 (0)	646 (3.5 %)	482 (9.4%)	431 (4.7%)	257 (4.4%)
500	130 (104-152)	666 (2.8%)	481 (2.4%)	446 (6.0%)	261 (5.7%)
5,000	1135 (846-1568)	607 (8.7%)	483 (5.4%)	446 (5.8%)	266 (3.8%)
16,650	2549 (1829-2987)	652 (2.6%)	469 (7.6%)	451 (6.6%)	282 (9.2%)
42,500	3492 (2521-4116)	661 (2.5%)	512 (3.4%)	465 (4.5%)	276 (7.6%)

Reviewer's Comments:

- Due to the high initial TU concentrations and sensitivity of the assay, the in vitro experiments using measured T concentrations (appearance of T rather than disappearance of TU) is more sensitive in estimating TU conversion rates. Therefore, the data presented from the Project RBJF2, Method LCMSC 521.1 (noted as Study #1 in this review) was used to assess ex vivo conversion of TU to T.
- Based upon the reported rate of TU to T conversion and the observed TU concentrations from phase 3 study LPCN 1021-16-002, there may be a significant difference in the currently reported T concentrations and the actual T concentrations (without ex vivo TU conversion). For example, if using the mean Cavg for TU of 11100 ng/dL and a 3.95% ex vivo conversion of TU to T, this can result in an overestimation of serum T Cavg concentration of 276 ng/dL. This suggests that the currently reported T concentrations from study LPCN 1021-16-002 may not be reliable.
- Based upon the new in vitro data, the Applicant states that ex vivo conversion of TU to T during the sample handling period based is not expected to occur.
- However, this reviewer notes the following concerns with the preliminary data:
    - Measured TU concentration in the spiked samples was significantly lower than expected TU concentration (e.g., the highest spike TU concentration was expected to be 42,500 ng/dL, but the mean (range) measured TU concentration was 3492 (2521-4116) ng/dL). The discrepancy in the expected and measured concentration suggests that there may be an issue with assay recovery. The full report was not submitted to the NDA; therefore, a thorough review of the results from study #2 is not possible at the time of this review cycle.

- Mean TU concentrations in spiked samples were significantly lower than TU Cavg from phase 3 study LPCN 1021-16-002 (3,492 vs. 11,106 ng/dL) (but was still relatively high compared to T Cavg observed in phase 3 study LPCN 1021-16-002).

- In summary, there is conflicting information about the potential ex vivo TU to T conversion based upon in vitro results as follows:
  - Wang et al.
    - Showed no T increase when TU was added to whole blood
    - Showed T increased up to 740 ng/dL when TE was added to whole blood
  - Lachance et al.
    - Showed T increased ~130-230 ng/dL when TU (10,000 ng/dL) was added to whole blood
    - Attempted to explain why Wang et al. did not observe ex vivo TU to T conversion
  - Lipocine Inc.
    - Study #1 showed TU converted to T at a rate of 0.85 to 3.95% resulting in possible T increase of up to 276 ng/dL
    - Study #2 showed no increase in T when TU (2521 to 4117 ng/dL) was added to whole blood

- The data from the two publications and the Applicant's two studies were presented at the Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting on January 10, 2018. The discrepancy in the findings and conclusions were discussed with panel members stating that additional work is needed to address the potential ex vivo TU to T conversion.

- This reviewer recommends the Applicant provide addition information about the ex vivo conversion to confirm the reliability of the phase 3 data.

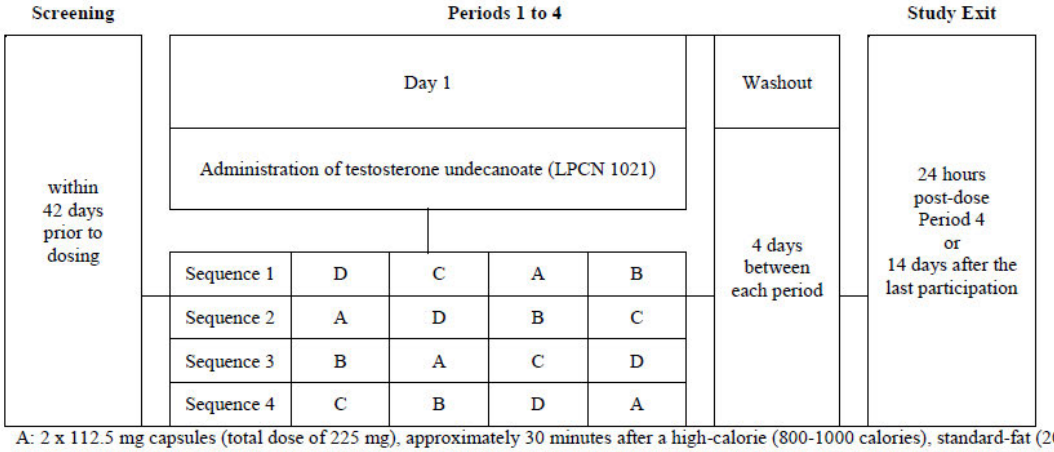
4.2.3 Food Effect

The Applicant evaluated the effect of food and fat content on the bioavailability of a single oral dose of Tlando. This was an open-label, randomized, four-period, four-treatment, crossover study in hypogonadal males.

Hypogonadal men were served low-fat, moderate-fat, and high-fat meals consisting of 800-1000 calories, or fasted overnight for at least 10 hrs. A total of up to 16 hypogonadal adult men received a 225-mg oral dose (2 x 112.5 mg capsules) of Tlando approximately 30 min after the meal had started and fasted for no less than 4 hrs after drug administration. Water 240 mL was given with drug administration.

Treatment A = standard (20-35%) fat meal
Treatment B = low (~15%) fat meal
Treatment C = high (~50%) fat meal
Treatment D = fasting conditions

Figure 4.2.3-1: Study design schematic



A: 2 x 112.5 mg capsules (total dose of 225 mg), approximately 30 minutes after a high-calorie (800-1000 calories), standard-fat (20-35%) meal.
B: 2 x 112.5 mg capsules (total dose of 225 mg), approximately 30 minutes after a high-calorie (800-1000 calories), low-fat (approximately 15%) meal.
C: 2 x 112.5 mg capsules (total dose of 225 mg), approximately 30 minutes after a high-calorie (800-1000 calories), high-fat (approximately 50%) meal.
D: 2 x 112.5 mg capsules (total dose of 225 mg), under fasting conditions.

Total Serum Testosterone

The data from this food effect study are illustrated in figures and tables below, followed by the reviewer's summary and interpretation of the data.

Figure 4.2.3-2: Mean (±SD) Serum Testosterone Concentration-Time Profiles Following Various Fat Content Meals (Treatments A, B and C (N=13)) and Fasting Conditions (Treatment D (N=14)) (Applicant's analysis).

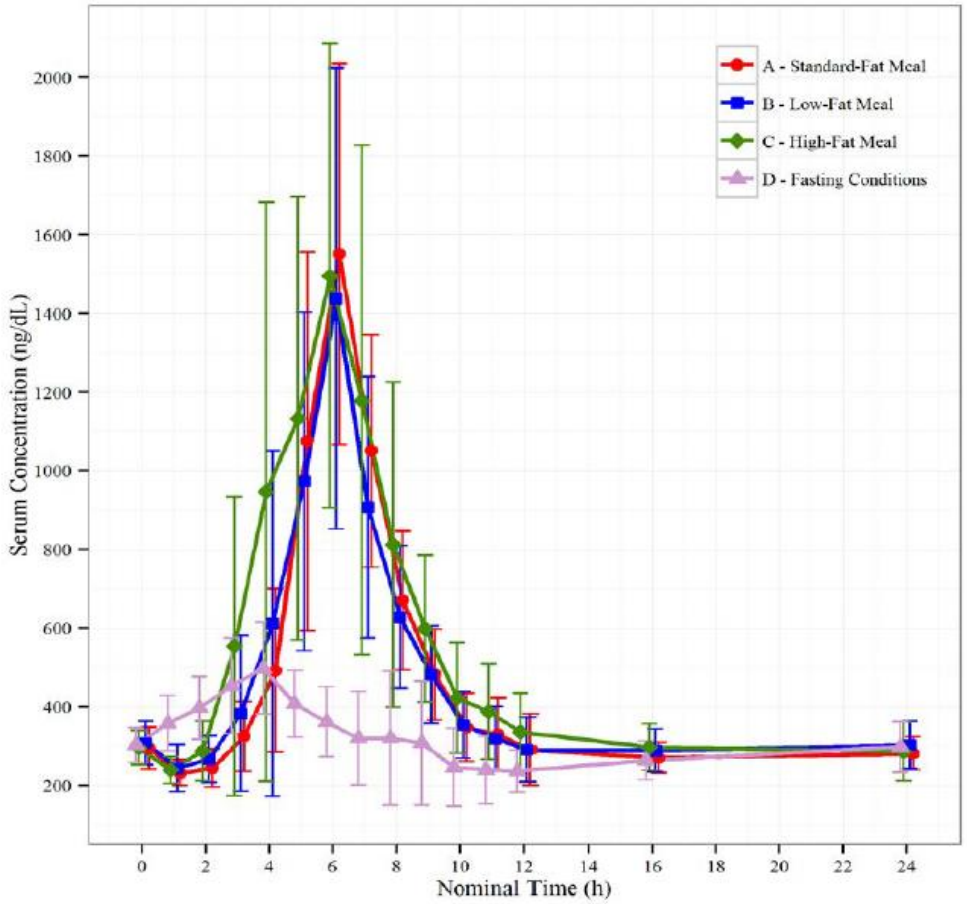


Figure 4.2.3-3. Mean (±SD) Baseline-Adjusted (BA) Testosterone Concentration-Time Profiles Following Various Fat Content Meals Types (Treatments A, B and C (N=13)) and Fasting Conditions (Treatment D (N=14)) (Applicant's analysis).

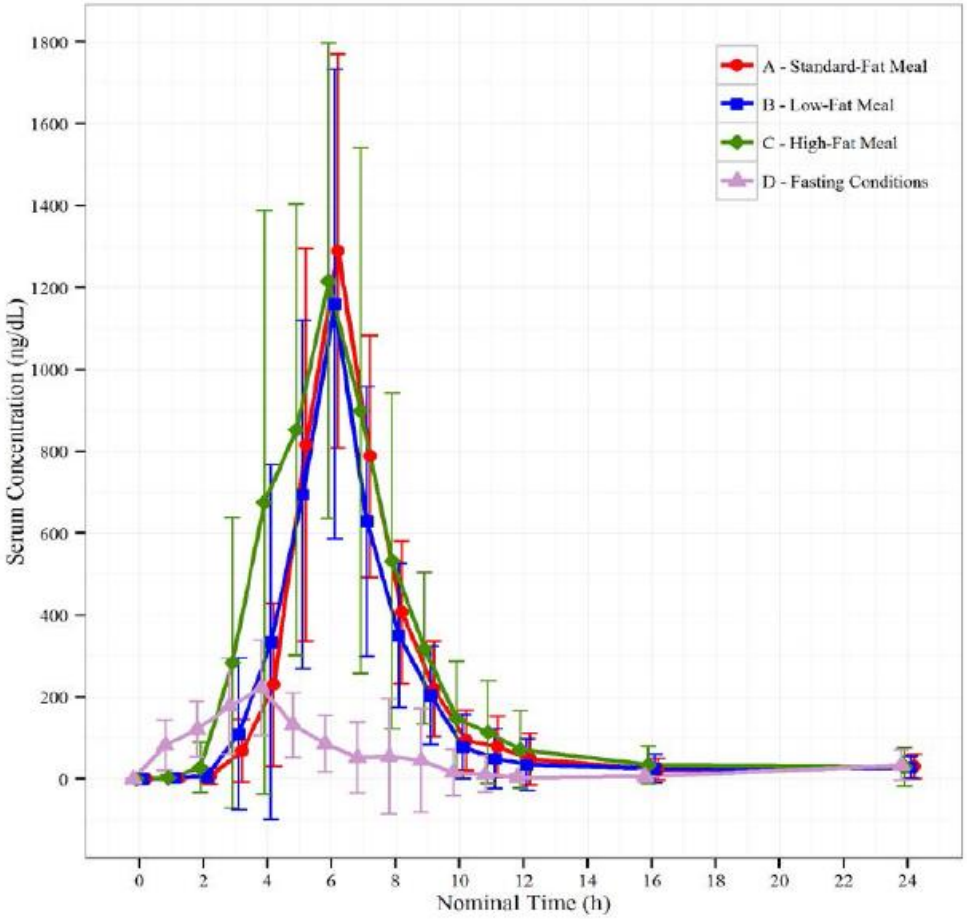


Figure 4.2.3-4. Effect of Fat Content on Testosterone AUC0-t

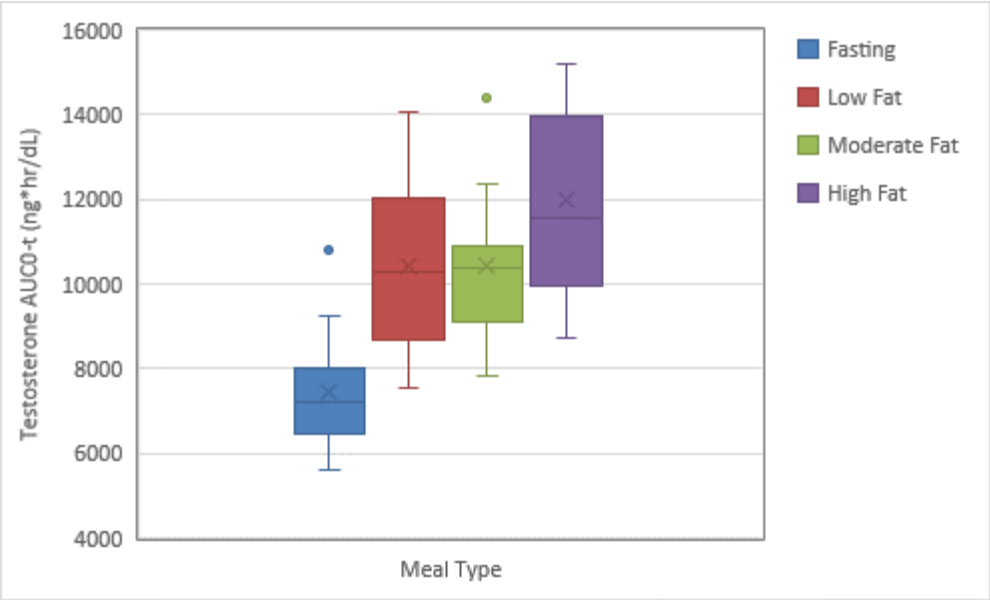


Figure 4.2.3-5. Effect of Fat Content on Testosterone Cmax

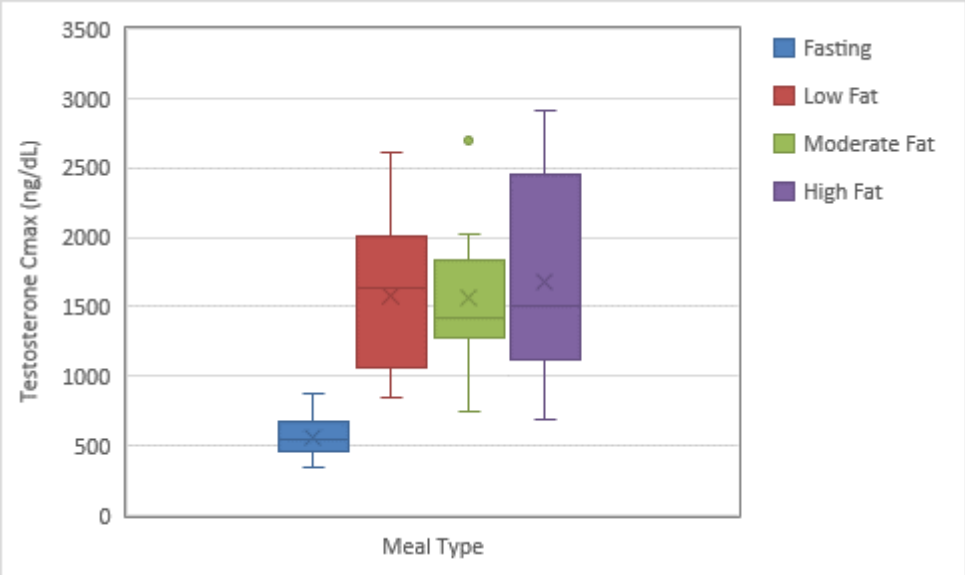


Figure 4.2.3-6. Effect of Fat Content on Baseline Adjusted Testosterone AUC0-t

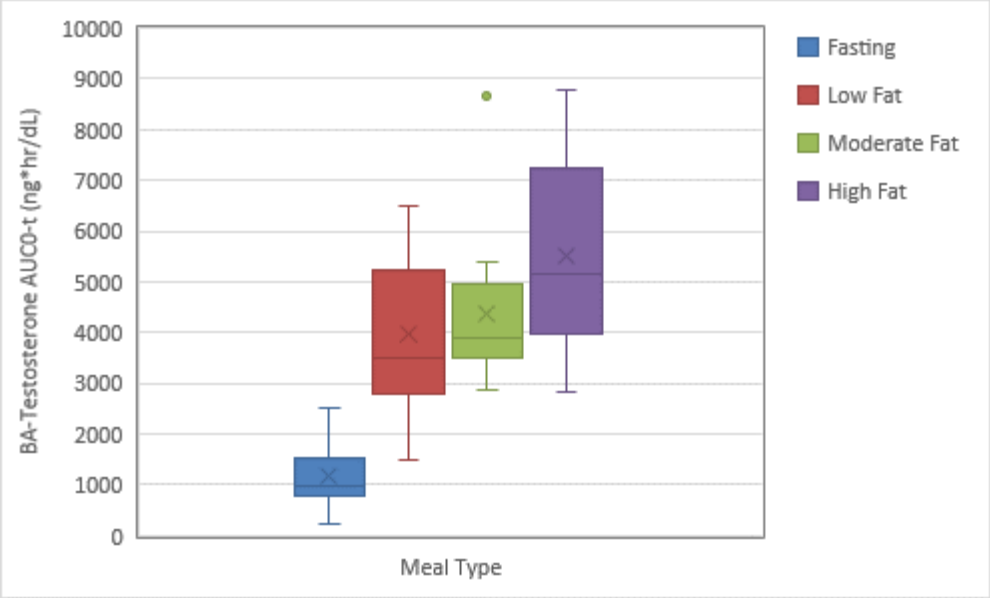


Figure 4.2.3-7. Effect of Fat Content on Baseline Adjusted Testosterone Cmax

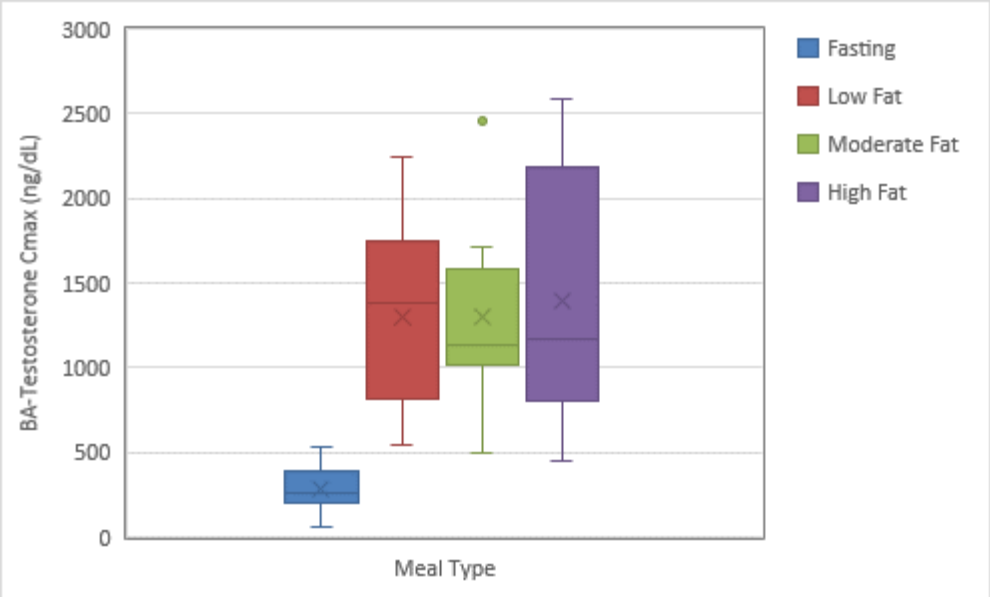


Table 4.2.3-1: Pharmacokinetic Parameters for Testosterone Following Various Meal Types in Hypogonadal men (Applicant's analysis).

Parameter	Statistic	Treatment			
		A Standard-Fat Meal	B Low-Fat Meal	C High-Fat Meal	D Fasting Conditions
C_{max} (ng/dL)	N	13	13	13	14
	Mean	1560	1570	1680	562
	SD	476	556	738	146
	CV%	30.5	35.3	44.0	26.0
	Geo. Mean	1500	1480	1530	546
T_{max} (h)	N	13	13	13	14
	Median	5.99	5.99	6.00	3.99
	Min	5.00	4.00	3.99	1.00
	Max	6.99	6.01	8.00	8.00
AUC_{0-t} (ng*h/dL)	N	13	13	13	14
	Mean	10420.50	10428.72	11974.41	7423.05
	SD	1670.89	1963.10	2205.83	1393.80
	CV%	16.03	18.82	18.42	18.78
	Geo. Mean	10303.29	10259.07	11785.39	7310.03

Table 4.2.3-2. Pharmacokinetic Parameters for Baseline-Adjusted Testosterone Following Various Meal Types in Hypogonadal men (Applicant's analysis).

Parameter	Statistic	Treatment			
		A Standard-Fat Meal	B Low-Fat Meal	C High-Fat Meal	D Fasting Conditions
C_{max} (ng/dL)	N	13	13	13	14
	Mean	1300	1300	1400	287
	SD	473	542	721	128
	CV%	36.5	41.8	51.7	44.8
	Geo. Mean	1220	1180	1220	255
T_{max} (h)	N	13	13	13	14
	Median	5.99	5.99	6.00	3.99
	Min	5.00	4.00	3.99	1.00
	Max	6.99	6.01	8.00	8.00
AUC_{0-t} (ng*h/dL)	N	13	13	13	14
	Mean	4371.91	3961.60	5510.66	1183.35
	SD	1496.11	1502.47	1978.80	641.77
	CV%	34.22	37.93	35.91	54.23
	Geo. Mean	4190.81	3670.45	5180.46	1019.18
AUC_{0-inf} (ng*h/dL)	N	5	7	9	5
	Mean	4818.91	3926.11	6064.43	1008.49
	SD	2228.12	1537.42	2271.21	631.49
	CV%	46.24	39.16	37.45	62.62
	Geo. Mean	4509.74	3708.60	5658.51	826.83
$T_{½ el}$ (h)	N	5	7	9	5
	Mean	2.86	3.76	2.47	3.33
	SD	2.93	3.10	1.97	4.25
	CV%	102.47	82.43	79.60	127.71
K_{el} (/h)	N	5	7	9	5
	Mean	0.5547	0.4252	0.5097	0.5502
	SD	0.4526	0.3718	0.4493	0.4095
	CV%	81.5967	87.4325	88.1531	74.4142

Table 4.2.3-3: Mean Testosterone Pharmacokinetics (AUC0-12hr) Following Various Meal Types (Treatments A, B, C and D) (Applicant's analysis).

Parameter	Statistic	Treatment			
		A Standard-Fat Meal	B Low-Fat Meal	C High-Fat Meal	D Fasting Conditions
AUC_{0-12} (ng*h/dL)	N	13	13	13	14
	Mean	7094.40	6899.14	8371.14	4178.07
	SD	1509.63	1512.01	2183.04	850.08
	CV%	21.28	21.92	26.08	20.35
	Geo. Mean	6957.59	6744.52	8117.09	4103.84

Table 4.2.3-4. Statistical Analysis of Testosterone Pharmacokinetic Parameters after Various Meal Intake.

PK Parameter	Treatment Comparisons	Geometric LSM Ratio
AUC0-t	high fat vs. fasting	161%
	high fat vs. mod fat	114%
	high fat vs. low fat	115%
AUC0-12hr	high fat vs. fasting	198%
	high fat vs. mod fat	117%
	high fat vs. low fat	120%
Cmax (0-t)	high fat vs. fasting	286%
	high fat vs. mod fat	103%
	high fat vs. low fat	103%

LSM=least square means

Table 4.2.3-5. Statistical Analysis of Baseline-Adjusted Testosterone PK Parameters after Various Meal Intake.

PK Parameter	Treatment Comparisons	Geometric LSM Ratio
AUC0-t	high fat vs. fasting	508%
	high fat vs. mod fat	124%
	high fat vs. low fat	141%
Cmax (0-t)	high fat vs. fasting	478%
	high fat vs. mod fat	100%
	high fat vs. low fat	103%

LSM=least square means

- The objective of the study was to evaluate the effect of food content on the bioavailability of TU, T, and DHT in 4 treatment groups – fasting, low fat, medium fat, and high fat.
- Comparing the two extreme cases of fat content – high-fat vs. low-fat –the geometric mean ratio for T AUC0-t, AUC0-12h, and Cmax was 1.15, 1.20 and 1.03, respectively.

- Comparing high-fat vs. moderate-fat, the geometric mean ratio for T AUC0-t, AUC0-12h, and Cmax was 1.14, 1.17, and 1.03, respectively.
- Comparing high-fat food vs. fasting condition, the geometric mean ratio for T AUC0-t, AUC0-12h, Cmax was 1.61, 1.98 and 2.86, respectively.
- TU and T bioavailability is significantly affected by the absence of food. The product is proposed to be administered with food without reference to a specific fat content.
- When endogenous baseline T concentrations were subtracted, the magnitude of food effects appeared larger than without baseline subtraction (Table 12).
- The phase 3 study was conducted irrespective of fat content. Overall, the range of fat content in food does not appear to have a significant effect on T bioavailability as the presence of fat in food to even a modest extent increases the bioavailability versus fasting.

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

/s/

LAI M LEE
02/26/2018

DOANH C TRAN
02/26/2018

GILBERT J BURCKART
02/26/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supporting Doc #:	208088/27 (eCTD Sequence #: 0026)
Drug Name:	TLANDO (Testosterone undecanoate oral capsule)
Indication(s):	Treatment of primary and secondary hypogonadism
Applicant:	Lipocine Inc.
Date(s):	Submission Date: August 8, 2017
	PDUFA Goal or Action Date: March 22, 2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Weiya Zhang, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Martin Kaufman, M.D., Clinical Reviewer
	Suresh Kaul, M.D., Clinical Team Leader
Project Manager:	Jeannie Roule

Keywords: Clinical studies, NDA review

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

The Applicant, Lipocine Inc., submitted safety and efficacy data from two studies in support of TLANDO for the treatment of primary and secondary hypogonadism. One study provided evidence demonstrating efficacy of a BID (two 112.5 mg twice daily) LPCN 1021 testosterone undecanoate oral capsules, while a second study did not provide evidence in support of a (b) (4) LPCN 1021 testosterone undecanoate oral capsules.

The primary efficacy evidence was based on achieving 24-hour average (C_{avg}) serum testosterone concentration within the normal range after 24 days of treatment in at least 75% of the subjects with the lower bound of the 95% confidence interval for the point estimate not below 65%. The secondary efficacy evidences were based on at least 85% subjects with C_{max} less than 1500 ng/dL, 5% subjects with C_{max} between 1800 to 2500 ng/dL, and no subject with C_{max} greater than 2500 ng/dL.

In study LPCN 1021-16-002 (hereafter referred to as study 002), 80% of the subjects achieved Cavg in the normal rage after 24 days of treatment with a 95% confidence interval of 72% to 88%; 74% subjects had C_{max} less than 1500 ng/dL, 14% subjects had C_{max} between 1800 and 2500 ng/dL, and one subject had C_{max} greater than 2500 mg/dL.

In study LPCN 1021-16-003 (hereafter referred to as study 003), 69% of the subjects achieved C_{avg} in the normal range after 24 days of treatment with a 95% confidence interval of 60% to 78%; 92% subjects had C_{max} less than 1500 ng/dL, 1% subjects had C_{max} between 1800 and 2500 ng/dL, and no subject had C_{max} greater than 2500 mg/dL.

From a statistical perspective, BID LPCN 1021 oral capsules demonstrated efficacy based on the pre-specified efficacy criteria.

2 INTRODUCTION

2.1 Overview

This is a resubmission of NDA 208088 after a complete response letter issued on June 28, 2016. The major deficiency in the original NDA was that the proposed titration scheme for clinical practice in the product label was significantly different from the one used in the Phase 3 trial. The Division recommended that the Applicant uses modeling and simulation data from the completed Phase 3 trial to select the titration scheme to be used for real-world use.

Following a post-action meeting and a special protocol assessment, the Applicant conducted a pivotal study 002 with a fixed dose of 225 mg BID to validate the fixed dosing regimen to support the indication of LPCN 1021 as a testosterone replacement therapy for the primary and secondary hypogonadism, and a supportive study 003 with a fixed dose of 150 mg TID to evaluate the dosing flexibility. Table 1 presents a brief study summary.

Table 1: Brief summary of clinical study for LPCN 1021

Study Number (Country/#Sites) Date First Subject Enrolled, Date last Subject Completed	Subject Population	Treatment	Safety Set
LPCN 1021-16-002 (US/12) January 12, 2017 April 6, 2017	Male subjects aged 18 to 80 years of age with documented onset of hypogonadism before age 65 whose morning serum total testosterone < 300 ng/dL	BID LPCN 1021 oral testosterone undecanoate capsule	95
LPCN 1021-16-003 (US/17) February, 2017 June 15, 2017	Male subjects aged 18 to 80 years of age with documented onset of hypogonadism before age 65 whose morning serum total testosterone < 300 ng/dL	TID LPCN 1021 oral testosterone undecanoate capsule	100

Source: Statistical Reviewer's listing.

2.2 Data Sources

The application was submitted electronically on August 8, 2017. The submitted SAS datasets were complete and well documented. The review items are located in the CDER Electronic Document Room as described below:

- The completed study report is located at \\CDSESUB1\evsprod\NDA208088\0026\m5\53-clin-stud-rep\535-rep-effic-safety-stud\testostero\5352-stud-rep-uncontr under eCTD Sequence Number 0026
- Raw and derived datasets used for analysis and the datasets define files are located at \\CDSESUB1\evsprod\NDA208088\0026\m5\datasets under eCTD Sequence Number 0026

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets and definition files are accessible. I was able to reproduce the efficacy results as presented in the study reports.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies 002 and 003 followed an identical but separate study design. Both were multicenter, Phase 1, open-label studies with 24 days of treatment. Eligible subjects were adult men between 18 and 80 years of age with documented onset of hypogonadism before age 65 who had morning serum testosterone < 300 ng/dL based on 2 consecutive blood samples on 2 separate days. Subjects were also to be naïve to androgen replacement or had discontinued current treatment and completed a washout period.

In Study 002, 95 subjects were enrolled and received LPCN 1021 (oral TU) 225 mg (two capsules of 112.5 mg) taken twice daily (total daily dose of 450 mg) for 24 days. In Study 003, 100 subjects were enrolled and received LPCN 1021 150 mg (two capsules of 75 mg) taken three times daily (total daily dose of 450 mg) for 24 days. The intensive PK sampling was performed at Day 24 in both studies.

Efficacy Endpoints

The primary efficacy endpoint for both studies was the percentage of subjects who achieved a 24-hour average (C_{avg}) serum testosterone concentration within the normal range of 300 to 1080 ng/dL upon completion of 24 days of treatment.

The secondary efficacy endpoints for both studies were the percentage of subjects who exhibited 24-hour maximum serum testosterone concentrations (C_{max}) within pre-specified limits upon completion of 24 days of study treatment. These limits for C_{max} are the following:

- $\geq$ 85% of subjects had C_{max} < 1500 ng/dL
- $\leq$ 5% of subjects had C_{max} between 1800 and 2500 ng/dL
- No subjects had C_{max} $\leq$ 2500 ng/dL

3.2.2 Statistical Methodologies

Analysis Datasets

Safety Set (SS) included all subjects who received at least one dose of study drug. The Full Analysis Set (FAS) included all subjects enrolled into the study with at least one post-baseline efficacy variable response (C_{avg} or C_{max}). The Pharmacokinetic (PK) Set included all subjects in the FAS who completed the study without major protocol deviations.

Assessment of Primary Efficacy Endpoints

The acceptable efficacy endpoint was the 75% of the subject achieving C_{avg} in the normal range with the lower bound of the 95% (2-sided) confidence interval of this estimate of 65% or more to conclude that the LPCN 1021 treatment was efficacious. The primary efficacy analysis was conducted using the Safety Set with the last observation carried forward (baseline values) in case the PK sampling on Day 24 was missing. The primary analysis was also conducted using the FAS and PK set. In addition, sensitivity analysis was performed for the primary endpoint using model-based imputation of missing data in the Safety Set.

Sample Size Calculation

Sample size for the study was based on the primary endpoint, the incidence of binomial confidence interval for the percentage of subjects achieving 24-hour serum testosterone concentrations within the normal range. In order to meet the 95% confidence lower bound of at least 65% for 75% efficacy point estimate, a sample size of approximately 100 subjects was selected.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

In study 002, a total of 95 subjects were enrolled to the study. 94 (98.9%) subjects completed the study. One subject early discontinued the study due to adverse event. In study 003, a total of 100 subjects were enrolled to the study and two patients early discontinued the study due to other reason.

Table 2: Subject disposition

Status	Study 002	Study 003
Subjects enrolled to the trial	95	100
Subjects in safety set	95 (100%)	100 (100%)
Total subjects who completed the study	94 (98.9%)	98 (98%)
Total subjects who discontinued early from the study	1 (1.1%)	2 (2%)
Reason for early discontinuation		
Adverse event	1 (1.1%)	0
Other (one subject – scheduling conflict; one subject – not reachable/lost to follow-up)	0	2 (2%)

Source: Table 14.1.1 in study 002 clinical study report (CSR). Table 14.1.1 in study 003 CSR.

The number of subject in the analysis datasets are summarized in Table 3. There were 95 subjects in the Safety Set from study 002 and 100 subjects in the Safety Set from study 003.

Table 3: Datasets for analysis

Status	Study 002	Study 003
Subjects enrolled to the trial	95	100
Safety Set	95 (100%)	100 (100%)
Full Analysis Set	94 (98.9%)	98 (98%)
Pharmacokinetic Set	90 (94.7%)	88 (88%)

Source: Table 14.1.1 in study 002 clinical study report (CSR). Table 14.1.1 in study 003 CSR.

Demographic data and baseline characteristics are summarized in Appendix Table 8 for both studies.

In study 002, subjects mean age at baseline was 56 years, with about 16% subjects older than 65. Mean weight and BMI of subjects at baseline were 103.6 kg and 32.8 kg/m^2, respectively. Most of the subjects enrolled were white (81.1%), followed by black or African American (15.8%).

In study 003, subjects mean age at baseline was 54.1 years, with about 9% subjects older than 65. Mean weight and BMI of subjects at baseline were 106.6 kg and 33.4 kg/m^2, respectively. Most of the subjects enrolled were white (84%), followed by black or African American (13%).

3.2.4 Results and Conclusions

Primary efficacy Endpoint

In study 002, 80% of subjects achieved a 24-hour average serum testosterone concentration within the normal range after 24 days of treatment with the lower bound of the 95% CI of 72% (Table 4). It met the criterion of demonstrating efficacy.

In study 003, 69% of subjects achieved a 24-hour average serum testosterone concentration within the normal range after 24 days of treatment with the lower bound of the 95% CI of 60% (Table 4). It did not meet the criterion of demonstrating efficacy.

Table 4: Proportion of subjects achieving 24-hour average serum testosterone concentration within normal range (SS)

Measure	Target	Study 002 N=95	Study 003 N=100
Subjects achieving 24-hour average serum testosterone concentration within [300, 1080] ng/dL, n (%)	≥ 75%	76 (80%)	69 (69%)
95% Confidence Interval	≥ 65% (Lower Bound)	72%, 88%	60%, 78%

Source: Table 14.2.4.4 in both CSRs. 95%, 2-sided, binomial CI surrounding the point estimate was calculated.

Sensitivity analyses were conducted for both studies (Table 5). The results were consistent with the primary analyses.

Table 5: Sensitivity analyses for proportion of subjects achieving 24-hour average serum testosterone concentration within normal range

	Study 002			Study 003		
Analysis dataset	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
Safety Set with LOCF	95	80%	72%, 88%	100	69%	60%, 78%
Full Analysis Set	94	81%	73%, 89%	98	70%	61%, 80%
PK Set	90	81%	73%, 89%	88	72%	62%, 81%
Multiple Imputation based on safety set	95	81%	72%, 88%	100	70%	60%, 78%

Source: Tables 14.2.4.1 to 14.2.4.4 in both CSRs.

Secondary efficacy Endpoint(s)

The results for subjects who achieved C_{max} values within the pre-specified limits for both studies are displayed in Table 6.

In study 002, 74% subjects had C_{max} less than 1500 ng/dL, 14% subjects had C_{max} between 1800 and 2500 ng/dL, and one subject had C_{max} greater than 2500 mg/dL. None of the C_{max} Criteria were met. In study 003, all three C_{max} criteria were met.

Table 6. Proportion of subjects achieving 24-hour maximum serum testosterone concentration within pre-specified limits (SS)

Measure	Target	Study 002 N = 95	Study 003 N = 100
C_{max} <1500 ng/dL	≥ 85%	69 (73%)	92 (92%)
$1800 \leq C_{max} \leq 2500$ ng/dL	≤ 5%	13 (14%)	1 (1%)
C_{max} > 2500 ng/dL	0	1 subject	0

Source: Table 14.2.5.4 in study 002 CSR, Table 14.2.5 1.4 in study 003 CSR, and reviewer's analysis.

3.3 Other Special/Subgroup Populations

Subgroup analyses were conducted on the primary efficacy endpoint to evaluate consistency in efficacy by BMI in the FAS. The proportions of subjects by BMI category achieving a C_{avg} within the normal range after 24 days of treatment in both studies are presented in Table 7.

In study 002, 93% of non-obese subjects (BMI < 30 kg/ m^2) and 75% of obese subjects (BMI ≥ 30 kg/ m^2) achieved C_{avg} within the normal range. In study 003, 90% of non-obese subjects (BMI < 30 kg/ m^2) and 61% of obese subjects (BMI ≥ 30 kg/ m^2) achieved C_{avg} within the normal range. Proportion of subjects with C_{avg} within normal range was numerically higher in the non-obese subjects than the obese subjects in both studies.

Table 7. Proportion of subjects achieving 24-hour average serum testosterone concentrations within normal range by BMI category (FAS)

BMI Category	Statistic	Study 002	Study 003
< 30 kg/m²	**N**	**29**	**31**
	n (%)	27 (93%)	28 (90%)
	95% CI	84%, 100%	(80%, 100%)
≥ 30 kg/ m²	**N**	**65**	**67**
	n (%)	49 (75%)	41 (61%)
	95% CI	65%, 86%	(50%, 73%)

Source: Table 14.2.4.2.2 in both CSRs.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

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

4.2 Collective Evidence

Study 002 provided evidence demonstrating the efficacy of BID LPCN 1021 testosterone undecanoate oral capsules for the treatment of primary and secondary hypogonadism based on the proportion of subjects who achieved 24-hour C_{avg} within the normal range while the C_{max} did not meet the pre-specified criteria. Study 003 did not provide evidence supporting the efficacy of TID LPCN 1021 testosterone undecanoate oral capsules based on C_{avg}.

In study 002, 80% of the subjects achieved C_{avg} in the normal rage after 24 days of treatment with a 95% confidence interval of 72% to 88%; 74% subjects had C_{max} less than 1500 ng/dL, 14% subjects had C_{max} between 1800 and 2500 ng/dL, and one subject had C_{max} greater than 2500 mg/dL.

In study 003, 69% of the subjects achieved C_{avg} in the normal range after 24 days of treatment with a 95% confidence interval of 60% to 78%; 92% subjects had C_{max} less than 1500 ng/dL, 1% subjects had C_{max} between 1800 and 2500 ng/dL, and no subject had C_{max} greater than 2500 mg/dL.

4.3 Conclusions and Recommendations

From a statistical perspective, study 002 provided evidence demonstrating efficacy of a BID LPCN 1021 testosterone undecanoate oral capsule in the treatment of primary and secondary hypogonadism while C_{max} did not reach the pre-specified criteria. Study 003 did not provide evidence in support of a (b) (4) LPCN 1021 testosterone undecanoate oral capsule for the indication.

APPENDIX

Table 8. Demographic and baseline characteristics

Characteristic	Study 002 (N=95)	Study 003 (N=100)
Sex		
Male, n (%)	95 (100%)	100 (100%)
Age (years)		
Mean (SD)	56.0 (8.9)	54.1 (8.8)
≤ 65, n (%)	79 (83.2%)	91 (91%)
> 65, n (%)	16 (16.8%)	9 (9%)
Weight (kg)		
Mean (SD)	103.6 (18.7)	106.6 (19.3)
BMI (kg/m^2)		
Mean (SD)	32.8 (5.5)	33.4 (5.5)
< 25, n (%)	3 (3.2%)	3 (3%)
≥ 25 and < 30, n (%)	26 (27.4%)	28 (28%)
≥ 30, n (%)	66 (69.5%)	69 (69%)
Race n (%)		
Asian	1 (1.1%)	1 (1%)
Black or African American	15 (15.8%)	13 (13%)
White	77 (81.1%)	84 (84%)
Multiple	2 (2.1%)	2 (2%)

Key: BMI = body mass index; SD = standard deviation.
Note: Percentages were based on N
Source: Table 14.1.2 in both CSRs.

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

/s/

WEIYA ZHANG
02/22/2018

MAHBOOB SOBHAN
02/22/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Memorandum

PHARMACOLOGY/TOXICOLOGY MEMO TO FILE

Date:	16th February 2018
NDA #	208-088
Sponsor:	Lipocine, Inc.
Drug:	Testosterone Undecanoate
Reviewer:	Laurie McLeod-Flynn, PhD
Note:	

Background

The Sponsor is seeking marketing approval for the use testosterone undecanoate (TU) capsules (BID) as a pro-drug for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Lipocine, Inc. originally filed NDA 208-088 as a 505(b)(2) application on 28th August 2015, relying on referenced literature for the long-term safety and reproductive and developmental effects of testosterone in addition to original toxicology studies in rats and dogs. NDA 208-088 received a complete response (CR) on 28 June 2016 due primarily to deficiencies in demonstrating an adequate dose titration scheme.

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.

Conclusion:

At this time, there is no impediment to Approval of this drug from a Pharmacology/Toxicology perspective.

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

/s/

LAURIE L MCLEOD FLYNN
02/16/2018

MUKESH SUMMAN
02/16/2018
I concur

CLINICAL REVIEW

Application Type	NDA
Application Number	208088
Priority or Standard	Standard
Submit Date	August 28,2015
Received Date	August 28, 2015
PDUFA Goal Date	June 28, 2016
Division / Office	DBRUP/ODE 3
Reviewer Name	Martin Kaufman, DPM, MBA
Review Completion Date	June 7, 2016
Established Name	Testosterone undecanoate
(Proposed) Trade Name	Tlando
Therapeutic Class	Androgens
Applicant	Lipocine Inc.
Formulation	Capsules
Dosing Regimen	225 mg BID (b) (4) (b) (4)
Indication	Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Intended Population	Adult (18 years or older) males

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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 single blood draw titration scheme 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.

1.2 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 a titration scheme based on a single blood draw that it proposed to use for the dosing recommendations in labeling. To ensure that the results of the Phase 3 study are generalizable to "real world" use of Tlando, one of the goals of the single blood draw titration scheme is to maintain reasonable agreement between titration decisions made in the Phase 3 study using Cavg0-24h and Cmax0-24h and titration decisions made using the titration scheme based on a single blood draw.

Comparison of the titration decisions made using the single blood draw titration 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 amendments to the original single blood draw titration scheme failed to meaningfully change this finding.

Therefore, the applicant has not provided a single blood draw titration scheme that results in titration decisions with a reasonable level of agreement with the titration decisions actually made in the Phase 3 study. Without an acceptable single blood draw titration scheme, it is not possible to make dosing recommendations for Tlando in labeling and the drug cannot be approved at this time.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Recommendations for postmarket risk evaluation and mitigation strategies (REMS) are deferred to the next review cycle.

1.4 Recommendations for Postmarket Requirements and Commitments

Recommendations for clinical postmarket requirements and commitments are deferred to the next review cycle.

2 Introduction and Regulatory Background

2.1 Product Information

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; and 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.

Tlando (testosterone undecanoate) capsules is an oral product containing (b) (4) 112.5 mg of testosterone undecanoate (TU) in a lipid formulation. Tlando 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 present in the body. In the US, TU is approved as an injectable formulation, but has not been approved for oral administration.

2.2 Table of Currently Available Treatments for Proposed Indications

Table 1: Currently Available Products for the Treatment of Male Hypogonadism

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
Parenteral	Depo-testosterone/ testosterone cypionate	50–400 mg every 2 – 4 weeks		085635
	testosterone cypionate	50–400 mg every 2 – 4 weeks		090387 091244 040652 040530 040615 086030 201720
	Delatestryl/testosterone enanthate	50–400 mg every 2 – 4 weeks	009165	
	testosterone enanthate	50–400 mg every 2 – 4 weeks		091120 040647 040575 085598
	Aveed/testosterone undecanoate	750 mg: second dose after 4 weeks, subsequent doses every 10 weeks	022219	
Oral	Testred/methyltestosterone	10-50 mg daily		083976
	Android/methyltestosterone	10-50 mg daily		087147
	methyltestosterone	10-50 mg daily		080767 204851
	Androxy/fluoxymesterone	5-20 mg daily		088342
Implant	Testopel/testosterone	150-450 mg every 3 to 6 months		080911
Transbuccal	Striant/testosterone	30 mg twice daily	021543	
Transdermal Patch	Androderm/testosterone	2-6 mg daily	020489	
Transdermal Gel	AndroGel/testosterone 1.62%	20.25-81 mg daily	022309	
	testosterone 1.62%	20.25-81 mg daily		204268
	AndroGel/testosterone 1%	50-100 mg daily	021015	
	testosterone gel 1%	50-100 mg daily		076737 076744
	Testim/testosterone 1%	50-100 mg daily	021454	
	Fortesta/testosterone	10-70 mg daily	021463	
	testosterone gel	10-70 mg daily		204571
	testosterone gel (Teva)	50-100 mg daily	202763	
	testosterone gel (Perrigo)	50-100 mg daily	203098	
	Vogelxo/testosterone gel	50-100 mg daily	204399	
Transdermal Solution	Axiron/testosterone	30-120 mg daily	022504	
Nasal Gel	Natesto/testosterone	11 mg thrice daily	205488	

Source: Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), electronic version accessed May 26, 2016. Product labeling accessed at the DailyMed website and the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) May 26, 2016.

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

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 adhere to 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.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Abbott Laboratories opened the original IND for Tlando (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 Tlando 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.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant indicated that studies were conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6) and applicable regulatory requirements including the archiving of essential documents.

3.2 Compliance with Good Clinical Practices

The applicant indicated that their studies were conducted in accordance with the ethical principles promulgated in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements.

In addition, the Office of Study Integrity and Surveillance (OSIS) conducted inspections of the bioanalytical laboratory used in the Phase 3 study (LPCN 1021-13-001) and two of the clinical sites that participated in that study.

Based on their inspections, OSIS had the following recommendations:

[redacted] (Bioanalytical laboratory)

- OCP and DBRUP reviewers should evaluate consequences of [redacted] (Subjects [redacted] and
- All other bioanalytical data from the bioanalytical laboratory in this study should be accepted for further Agency review.

Reviewer comment: [redacted] *and* [redacted]

Los Angeles BioMedical Research Institute at Harbor UCLA, Torrance, CA (Site 105)

- Data from the clinical portion of study LPCN 1021-13-001 conducted at this site should be accepted for further Agency review.

UTSW Medical Center Urology Lewisville, Lewisville, TX (Site 154)

- Data from the clinical portion of study LPCN 1021-13-001 conducted at this site should be accepted for further Agency review. However, DBRUP and OCP reviewers should evaluate the unexpected elevations of Lipoprotein-Associated Phospholipase (LAP-A2) found in some samples from patients enrolled at this site.

Reviewer comment: Lipoprotein-Associated Phospholipase (LAP-A2) was assessed during the Phase 3 study. Mean LAP-A2 values were similar for the Tlando and AndroGel 1.62% treatment arms throughout the study. Sporadic elevations above the upper limit of the normal range (235 ng/mL) were reported in both treatment groups. In the Tlando treatment group 36% of the subjects had at least one LAP-A2 value greater than 235 ng/mL compared to 44% in the AndroGel 1.62% group. The percentage of subjects with at least one LAP-A2 elevation who were enrolled at site 154 was greater than the percentage for the study in general. The reason for this is not clear.

3.3 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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The quality review team conducted a review of chemistry, manufacturing and controls (CMC). The 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. Though there are no other outstanding CMC deficiencies, the biopharmaceutics review team requested additional dissolution data using revised methodology to confirm the acceptance criterion.

However, because labeling (package insert, container/carton) negotiations were not completed and, in its present form, the labeling does not comply with the requirements under 21 CFR 201, the quality review team concluded that the NDA is not ready for approval.

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology review team conducted a review of preclinical pharmacology and toxicology.

The nonclinical 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.

4.4 Clinical Pharmacology

The clinical pharmacology review team conducted a clinical pharmacology review of the application. The reviewers reached the following conclusions:

- As conducted, 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 in a clinical setting and cannot support labeling, nor has the proposed single point titration scheme been shown to be acceptable.

- None of the proposed single point titration schemes 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 their associated safety issues), it is not possible to develop appropriate labeling at this time.

The clinical pharmacology review team recommended that the application receive a Complete Response action.

4.4.1 Mechanism of Action

Testosterone is the principal androgen secreted by the testis and main androgenic steroid in males. Endogenous androgens including T and DHT are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of 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; and alterations in body musculature and fat distribution. T and DHT are necessary for the normal development of secondary sex characteristics.

The proposed indication for Tlando is treatment of hypogonadism, a clinical syndrome that results from insufficient secretion of T, and 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), luteinizing hormone (LH)). Signs and symptoms associated with male hypogonadism may include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis.

Tlando was developed as an oral T replacement in hypogonadal men > 18 years of age with the goal of achieving serum T concentrations of approximately 300-1140 ng/dL following twice daily administration. TU is absorbed mainly through the lymphatic system and is converted to T via de-esterification of TU by non-specific esterases. Thus, TU is the prodrug of T. Dihydrotestosterone undecanoate (DHTU) is formed through the 5α-reduction of TU.

4.4.2 Pharmacodynamics

There were no pharmacodynamic assessments conducted.

4.4.3 Pharmacokinetics

The clinical pharmacology reviewer evaluated the pharmacokinetics of Tlando in three Phase 1 studies as well as the pharmacokinetic results of the single Phase 3 study. In

addition, the clinical pharmacology reviewer also reviewed a food effect study evaluating the effect of fat/caloric content on the bioavailability of T.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Tlando clinical development program included eight Phase 1 studies and one Phase 3 study. These studies are summarized in Table 2. The Phase 3 clinical study, LPCN 1021-13-001, 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.

Table 2: Studies Submitted To Support the Application

Study Number	Study Objective	Study Design	Test Product	N	Type of Subjects
Bioavailability Studies					
LPCN 1021-05-001	(1) Assess BA/PK of T following oral administration of LPCN1021 TU capsule formulations; (2) Compare BA/PK of T following LPCN1021 TU capsules to Andriol.	BA/PK of four oral TU capsule formulations	LPCN 1021-01 LPCN 1021-02 LPCN 1021-05 LPCN 1021-06 Andriol	LPCN 24 Andriol: 24	Post-menopausal women
LPCN 1021-09-001	Determine BA/PK of T after single, multiple dosing oral TU capsules. Assess dose proportionality. Evaluate the PK of two LPCN formulations.	Randomized, open-label, single and multiple dose pilot BA/PK study of two oral TU capsule formulations	LPCN 1021-07 LPCN 1021-08 Andriol	36	Hypogonadal males
S361.1.002	Determine the bioavailability and PK of TU, T, DHT, and DHTU after single dose administration under fasted, no-fat, low-fat, normal-fat, and high-fat conditions	Open-label, single dose, pilot food effect study	LPCN 1021-07 LPCN 1021-10	20	Post-menopausal women
LPCN 1021-14-001	Compare rate and extent of absorption of T, DHT, TU, and DHTU following administration of a single oral dose of LPCN as 2 x 112.5 mg capsules under various food and fat content conditions.	Open-label, randomized, four-period, four-treatment, crossover, single-dose BA/PK	LPCN 1021 Registration Lot	14	Hypogonadal males

Comparative Bioavailability Studies					
S361.1.001	Determine BA/PK of T, TU, E2, DHT, DHTU after 75 mg, 150 mg, 225 mg single doses of oral TU capsules	Open-label, single dose BA/ PK	LPCN 1021-07 LPCN 1021-10	24	Hypogonadal males
M13-298	Assess the relative BA of four LPCN formulations after a single dose and 14 days of BID dosing	Single and multiple dose relative BA	LPCN 1021-11 LPCN 1021-12 LPCN 1021-13 LPCN 1021-14 225 mg oral TU BID	32	Hypogonadal males
M12-868	Determine BA of TU capsules from two different lots after single-dose admin.	Open-label, crossover	LPCN 1021-07 75 mg oral TU	12	Post-menopausal women
Pharmacokinetic Study					
M12-778	Assess safety and tolerability of escalating multiple oral doses	Randomized double-blind, pbo-controlled dose escalating	LPCN 1021-07 75, 150, 225 300 mg BID Placebo	84	Hypogonadal males
Efficacy and Safety in Indication					
LPCN 1021-13-001	(1) Determine proportion of LPCN treated subjects who achieved T Cavg0-24h within normal range after ~13 weeks of study treatment. (2)Determine % LPCN treated subjects with Cmax:<1500 ng/dL; 1800-2500 ng/dL; and > 2500 ng/dL after ~ 13 weeks Assess CFB in safety parameters for LPCN and active control, groups. Evaluate CFB in the I-PSS, SF-36 QOL questionnaire, and PDQ for LPCN and control groups.	Multicenter, randomized, open-label, active-control, parallel-group,	LPCN 1021 To-be-Marketed Formulation 225 mg TU titrated to 150 mg or 300 mg oral TU BID, as needed Active Control: AndroGel 1.62%, topical	LPCN 1021: 210 Andro Gel 1.62%: 105	Hypogonadal males
Source: NDA 208088 (seq 000), Module 5.2, Table 5.2 p 1-3.					

5.2 Review Strategy

The primary focus of the clinical review was data derived from Study LPCN 1021-13-001. This Phase 3 study 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.

Supportive safety data was derived from Studies LPCN 1021-09-001, S361.1.001, M12-778, M13-298, and LPCN 1021-14-001, the five Phase 1 studies conducted in hypogonadal males.

5.3 Discussion of Individual Studies/Clinical Trials

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 received Tlando (oral testosterone undecanoate [TU]) or AndroGel 1.62% (testosterone topical gel, active control) for 52 weeks.

Inclusion Criteria
A subject was eligible for study participation if he met all of the following:

- Voluntarily signed and dated the study consent form(s) that had been approved by an Institutional Review Board. Written consent must have been obtained before the initiation of any study procedures.
- Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism before age 65.
- Documented diagnosis of primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired).
- Serum total testosterone < 300 ng/dL based on 2 consecutive blood samples obtained between 6 and 10 AM, on 2 separate days at approximately the same time of day (between 6 and 10 AM), after an appropriate washout of current androgen replacement therapy.
- Naive to androgen replacement or had discontinued current treatment and completed a washout of 12 weeks after intramuscular androgen injections; 4 weeks after topical or buccal androgens; 3 weeks after oral androgens, or, in the opinion of the investigator, the subject had an adequate washout window to be eligible. Washout must have been completed before collection of serum testosterone samples to determine study eligibility.
- Judged to be in good general health as determined by the principal investigator based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG) performed at screening.

Exclusion Criteria
In order to participate in the study, subjects should not have met any of the following criteria:

- History of significant sensitivity or allergy to androgens or product excipients.
- Clinically significant findings in the pre-study examinations including abnormal breast examination requiring follow-up, abnormal ECG.
- Abnormal prostate digital rectal examination (DRE) with palpable nodule(s) or I-PSS score > 19 points.
- Body mass index (BMI) ≥ 38 kg/m^2.

- Clinically significant abnormal laboratory value, in the opinion of the investigator, in serum chemistry, hematology, or urinalysis including but not limited to:
  a. Baseline hemoglobin < 11.5 g/dL or > 16.5 g/dL (the upper limit for the baseline hemoglobin was 16 g/dL for subjects enrolled before Protocol Amendment 3 [Version 4]).
  b. HCT < 35% or > 54%
  c. Serum transaminases > 2.5 times upper limit of normal
  d. Serum bilirubin > 2.0 mg/dL
  e. Creatinine > 2.0 mg/dL
  f. PSA > 2 ng/mL
  g. Prolactin > 17.7 ng/mL
- Positive test result for hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) antibodies.
- History of seizures or convulsions, including alcohol or drug withdrawal seizures. (History of febrile seizures was an exclusion criterion for subjects who were enrolled in the study before Protocol Amendment 3.)
- History of gastric surgery, cholecystectomy, vagotomy, bowel resection, or any surgical procedure that might have interfered with gastrointestinal motility, pH, or absorption.
- History of any clinically significant illness, infection, or surgical procedure within 1 month before study drug administration.
- History of stroke or myocardial infarction within the past 5 years.
- History of, or current or suspected, prostate or breast cancer.
- History of diagnosed, severe, untreated, obstructive sleep apnea.
- History of abuse of alcohol or any drug substance in the opinion of the investigator within the previous 2 years.
- History of long QT syndrome or unexplained sudden death in a first-degree relative (parent, sibling, or child).
- Concurrent treatment with medications that may have impacted the absorption, distribution, metabolism, or excretion of TU or placed the subject at risk for treatment with testosterone within 30 days before study drug administration and through the end of the study without PI and/or sponsor approval. Examples of prohibited concurrent medications include lipase inhibitors, saw palmetto, androgenic or androgenic-modifying supplements, anti-androgens, estrogens, oral cytochrome P450 3A4 inducers or inhibitors, and long-acting opioid analgesics.
- Dose changes of antihypertensive, lipid-lowering, or hypoglycemic agents during the past 3 months before study entry.
- Donation or loss of 550 mL or more blood volume (including plasmapheresis) or receipt of a transfusion of any blood product within 3 months before the start of treatment.

- Inadequate venous access for collection of serial blood samples required for PK profiles.
- Receipt of any investigational product within 1 month or within 5 half-lives before the start of treatment.
- Inability to understand and provide written informed consent for the study.
- Considered by the investigator or the sponsor-designated physician, for any reason, that the subject was an unsuitable candidate to receive Tlando.
- Subject had a partner of childbearing potential who was not willing to use adequate contraception for the duration of the study (acceptable methods of birth control included the following methods: abstinence, barrier methods, hormonal contraception, intrauterine devices, fallopian tube occlusion devices, and sterilization either of the male or female partner).
- Subject had a partner who was currently pregnant or planning pregnancy during the course of the clinical study.

Treatments

Tlando Treatment Arm

All subjects started at the same dose of 225 mg (2 capsules of 112.5 mg) taken BID approximately 12 hours apart (total daily dose of 450 mg) and approximately 30 minutes after morning and evening meals with water. Meal recommendations and dietary guidance were provided to subjects throughout the study.

Dose titration was based on an evaluation of the subject's serum total T concentrations obtained after approximately 3 and 7 weeks of treatment. For the Week 3 and Week 7 visits, subjects were confined to the clinic for approximately 26 hours to undergo intensive 24-hour PK profile blood sampling.

Dose adjustments were implemented approximately 1 week after the intensive PK sampling performed during the Week 3 and Week 7 visits (i.e., dose changes were made during the Week 4 and Week 8 visits). Subjects remained at the starting dose of 225 mg BID for approximately 21 days before the Week 3 titration blood draw. Subjects remained at the Week 4 dose for approximately 21 days before the Week 7 titration blood draw. Subjects remained at the Week 8 dose for a minimum of 21 days before an additional confinement period took place at approximately Week 13 for blood draws and efficacy analysis.

Dose titration was based on the maximum measured serum T concentration (Cmax) and the 24-hour average serum T concentration (Cavg0-24h) as follows:

- If Cavg0-24h < 300 ng/dL, dose was titrated upward by 75 mg/dose; or
- If Cavg0-24h > 1140 ng/dL, dose was titrated downward by 75 mg/dose; or
- If Cmax > 1500 ng/dL, dose was titrated downward by 75 mg/dose regardless of the Cavg0-24h; or

- If Cavg0-24h = 300 to 1140 ng/dL and Cmax ≤ 1500 ng/dL, dose was not changed.

Subjects whose serum T Cmax exceeded 1500 ng/dL when receiving the minimum dose (i.e., 150 mg Tlando) at Week 7 did not have their dose titrated downward, but were discontinued from the study at the Week 8 visit (time of second dose adjustment).

Additional clinic visits were conducted during the study at Week 26, Week 39, and Week 52 for safety and laboratory evaluations.

AndroGel 1.62% Treatment Arm
Subjects who were assigned to the AndroGel 1.62% treatment arm received treatment according to the approved package insert for the product. The starting dose of AndroGel 1.62% was 40.5 mg of testosterone (2 pump actuations) applied topically once daily in the morning to the shoulders and upper arms.

Dose titration was based on a single serum T concentration measured in a morning blood sample obtained before application of the gel on Day 14 and Day 28 in accordance with the approved package insert. Dose adjustments were made on the basis of the serum T concentration as follows:

- > 750 ng/dL: daily dose decreased by 1 pump actuation (equivalent of 20.25 mg)
- ≥ 350 and ≤ 750 ng/dL: no change
- < 350 ng/dL: daily dose increased by 1 pump actuation (equivalent of 20.25 mg)

The study dose could have been adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation) and a maximum of 81 mg of testosterone (4 pump actuations).

Efficacy Endpoints
Primary Endpoint
The primary endpoint was defined as the percentage of Tlando-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 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. between 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), and
- Psychosexual Daily Questionnaire (PDQ).

Safety Evaluation
Safety assessments were conducted throughout the study. Patients reported adverse events during weeks 1, 3, 4, 7, 8, 13, 26, 39, and 52 in the Tlando arm; and weeks 1, 2, 3, 4, 5, 7, 13, 26, 39, and 52 in the AndroGel 1.62% arm.

Other key safety endpoints included physical examination results, clinical laboratory test results, and changes in hematocrit (HCT), lipids (LDL and HDL), serum transaminases, and PSA. Safety assessments also included vital sign measurements and ECG results.

Other Studies

Safety Information from the following Phase 1 bioavailability and pharmacokinetic studies was reviewed:

- LPCN 1021-09-001 – Bioavailability and PK following single and multiple oral doses of two TU capsule formulations and Andriol; N = 36 (hypogonadal males).
- LPCN 1021-14-001 – Bioavailability and PK following single oral dose of Tlando as a function of food and fat content; N = 14 (hypogonadal males).
- S361.1.001 – Bioavailability and PK following single oral doses of two TU capsule formulations; N = 24 (hypogonadal males).
- M13-298 – Single and multiple dose relative bioavailability study of four TU capsule formulations; N = 32 (hypogonadal males).
- M12-778 – PK study following escalating multiple doses of one formulation of TU capsules; N = 84 (hypogonadal males).

6 Review of Efficacy

Efficacy Summary

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.

6.1 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.

6.1.1 Methods

The design of Study LPCN 1021-13-001 was discussed in Section 5.3.

6.1.2 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 with a BMI less than 38 kg/m^2. The mean age at baseline was 53.1 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 3 summarizes the demographic data and baseline characteristics of all randomly assigned subjects.

Table 3: Demographic and Baseline Characteristics (Randomized Subjects)

Parameter	Tlando 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	44 (21.0%)	22 (21.0%)	66 (21.0%)
Not Hispanic or Latino	166 (79.0%)	83 (79.0%)	249 (79.0%)
Age			
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)			
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)

Source: NDA 208088 (seq 000), Module 5.3.5.1, Table 14.1.2.1.

Reviewer Comment: In general, the demographic and baseline characteristics of subjects randomized in Study LPCN 1021-13-001 were similar within 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. Most of the medical history of hypogonadism was categorized in either endocrine/metabolic or genitourinary body systems.

Of the 315 subjects randomly assigned to treatment in the study, 47.3% had no history of previous treatment with androgens. Both the treatment groups had a similar percentage of patients without previous androgen treatment (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.

6.1.3 Subject Disposition

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; therefore, 104 subjects received treatment with AndroGel 1.62% and 210 subjects received treatment with Tlando. Overall, 130 subjects (61.9%) in the Tlando and 71 subjects (67.6%) of subjects 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 Table 4.

Table 4: Subject Disposition (All Enrolled Subjects)

Status	Tlando 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 Tlando 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)

[a] Any event, in the judgment of the investigator, where continuation of the subject in the study could have put the subject at health risk.
[b]Continued study participation put the subject at health risk, including significant changes in medical history or reported or observed adverse events, where continuation of the subject on the treatment could have put the subject at health risk.
Source: NDA 208088 (seq 000), Module 5.3.5.1, Table 14.1.1.

The most common reason for discontinuation in the category “other reasons” was that the subject had screened and/or been randomly assigned at a another study site before enrolling at the current site, which occurred in 4 subjects in the Tlando 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 Tlando 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 Tlando 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 Tlando 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) (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 Tlando 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 Tlando included peripheral edema and weight increased (Subject (b) (6) abdominal discomfort (Subject (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)

Thirteen subjects (6.2%) in the Tlando group and 12 subjects (11.4%) in the AndroGel 1.62% group withdrew from the study prematurely with a reason of "lost to follow-up." Eight of the 13 Tlando-treated subjects reported no AEs during the study and 2 subjects (Subject (b) (6) and Subject (b) (6) reported AEs that were considered by the investigator to be unrelated to study drug and had resolved at least 2 months before the early termination. Three Tlando-treated subjects had ongoing AEs at the time they were lost to follow-up; all of the AEs were considered by the investigator to be unrelated to study drug. Ongoing AEs at the time of Tlando discontinuation included peripheral neuropathy (mild) and iron deficiency anemia (moderate) in Subject (b) (6) headache (mild), muscle spasms (mild), and cough (mild) in Subject (b) (6) and eye inflammation (mild) in Subject (b) (6)

Five of the 12 AndroGel 1.62%-treated subjects who were lost to follow-up reported no AEs during the study and 3 subjects (Subject (b) (6) Subject (b) (6) and Subject (b) (6) reported AEs that were considered by the investigator to be unrelated to study drug and had resolved at least 4 months before the early termination. Four AndroGel 1.62%-treated subjects had ongoing AEs at the time they were lost to follow-up; 1 of these subjects had AEs that were considered by the investigator to be related to the study drug. Ongoing AEs at the time of AndroGel 1.62% discontinuation included application site reaction (mild, related), seborrhea (mild, related), hypertrichosis (mild, related), flushing (mild, related), and skin mass (mild, not related) in Subject (b) (6) hypertension (mild, not related) in Subject (b) (6) tachycardia (mild, not related) in Subject (b) (6) and irritability (mild, not related) and nocturia (mild, not related) in Subject (b) (6)

Adverse events leading to study drug discontinuation are reviewed in Section 7.3.3.

Twenty-nine subjects (13.8%) in the Tlando group and 9 subjects (8.6%) in the AndroGel 1.62% group withdrew their consent to continue participating in the study. When this reason was cited for withdrawal, the electronic Case Report Form used in the study did not capture more detailed information for the withdrawal. Therefore, at the end of the study, after the database had been locked, the applicant requested that study sites provide any additional information from source documents that might provide specific details about why these subjects had withdrawn their consent.

Based on the additional information obtained from the study sites after study completion, the applicant reclassified the reasons for discontinuation for some of the subjects in the study. The applicant also created discontinuation categories for the Phase 3 study that were more consistent with the Phase 1 studies included in the integrated analyses. Table 5 provides a summary of subject withdrawals based on the applicant's classification for discontinuation.

Table 5: Summary of Subject Discontinuation Based on Applicant's Reclassification

Status	Tlando 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)
Reason for Early Discontinuation[1]		
Consent Withdrawn	24 (11.4)	5 (4.8)
Confinement or Schedule Conflict	14 (6.7)	3 (2.9)
Reason other than Confinement or Schedule Conflict	10 (4.8)	2 (1.9)
Protocol Deviation	7 (3.3)	3 (2.9)
Lost to Follow Up	14 (6.7)	12 (11.4)
Cmax or Cavg not Achieved; Met the Stopping Criteria[2]	9 (4.3)	NA
Hematocrit >54%	3 (1.4)	1 (1.0)
Prostate Specific Antigen >4 ng/mL	1 (0.5)	1 (1.0)
Weight Gain	3 (1.4)	0
Adverse Event	7 (3.3)	5 (4.8)
Serious Adverse Event	3 (1.4)	0
Other, Lack of Efficacy	5 (2.4)	4 (3.8)
Other, Duplicate Subject[3]	4 (1.9)	3 (2.9)

Key: Cavg = average serum concentration; Cmax = maximum observed serum concentration
[1]Specific reasons for discontinuation were reclassified by the applicant.
[2]Cmax > 1500 ng/dL when lowered to Tlando 150 BID or Cavg < 300 ng/dL at Week 7 while on highest Tlando dose.
[3]Subjects who enrolled at more than one site. In cases where this occurred, subjects were withdrawn at both study sites.
Source: NDA 208088 (seq 000), Module 2.7.3, Table 3

The applicant believes that the higher rate of dropouts in the Tlando arm of the study was likely due to the design of the study rather than study drug-related issues. Before Week 13, the Tlando 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 Tlando 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. In addition, 4.3% of Tlando

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.

To further evaluate the reason for the higher rate of dropouts in the Tlando arm of the study, the applicant also submitted discontinuation data based on whether the discontinuation occurred before or after the week 13 visit. Table 6 summarizes discontinuations before and after the week 13 visit.

Table 6: Summary of Subject Discontinuation Before and After Completing Week 13 Visit Based on Applicant Classification

Status	Entire Study			
	Tlando 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	
	Tlando n (%)	AndroGel 1.62% n (%)	Tlando 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 Confinement or Schedule Conflict	4 (1.9)	1 (1.0)	6 (2.9)	1 (1.0)
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.

Reviewer comment: The overall dropout rate during the entire study was similar for the Tlando and AndroGel 1.62% arms. However, during the initial 13 weeks of the study, when subjects in the Tlando, but not 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 discontinuation categories with the greatest difference between Tlando and AndroGel 1.62% subjects were confinement/schedule conflict, met the stopping criteria for the study, lost to follow up, and adverse events. The percentage of subjects discontinuing for reasons other than those four was, in general, similar for both treatment arms. During the remainder of the study, the discontinuation rate for the AndroGel 1.62% arm was greater than for the Tlando arm.

The applicant's explanation that the imbalance in discontinuation between the Tlando and AndroGel 1.62% arm during the first 13 weeks of the study was likely due to the design of the study rather than study drug related issues is partially supported by this analysis. However, the imbalance in adverse events occurring during the initial 13 weeks of the study (but not in the remainder of the study) may also be a factor.

6.1.4 Analysis of Primary Endpoint

Datasets Analyzed
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 Tlando, 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.

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. The Safety Set constitutes the population for all analyses of safety endpoints.

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.

Table 7 summarizes the number of subjects included in each of the datasets that were analyzed.

Table 7: Datasets Analyzed in Study LPCN 1021-2013-001–Subjects Randomized to Tlando (N = 210)

Dataset	Tlando 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 Tlando group.
Source: NDA 208088 (seq 0000), 2.7.3, Table 4, p.21.

Results

The efficacy analysis of Tlando 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 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 the efficacy endpoint of the study to be met, the minimum acceptable percentage was 75%. A 95%, 2-sided, binomial confidence interval surrounding the point estimate was required to have a lower bound of 65% or more to conclude that the Tlando treatment was efficacious. The primary analysis dataset was the EPS.

The results for the analysis of the primary endpoint for the EPS and FAS populations are summarized in Table 8.

Table 8: Proportion of Tlando-Treated Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range at Week 13 – EPS and FAS

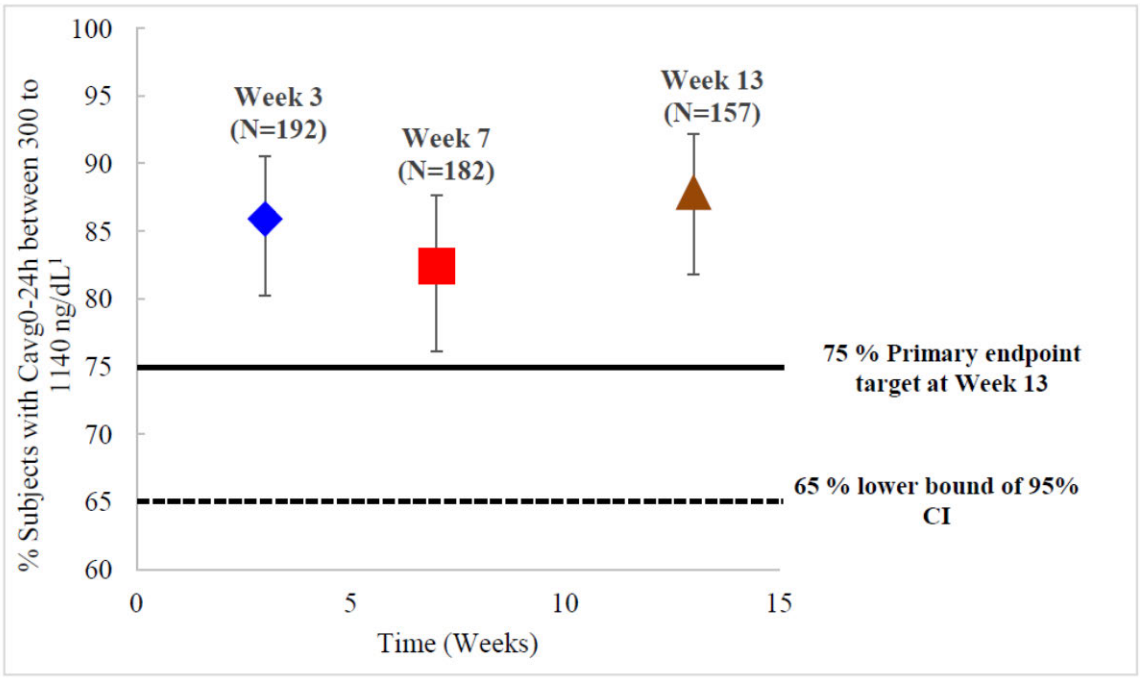
Parameter	Target	EPS N=151	FAS N=193
Percentage (No.) subjects achieving 24-hour average serum T concentration within normal range[1]	≥ 75%	87.4% (132/151)	87.0% (168/193)
95% Confidence interval	≥ 65% (Lower Bound)	81.70%, 92.73%	81.97%, 91.82%

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.

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.

Reviewer comment: For the primary endpoint, the results of Study LPCN 1021-13-001 met the criteria for efficacy. This was the case for 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.

6.1.5 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.

Tlando 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).

The target for the proportion of subjects with T Cmax <1500 ng/dL (≥ 85%) was met when T Cmax0-12h and T Cmax12-24h values were used. However, the proportion was below the target (83% vs ≥ 85%) for T Cmax0-24h values. The proportion of subjects with T Cmax between 1800 and 2500 ng/dL met the target (≤ 5%) for T Cmax0-12h, T Cmax12-24h, and T Cmax0-24h. Three subjects had T Cmax > 2500 ng/dL. Table 9 summarizes the Cmax responder analysis for subjects who were within the predetermined targets for the three T Cmax values (Cmax0-12h, Cmax12-24h, and Cmax0-24h of serum T).

Table 9: Proportion of Tlando-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.				

The target for one of the secondary endpoints was that no subject should have a Cmax > 2500 ng/dL. 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 10 and discussed in detail below.

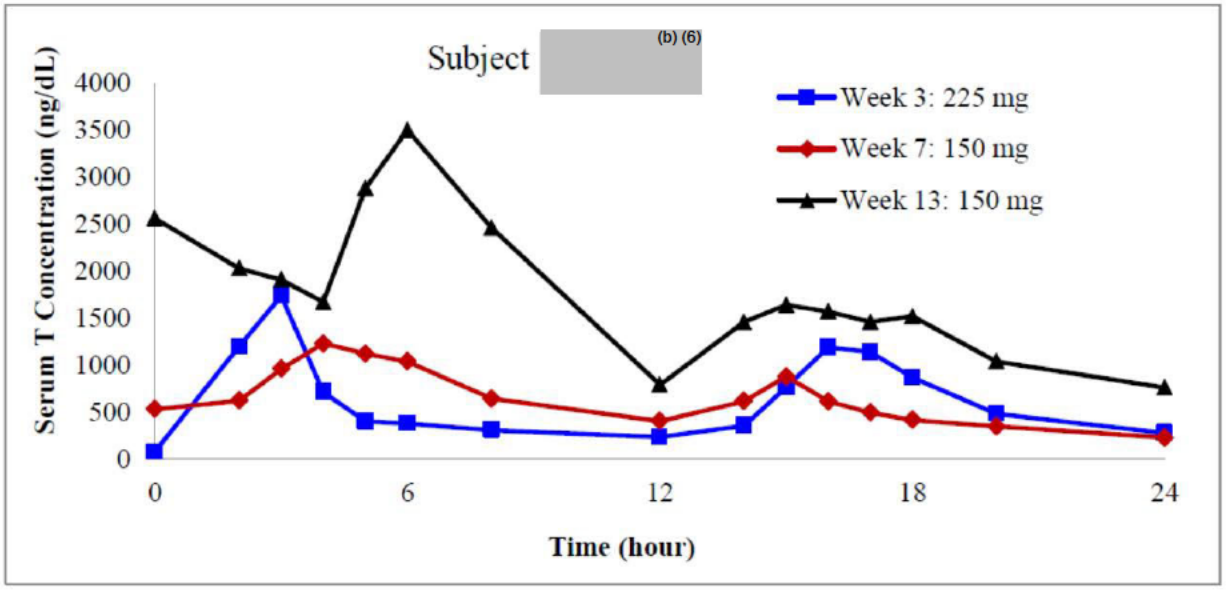
Table 10: Subjects with Cmax > 2500 ng/dL – EPS (N = 151)

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
(b) (6)	67	Black or African American/ Not Hispanic or Latino	28.9	300 mg	3390	2.0	Week 13
(b) (6)	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.

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.

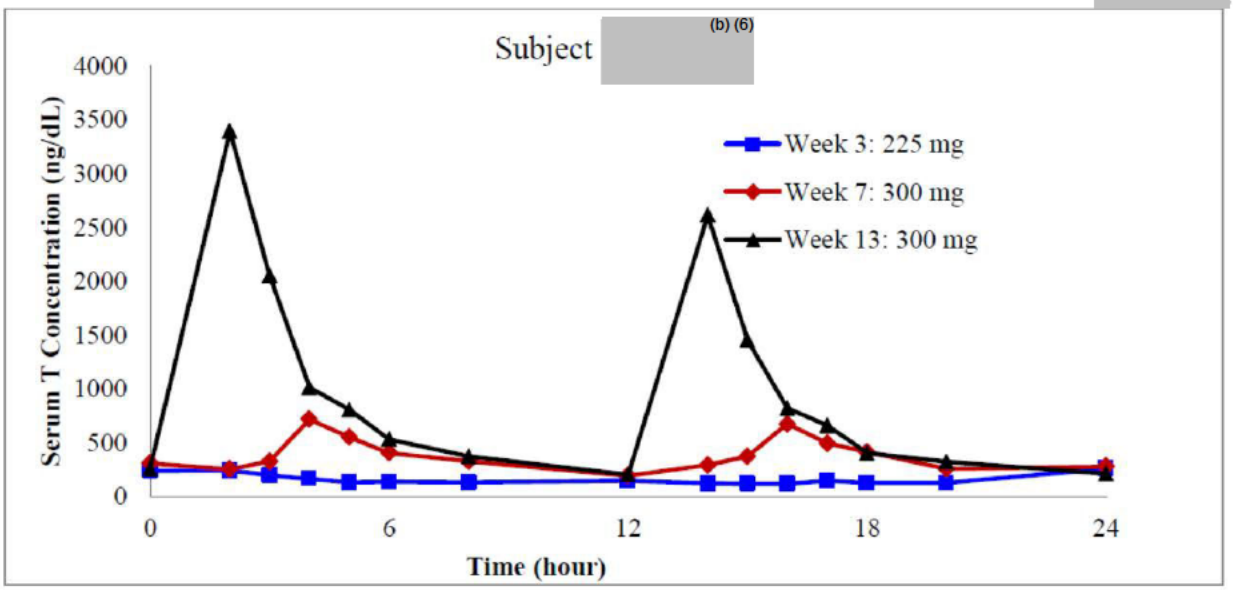
- The pre-dose value at Week 13 was unusually high at 2560 ng/dL.
- Unusual serum testosterone levels at Week 13 compared to Week 3 and Week 7.
- Serum testosterone levels declined following the pre-dose measurement for Week 13 and then increased after 4 hours, which was not a typical observation of 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.

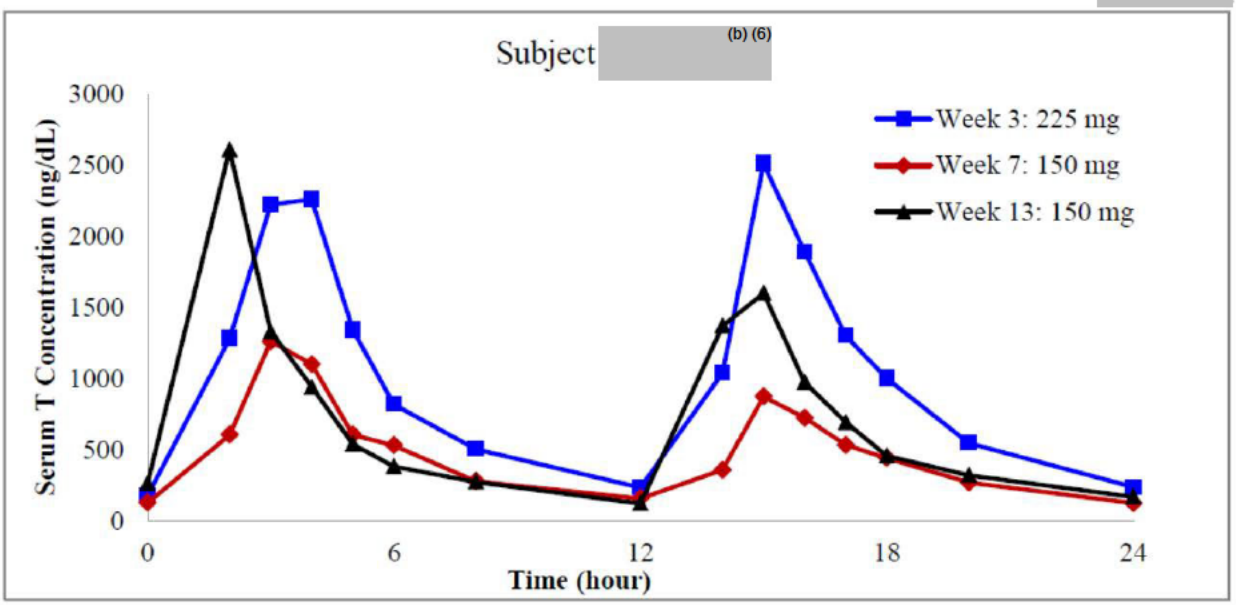
- Based on the Week 3 Cavg of 157 ng/dL, the subject was up titrated to 300 mg BID.
- At the 300 mg BID TU dose at Week 7, which was the same dose as Week 13, Cmax value was 715 ng/dL (low).
- At Week 13, testosterone concentration peaked 2 hours following both the morning and evening doses with testosterone 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 year 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.

- 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.

Reviewer 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 T concentration > 2500 ng/dL at time point 0 (before the am dose of the drug). The T value declined following the pre-dose measurement and then started to increase after four hours, reaching Cmax of 3500 ng/dL six hours post-dose. 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 at Week 13.*

An assessment of Cmax > 2500 ng/dL excursions was also done using the Full Analysis Set: five additional subjects were found who met that criterion. Information for these subjects is summarized in Table 11 and discussed in detail below.

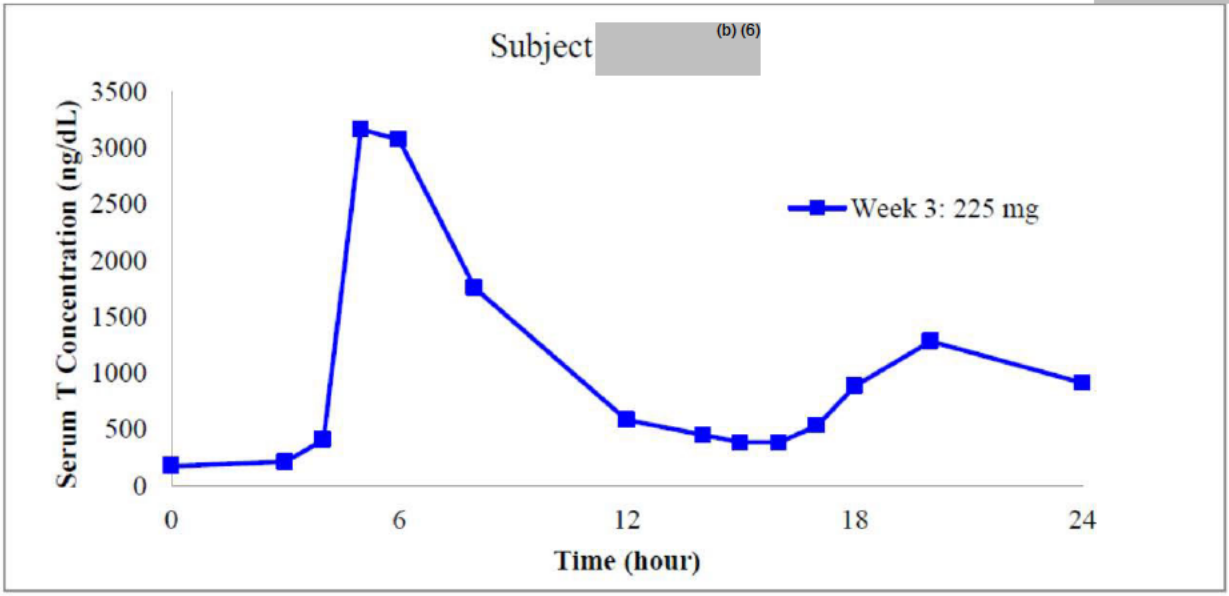
Table 11: Additional Subjects with Cmax > 2500 ng/dL (based on last observed PK profile) - FAS (N = 193)

Subject Number	Age (years)	Race / Ethnicity	BMI (kg/m2)	Dose at Cmax > 2500 ng/dL	Cmax (ng/dL)	Tmax (hr)	PK day
(b) (6)	55	White/ Not Hispanic or Latino	35.7	225 mg	3160	4.9	Week 3
	49	Other/ Not Hispanic or Latino	32.3	300 mg	2700	0	Week 13
	55	Black or African American/ Not Hispanic or Latino	31.6	150 mg	3050	14.1	Week 7
	59	White/ Hispanic or Latino	29.9	225 mg	3390	3.0	Week 13
	63	White/ Not Hispanic or Latino	30.9	225 mg	2590	3.0	Week 13

Source: NDA 208088 (seq 0000), 2.7.3, Table 12, p. 31.

Subject (b) (6) The subject is a 55 year-old male. A Cmax of 3160 ng/dL was seen at Week 3 when the subject was on the 225 mg BID TU dose.

Figure 5: Total Serum Testosterone Concentration-Time Profile, Subject (b) (6)



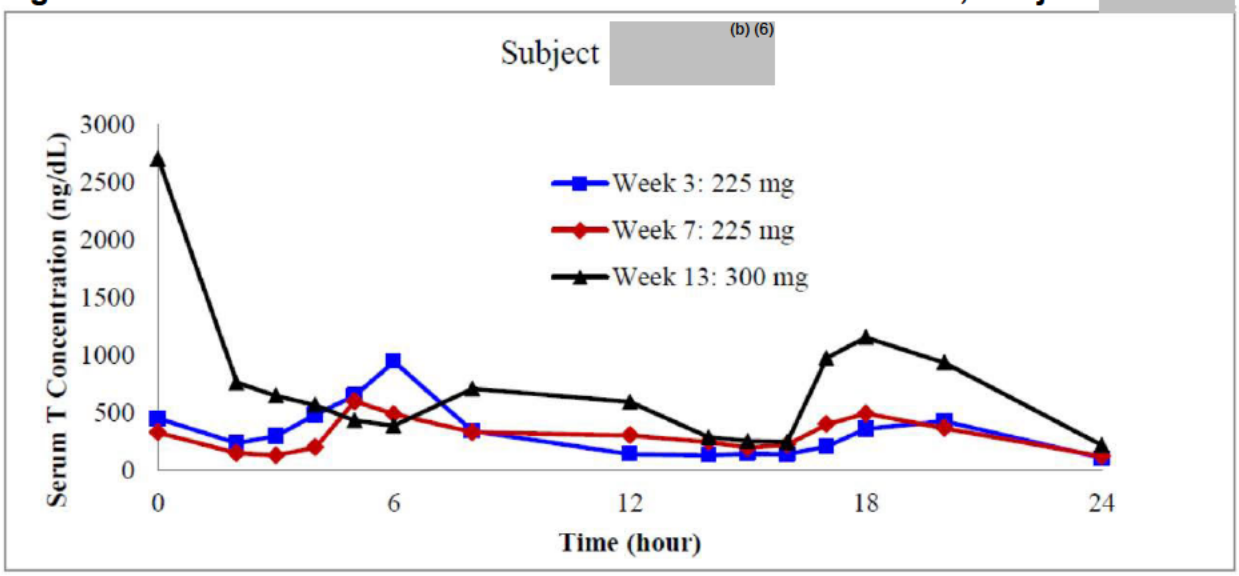
Source: NDA 208088 (seq 0000), 2.7.3, Figure 7, p. 37.

- At Week 3 the testosterone concentrations were 3160 and 3070 ng/dL at 5 and 6 hours, respectively; the testosterone concentration did not exceed 2500 ng/dL at any other time points suggesting transient occurrence.
- The PK data indicate that the dose was to be reduced to 150 mg BID at the Week 4 visit. However, the subject did not return to the clinic for the Week 7 visit, and after repeated attempts to contact the subject, the subject was lost to follow up and withdrawn from the study
- No adverse events were reported for this subject.
- The evening PK profile of the subject shows normal levels of serum testosterone.

Applicant's assessment: Based on the Week 3 testosterone levels, this subject appears to have needed a downward titration, but there was no opportunity to assess testosterone levels after the subject was down titrated to 150 mg BID dose. The observed excursion with this subject does not appear to have any significant clinical relevance with no AE reports.

Subject (b) (6) The subject is a 49 year-old male. A Cmax value of 2700 ng/dL was observed at Week 13 when the subject was on the 300 mg BID TU dose.

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



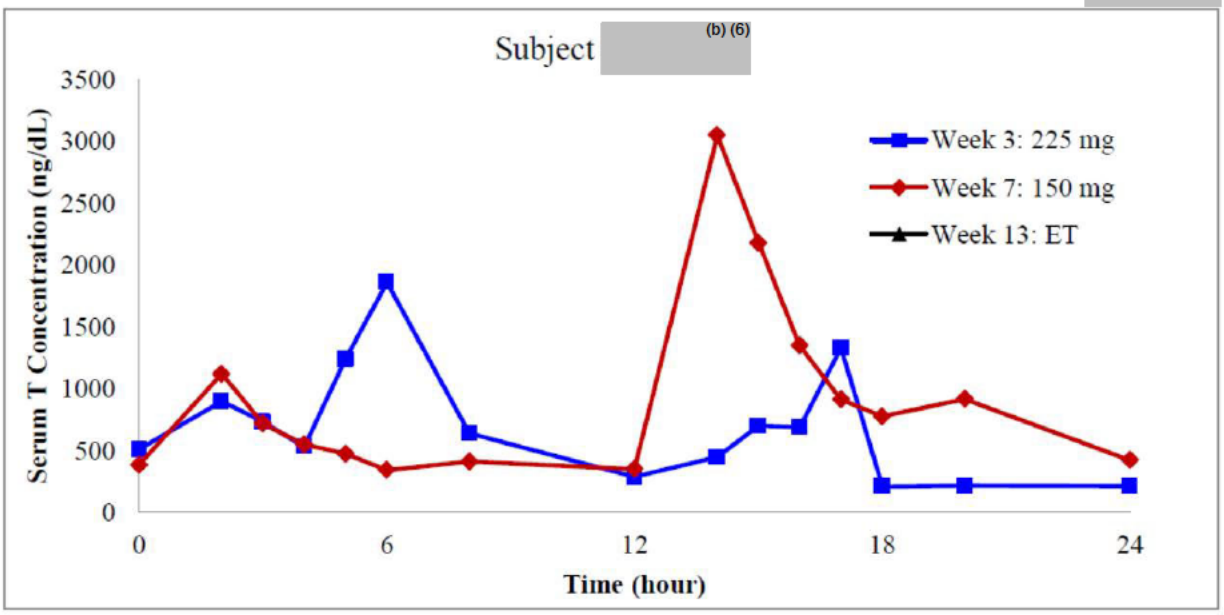
Source: NDA 208088 (seq 0000), 2.7.3, Figure 4, p. 34.

- Cmax occurred at the pre-dose time point and was unusually high; subsequent testosterone concentrations showed a rapid decline, which is not a typical observation with Tlando T level profiles.
- Testosterone concentrations did not exceed 2500 ng/dL at any other measured time point.
- Testosterone concentrations at all other time periods (Week 3, 7 or other times during Week 13) were within the expected normal range suggesting this to be outlier event.
- The subject reported strep B-Lesion Corona penis and elevated triglycerides adverse events; both adverse events were considered by the investigator to be non-drug related and moderate in severity.

Applicant's assessment: It appears that the high Cmax value in this subject is an outlier with no clinical relevance. Because of the high Cmax occurring pre-dose, the subject may have taken an unscheduled testosterone dose before his clinic visit, although this was not confirmed by the subject or the investigator. Based on the data available, 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 55 year-old male. A Cmax value of 3050 ng/dL was seen when the subject was on the 150 mg BID TU dose.

Figure 7: Total Serum Testosterone Concentration-Time Profile, Subject (b) (6)



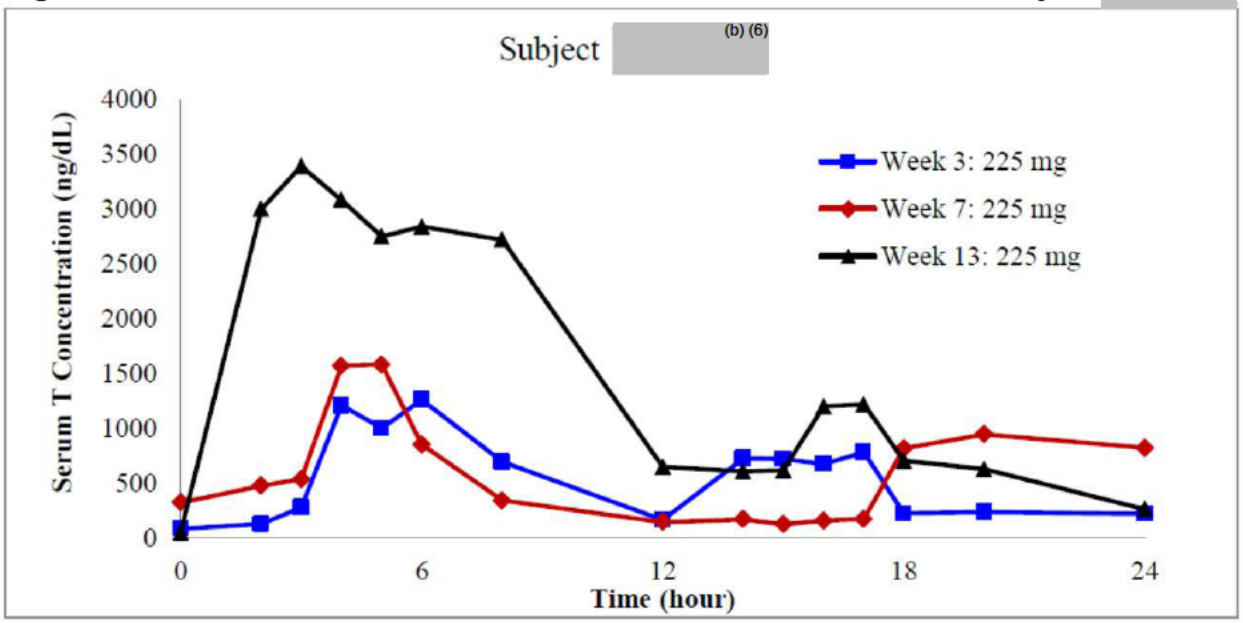
Source: NDA 208088 (seq 0000), 2.7.3, Figure 10, p. 40.

- At Week 3, the Cmax was 1860 ng/dL while the subject was on the 225 mg BID dose and the dose was reduced to 150 mg BID at Week 4.
- At Week 7, the Cmax was 3050 ng/dL occurring at 14 hours post dose (Cmax0-12h was 1120 ng/dL).
- The testosterone concentration did not exceed 2500 ng/dL at any other time point (prior time points at same week or prior week at higher 225 mg BID dose).
- As a result of the Cmax exceeding 1500 ng/dL despite the Tlando dose being lowered to 150 mg BID, the subject was withdrawn from the study at the Week 8 visit in accordance with protocol-specified stopping criteria of T Cmax > 1500 ng/dL when at 150 mg dose.
- No adverse events were reported for this subject.

Applicant's assessment: The subject showed an increased Cmax level upon reducing the dose and the profile levels were not consistent with other times or periods. This subject's Cmax at Week 7 was not observed at Week 3 even at a higher 225 mg dose, suggesting the excursion to be an isolated/sporadic event with a transient increase in Cmax as an outlier observation possibly due to errors in dosing, with no meaningful clinical significance.

Subject (b) (6) The subject is a 59 year-old male. A Cmax value of 3390 ng/dL occurred at Week 13 when at the 225 mg BID TU dose.

Figure 8: Total Serum Testosterone Concentration-Time Profile, Subject (b) (6)



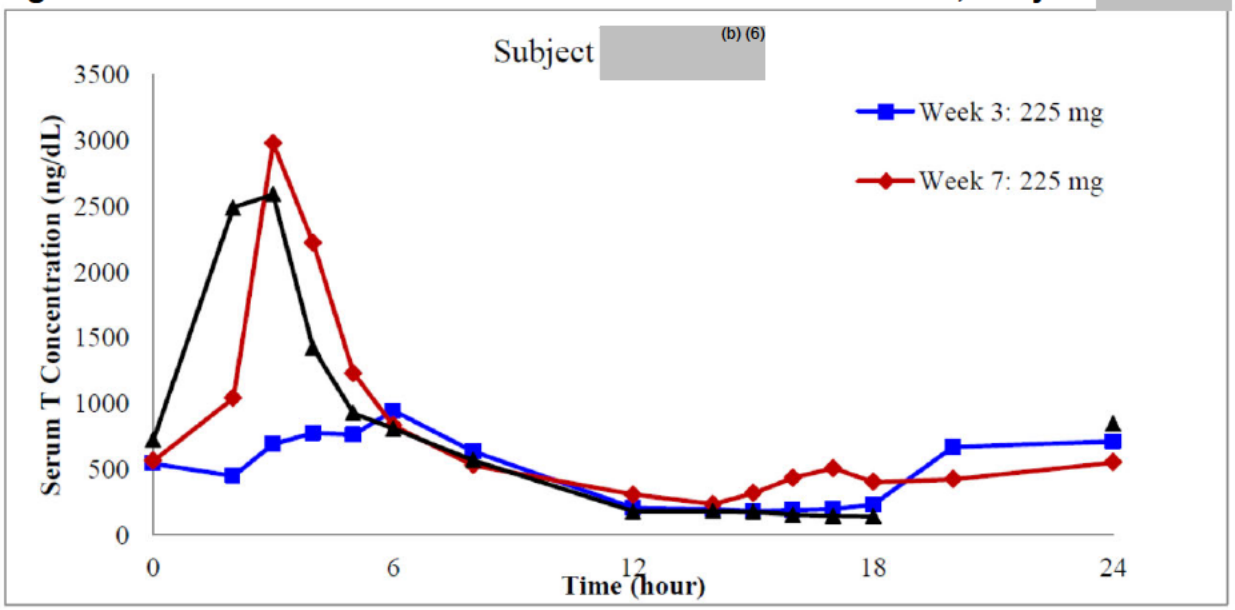
Source: NDA 208088 (seq 0000), 2.7.3, Figure 5, p. 35.

- At Week 3, the Cmax was 1260 ng/dL. Although the dose should have remained at 225 mg BID based on protocol-specified dosing guidelines, a dosing-related protocol deviation occurred in which the dose was mistakenly increased to 300 mg BID at the Week 4 visit and then changed back to 225 mg BID 13 days later
- At Week 7, Cmax was 1580 ng/dL and the dose should have been reduced to 150 mg BID at Week 8 based on protocol-specified dosing criteria. However, a protocol deviation occurred in which the dose was not reduced at the Week 8 visit and the subject continued to receive 225 mg BID.
- At Week 13, Cmax was 3390 ng/dL and serum testosterone concentrations exceeded 2500 ng/dL from 2 through 8 hours post dose.
- Of note, Cmax values were higher following the morning dose (i.e., Cmax0-12h: 3390 ng/dL) than following the evening dose (i.e., Cmax12-24h: 1220 ng/dL) thus demonstrating that the high testosterone values observed in the morning were not repeated in the evening.
- No adverse events were reported for this subject.

Applicant's assessment: This subject appears to be a candidate for down titration; however, the subject failed to down titrate due to a site error. It appears that this Cmax excursion was an outlier event possibly related to failure to down titrate with no meaningful clinical relevance.

Subject (b) (6) The subject is a 63 year-old male. Cmax value of 2590 ng/dL was seen at Week 13 when the subject was at 225 mg BID TU dose.

Figure 9: Total Serum Testosterone Concentration-Time Profile, Subject (b) (6)



Source: NDA 208088 (seq 0000), 2.7.3, Figure 6, p. 36.

- The subject started Tlando at a dose of 225 mg BID. At Week 3 Cmax was 944 ng/dL and the dose remained at 225 mg BID.
- At Week 7, Cmax was 2980 ng/dL and the Tlando dose should have been reduced to 150 mg BID. However, a protocol deviation occurred in which the dose was not reduced due to clinic oversight.
- At Week 13, Cmax was 2590 ng/dL at the 3 hour time point, but was transient as testosterone levels did not exceed 2500 ng/dL at any other time point.
- The subject continued to receive Tlando at a dose of 225 mg BID throughout the study. The subject was a candidate for down titration but failed to down titrate due to a site error.
- No adverse events were reported and the subject completed the 52 week study.
- Testosterone concentrations were measured 3 to 6 hours post dose at Week 26, 39, and 52 were 245, 465, and 282 ng/dL, respectively and are well below the high levels seen at Week 13.

Applicant's assessment: Overall, it appears that this Cmax excursion in this subject was transient and sporadic suggesting an outlier event contributed by the site failing to down titrate the subject at Week 8 with no meaningful clinical relevance.

Reviewer comment: There were five additional subjects in the FAS (but not the EPS) with T Cmax excursions > 2500: three had titration errors, one had an unusually high pre-dose T concentration, and one had no apparent reason for the excursion.

Subjects [redacted] *were not titrated or titrated incorrectly prior to the Cmax excursion.*

Subject [redacted] *had Cmax > 2500 ng/dL during the Week 3 PK assessment. Based on that assessment, the subject's dose was to be reduced from 225 mg BID to 150 mg BID. However, the subject did not return to the clinic for the Week 7 visit, and was lost to follow. The applicant notes that this subject appears to have needed a downward titration, but there was no opportunity to assess testosterone levels after the subject was down titrated to the 150 mg BID dose. I believe that this subject had a Cmax excursion > 2500 ng/dL and that it is possible that this excursion was due to lack of titration. Whether titration would have been successful in preventing additional Cmax excursions > 2500 ng/dL is unknown due to missing data.*

Subject [redacted] *had a Cmax excursion > 2500 ng/dL during the Week 13 PK assessment. The subject was incorrectly titrated twice prior to Week 13: at Week 4 his dose was mistakenly increased to 300 mg BID for 13 days and at Week 8 his dose was to be reduced to 150 mg BID, but was continued at 225 mg BID. The applicant attributes the Cmax excursion to failure to down titrate. I believe it is possible that the Cmax excursion resulted from the lack of titration.*

Subject [redacted] *had Cmax excursions > 2500 ng/dL during the Week 7 and Week 13 PK assessments. At Week 7, Cmax was 2980 ng/dL and the dose should have been reduced to 150 mg BID, but was not reduced due to clinic oversight. The applicant attributes the Week 13 Cmax excursion to the failure of the clinic to down titrate. I believe it is possible that the Week 13 Cmax excursion may have resulted from lack of titration. Regarding the Week 7 excursion, which is not included in the assessment of the secondary endpoint, this excursion appears to have occurred for no apparent reason.*

Subject [redacted] *had a pre-dose T value that was unusually high. The pre-dose (time point 0) T value was > 2500 ng/dL, and declined to the normal range at the 2 hour time point. The applicant attributes this subject's Cmax excursion to an unscheduled testosterone dose before his clinic visit. I believe that unscheduled dosing could result in the PK plot seen for this subject and is a reasonable explanation for the Cmax excursion.*

Subject [redacted] *had a Cmax excursion for which there was no apparent reason. The Cmax excursion occurred during the Week 7 PK assessment after the subject was down titrated to the 150 mg BID dose at Week 4. The subject met the stopping criteria of the study (Cmax > 1500 at the 150 mg BID dose) and was withdrawn from the study. There was no apparent reason for the Cmax excursion.*

Reviewer summary comments regarding Cmax excursions >2500 ng/dL: There were eight subjects with Cmax excursion > 2500 ng/dL in the FAS of the study, three of these subjects were also included in the EPS. For five of the subjects, there were possible

explanations for the excursions that I believe are reasonable: two subjects ([(b) (6)] and [(b) (6)] had unusually high pre-dose T values that may have been caused by unscheduled dosing; three subjects [(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)] 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 2 hours after dosing, 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 my opinion, there is a risk that some patients treated with Tlando will have sporadic Cmax excursions > 2500 ng/dL. During these excursions, the duration of time in which T levels are elevated is expected to be in the range of 1-2 hours. No factors were identified that would predict which patients might be at risk for these excursions.

6.1.6 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).

The I-PSS is a questionnaire used to assess the severity and impact of urinary symptoms. The I-PSS symptom scores could range from 0 to 35 with higher scores representing more severe and greater impact of urinary symptoms. In the study, it was used to exclude men with moderate to severe symptoms of benign prostate hypertrophy. Subjects completed the I-PSS at screening and at the end of the study. The screening I-PSS score must have been ≤ 19 to meet eligibility requirements. I-PSS total symptom scores increased slightly from baseline to end-of-study in both the Tlando and AndroGel 1.62% treatment groups (mean change: 1.0 vs 2.3, respectively). Mean I-PSS Quality of Life scores were essentially unchanged from baseline to end-of-study for both groups.

The SF-36 is a multipurpose, short-form health survey comprising 36 questions that yields an 8-scale profile of functional health and well-being scores as well as psychometrically based physical and mental health summary measures and a preference-based health utility index. Subjects completed the SF-36 at screening and at the end of the study. Scores for each subscale could range from 0 to 100 with higher

scores representing a more favorable health state. Mean scores at the end of the study (or early termination) for most of the subscales were within 1 to 2 points of the baseline mean scores for both Tlando and AndroGel 1.62% treatments. However, mean change from baseline to end of study for the Vitality subscale was numerically higher for Tlando than AndroGel 1.62% (6.89 vs 3.82) as was the Mental Health subscale score (2.91 vs -0.10).

The PDQ is a self-reporting instrument designed to assess sexual function and mood on a daily basis for seven days. The PDQ comprises three different domains representing 1) sexual desire, enjoyment, and performance; 2) sexual activity; and 3) mood. Subjects completed the PDQ during the screening period and at the end of the study over a 7-day period. Improvements were noted for the Tlando and AndroGel 1.62% groups with increases in mean change from baseline for weekly sexual activity (1.72 vs 1.71, respectively), maintained satisfactory erection (1.59 vs 1.09), overall sexual desire (1.38 vs 1.35) and percent full erection (19.62 vs 12.93).

Reviewer comment: Interpretation of the results from the patient reported instruments is not clear due to the lack of a placebo control.

6.1.7 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).

Body Mass Index

Study entry criteria in the Phase 3 study allowed men who had a BMI less than 38 kg/m^2 to enroll in the study. Of the 151 subjects in the EPS, 87 (57.6%) had a BMI ≥30 kg/m^2, which meets the criteria for obesity. For the EPS, 92.2% of non-obese subjects and 83.9% of obese subjects achieved T Cavg0-24 between 300 to 1140 ng/dL with corresponding lower bound 95% confidence intervals of 82.70% and 75.54%, respectively. The results of this analysis are summarized in Table 12.

Table 12: Proportion of Tlando Treated Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range at Week 13 in Non-Obese (BMI < 30 kg/m2) and Obese Subjects (BMI ≥ 30 kg/m2) – Efficacy Population Set (N = 151)

Parameter	BMI < 30 kg/m^2 (N=64)	BMI ≥ 30 kg/m^2 (N=87)
Percentage (No.) subjects achieving 24-hour average serum T concentration within normal range	92.2% (59/64)	83.9% (73/87)
95% Confidence interval	82.70%, 97.41%	75.54%, 91.70%
Source: NDA 208088 (seq 0000), 2.7.3, Table 29, p. 63.		

An analysis of average and maximum serum testosterone concentrations by BMI was also performed using the PK set. The mean T Cavg0-24h was 448.73 ng/dL for the 54 non-obese subjects compared to 444.77 ng/dL for the 76 obese subjects; the mean T Cmax0-24h was 1159.94 for non-obese subjects compared to 1115.68 ng/dL for obese subjects. The results are summarized in Table 13.

Table 13: Average Serum Testosterone Concentration and Maximum Serum Testosterone Concentration at Week 13 in Non-Obese (BMI < 30 kg/m2) and Obese Subjects (BMI ≥ 30 kg/m2) – Pharmacokinetic Set (N = 130)

Parameter	Statistic	All BMI (N=130)	BMI < 30 kg/m^2 (N=54)	BMI ≥ 30 kg/m^2 (N=76)
Cavg0-24h, ng/dL	Mean (SD)	446.41 (171.46)	448.73 (147.32)	444.77 (187.68)
Cmax0-24h, ng/dL	Mean (SD)	1134.07 (526.18)	1159.94 (532.23)	1115.68 (524.61)
Source: NDA 208088 (seq 0000), 2.7.3, Table 30, p. 64.				

Reviewer comment: Based on the subgroup analysis of obese (BMI ≥ 30 kg/m$^{2)}$ and non-obese (BMI < 30 kg/m$^{2)}$ subjects, the drug is expected to be effective in both obese and non-obese patients.

Prior Androgen Therapy

The Phase 3 study enrolled subjects who were on a prior androgen therapy (non-naive) and subjects who never received prior androgen therapy (naive). Non-naive subjects completed an appropriate washout of their current androgen replacement therapy before being randomized to the study drug. Of the 151 subjects in EPS, 70 subjects were naive to androgen therapy while 81 were non-naive. For the EPS, 94.29% of naive subjects and 81.48% of non-naive subjects achieved T Cavg0-24 between 300 to 1140 ng/dL with corresponding lower bound 95% confidence intervals of 87.86% and 71.89%, respectively. The results of this analysis are summarized in Table 14.

Table 14: Proportion of Tlando-Treated Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range at Week 13 in Androgen Naive and Non-Naive Subjects – Efficacy Population Set (N = 151)

Parameter	Efficacy Population Set	
	Naive (N=70)	Non-Naive (N=81)
Percentage (No.) subjects achieving 24-hour average serum T concentration within normal range	94.3% (66/70)	81.5% (66/81)
95% Confidence interval	86.01 %, 98.42%	72.38%, 90.09%
Source: NDA 208088 (seq 0000), 2.7 3, Table 31, p. 65.		

An analysis of average and maximum serum testosterone concentrations by prior androgen therapy was also performed using the PK set. The mean T Cavg0-24h was 444 ng/dL for the 62 naive subjects compared to 449 ng/dL for the 68 non-naive subjects; the mean Cmax0-24h was 1075 ng/dL for naïve subject compared to 1188 ng/dL for the non-naïve subjects. The results are summarized in Table 15.

Table 15: Average Serum Testosterone Concentration and Maximum Serum Testosterone Concentration at Week 13 in Androgen Naïve and Non-Naïve Subjects – Pharmacokinetic Set (N = 130)

Parameter	Statistic	All Subjects N=130	Naïve N=62	Non-Naïve N=68
T Cavg0-24h, ng/dL	Mean (SD)	446.41 (171.46)	443.73 (118.12)	448.86 (209.49)
T Cmax0-24h, ng/dL	Mean (SD)	1134.07 (526.18)	1074.73 (450.19)	1188.18 (585.08)
Source: NDA 208088 (seq 0000), 2.7.3, Table 32, p. 65.				

Reviewer comment: Based on the subgroup analysis of naive and non-naive subjects, the drug is expected to be effective in both naive and non-naive patients.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

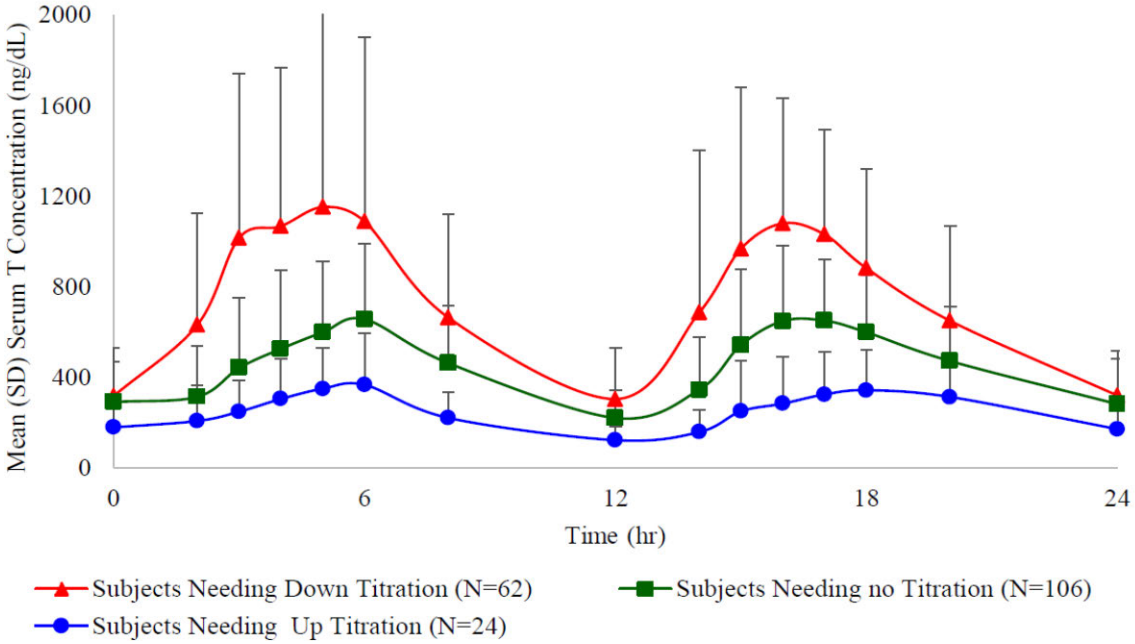
Dose Titration During the Phase 3 Study

During the Phase 3 study, three dose levels of Tlando (150 mg, 225 mg and 300 mg TU) were administered twice daily to randomized subjects. All subjects started Tlando 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 were receiving the 225 mg BID starting dose and 41% (65/157) of the subjects had required no titration; 89% (140/157) of the subjects had required no more than one titration and about 10% of the subjects had 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.

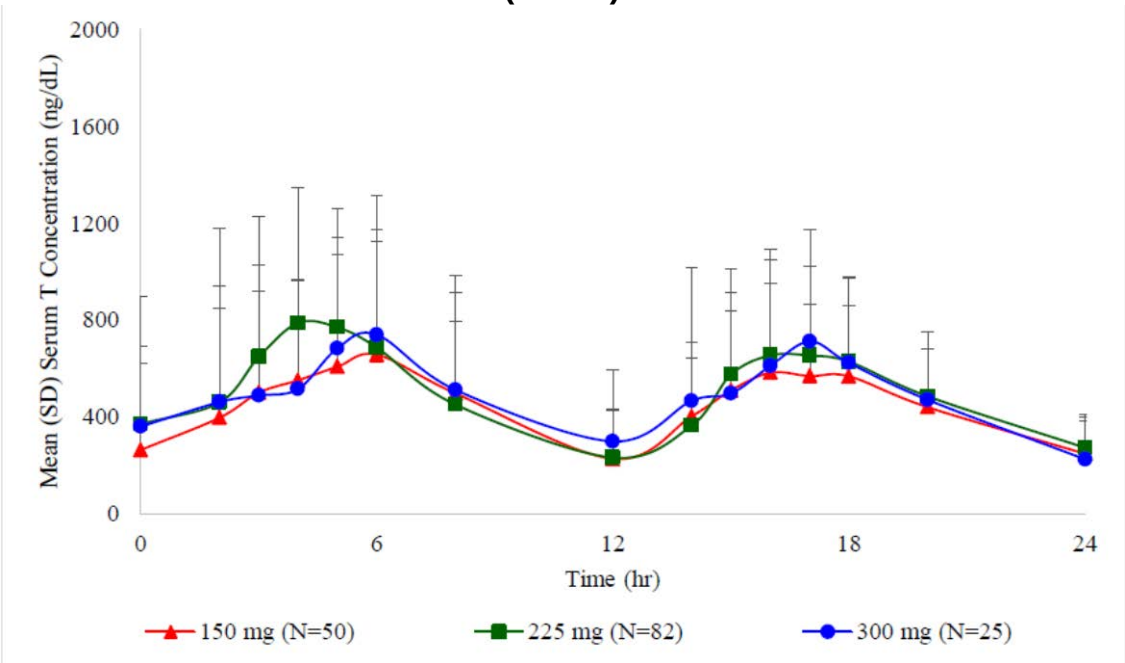
Figure 10 shows the mean serum testosterone concentration-time profile of subjects at Week 3 stratified by titration requirement at Week 4. Figure 11 shows the mean serum testosterone concentration-time profile of subjects at Week 13 stratified by final dose at Week 13.

Figure 10: 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)



Source: NDA 208088 (seq 0000), 2.7.3, Figure 20, p. 68.

Figure 11: 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)



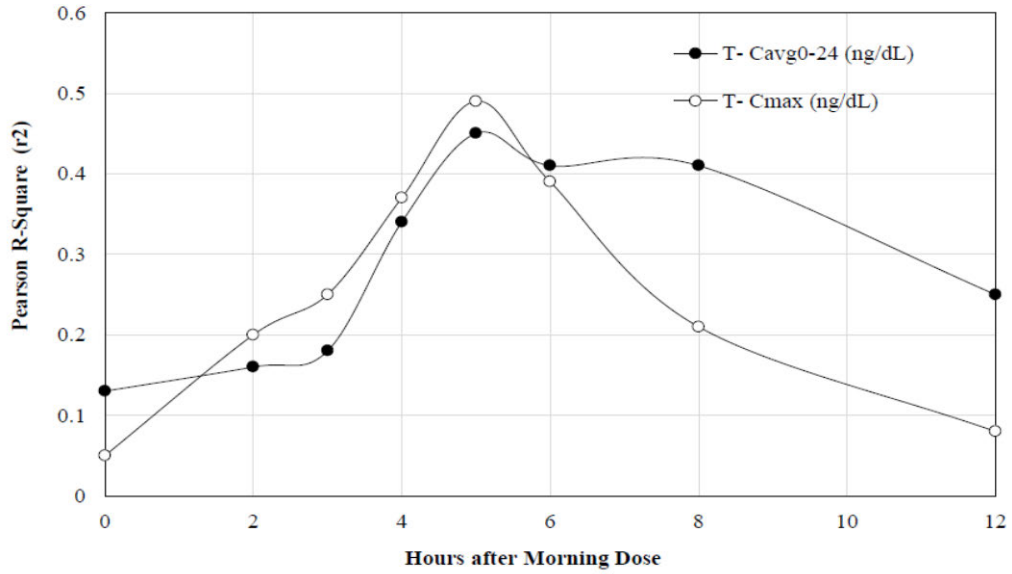
Source: NDA 208088 (seq 0000), 2.7.3, Figure 21, p. 69.

Reviewer comment: The convergence at Week 13 of the concentration-time profiles for the final doses suggests 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. Figure 12 shows the correlation between serum testosterone concentration at single time points and Cavg0-24h and Cmax at Week 3 and Week 7. 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 12: 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

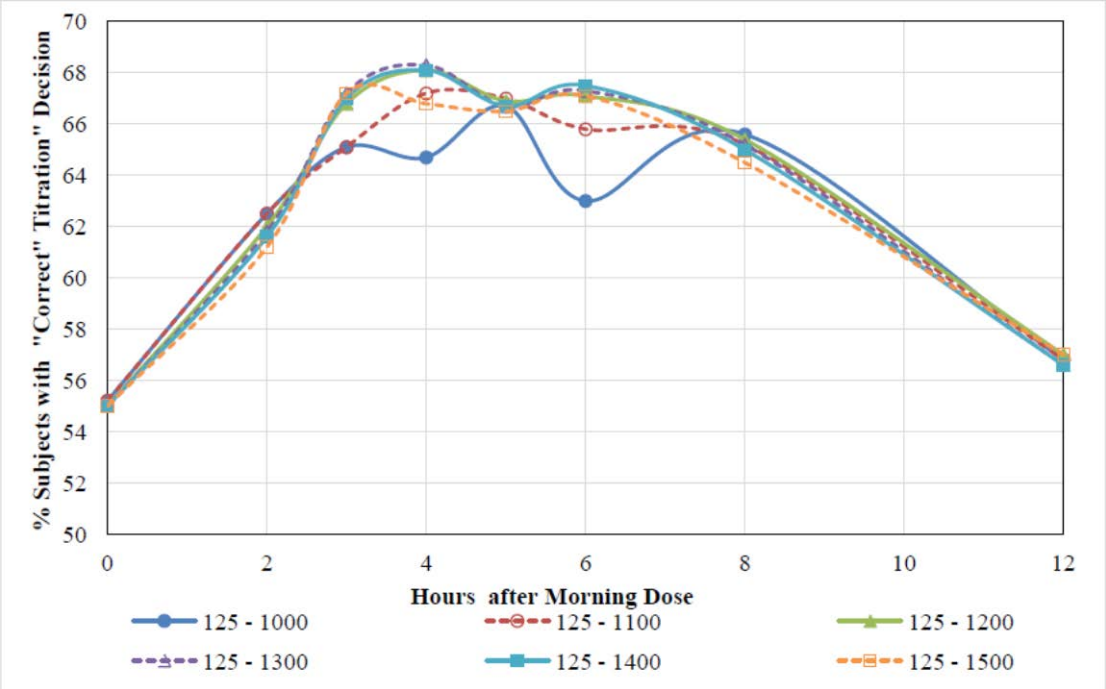
0.72. Based on this analysis, the applicant concluded that Cavg0-24 provides a good representation of Cmax data when used for titration decisions.

Reviewer 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.

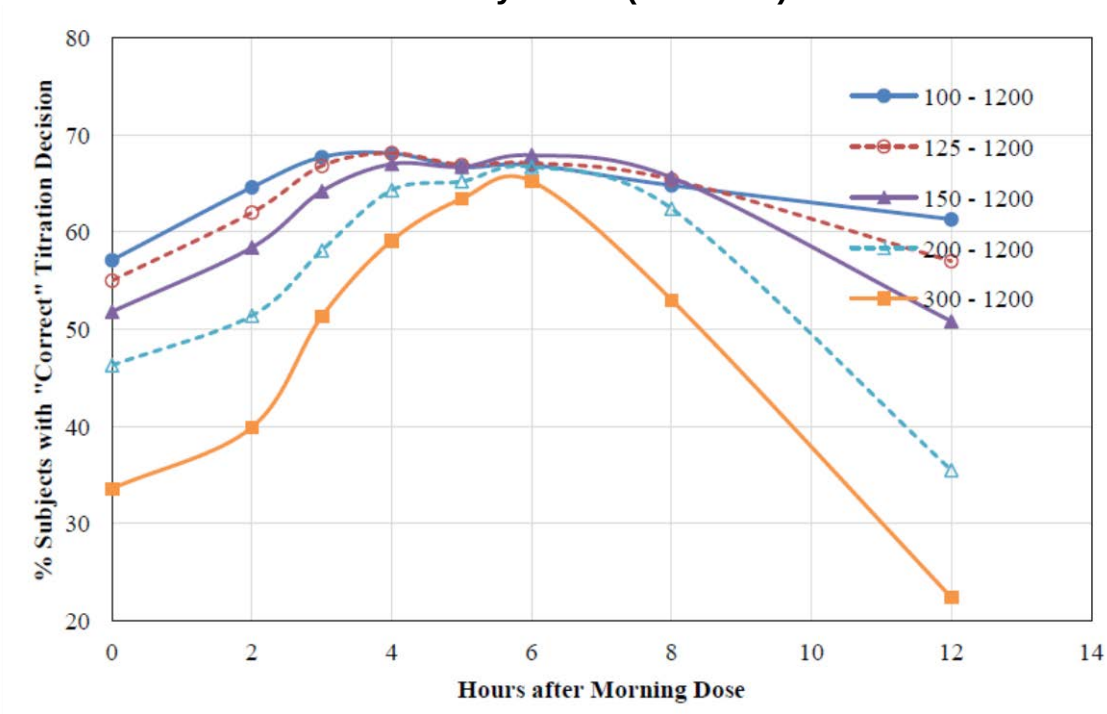
For this analysis, various testosterone concentrations were set as an upper bound (1000, 1100, 1200, 1300, 1400, and 1500 ng/dL) and a lower bound (100, 125, 150, 200, and 300 ng/dL) and an evaluated to determine the combination of upper and lower boundaries at which a single blood draw titration decision outcome would most often match the "correct" titration decision. Figure 13 and Figure 14 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 13: Percentage of Subject Where a Single Testosterone Level Led to the "Correct" Titration Decision Using a Lower Bound of 125 ng/dL and Various Upper Bounds Ranging from 1000 to 1500 ng/dL – Full Analysis Set (N = ~ 532)



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 14: Percentage of Subjects Where a Single Testosterone Level Led to the "Correct" Titration Decision Using Various Lower Bounds Ranging from 100 to 300 ng/dL and an Upper Bound of 1200 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 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 125 ng/dL and an upper limit of 1200 ng/dL.

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

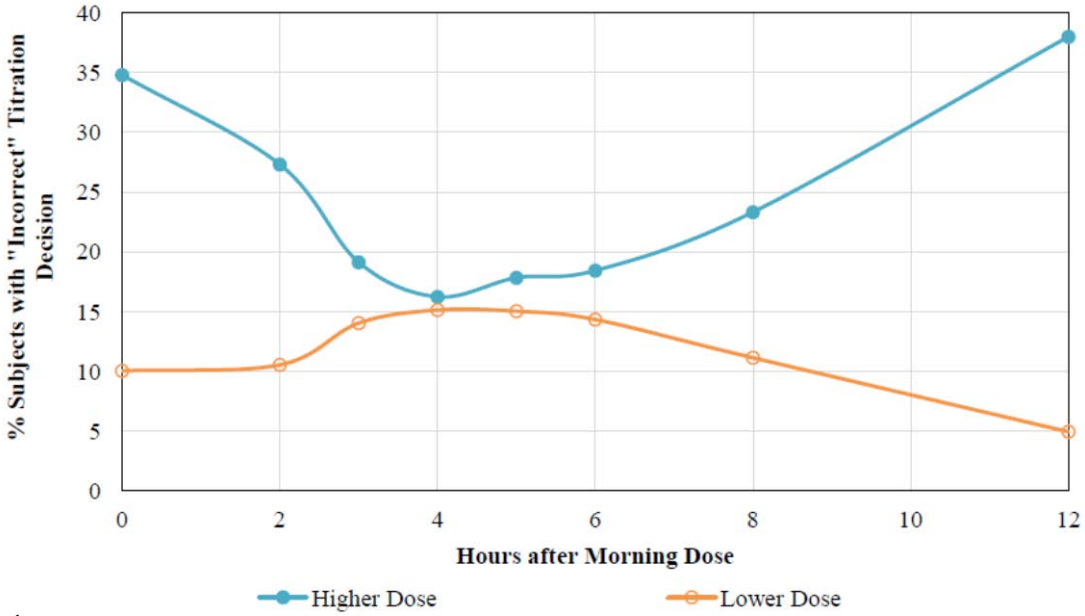
Based on these results, the following titration criteria were proposed:

- 3 to 6 hours after morning dose administration as the appropriate titration window
- 125 ng/dL as the lower bound for recommending an upward titration
- 1200 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. Figure 15 shows the percent of subjects who would have been wrongly titrated up or down using the 125 to 1200 ng/dL bounds.

Figure 15: Percentage of Subjects Where a Lower Bound of 125 ng/dL and an Upper Bound of 1200 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.

Reviewer 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 generalizable to 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 (125 to 1200 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:

- 4 to 6 hours after morning dose administration as the appropriate titration window
- 300 ng/dL as the lower bound for recommending an upward titration

- 1200 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.

Table 16 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 16: 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 125 ng/dL Upper bound of 1200 ng/dL**	**Lower bound of 300 ng/dL Upper bound of 1200 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 lower bound of 300 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.

Reviewer comment: The 300 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.

On May 31, 2016, the applicant submitted the following proposal for improving concordance between the single point titration scheme and the titration decisions made in the Phase 3 study.

- Correlate single time point post AM dose titration decisions to the titration decision in Phase 3 based on only the AM PK profile

The applicant provided concordance analyses for titration based on Cavg/Cmax over 12 hours following the morning dose and the single time point titration initially proposed in the NDA and the revised single point titration scheme proposed in the May 20, 2016 submission. These analyses are summarized in Table 17 and Table 18, respectively.

Table 17: Subjects where single point titration is in agreement with Phase 3 Titration Bounds: 125 ng/dL to 1200 ng/dL

Visit	N	Cavg/Cmax0-24 % Agreement*	Cavg/Cmax0-12 % Agreement*
Week 03	192	64.7	63.2
Week 07	182	68.8	71.2
Week 13	157	68.0	66.6
*Average % for time window (3 to 6 hours) Source: NDA 208088 (seq 0020), 1.2, Table 1.b.1 and 1.c.1, p. 2-3.			

Table 18: Subjects where single point titration is in agreement with Phase 3 Titration Bounds: 300 ng/dL to 1200 ng/dL

Visit	N	Cavg/Cmax 0-24 % Agreement*	Cavg/Cmax 0-12 % Agreement*
Week 03	192	57.5	64.8
Week 07	182	66.3	76.4
Week 13	157	64.1	66.7
*Average % for time window (4 to 6 hours) Source: NDA 208088 (seq 0020), 1.2, Table 1.b.2 and 1.c.2, p. 3-4.			

Reviewer comment: The new proposal increased concordance for most time points. However, except for Week 7, the number of "incorrect" decisions continues to be greater than 33%.

The applicant also offered the following suggestions for improving concordance:

- The sampling time window could be narrowed from 4 - 6 hours to 5 - 6 hours for the 300-1200 ng/dL single point titration bounds.
- Considering subjects at the borderline testosterone levels (in between 275 to 300 ng/dL) as not truly discordant improves concordance of single point to Phase 3.

Reviewer comment: Reducing the titration window to one hour is not considered feasible in "real-world" use of the drug. Other than improving concordance, the rationale for considering T levels between 275 and 300 ng/dL as "not being discordant" is not clear.

Reviewer summary comment regarding dosing recommendations: 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 that can be used in labeling.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

During the Phase 3 study, no efficacy measurements were conducted after the week 13 PK assessment. Single point blood samples were collected 3 to 6 hours after the AM dose at weeks 26, 39, and 52. The mean serum testosterone concentration at each of those time points was within the normal range.

6.1.10 Additional Efficacy Issues/Analyses

Free testosterone

During the Phase 3 study, free testosterone was calculated using the method described by Vermeulen et.al.[1] Calculated mean free testosterone levels for Tlando and AndroGel 1.62% are shown in Table 19.

Table 19: Calculated Free Testosterone (ng/dL) Levels following Tlando and AndroGel 1.62% Administration – All Available Data

	Tlando		AndroGel 1.62%	
Visit	N[1]	Free T (ng/dL) Mean (SD)	N[1]	Free T (ng/dL) Mean (SD)
Baseline	191	5.5 (2.1)	89	5.58 (1.98)
Week 13[2]	145	12.9 (5.0)	84	12.5 (8.2)
Week 26[3]	139	12.7 (10.0)	79	13.4 (13.6)
Week 39[3]	133	14.0 (11.8)	74	10.0 (6.4)
Week 52[3]	124	14.0 (15.0)	65	9.8 (5.4)

[1]N = Number of subjects in the safety population at the respective visit.
[2]For Week 13 Cavg is used.
[3]For Week 26, 39 and 52, 3 to 6 hour value is used.
Source: NDA 208088 (seq 0000), 2.7.3, Table 18, p. 48.

Reviewer comment: For subjects treated with Tlando, 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 arithmetic mean baseline DHT concentrations for the Safety Set were 23.7 ng/dL (N=185) for the Tlando group and 22.7 ng/dL (N= 89) for the AndroGel 1.62% group. Measured DHT concentrations increased as T concentrations increased. The overall

[1]Vermeulen A Verdonck L et al. A Critical Evaluation of Simple Methods for the Estimation of Free Testosterone in Serum. J Clin Endocrinol Metab 1999 84(10): 3666-3672.

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. Table 20 shows the PK parameters for DHT at Week 13 for the PK set in subjects receiving Tlando (PK assessments were not conducted on subjects in the AndroGel 1.62% group).

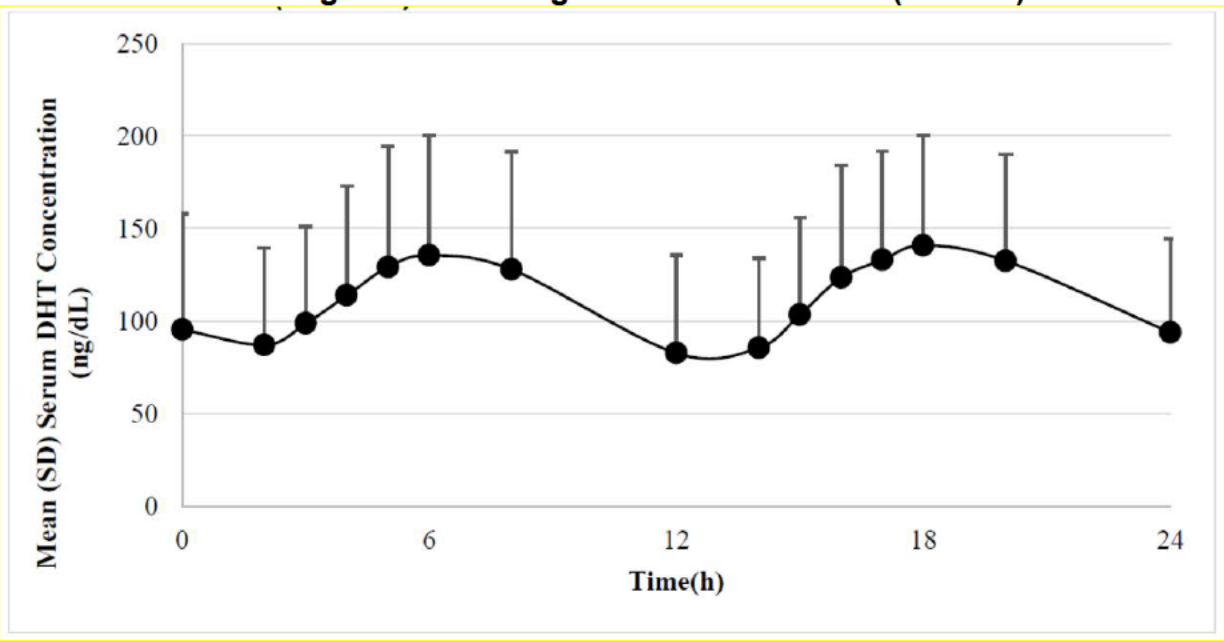
Table 20: Serum DHT PK (Cavg0-24h and Cmax, ng/dL) by Dose at Weeks 3, 7, and 13 – Pharmacokinetic Set (N = 130)

PK Parameters	Statistic	Dose of Tlando (BID)				
		150 mg	225 mg	300 mg	Overall	Overall DHT/T
Week 3	**n**		**130**		**130**	**130**
Cavg0-24h, ng/dL	Mean (SD)	--	116 (42)	--	116 (42)	0.24 (0.06)
Cmax, ng/dL	Mean (SD)	--	195 (69)	--	195 (69)	0.16 (0.06)
Week 7	**n**	**36**	**78**	**16**	**130**	**130**
Cavg0-24h, ng/dL	Mean (SD)	106 (38)	114 (49)	107 (28)	111 (44)	0.26 (0.07)
Cmax, ng/dL	Mean (SD)	181 (53)	192 (68)	182 (59)	188 (63)	0.18 (0.06)
Week 13	**n**	**47**	**65**	**18**	**130**	**130**
Cavg0-24h, ng/dL	Mean (SD)	114 (48)	112 (36)	108 (47)	112 (42)	0.26 (0.07)
Cmax, ng/dL	Mean (SD)	190 (75)	182 (60)	191 (71)	186 (67)	0.18 (0.07)

Source: NDA 208088 (seq 0000), 2.7.3, Table 19, p. 49.

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. Figure 16 shows serum DHT concentrations at Week 13 after subjects had been on their final Tlando dose (150, 225, or 300 mg TU BID) for at least 21 days.

Figure 16: Mean (+SD) Serum Dihydrotestosterone Concentrations over Time following Tlando Dosing at Week 13 – PK Set (N = 130)



Source: NDA 208088 (seq 0000), 2.7.3, Figure 15, p. 50.

At Weeks 26, 39, and 52 of the Phase 3 study, DHT levels were measured from a single blood sample obtained 3 to 6 hours following the morning dose of Tlando. The rationale for this sampling time point is discussed in Section 6.1.8. Table 21 summarizes 3 to 6 hour DHT concentrations for Tlando and AndroGel 1.62% in the Phase 3 study.

Table 21: Serum Concentrations (3 to 6 hour Sampling) for DHT, and DHT:T in Subjects Dosed with Tlando and AndroGel 1.62%, – All Available Data from Phase 3 Study (PK Set)

Analyte	Treatment Arm	Week 13	Week 26	Week 39	Week 52
DHT (ng/dL), Mean (SD)	Tlando	112 (42)*	91 (49)	93 (44)	92 (58)
	AndroGel 1.62%	99 (56)	102 (70)	86 (51)	87 (49)
DHT:T Ratio AUC0-24h, Mean (SD)	Tlando	0.26 (0.07)*	0.23 (0.11)	0.22 (0.12)	0.23 (0.12)
	AndroGel 1.62%	0.20 (0.06)	0.19 (0.06)	0.19 (0.08)	0.20 (0.07)

*Based on Cavg0-24h value
Source: NDA 208088 (seq 0000), 2.7.3, Table 20, p. 51.

Reviewer comment: The laboratory used by the applicant to measure DHT concentrations did not have 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 Tlando treatment group, but not on subjects treated with AndroGel 1.62%, so comparisons of Cavg between Tlando 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 Tlando maintains DHT within the normal range. In my opinion, based on the available data there is a potential risk that DHT levels may be slightly to moderately elevated in patients treated with Tlando. To further assess this issue, the applicant submitted a literature review to evaluate safety in clinical trials of transdermal DHT gel (see Section 9: Literature Review/References).

Estradiol

The arithmetic mean baseline E2 concentrations for the Safety Set (N=202) were 17.8 pg/mL for Tlando. 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 redoes levels after approximately 12 hours. The E2 concentration profile after the evening dose was similar to the profile observed after the morning dose. Table 22 summarizes the pharmacokinetic parameters for E2 after Tlando administration.

Table 22: Serum Estradiol Pharmacokinetics (Cavg0-24h and Cmax) by Dose at Weeks 3, 7, and 13 – Pharmacokinetic Set (N = 130)

PK Parameters	Statistic	Dose of Tlando (BID)			
		150 mg	225 mg	300 mg	Overall
Week 3	**n**		**130**		**130**
Cavg0-24h, pg/mL	Mean (SD)	--	29.3 (12.6)	--	29.3 (12.6)
Cmax, pg/mL	Mean (SD)	--	44.2 (18.1)	--	44.2 (18.1)
Week 7	**n**	**36**	**78**	**16**	**130**
Cavg0-24h, pg/mL	Mean (SD)	26.8 (12.1)	31.8 (13.4)	26.8 (10.2)	29.8 (12.9)
Cmax, pg/mL	Mean (SD)	38.3 (15.1)	51.3 (37.5)	41.1 (16.2)	46.5 (13.1)
Week 13	**n**	**47**	**65**	**18**	**130**
Cavg0-24h, pg/mL	Mean (SD)	26.4 (13.0)	29.9 (12.4)	26.5 (9.2)	28.2 (12.3)
Cmax, pg/mL	Mean (SD)	38.6 (18.0)	45.1 (20.5)	44.8 (17.1)	42.7 (19.3)

Source: NDA 208088 (seq 0000), 2.7.3, Table 25, p. 58.

Reviewer comment: For subjects treated with Tlando, the mean overall Cavg0-24 for estradiol was within the normal range at week 13.

7 Review of Safety

Safety Summary

The applicant conducted one 52-week Phase 3 study providing safety and efficacy data for Tlando. In addition, five Phase 1 studies in the target population of hypogonadal men were also conducted. Review of the adverse event, clinical laboratory, and vital sign data generated during these studies indicate that Tlando can be safely used for testosterone replacement therapy in properly selected men 18 years of age or older.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies LPCN 1021-13-001, LPCN 1021-09-001, S361.1.001, M12-778, M13-298, and LPCN 1021-14-001 are the source of safety information for this NDA. These studies were performed in the target population of hypogonadal men.

7.1.2 Categorization of Adverse Events

Different MedDRA versions were used in the coding of AE terms in the clinical trials. Phase 3 study events were coded using MedDRA 16.1, LPCN 1021-14-001 study events were coded using MedDRA 17.1 while earlier Phase 1 studies used even earlier versions. In the ISS, all AEs reported in Phase 1 and Phase 3 studies were up-coded to MedDRA 17.1. Therefore, for Phase 3 data presented alone, adverse events are reported using MedDRA 16.1 and where Phase 1 and Phase 3 data are integrated, adverse events are reported using MedDRA 17.1. Seven AEs that occurred during the Phase 3 study were affected by differences in MedDRA coding and are summarized in Table 23.

Table 23: Adverse Events Affected by Different MedDRA Versions for Phase 3 Study Coding

AE Verbatim	MedDRA 16.1 Preferred Term	MedDRA 16.1 System Organ Class	MedDRA 17.1 Preferred Term	MedDRA 17.1 System Organ Class
Balantitis	Balanitis	Reproductive System And Breast Disorders	Balanoposthitis	Reproductive System And Breast Disorders
Epididymitis	Epididymitis	Reproductive System And Breast Disorders	Epididymitis	Infections And Infestations
Irritability	Irritability	General Disorders And Administration Site Conditions	Irritability	Psychiatric Disorders
Seasonal Allergic Rhinitis	Rhinitis Seasonal	Respiratory, Thoracic And Mediastinal Disorders	Seasonal Allergy	Immune System Disorders
Therapeutic Response Unexpected	Therapeutic Response Unexpected	General Disorders And Administration Site Conditions	Therapeutic Response Changed	General Disorders And Administration Site Conditions
Soft Stools	Diarrhoea	Gastrointestinal Disorders	Faeces Soft	Gastrointestinal Disorders
Skin Abrasion	Excoriation	Injury, Poisoning And Procedural Complications	Skin Abrasion	Injury, Poisoning And Procedural Complications

Source: NDA 208088 (seq 0000), 2.7.4, Table 24, p. 52.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The following five Phase 1 studies, performed in the target population of hypogonadal men, were integrated into a pooled database for summary analyses.

- LPCN 1021-09-001 was a single oral dose and multiple dose (more than one day) study (5 days)
- S361.1.001 was a single oral dose study
- M12-778 was a single oral dose followed by multiple dose study (three groups: 14 days, two groups: 28 days)
- M13-298 was a multiple oral dose study (14 days)
- LPCN 1021-14-001 was a single oral dose study

These studies used a range of TU doses (50 to 300 mg), most enrolled a small number of subjects and had a short treatment duration.

In addition, data from the Phase 3 study (LPCN 1021-13-001) were added to the database of pooled Phase 1 studies for selected baseline and safety data for integrated analysis.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

Phase 1 and Phase 3 Studies

Duration (days) and amount (mg) of exposure were summarized for each treatment/dose group. The denominators for calculating the percentages were based on the number of patients with exposure data for each treatment/dose group.

For the 381 hypogonadal men who received Tlando in the Phase 1 and 3 studies (single and multiple dose periods), Tlando was received for a median 33.0 days (range of 1 to 382 days) with 44.6% of the subjects receiving study drug for 4 weeks or less and 34.6% of subjects receiving study drug for more than 39 weeks. Table 24 summarizes the extent of exposure for the Phase 1 and Phase 3 studies.

Table 24: Summary of Extent of Exposure for Phase 1 and 3 Studies (Single and Multiple Dose Periods) – Safety Population

Assessment	Tlando N = 381	Andriol N = 34	AndroGel 1.62% N = 104	Placebo N = 18
Extent of Exposure (days)				
N	381	34	104	18
Mean (SD)	148.6 (163.46)	3.1 (3.24)	290.5 (123.16)	19.4 (7.01)
Median	33.0	1.0	364.0	15.0
Q1, Q3	15.0, 364.0	1.0, 8.0	189.5, 366.0	15.0, 29.0
Min, Max	1, 382	1, 8	1, 382	11, 29
Interval (weeks), n (%)				
[0,4]	170 (44.6)	34 (100)	7 (6.7)	12 (66.7)
(4,13]	54 (14.2)	0	8 (7.7)	6 (33.3)
(13,26]	14 (3.7)	0	9 (8.7)	0
(26,39]	11 (2.9)	0	7 (6.7)	0
>39	132 (34.6)	0	73 (70.2)	0
Total Dose (mg)				
N	3781	34	101	18
Mean (SD)	59793.65 (68108.89)	338.82 (407.00)	18015.52 (8687.05)	7850.00 (5551.37)
Median	17100.00	80.00	18759.60	6525.00
Q1, Q3	2475.00, 118125.00	80.00, 960.00	12457.80, 23571.00	4350.00, 12825.00
Min, Max	0.0, 217050.0	80.0, 960.0	874.8, 39317.4	1500.0, 17100.0

Source: NDA 208088 (seq 0000), 2.7.4, Table 8, p. 31.

Table 25 displays extent of exposure data for the combined Phase 1 and Phase 3 studies with multiple dose periods by Tlando dose level. The most commonly used Tlando dose in these studies was the 225 mg dose (170 subjects), which had a median exposure of 73.5 days (ranging from 1 to 382 days) with 40.6% of subjects receiving study drug for more than 39 weeks and 38.2% of subjects receiving study drug for 4 weeks or less.

Table 25: Summary of Extent of Exposure by Dose Level for Phase 1 and 3 Studies (Multiple Tlando Dose Period) – Safety Population

Assessment	75 mg BID N = 16	100 mg BID N = 19	150 mg BID N = 82	225 mg BID N = 170	300 mg BID N = 40
Days of Exposure, n	16	19	82	170	40
Mean (SD)	15.0 (0.00)	7.9 (0.23)	217.4 (157.39)	171.7 (166.45)	226.2 (155.15)
Median	15.0	8.0	320.5	73.5	363.5
Q1, Q3	15.0, 15.0	8.0, 8.0	52.0, 365.0	15.0, 365.0	52.5, 366.0
Minimum, Maximum	15, 15	7, 8	14, 374	1, 382	29, 373
Interval (weeks), n (%)					
[0,4]	16 (100)	19 (100)	16 (19.5)	65 (38.2)	0
(4,13]	0	0	16 (19.5)	23 (13.5)	15 (37.5)
(13,26]	0	0	4 (4.9)	8 (4.7)	2 (5.0)
(26,39]	0	0	4 (4.9)	5 (2.9)	2 (5.0)
>39	0	0	42 (51.2)	69 (40.6)	21 (52.5)
Total Dose (mg), n	16	19	82	168	39
Mean (SD)	2175.00 (0.00)	1194.74 (22.94)	66103.35 (46826.25)	73841.52 (69786.47)	120340.38 (84310.23)
Median	2175.00	1200.00	87900.00	35100.00	126075.00
Q1, Q3	2175.00, 2175.00	1200.00, 1200.00	21300.00, 113025.00	6525.00, 153450.00	17100.00, 205837.50
Min, Max	2175.0, 2175.0	1100.0, 1200.0	3900.0, 130050.0	0.0, 176400.0	4500.0, 217050.0

Source: NDA 208088 (seq 0000), 2.7.4, Table 10, p. 33.

Phase 3 Study (LPCN 1021-13-001)

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 Tlando 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 Tlando, 130 were exposed for 52 weeks. Table 26 summarizes the extent of exposure for the Phase 3 study.

Table 26: Summary of Extent of Exposure for the Phase 3 Study – Safety Population

Assessment	Tlando N = 210	AndroGel 1.62% N = 104[1]
Extent of Exposure (days)		
n	210	104
Mean (SD)	260.0 (144.01)	290.5 (123.16)
Median	364.0	364.0
Q1, Q3	88.0, 366.0	189.5, 366.0
Min, Max	1, 382	1, 382
Interval (weeks), n (%)		
[0,4]	17 (8.1)	7 (6.7)
(4,13]	36 (17.1)	8 (7.7)
(13,26]	14 (6.7)	9 (8.7)
(26,39]	11 (5.2)	7 (6.7)
>39	132 (62.9)	73 (70.2)
Total Dose (mg)		
N[2]	207	101
Mean (SD)	105678.99 (61612.71)	18015.52 (8687.05)
Median	113887.50	18759.60
Q1, Q3	40950.00, 156712.50	12457.80, 23571.00
Min, Max	0.0, 217050.0	874.8, 39317.4

[1]One subject was randomized to AndroGel 1.62% but did not receive treatment.
[2]Three subjects each in Tlando and AndroGel treatment arms did not have their final dose data available at 52 Weeks / early termination and therefore their total exposure was not estimated.
Source: NDA 208088 (seq 0000), 2.7.4, Table 5, p. 29.

Slightly more than half of subjects in the safety set (113 of 210, 53.8%) were on the final dose of 225 mg and had a median exposure of 364.0 days. For subjects with a final Tlando dose of 225 mg, 69 (61.1%) received the dose for more than 39 weeks and the median total dose received was 144,000.00 mg. For subjects with a final dose of 150 mg Tlando, the median number of days of exposure was 363.0 days, the median dose was 102,000.00 mg, and 42 (63.6%) subjects received the dose for more than 39 weeks. For subjects with a final dose of 300 mg Tlando, the median number of days of exposure was 365.0 days, the median dose was 197,475.00 mg, and 21 (67.7%) subjects received the dose for more than 39 weeks. Table 27 displays extent of exposure data for the Phase 3 study by final Tlando dose level.

Table 27: Summary of Extent of Exposure by Final Dose Level for Phase 3 Study (Multiple Tlando Dose Period) – Safety Population

Assessment	150 mg N = 66	225 mg N = 113	300 mg N = 31
Extent of Exposure (days)			
n	66	113	31
Mean (SD)	266.5 (135.41)	249.9 (153.07)	283.5 (127.41)
Median	363.0	364.0	365.0
Q1, Q3	93.0, 365.0	77.0, 366.0	182.0, 367.0
Min, Max	36, 374	1, 382	49, 373
Interval (weeks), n (%)			
[0,4]	0	17 (15.0)	0
(4,13]	16 (24.2)	14 (12.4)	6 (19.4)
(13,26]	4 (6.1)	8 (7.1)	2 (6.5)
(26,39]	4 (6.1)	5 (4.4)	2 (6.5)
>39	42 (63.6)	69 (61.1)	21 (67.7)
Total Dose (mg)			
n	66	111	30
Mean (SD)	81080.68 (39561.44)	107971.62 (62658.69)	151312.50 (70809.80)
Median	102000.00	144000.00	197475.00
Q1, Q3	36150.00, 113587.50	38137.50, 160312.50	85875.00, 207300.00
Min, Max	9450.0, 130050.0	0.0, 176400.0	4500.0, 217050.0

Source: NDA 208088 (seq 0000), 2.7.4, Table 6, p. 30.

Phase 1 Studies

Table 28 displays extent of exposure data for the Phase 1 studies with single and multiple dose periods.

Table 28: Summary of Extent of Exposure Phase 1 Studies (Single and Multiple Dose Periods) – Safety Population

Assessment	Tlando N = 171	Andriol N = 34	Placebo N = 18
Extent of Exposure (days)			
n	171	34	18
Mean (SD)	11.8 (7.98)	3.1 (3.24)	19.4 (7.01)
Median	15.0	1.0	15.0
Q1, Q3	4.0, 15.0	1.0, 8.0	15.0, 29.0
Min, Max	1, 29	1, 8	11, 29
Interval (weeks), n (%)			
[0,4]	153 (89.5)	34 (100)	12 (66.7)
(4,13]	18 (10.5)	0	6 (33.3)
(13,26]	0	0	0
(26,39]	0	0	0
>39	0	0	0
Total Dose (mg)			
N	171	34	18
Mean (SD)	4248.25 (4483.468)	338.82 (407.00)	7850.00 (5551.37)
Median	2175.00	80.00	6525.00
Q1, Q3	900.00, 6525.00	80.00, 960.00	4350.00, 12825.00
Min, Max	50.0, 17100.0	80.0, 960.0	1500.0, 17100.0

Source: NDA 208088 (seq 0000), 5.3.5.3 Table 4.1, p. 48-49.

Reviewer comment: Exposure to Tlando appears to be adequate. The applicant met the goal of having at least 100 subjects exposed to Tlando 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 (See Section 8 Postmarketing Experience).

Demographics

Phase 3 Study (LPCN 1021-13-001)

Table 29 summarizes the baseline and demographic data of subjects who were randomized in the Phase 3 study.

Table 29: Demographic and Baseline Characteristics of Subjects in the Phase 3 Study – Randomized Subjects

Characteristic	Tlando N = 210	AndroGel 1.62% N = 105
Age, Mean (SD)	52.6 (10.24)	54.2 (9.39)
≤ 65 Years, n (%)	190 (90.5)	96 (91.4)
> 65 Years, n (%)	20 (9.5)	9 (8.6)
Race, n (%)		
Asian	3 (1.4)	3 (2.9)
Black or African American	32 (15.2)	10 (9.5)
White	172 (81.9)	92 (87.6)
Other	3 (1.4)	0
Ethnicity, n (%)		
Hispanic or Latino	44 (21.0)	22 (21.0)
Not Hispanic or Latino	166 (79.0)	83 (79.0)
Body Mass Index, Mean (SD)	30.83 (3.88)	30.98 (3.88)
< 25 kg/m², n (%)	12 (5.7)	5 (4.8)
≥ 25 to < 30 kg/m², n (%)	80 (38.1)	33 (31.4)
≥ 30 kg/m², n (%)	118 (56.2)	67 (63.8)
Weight (kg), Mean (SD)	97.09 (14.96)	99.20 (14.78)
Prior Androgen Therapy, n (%)	108 (51.4)	58 (55.2)

Source: NDA 208088 (seq 0000), 2.7.4, Table 16, p. 43.

Reviewer comment: In general, the baseline characteristics of subjects randomized to the two treatment groups in the Phase 3 study was similar and representative of patients likely to use the drug. The percentage of subjects older than 65 years of age was less than 10% for both treatment arms.

Screening testosterone levels of subjects in the Phase 3 study are summarized in Table 30.

Table 30: Screening Testosterone Levels of Subjects in the Phase 3 Study – Safety Set (N = 314)

Characteristic	Tlando N=210	AndroGel 1.62% N=104	Overall N=314
Testosterone (ng/dL)			
N	210	104	314
Mean (SD)	205.6 (66.3)	201.9 (71.9)	204.4 (68.2)
Minimum, Maximum	10, 302[a]	10, 444[a]	10, 444[a]

[a]One subject in the AndroGel arm had three screening T measurements, one of which was 444 ng/dL, whereas the other two were less than 300 ng/dL. Two subjects in the Tlando arm had three measurements of T at screening and one of the values was above 300 ng/dL in each of the subjects (one subject had one value of 301 ng/dL and another had 302 ng/dL) whereas the other two values were less than 300 ng/dL in both the subjects. The protocol specified that serum T < 300 ng/dL based on two consecutive blood samples obtained on two separate days is required as an inclusion criteria. Due to some sites misinterpreting this requirement, they enrolled these subjects following determination that two samples were < 300 ng/dL.
Source: NDA 208088 (seq 0000), 2.7.4, Table 17, p. 44.

Reviewer comment: Screening T levels were similar between the Tlando and AndroGel 1.62% treatment groups.

7.2.2 Explorations for Dose Response

The applicant conducted study M12-778 to assess the safety, tolerability, and PK of escalating doses of Tlando. In addition, the dose of Tlando in Study LPCN 1021-2013-001 was titrated based on the Cavg 0-24 and Cmax 0-24 during the PK assessments that occurred during weeks 3 and 7.

Reviewer comment: The dose response was adequately evaluated.

7.2.3 Special Animal and/or In Vitro Testing

The applicant submitted an in vitro study (8030765) titled “The Effects of 3 Compounds in the Human AR Binding Assay” to investigate the effects of testosterone undecanoate (TU), dihydrotestosterone undecanoate (DHTU), and testosterone in the in vitro human AR receptor binding assay. The study was reviewed by the pharmacology/toxicology reviewer.

7.2.4 Routine Clinical Testing

Routine clinical testing of subjects was conducted throughout the Phase 3 study and appears to be adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific metabolic, clearance or interaction evaluations were submitted for this application.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following adverse events have been identified for the testosterone class of drug products: worsening of benign prostatic hyperplasia; polycythemia; venous thromboembolism, including deep vein thrombosis and pulmonary embolism; edema; gynecomastia; worsening of sleep apnea; and changes in serum lipid profile. In addition, the potential risks of prostate cancer and cardiovascular adverse events have also been identified.

During the clinical studies, these adverse events were evaluated by adverse event and clinical laboratory monitoring.

7.3 Major Safety Results

7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

Phase 3 Study
During the Phase 3 study, a total of 19 treatment-emergent serious adverse events (SAE) were reported for 14 subjects (4.5%). For the Tlando 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 Tlando and AndroGel 1.62% groups. Table 31 summarizes the treatment-emergent SAEs during Study LPCN 1021-13-001.

Table 31: Summary of Treatment-emergent Serious Adverse Events in the Phase 3 Study (Safety Set)

System Organ Class Preferred Term	Tlando (N = 210) n (%)	AndroGel 1.62% (N = 104) n (%)	Overall (N = 314) n (%)
Any treatment-emergent SAE	12 (5.7)	2 (1.9)	14 (4.5)
Infections and infestations	3 (1.4)	1 (1.0)	4 (1.3)
Sepsis	1 (0.5)	1 (1.0)	2 (0.6)
Cholecystitis infective	0	1 (1.0)	1 (0.3)
Osteomyelitis	1 (0.5)	0	1 (0.3)
Pneumonia	0	1 (1.0)	1 (0.3)
Pneumonia streptococcal	1 (0.5)	0	1 (0.3)
Staphylococcal bacteraemia	1 (0.5)	0	1 (0.3)
Musculoskeletal and connective tissue disorders	3 (1.4)	0	3 (1.0)
Arthritis	1 (0.5)	0	1 (0.3)
Osteonecrosis	1 (0.5)	0	1 (0.3)
Spinal osteoarthritis	1 (0.5)	0	1 (0.3)
Gastrointestinal disorders	2 (1.0)	0	2 (0.6)
Abdominal pain	1 (0.5)	0	1 (0.3)
Gastrooesophageal reflux disease	1 (0.5)	0	1 (0.3)
General disorders and administration site conditions	1 (0.5)	1 (1.0)	2 (0.6)
Chest pain	0	1 (1.0)	1 (0.3)
Non-cardiac chest pain	1 (0.5)	0	1 (0.3)
Injury, poisoning and procedural complications	2 (1.0)	0	2 (0.6)
Cervical vertebral fracture	1 (0.5)	0	1 (0.3)
Face injury	1 (0.5)	0	1 (0.3)
Nervous system disorders	2 (1.0)	0	2 (0.6)
Ataxia	1 (0.5)	0	1 (0.3)
Balance disorder	1 (0.5)	0	1 (0.3)
Syncope	1 (0.5)	0	1 (0.3)

Adverse event classification using MedDRA 16.1.
Source: NDA 208088 (seq 0000), 5.3.5.1, Table 58, p. 116.

Table 32 lists by subject the SAEs that occurred during Study LPCN 1021-13-001. Narratives for each of the Tlando subjects follow the table. No SAEs were considered by the investigator to be related to the study drug. Subject (b) (6) experienced four SAEs prior to receiving the first dose of study drug.

Table 32: Serious Adverse Events during the Phase 3 Study – Safety Set

Subject Number	Study Drug Dose	MedDRA Preferred Term	Study Day SAE Onset	SAE Duration (days)	Relationship to Study Drug/ Severity
Tlando					
(b) (6)	225 mg	Face injury	362	2	NR/Moderate
	150 mg	Abdominal pain	286	4	NR/Severe
	225 mg	Osteonecrosis	147	3	NR/Severe
	225 mg	Sepsis	218	3	NR/Severe
	150 mg	Cervical vertebral fracture Spinal osteoarthritis	359 386	11 5	NR/Severe NR/Severe
	225 mg	Staphylococcal bacteraemia Osteomyelitis	49 49	6 51	NR/Moderate NR/Moderate
	300 mg	Noncardiac chest pain	134	2	NR/Moderate
	225 mg	Pneumonia streptococcal	54	12	NR/Severe
	225 mg	Arthritis	45	5	NR/Severe
	225 mg	Syncope	231	2	NR/Mild
	150 mg	GERD	139	3	NR/Severe
	225 mg	Balance disorder Ataxia	79 79	2 2	NR/Moderate NR/Moderate
AndroGel 1.62%					
(b) (6)	81 mg	Chest pain	165	2	NR/Severe
	NA	Rib fracture Pneumothorax Lumbar vertebral fracture Splenic rupture	-24 -24 -24 -24	53 53 53 53	NR/Moderate NR/Moderate NR/Moderate NR/Moderate
	81 mg	Cholecystitis infective Pneumonia Sepsis	45 45 45	8 8 8	NR/Severe NR/Severe NR/Severe

NR = not related; GERD = Gastrooesophageal reflux disease
[a]Subject (b) (6) provided written informed consent, but experienced SAEs prior to receiving the first dose of study drug and later was randomized to AndroGel 1.62%
Source: Source: NDA 208088 (seq 0000), 2.7.4, Table 29, p. 60.

Reviewer comment: Each of the serious adverse events reported during the Phase 3 study was reviewed. I agree that these events do not appear to be related to the study drug.

Phase 1 Studies
No serious adverse events (SAE) occurred during the Phase 1 studies in the target population.

7.3.3 Dropouts and/or Discontinuations

Phase 3 Study
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 Tlando 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 Tlando group), libido decreased (2

subjects in the Tlando group), and polycythemia (1 subject in each of the Tlando 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 Tlando group and 3 events in 3 subjects in the AndroGel 1.62% group.

Three subjects who received Tlando 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.

As described in Section 6.1.3 Subject Disposition, the applicant conducted an investigation for subjects who discontinued the study prematurely with a reason of withdrew consent. Information obtained after the study had ended revealed that the specific reasons for the withdrawn consent included weight gain for Subject (b) (6) who had received Tlando and worsening insomnia for Subject (b) (6) who had received AndroGel 1.62%. In addition, adverse events that had an action taken as study drug discontinued were not always considered the reason for study discontinuation in terms of disposition. For example, Subject (b) (6) was prematurely withdrawn from the study for the reason of meeting the Cmax or Cavg stopping criteria. Subjects (b) (6) (b) (6) and (b) (6) were withdrawn by the investigator due to a reason of consent withdrawn (subsequently classified by the applicant as a confinement or schedule conflict). The additional information obtained by the applicant from the study sites after completion of the study revealed that the Subject (b) (6) s reason for withdrawing from the study was that the previous PK visit had taken too much time and he couldn't take 2 days off work anymore. Subject (b) (6) s reason for withdrawing was that he withdrew his consent due to his work schedule. Because these subjects had been experiencing adverse events during their discontinuation, the action taken for these adverse events was study drug discontinued.

Table 33 lists subjects, including the subjects re-classified by the applicant, who experienced an adverse event immediately preceding drug discontinuation.

Table 33: Adverse Events Leading to Study Discontinuation, Phase 3 Study - Safety Set

Subject Number	Study Drug Dose	MedDRA Preferred Term	Relationship to Study Drug/ Severity	Discontinuation Reason (Sponsor Classification)
Tlando				
(b) (6)	225 mg	Libido Decreased	NR/Mild	Confinement or schedule conflict
	225 mg	Weight Increased	NR/Mild	Weight gain

Subject Number	Study Drug Dose	MedDRA Preferred Term	Relationship to Study Drug/ Severity	Discontinuation Reason (Sponsor Classification)
(b) (6)	225 mg	Polycythaemia	Related/Mild	Hematocrit >54%
	NA	ECG Abnormal	Related/Moderate	Adverse event
	225 mg	Weight Increased	NR/Mild	Weight gain
	300 mg	NA[1]	NA[1]	Weight gain
	225 mg 225 mg	Abdominal Pain Libido Decreased	NR/Moderate Related/Moderate	Adverse event
	150 mg	Acne	Related/Mild	Cmax or Cavg not achieved; met stopping criteria
	225 mg 225 mg	Oedema Peripheral Weight Increased	Related/Mild Related/Moderate	Adverse event
	150 mg 150 mg 150 mg	Spinal Cord Oedema Cervical Vertebral Fracture Muscle Spasms	NR/Moderate NR/Severe NR/Mild	Serious adverse event
	225 mg	Abdominal Discomfort	Related/Moderate	Adverse event
	225 mg 225 mg	Staphylococcal Bacteraemia Osteomyelitis	NR/Moderate NR/Moderate	Serious adverse event
	225 mg 225 mg 225 mg	Diarrhoea Fatigue Irritability	NR/Mild NR/Mild NR/Mild	Confinement or schedule conflict
	225 mg 225 mg 225 mg 225 mg	Feeling Hot Flushing Agitation Insomnia	Related/Moderate Related/Moderate Related/Moderate Related/Mild	Adverse event
	150 mg	RBC Count Increased	NR/Mild	Hematocrit >54%
	150 mg	PSA Increased	Related/Moderate	PSA > 4 ng/mL
	NA NA	Ataxia Balance Disorder	NR/Moderate NR/Moderate	Serious adverse event
	150 mg	APTT Prolonged	Related/Moderate	Adverse event
	150 mg	Dyspnoea	Related/Mild	Adverse event
	150 mg	Haematocrit Increased	Related/Mild	Hematocrit >54%
AndroGel 1.62%				
(b) (6)	60.75 mg	Polycythaemia	Related/Mild	Hematocrit > 54%
	40.5 mg	Anger	Related/Moderate	Adverse event
	81 mg 81 mg	Joint Stiffness Musculoskeletal Stiffness	NR/Mild NR/Mild	Adverse event
	81 mg	Headache	Related/Mild	Adverse event
	40.5 mg	Insomnia[2]	NR/Mild	Adverse event
	81 mg	Prostate Cancer	NR/Moderate	Adverse event

NR = not related; APTT = Activated Partial Thromboplastin Time
[1]Information obtained from the site after the study had ended indicated that the subject withdrew due to an increase in weight gain. An adverse event of weight gain had not been recorded for this subject in the eCRF.
[2]Information obtained from the site after the study had ended indicated that the subject withdrew from the study due to worsening insomnia. The adverse event of insomnia for this subject had an action taken of "dose not changed" in the eCRF.
Source: NDA 208088 (seq 0000), 2.7.4, Table 30, p. 62-63.

Reviewer comment: The percentage of subjects who discontinued the Phase 3 study due to an adverse event is greater in the Tlando 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 applicant'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 Tlando 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 Tlando group), hematocrit > 54% (3 subjects in the Tlando group and 1 subject in the AndroGel 1.62% group), and libido decreased (2 subjects in the Tlando group).

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 been the result of the study design. 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.

The discontinuations that resulted from hematocrit > 54% are discussed in detail in Section 7.4.2 Laboratory Findings.

Phase 1 Studies

In the Phase 1 studies in the target population, 4 subjects withdrew from the study prematurely due to an adverse event. Three subjects participating in Study LPCN 1021-09-001 withdrew due to respiratory tract infections, all of which were considered unrelated to study drug by the investigator; and 1 subject participating in Study M12-778 withdrew due to abdominal pain, which was considered by the investigator to be mild in severity and possibly related to study treatment. Table 34 summarizes AEs leading to study discontinuation in the Phase 1 studies.

Table 34: Summary of Subjects with Adverse Events that Lead to Study Discontinuation – Phase 1 Studies in Target Population

Subject Number	Study Treatment	Preferred Term	Relationship to Study Drug/Severity
LPCN 1021-09-001			
(b) (6)	Andriol	Respiratory tract infection	NR/Moderate
	Andriol	Respiratory tract infection	NR/Moderate
	Tlando	Upper respiratory tract infection	NR/Mild
M12-778			
(b) (6)	Placebo	Abdominal pain	Possibly related/Mild

NR = not related
Source: NDA 208088 (seq 0000), 2.7.4, Table 31, p. 63.

7.3.4 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 Tlando 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. Treatment emergent adverse events of special interest for the integrated Phase 1 and 2 studies are summarized in Table 35.

Table 35: Treatment-Emergent Adverse Events of Special Interest for Testosterone Replacement Therapy – Safety Population

Sponsor Defined Groups MedDRA Preferred Term[1]	Tlando N = 381	Andriol 80 mg N = 34	AndroGel 1.62% N = 104	Placebo N = 18
Cardiac and Cerebrovascular Disorders				
Atrial Fibrillation	1 (0.3)	0	2 (1.9)	0
Blood Pressure Increased	3 (0.8)	0	2 (1.9)	0
Blood Creatine Phosphokinase Increased	1 (0.3)	0	0	0
Bradycardia	0	0	1 (1.0)	0
Bundle Branch Block Bilateral	0	0	1 (1.0)	0
Cardiac Flutter	1 (0.3)	0	0	0
Electrocardiogram Abnormal	1 (0.3)	0	1 (1.0)	0
Electrocardiogram Change	1 (0.3)	0	0	0
Electrocardiogram T Wave Inversion	1 (0.3)	0	0	0
Enzyme Level Increased	3 (0.8)	0	0	0
Heart Rate Increased	2 (0.5)	1 (2.9)	0	0
Hypertension	6 (1.6)	0	5 (4.8)	0
Left Atrial Dilatation	0	0	1 (1.0)	0
Mitral Valve Incompetence	1 (0.3)	0	0	0
Palpitations	2 (0.5)	1 (2.9)	0	0
Sinus Tachycardia	0	0	1 (1.0)	0
Tachycardia	2 (0.5)	0	1 (1.0)	0
Tricuspid Valve Incompetence	1 (0.3)	0	0	0
Ventricular Extrasystoles	0	0	1 (1.0)	0
Ventricular Hypertrophy	1 (0.3)	0	0	0
Blood and Lymphatic System				
Anaemia	2 (0.5)	0	0	0
Blood Cholesterol Increased	0	1 (2.9)	0	0
Blood Triglycerides Increased	3 (0.8)	0	2 (1.9)	0
Haematocrit Increased	4 (1.0)	0	0	0
Haemoglobin Increased	1 (0.3)	0	0	0
High Density Lipoprotein Decreased	1 (0.3)	0	0	0
Hypercholesterolaemia	2 (0.5)	0	0	0
Hyperlipidaemia	1 (0.3)	0	2 (1.9)	0
Lipids Increased	2 (0.5)	0	0	0
Polycythaemia	1 (0.3)	0	1 (1.0)	0
Red Blood Cell Count Increased	1 (0.3)	0	0	0
Hepatic System				
Alanine Aminotransferase Increased	1 (0.3)	0	0	0
Blood Bilirubin Increased	0	0	1 (1.0)	0
Hepatic Enzyme Increased	0	0	1 (1.0)	0
Renal and Reproductive System				
Dysuria	0	0	1 (1.0)	0
Enuresis	0	0	1 (1.0)	0
Nocturia	0	0	2 (1.9)	0
Prostate Cancer	0	0	1 (1.0)	0

Sponsor Defined Groups MedDRA Preferred Term[1]	Tlando N = 381	Andriol 80 mg N = 34	AndroGel 1.62% N = 104	Placebo N = 18
Prostatic Specific Antigen Increased	4 (1.0)	0	0	0
Prostatitis	1 (0.3)	0	1 (1.0)	0
Prostatomegaly	2 (0.5)	0	0	0
Testicular Atrophy	0	0	1 (1.0)	0
Testicular Disorder	0	0	1 (1.0)	0
Urinary Retention	1 (0.3)	0	0	0
Nervous System				
Dizziness	4 (1.0)	0	2 (1.9)	1 (5.6)
Headache	19 (5.0)	1 (2.9)	5 (4.8)	2 (11.1)
Sleep Apnoea Syndrome	3 (0.8)	0	1 (1.0)	0
Tension Headache	1 (0.3)	0	0	0
Transient Ischaemic Attack	1 (0.3)	0	0	0
Psychiatric System				
Abnormal Dreams	1 (0.3)	0	0	0
Agitation	1 (0.3)	0	0	0
Anger	0	0	1 (1.0)	0
Anxiety	3 (0.8)	1 (2.9)	1 (1.0)	0
Depression	0	0	1 (1.0)	0
Insomnia	5 (1.3)	0	1 (1.0)	0
Irritability	2 (0.5)	0	2 (1.9)	0
Libido Decreased	3 (0.8)	0	0	0
Major Depression	0	0	1 (1.0)	0
Middle Insomnia	0	0	1 (1.0)	0
Mood Altered	1 (0.3)	0	0	0
Panic Attack	1 (0.3)	0	0	0
Restlessness	1 (0.3)	0	0	0
Other Potential Androgen Effects				
Acne	7 (1.8)	0	3 (2.9)	0
Alopecia	0	0	1 (1.0)	0
Gynaecomastia	0	0	1 (1.0)	0
Hirsutism	1 (0.3)	0	0	0
Oedema	1 (0.3)	0	0	0
Oedema Peripheral	3 (0.8)	0	1 (1.0)	0

[1]MedDRA version 17.1
Source: NDA 208088 (seq 0000), 2.7.4, Table 33, p. 66-67.

Reviewer comment: Except for the event of headache, all TEAEs of special interest occurred in less than 2.0% of Tlando subjects.

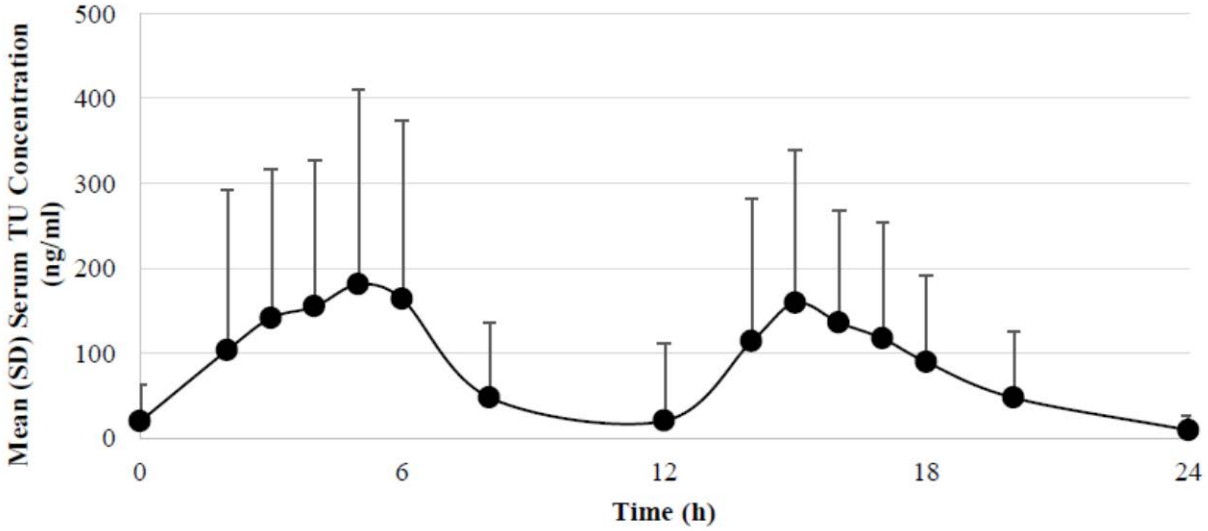
7.3.5 Submission Specific Primary Safety Concerns

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.

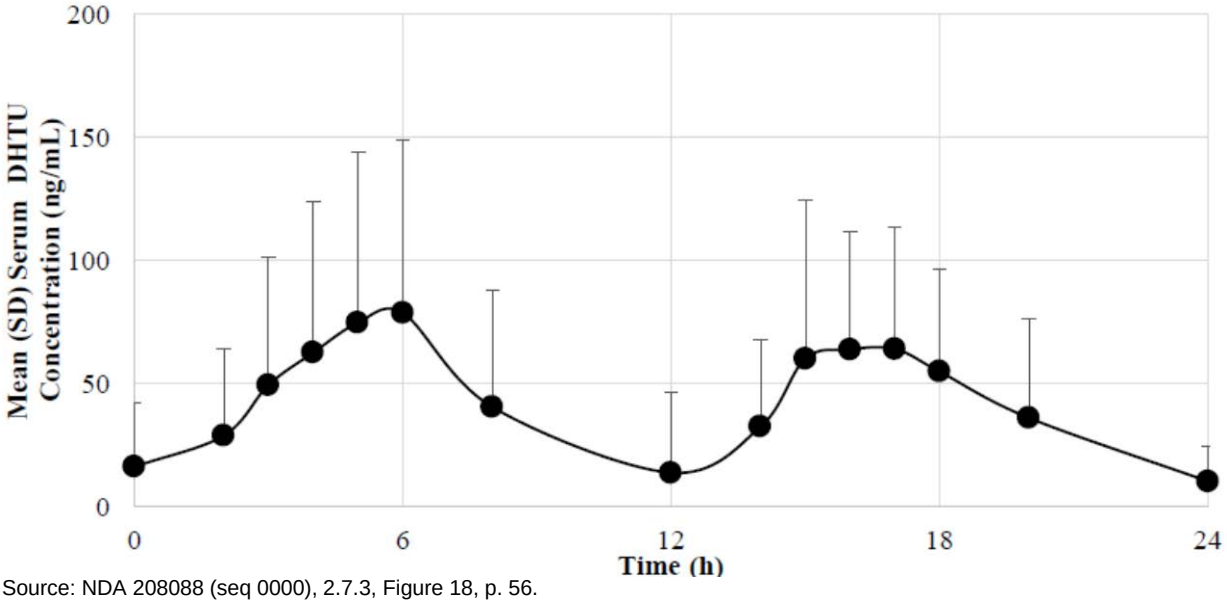
At Week 13, after subjects had been on their final Tlando dose (150, 225, or 300 mg BID) for at least 21 days, mean serum TU and DHTU concentrations pre-dose were 19.69 ng/mL and 16.25 ng/mL, respectively. Peak concentrations of TU and DHTU were 181.03 ng/mL and 78.68 ng/mL, respectively, and then declined to steady state pre-dose levels (20.30 ng/mL and 13.82 ng/mL at 12 hours post previous dose, respectively). Figure 17 and Figure 18 show serum concentrations of TU and DHTU at Week 13.

Figure 17: Mean (SD) Serum TU Concentration (ng/mL) over Time after Tlando Dosing at Week 13 – PK Set (N = 130)



Source: NDA 208088 (seq 0000), 2.7.3, Figure 17, p. 55.

Figure 18: Mean (SD) Serum DHTU Concentration (ng/mL) over Time after Tlando Dosing at Week 13 – PK Set (N = 130)



Source: NDA 208088 (seq 0000), 2.7.3, Figure 18, p. 56.

Table 36 and Table 37 show PK parameters by study week for TU and DHTU. Mean TU and DHTU Cmax0-24h, Cavg0-24h, and AUC0-24h for Week 3 (pre-titration) were higher than for Weeks 7 and 13.

Table 36: Serum PK Parameters of TU after Tlando Dosing by Visit through Week 13 – PK Set (N = 130, Overall)

Parameter	Statistic	Week 3	Week 7	Week 13
Cmax0-24h, ng/mL	Mean (SD)	498.75 (290.17)	444.67 (325.07)	428.50 (264.58)
Tmax, h	Median (Min, Max)	6.00 (0.0, 20.0)	6.00 (0.0, 20.0)	5.90 (0.0, 24.0)
AUC0-24h, ng·h/mL	Mean (SD)	2450.42 (1337.35)	2065.40 (1161.14)	2005.49 (980.62)
Cavg0-24h, ng/mL	Mean (SD)	102.13 (55.77)	86.15 (48.43)	83.62 (40.84)
Source: NDA 208088 (seq 0000), 2.7.3, Table 22, p. 56.				

Table 37: Serum PK Parameters of DHTU after Tlando Dosing by Visit through Week 13 – PK Set (N = 130)

Parameter	Statistic	Week 3	Week 7	Week 13
Cmax0-24h, ng/mL	Mean (SD)	162.25 (79.41)	141.62 (76.63)	140.94 (78.19)
Tmax, h	Median (Min, Max)	10.05 (2.0, 24.0)	8.00 (0.0, 20.0)	6.00 (0.0, 24.0)
AUC0-24h, ng·h/mL	Mean (SD)	1135.34 (539.23)	1009.86 (571.44)	976.42 (501.58)
Cavg0-24h, ng/mL	Mean (SD)	47.31 (22.48)	42.12 (23.85)	40.71 (20.89)
Source: NDA 208088 (seq 0000), 2.7.3, Table 23, p. 57.				

Table 38 shows the mean serum TU and DHTU concentration from a single blood draw taken 3 to 6 hours after morning dosing of Tlando at Weeks 26, 39, and 52.

Table 38: Serum TU and DHTU Concentration Obtained from a Single Blood Draw 3 to 6 Hours after Tlando Dosing by Visit after Week 13 – Full Analysis Set (All Available Data for Visit)

Visit	Statistic	Tlando	
		TU (ng/mL)	DHTU (ng/mL)
Week 26	N	143	143
	Mean (SD)	123.73 (143.15)	47.73 (43.70)
Week 39	N	137	137
	Mean (SD)	147.58 (225.14)	52.33 (60.89)
Week 52	N	143	143
	Mean (SD)	140.09 (223.27)	49.19 (57.12)

Source: NDA 208088 (seq 0000), 2.7.3, Table 23, p. 57.

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 provides the following 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 (8030765). 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 (S361.7.014).

Reviewer 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. Please refer to the pharmacology/toxicology review for a detailed review of the nonclinical studies.

In addition, during the Tlando 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.

Reviewer comment: While the laboratory findings and adverse event profile of Tlando and AndroGel 1.62% were in general similar, there were some differences.

- *The mean increase in PSA in the Tlando group was greater than the increase in the AndroGel 1.62% group.*

- *The decrease in HDL levels was greater in the Tlando group than in the AndroGel 1.62% group.*

Whether elevated levels of TU and DHTU played a role in the differences observed for these androgenic mediated events is not clear, however, given the lack of binding affinity of TU and DHTU for the androgen receptor, it seems unlikely.

In addition, because DHTU is metabolized to DHT, there is at least a theoretical concern that DHTU may contribute to increased levels of DHT. Due to the lack of a reference range for DHT in the Phase 3 study, it did not provide convincing evidence that DHT levels are within the normal level in subjects treated with Tlando.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase 3 Study
Common (≥ 2%) Treatment-Emergent Adverse Events (TEAE) reported during the Phase 3 study are summarized in Table 39.

Table 39: Common (>2%) Treatment-Emergent Adverse Events (TEAE) Occurring During the Phase 3 Study (Safety Set)

System Organ Class Preferred Term	Tlando N=210		AndroGel 1.62% N=104		Overall N=314	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE occurring in ≥ 2% of subjects	68 (32.4%)	88	33 (31.7%)	48	101 (32.2%)	136
Infections and Infestations	25 (11.9%)	29	14 (13.5%)	16	39 (12.4%)	44
Upper Respiratory Tract Infection	11 (5.2%)	12	6 (5.8%)	6	17 (5.4%)	18
Nasopharyngitis	8 (3.8%)	8	5 (4.8%)	5	13 (4.1%)	13
Bronchitis	4 (1.9%)	4	3 (2.9%)	3	7 (2.2%)	7
Sinusitis	5 (2.4%)	5	1 (1.0%)	2	6 (1.9%)	7
Investigations	14 (6.7%)	15	2 (1.9%)	2	16 (5.1%)	17
Weight Increased	10 (4.8%)	10	1 (1.0%)	1	11 (3.5%)	11
HCT Increased	5 (2.4%)	5	1 (1.0%)	1	6 (1.9%)	6
Nervous System Disorders	10 (4.8%)	10	5 (4.8%)	6	15 (4.8%)	16
Headache	10 (4.8%)	10	5 (4.8%)	6	15 (4.8%)	16
Musculoskeletal and Connective Tissue Disorders	9 (4.3%)	11	6 (5.8%)	7	15 (4.8%)	18
Back Pain	6 (2.9%)	6	3 (2.9%)	3	9 (2.9%)	9
Arthralgia	3 (1.4%)	5	4 (3.8%)	4	7 (2.2%)	9
General Disorders and Administration Site Conditions	5 (2.4%)	5	7 (6.7%)	8	12 (3.8%)	13
Fatigue	5 (2.4%)	5	7 (6.7%)	8	12 (3.8%)	13
Vascular Disorders	6 (2.9%)	6	5 (4.8%)	5	11 (3.5%)	11
Hypertension	6 (2.9%)	6	5 (4.8%)	5	11 (3.5%)	11
Skin and Subcutaneous Tissue Disorders	7 (3.3%)	7	3 (2.9%)	3	10 (3.2%)	10
Acne	7 (3.3%)	7	3 (2.9%)	3	10 (3.2%)	10
Gastrointestinal Disorders	6 (2.9%)	6	1 (1.0%)	1	7 (2.2%)	7
Diarrhea	6 (2.9%)	6	1 (1.0%)	1	7 (2.2%)	7
Metabolism and Nutrition Disorders	5 (2.4%)	5	0 (0.0%)	0	5 (1.6%)	5
Diabetes mellitus	5 (2.4%)	5	0 (0.0%)	0	5 (1.6%)	5

Source: Reviewer analysis of NDA 208088 (seq 0000), 5.3.5.1, Table 14.3.1.3.2, p. 550-551 and dataset ADAE.

Reviewer comment: Except for the events of weight increase, acne, diarrhea, diabetes, hematocrit increase, and sinusitis, the incidence of common TEAEs for Tlando was similar or less than that of AndroGel 1.62%.

Of the 10 cases of weight increase reported in Tlando subjects, four were assessed by the investigator as mild in severity and considered not related to the study drug; two were assessed as mild and related to the study drug; and four were assessed as moderate in severity and related to the study drug. Three of the 10 subjects who reported the AE of weight increase discontinued the study due the AE. Though the cause of the imbalance in the number of subjects reporting weight increase in not entirely clear, I believe it may have resulted from differences in the dietary

recommendations that were given to the two treatment groups. Subjects in the Tlando group were required to eat a meal before each dose of the drug and instructed to include at least 25 – 30 grams of fat in the meal, while subjects in the AndroGel 1.62% group had no dietary restrictions or recommendations. For Tlando subjects who had lower fat diets before the study, the minimum fat recommendation may have caused them to increase the fat (and caloric) content of their meals.

Of the seven cases of acne reported in Tlando treated subjects, six were assess by the investigator as mild and one was assess as moderate in severity. One subject discontinued the study due to the AE. All but one of the cases was considered related to the study drug.

Of the six cases of diarrhea reported in the Tlando group, one was considered related to the study drug and was assessed as mild in severity. The other five cases were not considered related to the study drug, although one of these subjects discontinued from the study due to the AE; in that case the AE was assessed as mild.

Of the five cases of diabetes reported in Tlando treated subjects, one was considered related to the study drug and was assessed as mild in severity. The other four cases were not considered related to the drug. All subjects reporting this AE completed the study.

Five Tlando treated subjects had hematocrit values greater than 54%. These subjects are reviewed in detail in Section 7.4.2 Laboratory Findings.

None of the cases of sinusitis reported in Tlando subjects was considered related to the study drug. All subjects with this AE completed the study.

Phase 1 Studies
In the Phase 1 studies, three common (≥ 2%) AEs were reported by Tlando subjects: headache (5.3%), dry skin (4.1%), and constipation (3.5%). The incidence of headache in the Phase 1 studies was similar to the incidence in the Phase 3 study (5.3% vs 4.8%, respectively). The incidence of dry skin and constipation was greater in the Phase 1 studies (dry skin 4.1% vs 0; constipation 3.5% vs 0.5%).

Reviewer comment: The AE of dry skin was the only common AE that was reported in the Phase 1 studies but not in the Phase 3 study.

7.4.2 Laboratory Findings

During the Phase 3 study, a central laboratory performed screening and safety laboratory tests. After enrollment in the study, any laboratory test value outside the reference range that the investigator considered to be clinically significant was repeated to verify the out-of-range value and was followed to a satisfactory clinical resolution. A

laboratory test value that required a subject to be discontinued from the study or required a subject to receive treatment was recorded as an adverse event.

During the study, blood and urine samples for the clinical laboratory tests were collected for subjects in both treatment arms at screening and at the following visits: Week 7, Week 13, Week 26, Week 39, and Week 52. Samples for clinical laboratory tests were collected in the morning before meals and study drug administration. The test results from screening served as the baseline for future assessments.

Hematology

Increases were observed for hematocrit (HCT) in both the Tlando and AndroGel 1.62% treatment arms. Table 40 summarizes the changes in HCT from baseline.

Table 40: Hematocrit: Mean Baseline and Mean Change from Baseline Values of Hematocrit in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		HCT Value (%)		HCT Value Change from Baseline (%)			HCT Value (%)		HCT Value Change from Baseline (%)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	206	43.48	3.20	--	--	103	44.03	3.36	--	--
Week 7	177	44.47	3.73	1.13	3.03	96	44.99	3.26	0.90	2.72
Week 13	155	45.21	3.90	1.76	3.19	91	45.83	3.85	1.85	3.45
Week 26	144	45.86	3.62	2.46	3.10	81	46.67	3.78	2.63	3.15
Week 39	137	46.28	3.97	2.82	3.27	76	46.25	3.73	2.28	3.39
Week 52	128	46.10	3.83	2.90	3.45	67	46.25	3.47	2.16	3.39
Early Term	50	45.40	4.44	1.60	3.13	14	46.36	3.57	1.81	2.12

Source: Source: NDA 208088 (seq 0000), 5.3.5.1, Table 60, p. 122.

During the study, nine subjects had a HCT that was greater than 54%: eight in the Tlando group and one in the AndroGel 1.62% group. The data for those subjects are summarized in Table 41.

Table 41: Summary of Subjects with Elevated > 54%Hematocrit (HCT) in Phase 3 Study – Safety Population

Subject Number (Study Disposition)	Age (years)	Visit	HCT Result	Total Dose Taken	Adverse Event (Severity/Relationship/ Action Taken/ Resolution)
Tlando					
(b) (6) (Hematocrit >54%)	55	Screening Week 7 Week 13 ET	46.0% 49.7% 54.6% 52.9%	43088 mg	Polycythemia (Mild/Related/Drug withdrawn/ Not resolved)

(b) (6) (Completed study)	51	Screening Week 7 Week 13 Unscheduled Week 26 Week 39 Week 52	46.9% 51.3% 55.3% 50.8% 51.1% 48.8% 52.1%	130050 mg	No adverse events recorded due to lab value.
(b) (6) (Completed study)	57	Screening Week 7 Unscheduled Week 13 Week 26 Week 39 Week 52	47.4% 54.4% 48.9% 48% 53.5% 53.3% 53.1%	167850 mg	No adverse events recorded due to lab value.
(b) (6) (Adverse event, decreased libido)	54	Screening ET	45.3% 54.2%	24300 mg	No adverse events recorded due to lab value.
(b) (6) (Completed study)	53	Screening Week 7 Week 13 Week 26 Week 39 Week 52	45% 43.8% Not Done 50.5% 52.3% 54.5%	153900 mg	No adverse events recorded due to lab value.
(b) (6) (Hematocrit >54%)	68	Screening Unscheduled Week 7 Week 13 Unscheduled Week 26 Week 39 Unscheduled ET	49.5% 46.1% 53.1% 55% 54.9% 52.5% 55% 57.1% 53.6%	91275 mg	Red blood cell count increased (Mild/ Not related/Drug withdrawn/ Resolved)
(b) (6) (ET due to protocol violation)	57	Screening Week 7 Week 13 Unsch ET	47.4% 49.5% 54.1% 54.8% 51%	32175 mg	Hematocrit increased (Mild/Related/Dose not changed/ Resolved)
(b) (6) (ET due to hematocrit >54%)	54	Screening Week 7 ET	47.1% 54.3% 53.5%	24300 mg	Hematocrit increase (Mild/Related/Withdrawn / Not resolved)
AndroGel 1.62%					
(b) (6) (ET due to hematocrit >54%)	57	Screening Week 7 Week 13 Week 26 Week 39 ET	43.6% 45.7% 49.1% 50% 55.8% 51.3%	909 g	Polycythemia (Mild/Related/Drug Withdrawn/ Resolved)

Source: NDA 208088 (seq 0000), 2.7.4, Table 48, p. 85-86.

Reviewer comment: During the course of the study, mean HCT values were similar in both treatment groups. The mean percentage change from baseline to week 52 was 2.90% for Tlando subjects and 2.16% for AndroGel 1.62% subjects. However, a greater number of subjects in the Tlando group had a HCT value that was greater than 54%. Of the nine subjects with a HCT value greater than 54%, eight were in the Tlando group and one was in the AndroGel 1.62% group.

Of the eight subjects in the Tlando group with a HCT value greater than 54%, two subjects ([redacted] and [redacted] had HCT values that were less than 54% during a re-assessment done one week after the original assessment. Both subjects continued in the study and neither had a HCT value greater than 54% during the remainder of the study.

One subject ([redacted] discontinued from the study due to an unrelated AE (decreased libido) and had a HCT value of 54.2% at the early termination visit. It should be noted that the subject was exposed to the study drug for 32 days and that the early termination assessment was done 28 days after the last exposure to the drug.

Of the remaining five subjects, only one had a HCT value that exceeded 55%. Subject [redacted] had the highest HCT value (57.1%) reported in Tlando treated subjects. The subject was discontinued from the study due to the increase in HCT. At the early termination visit, which occurred 39 days after the date of last exposure to the drug, the HCT was 53.6%. This subject also reported one SAE during the study. On Study Day 139, the subject experienced worsening of GERD with esophagitis, which required hospitalization. The event was not considered related to the study drug by the investigator. During the event, the study drug was interrupted for three days. No additional AEs were reported for this subject.

Increases were also observed for hemoglobin in both the Tlando and AndroGel 1.62% treatment groups. Table 42 summarizes the changes in hemoglobin from baseline.

Table 42: Hemoglobin: Mean Baseline and Mean Change from Baseline Values of Hemoglobin in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		Hgb Value (g/L)		Hgb Value Change from Baseline (g/L)			Hgb Value (g/L)		Hgb Value Change from Baseline (g/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	206	143.9	10.94	--	--	103	146.1	11.03	--	--
Week 7	177	143.7	12.28	0.3	9.06	96	146.7	10.42	0.4	8.34
Week 13	155	144.9	12.82	1.1	10.15	91	148.3	12.47	2.3	10.53
Week 26	144	147.1	12.37	3.5	9.47	81	151.3	11.35	5.4	9.72
Week 39	137	149.1	13.42	5.3	10.33	76	150.6	12.30	4.7	10.60
Week 52	128	152.1	13.04	9.1	10.59	67	152.8	11.74	6.9	11.23
Early Term	50	146.6	14.02	2.3	9.19	14	151.0	12.37	2.3	8.54
Source: Source: NDA 208088 (seq 0000), 5.3.5.1, Table 61, p. 122.										

Reviewer comment: During the course of the study, mean hemoglobin values were similar in both treatment groups. The mean hemoglobin at week 52 was 152.1 g/L for Tlando subjects and 152.8 g/L for AndroGel 1.62% subjects. The mean change from baseline to week 52 was 9.1 g/L for Tlando subjects and 6.9 g/L for AndroGel 1.62% subjects.

Prostate-specific Antigen (PSA)

Increases were observed for PSA in both the Tlando and AndroGel 1.62% treatment arms. Table 43 summarizes the changes in PSA from baseline.

Table 43: PSA: Mean Baseline and Mean Change from Baseline Values of PSA in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		PSA Value (µg/L)		PSA Value Change from Baseline (µg/L)			PSA Value (µg/L)		PSA Value Change from Baseline (µg/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	208	0.70	0.47	--	--	104	0.62	0.40	--	--
Week 7	182	0.86	0.69	0.16	0.51	96	0.66	0.46	0.06	0.30
Week 13	156	0.82	0.58	0.12	0.37	91	0.67	0.53	0.08	0.35
Week 26	144	0.93	0.72	0.22	0.45	82	0.71	0.40	0.14	0.31
Week 39	137	0.89	0.57	0.18	0.36	76	0.68	0.41	0.11	0.33
Week 52	129	0.98	0.66	0.24	0.43	69	0.70	0.36	0.15	0.24
Early Term	50	1.08	1.73	0.35	1.69	14	0.89	0.57	0.06	0.21

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 67, p. 126.

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. The Tlando treated subjects with PSA values > 4 ng/ml are discussed below.

Reviewer comment: In general, mean PSA increased in both the Tlando and AndroGel 1.62% treatment groups, however, the increase in the Tlando group was greater than the increase in the AndroGel 1.62% group (0.24 ng/mL versus 0.15 ng/mL at week 52). Three subjects in the Tlando group had PSA > 4 ng/mL compared to two in the AndroGel 1.62% group. In two of the three subjects in the Tlando group, the increase in PSA was transient and the PSA level was < 4 ng/mL when it was re-checked one week after the increase. In the third subject, there was a rapid increase to 12.2 ng/mL that decreased to 7.8 ng/mL three days later. Based on the information provided, it is more likely that this increase was the result of a transient inflammatory process than of the study drug.

The labeling for currently approved testosterone products includes a recommendation to periodically monitor PSA. The labeling for Tlando should also include this recommendation.

Clinical Chemistry

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 greater than the decrease in subjects treated with AndroGel 1.62%. Mean HDL values and changes from baseline are summarized in Table 45.

Table 44: Mean Baseline and Mean Change from Baseline Values of HDL in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		HDL Value (mmol/L)		HDL Value Change from Baseline (mmol/L)			HDL Value (mmol/L)		HDL Value Change from Baseline (mmol/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	1.26	0.33	--	--	104	1.20	0.27	--	--
Week 7	182	1.02	0.26	-0.25	0.21	96	1.14	0.26	-0.07	0.18
Week 13	157	1.03	0.25	-0.22	0.20	91	1.14	0.25	-0.08	0.18
Week 26	144	1.08	0.25	-0.19	0.22	82	1.12	0.27	-0.08	0.20
Week 39	137	1.08	0.26	-0.19	0.21	76	1.16	0.27	-0.05	0.22
Week 52	128	1.12	0.27	-0.15	0.21	68	1.16	0.25	-0.05	0.23
Early Term	50	1.13	0.29	-0.13	0.24	14	0.99	0.24	-0.08	0.17
Source: NDA 208088 (seq 0000), 5.3.5.1, Table 62, p. 123.										

Table 46 shows the proportion of subjects with HDL levels greater than or equal to 40 mg/dL (the lower bound of the normal range) during 52 weeks of treatment with either Tlando or AndroGel. At each of the time points that HDL was assessed, the proportion of subjects with HDL $\geq$ 40 mg/dL was lower in the Tlando treatment group than in the AndroGel 1.62% group.

Table 45: Proportion of Subjects with HDL Values > 40 mg/dL in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando			AndroGel 1.62%		
		Subjects with HDL $\geq$ 40 mg/dL			Subjects with HDL $\geq$ 40 mg/dL	
	N	n (p)	SE	N	n (%)	SE
Baseline	207	161 (0.78)	0.03	104	76 (0.73)	0.04
Week 7	182	68 (0.37)	0.04	96	63 (0.66)	0.05
Week 13	157	68 (0.43)	0.04	91	57 (0.63)	0.05
Week 26	144	79 (0.55)	0.04	82	52 (0.63)	0.05
Week 39	137	76 (0.55)	0.04	76	53 (0.70)	0.05
Week 52	128	81 (0.63)	0.04	68	46 (0.68)	0.06
Early Term	50	31 (0.62)	0.07	14	7 (0.50)	0.14
Source: Reviewer analysis, NDA 208088 (seq 0000), 5.3.5.1, Dataset ADLB						

Mean LDL levels showed an initial drop in both treatment groups. In the Tlando group, levels returned to baseline by week 26 and then remained relatively stable through the end of the study. In the AndroGel 1.62% group, the initial drop was maintained through the end of the study. Mean LDL values and changes from baseline are summarized in Table 47.

Table 46: Mean Baseline and Mean Change from Baseline Values of LDL in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		LDL Value (mmol/L)		LDL Value Change from Baseline (mmol/L)			LDL Value (mmol/L)		LDL Value Change from Baseline (mmol/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	194	2.94	0.80	--	--	97	2.85	0.94	--	--
Week 7	175	2.81	0.92	-0.17	0.62	90	2.61	0.76	-0.25	0.70
Week 13	150	2.84	0.94	-0.10	0.59	81	2.58	0.84	-0.27	0.55
Week 26	140	2.93	0.96	0.01	0.66	77	2.58	0.72	-0.27	0.61
Week 39	134	2.92	0.95	0.00	0.77	70	2.74	0.81	-0.05	0.72
Week 52	124	2.92	0.97	-0.01	0.68	64	2.66	0.93	-0.21	0.74
Early Term	49	2.95	0.84	-0.17	0.58	13	2.49	0.62	-0.19	0.38

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 63, p. 124.

Mean triglycerides decreases from baseline were observed for the Tlando group during the course of the study, while mean increases were observed for the AndroGel 1.62% group through week 39. Mean triglyceride values and changes from baseline are summarized in Table 48.

Table 47: Triglycerides: Mean Baseline and Mean Change from Baseline Values of Triglycerides in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		TG Value (mmol/L)		TG Value Change from Baseline (mmol/L)			TG Value (mmol/L)		TG Value Change from Baseline (mmol/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	2.17	1.61	--	--	104	2.11	1.29	--	--
Week 7	182	2.03	1.28	-0.12	1.27	96	2.22	1.27	0.12	0.90
Week 13	157	1.94	1.09	-0.14	1.19	91	2.35	1.60	0.21	1.12
Week 26	144	1.93	1.47	-0.18	1.74	82	2.50	2.68	0.33	2.41
Week 39	137	1.84	1.11	-0.18	0.95	76	2.26	1.69	0.12	1.13
Week 52	128	1.79	1.17	-0.21	1.06	68	2.02	1.48	-0.08	1.07
Early Term	50	2.43	1.63	-0.11	1.32	14	3.18	3.08	1.05	2.39

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 64, p. 124.

Mean total cholesterol decreased from baseline for both the Tlando and AndroGel 1.62% group. Mean total cholesterol values and changes from baseline are summarized in Table 49.

Table 48: Total Cholesterol: Mean Baseline and Mean Change from Baseline Values of Total Cholesterol in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		TC Value (mmol/L)		TC Value Change from Baseline (mmol/L)			TC Value (mmol/L)		TC Value Change from Baseline (mmol/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	5.12	0.97	--	--	104	4.97	1.12	--	--
Week 7	182	4.73	1.06	-0.43	0.73	96	4.75	0.96	-0.25	0.77
Week 13	157	4.74	1.06	-0.35	0.72	91	4.73	1.12	-0.28	0.74
Week 26	144	4.84	1.08	-0.25	0.75	82	4.78	1.06	-0.24	0.86
Week 39	137	4.79	1.04	-0.27	0.90	76	4.92	1.15	-0.08	0.92
Week 52	129	4.80	1.07	-0.24	0.86	69	4.71	1.12	-0.28	0.88
Early Term	50	5.16	1.11	-0.24	0.71	14	4.80	0.90	0.14	0.87

Source: NDA 208088 (seq 0000), 5.3.5.1, Table 65, p. 125.

Reviewer comment: HDL levels decreased in both treatment groups, however, the decrease was greater in the Tlando group. After 52 weeks of treatment, mean HDL levels decreased from 48.7 to 43.3 mg/dL in Tlando treated subjects and from 46.4 to 44.9 mg/dL in AndroGel 1.62% treated subjects. At each of the time points that HDL was assessed, the proportion of subjects with HDL $\geq$ 40 mg/dL was lower in the Tlando treatment group than in the AndroGel 1.62% group. Decreased HDL is considered a risk factor for cardiovascular disease. Levels of other lipids assessed during the study (triglycerides, total cholesterol, and LDL) decreased or remained unchanged during treatment with Tlando.

The labeling for currently approved testosterone products includes a recommendation to periodically monitor lipids. The labeling for Tlando should also include this recommendation.

C-reactive protein (CRP) was assessed at baseline and at weeks 7, 13, 26, 39, and 52 during the Phase 3 study. Mean CRP values and changes from baseline (in nmol/L) are summarized in Table 50.

Table 49: Mean Baseline and Mean Change from Baseline Values of CRP in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		CRP Value (nmol/L)		CRP Value Change from Baseline (nmol/L)			CRP Value (nmol/L)		CRP Value Change from Baseline (nmol/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	196	23.38	19.44	--	--	99	21.28	18.82	--	--
Week 7	175	25.78	19.29	-3.20	32.99	92	19.62	15.68	-9.57	49.22
Week 13	150	25.88	20.27	-3.48	30.35	88	20.14	18.18	-9.89	49.64
Week 26	140	25.06	20.26	-5.84	29.92	80	21.10	18.76	-4.01	32.77
Week 39	122	24.03	17.85	-4.10	29.95	76	23.62	19.54	-4.02	39.93
Week 52	120	23.06	18.27	-4.12	22.74	68	22.85	20.42	-3.69	39.31
Early Term	48	24.59	19.55	-6.05	45.50	14	22.73	19.60	-26.32	103.14

Note: The last nonmissing measurement at screening served as the baseline. Based on Centers for Disease Control and American Heart Association recommendations, CRP values > 95.23 nmol/L were excluded, as such a high CRP level is poss bly related to acute inflammation.
Source: NDA 208088 (seq 0000), 5.3.5.1, Table 66, p. 125.

For clinical chemistry analytes not specifically mentioned in this section, there were no notable differences between the Tlando and AndroGel 1.62% groups at baseline or at other time points.

Sex hormone binding globulin (SHBG)

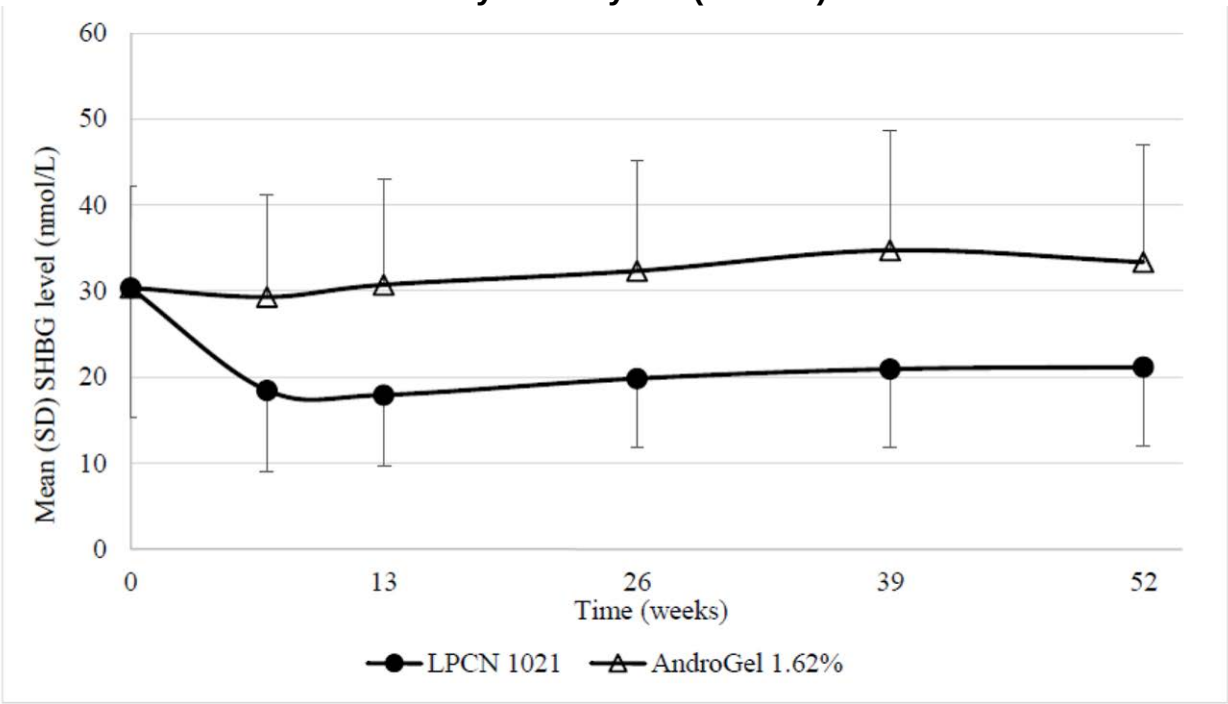
Serum sex hormone binding globulin (SHBG) concentration was measured at baseline, Week 7, Week 13, Week 26, Week 39 and Week 52 of the Phase 3 study. Mean SHBG levels showed a decrease at each post-baseline visit in subjects receiving Tlando while mean SHBG levels showed no significant decrease from baseline in subjects receiving AndroGel 1.62%. Mean SHBG results from subjects treated with Tlando and AndroGel 1.62% are shown in Table 51 and Figure 19.

Table 50: Sex Hormone Binding Globulin (SHBG) Levels (nmol/L) and Change from Baseline through Week 52 during Phase 3 Study – Safety Set

	Tlando					AndroGel 1.62%				
		SHBG Level (nmol/L)		SHBG Change from Baseline (nmol/L)			SHBG Level (nmol/L)		SHBG Change from Baseline (nmol/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	204	30.34	15.01	--	--	99	30.35	11.79	--	--
Week 7	115	18.44	9.40	-11.49	7.82	93	29.27	11.87	-0.69	6.56
Week 13	145	17.90	8.18	-11.75	7.16	86	30.70	12.29	0.03	5.55
Week 26	140	19.81	7.93	-9.74	8.71	81	32.31	12.86	1.77	6.60
Week 39	136	20.91	9.09	-8.75	10.15	76	34.71	13.97	3.89	8.15
Week 52	126	21.14	9.20	-8.91	9.74	67	33.33	13.65	2.39	7.91
Early Term	48	24.97	11.67	-5.40	9.61	13	29.36	12.27	0.43	6.66

Source: NDA 208088 (seq 0000), 2.7.4, Table 63, p. 107.

Figure 19: Change (+/- SD) in SHBG (nmol/L) Values over Time during the Phase 3 Study – Safety Set (N = 314)



Source: NDA 208088 (seq 0000), 2.7.4, Figure 4, p. 106.

The largest decrease in SHBG during treatment with Tlando was observed at Week 13 (change from baseline of -11.75 nmol/L), after which SHBG levels increased slightly and remained relatively stable. The mean SHBG values of Tlando treated subjects remained within the normal range of 17.3 to 65.8 nmol/L.

Reviewer comment: The effect of the reduction in SHBG on free testosterone levels is discussed in Section 6.1.10 - Additional Efficacy Issues/Analyses.

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)
LH and FSH decreased in both the Tlando and AndroGel 1.62% treatment groups. Decreases in the Tlando group were greater than decreases in the AndroGel 1.62% group. Table 52 and Table 53 show mean values and changes from baseline for LH and FSH, respectively, during the Phase 3 study.

Table 51: Mean Baseline and Mean Change from Baseline Values of LH in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		LH Value (IU/L)		LH Value Change from Baseline (IU/L)			LH Value (IU/L)		LH Value Change from Baseline (IU/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	5.75	7.34	--	--	104	4.75	4.40	--	--
Week 7	119	1.43	4.30	-4.05	5.75	95	1.74	2.97	-2.80	2.53
Week 13	152	1.61	3.90	-3.98	5.35	89	1.54	2.64	-3.11	2.14
Week 26	144	1.77	3.38	-4.07	6.42	82	1.20	1.79	-3.30	2.54
Week 39	137	2.12	4.05	-3.77	6.67	76	1.82	2.35	-2.77	2.60
Week 52	128	2.35	4.48	-3.75	7.23	69	1.59	2.42	-2.95	2.61
Early Term	50	3.41	4.02	-1.50	4.87	14	1.78	1.50	-2.62	2.55
Source: NDA 208088 (seq 0000), 5.3.5.1, Table 69, p. 127.										

Table 52: Mean Baseline and Mean Change from Baseline Values of FSH in Tlando- and AndroGel 1.62%-Treated Subjects (Safety Set)

	Tlando					AndroGel 1.62%				
		FSH Value (IU/L)		FSH Value Change from Baseline (IU/L)			FSH Value (IU/L)		FSH Value Change from Baseline (IU/L)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	8.43	10.30	--	--	104	7.20	7.61	--	--
Week 7	119	2.29	5.02	-5.50	8.06	95	3.26	5.47	-3.93	5.29
Week 13	152	2.88	7.70	-5.15	6.66	89	3.02	5.65	-4.26	4.47
Week 26	144	3.37	6.94	-5.08	8.21	82	2.44	3.90	-4.21	4.59
Week 39	136	3.76	8.02	-4.86	8.01	76	3.51	5.01	-3.31	4.86
Week 52	128	3.97	9.25	-4.93	9.50	69	3.08	4.44	-3.92	5.13
Early Term	50	5.15	7.55	-2.68	9.29	14	3.35	3.12	-3.77	5.40
Source: NDA 208088 (seq 0000), 5.3.5.1, Table 70, p. 128.										

Reviewer comment: A decrease in LH and FSH is expected during treatment with testosterone.

7.4.3 Vital Signs

During the Phase 3 study, vital signs were measured at each visit after the subject had been sitting at rest for at least 5 minutes. Mean change from baseline values in vital sign measurements show no clinically meaningful changes for heart rate or temperature. Mean body weight was similar between the 2 groups at baseline and showed slight increases during the study (mean [SD] increase of 0.89 [5.27] kg for the Tlando group compared to 1.37 [7.80] kg for the AndroGel 1.62% group).

Blood pressure was monitored during the study. Mean and change from baseline values for systolic and diastolic blood pressures are shown in Table 54 and Table 55, respectively.

Table 53: Mean Baseline and Mean Change from Baseline Values for Systolic Blood Pressure in Tlando-Treated Subjects during Phase 3 Study – Safety Set

	Tlando					AndroGel 1.62%				
		Value (mm Hg)		Value Change from Baseline (mm Hg)			Value (mm Hg)		Value Change from Baseline mm Hg)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	210	132.6	13.99	--	--	104	132.6	14.50	--	--
Week 7	182	131.4	14.33	-0.9	13.79	97	129.9	12.56	-3.1	13.47
Week 13	157	131.3	12.65	-0.8	12.57	92	130.7	12.47	-2.6	12.37
Week 26	144	130.7	13.28	-1.1	12.74	82	131.0	13.82	-2.0	14.35
Week 39	138	131.0	13.71	-0.5	13.92	76	132.8	13.86	-0.7	12.87
Week 52	130	131.2	14.70	-0.3	14.36	71	133.5	13.76	0.0	13.43
Early Term	49	130.2	11.17	-3.5	12.25	15	131.1	12.06	1.0	15.46
Source: NDA 208088 (seq 0000), 2.7.4, Table 65, p. 109.										

Table 54: Mean Baseline and Mean Change from Baseline Values for Diastolic Blood Pressure in Tlando-Treated Subjects during Phase 3 Study – Safety Set

	Tlando					AndroGel 1.62%				
		Value (mm Hg)		Value Change from Baseline (mm Hg)			Value (mm Hg)		Value Change from Baseline mm Hg)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	210	82.9	8.58	--	--	104	82.4	8.61	--	--
Week 7	182	79.7	8.93	-3.0	8.44	97	81.7	8.02	-0.9	7.67
Week 13	157	80.6	8.46	-2.5	7.47	92	82.6	9.37	0.0	9.42
Week 26	144	81.1	9.32	-1.9	8.17	82	82.1	8.95	-0.4	9.59
Week 39	138	82.1	8.27	-0.8	7.80	76	83.6	8.07	1.1	7.21
Week 52	130	81.4	9.18	-1.3	8.32	71	83.0	9.11	0.4	9.36
Early Term	49	81.3	7.85	-0.7	7.81	15	80.1	9.41	-1.6	8.58
Source: NDA 208088 (seq 0000), 2.7.4, Table 66, p. 109.										

Reviewer comment: In general, there were no clinically meaningful changes in vital signs in Tlando treated subjects during the course of the study.

7.4.4 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 at baseline. Shifts from normal to abnormal, not clinically significant occurred at Week 7 for 15.4% and 10.3% of the Tlando and AndroGel 1.62% subjects, respectively; at Week 13 for 17.2% and 11.8% of the subjects, respectively; at Week 26 for 13.1% and 11.0% of subjects, respectively; at Week 39 for 16.7% and 14.5% of subjects, respectively; at

Week 52 for 23.8% and 11.4% of subjects respectively; and at Early Termination for 5.9% and 0% of subjects, respectively.

Three subjects who received Tlando and two subjects who received AndroGel 1.62% had shifts from normal or abnormal (not clinically significant), at baseline to abnormal (clinically significant) during the study.

Reviewer comment: During the Phase 3 study, the number of subjects with shifts from normal or abnormal (not clinically significant) to abnormal (clinically significant) was similar for the Tlando and AndroGel 1.62% treatment groups. One subject treated with Tlando was discontinued from the study due to an AE of ECG abnormal. This subject had a history of systolic ejection murmur II/IV (since (b) (6)) and hypertension (since (b) (6)). His screening ECG was abnormal (not clinically significant).

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted to this NDA.

7.4.6 Immunogenicity

No studies of immunogenicity were done to support this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The percentage of subjects reporting at least one TEAE was lower for the 75 and 100 mg TU dose levels (18.8% and 15.8%) than for the higher dose levels (50.0% to 68.3% for the 150 mg to 300 mg dose levels). The 75 and 100 mg TU dose levels were used only in studies in which subjects were exposed to treatment for 0 to 4 weeks.

For most SOCs, no obvious dose dependency of AEs was noted. However, a decrease in the percentage of adverse events was noted with increasing dose for gastrointestinal disorders; respiratory, thoracic and mediastinal disorders; skin and subcutaneous disorders; and metabolism and nutritional disorders. In contrast, percentage of adverse events appeared to increase slightly with increasing dose for general disorders and administration site conditions and musculoskeletal and connective tissue disorders.

7.5.2 Time Dependency for Adverse Events

The highest percentage of subjects experiencing at least one TEAE for both the Tlando and AndroGel 1.62% groups occurred in subjects who remained in the study for 13 to 26 weeks (85.7% of Tlando subjects and 88.9% of AndroGel 1.62% subjects). For

Tlando and both active treatment groups, the lowest percentage of subjects experiencing at least one TEAE was for subjects enrolled in a study for 4 weeks or less.

7.5.3 Drug-Demographic Interactions

Age

Of the 381 hypogonadal men who received Tlando in a Phase 1 or 3 study, 28 (7.3%) were 65 years or older. Table 60 and Table 61 display TEAEs by SOC for subjects less than 65 years of age and at least 65 years of age, respectively, for the Phase 1 and 3 studies by treatment group.

Table 55: Treatment Emergent Adverse Events by System Organ Class for Subjects < 65 Years for Phase 1 and 3 Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	Tlando N = 353	Andriol 80 mg N = 34	AndroGel 1.62% N = 92	Placebo N = 17
Any TEAE	174 (49.3)	12 (35.3)	59 (64.1)	8 (47.1)
Infections and Infestations	43 (12.2)	3 (8.8)	19 (20.7)	0
Gastrointestinal Disorders	40 (11.3)	2 (5.9)	9 (9.8)	8 (47.1)
Investigations	37 (10.5)	3 (8.8)	11 (12.0)	0
Musculoskeletal and Connective Tissue Disorders	30 (8.5)	0	12 (13.0)	1 (5.9)
Nervous System Disorders	29 (8.2)	2 (5.9)	8 (8.7)	3 (17.6)
Skin and Subcutaneous Tissue Disorders	28 (7.9)	1 (2.9)	8 (8.7)	2 (11.8)
General Disorders and Administration Site Conditions	21 (5.9)	1 (2.9)	12 (13.0)	1 (5.9)
Injury, Poisoning and Procedural Complications	19 (5.4)	2 (5.9)	9 (9.8)	0
Respiratory, Thoracic and Mediastinal Disorders	16 (4.5)	0	7 (7.6)	0
Psychiatric Disorders	14 (4.0)	1 (2.9)	5 (5.4)	0
Metabolism and Nutrition Disorders	13 (3.7)	0	7 (7.6)	0
Vascular Disorders	8 (2.3)	1 (2.9)	6 (6.5)	0
Cardiac Disorders	7 (2.0)	1 (2.9)	5 (5.4)	0
Blood and Lymphatic System Disorders	6 (1.7)	0	2 (2.2)	0
Eye Disorders	5 (1.4)	0	2 (2.2)	0
Renal and Urinary Disorders	5 (1.4)	0	7 (7.6)	0
Reproductive System and Breast Disorders	5 (1.4)	0	6 (6.5)	0
Congenital, Familial and Genetic Disorders	1 (0.3)	0	0	0
Ear and Labyrinth Disorders	1 (0.3)	0	1 (1.1)	0
Immune System Disorders	1 (0.3)	0	1 (1.1)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.3)	0	1 (1.1)	0
Surgical and Medical Procedures	1 (0.3)	0	1 (1.1)	0
Endocrine Disorders	0	0	1 (1.1)	0

Studies included: LPCN 1021-13-001, LPCN 1021-09-001, LPCN 1021-14-001, M12-778, M13-298, and S361.1.001
Source: NDA 208088 (seq 0000), 2.7.4, Table 72, p. 119.

Table 56: Treatment Emergent Adverse Events by System Organ Class for Subjects ≥ 65 Years for Phase 1 and 3 Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	Tlando N = 28	Andriol 80 mg N = 0	AndroGel 1.62% N = 12	Placebo N = 1
Any TEAE	16 (57.1)	0	9 (75.0)	1 (100)
Investigations	5 (17.9)	0	1 (8.3)	0
Nervous System Disorders	5 (17.9)	0	0	0
Gastrointestinal Disorders	3 (10.7)	0	2 (16.7)	0
Infections and Infestations	2 (7.1)	0	3 (25.0)	0
Injury, Poisoning and Procedural Complications	2 (7.1)	0	2 (16.7)	0
Musculoskeletal and Connective Tissue Disorders	2 (7.1)	0	0	0
Renal and Urinary Disorders	2 (7.1)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	2 (7.1)	0	2 (16.7)	0
Blood and Lymphatic System Disorders	1 (3.6)	0	0	0
General Disorders and Administration Site Conditions	1 (3.6)	0	1 (8.3)	1 (100)
Skin and Subcutaneous Tissue Disorders	1 (3.6)	0	0	0
Surgical and Medical Procedures	1 (3.6)	0	0	0
Vascular Disorders	1 (3.6)	0	0	0
Cardiac Disorders	0	0	1 (8.3)	0
Ear and Labyrinth Disorders	0	0	1 (8.3)	0
Immune System Disorders	0	0	1 (8.3)	0
Metabolism and Nutrition Disorders	0	0	2 (16.7)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	1 (8.3)	0
Psychiatric Disorders	0	0	1 (8.3)	0

Studies included: LPCN 1021-13-001, LPCN 1021-09-001, LPCN 1021-14-001, M12-778, M13-298, and S361.1.001
Source: NDA 208088 (seq 0000), 2.7.4, Table 73, p. 120.

Of subjects who were treated with Tlando, 49.3% of younger subjects experienced at least one TEAE compared with 57.1% of older subjects. A higher percentage of older subjects experienced at least one TEAE with AndroGel 1.62% compared with younger subjects (75.0% vs 64.1%, respectively). For older subjects who received Tlando, adverse events occurred most frequently in the SOCs of investigations (17.9% of older subjects vs 12.2% of younger subjects), nervous system disorders (17.9% vs 8.2%, respectively), gastrointestinal disorders (10.7% vs 11.3%), infections and infestations (7.1% vs 12.2%, respectively), injury, poisoning, and procedural complications (7.1% vs 5.4%, respectively), musculoskeletal and connective tissue disorders (7.1% vs 8.5%, respectively), and respiratory, thoracic, and mediastinal disorders (7.1% vs 4.5%).

Body Mass Index

Of the 381 hypogonadal men who received Tlando in a Phase 1 or Phase 3 study, 176 (46.2%) had a BMI of 30 kg/m2 or greater, which meets the criteria of obesity. Table 62 and Table 63 display TEAEs by SOC for subjects with BMI less than 30 kg/m^2 (non-obese) and at least 30 kg/m^2 (obese), respectively, for Phase 1 and 3 studies by treatment.

Table 57: Treatment Emergent Adverse Events by System Organ Class for Subjects with Body Mass Index < 30 kg/m2 for Phase 1 and 3 Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class, n (%)	Tlando N = 205	Andriol 80 mg N = 29	AndroGel 1.62% N = 37	Placebo N = 16
Any TEAE	91 (44.4)	12 (41.4)	26 (70.3)	8 (50.0)
Gastrointestinal Disorders	22 (10.7)	2 (6.9)	4 (10.8)	7 (43.8)
Infections and Infestations	20 (9.8)	3 (10.3)	9 (24.3)	0
Nervous System Disorders	19 (9.3)	2 (6.9)	4 (10.8)	3 (18.8)
Investigations	18 (8.8)	3 (10.3)	6 (16.2)	0
Musculoskeletal and Connective Tissue Disorders	14 (6.8)	0	6 (16.2)	1 (6.3)
Skin and Subcutaneous Tissue Disorders	14 (6.8)	1 (3.4)	3 (8.1)	2 (12.5)
Injury, Poisoning and Procedural Complications	11 (5.4)	2 (6.9)	6 (16.2)	0
General Disorders and Administration Site Conditions	8 (3.9)	1 (3.4)	3 (8.1)	2 (12.5)
Respiratory, Thoracic and Mediastinal Disorders	7 (3.4)	0	3 (8.1)	0
Psychiatric Disorders	6 (2.9)	1 (3.4)	2 (5.4)	0
Cardiac Disorders	5 (2.4)	1 (3.4)	0	0
Metabolism and Nutrition Disorders	4 (2.0)	0	3 (8.1)	0
Eye Disorders	3 (1.5)	0	0	0
Vascular Disorders	3 (1.5)	1 (3.4)	2 (5.4)	0
Blood and Lymphatic System Disorders	2 (1.0)	0	1 (2.7)	0
Renal and Urinary Disorders	2 (1.0)	0	2 (5.4)	0
Reproductive System and Breast Disorders	2 (1.0)	0	4 (10.8)	0
Congenital, Familial and Genetic Disorders	1 (0.5)	0	0	0
Immune System Disorders	1 (0.5)	0	0	0
Surgical and Medical Procedures	1 (0.5)	0	0	0
Ear and Labyrinth Disorders	0	0	1 (2.7)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	1 (2.7)	0

Studies included: LPCN 1021-13-001, LPCN 1021-09-001, LPCN 1021-14-001, M12-778, M13-298, and S361.1.001
Source: NDA 208088 (seq 0000), 2.7.4, Table 76, p. 123.

Table 58: Treatment Emergent Adverse Events by System Organ Class for Subjects with Body Mass Index ≥ 30 kg/m2 for Phase 1 and 3 Studies (Single and Multiple Dose Periods) — Safety Population

System Organ Class1, n (%)	Tlando N = 176	Andriol 80 mg N = 5	AndroGel 1.62% N = 67	Placebo N = 2
Any TEAE	99 (56.3)	0	42 (62.7)	1 (50.0)
Infections and Infestations	25 (14.2)	0	13 (19.4)	0
Investigations	24 (13.6)	0	6 (9.0)	0
Gastrointestinal Disorders	21 (11.9)	0	7 (10.4)	1 (50.0)
Musculoskeletal and Connective Tissue Disorders	18 (10.2)	0	6 (9.0)	0
Nervous System Disorders	15 (8.5)	0	4 (6.0)	0
Skin and Subcutaneous Tissue Disorders	15 (8.5)	0	5 (7.5)	0
General Disorders and Administration Site Conditions	14 (8.0)	0	10 (14.9)	0
Respiratory, Thoracic and Mediastinal Disorders	11 (6.3)	0	6 (9.0)	0
Injury, Poisoning and Procedural Complications	10 (5.7)	0	5 (7.5)	0
Metabolism and Nutrition Disorders	9 (5.1)	0	6 (9.0)	0
Psychiatric Disorders	8 (4.5)	0	4 (6.0)	0
Vascular Disorders	6 (3.4)	0	4 (6.0)	0
Blood and Lymphatic System Disorders	5 (2.8)	0	1 (1.5)	0
Renal and Urinary Disorders	5 (2.8)	0	5 (7.5)	0
Reproductive System and Breast Disorders	3 (1.7)	0	2 (3.0)	0
Cardiac Disorders	2 (1.1)	0	6 (9.0)	0
Eye Disorders	2 (1.1)	0	2 (3.0)	0
Ear and Labyrinth Disorders	1 (0.6)	0	1 (1.5)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.6)	0	1 (1.5)	0
Surgical and Medical Procedures	1 (0.6)	0	1 (1.5)	0
Endocrine Disorders	0	0	1 (1.5)	0
Immune System Disorders	0	0	2 (3.0)	0

Studies included: LPCN 1021-13-001, LPCN 1021-09-001, LPCN 1021-14-001, M12-778, M13-298, and S361.1.001.
Source: NDA 208088 (seq 0000), 2.7.4, Table 77, p. 124.

Of subjects who were treated with Tlando, 44.4% of non-obese subjects experienced at least one TEAE compared with 56.3% of obese subjects. In contrast, a higher percentage of non-obese subjects experienced at least one TEAE with AndroGel 1.62% compared with obese subjects (70.3% vs 62.7%, respectively). For obese subjects who received Tlando, adverse events occurred most frequently in the SOCs of infections and infestations (14.2% of obese subjects vs 9.8% of non-obese subjects), investigations (13.6% vs 8.8%, respectively), gastrointestinal disorders (11.9% vs 10.7%, respectively), musculoskeletal and connective tissue disorders (10.2% vs 6.8%, respectively), nervous system disorders (8.5% vs 9.3%, respectively), skin and

subcutaneous tissue disorders (8.5% vs 6.8%, respectively), and general disorders and administration site conditions (8.0% vs 3.9%).

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies or analyses were performed.

7.5.5 Drug-Drug Interactions

No drug-disease interaction studies or analyses were performed.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Two subjects reported malignant neoplasms during the Phase 3 study: one in the Tlando treatment group (thyroid neoplasm-malignant) and one in the AndroGel 1.62% treatment group.

> Subject (b) (6) is a 41 year old white male randomized to the Tlando treatment group. The subject reported the adverse event of thyroid neoplasm-malignant on study day 272. The event was assessed as not related to the study drug by the investigator.
>
> Subject (b) (6) is a 66 year old white male randomized to the AndroGel 1.62% treatment group. The subject reported the adverse event of prostate cancer on study day 62. The event was assessed as not related to the study drug by the investigator.

7.6.2 Human Reproduction and Pregnancy Data

No studies on pregnancy or lactation were conducted as part of the clinical research program for Tlando. Exposure of a female fetus to androgens may result in varying degrees of virilization.

7.6.3 Pediatrics and Assessment of Effects on Growth

Tlando was not studied in males less than 18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose with Tlando were reported in the Phase 1 or Phase 3 clinical studies of Tlando, and no new data regarding overdose were generated for Tlando for

this submission. No formal abuse potential studies or studies to evaluate withdrawal or rebound were conducted as part of the clinical research program for Tlando.

7.7 Additional Submissions / Safety Issues

The applicant submitted a 120-day safety update report on January 27, 2016. The submission contained safety assessments including adverse events, clinical laboratory tests (b) (4)

(b) (4)

(b) (4)

Safety Findings

One (1/10, 10.0%) subject receiving LPCN 1021 capsules reported at least one treatment emergent adverse event (TEAE); headache was reported by one subject (1/10 subjects, 10.0%). The adverse event was assessed by the investigator as unrelated to the study drug. The TEAE resolved spontaneously. Two (2/10, 20.0%) subjects receiving LPCN 1021 tablets (alternate dosage form not proposed in this NDA) reported TEAEs; headache was reported by two subjects (2/10 subjects, 20.0%). The adverse events were assessed by the investigator as unrelated to the study drug.

No abnormal hematology, clinical chemistry, or urinalysis results were reported as adverse events or led to study drug discontinuation. No abnormal vital signs were observed after LPCN 1021 study drug administration (capsules or tablets) during the study. No clinically significant abnormalities were observed during the study for any ECG value. No cardiovascular adverse events were associated with any ECG changes throughout the study.

(b) (4)

8 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.

The applicant submitted a paper titled, "*The risk of adverse outcomes in association with use of testosterone products: a cohort study using the UK-based general practice research database*."[2] The paper describes a cohort study of men in the UK based General Practice Research Database who were users of oral testosterone undecanoate and injectable forms of testosterone. The study cohort included 5841 men who received at least one study testosterone preparation (injectable: n = 4190; oral: n = 1329; both oral and injectable n = 322). The paper reported the following results: adjusted relative risks for oral compared with injectable testosterone were 0.8 (95% CI 0.6, 1.2) for hypertension, 0.13 (0.05, 0.35) for polycythemia, 1.1 (0.7, 1.7) for prostate cancer, 1.5 (1.1, 2.2) for BPH and 1.1 (0.8, 1.4) for prostatism. The authors concluded that the risks of prostate cancer and prostatism were similar in users of the two preparations, but risks were higher for hypertension and polycythemia in the injectable compared with the oral testosterone users. The risk of BPH was slightly higher in the oral users, but the difference was small and could have been due to bias.

Reviewer comment: The formulation and dose of oral testosterone undecanoate capsules marketed in the UK are different from Tlando. Therefore, the results of the paper submitted by the applicant have limited applicability to the product under review. However, the results provide support for the long-term safety of oral testosterone undecanoate in general.

[2] Jick SS Hagberg KW. The risk of adverse outcomes in association with use of testosterone products: a cohort study using the UK-based general practice research database. Br J Clin Pharmacol 2012 75(1): 260-270.

9 Appendices

9.1 Literature Review/References

The applicant conducted a literature review to evaluate safety regarding the DHT levels observed in clinical trials. Five double-blind, placebo-controlled trials in which males were treated with a DHT gel are summarized in Table 64. The applicant believes that the studies support that DHT levels in excess of those observed in the LPCN 1021-13-001 study did not result in serious adverse events, or safety signals.

Table 59: Summary of Randomized Placebo-controlled Studies on Transdermal DHT-gel from the Literature

Duration Dosing (Month)	Subjects	DHT Gel Dose	Serum level in the DHT group**			Safety	Reference
			DHT (ng/dL)	T (ng/dL)	DHT/T ratio		
1	Healthy male 35-55 yrs N=l2D N=l5P	70mg /day	7x Base: 35	Decreased Base: 440	NA	No change in clinical labs. No difference in intra-prostate DHT, PSA, PV and androgen- related gene expression. Supraphysiologic increases in serum DHT did not significantly alter intraprostatic levels of DHT, testosterone, or prostate epithelial cell androgen-regulated gene expression in healthy men.	Page et al: *J Clin Endocrinol Metab* 96: 430-437, 2011.
3	Healthy male >60 yrs; N=l8D N=l9P	70 mg qd	490-534 Base: 41	144-210 Base: 432	2.4-3.7 Base: 0.09	Dihydrotestosterone treatment had no adverse effects on prostate (unchanged prostate volumes and prostate-specific antigen) and cardiovascular (no adverse change in vascular reactivity or lipids) safety markers. Increased Hct/Hb (in normal range.	Ly et al: *J Clin Endocrinol Metab* 86: 4078-4088, 2001.
6	Healthy male 50-70 yrs; N=60D N=60P	125-250 mg /day	238 Base: 44	170 Base: 464	1.4 Base: 0.09	No adverse effects on prostate; no changes on lipids. Hemoglobin concentrations increased from 146.0 +/- 8.2 to 154.8 +/- 11.4 g/liter, and hematocrit from 43.5 +/- 2.5% to 45.8 +/- 3.4% (P < 0.001). Prostate weight and prostate-specific antigen levels did not change during the treatment. No major adverse events were observed.	Kunelius et al: *J Clin Endocrinol Metab* 87: 1467- 1472, 2002.
6	Hypogonadal male, 55-80 yrs; N=43D N=44D N=41P	35mg /day 70mg /day	244-300 Base: NA	106-124 Base: 226-231	2.3-2.4 Base: NA	2 deaths (unrelated), n=l 5 SAEs (2 related: prostate cancer and one increased PSA); no effects on prostate volume but increase PSA (3.4% on DHT-gel vs. 0% on placebo); increased Hct/Hb, polycythemia; no effects on BP	A Phase 2 trial from *Ascend Therapeutics, Inc. Clintrial.gov: NCT00490022*
24	Healthy male without prostate disease >50 yrs; N=55D N=58P	70mg /day	730 Base: 64	69 Base: 490	10.5 Base: 0.1	Slightly increased PSA and prostate volume; no changes on lipids; Dihydrotestosterone increased hemoglobin levels (7% [CI, 5% to 9%]), serum creatinine levels (9% [CI, 5% to 11%]), and lean mass (2.4% [CI, 1.6% to 3.1%) but decreased fat mass (5.2% [CI, 2.6% to 7.7%]) (P <0.001 for all). Protocol-specific discontinuations due to DHT were asymptomatic increased hematocrit (n = 8), which resolved after stopping treatment, and increased prostate-specific antigen levels (n = 3; none with prostate cancer) in the DHT group. No serious adverse effects due to DHT occurred	Idan et al: *Ann Intern Med* 153:621-632, 2010.

D=DHT Gel; P=Placebo; Base=baseline; NA=not available
**Serum DHT and T were stable over the course of treatment;
Source: NDA 208088 (seq 0000), 2.7.3, Table 21, p. 53.

Reviewer comment: Except for the Idan study, the reviewed studies were six months or less in duration. Two of the studies had less than 20 treated subjects and all but one were conducted in healthy men.

During the 24 month study by Idan et al., two subjects in the DHT treatment group reported serious adverse events of concern: one subject reported the event of pulmonary embolism, another reported the event of deep venous thrombosis. There

were no reports of pulmonary embolism or deep venous thrombosis in the placebo group.

This reviewer did not find these studies to be supportive of the safety of long-term exposure to elevated levels of DHT.

9.2 Labeling Recommendations

Labeling was deferred to the next review cycle.

9.3 Advisory Committee Meeting

A new drug application (NDA) for another oral testosterone undecanoate product for the proposed indication of testosterone replacement therapy in males was discussed by an Advisory Committee on September 18, 2014. Therefore, there did not appear to be a need to evaluate this product with an Advisory Committee.

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

/s/

MARTIN E KAUFMAN
06/23/2016

SURESH KAUL
06/23/2016

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA #	208088
Submission Dates	August 28, 2015, May 26, 2016, June 1, 2016
Brand Name	Tlando® (approved by DMEPA 4/11/16)
Generic Name	Testosterone undecanoate
Strength and Formulation; Regimen	[redacted] (b) (4) 112.5 mg capsules; 225 mg orally twice daily taken with food; [redacted] (b) (4)
Sponsor	Lipocine Inc.
Proposed Indication	Treatment of Hypogonadism
Submission Type	Original NDA; standard review
Relevant IND	106,476
Clinical Pharmacology Review Team	LaiMing Lee, PhD; Myong-Jin Kim, PharmD; Luning (Ada) Zhuang, PhD; Jeffry Florian, PhD; and E. Dennis Bashaw, PharmD
OCP Divisions	Division of Clinical Pharmacology-3 and Division of Pharmacometrics
OND Division	Division of Bone, Reproductive, and Urologic Products

An OCP Office-Level Required briefing was held on May 23, 2016. Attendees included Issam Zineh, Shiew-Mei Huang, Hae-Young Ahn, Kellie Reynolds, Yaning Wang, Darrell Abernethy, Myong-Jin Kim, Jeffry Florian, Luning (Ada) Zhuang, LaiMing Lee, Chongwoo Yu, Jihong Shon, Rajnikanth Madabushi, Lauren Brum, Julie Beitz, Amy Egan, Hylton Joffe, Suresh Kaul, Martin Kaufman, and Samantha Bell.

TABLE OF CONTENTS

1 Executive Summary

The Applicant developed testosterone undecanoate (TU [redacted] 112.5 mg oral capsules for the treatment of hypogonadism in adult men with a deficiency or absence of endogenous testosterone (T). Oral TU (also referred to as LPCN) is a testosterone ester. As a prodrug, TU is de-esterified to T to replace deficient or absent T hormone in hypogonadal males.

The bioavailability of oral TU capsules was evaluated in various formulations in early phase 1 studies in both postmenopausal women and hypogonadal men. This NDA includes a total of eight phase 1 and 2 studies, and one phase 3 study. Formulation LPCN 1021-07 was selected for bioavailability and dose proportionality study (S361.1.001) and dose finding study (M12-778) based upon achieving T concentrations (24-hr Cavg) within the eugonadal range (approximately 300-1100 ng/dL). The to-be-marketed formulation is qualitatively and quantitatively the same as formulation LPCN 1021-07. The to-be-market formulation was evaluated in the pivotal food effect (LPCN 1021-14-001) and phase 3 (LPCN 1021-13-001) studies.

The Applicant demonstrated efficacy based upon the pre-specified and agreed upon primary efficacy endpoint of at least 75% of patients achieving a 24-hr Cavg between 300-1140 ng/dL based upon the primary efficacy population. Two of the three secondary endpoints for safety (based upon Cmax) were met. However, 3 of 151 patients (2%) had a Cmax >2500 ng/dL when acceptance criteria should be 0%. The secondary endpoints are based upon safety concerns for Cmax above 1500 ng/dL.

The titration scheme used in the pivotal phase 3 study was based upon 24-hr Cavg with additional criteria for down titration based upon Cmax outliers after the morning and evening doses. The proposed label recommends [redacted] However, a cursory review provided of the new material suggests that the proposed alterations to the single time point sampling scheme provide only a marginal improvement in agreement with the Phase 3 titration scheme. Approvability of the NDA is dependent upon deriving a dosing algorithm for the label that: (1) will provide clinicians and users with a practical titration scheme; (2) will ensure patients are effectively treated (within the eugonadal range); and (3) avoids excessively high T concentrations in patients. Currently, the lack of agreement between the two titration schemes precludes the translation of the phase 3 results into labeling.

1.1 Recommendation

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 [redacted] 112.5 mg oral capsules submitted to the Agency on August 28, 2015. As conducted, 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 in 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 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 their associated safety issues), it is not possible to develop appropriate labeling at this time and a Complete Response is recommended.

1.2 Phase IV Commitments/Requirements

Not Applicable

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

General PK characteristics of TU and T

TU is a prodrug for T and circulates freely in the plasma. Following 13 weeks of oral TU 225 mg BID dosing in 65 hypogonadal men, mean serum TU Cmax, Tmax, AUC0-24 hr, and Cavg0-24hr values were 412 ng/mL, 5.0 hrs, 2043 ng.hr/mL, and 85 ng/mL. In the plasma TU is converted to T by non-specific esterases, the apparent half-life of TU is 1.7hrs. Correspondingly, the resulting mean pharmacokinetic values for serum T Cmax, Tmax, AUC0-24 hr, and Cavg0-24hr values were 1117 ng/dL, 6.0 hrs, 10720 ng.hr/dL, and 447 ng/dL in the same subjects.

T is then metabolized by CYP3A4, aromatase, and 5-α-reductase. CYP3A4 metabolism of testosterone occurs primarily in the liver, aromatase in adipose tissues, and 5-α-reductase in many sites including the skin.

Dose Selection

Study S361.1.001 (single-dose) provided the preliminary bioavailability data for the dose-finding/dose escalation study M12-778.

Study S361.1.001 was an open-label, single dose bioavailability study of two oral TU capsule formulations in hypogonadal men with doses of 75, 150, and 225 mg taken with 240 mL water 30 min after starting a high-fat breakfast. The 24-hr and 12-hr T Cavg following a single dose administration oral TU were within the commonly recognized target eugonadal range (e.g., 300-1100 ng/dL). Additionally, at all three doses, the mean Cmax was less than 1500 ng/dL – the upper limit of normal. This study provided the preliminary bioavailability data for a dosing-finding study and titration scheme development (Study M12-778).

Mean (SD) serum T pharmacokinetics following single dose administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07

	TU Dose		
PK Parameter	75 mg (N=12)	150 mg (N=11)	225 mg (N=11)
Cmax (ng/dL)	545 (202)	979 (415)	1155 (423)
Tmax* (hr)	6.5 (4-12)	7 (4-10)	6 (4-10)
$AUC_{0\text{-}24}$ (ng hr/dL)	7498 (2953)	9632 (3584)	10103 (3135)
$Cavg_{0\text{-}24\ hr}$ (ng/dL)	**312 (123)**	**401 (149)**	**421 (131)**
$Cavg_{0\text{-}12\ hr}$ (ng/dL)	**348 (132)**	**497 (207)**	**568 (201)**

*median (range)

Study M12-778 was a single-center, randomized, double-blind, placebo-controlled, ascending multiple-dose, serial-group study in adult hypogonadal male subjects (N=84) with a confirmed serum T < 300 ng/dL on two separate occasions. The study consisted of 5 groups with 3 groups of 20 subjects and 2 groups of 12 subjects each. Subjects in Groups 1, 2 and 3 were randomly assigned in a 4:1 ratio to receive oral TU (75 mg for Group 1, 150 mg for Group 2, and 225 mg for Group 3) or matching placebo. Groups 1-3 received oral TU or placebo daily for 14 days starting on Day 1 through Day 15 am dose. Subjects in Groups 4 and 5 were randomly assigned in a 3:1 ratio to receive oral TU (300 mg for Group 4 and 225 mg for Group 5) or matching placebo and dosed for 28 days.

From Study M12-778, the 12-hr T Cavg was 381 and 661ng/mL following 21 days of BID dosing administration oral TU 225 mg and 300 mg, respectively. The T Cavg was within the commonly recognized target eugonadal range; however, the mean T Cmax was 1447 ng/dL +/- 694 ng/dL following 300 mg BID which is near the upper limit of normal (~1500 ng/dL). This study provided the preliminary bioavailability data for a dosing-finding study and titration scheme development using formulation LPCN 1021-07.

Mean (SD) serum T pharmacokinetics following multiple dose (BID x 14 days) administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07 on Day 15

	TU Dose			
PK Parameter	75 mg (N=16) Group 1	150 mg (N=16) Group2	225 mg (N=16) Group 3	300 mg (N=9) Group 4
Cmax (ng/dL)	**544 (169)**	**792 (276)**	**1169 (356)**	**1447 (694)**
Tmax (hr)	7.8 (4.8)	8.7 (6.3)	8.7 (4.7)	4.9 (1.5)
$AUC_{0\text{-}24\ hr}$ (ng.hr/dL)	6488(2265)	7652 (1839)	10693 (3872)	7329 (3264)
$Cavg_{0\text{-}24\ hr}$ (ng/dL)	**270 (94.4)**	**319 (77)**	**446 (161)**	**611 (272)**

Based upon the data from Study M12-778, the starting dose for the phase 3 study was selected as 225 mg BID with titration increments of 75 mg BID.

Efficacy Endpoints

Efficacy for Lipocine's oral TU was demonstrated in Phase 3 study LPCN 1021-13-001. The efficacy endpoint is the percentage (≥75%) of patients achieving 24-hr average serum T within the normal range range (300-1140 ng/dL) upon completion of 13 weeks of treatment. In this phase 3 study, the percentage was 87.4% (132 of 151 patients) based on the efficacy population. The lower bound of the 95% CI should be ≥ 65%; in this study, the lower bound was 81.7%. The Applicant demonstrated efficacy based upon the defined endpoints.

Parameter	Target	Efficacy Population N=151	Full Analysis Set 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%

Safety Findings

Safety assessment is partially based on PK assessment of Cmax. The secondary endpoint Cmax was nearly met with T 24-hr Cmax < 1500 ng/dL of greater than 85% patients; in this study, 82.8% (125 of 151 patients) had a Cmax < 1500 ng/dL. For those with Cmax between 1800 and 2500 ng/dL was 4.6% (7 of 151 patients), which is less than the 5% cutoff. No patients should have achieved a Cmax>2500 ng/dL to satisfy the secondary endpoint; however, in this study, 2% (3 of 151) of patients had an unacceptably high Cmax. The Clinical Reviewer Martin Kaufman found no T-related AEs (e.g. increases in hematocrit, hemoglobin, or PSA) that were different from the approved active comparator.

Dose Proportionality

Dose proportionality was assessed with the Power Model with the open-label, single-dose escalation study in hypogonadal men (S361.1.001). For TU, the increase in AUC_{0-24}, AUC_{0-12}, and Cmax was proportional for doses 75, 150, and 225 mg LPCN 1021-07. For total T, the increase in AUC_{0-24}, AUC_{0-12}, and Cmax was less than proportional to the increase in dose of LPCN 1021-07

Metabolizing Enzymes

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, due to the ubiquitous nature of non-specific esterases in the body, the Applicant did not conduct in vitro and in vivo studies to assess potential drug-drug interactions.

Intrinsic Factors

There were no dedicated phase 1 studies to evaluate the effect of intrinsic factors such as organ impairment, race, and age on the bioavailability of TU or T. The phase 3 study excluded patients with a history of any clinically significant illness and enrolled approximately 10% of men over the age of 65 years. The composition of patients in the phase 3 consisted of approximately 84% White, 13% Black or African American, and 2% Asian. Efficacy and safety of LPCN 1021 were not evaluated in patients less than 18 years of age and is not indicated for women. The phase 3 study excluded patients with history of clinically significant illness, which may include hepatic and renal impairment.

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

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

Geriatric Use: The Applicant's proposed product label states [redacted] (b) (4)

Pediatric Use: The Applicant's proposed product label states [redacted] (b) (4)

Extrinsic Factors

The effects of extrinsic factors such as prescription drugs and herbal products have not been studied by the Applicant. The phase 3 study protocol excluded use of CYP3A4 inhibitors and inducers, yet the proposed label does not address the potential concomitant use with oral TU.

Effect of Food (low-fat, moderate-fat, and high-fat) on T PK

The Applicant evaluate 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 male received a 225 mg oral dose of LPCN ~30 min after the meal had started and fasted for no less than 4 hrs after drug administration.

The following table summarizes the mean (%CV) serum T pharmacokinetics following various food types.

	Meal Type/Fat Content			
PK Parameter	Fasting Condition (N=14)	Low-Fat (N=13)	Moderate-Fat (Standard Meal) (N=13)	High-Fat (N=13)
$C_{max0\text{-}24}$ (ng/dL)	562 (26)	1570 (35)	1560 (31)	1680 (44)
Tmax* (hr)	4.0 (1-8)	6.0 (4-6)	6 (5-7)	6 (4-8)
$AUC_{0\text{-}12}$ (ng hr/dL)	4178 (20)	6899 (22)	7094 (21)	8371 (26)

*median (range)

2 Question-Based Review

2.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

TU capsules, (b) (4) (b) (4) 112.5 mg, are proposed by Lipocine as an oral T replacement product for the treatment of hypogonadism. Currently, the majority of FDA-approved T products are available for transdermal delivery. Oral TU is a prodrug ester of T and is approved outside of the United States, including Canada, as Andriol® Testocaps by Organon.

An End-of-Phase 2 meeting with the Applicant was held on November 15, 2012 to discuss the phase 3 study, proposed phase PK studies, preclinical program, and Chemistry program. There was agreement that Cavg was an acceptable primary efficacy endpoint and that the normal range for T be established. The Applicant was informed that fat content and/or food type can impact TU bioavailability; therefore, the review team recommended the Applicant conduct the food effect study before initiating the phase 3 study.

A pre-NDA meeting was held on March 19, 2015 to discuss the preliminary data from the phase 3 study. It appears that the sponsor met the specified endpoints of $\geq$ 75% of patients having a Cavg of serum T within the normal range at Week 13. A brief summary of the phase 3 study results provided by the Applicant showed that there were 8 patients who had a Cmax > 2500 ng/dL (acceptance criteria is 0 patients with Cmax > 2500 ng/dL). The Division stated that the number of subjects with Cmax greater than 2500 ng/dL would be a review issue during the NDA review process. The Division expressed concerns that the proposed titration for the label using a single time point that will be correlated to Cavg does not reflect the titration scheme used in the completed phase 3 study that included both Cavg and Cmax. The phase 3 study was not reviewed under a Special Protocol Assessment.

Currently, demonstration of efficacy for all T products is based upon a PK endpoint – at least 75% of patients with Cavg within the eugonadal range. The most commonly used T products are the transdermal gels where the PK profile is relatively flat; however, the PK profile for oral TU shows a significant a rapid increase in T followed by a decline over the 12 hr dosing duration and does not mimic the PK profiles of transdermal products.

2.2 General Attributes of the Drug

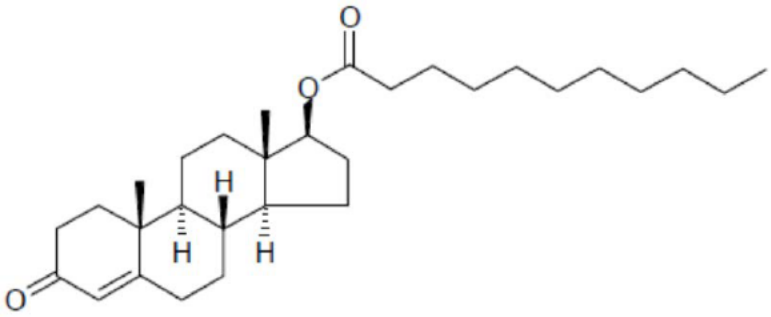
2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

TLANDO (TU) is an ester of an androgen, T developed for oral administration. TLANDO contains TU, (b) (4) polyoxyl 40 hydrogenated castor oil, polyethylene glycol, ascorbyl palmitate, gelatin, titanium dioxide, black iron oxide, and imprint ink. This oral TU product is referred to as LPCN 1021, SLV-361 and/or ABT-SLV361 in study reports.

The drug product TLANDO is available as capsules [redacted]

- [redacted]
- 112.5 mg TU oral, light gray capsule containing [redacted]

Testosterone undecanoate chemical structure is:



The chemical name is 17β-undecanoyloxy-4-androsten-3-one.
The molecular weight is 456.7 daltons.
The molecular formula is $C_{30}H_{48}O_3$.
The aqueous solubility is <0.1 mcg/mL; soluble in methanol, isopropanol, and acetone

The to-be-marketed product was used in the pivotal food effect (LPCN 1021-14-001) and phase 3 (LPCN 1021-13-001) studies. [redacted] ormulation LPCN 1021-07 was used in single-, multiple-dose, and dose-finding PK studies (Studies LPCN 1021-09-001, S361.001.1, and M12-778).

2.2.2 What are the proposed mechanism of action and therapeutic indication?

T is the principal androgen secreted by the testis and main androgenic steroid in males. Endogenous androgens including T and DHT are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics.

These effects include the growth and maturation of 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. T and DHT are necessary for the normal development of secondary sex characteristics.

The proposed indication is treatment of hypogonadism, a clinical syndrome results from insufficient secretion of T, and 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), luteinizing hormone (LH)).

Signs and symptoms associated with male hypogonadism may include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

TLANDO was developed as an oral T replacement in hypogonadal men ≥ 18 years of age with the desired serum T concentrations of approximately 300-1140 ng/dL following twice daily oral administration. TU is absorbed mainly through the lymphatic system and is converted to T via the de-esterification of TU by non-specific esterases. Thus, TU is the prodrug of T. Dihydrotestosterone undecanoate (DHTU) is formed through the 5α-reduction of TU.

TLANDO, including all other T replacement products, is not indicated to treat age-related hypogonadism (also referred to as late-onset hypogonadism" or andropause).

2.2.3 What are the proposed dosages and routes of administration?

TLANDO is proposed as oral capsules containing (b) (4) 112.5 mg TU (b) (4) The proposed (b) (4) dose is 225 mg TU twice daily (450 mg total daily TU dose) to be administered with food. The sponsor is proposing serum T concentrations be measured after initiation of therapy to ensure that the desired concentrations are achieved. (b) (4)

(b) (4)

(b) (4)

In the phase 3 study, all patients started at 225 mg BID (2 x 112.5 mg AM and 2 x 112.5 mg PM). If the dose was reduced to 150 mg BID, patients took 2 x 75 mg capsules BID. If the dose was increased to 300

mg BID, patients took 4 x 75 mg capsules BID. At all dose levels the morning and evening doses were the same.

(b) (4) the titration scheme used in pivotal phase 3 study. The basis for dosing changes in the pivotal phase 3 study was dictated by deviations from a 24-hr Cavg range of 300-1140 ng/dL or Cmax of greater than 1500 ng/dL irrespective of the 24-hr Cavg.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and clinical studies used to support dosing or claims?

The primary basis to support the clinical efficacy and safety comes from Study LPCN 1021-13-001 - a multi-center, phase 3, randomized, open-label, active controlled, parallel group study in adult hypogonadal men. The initial TU dose was 225 mg BID with a target 24 hr Cavg of 300-1140 ng/dL. Extensive PK was taken at Weeks 3 and 7, with titrations made on Weeks 4 and 8, respectively.

Clinical Pharmacology studies were initially conducted to evaluate bioavailability of T with multiple formulations and effect of food in both postmenopausal women and hypogonadal men. Once the lead formulation was selected, the sponsor conducted pivotal Clinical Pharmacology assessments that included single and multiple-dose studies in patients, pivotal fat/food effect studies, and the pivotal phase 3 study.

Study Identifier (Study Dates)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	# Subjects by Arm; Planned/ Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Bioavailability Studies						
LPCN 1021-05-001 Synopsis (February 2006 to March 2006)	Primary: Assess bioavailability and PK of T following oral administration of LPCN 1021 TU capsule formulations. Secondary: Compare bioavailability and PK of T following LPCN 1021 TU capsules to bioavailability and PK of T following Andriol. Evaluate relative safety of LPCN 1021 capsule formulations.	Bioavailability and PK of four oral TU capsule formulations	LPCN 1021-01[2] LPCN 1021-02 LPCN 1021-05 LPCN 1021-06 120 mg oral TU Active Control: Andriol, oral	24/24 Andriol: 24/24	Postmeno-pausal women	Single dose
LPCN 1021-09-001 Synopsis (October 2009 to February 2010)	Determine the bioavailability and PK of T after single and multiple dosing of oral TU capsules. Assess dose proportionality of oral TU capsules. Evaluate the PK of two oral TU capsule formulations. Assess safety and tolerability of oral TU.	Randomized, open-label, single and multiple dose pilot bioavailability and PK study of two oral TU capsule formulations	LPCN 1021-07[1] LPCN 1021-08 50 and 100 mg oral TU (QD on Day 1 and 8; BID on Day 3-7) Active Control: Andriol, oral	LPCN 1021: 36/36 Andriol (commercial Canadian oral product) 36/36	Hypo-gonadal men	Single and multiple dose (5 days)
S361.1.002 Synopsis (June 2010 to July 2010)	Primary: Determine the bioavailability and PK of TU, T, DHT, and DHTU after single dose administration under fasted, no-fat, low-fat, normal-fat, and high-fat conditions in postmenopausal females. Explore within group PK of oral TU capsules under different fed conditions. Explore between group PK of two oral TU capsule formulations under different fed conditions. Safety: Assess safety and tolerability of oral TU capsules in postmenopausal females.	Open-label, single dose, pilot food effect study on the bioavailability and PK of two oral TU capsule formulations	LPCN 1021-07[1] LPCN 1021-10 75 mg oral TU	20/20	Postmeno-pausal women	Single dose

LPCN 1021-14-001 Synopsis (March 2015 to April 2015)	Compare rate and extent of absorption of T, DHT, TU, and DHTU following administration of a single oral dose of LPCN 1021 as 2 x 112.5 mg capsules under various food and fat content conditions (low to high) in hypogonadal males. Assess safety and tolerability of LPCN 1021 in hypogonadal males.	Open-label, randomized, four-period, four-treatment, crossover, single-dose bioavailability and PK study of oral TU capsule as a function of food and fat content	LPCN 1021 Registration Lot 225 mg oral TU	16/14	Hypo-gonadal men	Single dose
Comparative Bioavailability Studies						
S361.1.001 Synopsis (June 2010 to August 2010)	Determine bioavailability and PK of T, TU, E2, DHT, and DHTU after 75 mg, 150 mg, and 225 mg single doses of oral TU capsules in hypogonadal males. Assess dose proportionality of oral TU capsules Compare the PK of two oral TU capsule formulations Assess safety and tolerability of oral TU capsules in hypogonadal males.	Open-label, single dose bioavailability and PK study of two oral TU capsule formulations	LPCN 1021-07[1] LPCN 1021-10 75, 150, and 225 mg oral TU	24/24	Hypo-gonadal men	Single dose
M13-298 Synopsis (October 2011 to January 2012)	Assess the relative bioavailability of four LPCN 1021 formulations after a single dose and 14 days of BID dosing at 225 mg in hypogonadal males.	Single and multiple dose relative bioavailability study of four TU capsule formulations	LPCN 1021-11 LPCN 1021-12 LPCN 1021-13 LPCN 1021-14 225 mg oral TU BID	32/32	Hypo-gonadal men	Multiple doses (14 days)
M12-868 Synopsis (April 2011 to May 2011)	Determine the bioavailability of TU capsules from two different lots in postmenopausal females after single-dose administration.	Open-label, crossover study to compare relative bioavailability of 2 lots of TU capsules	LPCN 1021-07[1] 75 mg oral TU	12/12	Postmeno-pausal women	Single dose
Patient Pharmacokinetic Study						
M12-778 Synopsis (March 2011 to September 2011)	Assess safety and tolerability of escalating multiple oral doses of LPCN 1021 in hypogonadal males. Determine the PK of T, DHT, TU, DHTU, and E2 after multiple oral doses of LPCN 1021 in hypogonadal males.	Randomized double-blind, placebo-controlled dose escalating study of safety, tolerability and PK of oral TU	LPCN 1021-07[1] 75, 150, 225 and 300 mg oral TU BID Placebo	84/84	Hypo-gonadal men	
Efficacy and Safety in Indication						
LPCN 1021-13-001 Synopsis (February 2014 to April 2015)	Primary Determine the proportion of LPCN 1021-treated subjects who achieved a 24-hour average serum T concentration (Cavg0-24h) within the normal range after approximately 13 weeks of study treatment. The normal range for serum T (Cavg0-24h) was defined as 300 to 1140 ng/dL. Secondary Determine percentage of LPCN 1021 treated subjects with serum T concentrations (maximum observed serum concentration [Cmax]) < 1500 ng/dL; the percentage of subjects with Cmax between 1800 and 2500 ng/dL; and the percentage of subjects with Cmax > 2500 ng/dL after approximately 13 weeks. Assess CFB in safety parameters for the LPCN 1021 and active control, AndroGel 1.62%, groups over the course of treatment.[3] Evaluate CFB to endpoint in the I-PSS, the SF-36 quality-of-life questionnaire, and the PDQ for the LPCN 1021 and AndroGel 1.62% groups.	Multicenter, randomized, open-label, active-control, parallel-group, efficacy and safety study or oral TU	LPCN 1021 To-be-Marketed Formulation 225 mg TU titrated to 150 mg or 300 mg oral TU BID, as needed Active Control: AndroGel 1.62%, topical	LPCN 1021: 200/210 AndroGel 1.62%: 100/105	Hypo-gonadal men	

The following Clinical Pharmacology studies were reviewed:

LPCN 1021-09-001: single- and multiple-dose study in hypogonadal men to assess the bioavailability of formulation LPCN 1021-07 (50 and 100 mg capsules)

S361.1.001: single-dose study in hypogonadal men to assess the bioavailability and dose proportionality of formulation LPCN 1021-07 (75, 150, and 225 mg capsules)

M12-778: multiple-dose, dose-escalation study in hypogonadal men with formulation LPCN 1021-07 (75, 150, 225, and 300 mg capsules)

LPCN 1021-14-001: single-dose, pivotal food effect study in hypogonadal men with the to-be-marketed formulation (225 mg capsules)

The following Phase 3 study was reviewed:

LPCN 1021-13-001: randomized, open-label, multi-center, active-control, safety and efficacy study in hypogonadal men with the to-be-marketed formulation ([(b) (4)] dose: 225 mg BID)

The following Clinical Pharmacology studies were not reviewed because the formulations are not relevant to the to-be-marketed formulation or the intended population:

LPCN 1021-05-001: single dose PK study evaluating early formulations in postmenopausal women
S361.1.001: single-dose, pilot food effect study in postmenopausal women
M13-298: single- and multiple-dose PK study evaluating alternative formulations in hypogonadal men
M12-868: single dose PK study in postmenopausal women

2.3.2 What is the basis for selecting the response endpoints (i.e. clinical endpoints or biomarkers) and how are they measured in clinical pharmacology and clinical studies?

The Endocrine Society defines hypogonadism in men as a clinical syndrome that results from failure of the testis to produce physiological concentrations of T, which is typically 24-hr Cavg of 300-1000 ng/dL. The Endocrine Society guidelines suggest that the diagnosis of androgen deficiency in adult men be based on a patient's symptoms and signs (e.g. deficiency in secondary sex characteristics, bone mineral density, asexual function, well-being, and muscle mass and strength, etc.) and measurement of serum T concentrations.

For drug products developed for T replacement therapy, including oral TU, the target response endpoint in Clinical efficacy and safety clinical studies is a 24-hr serum T concentration in the eugonadal range. Lipocine selected their 24-hr T Cavg of 300-1140 ng/dL to be representative of eugonadal concentrations.

The primary endpoint for clinical efficacy is established when at least 75% of patients achieve a 24-hr T Cavg within the pre-specified eugonadal range (300-1140 ng/dL in this NDA) and the lower bound of the corresponding 95% confidence interval (CI) for the point estimate is at least 65%. Secondary endpoints included 24-hr T Cmax limits: $\geq$ 85% of all patients <1500 ng/dL; $\leq$ 5% of all patients between 1800 and 2500 ng/dL; 0% $\geq$ 2500 ng/dL.

The phase 3 study included an active comparator, AndroGel 1.62%, an approved transdermal T product.

At Week 3 and Week 7, patients had 24-hour intensive blood sampling relative to the morning dose to evaluate serum PK. Blood samples were taken at 0, 2, 3, 4, 5, 6, 8, 12, 14, 15, 16, 17, 18, 20 and 24 hours post-dose. Based on the 24-hour T Cavg and 24-hr peak serum total T Cmax, subjects were assessed for possible dose adjustment based on the following titration algorithm:

- If T Cavg < 300 ng/dL, dose was titrated upward by 75 mg
- If T Cavg > 1140 ng/dL, dose was titrated downward by 75 mg

- If T Cavg was between 300 to 1140 ng/dL and T Cmax < 1500 ng/dL, dose was not changed
- If T Cmax > 1500 ng/dL, dose was titrated downward by 75 mg/dose regardless of the 24-hr Cavg

Dose adjustments were implemented ~1 week after the intensive PK sampling was performed following the Week 3 and Week 7 visits (i.e., dose changes were made during the Week 4 and Week 8 visits).

At Week 13 all subjects receiving TLANDO underwent intensive PK blood draws for efficacy evaluation. The study doses could have been 225 mg TU or 150 mg TU or 300 mg TU, taken twice daily.

2.3.3 Are the active moieties in the serum and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters?

TU is de-esterified to T, the active moiety for the treatment of hypogonadism. Blood samples were taken for determination of TU, T, dihydrotestosterone undecanoate (DHTU), dihydrotestosterone (DHT), and estradiol (E2) concentrations. PK parameters were reported for the majority of the phase 1 studies and the phase 3 study. In this NDA review, TU and T are the primary moieties reported because TU is the drug substance and T is the pharmacologically active moiety. Baseline-corrected T, other hormones, and metabolites of T, may be reported where relevant.

DHT is synthesized from T by 5-reductase and is strong androgen. High concentrations of DHT are associated with the development benign prostatic hyperplasia (BPH) and prostate cancer; therefore, DHT monitoring is an important measure for safety. Normal serum DHT concentration is approximately 10-20% of T concentrations. The DHT:T ratio in the Clinical Pharmacology studies were briefly reviewed and confirmed to be within the normal range.

2.3.4 How were the dose(s) selected for the Phase 3 trial?

The data obtained from the Clinical Pharmacology studies S361.1.001 and M12-778 formed the basis for the initial dose and dose titration scheme for the phase 3 trial.

Study S361.1.001 was an open-label, single dose bioavailability study of two oral TU capsule formulations in hypogonadal men with doses of 75, 150, and 225 mg taken with 240 mL water 30 min after starting a high-fat breakfast. Subjects were randomized to either Group 1 (Formulation LPCN 1021-07) or Group 2 (Formulation LPCN 1021-10) groups. Formulation LPCN 1021-07 capsules (b) (4) (b) (4) (b) (4), but are otherwise the same as the to-be-marketed capsules used in the Phase 3 and pivotal food effect studies. (b) (4)

Mean (SD) serum TU pharmacokinetics following single dose administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07

	TU Dose		
PK Parameter	75 mg (N=12)	150 mg (N=11)	225 mg (N=11)
Cmax (ng/dL)	11528 (6139)	35418 (22646)	35709 (20044)
Tmax* (hr)	5 (5-12)	5 (4-10)	5 (5-10)
$AUC_{0\text{-}24}$ (ng hr/dL)	39785 (13455)	102795 (35029)	123481 (55676)
$Cavg_{0\text{-}24\ hr}$ (ng/dL)	2750 (1253)	6016 (2521)	7235 (3518)
$T_{1/2}$ (hr)	1.4 (0.4)	1.4 (0.4)	1.7 (0.8)

*median (range)

Mean (SD) serum T pharmacokinetics following single dose administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07

	TU Dose		
PK Parameter	75 mg (N=12)	150 mg (N=11)	225 mg (N=11)
Cmax (ng/dL)	545 (202)	979 (415)	1155 (423)
Tmax* (hr)	6.5 (4-12)	7 (4-10)	6 (4-10)
$AUC_{0\text{-}24}$ (ng hr/dL)	7498 (2953)	9632 (3584)	10103 (3135)
$Cavg_{0\text{-}24\ hr}$ (ng/dL)	**312 (123)**	**401 (149)**	**421 (131)**
$Cavg_{0\text{-}12\ hr}$ (ng/dL)	**348 (132)**	**497 (207)**	**568 (201)**

*median (range)

Reviewer's Comment: The 24-hr and 12-hr T Cavg following a single dose administration oral TU were within the commonly recognized target eugonadal range (e.g., 300-1100 ng/dL). Additionally, at all three doses, the mean Cmax was less than 1500 ng/dL – the upper limit of normal. This study provided the preliminary bioavailability data for a dosing-finding study and titration scheme development (Study M12-778) using formulation LPCN 1021-07.

The T Cavg over a 12- and 24-hr duration following a single 75 mg dose was near the lower end of the eugonadal range. T Cavg over a 24-hr duration is a relevant PK parameter to consider as the primary efficacy endpoint is based upon ≥75% of patients achieving T Cavg0-24hr within the pre-specified eugonadal range.

Based on the 12-hr T Cavg, subjects can potentially be within the eugonadal range while avoiding Cmax greater than 1500 ng/dL. Based upon these findings, Study M12-778 incorporated a BID dosing regimen with the same doses evaluated in Study S361.1.001.

Study M12-778 was a single-center, randomized, double-blind, placebo-controlled, ascending multiple-dose, serial-group study in adult hypogonadal male subjects (N=84) who met the selection criteria. The study consisted of 5 groups with 3 groups of 20 subjects and 2 groups of 12 subjects each. Subjects in

Groups 1, 2 and 3 were randomly assigned in a 4:1 ratio to receive oral TU (75 mg for Group 1, 150 mg for Group 2, and 225 mg for Group 3) or matching placebo. Groups 1-3 received oral TU or placebo daily for 14 days starting on Day 1 through Day 15 am dose. Subjects in Groups 4 and 5 were randomly assigned in a 3:1 ratio to receive oral TU (300 mg for Group 4 and 225 mg for Group 5) or matching placebo and dosed for 28 days. The sponsor noted a difference in the PK profiles for the 225 mg group (Group 3) on Day 8 vs. Day 15 so they added an additional 225 mg dose group (Group 5) with a 28-day dosing duration. All subjects were dosed BID 30 min after a standard meal (moderate fat content).

Mean (SD) serum TU pharmacokinetics following multiple dose (BID dosing x 14 days) administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07 on Day 15

	TU Dose		
PK Parameter	75 mg (N=16) Group 1	150 mg (N=15) Group2	225 mg (N=16) Group 3
Cmax (ng/dL)	12323 (4135.4)	19209 (10303)	36333 (12635)
Tmax (hr)	7.0 (4.6)	7.7 (5.7)	7.9 (4.6)
$AUC_{0\text{-}24\ hr}$ (ng.hr/dL)	61849 (17643)	101369 (37256)	192284 (56236)
$Cavg_{0\text{-}24\ hr}$ (ng/dL)	**2577 (735)**	**4224 (1552)**	**8012 (2343)**

Mean (SD) serum T pharmacokinetics following multiple dose (BID x 14 days) administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07 on Day 15

	TU Dose		
PK Parameter	75 mg (N=16) Group 1	150 mg (N=16) Group2	225 mg (N=16) Group 3
Cmax (ng/dL)	**544 (169)**	**792 (276)**	**1169 (356)**
Tmax (hr)	7.8 (4.8)	8.7 (6.3)	8.7 (4.7)
$AUC_{0\text{-}24\ hr}$ (ng.hr/dL)	6488(2265)	7652 (1839)	10693 (3872)
$Cavg_{0\text{-}24\ hr}$ (ng/dL)	**270 (94.4)**	**319 (77)**	**446 (161)**

Reviewer's Comment: The 24-hr T Cavg was 319 and 446 ng/mL (above 300 ng/dL) following 14 days of BID dosing administration oral TU 150 mg BID and 225 mg BID and the Cmax was less than 1500 ng/dL. The dose escalation study continued up to 300 mg BID and was extended in duration.

Mean (SD) serum TU pharmacokinetics following multiple dose (BID dosing x 21 days) administration 225 mg and 300 mg oral TU with formulation LPCN 1021-07 on Day 22

	TU Dose	
PK Parameter	225 mg (N=9) Group 5	300 mg (N=9) Group 4
Cmax (ng/dL)	19322 (7997)	62533 (49122)
Tmax (hr)	3.6 (1.7)	3.8 (1.9)
$AUC_{0\text{-}12\ hr}$ (ng.hr/dL)	69525 (19641)	191493 (109030)
$Cavg_{0\text{-}12\ hr}$ (ng/dL)	**69525 (19641)**	**15958 (9086)**

Mean (SD) serum T pharmacokinetics following multiple dose (BID dosing x 21 days) administration 225 mg and 300 mg oral TU with formulation LPCN 1021-07 on Day 22

	TU Dose	
PK Parameter	225 mg (N=9) Group 5	300 mg (N=9) Group 4
Cmax (ng/dL)	**835 (329)**	**1447 (694)**
Tmax (hr)	4.7 (1.7)	4.9 (1.5)
$AUC_{0\text{-}12\ hr}$ (ng.hr/dL)	4576 (1512)	7329 (3264)
$Cavg_{0\text{-}12\ hr}$ (ng/dL)	**381 (126)**	**611 (272)**

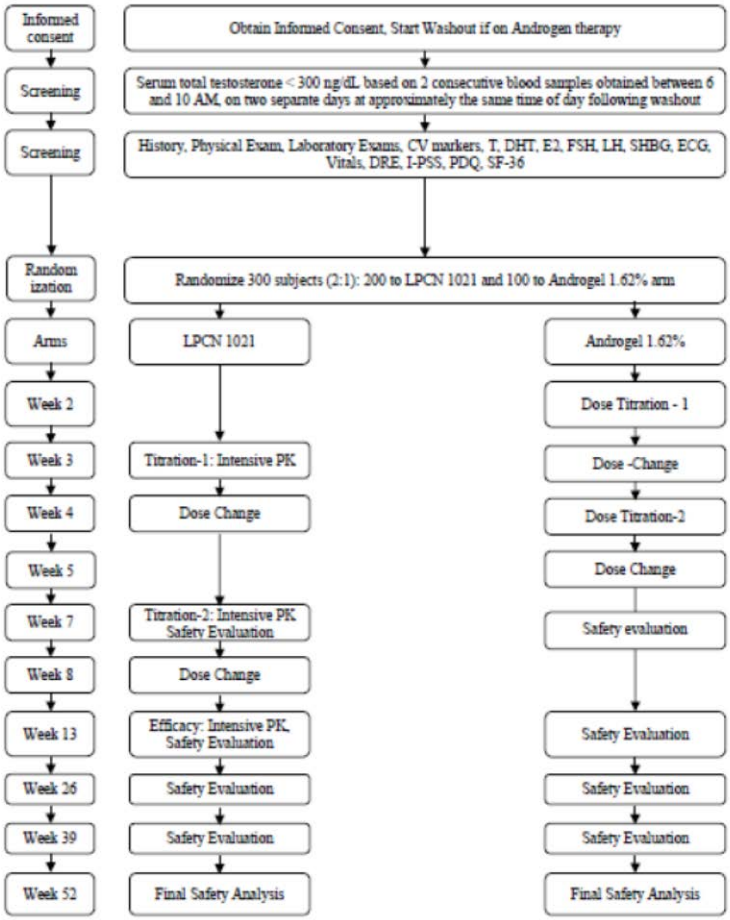
Reviewer's Comment: The 12-hr T Cavg was 381 and 661ng/mL following 21 days of BID dosing administration oral TU 225 mg and 300 mg, respectively. The T Cavg was within the commonly recognized target eugonadal range; however, the mean T Cmax was 1447 ng/dL following 300 mg BID which is near the upper limit of normal (~1500 ng/dL).

Study S361.1.001 (single dose) provided the preliminary bioavailability data for the dose-finding/dose escalation study M12-778. Based upon the data from Study M12-778, the starting dose for the phase 3 study was selected as 225 mg BID with titration increments of 75 mg BID.

2.3.5 How was the efficacy and safety of oral TU assessed and what were the findings?

Clinical Efficacy Based on 24-hr Cavg in Phase 3 Study LPCN 1021-13-001

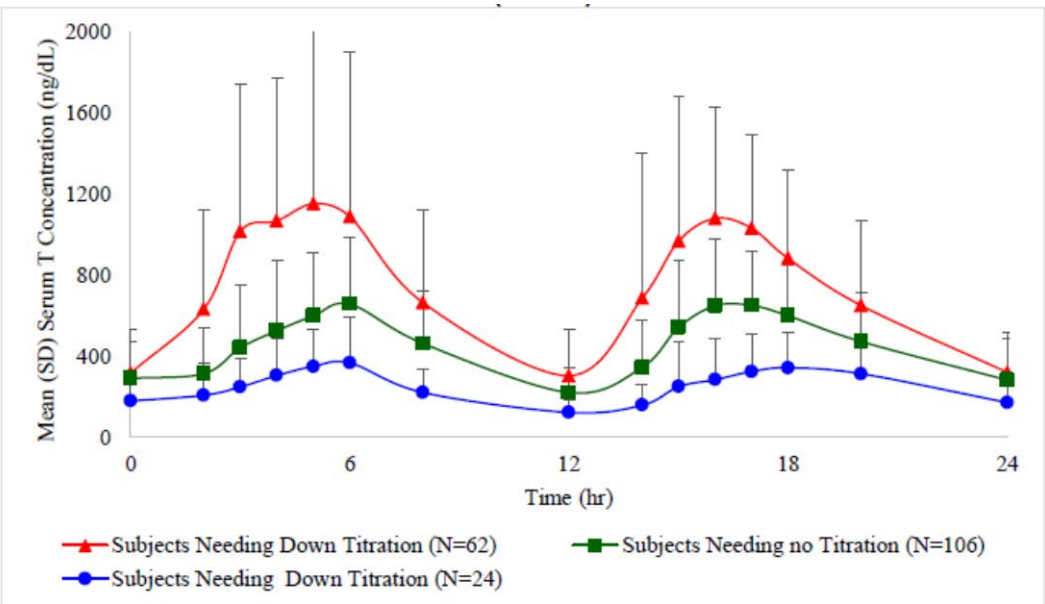
Effectiveness of T replacement is based upon achieving 24-hr average within the eugonadal range (i.e. 300-1140 ng/dL). The Phase 3 study design is shown in the following figure.



All patients in the treatment arm started at the same dose of 225 mg (2 x 112.5 mg) BID with administration approximately 12 hrs apart (total daily dose of 450 mg) and ~ 30 min after morning and evening meals with water. Dose titration was based on an assessment of the patient's total serum T concentration over 24 hrs (24-hr Cavg) and maximum serum T concentration (Cmax) over 24 hr period obtained after approximately 3 and 7 weeks of treatment. For the Week 3 (-2 to +5 days) and Week 7 (-2 to +5 days) visits, serial blood samples were taken at 0 (up to 30 min before dosing), 2, 3, 4, 5, 6, 8, 12, 14, 15, 16, 17, 18, 20, and 24 hrs after the morning dose. The 24-hr Cavg and Cmax were calculated and used for dose adjustment on Week 4 and Week 8 based upon the following titration algorithm:

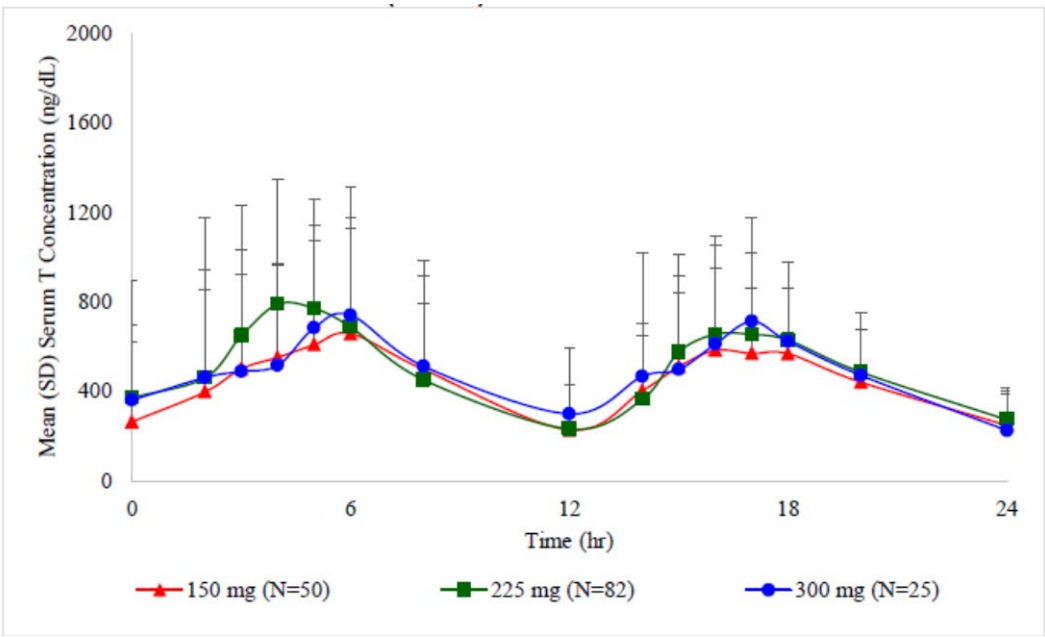
- If T Cavg < 300 ng/dL, dose was titrated upward by 75 mg
- If T Cavg > 1140 ng/dL, dose was titrated downward by 75 mg
- If T Cavg between 300 to 1140 ng/dL and T Cmax < 1500 ng/dL, dose was not changed
- If T Cmax > 1500 ng/dL, dose was titrated downward by 75 mg/dose regardless of the 24-hr Cavg

Mean serum T concentration-time profile of patients at Week 3 stratified by titration requirement at Week 4 (N=192*) (sponsor's figure 20, Module 2.73).



* Total 193 patients had week 3 visit but one patient had inadequate PK samplings.

Mean serum T concentration-time profile of patients at Week 13 stratified by final dose at Week 13 (N=157*) (sponsor's figure 21, Module 2.73).



150 mg = patients who down-titrated either at Week 4 or Week 8 based on Cmax or Cavg
225 mg = patients who ended up at the starting dose
300 mg = patients who up-titrated either at Week 4 or Week 8 based on Cavg
* Total 157 patients had week 13 visit.

Primary efficacy endpoint for this study was the percentage of patients in the treatment arm who achieved a 24-hr Cavg serum T concentration within the normal range (300-1140 ng/dL) upon completion of 13 weeks of treatment. To establish efficacy, the Applicant was informed that the primary efficacy endpoint is that at least 75% of patients had to achieve a 24-hr Cavg within 300-1140 ng/dL and the lower bound of the corresponding 95% CI for this point estimate is at least 65%.

Proportion of Patients Treated with oral TU Achieving 24-hr serum T Concentrations within Predetermined Normal Range at Week 13

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 is Efficacy Population Set and FAS is Full Analysis Set

Reviewer's Comments: The primary efficacy endpoint was achieved with 87.4% of patients within the targeted 24-hr T Cavg 300-1140 ng/dL with the lower bound of the 95% CI of 81.7%. See the Clinical Review by Martin Kaufman for additional details. The majority of down-titrations were due to Cmax >1500 ng/dL, not Cavg.

Secondary endpoints are based on 24-hr T Cmax at Week 13. The predetermined limits were:

- T Cmax < 1500 ng/dL: ≥ 85% of patients
- T Cmax between 1800 and 2500 ng/dL: ≤ 5% of patients
- T Cmax > 2500 ng/dL: 0% of patients

Proportion of Patients Treated with oral TU Achieving Maximum Total T Concentrations within Predetermined Limits at Week 13 (N=151) (sponsor's table 24, Study LPCN 1021-13-001)

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)

Reviewer's Comments:

The secondary endpoint of patients with a 24-hr Cmax between 1800 and 2500 ng/dL was 4.6%, which meet the target of ≤ 5%. However, the percentage of patients with a 24-hr Cmax < 1500 ng/dL was 82.8% (below the target of ≥ 85%) and the percentage of patients with a 24-hr Cmax > 2500 ng/dL was 2.0% (above the target of 0%). It is evident from the PK profile of oral TU capsules with a twice daily regimen, a peak and trough will follow each administration.

The following table summarizes the serum T parameters at the final dose of 150, 225, and 300 mg BID at Week 13 (sponsor's table 34).

	Pharmacokinetic Parameter			
LPCN 1021 Dose	Cmax (ng/dL) Mean (SD)	Tmax (h) Med (Min, Max)	AUC0-24h (ng·h/dL) Mean (SD)	Cavg0-24h (ng/dL) Mean (SD)
150 mg, N = 47	1065.06 (535.93)	6.0 (2.0, 20.0)	10662.74 (5457.72)	444.77 (227.37)
225 mg, N = 65	1116.77 (427.98)	6.0 (0.0, 20.0)	10720.11 (2957.92)	446.85 (123.28)
300 mg, N = 18	1376.72 (746.68)	5.6 (2.0, 24.0)	10753.35 (3866.91)	449.12 (161.13)
Overall, N = 130	1134.07 (526.18)	6.0 (0.0, 24.0)	10703.97 (4115.09)	446.41 (171.46)

Reviewer's Comments:

The table above shows the 24-hr testosterone concentrations at the final doses of 150 mg, 225 mg, or 300 mg BID for 130 patients after 13 weeks of treatment with oral TU. The final dose for each patient was the result of two prior PK assessments at Weeks 3 and 7 with possible dose adjustment at Weeks 4 and 8, respectively, if the 24-hr Cavg was outside of range 300-1140 ng/dL or Cmax was >1500 ng/dL. Of the patients who completed the study and were treated with oral TU, the mean 24-hr Cavg was 445, 447, and 449 ng/dL at doses 150, 225, and 300 mg BID, respectively, at Week 13.

The following table summarizes the mean (min, max) serum T concentrations at each scheduled time point stratified by the final dose of 150, 225, and 300 mg BID at Week 13 (sponsor's table 14.2.1.1).

					Testosterone serum concentration (ng/dL)					
LPCN 1021 dose (BID)	Visit	Scheduled time	n	nmiss	Mean	SD	CV (%)	Minimum	Median	Maximum
150 mg N = 47	Week 13	Pre-dose	47	0	259.7021	363.9992	140.2	0.000	210.0000	2560.000
		2 hr	46	1	407.0326	464.2517	114.1	35.500	262.000	2610.000
		3 hr	47	0	499.8255	410.2075	82.1	30.200	353.0000	1910.000
		4 hr	47	0	539.8787	382.0137	70.8	58.000	413.0000	1670.000
		5 hr	44	3	609.6500	466.9663	76.6	57.900	507.5000	2880.000
		6 hr	47	0	662.6851	530.1568	80.0	44.600	567.0000	3500.000
		8 hr	47	0	500.3702	423.5373	84.6	37.400	342.0000	2460.000
		12 hr	47	0	225.0574	206.7123	91.8	17.900	178.0000	1160.000
		14 hr	47	0	408.6702	311.5265	76.2	57.500	307.0000	1460.000
		15 hr	47	0	524.7298	409.9501	78.1	58.300	365.0000	1640.000
		16 hr	47	0	597.5766	373.2206	62.5	80.000	527.0000	1570.000
		17 hr	47	0	571.4468	301.3941	52.7	52.000	540.0000	1460.000
		18 hr	47	0	569.7596	299.4373	52.6	35.700	540.000	1600.000
		20 hr	47	0	439.9638	238.9838	54.3	41.600	386.0000	1380.000
		24 hr	47	0	241.1468	138.3761	57.4	35.600	201.0000	762.000
225 mg N = 65	Week 13	Pre-dose	64	1	322.5516	224.3142	69.5	43.600	265.0000	1290.000
		2 hr	65	0	384.4138	303.7429	79.0	33.600	276.000	1700.000
		3 hr	65	0	555.8169	431.8179	77.7	57.600	427.0000	1870.000
		4 hr	65	0	663.2492	408.4916	61.6	55.200	650.0000	1940.000
		5 hr	64	1	708.4875	441.2411	62.3	97.200	603.0000	2300.000
		6 hr	65	0	636.8077	363.5838	57.1	47.800	587.0000	2310.000
		8 hr	65	0	417.0615	248.1148	59.5	50.000	366.0000	1420.000
		12 hr	65	0	218.9708	206.1911	94.2	76.500	172.0000	1670.000
		14 hr	65	0	330.7292	253.9457	76.8	32.200	269.0000	1580.000
		15 hr	65	0	544.7046	407.5112	74.8	47.800	381.0000	1580.000
		16 hr	64	1	611.2234	349.0895	57.1	78.300	539.5000	1450.000
		17 hr	64	1	600.3375	300.1305	50.0	82.600	555.0000	1820.000
		18 hr	65	0	586.4892	285.9401	48.8	98.800	535.000	1650.000
		20 hr	64	1	462.7484	241.5896	52.2	65.900	412.0000	1370.000
		24 hr	64	1	259.8859	124.8743	48.0	99.700	249.5000	615.000
300 mg N = 18	Week 13	Pre-dose	18	0	186.4611	124.5418	66.8	26.800	155.5000	506.000
		2 hr	18	0	437.7444	789.6671	180.4	32.500	183.500	3390.000
		3 hr	18	0	485.9778	575.5031	118.4	47.600	254.5000	2050.000
		4 hr	18	0	524.3111	438.5086	83.6	51.600	363.5000	1750.000
		5 hr	18	0	684.5889	460.4951	67.3	50.600	591.5000	1450.000
		6 hr	18	0	655.1333	436.8674	66.7	76.400	488.0000	1540.000
		8 hr	18	0	493.0000	509.3525	103.3	107.000	405.0000	2380.000
		12 hr	18	0	287.0833	335.4772	116.9	67.300	172.5000	1420.000

14 hr	18	0	460.6611	589.8953	128.1	77.900	298.5000	2610.000
15 hr	18	0	512.8833	334.1854	65.2	70.900	538.0000	1450.000
16 hr	18	0	664.9444	536.3663	80.7	109.000	600.0000	2440.000
17 hr	17	1	671.8824	466.0029	69.4	158.000	597.0000	2020.000
18 hr	18	0	538.6111	220.9006	41.0	222.000	514.5000	998.000
20 hr	18	0	396.4444	180.1138	45.4	121.000	367.0000	920.000
24 hr	18	0	187.9222	101.0981	53.8	75.000	170.5000	433.000

There were patients within each dose group with a maximum T concentration that exceeded 1500 ng/dL (up to 3390 ng/dL). These excursions from the physiological range occurred as early as 2 hrs and up to 18 hrs after the last dose. This data highlight the complexities of using the mean data to assess treatment outcomes at a population level for an indication that requires individual dose titration. The inter-subject variability was high with a %CV ranging from ~60% to 180% within the first 12 hrs after the last TU dose.

Chemiluminescence Immunossay (CLIA) for Phase 3 Enrollment

Enrollment in the phase 3 study required patients have a baseline testosterone concentration less than 300 ng/dL on two consecutive readings at approximately the same time (between 6 am and 10 am) on two separate days. The reference range for CLIA 241-827 ng/dL for determination of eugonadal state was used to confirm a patient's diagnosis of hypogonadism with a reference range of. With CLIA, patients with a T concentration < 241 ng/dL is considered hypogonadal and was permitted to enter the study. The CLIA method and other immune assays are typically used in the clinical setting as the LC-MS/MS method is not as easily accessible for rapid assessment of baseline testosterone concentration.

LC-MS/MS for PK Assessment in the Phase 3 Study

T concentrations from extensive 24-hr blood sampling were determined by LC-MS/MS. For dose adjustments at Weeks 4 and 8, and for efficacy assessment at Week 13, extensive blood sampling was conducted at Weeks 3, 7, and 13, respectively. PK parameters used to guide dose titrations included 24-hr Cavg and Cmax during the 24-hr period.

Difference in T Concentration as Assessed by CLIA and LC-MS/MS

The reviewers from the Office of Clinical Pharmacology and Office of Statistics observed inconsistence values for baseline T concentrations for the same patient from two database files. The database files showed that adlb.xpt showed the T baseline concentrations were higher than the values in the adpc.xpt database for the same patient taken on the same day.

In response to an Information Request sent by DBRUP on May 18, 2016, the Applicant clarified that the data from adlb.xpt were from samples assayed by CLIA, while the data from adpc.xpt were from samples assayed by LC-MS/MS which tended to result in higher concentrations. While there is an absolute difference in the two assay methods, the sponsor conducted a sensitivity analysis of responders using the subset of subjects with T < 300 ng/dL based on the adpc.xpt. The results showed that > 85% of patients had achieved 24-hr Cavg of 300-1140 ng/dL and thus meeting the primary efficacy endpoint (see the sponsor's table 5 below).

Subject population	Full Analysis Set (LOCF)	Efficacy Population Set (LOCF)
N	136	106
Percentage subjects achieving 24-hour average serum Total testosterone concentration within 300 to 1140 ng/dL	85.29 %	85.85%
95% Confidence interval[1]	78.30 %, 90.31%	77.84 %, 91.29%
[1]A 95%, 2-sided, binomial confidence interval surrounding the point estimate was calculated.		

2.3.6 What are the proposed dosing regimen and administration instructions?

Proposed Titration Scheme (b) (4)

(b) (4)

2.3.7 Did the Applicant submit adequate data supporting the proposed dose titration scheme?

Proposed Sampling Time (b) (4) hrs post-AM dose

(b) (4)

(b) (4)

Proposed Titration Algorithm

(b) (4)

Office of Clinical Pharmacology 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 have Cmax higher than 1500 ng/dL at the Week 3 visit, so the dose was reduced to 150 ng/dL. 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.

Comparison of the percentage of the patients that would be down-titrated, have no change in dose, or be up-titrated based on a single serum T sample between (b) (4) h after morning administration for all the patients within each group for titration thresholds in Phase 3 study and proposed in (b) (4) (table below). The percentage of the patients who would have same dose adjustment based on both Cavg and C3-6h are highlighted.

Concordance by dosing subgroup between full profile (C_{avg}) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of 300 and 1140 ng/dL (bounds in Phase 3) and (b) (4) and (b) (4) ng/dL (b) (4) (b) (4)

C_{avg} Titration Results from Phase 3	$C_{3\text{-}6h}$ Titration	Titration threshold of 300 and 1140 ng/dL	Titration threshold of (b) (4) and (b) (4) ng/dL (b) (4)
Down Titration (n=61*)	Down Titration	43%	
	No Change	44%	
	Up Titration	13%	
No Change (n=105)	Down Titration	7%	
	No Change	65%	
	Up Titration	28%	
Up Titration (n=25)	Down Titration	0%	
	No Change	47%	
	Up Titration	53%	

* N=191, two patients do not have dose adjustment due to inadequate PK samplings.

The results verified the sponsor's concordance analysis that the thresholds of (b) (4) to (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. At least a 35% discordance was identified between two titration schemes, and the percentage cannot be improved upon for some groups (e.g. down titration group).

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of testosterone undecanoate and testosterone in hypogonadal men?

Single Dose PK

Study S361.1.001 was an open-label, single dose bioavailability study of two oral TU capsule formulations in hypogonadal men with doses of 75, 150, and 225 mg taken with 240 mL water 30 min after starting a high-fat breakfast. Subjects were randomized to either Group 1 (Formulation LPCN 1021-07) or Group 2 (Formulation LPCN 1021-10) groups. Formulation LPCN 1021-07 capsules (b) (4) (b) (4) (b) (4), but are otherwise the same as the to-be-marketed capsules used in the Phase 3

and pivotal food effect studies. Formulation LPCN 1021-10 differs from LPCN 1021-07 by containing a (b) (4)

Mean (SD) serum TU pharmacokinetics following single dose administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07

	TU Dose		
PK Parameter	75 mg (N=12)	150 mg (N=11)	225 mg (N=11)
Cmax0-24 (ng/dL)	11528 (6139)	35418 (22646)	35709 (20044)
Tmax* (hr)	5 (5-12)	5 (4-10)	5 (5-10)
AUC0-24 (ng hr/dL)	39785 (13455)	102795 (35029)	123481 (55676)
Cavg0-24 hr (ng/dL)	2750 (1253)	6016 (2521)	7235 (3518)
T1/2 (hr)	1.4 (0.4)	1.4 (0.4)	1.7 (0.8)

*median (range)

Mean (SD) serum T pharmacokinetics following single dose administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07

	TU Dose		
PK Parameter	75 mg (N=12)	150 mg (N=11)	225 mg (N=11)
Cmax0-24 (ng/dL)	545 (202)	979 (415)	1155 (423)
Tmax* (hr)	6.5 (4-12)	7 (4-10)	6 (4-10)
AUC0-24 (ng hr/dL)	7498 (2953)	9632 (3584)	10103 (3135)
Cavg0-24 hr (ng/dL)	**312 (123)**	**401 (149)**	**421 (131)**
Cavg0-12 hr (ng/dL)	**348 (132)**	**497 (207)**	**568 (201)**

*median (range)

Reviewer's Comment: The 24-hr and 12-hr T Cavg following a single dose administration oral TU were within the commonly recognized target eugonadal range (e.g., 300-1100 ng/dL). Additionally, at all three doses, the mean Cmax was less than 1500 ng/dL – the upper limit of normal. This study provided the preliminary bioavailability data for a dosing-finding study and titration scheme development (Study M12-778) using formulation LPCN 1021-07.

The T Cavg over a 12- and 24-hr duration following a single 75 mg dose was near the lower end of the eugonadal range. T Cavg over a 24-hr duration is a relevant PK parameter to consider as the primary efficacy endpoint is based upon ≥75% of patients achieving T Cavg0-24hr within the pre-specified eugonadal range.

Based on the 12-hr T Cavg, subjects can potentially be within the eugonadal range while avoiding Cmax greater than 1500 ng/dL. Based upon these findings, Study M12-778 incorporated a BID dosing regimen with the same doses evaluated in Study S361.1.001.

Single and Multiple Dose PK

The PK of TU and T following single and multiple-dose administration of oral TU 225 mg BID was determined in a randomized single center, double-blind, placebo-controlled dose, single and multiple-dose, escalating study in adult hypogonadal males with a mean age of ~43 years (Study M12-778).

The study consisted of 5 groups with 3 groups of 20 subjects and 2 groups of 12 subjects each. Subjects in Groups 1, 2 and 3 were randomly assigned in a 4:1 ratio to receive oral TU (75 mg for Group 1, 150 mg for Group 2, and 225 mg for Group 3) or matching placebo. Groups 1-3 received oral TU or placebo daily for 14 days starting on Day 1 through Day 15 am dose. Subjects in Groups 4 and 5 were randomly assigned in a 3:1 ratio to receive oral TU (300 mg for Group 4 and 225 mg for Group 5) or matching placebo and dosed for 28 days. The sponsor noted a difference in the PK profiles for the 225 mg group (Group 3) on Day 8 vs. Day 15 so they added an additional 225 mg dose group (Group 5) with a 28-day dosing duration. All subjects were dosed BID 30 min after a standard meal (moderate fat content).

Mean (SD) serum TU pharmacokinetics following multiple dose (BID dosing x 14 days) administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07 on Day 15

	TU Dose		
PK Parameter	75 mg (N=16) Group 1	150 mg (N=15) Group2	225 mg (N=16) Group 3
Cmax0-24 (ng/dL)	12323 (4135.4)	19209 (10303)	36333 (12635)
Tmax (hr)	7.0 (4.6)	7.7 (5.7)	7.9 (4.6)
AUC0-24 hr (ng hr/dL)	61849 (17643)	101369 (37256)	192284 (56236)
Cavg0-24 hr (ng/dL)	**2577 (735)**	**4224 (1552)**	**8012 (2343)**

Mean (SD) serum T pharmacokinetics following multiple dose (BID x 14 days) administration of 75 mg, 150 mg, and 225 mg oral TU with formulation LPCN 1021-07 on Day 15

	TU Dose		
PK Parameter	75 mg (N=16) Group 1	150 mg (N=16) Group2	225 mg (N=16) Group 3
Cmax0-24 (ng/dL)	**544 (169)**	**792 (276)**	**1169 (356)**
Tmax (hr)	7.8 (4.8)	8.7 (6.3)	8.7 (4.7)
AUC0-24 hr (ng hr/dL)	6488(2265)	7652 (1839)	10693 (3872)
Cavg0-24 hr (ng/dL)	**270 (94.4)**	**319 (77)**	**446 (161)**

Reviewer's Comment: The 24-hr T Cavg was 319 and 446 ng/mL (above 300 ng/dL) following 14 days of BID dosing administration oral TU 150 mg BID and 225 mg BID and the Cmax was less than 1500 ng/dL. The dose escalation study continued up to 300 mg BID and was extended in duration.

Mean (SD) serum TU pharmacokinetics following multiple dose (BID dosing x 21 days) administration 225 mg and 300 mg oral TU with formulation LPCN 1021-07 on Day 22

	TU Dose	
PK Parameter	225 mg (N=9) Group 5	300 mg (N=9) Group 4
Cmax0-24 (ng/dL)	19322 (7997)	62533 (49122)
Tmax (hr)	3.6 (1.7)	3.8 (1.9)
AUC0-12 hr (ng.hr/dL)	69525 (19641)	191493 (109030)
Cavg0-12 hr (ng/dL)	**69525 (19641)**	**15958 (9086)**

Mean (SD) serum T pharmacokinetics following multiple dose (BID dosing x 21 days) administration 225 mg and 300 mg oral TU with formulation LPCN 1021-07 on Day 22

	TU Dose	
PK Parameter	225 mg (N=9) Group 5	300 mg (N=9) Group 4
Cmax0-24 (ng/dL)	**835 (329)**	**1447 (694)**
Tmax (hr)	4.7 (1.7)	4.9 (1.5)
AUC0-12 hr (ng.hr/dL)	4576 (1512)	7329 (3264)
Cavg0-12 hr (ng/dL)	**381 (126)**	**611 (272)**

Reviewer's Comment: The 12-hr T Cavg was 381 and 661ng/mL following 21 days of BID dosing administration oral TU 225 mg and 300 mg, respectively. The T Cavg was within the commonly recognized target eugonadal range; however, the mean T Cmax was 1447 ng/dL following 300 mg BID which is near the upper limit of normal (~1500 ng/dL).

The accumulation ratio for T at 225 mg was approximately 1.0 based on the Day 14/Day 1 $AUC_{0\text{-}24hr}$ ratio.

The following table summarizes the TU:T ratio from all dose groups following BID dosing.

	TU Dose (administered BID) on Day 15				
	75 mg (Group 1) N=16	150 mg (Group 2) N=15	225 mg (Group 3) N=15	225 mg (Group 4) N=9	300 mg (Group 5) N=9
AUC0-24hr (ng.hr/dL)					
TU	61849	101369	192284	152433	351913
T	6488	7652	10693	8593	15466
TU:T ratio	**9.5**	**13.2**	**18.0**	**17.7**	**22.8**
Cmax (0-24hr) (ng/dL)					
TU	12323	19209	36333	24846	77100
T	544	792	1169	798	1923
TU:T ratio	**22.7**	**24.3**	**31.1**	**31.1**	**22.8**

Reviewer's Comments:
The TU:T ratio for AUC0-24 is based upon the AUC0-24 for TU divided by the AUC0-24 for T. For example: at 300 mg, TU:T ratio for AUC0-24 is 351913/15466 = 22.8.

The TU:T ratio for AUC0-24 for the proposed doses is approximately 13, 18, and 23 for 150 mg, 225 mg, and 300 mg BID, respectively. The TU:T ratio for Cmax0-24 for the proposed doses is approximately 24, 31, and 23 for 150 mg, 225 mg, and 300 mg BID, respectively.

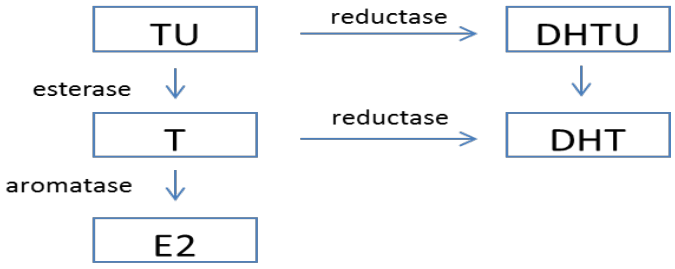
The high TU:T ratios show that there is incomplete conversion of TU tot T.

2.5.2 What are the characteristics of drug absorption?

Oral administration of T results in low bioavailability as it is extensive metabolized by first-pass liver metabolism. Published literature states that the bioavailability of oral TU administration is approximately 7% due to the extensive first pass effect. During the absorption process, TU is reduced to 5α-dihydrotestosterone undecanoate (DHTU), which is also absorbed via the lymphatic system. From the lymphatic system, TU and DHTU are released into the circulation via the thoracic duct. Both TU and DHTU are hydrolyzed to yield T and 5α-dihydrotestosterone (DHT). T is also metabolized to other pharmacologically active metabolites such as estradiol (E2).

2.5.3 What are the characteristics of drug metabolism?

TU is a lipophilic molecule and is a fatty-acid ester prodrug of T that must undergo hydrolysis by esterases to release T. It is formulated in a lipid-based capsule to be absorbed primarily via the lymphatic system to avoid the first-pass metabolism in the liver. With oral TU therapy, E2 and DHT increased from baseline but are within the normal range at the end of treatment.



2.5.4 What are the characteristics of drug excretion in urine?

Approximately 40% of the ^{3}H-radiolabeled TU were excreted in the urine after 24 hrs, according to publication by Horst HJ et. al. 1976.

2.6 Intrinsic Factors

2.6.1 What intrinsic factors (age, race, and organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

There were no dedicated phase 1 studies to evaluate the effect of intrinsic factors such as organ impairment, race, and age on the bioavailability of TU or T. The phase 3 study excluded patients with a history of any clinically significant illness and enrolled approximately 10% of men over the age of 65 years. The composition of patients in the phase 3 consisted of approximately 84% White, 13% Black or African American, and 2% Asian. Efficacy and safety of LPCN 1021 were not evaluated in patients less than 18 years of age and is not indicated for women. The phase 3 study excluded patients with history of clinically significant illness, which may include hepatic and renal impairment.

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

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

Geriatric Use: The Applicant's proposed product label states (b) (4)

Pediatric Use: The Applicant's proposed product label states (b) (4)

2.7 Extrinsic Factors

2.7.1 What extrinsic factors influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as prescription drugs and herbal products have not been studied by the Applicant. The phase 3 study protocol excluded use of CYP3A4 inhibitors and inducers, yet the proposed label does not address the potential concomitant use with oral TU.

2.7.2 Drug-Drug Interactions

2.7.2.1 Is there an in vitro basis to suspect in vivo 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 Applicant did not conduct in vitro and in vivo studies to assess potential drug-drug interactions.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutics classification system principles, in what class is this drug and formulation? What solubility and permeability support this classification?

There has been no formal classification of TU solubility and permeability based on the biopharmaceutics classification system.

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical trial formulation?

The to-be-marketed formulation was used in the pivotal phase 3 study (LPCN 1021-14-001) and definitive food-effect study (LPCN 1021-13-001) and included the (b) (4) ascorbyl palmitate (b) (4) (b) (4) (b) (4) Ascorbyl palmitate serves as an (b) (4) The Chemistry Reviewer had previously concluded this addition is an insignificant formulation change and no bridging between the two formulations is required.

Composition of the to-be-marketed oral TU capsules ((b) (4) (b) (4) 112.5 mg) is presented in the following table (sponsor's table 1 from Module 2.3).

Component	Quality Standard	Function	% in Fill	(b) (4) 112.5 mg dose strength
Capsule Fill				Amount (mg) per capsule
Testosterone Undecanoate	In-house	Drug substance	(b) (4)	112.5
(b) (4) (Glyceryl Monolinoleate)	NF	(b) (4)		(b) (4)
Polyoxyl 40 Hydrogenated Castor Oil	NF			
Ascorbyl Palmitate	NF			
Polyethylene Glycol, 8000	NF			
Total	(b) (4)			
Capsule, gelatin (b) (4) (b) (4)	In-house	Capsule shell		1 capsule
Gelatin Banding (b) (4)				(b) (4)
Gelatin (b) (4) Pharmaceutical Grade	NF	Capsule Banding	(b) (4)	

2.8.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

TU is a lipophilic substance. Therefore, it is recommended that the capsules are taken with meals containing some lipids in order to increase absorption and bioavailability of testosterone. The Applicant evaluate 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 male 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 drug administration. Blood samples for determination of T, DHT, TU, and DHTU concentrations were collected at approximately 12 hr, approximately 2 hr, and pre-dose (within 45 min prior to dosing) of dosing, and between 1 and 24 hrs 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.

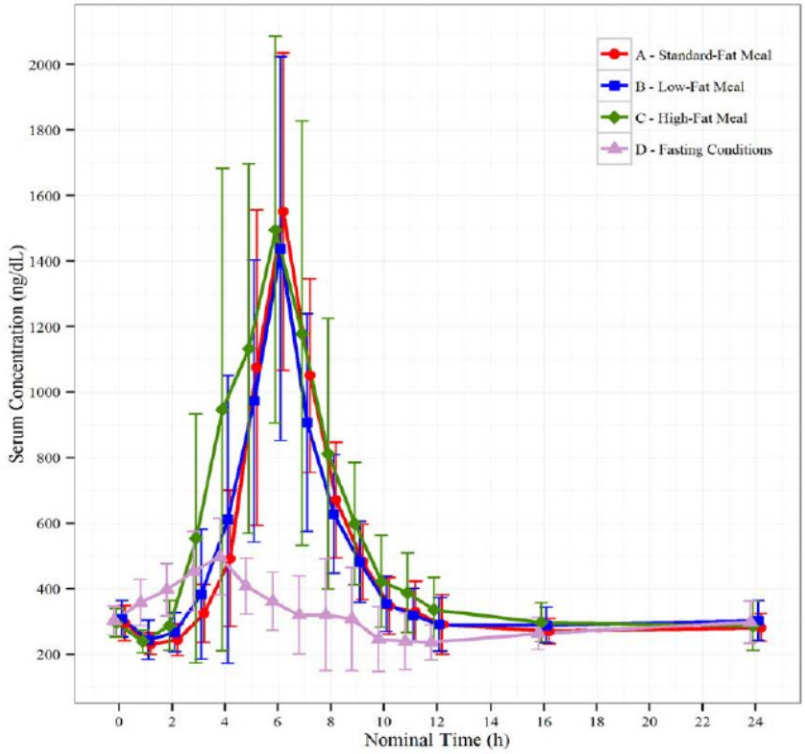
Fat and Caloric Description of the Meals

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%)

Standard Fat refers to a moderate-fat meal.

Total Testosterone (T)

The following figure is the mean (SD) T serum concentration-time profiles following various food intake (Treatments A, B and C (N=13) and Treatment D (N=14)) (sponsor's figure 11.4.2.4-3).



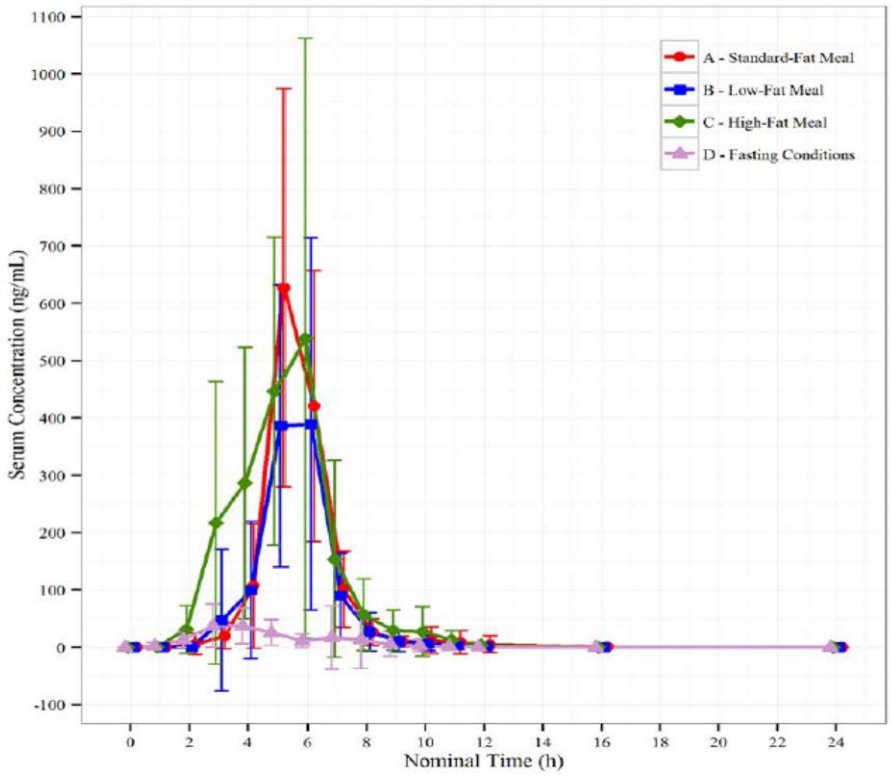
Mean (%CV) testosterone (T) serum pharmacokinetics following various food type.

	Meal Type/Fat Content			
PK Parameter	Fasting Condition (N=14)	Low-Fat (N=13)	Moderate-Fat (Standard Meal) (N=13)	High-Fat (N=13)
Cmax0-24 (ng/dL)	562 (26)	1570 (35)	1560 (31)	1680 (44)
Tmax* (hr)	4.0 (1-8)	6.0 (4-6)	6 (5-7)	6 (4-8)
AUC0-12 (ng hr/dL)	4178 (20)	6899 (22)	7094 (21)	8371 (26)

*median (range)

Testosterone Undecanoate (TU)

The following figure is the mean (SD) TU serum concentration-time profiles following various food intake (Treatments A, B and C (N=13) and Treatment D (N=14)) (sponsor's figure 11.4.2.4-3).



Mean (%CV) testosterone (TU) serum pharmacokinetics following various food type.

	Meal Type/Fat Content			
PK Parameter	Fasting Condition (N=14)	Low-Fat (N=13)	Moderate-Fat (Standard Meal) (N=13)	High-Fat (N=13)
Cmax0-24 (ng/dL)	71.2 (73.2)	553 (46.9)	685 (48.7)	728 (64.0)
Tmax* (hr)	4.0 (3.0-7.0)	5.0 (3.0-6.0)	5.0 (5.0-7.0)	5.0 (3.0-8.0)
AUC0-12 (ng hr/dL)	169 (82)	1060 (39)	1333 (33)	1802 (36)

*median (range)

Reviewer's Comments:

- *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 4 treatment groups – fasting, low-fat, medium-fat, and high-fat.*

- *Comparing the two extreme cases of fat content – low-fat vs. high-fat –the geometric mean ratio for T for AUC0-12h was 0.83and for Cmax was 0.96.*
- *Comparing high-fat vs. moderate-fat, the geometric mean ratio for T for AUC0-12h was 1.17 and for Cmax was 1.03.*
- *Comparing high-fat food vs. fasting condition, the geometric mean ratio for TU for AUC0-12h was 12.6 and for Cmax was 11.0.*
- *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.*

2.9 Analytical Section

2.9.1 What bioanalytical methods are used to assess drug concentrations? Briefly describe the methods and summarize the assay performance.

Serum TU and DHTU were analyzed by LC-MS/MS following protein precipitation with solid phase extraction. The validated assay range for TU was 0.203 to 154 ng/dL (8 standards) and for DHTU (8 standards) was 0.582 to 442 ng/dL. The mean % bias for TU was between 0.5% and 1.8% and for DHTU was between 1.6 and 4.6%. The QC samples for TU ranged from 2 to 1000 ng/mL and for DHTU were 1 to 500 ng/mL. The acceptance criteria (%CV) ranged from 1.2% to 4.7% for TU and from 2.5% to 6.8% for DHTU.

The HPLC method for TU and DHTU is presented in the following table:

Injection Volume	50 µL
Mobile Phase	94/6/0.2 (*v/v/v*) Methanol/Water/Acetic Acid
Reference Solution	Approximately 10 ng/mL each of TU, TUd3, DHTU, and DHTUd3 in 75/25 (*v/v*) Acetonitrile/Water
Analytical Column	Sigma-Aldrich, Ascentis Express C18 2.7µm 2.1x100mm
Flow Rate (Analytical)	0.5 mL/min
Column Temperature	50 ºC
Autosampler Temperature	Cool (set point 4ºC)
Run Time	Approximately 3 minutes

Stability of TU and DHTU following multiple cycles of freeze-thaw was evaluated. The first cycle evaluation samples were frozen for at least 24 hrs at ~ -20°C. All subsequent evaluation cycles were frozen for at least 12 hrs at ~ -20°C. After 4 cycles of freeze-thaw and at least 16 hrs of room temperature, the mean % bias for TU was between 0.5% and 5% and for DHTU was 1.6% and 2.2%.

Serum T and DHT were analyzed by LC-MS/MS following protein precipitation with solid phase extraction. QC samples ranged from 10 to 3750 ng/dL for T and 2 to 750 ng/dL for DHT. The acceptance criteria (%CV) ranged from 4.6% to 9.2% for T and from 3.0% to 11.4% for DHT.

Serum E2 were analyzed by LC-MS/MS following protein precipitation with solid phase extraction. QC samples ranged from 1 to 750 ng/mL for E2. The acceptance criteria (%CV) ranged from (b) (4)% to (b) (4)% for E2.

Reviewer's comment: Percent bias for TU, DHTU, T, and DHT were all below 15%. For E2, the %CV for one QC sample fell slightly outside the FDA acceptance criteria of 15%. The analytical method and acceptance criteria are acceptable per the FDA's Guidance on Bioanalytical Method Validation.

2.9.2 Which metabolites have been selected for analysis and why?

DHTU, T, DHT, and E2 are all metabolites of TU. T is the active metabolite contributing to the efficacy endpoint of TU therapy and is used in the endpoint efficacy analysis.

2.9.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The calibration standards were within the ranges anticipated for patient concentration. The correlation coefficient for TU, DHTU, T, DHT, and E2 were near unity (1.0).

Calibration Standards and Curve Fit for TU

Run Number	Slope	Intercept	r^2
1	0.092387	0.001413	0.996285
2	0.094060	-0.000864	0.999097
3	0.095977	-0.000757	0.999417
4	0.094838	-0.001612	0.998742
6	0.096673	-0.004486	0.998089

Calibration Standards and Curve Fit for DHTU

Run Number	Slope	Intercept	r^2
1	0.034197	0.010103	0.999143
2	0.033774	0.010442	0.998740
3	0.035701	0.007137	0.993909
4	0.034174	0.008490	0.998278
6	0.034823	0.006866	0.998987

Calibration Standards and Curve Fit for T

Run ID	Line Equation	R
1RBJE2-A-2	Y = -1.532515E-03 + 4.337119E-01 * X	0.9983
2RBJE2-A-2	Y = -1.511228E-04 + 4.362857E-01 * X	0.9981
3RBJE2-A-2	Y = 3.200280E-04 + 4.464363E-01 * X	0.9990
5RBJE2-B-2	Y = -1.192464E-03 + 4.282691E-01 * X	0.9974
6RBJE2-A-2	Y = -3.997198E-04 + 4.439190E-01 * X	0.9988
8RBJE2-A-2	Y = 2.528093E-03 + 4.880815E-01 * X	0.9988
11RBJE2-A-2	Y = -6.833360E-04 + 4.749844E-01 * X	0.9989
	Average Correlation Coefficient	0.9985

Calibration Standards and Curve Fit for DHT

Run ID	Line Equation	R
1RBJE2-A-1	Y = -7.839303E-04 + 8.273021E-01 * X	0.9978
2RBJE2-A-1	Y = -1.124412E-03 + 8.358796E-01 * X	0.9990
3RBJE2-A-1	Y = 6.185824E-03 + 8.535966E-01 * X	0.9987
5RBJE2-B-1	Y = -1.912112E-03 + 8.320710E-01 * X	0.9994
6RBJE2-A-1	Y = 1.049851E-03 + 8.329089E-01 * X	0.9992
8RBJE2-A-1	Y = -3.288973E-03 + 8.068084E-01 * X	0.9986
11RBJE2-A-1	Y = 1.740335E-03 + 7.913881E-01 * X	0.9979
	Average Correlation Coefficient	0.9987

Calibration Standards and Curve Fit for E2

Run ID	Line Equation	R
3JNZ2-2-A	Y = -1.476609E-06 * X^2 + 1.045859E-02 * X + 1.704595E-03	0.9993
5JNZ2-2-B	Y = -1.397770E-06 * X^2 + 1.056992E-02 * X + 1.645856E-03	0.9988
6JNZ2-2-A	Y = -1.287451E-06 * X^2 + 1.056344E-02 * X + 2.060203E-03	0.9991
8JNZ2-2-A	Y = -1.032186E-06 * X^2 + 1.016170E-02 * X + 1.241217E-03	0.9994
9JNZ2-2-A	Y = -1.489687E-06 * X^2 + 1.072432E-02 * X + -1.038729E-04	0.9981
10JNZ2-2-A	Y = -1.728794E-06 * X^2 + 1.111711E-02 * X + -4.477087E-04	0.9993
	Average Correlation Coefficient	0.9990

2.9.4 What are the lower and upper limits of quantification (LLOQ/ULOQ)? What are the accuracy, precision and selectivity at these limits?

For TU and DHTU, the LLOQ were 2 and 1 ng/mL, respectively. For TU and DHTU, the ULOQ were 1000 and 500 ng/mL, respectively. The LLOQ was 10 ng/dL for T and 5 ng/dL for DHT. For E2, the LLOQ and ULOQ were 1 and 750 ng/mL, respectively. These ranges cover the anticipated concentration ranges.

2.9.5 Does TU convert to T in the blood/serum samples during sample processing and before analysis?

The conversion of TU to T by non-specific esterases in blood can potentially occur during processing of samples before analysis of the moieties can occur. If TU is converted to T in blood samples before the sampling process is completed, the reported T concentrations can be artificially inflated and result in an overestimation of T replacement by oral TU capsules.

The phase 3 study design specified that whole blood samples were allowed to clot at room temperature for 20 min (up to 60 min) before centrifugation ~ 1000 g for 10-15 min. The resulting serum was transferred into 3 separate tubes for immediate freezing at -20°C, and maintained frozen during shipment to (b) (4) for bioanalysis.

The Applicant assessed the potential conversion of TU to T with whole blood samples fortified with TU (1000 ng/mL) (Method Validation Report LCMSC 521.1). Whole blood was drawn into heparinized

blood tubes and sub-aliquotted from three donors. All samples were incubated at room temperature for 30 min to mimic typical processing time. Following the 30 min at room temperature, one set of samples was processed to plasma in a 2 to 8°C centrifuge (Controls), one set was placed on ice and processed to plasma after 60 min and 120 min on ice, one set of samples was placed at room temperature and processed to plasma after 120 min.

Blood samples were aliquotted and treated as follows:

- Blood samples without TU or DHTU incubated for 30 min at room temperature → processed for plasma (for endogenous T and DHTconcentrations)
- Blood samples fortified with TU and DHTU incubated for 30 min at room temperature → processed for plasma (sponsor referred to these samples as Controls)
- Blood samples fortified with TU and DHTU incubated for 90 min (30 min + 60 min) at room temperature → processed for plasma
- Blood samples fortified with TU and DHTU incubated for 150 min (30 min + 120 min) at room temperature → processed for plasma
- Blood samples fortified with TU and DHTU incubated for 30 min at RT + 60 min on ice → processed for plasma
- Blood samples fortified with TU and DHTU incubated for 30 min at RT + 120 min on ice → processed for plasma

	30 min at RT*	30 min at RT + 60 min on ice	30 min at RT + 120 min on ice	90 min at RT	150 min at RT
Donor 1					
T (ng/mL)	19.9	26.1	29.1	30.8	52.9
BA-T (ng/mL)	NA	6.2	9.2	10.9	33.0
% TU conversion	NA	0.99	1.46	1.73	5.22
Donor 2					
T (ng/mL)	19.6	26.8	28.1	41.8	61.1
BA-T (ng/mL)	NA	7.2	8.5	22.2	41.4
% TU conversion	NA	1.14	1.34	3.51	6.56
Donor 3					
T (ng/mL)	9.3	10.8	13.3	19.6	33.9
BA-T (ng/mL)	NA	1.4	4.0	10.2	24.6
% TU conversion	NA	0.23	0.63	1.62	3.89

NA = not applicable
RT= room temperature
T= testosterone concentration
BA-T= baseline-adjusted testosterone
*referred to as Control by the Applicant

Reviewer's Comments:

- *The determination of T concentrations was calculated using a calibration curve from an earlier run for the stability assessments. This is acceptable.*

- *Percent conversion of TU to T is based upon the 1 to 1 molar conversion of TU to using molecular weight of T = 288.42 and molecular weight of TU = 456.70. This is acceptable.*
- *The Applicant considers the samples incubated for 30 min at room temperature to be the baseline/ endogenous T concentration. While this reflects the standard sampling processing procedure, the baseline concentration of T can be affected by the potential conversion of TU to T by esterases during the 30 min period and may not accurately reflect the baseline T concentrations.*
- *Control samples included 30 min of TU incubated in whole blood in the presence of esterase; this is not equivalent to immediately removing non-specific esterases from the blood.*
- *The conversion of TU to T is approximately 1% of the TU dose once the samples are placed on ice, compared to 30 min at room temperature.*
- *The conversion of TU to T is approximately 2% and 5% of the TU dose for samples incubated at room temperature for up to 90 min and up to 150 min, respectively. This suggests that at room temperature, an additional 3% of TU dose is converted to T as the incubation time increased from 90 to 150 min.*
- *While this approach to assess the conversion of TU to T does not assess the impact of esterases on TU while the blood remains tubes for first 30 min (time between blood collection and plasma preparation), it does show that there is approximately 3% conversion of TU within 60 min (90 to 150 min). This is not significant considering the assay variability and intra-subject variability.*

3 Appendices

APPEARS THIS WAY ON ORIGINAL

Pharmacometrics Review

1 SUMMARY OF FINDINGS

LPCN 1021 is an oral capsule of testosterone undecanoate, a prodrug of testosterone, with a proposed indication for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The proposed (b) (4) dosing regimen is 225 mg TU BID to be administered with food. (b) (4) .

Serum testosterone concentration should be assessed periodically thereafter. Based on the single serum testosterone measurement, the following dose adjustments are proposed:

(b) (4)

The proposed titration scheme (b) (4) differs from the titration scheme in the single registrational Phase 3 study (LPCN 1021-13-001). The Phase 3 study design is shown in Figure 1. All subjects in the treatment arm started at the same dose of 225 mg (2 capsules of 112.5 mg) BID with administration approximately 12 hours apart (total daily dose of 450 mg) and approximately 30 minutes after morning and evening meals with water. Dose titration was based on an assessment of the subject's total serum T concentration over 24 h ($C_{avg0\text{-}24h}$) and maximum serum T concentration over 24 h ($C_{max0\text{-}24}$) obtained after approximately 3 and 7 weeks of treatment. For the Week 3 (-2 to +5 days) and Week 7 (-2 to +5 days) visits, serial blood samples were taken at 0 (up to 30 minutes before dosing), 2, 3, 4, 5, 6, 8, 12, 14, 15, 16, 17, 18, 20, and 24 hours after the morning dose. The $C_{avg0\text{-}24h}$ and $C_{max0\text{-}24h}$ were calculated and used for dose adjustment on Week 4 and Week 8:

- If $C_{avg0\text{-}24h} < 300$ ng/dL, dose was titrated upward by 75 mg/dose; or
- If $C_{avg0\text{-}24h} > 1140$ ng/dL, dose was titrated downward by 75 mg/dose; or
- If $C_{max} > 1500$ ng/dL, dose was titrated downward by 75 mg/dose regardless of the $C_{avg0\text{-}24h}$; or
- If $C_{avg0\text{-}24h} = 300$ to 1140 ng/dL and $C_{max} \leq 1500$ ng/dL, dose was not changed.

An additional visit took place at approximately Week 13 (-2 to +5 days) using the intensive blood sampling schedule listed above. Efficacy was evaluated by the Applicant at this time point for all patients remaining on treatment.

The primary efficacy endpoint for this study was the percentage of patients who achieved a $C_{avg0-24h}$ serum T concentration within the normal range (300-1140 ng/dL) upon completion of 13 weeks of treatment.

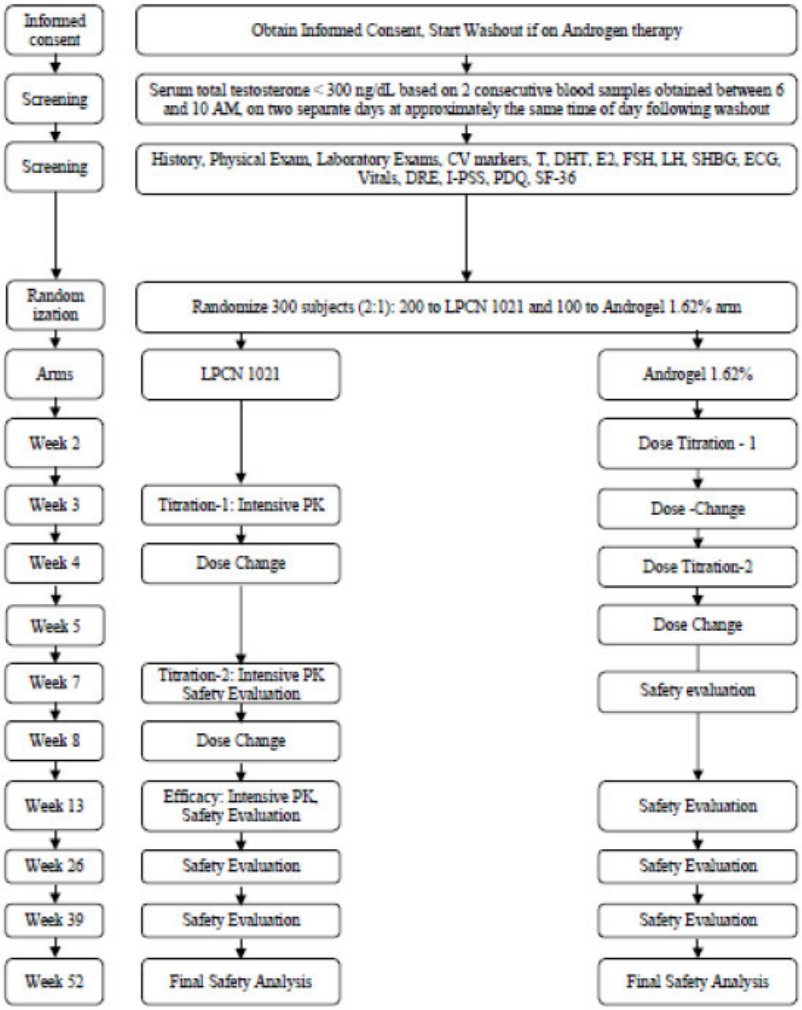


Figure 1: Phase 3 study design

Source: Applicant's study report for LPCN 1021-13-001, Page 22, Figure 1

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 Is the Applicant's proposed titration scheme [redacted] (b) (4) after the morning dose appropriate?

The proposed titration scheme [redacted] (b) (4) [redacted] (b) (4) is unable to capture the full PK information of oral testosterone over 24 h, including $C_{avg0-24h}$ and $C_{max0-24h}$. Not all the patients would have the same dose adjustment based on a single T concentration between [redacted] (b) (4) h after morning dose as would have been performed based on $C_{avg0-24h}$ and $C_{max0-24h}$ in Phase 3 trial. Although the proposed

titration threshold and sampling time would result in the greatest percentage of patients being titrated as occurred in the Phase 3 trial, there are still a considerable percentage of patients whose dose adjustment would be discordant between the single T titration and $C_{avg0-24h}$ and $C_{max0-24h}$ based titration.

The reviewer assessed the appropriateness of the proposed titration scheme (b) (4) by evaluating whether patients from the Phase 3 trial would have been titrated in the same manner using a single serum T sample. The Reviewer's analysis was based on PK information from 193 patients on active treatment from the Phase 3 study.

1. Titration threshold

The reviewer's titration analysis was based on intensive PK data obtained in Week 3. This represents the only on treatment assessment before patients were adjusted from the starting dose and is appropriate for comparing differences between the two titration algorithms. The reviewer considered the Applicant's proposed titration scheme as well as titration schemes where the upper or lower titration thresholds were altered (b) (4) Concordance assessments are shown for each time point with a concentration sample available.

The patients were divided into three groups based on changes to dosing at the Week 3 visit: i) down-titrated due to high $C_{max0-24h}$ (b) (4) ii) no-change in dose as $C_{avg0-24h}$ was within the normal range with no C_{max} outliers (b) (4) and iii) up-titrated in dose as $C_{avg0-24h}$ 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 have $C_{max0-24h}$ higher than 1500 ng/dL at the Week 3 visit, so the dose was reduced to 150 ng/dL. Also, 105 patients had $C_{avg0-24h}$ 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 $C_{avg0-24h}$ lower than normal range, so the dose was up-titrated to 300 mg BID.

The reviewer compared the percentage of the patients that would be down-titrated, have no change in dose, or be up-titrated (b) (4) between (b) (4) h after morning administration for all the patients within each group for titration thresholds in Phase 3 study (b) (4) (b) (4) The percentage of the patients who would have same dose adjustment based on both $C_{avg0-24h}/C_{max0-24h}$ and C_{3-6h} are highlighted. More detailed information are provided in Table 2-4 for the proposed titration thresholds (Table 2) and other titration threshold investigated by the review as a sensitivity analysis (Table 3-4).

Table 1: Concordance by dosing subgroup between full profile ($C_{avg0\text{-}24h}$ and $C_{max0\text{-}24h}$) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of 300 and 1140 ng/dL (bounds in Phase 3) and (b) (4) and (b) (4) ng/dL (b) (4)

C_{avg}/C_{max} over 24h Titration Results from Phase 3 at week 3	$C_{3\text{-}6h}$ Titration	Titration threshold of 300 and 1140 ng/dL	Titration threshold of (b) (4) and (b) (4) ng/dL (b) (4)
Down Titration (n=61*)	Down Titration	43%	
	No Change	44%	
	Up Titration	13%	
No Change (n=105)	Down Titration	7%	
	No Change	65%	
	Up Titration	28%	
Up Titration (n=25)	Down Titration	0%	
	No Change	47%	
	Up Titration	53%	

* N=191, two patients do not have dose adjustment due to inadequate PK samplings.

Source: Reviewer's analysis

Table 2: Concordance comparison between full profile ($C_{avg0\text{-}24h}$ and $C_{max0\text{-}24h}$) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of (b) (4) and (b) (4) ng/dL

(b) (4)

Source: Reviewer's analysis

Table 3: Concordance comparison between full profile ($C_{avg0\text{-}24h}$ and $C_{max0\text{-}24h}$) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of (b) (4) and 1140 ng/dL

(b) (4)

* N=191, two patients do not have dose adjustment due to inadequate PK samplings.
Source: Reviewer's analysis

Table 4: Concordance comparison between full profile (C_{avg}) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of 300 and 1140 ng/dL

(b) (4)

Source: Reviewer's analysis

The results in Tables 2 and 3 show that a higher upper bound would not alter the titration decision for a majority of the patients. A few more patients in the down-titration group would be titrated as occurred in the Phase 3 trial based on a single T concentration compared to those based on $C_{avg0\text{-}24h}$ and $C_{max0\text{-}24h}$ with upper bound of 1140 ng/dL. Subsequently, a few more patients in the no-change group would be down-titrated with an upper bound of 1140 ng/dL. The total numbers of patients titrated similarly with a single T sample were 124 for both upper titration bounds.

In contrast, when the lower bound was increased from (b) (4) ng/dL to (b) (4) ng/dL, the number of patients who would be titrated in the same manner was dramatically reduced as shown in Tables 3 and 4. Only 108 patients would receive the same dose adjustment with a lower bound of 300 ng/dL and upper bound of 1140 ng/dL. Due to the change of lower bound, the percentage of patients with the same dose adjustment in the no-change group would decrease from more than 90% to less than 70%. Although there was increase in up-titration group from 10% to more than 50%, the majority of the patients in the no-change group would result in an overall reduction in the percentage of patients titrated similar to the Phase 3.

The reviewer also evaluated other lower bound including 150 ng/dL, 200 ng/dL and 250 ng/dL, as shown in Tables 5-7. As expected, a higher lower bound results in a greater percentage of patients with the same dose adjustment in up-titration group but less percentage of patients with the same dose adjustment in no-change group. Overall 124, 119, and 112patients would be titrated similarly to what occurred in Phase 3 with a lower bound of 150 ng/dL, 200 ng/dL and 250 ng/dL, respectively. There is a trend of greater concordance as the lower threshold bound is decreased from 300 ng/dL to (b) (4) ng/dL. Although a lower bound of (b) (4) ng/dL and 150 ng/dL would result in a similar number of patients having concordant dose adjustments with that in Phase 3, the percentage of patients who would be up titrated in down-titration group is lower with lower bound of (b) (4) ng/dL.

Table 5: Concordance comparison between full profile (C_{avg}) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of 150 and (b) (4) ng/dL

(b) (4)

Source: Reviewer's analysis

Table 6: Concordance comparison between full profile (C_{avg}) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of 200 and (b) (4) ng/dL

(b) (4)

Source: Reviewer's analysis

Table 7: Concordance comparison between full profile (C_{avg}) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of 250 and (b) (4) ng/dL

(b) (4)

Source: Reviewer's analysis

The percentage of patients in the down-titration group with the same dose adjustment as that in Phase 3 remained constant regardless of the evaluated titration thresholds. To further explore what was happening for these patients, the Reviewer plotted the distribution of T_{max} for the patients in the down-titration group (n=61) and all the other patients (n=130) in the dataset (Figure 2). The results show that $C_{max0-24h}$ was observed with relatively similar frequency following the morning and evening doses. The PK profile over 24 hours for all the patients in Figure 3 also illustrates that the $C_{max0-24h}$ values after morning dose and evening dose were comparable. In other words, it is possible that some patients that would be down-titrated based on $C_{avg0-24}$ and $C_{max0-24h}$ may not be down-titrated based on a single T concentration 3 to 6 hours after morning dose.

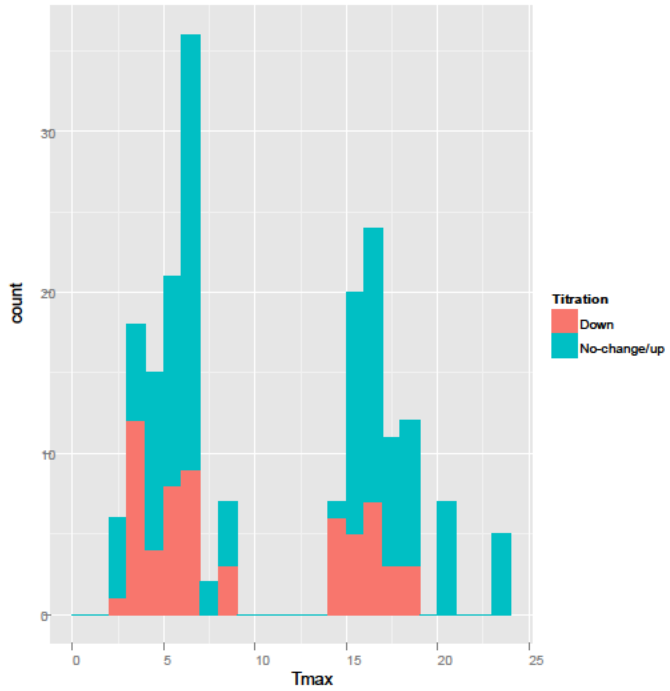


Figure 2: T_{max} distribution for patients in down-titration group (n=61) and no-change/up-titration patients (n=130)

Source: Reviewer's analysis

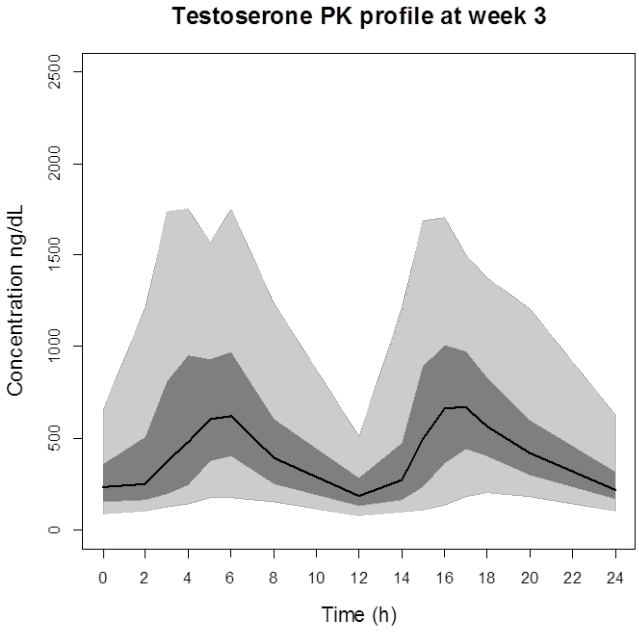


Figure 3: PK profile for all the patients in week 3 (n=193)

Source: Reviewer's analysis

To determine if the low concordance in down titration group is only due to $C_{max0-24}$ outliers after evening dose, the Reviewer compared the titration decision based on C_{avg}/C_{max} over 12 h to that based on a single T sample opened 3 to 6 hours after the morning dose (Table 8). The concordance in down titration group only marginally improves to 50% when the first 12 hours of the PK profile if evaluated. The total numbers of patients titrated similarly with a single T sample were 120 for both titration thresholds which is comparable to what was calculated based on C_{avg} and C_{max} over 24 h with lower bound of (b) (4) ng/dL (n=124), suggesting that the concordance calculation does not improve if only the morning dose is considered. The individual plots for each titration decisions based on single T concentration (4 h was used here as an example) with threshold of (b) (4) and (b) (4) ng/dL separated by $C_{avg0-12h}$ and $C_{max0-12h}$ titration results are shown in Figure 4. The plots clearly show that a single T concentration at one time point is unable to capture the C_{max} outliers after morning dosing.

Table 8: Concordance by dosing subgroup between morning PK profile ($C_{avg0\text{-}12h}$ and $C_{max0\text{-}12h}$) and single time point ($C_{3\text{-}6h}$) titrations using a titration threshold of 300 and 1140 ng/dL (bounds in Phase 3) and [redacted] and [redacted] ng/dL [redacted]

C_{avg}/C_{max} over 12 h Titration Results from Phase 3 at week 3	$C_{3\text{-}6h}$ Titration	Titration threshold of 300 and 1140 ng/dL	Titration threshold of [redacted] and [redacted] ng/dL
Down Titration (n=46)	Down Titration	50%	[redacted]
	No Change	42%	
	Up Titration	7%	
No Change (n=108)	Down Titration	10%	
	No Change	68%	
	Up Titration	22%	
Up Titration (n=38)	Down Titration	0%	
	No Change	37%	
	Up Titration	63%	

* N=192, one patient do not have dose adjustment due to inadequate PK samplings after morning dose.

Source: Reviewer's analysis

[redacted]

down-titrated based on the $C_{avg0\text{-}12h}$ and $C_{max0\text{-}12h}$ titration algorithm but who would have no change in dosing based on the single T sample titration algorithm.

Source: Reviewer's analysis

The results verified the sponsor's concordance analysis that the thresholds of (b) (4) to (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. At least a 35% discordance was identified between two titration schemes, and the percentage cannot be improved upon for some groups (e.g. down titration group).

In order to determine if concordance could be improved, the review team sent the Applicant two information requests on 5/18/2016 and 5/26/2016. Responses to these two information requests were received on 5/26/2016 and 6/1/206, respectively. As part of these responses, the Applicant proposed a new titration scheme (sampling between 4 to 6 h after the morning dose with titration thresholds of (b) (4) to (b) (4) ng/dL). Due to the close proximity of these responses to the end of the review cycle, the submitted analyses were not reviewed. However, top line assessment of the provided responses did not indicate that alterations to the proposed titration scheme would improve concordance with titration decisions from the Phase 3 trial. As the current decision is to issue a complete response for this submission, items included as part of these information requests will be evaluated in a subsequent review cycle, if applicable.

2. Single Serum Sampling Time

The sampling time for a single T concentration was chosen by Applicant according to a correlation analysis based on a Phase 2 study (M12-778). The relationship between serum testosterone concentration (C_t) at 2, 4, 6, 8, and 12 hours post dose (30 min after standard dinner) (i.e., C_{2h}, C_{4h}, C_{6h}, C_{8h} and C_{12h}) and $C_{avg0\text{-}24h}$ and 24 hour C_{max} was evaluated for Days 8, 15, and 29. The observed correlation coefficient values between C_t and C_{max} and between C_t and $C_{avg0\text{-}24h}$ are plotted in Figure 5. The correlation coefficient was highest after 2 hours and declined rapidly after 6 hours following the morning dose. This analysis suggests that the testosterone concentration observed between 3 and 6 hours after morning dosing have the highest correlation with C_{max} and $C_{avg0\text{-}24h}$. Based on these results, a range of 3 to 6 hours post morning dose was selected for single blood sampling at Weeks 26, 39, and 52 in the Phase 3 study.

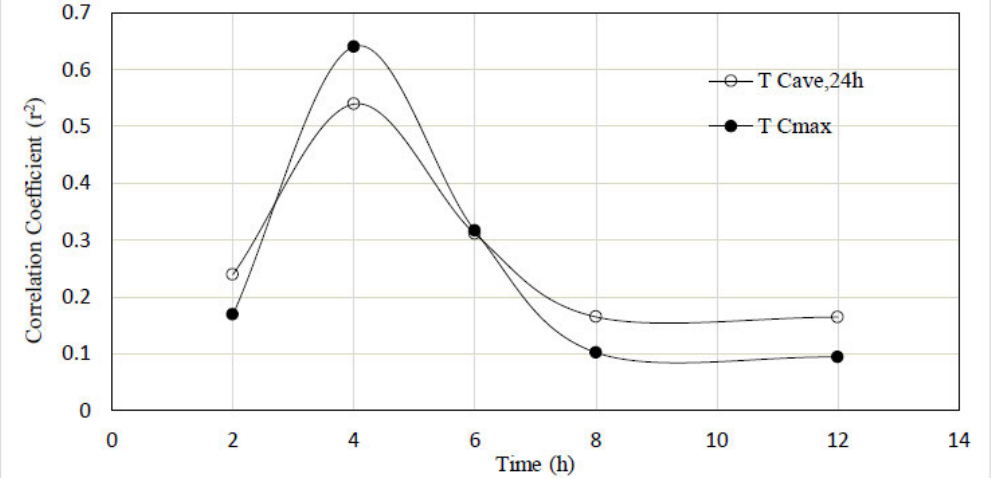


Figure 5: Correlation between Serum Testosterone Concentration at Single Time Points and C_{avg} (ng/dL) and C_{max} (ng/dL) at Day 8, 15, and 29 (N = 48)

Source: Applicant's Summary of Clinical Pharmacology, Page 19, Figure 3.

The Reviewer conducted a similar analysis based on the Week 3 PK data from the Phase 3 study as shown in Table 9. The results show the $C_{5\text{-}8h}$ has the highest correlation with C_{avg} and $C_{4\text{-}6h}$ has the highest correlation with C_{max}. The C_{max} result is consistent with Applicant's conclusion.

Table 9: Correction between C2-12h after morning dose and C_{avg} and C_{max} on Week 3

	C_{2h}	C_{3h}	C_{4h}	C_{5h}	C_{6h}	C_{8h}	C_{12h}
C_{avg}	0.41	0.48	0.60	0.68	0.63	0.65	0.59
C_{max}	0.42	0.51	0.61	0.74	0.67	0.50	0.38

Source: Reviewer's analysis

To assess the impact of the Applicant's proposed sampling window (3 to 6 h) compared to the identified window 5 to 8 h), the Reviewer summarized the percentage of patients with the same dose adjustment with sampling time within 5 to 8 hours in Table 10 and compared it to the Table 2.

Table 10: Concordance comparison between full profile (C_{avg}) and single time point ($C_{3\text{-}6h}$) titrations using a threshold of (b) (4) and (b) (4) ng/dL

(b) (4)

The total number of patients with concordant dose adjustments with Phase 3 decisions for the new sampling time will be 121, which is comparable to the number concordant patients for a sampling time between 3 to 6 h. The result demonstrated that the sampling time chosen by the Applicant is acceptable and unlikely to be improved upon by selected a different time window.

1.1.2 How often should patients have serum testosterone concentrations assessed after initiation of therapy?

The Applicant proposes an initial serum testosterone assessment at least 14 days after initiation of therapy with periodic assessments thereafter. An initial assessment after 14 days is appropriate as steady state testosterone levels from the regimen will have been achieved and the results from the Phase 3 trial suggest that about half of patients need at least one titration to satisfy the $C_{max0\text{-}24h}$ and $C_{avg0\text{-}24h}$ titration constraints. However, it was observed that patients may have required multiple titrations or patients continued to be titrated up to the last visit. As such, periodic assessments would be needed to maintain patients within the normal range. The reviewer proposed assessments every 3 to 6 months.

Based on observations from Phase 3 study, some patients continue to require dose adjustments at each subsequent visit. Shown below are the concordance tables between the dose a patient was on at the: i) Week 3 and Week 7 visit (Table 11); Week 7 and Week 13 visit (Table 12); and iii) Week 13 and a theoretical future visit based on how the patient would be titrated at Week 13 (Table 13). All patients started on 225 mg BID and remained on this dose through the Week 3 visit. At Week 7, only 105 patients would remain on 225 mg BID (no change in dosing, highlighted), 51 patients were down-titrated, 26 patients were up-titrated, and 11 patients had discontinued. Six weeks later, a total of 106 patients would remain on the same dose as their Week 7 (highlighted) with an additional 26 patients having dropped out of the study. There are 28 patients down-titrated and 22 patients up-titrated. Based on $C_{avg0\text{-}24h}$ and $C_{max0\text{-}24h}$ at week 13, 97 patients would remain on the same dose going forward from week 13 (highlighted) and 10 more patients discontinued from the study. There were still 33 patients down-titrated and only 16 patients up-titrated. The majority of these dosing alterations (down titrations) were due to high $C_{max0\text{-}24h}$ observed in the study.

Table 11 Number of patients at each dose level for Week 3 and Week 7

		Week 7 dose			
		Discontinued	150 mg	225 mg	300 mg
Week 3 dose	Discontinued				
	150 mg				
	225 mg	11	51	105	26
	300 mg				

Source: Reviewer's analysis

Table 12 Number of patients at each dose level for Week 7 and Week 13

		Week 13 dose			
		Discontinued	150 mg	225 mg	300 mg
Week 7 dose	Discontinued	11	0	0	0
	150 mg	12	28	11	0
	225 mg	8	22	64	11
	300 mg	6	0	6	14

Source: Reviewer's analysis

Table 13 Number of patients at each dose level for Week 13 and a theoretical next visit (titration based on Week 13 data)

		Dose moving forward if titration occurred at Week 13			
		Discontinued	150 mg	225 mg	300 mg
Week 13 dose	Discontinued	37	0	0	0
	150 mg	6	34	10	0
	225 mg	0	24	51	6
	300 mg	4	0	9	12

Source: Reviewer's analysis

These results indicate that the serum testosterone concentrations should be assessed periodically after initiation of the therapy to ensure adequate titration of dosing. When switching to single T concentration for titration, the measurement of T concentration in the patients periodically becomes even more important to reduce the possibility of overdosing or underdosing due to high intra-subject variability. The reviewer recommends assessments every 3 to 6 months for patients. This is longer than the interval between visits in the Phase 3 trial and exceeds the time to achieve steady state following a dosing change.

1.2 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application and concludes that the Phase 3 trial, as conducted, supports the efficacy and safety of testosterone undecanoate (112.5 mg, [redacted] (b) (4)) administered as two tablets twice daily with titration based on $C_{avg0\text{-}24h}$ and $C_{max0\text{-}24h}$. The reviewer agrees that titration thresholds of (b) (4) ng/mL for up-titration and (b) (4) ng/mL for down-titration in a window of 3 to 6 hours following the morning dose maximizes the percentage of patients with a similar dose adjustment as occurred in the Phase 3 trial. However, at least 35% discordance was identified between these two titration schemes, which cannot be further improved based on selection of a different sampling time interval or titration thresholds. This discordance hinders the ability to translate the Phase 3 results into labeling. The reviewer agrees that testosterone concentrations should continue to be assessed periodically after

initiation of therapy and proposes assessments every 3 to 6 months given that patients continued to require titration at each on-treatment assessment.

15 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

LAI M LEE
11/03/2015

MYONG JIN KIM
11/03/2015

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

/s/

LAI M LEE
06/14/2016

LUNING ZHUANG
06/14/2016

JEFFRY FLORIAN
06/14/2016

MYONG JIN KIM
06/14/2016

EDWARD D BASHAW
06/14/2016
Concur with C/R based on lack of appropriate titration scheme.

Memorandum

PHARMACOLOGY/TOXICOLOGY SUPERVISOR MEMO

Date:	5th June 2016
NDA #	208088
Sponsor:	Lipocine Inc.
Drug/Indication:	Testosterone Undecanoate/ Hypogonadism
Reviewer:	Mukesh Summan, PhD, DABT

Background: The Sponsor is seeking marketing approval for the use testosterone undecanoate (TU) capsules (BID) as a pro-drug for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

NDA 208088 was submitted as a 505(b)2 NDA on August 28th 2015 and relies on the FDA's previous findings of safety and efficacy of approved testosterone products. Testosterone is currently marketed as topical, buccal, intranasal, intramuscular and subcutaneously implanted pellets. Another TU product (AVEED™) given via the intramuscular route, was recently approved under NDA 22219 and provides evidence of use of TU in hypogonadal men. In addition, oral TU products (Andriol®/ Andriol® Testocaps) have been marketed outside of the USA for decades. Thus, if approved, Lipocine Inc.'s capsule product will be the first oral product on the market in the USA.

Summary of nonclinical data:

Androgenic effects on male reproductive tissues were observed in the chronic (26-week) rat study at all exposures, including the low dose which is equivalent to the blood levels of the maximum recommended clinical exposure to testosterone, and are considered expected effects of exogenous testosterone exposure to eugonal male rats. In non-reproductive tissues, ductular dilation of the mammary gland (minimal to slight) was observed at 2- and 6-fold the maximum recommended clinical exposure to testosterone. In addition, diffuse adrenal cortical vacuolation, thymic atrophy and lacrimal gland acinar cell hypertrophy/hyperplasia was present in the treated rats at 0.6- to 6-fold, the maximum recommended clinical exposure to testosterone. The significance of these observations is unknown and is likely related exaggerated pharmacology of testosterone.

Androgenic effects on male reproductive tissues were also observed in the chronic (90-day) dog study at all exposures, including the low dose which is equivalent to 5-fold the maximum recommended clinical exposure to testosterone, and are considered expected effect of exogenous testosterone exposure. In non-reproductive tissues, cortical atrophy (slight to moderate), dose-dependent lymphoid depletion and dose-dependent increased absolute and relative kidney weights was noted in all treated

males. Exposure to TU at 29-fold the maximum human testosterone exposure resulted in increased parathyroid/thyroid absolute and relative weights (all males) and hepatocellular (minimal focal) degeneration/necrosis in a small subset of animals. The significance of these observations is unknown and is likely related exaggerated pharmacology of testosterone.

TU was negative in a standard battery of genotoxicity assays.

Label: Reliance on the nonclinical sections of the approved testosterone products (class labeling) are appropriate. No significant nonclinical labeling issues were identified and significant changes to the label are not required.

Outstanding Nonclinical Issue: None.

Conclusion(s): Dr. Laurie McLeod-Flynn, the primary nonclinical reviewer, concludes that the pharmacology and toxicology data support approval of testosterone undecanoate (TU). I concur with Dr. McLeod-Flynn's assessment.

Based on the extensive clinical experience with testosterone, the nonclinical studies conducted by the sponsor, and the findings of safety and efficacy of approved testosterone products Pharmacology and Toxicology recommends approval of Lipocine Inc.'s testosterone undecanoate (TU) capsules.

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

/s/

MUKESH SUMMAN
06/06/2016
Nonclinical Supports AP

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	208088
Supporting document/s:	0000
Applicant's letter date:	28 August 2015
CDER stamp date:	28 August 2015
Product:	Testosterone undecanoate
Indication:	Testosterone replacement in hypogonadal men
Applicant:	Lipocine, Inc.
Review Division:	DBRUP
Reviewer:	Laurie McLeod-Flynn
Supervisor/Team Leader:	Lynnda Reid, PhD
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Jeannie Roule

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208088 are owned by Lipocine, Inc. or are data for which Lipocine, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 208088 that Lipocine, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208088.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

Testosterone is currently marketed as topical, buccal, intranasal, intramuscular, and subcutaneously implanted pellet formulations. However, orally administered testosterone, such as methyltestosterone, has been difficult to develop due to concerns for hepatotoxicity due to first pass metabolism of testosterone.

Testosterone undecanoate (TU), is a prodrug being developed for testosterone replacement therapy in hypogonadal men. As an ester of testosterone to undecanoic acid at the C17β-hydroxyl position, it is subject to intestinal lymphatic absorption. It is deesterified to yield systemic levels of testosterone and an endogenous compound, undecanoic acid. Although an oral TU formulation is not available in the USA, oral TU products have been marketed outside of the USA for decades and an intramuscular TU product, AVEED™, is approved in the United States to treat male hypogonadism. Undecanoic acid is an approved food additive in the United States.

1.2 Brief Discussion of Nonclinical Findings

TU has a relatively high binding constant for the androgen receptor, compared to that of testosterone and has little potential for androgenic activity.

Testosterone and TU have low potentials for acute toxicity. Undecanoic acid is a naturally occurring 11-carbon fatty acid, metabolized by beta-oxidation and the tricarboxylic acid pathways.

TU is very poorly absorbed; administration of TU with food was shown to increase oral absorption into the intestinal lymphatics in rats and dogs. After absorption, a fraction of TU is metabolized in the intestinal wall to DHTU. TU and DHTU are distributed systemically and are metabolized to undecanoic acid, T, DHT, estradiol (E2), as well as to other steroid metabolites and glucuronide and sulfate conjugates. TU and DHTU are the major blood components, with testosterone, the active androgen, accounting for only about 1 and 3.7% of circulating drug in rats and dogs, respectively.

<u>26-Week rat toxicology study</u>
A no observed adverse effect level (NOAEL) for androgenic effects was not observed in rats, even at the low dose, which was approximately equivalent in blood levels to the maximum recommended clinical dose exposure to testosterone. Findings were observed in the testis, epididymis, prostate, seminal vesicle, mammary gland, thyroid gland, adrenal gland, thymus, lacrimal gland, and parotid gland. The changes in male reproductive organs (interstitial cell atrophy in the testes, distension of the seminal vesicles and prostate), along with increased reproductive organ weights, are considered to be expected effects of exogenous testosterone. Levels of active testosterone will be monitored and adjusted to specified physiological levels during clinical use.

In the mammary gland, minimal to slight ductular dilation was observed at about 2-fold the maximum clinical levels of testosterone and above, characterized by an increase in the number of distended ducts lined by cuboidal to columnar epithelium, with or without secretion. A minimal increase in follicular cell hypertrophy was observed in the thyroid gland at about 6-fold. In the adrenal gland, at all dose levels, 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. Thymic atrophy and lacrimal gland acinar hypertrophy/hyperplasia , and an increase in fat infiltration of the parotid gland were also observed. The relevance of these effects at clinical dose levels and exposures are not known. However, no similar effects were observed in clinical studies.

90-Day dog toxicology study

A no observed adverse effect level (NOAEL) for androgenic effects was not observed even at the low dose, which was approximately equivalent in blood levels to 5-fold the maximum recommended clinical dose exposure to testosterone. Androgenic effects on male reproductive tissues observed in all treated groups included Leydig cell atrophy, decreased spermatogenesis, and prostate hypertrophy. The changes in male reproductive organs (interstitial cell atrophy in the testes, distension of the seminal vesicles and prostate), along with increased reproductive organ weights, are considered to be expected effects of exogenous testosterone.

Absolute and relative kidney weights were increased at all doses and slight increases in the absolute and relative weights of thyroid/parathyroid glands were observed at approximately 29-fold the maximum recommended clinical exposure. In the adrenal, slight to moderate cortical atrophy was observed in all treated animals, and in the thymus, a dose dependent increase from slight to severe lymphoid depletion was observed in all treated animals. Minimal focal hepatocellular degeneration / necrosis with hemorrhage, inflammation and periportal acute/subacute inflammatory cell infiltrate were observed in two animals at 29-fold, and one of these males also had minimal periportal acute/subacute inflammation and minimal bile duct hyperplasia. The relevance of these effects at clinical dose levels and exposures are not known. However, no similar effects were observed in clinical studies.

Reproductive effects

The risk for reproductive toxicity is considered to be similar to those for other approved testosterone products.

Mutagenesis/ Carcinogenicity

The risk for carcinogenicity is considered to be similar to those for other approved testosterone products. TU was negative in a reverse mutation assay in bacteria, a chromosome aberration assay in cultured human peripheral blood lymphocytes, and a micronucleus assay in rats.

TU metabolism/elimination

TU related radioactivity was widely distributed among tissues in a rat study. No accumulation or retention was of note in adrenal or other glandular tissue or in any reproductive tissue. TU was among the least polar entities, (with a few less polar unidentified metabolites), and it is reasonable to assume that TU accounted for a large proportion of the observed distribution. By seven days post dose, radioactivity was cleared from most rat tissues. No determination of the subcellular distribution of TU was made, and it 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. Clinically, no adverse effects on the adrenals or other glandular tissue or on reproductive tissues at physiological blood levels have been identified.

1.3 Recommendations

1.3.1 Approvability

There is no impediment to approval from a Pharmacology/Toxicology perspective. It is appropriate that class labeling used for other testosterone replacement products also be used for this product.

1.3.3 Labeling

Proposed Carcinogenesis, Mutagenesis, Impairment of Fertility Labeling:

(class labeling)

Subheadings, in red, were added.

(b) (4)

2.3 Drug Formulation

Composition of Testosterone Undecanoate Capsules ([b) (4)] 112.5 mg)

Component	Quality Standard	Function	% in Fill	[b) (4)]	112.5 mg dose strength
Capsule Fill				**Amount (mg) per capsule**	
Testosterone Undecanoate	In-house	Drug substance	[b) (4)]	[b) (4)]	112.5
[b) (4)] (Glyceryl Monolinoleate)	NF	[b) (4)]			[b) (4)]
Polyoxyl 40 Hydrogenated Castor Oil	NF				
Ascorbyl Palmitate	NF				
Polyethylene Glycol, 8000	NF				
Total					
[b) (4)]	In-house				-
Capsule, gelatin, [b) (4)] [b) (4)]	In-house	Capsule shell			1 capsule
Gelatin Banding [b) (4)]					
Gelatin [b) (4)] Pharmaceutical Grade	NF	Capsule Banding			*
					[b) (4)]

2.4 Comments on Novel Excipients

There are no novel excipients included in the manufacture of testosterone undecanoate capsules.

2.5 Comments on Impurities/Degradants of Concern

No assessment was possible from a QSAR evaluation of the mutagenicity and rodent carcinogenicity of the [b) (4)] impurity, due to poor coverage of the model. QSAR evaluation of the [b) (4)] impurities, which are the basis of formation of the [b) (4)] were negative, however. [b) (4)] are common degradants for which many biological protective systems have developed. Although high concentrations of [b) (4)] have been shown to be promoters of carcinogenesis under some conditions, a permissible daily exposure of [b) (4)] [b) (4)] has been set at [b) (4)] µg/day (based on threshold [b) (4)] where [b) (4)] mechanisms are overwhelmed; M7(R1) Addendum to ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk - Application of the Principles of the ICH M7 Guidance to Calculation of Compound-Specific Acceptable Intakes (ICH-M7(R1); Step 2; June

2015.) Therefore, the levels of (b) (4) degradants of testosterone, previously approved by the Division, are acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

Twice per day, at doses up to (b) (4) mg/kg/day, in hypogonadal men, with monitoring of blood levels of T.

2.7 Regulatory Background

A pre-IND meeting was held on January 11, 2010, at which a battery of nonclinical pharmacology and toxicology studies and supporting literature references were recommended by DBRUP. The IND was submitted on April 2, 2010. On May 9, 2011, the division concurred that a 9- month dog study was not necessary to support the safety of an oral TU. The rights to SLV361 were transferred from Abbott Laboratories to Lipocine, Inc., on May 14, 2012.

3 Studies Submitted

3.1 Studies Reviewed

Toxicology
SLV361: 26 Week Oral (Gavage)14 Day Oral (Gavage) Administration Toxicity Study in the Male Rat (S361.7.013)

SLV361: 28 Day Oral (Gavage) Administration Toxicity Study in the Male Rat (S361.7.008)

A 90 Day Oral (Gavage) Toxicity and Toxicokinetic Study in Dogs (S361.7.014)

A 28 Day Oral (Gavage) Toxicity and Toxicokinetic Study in Dogs (S361.7.012)

Reverse Mutation in Five Histidine Requiring Strains of Salmonella typhimurium (S361.7.005)

Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes (S361.7.006)

Induction of Micronuclei in the Bone Marrow of Treated Rats (S361.7.007)

Pharmacology
In Vitro Pharmacology: The Effects of 3 Compounds in the Human AR Binding Assay (S361.5.003)

PK/ADME

[^{14}C]-SLV361: A Study of Distribution in the Rat by Quantitative Whole-Body Autoradiography (S361.6.0100)

[14C]-SLV361 - A study of absorption, metabolism and excretion following oral and intravenous administration to the male dog (S361.6.005)

[14C]-SLV361 - A study of absorption, metabolism and excretion following oral and intravenous administration to the male rat (S361.6.006)

The Validation of the Determination of Testosterone, Dihydrotestosterone, Testosterone Undecanoate and Dihydrotestosterone Undecanoate in Rat Heparin Plasma Using LC-MS/MS (S361.6.001)

The Validation of the Determination of Testosterone, Dihydrotestosterone, Testosterone Undecanoate and Dihydrotestosterone Undecanoate in Dog Heparin Plasma Using LC-MS/MS (S361.6.002)

The Validation of the Determination of 17β-Estradiol in Rat Heparin Plasma, Using LC-MS/MS (S361.6.003)

The Validation of the Determination of 17β-Estradiol in Dog Heparin Plasma, Using LC-MS/MS (S361.6.004)

3.2 Studies Not Reviewed

Testosterone Undecanoate: An Oral (Gavage) Pharmacokinetic Study in Rats (non-GLP) 09-2169

Testosterone Undecanoate: An Oral (Gavage) Pharmacokinetic Study in Rats (non-GLP) 09-2179

Testosterone Undecanoate: An Oral (Gavage) Pharmacokinetic Study in Dogs (non-GLP) 09-3438

3.3 Previous Reviews Referenced

30 April 2013 Review by Jeffrey Bray, Ph.D.

4 Pharmacology

Testosterone undecanoate (TU), is a prodrug ester of testosterone bound to undecanoic acid at the C17β-hydroxyl position. It is hydrolyzed to yield systemic levels of testosterone (T) and an endogenous fatty acid, undecanoic acid.

Pharmacology information is based on a binding study of TU in a human androgen receptor (AR) binding assay and on literature references of testosterone products.

TU is converted to testosterone by circulating esterases in the blood. It is believed that TU should be relatively inactive because the large undecanoate group may interfere with binding to the androgen receptor, and this is supported by early bioassay studies of various C17-testosterone esters[1,2]. Although dihydrotestosterone undecanoate (DHTU) is also present in plasma, and its biological activity is not known, it also is likely to be relatively inactive because of the large undecanoate group. Whether DHTU can be de-esterified to dihydrotestosterone (DHT) is also not known. It is thought that T and DHT are the primary active hormones derived from orally-administered TU.

Testosterone's activity derives primarily from the actions of T combined with the activity of its primary active metabolite, DHT. In most tissues (including muscle, testis and liver), T is the principle androgen. However, DHT has predominant activity in prostate, seminal vesicle, and skin due to its local formation there via conversion from T by 5α-reductase. In addition, T may cause estrogenic action in some tissues such as adipose tissue, bone, breast and specific regions of the brain after its conversion to estradiol by aromatase in those tissues.

A predominant effect of endogenous T at normal-range blood concentrations is to promote the development and maintenance of male reproductive anatomy and physiology (e.g., spermatogenesis; maturation and maintenance of the prostate, seminal vesicles, penis and vas deferens). Additionally, T can cause a wide range of beneficial effects in males and females on bone, muscle mass, hematopoiesis, skin, lacrimal glands, the cardiovascular system, and nervous system.

1 Miescher, K., Wettstein, A., and Tschopp, E. CCLXXCII. The activation of the male sex hormones. II. Biochemical Journal. 1936; 30: 1977-1990.
2 Ott, A.C., Kuizenga, M.H., Lyster, S.C., and Johnson, B.A. Testosterone β-cyclopentylpropionate: a new long-acting androgen. J Clinical Endocrinol Metabolism. 1952; 12: 15-27.

4.1 Primary Pharmacology

In Vitro Pharmacology: The Effects of 3 Compounds in the Human AR Binding Assay (Non-GLP Study No. S361.5.003, CEREP Celle l'Evescault, France, 14 June 2010)

The binding of SLV361 (lot # ST-090803, 98.20% pure,) dihydrotestosterone undecanoate (DHTU), and testosterone to the human androgen receptor (AR) was evaluated using a competition binding assay against 1 nM [^{3}H] methyltrienolone for 24 h at 4°C. SLV361 and DHTU did not effectively bind to the AR under the conditions of the assay with IC_{50} values >10 mM and no measurable inhibition constant (K_i).

Table 1 Androgen Receptor Binding Characteristics of SLV361

Compound	IC50 (nM)	Ki (nM)
Testosterone	**6.1**	**2.7**
Dihydrotestosterone undecanoate	**>10,000**	**ND**
SLV361 (testosterone undecanoate)	**>10,000**	**ND**

4.3 Safety Pharmacology

No safety pharmacology studies were submitted or conducted by the sponsor. It is well known clinically that testosterone may cause a wide range of side effects, including hematopoiesis, enlarged kidneys, cardiovascular effects (including myocardial infarction) and nervous system effects (including nervousness, irritability, aggression and mood changes.)

5 Pharmacokinetics/ADME/Toxicokinetics

Testosterone undecanoate (TU) is one of a several 17β-esterified androgens that have been studied for clinical use (others include testosterone enanthate and testosterone propionate), which are typically administered intramuscularly. TU is converted to testosterone by circulating esterases in the blood. Rat and dog studies demonstrate systemic levels of testosterone undecanoate (TU), testosterone (T), dihydrotestosterone undecanoate (DHTU), and dihydrotestosterone (DHT) following oral TU administration.

5.1 PK/ADME

[^{14}C]-SLV361: A Study of Distribution in the Rat by Quantitative Whole-Body Autoradiography (GLP/QA Study No. S361.6.010, (b) (4) (b) (4) 4 October 2010). As reviewed by Dr. Bray and summarized here (DARRTS 30 April 2013).

Methods:
Male albino (Han Wistar) or pigmented (Lister-Hooded) rats were administered a single oral dose of ~5 MBq/kg of [^{14}C]-SLV361 mixed with unlabeled SLV361 for a nominal dose of 120 mg/kg (actual: 115 -130 mg/kg) in oleic acid in a volume of 5 mL/kg. Animals were given 5 mL/kg corn oil/olive oil (50:50, v/v) approximately 0.5 to 1 hour before drug to aid in absorption. Albino rats (1/timepoint) were sacrificed at 2 and 6 hours, and 1, 3, and 7 days post-dose with blood collected and stored. Pigmented rats were sacrificed at 6 hours, and 1, 3, 7, 21, and 35 days post-dose.

Results: At 2 hours, quantifiable label was detected only in the GI tract and excretory system of albino rats, as well as in plasma. By 6 hours, most tissues had quantifiable levels of radioactivity in both albino and pigmented male rats. A comparison of peak levels at 6 hours showed that albino rats had higher levels of radioactivity in most

tissues than did pigmented rats. At 24 hours, bile duct, intestines, rectum, kidney, liver, skin, stomach, urinary bladder contained the highest levels of label. After 3 days, the trachea, intestinal mucosa, kidney, urinary bladder, liver, bile duct, and skin in both types of rats, the aortic wall of albino rats, and the non-fundic stomach mucosa of pigmented rats still had significant quantified radioactivity, although higher in pigmented rats. These same tissues and the adrenals had tissue:plasma ratios of ≥2 at 6, 24, or 72 hours. No radioactivity was quantifiable by Day 7 in either strain of rat. The temporal pattern of labeling suggests transit through the GI tract and elimination via hepatic clearance with both fecal and urinary routes of excretion. There was no significant exposure or retention in male reproductive tissues (prostate, epididymis, seminal gland, preputial gland, testes).

Table 2 Concentrations of radioactivity in selected tissues at 6 hours following an oral dose of 120 mg/kg SLV361 to male albino and pigmented rats

Tissue	Albino Rats		Pigmented Rats	
	µg equiv./g of tissue	Tissue:plasma ratio	µg equiv./g of tissue	Tissue:plasma ratio
Plasma	4.81	--	2.48	--
Nasal mucosa	12.3	2.55	BLQ	NC
Trachea	1.07	0.22	BLQ	NC
Esophageal wall	2.91	0.6	0.84	0.34
Stom. muc.fundus	10.2	2.12	17.7	7.15
Stomach mucosa	40.7	8.44	10.6	4.29
Sm.intest.mucosa	60.7	13.3	64.7	26.1
Caecum mucosa	26.6	5.52	3.54	1.43
Lge.intest.mucosa	1.27	0.26	3.35	1.35
Rectum mucosa	0.89	0.19	BLQ	NC
Urinary blad. wall	90.8	18.9	3.84	1.55
Kidney cortex	6.05	1.26	2.65	1.07
Kidney medulla	13.3	2.75	5.96	2.41
Liver	23.1	4.80	12.9	5.21
Bile ducts	641	133	395	159
Aortic wall	7.07	1.47	2.22	0.90
Adrenal cortex	4.65	0.97	2.59	1.04
Adrenal medulla	5.23	1.09	2.35	0.95
Epididymis	1.35	0.28	BLQ	NC
Preputial gland	1.99	0.41	1.66	0.67
Prostate	0.84	0.17	0.91	0.37
Seminal vesicles	0.85	0.21	0.84	0.34
Testis	BLQ	NC	BLQ	NC
Skin, nonpigment.	27.8	0.36	BLQ	NC
Skin pigmented	n/a	--	BLQ	NC
Uveal tract/retina	0.90	0.19	1.22	0.49

BLQ, Below Limit of Quantification; NC, Not Calculable; n/a, Not Applicable

Table 3 Concentrations of radioactivity in selected tissues at 24 hours following an oral dose of 120 mg/kg SLV361 to male albino and pigmented rats

Tissue	Albino Rats		Pigmented Rats	
	µg equiv./g of tissue	Tissue:plasma ratio	µg equiv./g of tissue	Tissue:plasma ratio
Plasma	0.85	--	0.34	--
Nasal mucosa	BLQ	NC	BLQ	NC
Trachea	0.98	1.15	1.09	3.20
Esophageal wall	BLQ	NC	BLQ	NC
Stom. muc.fundus	2.0	2.37	BLQ	NC
Stomach mucosa	6.83	8.07	14.3	42.1
Sm.intest.mucosa	9.64	11.2	8.38	24.6
Caecum mucosa	11.6	13.8	14.5	42.5
Lge.intest.mucosa	28.5	33.7	18.3	53.8
Rectum mucosa	19.1	22.6	BLQ	NC
Urinary blad. wall	20.2	23.9	2.86	8.40
Kidney cortex	5.58	6.60	2.07	6.08
Kidney medulla	1.39	1.64	BLQ	NC
Liver	9.55	11.3	4.39	12.9
Bile ducts	73.7	87.1	92.2	271
Aortic wall	BLQ	NC	BLQ	NC
Adrenal cortex	1.66	1.96	BLQ	NC
Adrenal medulla	0.92	1.09	BLQ	NC
Epididymis	0.93	1.09	BLQ	NC
Preputial gland	1.02	1.21	1.74	5.12
Prostate	1.03	1.22	BLQ	NC
Seminal vesicles	0.85	1.01	BLQ	NC
Testis	BLQ	NC	BLQ	NC
Skin, nonpigment.	27.8	32.9	BLQ	NC
Skin pigmented	n/a	--	1.51	4.43
Uveal tract/retina	BLQ	NC	BLQ	NC

BLQ, Below Limit of Quantification; NC, Not Calculable; n/a, Not Applicable

[14C]-SLV361 - A study of absorption, metabolism and excretion following oral and intravenous administration to the male dog (Study no. S361.6.005, (b) (4) (b) (4) 13 August 2010)

Male Beagle dogs were administered a single intravenous dose (5 mg/kg in soybean oil:Intralipid 20 (1:9 w/w; intravenous),) or a single oral dose (120 mg/kg in oleic acid) of [^{14}C]-SLV361 in? . No overt toxicological signs were observed in any animal.

Following both intravenous and oral administrations of SLV361, the ratios of radioactivity in blood compared to plasma were fairly constant (typically 0.5 or 0.6), indicating there was little if any association of radioactive material with the cell phase of blood.

Following an intravenous dose of SLV361 (5 mg/kg, slow bolus injection), mean peak concentrations of radioactivity of 318 (blood) and 510 (plasma) ng equiv/g were observed at 5 minutes. Mean levels of radioactivity were about half at 2 hours and about 30% (blood) and 29% (plasma) at 48 hours. Due to the relatively high levels of

radioactivity at 48 hours, AUC extrapolations to infinity were 63% and 62%, for blood and plasma respectively. The approximate half life values for total radioactivity were 74 hours (blood) and 71 hours (plasma).

Following an oral dose of SLV361 (120 mg/kg, gavage), mean levels of radioactivity reached a maximum at 6 hours in blood (6140 ng equiv/g) and 7 hours in plasma (10900 ng equiv/g). Concentrations were about 10% by 24 hours and about 3% by 48 hours, in both blood and plasma. It was not possible to characterize a terminal phase due to a low number of sampling points. Based on AUC comparisons with the intravenous phase, an oral dose of SLV361 at 120 mg/kg was approximately 50% or 55% absorbed, in blood and plasma, respectively. These bioavailability values were based on total radioactivity and therefore are a measure of exposure to SLV361 and its circulating labeled metabolites combined.

Following both intravenous and oral administrations of SLV361, recoveries of radioactivity were 53% (intravenous) and 68% (oral) after 168 hours. Radioactivity was still detectable at the time of the last collection (144-168 hours) in all urine and feces samples. It is expected that additional radioactivity was associated with tissues and the residual carcass. Several metabolites more polar than TU were observed in feces.

Biliary excretion of SLV361 and metabolites is expected to be significant since about a quarter of the intravenous dose was recovered in feces. Unchanged SLV361 was nearly always the major component in plasma and feces, but was absent in urine samples. It was surmised that the dealkylation of SLV361 (to produce testosterone) occurred predominantly in the systemic circulation, prior to renal excretion.

The major routes of biotransformation for SLV361 were dealkylation (loss of undecanoyl moiety) to testosterone, with subsequent hydroxylations, reductions (loss of oxygen and/or addition of hydrogen) and glucuronidation. Testosterone and reduced testosterone were the predominant entities observed in urine. SLV361 (presumed unabsorbed) or dihydrotestosterone were the major entities in feces. In plasma, glucuronides of C3 or C16 of the testosterone tetracyclic nucleus were observed along with two reduced forms of testosterone (which were also observed in urine).

[14C]-SLV361 - A study of absorption, metabolism and excretion following oral and intravenous administration to the male rat (Study no. S361.6.006, (b) (4) (b) (4) 13 August 2010)

Male rats were administered a single intravenous (5 mg/kg in soybean oil:Intralipid 20 (1:9 w/w; intravenous) or a single oral (120 mg/kg in oleic acid) of [14C]-SLV361. No overt toxicological signs were observed in any animal

Following both intravenous and oral administrations of SLV361, the mean ratios of radioactivity in blood compared to plasma were about 0.6 to 1.1, indicating little or no association of radioactive material with the cell phase of blood.

Following an intravenous dose of SLV361 (5 mg/kg, slow bolus injection), mean peak concentrations of radioactivity of 847 (blood) and 1130 (plasma) ng equiv/g were observed at 5 minutes. Mean levels of radioactivity were about half of these peak concentrations by 0.25 hour (blood) and 0.5 hour (plasma) after dosing. Levels were about 2% (blood) and 3% (plasma) of the observed maxima at 48 hours. After 48 hours, radioactivity was not detectable in blood, but in plasma, intermittent low detectable levels were observed up to 168 hours. The approximate half life values for total radioactivity were 15 hours in blood and 29 hours in plasma.

Following an oral dose of SLV361 (120 mg/kg, gavage), mean levels of radioactivity reached a maximum at 4 hours in blood (3260 ng equiv/g) and 8 hours in plasma (3700 ng equiv/g). Concentrations were about half by 24 hours and about 11% by 48 hours, in both blood and plasma. The terminal phase half life in plasma was about 10 hours, and in blood, about 19 hours. However, in blood, there was a non-linear terminal phase between the maximum concentration (at 4 hours) and the end of the sampling phase (at 48 hours), with multiple maxima observed.

Based on AUC comparisons with the intravenous phase, an oral dose of SLV361 at 120 mg/kg was approximately 78% and 65% absorbed, in blood and plasma, respectively. These bioavailability values were based on total radioactivity and therefore are a measure of exposure to SLV361 and its circulating labeled metabolites combined.
.
About one third of administered radioactivity following an intravenous dose was recovered in the residual carcass at 168 h suggesting extensive tissue distribution and retention. Biliary excretion of radioactive material accounted for nearly half of the intravenous dose. SLV361 (TU) was present in nearly all plasma samples by both dose routes and in all feces samples by oral dose but was absent from all urine samples. At least one metabolite more polar than TU was observed in feces.

The major route of biotransformation for SLV361 was dealkylation (loss of C_6H_{14}, and loss of undecanoyl moiety), the latter to testosterone or an isomer, with subsequent hydroxylations and decarboxylation. Products of second phase metabolism were not detected in plasma. SLV361 also underwent decarboxylation and loss of a C_6H_{14} moiety.

6 General Toxicology

6.1 Single-Dose Toxicity

Testosterone possesses low potential for acute toxicity, with single doses on the order of grams per kg of body weight required for lethality in rodents (RTECS). The acute oral LD50 of TU is 4 g/kg.

6.2 Repeat-Dose Toxicity

***SLV361:* 28 Day Oral (Gavage) Administration Toxicity Study in the Male Rat** (Study No. S361.7.008)

TU (SLV361) was administered for 28 days to male HsdHan™:WIST rats (4 groups of 10 animals/group,) at doses of 0, 50, 100, or 500 mg TU/kg of body weight/day. A priming dose of corn oil and olive oil (50:50 v/v) at 5 mL/kg was used to enhance absorption of TU. Toxicokinetics evaluations were performed on an additional 9 animals per group.

Repeat administration of TU to rats by oral gavage was generally well tolerated, although the vehicle was observed to be unpalatable. A marginal treatment related reduction in body weight gain and food consumption was observed. Hematological effects included slightly decreased mean white blood cell and lymphocyte counts, and moderately increased neutrophil counts in males at 100 and 500 mg/kg/day. Clinical chemistry effects included marginally decreased mean calcium concentrations and slightly decreased total cholesterol concentrations in males at 500 mg/kg/day.

Treatment related effects were observed in the mammary gland, adrenal gland, testis, epididymis, seminal vesicle, prostate, thymus, thyroid and lacrimal glands.

In the mammary gland, there was an increase in the incidence and severity of acinar hyperplasia in males at 100 and 500 mg/kg/day. In the adrenal gland, cortical vacuolation was observed in all treated groups. Interstitial cell atrophy was noted in the testis of all treated animals, characterized by a decrease in the number and size of interstitial (Leydig) cells, coupled with an increase in the incidence and severity of germ cell degeneration, tubular cell vacuolation and spermatid retention in treated animals. In the epididymis, there was an increase in the incidence and/or severity of cell debris in treated animals, compared with controls with an increase in the incidence and severity of oligospermia in animals dosed at 50 and 100 mg/kg/day. Hypertrophy of the seminal vesicles and prostate of animals at 50, 100 and 500 mg/kg/day was observed. Atrophy of the thymus was observed at 100 and 500 mg/kg/day and an increase in follicular cell hypertrophy was observed in all treated groups. In the lacrimal gland, acinar hypertrophy/hyperplasia was observed at 50, 100 and 500 mg/kg/day.

Maximum plasma concentrations of TU, T, DHTU, and DHT were achieved between 4 and 8 hours post dose. Systemic exposure to TU, DHTU, and DHT increased in a nonproportional manner with dose, while testosterone appeared to increase dose proportionately. There was evidence of accumulation of TU, DHTU, T and DHT based on AUC. Accumulation was greatest at 500 mg/kg/day based on AUC for TU, T, and DHT. Accumulation was similar

across the range of doses for DHTU. Plasma concentrations of 17β-estradiol were not quantifiable.

No no-effect level was observed in this study. Exposures at 50 mg/kg/day were: TU: AUC_{0-t} 5230 ng.hr/ml, Cmax 1010 ng/ml; DHTU: AUC_{0-t} 6440 ng.h/ml, Cmax 987 ng/ml; T: AUC_{0-t} 276 ng.hr/ml, Cmax 47.8 ng/m; and DHT: AUC_{0-t} 101 ng.h/ml, Cmax 14.8 ng/ml. Exposures at 100 mg/kg/day were: TU: AUC_{0-t} 7180 ng.hr/ml, Cmax 1600 ng/ml; DHTU: AUC_{0-t} 8030 ng.h/ml, Cmax 1310 ng/ml; T: AUC_{0-t} 385 ng.hr/ml, Cmax 86 ng/m; and DHT: AUC_{0-t} 150 ng.h/ml, Cmax 24.7 ng/ml. Exposures at 500 mg/kg/day were: TU: AUC_{0-t} 97400 ng.hr/ml, Cmax 12200 ng/ml; DHTU: AUC_{0-t} 37100 ng.h/ml, Cmax 4320 ng/ml; T: AUC_{0-t} 3640 ng.hr/ml, Cmax 480 ng/ml; and DHT: AUC_{0-t} 707 ng.h/ml, Cmax 60.0 ng/ml.

Study title: SLV361: 26 Week Oral (Gavage) Administration Toxicity Study in the Male Rat

Study no.:	(b) (4) (Abbott Reference Number: S361.7.013)
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4) (b) (4)
Date of study initiation:	27 October 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SLV361, Lot # X1-091001, 101.4%, based on LC with MS/MS detection

Key Study Findings

Findings were observed in the testis, epididymis, prostate, seminal vesicle, mammary gland, thyroid gland, adrenal gland, thymus, lacrimal gland, and parotid gland.

In the testis, germ cell degeneration/depletion, germ cell exfoliation and interstitial cell atrophy were observed in the majority of animals in all dose groups, along with distension of seminal vesicles and distension/hypertrophy of the prostate (at 0.6- to 6-fold the maximum proposed clinical exposure to testosterone by AUC.)

In the mammary gland, minimal to slight ductular dilation was observed in animals at 50 and 150 mg/kg/day (2- to 6-fold), characterized by an increase in the number of distended ducts lined by cuboidal to columnar epithelium, with or without secretion. A minimal increase in follicular cell hypertrophy was observed in the thyroid gland at 150 mg/kg/day (6-fold.)

In the adrenal gland, there was an increase in the incidence and severity of diffuse cortical vacuolation in treated animals (at 0.6- to 6-fold the maximum proposed clinical

exposure to testosterone by AUC), characterized by small to large cytoplasmic vacuoles within cortical adrenocytes, primarily in the zona fasciculata and reticularis. Thymic atrophy and lacrimal gland acinar hypertrophy/hyperplasia were also observed in all groups. An increase in fat infiltration of the parotid gland was observed at 50 and 150 mg/kg/day (2-to 6-fold).

The NOAEL could not be determined.

Methods

Doses:	0, 20, 50, and 150 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	Oleic acid
Species/Strain:	Rat/ Hsd Han™: WIST
Number/Sex/Group:	15 males/group
Age:	6-7 weeks
Weight:	163.6 - 235.5 g
Satellite groups:	9 males/group
Unique study design:	To enhance lymphatic absorption, each animal received a priming dose of 5 ml/kg corn oil: olive oil (50:50 v/v) 30 min before dosing.
Deviation from study protocol:	None significant

Observations and Results

Mortality

One animal in the 150 mg/kg group was sacrificed moribund on Day 104 due to eye rupture with ulceration reported as not related to treatment.

Clinical Signs

No treatment related effects were observed.

Body Weights

A marginal treatment-related reduction in body weight gain (22 and 27%) in animals that received 50 or 150 mg/kg/day was observed.

Feed Consumption

No treatment related effects were observed.

Ophthalmoscopy

No treatment related effects were observed.

Hematology

Group mean neutrophil counts were marginally increased at 50 or 150 mg/kg/day at Week 13 (1.36 to 1.64-fold)and at Week 26 (1.40 to 1.90-fold). Mean prothrombin time was minimally decreased (0.91-fold) at 150 mg/kg/day.

Clinical Chemistry

At Week 13, group mean inorganic phosphorus concentration was minimally increased at 50 or 150 mg/kg/day (1.19 to1.25-fold), and mean total cholesterol concentration was minimally decreased (0.85-fold) at150 mg/kg/day. At Week 26, group mean total cholesterol and phospholipid concentrations were minimally decreased (0.78 and 0.82-fold respectively) at 150 mg/kg/day

Urinalysis

No treatment related effects were observed.

Gross Pathology

Small and/or soft testis, small epididymis, large seminal vesicle and large prostate were observed in all treated animals.

Organ Weights

Decreases in group mean testes and epididymides weights (compared with body weights), were observed across all treatment groups (by 0.42, 0.46 and 0.59-fold). Increased kidney and liver weights (compared with body weights)(up to 1.3-fold) and increased group mean prostate and seminal vesicle weights (compared with body weights)(up to 2.2-fold) were observed at 50 and150 mg/kg/day. A dose related decrease in group mean thyroid/parathyroid and thymus weights (compared to body weight) was observed across all groups.

Histopathology

Adequate Battery: yes

Peer Review: yes

Histological Findings

Findings were observed in the testis, epididymis, prostate, seminal vesicle, adrenal gland, thymus, lacrimal gland, mammary gland, parotid gland, lung and thyroid gland.

In the testis, germ cell degeneration/depletion, germ cell exfoliation and interstitial cell atrophy were observed in the majority of animals in all dose groups. Spermatid retention was observed at 50 and 150 mg/kg/day. Germ cell degeneration/depletion was characterized by variable loss of cells including pachytene spermatocytes and round spermatids from mid-cycle (Stage VI–IX) tubules and spermatocytes undergoing meiotic

division (stage XIV). Tubules had variable vacuolation consistent with germ cell loss. Spermatid depletion was characterized by a reduction in primarily mature (elongated) spermatids. Germ cell exfoliation was characterized by separation of germinal epithelial cells with loss into the tubular lumen. Interstitial cell atrophy was characterized by a reduction in the size of interstitial (Leydig) cells. Spermatid retention was characterized by retention of spermatids within tubular epithelium beyond the stage when release normally occurs (stage VIIIIX). In the epididymis, there was cellular debris and oligospermia in the majority of treated animals. Cellular debris was characterized by variable numbers of exfoliated cells within epididymal tubular lumens. Oligospermia was characterized by a reduction in the number of mature spermatozoa in the epididymal tubules. There was distension in the seminal vesicles and distension/hypertrophy in the prostate in the majority of treated animals. Distension was characterized by acinar distension, causing an overall enlargement of the seminal vesicles; distension/ hypertrophy of the prostate was similar, with occasional focal areas of epithelial cells with increased amounts of cytoplasm.

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. In the lacrimal gland, there was acinar hypertrophy/hyperplasia in almost all treated animals, characterized by an increase in the size and number of cells present in the acini, with variably sized nuclei, fine to coarsely stippled chromatin, moderate amounts of apical eosinophilic granules and occasional mitoses. This was accompanied by occasional groups of foamy, Harderian gland-like cells (Harderian gland alteration) in animals dosed at 50 and 150 mg/kg/day. In the lacrimal gland, there was acinar hypertrophy/hyperplasia in almost all treated animals, characterized by an increase in the size and number of cells present in the acini, with variably sized nuclei, fine to coarsely stippled chromatin, moderate amounts of apical eosinophilic granules and occasional mitoses. This was accompanied by occasional groups of foamy, Harderian gland-like cells (Harderian gland alteration) in animals dosed at 50 and 150 mg/kg/day.

In the mammary gland, minimal to slight ductular dilation was observed in animals at 50 and 150 mg/kg/day, characterized by an increase in the number of distended ducts lined by cuboidal to columnar epithelium, with or without secretion. An increase in fat infiltration of the parotid gland was observed at 50 and 150 mg/kg/day, characterized by scattered adipocytes separating acini without an overall increase in glandular size. In the lung, foamy macrophages were observed in alveoli of control and treated groups with a minor increase in animals dosed at 150 mg/kg/day, characterized by small aggregates of macrophages with increased amounts of pale foamy cytoplasm within alveolar spaces, consistent with oil inhalation. Minimal increase in follicular cell hypertrophy was observed in the thyroid gland at 150 mg/kg/day compared with controls, characterized by follicles with pale cuboidal to columnar epithelium with increased cytoplasm.

Table 4 Histopathological findings in male rats administered oral TU for 26 weeks

		Males			
Testosterone undecanoate (mg/kg/day)		0	20	50	150
Testis	number examined	15	15	15	14
Spermatid depletion			13	15	13
Germ cell degeneration/depletion			13	15	13
Germ cell exfoliation			9	15	13
Interstitial cell atrophy			14	15	14
Spermatid retention				7	11
Agonal congestion/ hemorrhage			5	2	1
Epididymis	number examined	15	15	15	14
Cellular debris			13	15	13
Oligospermia			13	15	13
Tubular cell vacuolation			3	1	
Seminal vesicle	number examined	15	15	15	14
Distension			3	12	13
Prostate	number examined	15	15	15	14
Distension/hypertrophy			7	15	13
Kidney	number examined	15	15	15	14
Agonal congestion/ hemorrhage					3
Adrenal	number examined	15	15	15	14
Cortical vacuolation, diffuse		4	12	14	14
Thymus	number examined	15	15	15	14
Atrophy		1	8	12	12
Lacrimal gland	number examined	15	15	15	14
Acinar hypertrophy/hyperplasia			14	15	14
Mammary gland,	number examined	7	12	13	9
Tubular-alveolar differentiation				4	8
Thyroid	number examined	15	15	15	14
Follicular cell hypertrophy		2	1	1	7
Lung	number examined	15	15	15	14
Foamy macrophages		9	6	9	13
Agonal congestion/ hemorrhage		2	4	5	7
Parotid gland	number examined	15	15	15	14
Fatty infiltration		4	5	11	14
Acinar cell vacuolation			1	3	2

Special Evaluation

Seminology parameters were measured at Week 26. Mean sperm counts were 0.35 fold, 0.09 fold, and 0.66 fold control values at 20, 50, and 150 mg/kg/day, respectively. Mean sperm motility values were 0.14, 0.008, and 0.11 fold, respectively. Mean sperm velocity values were 0.19, 0.06, 0.21 fold, respectively

.

Mean percentage of abnormal sperm were increased by 55.5, 231.5, and 10.5 fold, respectively.

Toxicokinetics

A reported clinical mean Cav of 6.1 ng/ml (611 ng/dL) testosterone equates approximately to an AUC_{0-24} of about 6.1 ng/ml x 24 hours or about 147 ng•hr/ml, at the maximum recommended human dose. (Although testosterone levels were not measured in the control group in this study, the normal range of serum testosterone levels in intact male rats has been reported to be from 3.5 to 22 ng/ml.)

A reported clinical mean Cavg of 1.2 ng/ml DHT equates approximately to an AUC_{0-24} of about 27.8 ng•hr/ml.

A reported clinical mean Cavg of 160 ng/ml of testosterone undecanoate equates approximately to an AUC_{0-24} of about 3830 ng•hr/ml.

A reported clinical mean Cavg of 75 ng/ml of dihydrotestosterone undecanoate equates approximately to an AUC_{0-24} of about 1799 ng•hr/ml.

Multiples of exposure to clinical TU at 20, 50, and 150 mg/kg/day TU are estimated to be about 0.8X, 6X, and 10X, respectively. (TU is not expected to affect androgen sensitive tissues.)

Multiples of exposure to clinical testosterone at 20, 50, and 150 mg/kg/day TU are estimated to be about 0.6X, 2X, and 6X, respectively, in rats.

Multiples of exposure to clinical DHT at 20, 50, and 150 mg/kg/day TU are estimated to be about 1X, 3X, and 7X, respectively.

Multiples of exposure to clinical DHTU at 20, 50, and 150 mg/kg/day TU are estimated to be about 3X, 8X, and 23X, respectively.

Table 5 Mean AUC0-24h of Testosterone Undecanoate, Dihydrotestosterone Undecanoate, Testosterone, and Dihydrotestosterone in Male Rats

AUC_{0-24h} (ng•h/ml)	Males			
TU dose (mg/kg/day)	0	20	50	150
Testosterone undecanoate				
Day 1	ND	946	3070	11300
Week 26		2970	23800	39900
Dihydrotestosterone undecanoate				
Day 1	ND	2230	5880	13800
Week 26		4610	14300	41300
Testosterone				
Day 1	ND	51.9	101	478
Week 26		90.1	328	934
Dihydrotestosterone				
Day 1	ND	16.2	33.3	117
Week 26		26.7	92.0	204

Table 6 Mean Cmax of Testosterone Undecanoate, Dihydrotestosterone Undecanoate, Testosterone, and Dihydrotestosterone in Male Rats

Cmax (ng/ml)	Males			
TU dose (mg/kg/day)	0	20	50	150
Testosterone undecanoate				
Day 1	ND	67.9	401	1430
Week 26		373	1800	7060
Dihydrotestosterone undecanoate				
Day 1		171	645	1570
Week 26		638	1680	4170
Testosterone				
Day 1		4.21	7.99	36.9
Week 26		8.42	30.3	169
Dihydrotestosterone				
Day 1		1.31	2.70	9.31
Week 26		2.37	7.31	21.6

Table 7 Mean tmax of Testosterone Undecanoate, Dihydrotestosterone Undecanoate, Testosterone, and Dihydrotestosterone in Male Rats

Tmax (h)	Males			
TU dose (mg/kg/day)	0	20	50	150
Testosterone undecanoate				
Day 1	ND	8	8	8
Week 26		4	8	4
Dihydrotestosterone undecanoate				
Day 1		8	8	8
Week 26		4	8	4
Testosterone				
Day 1		4	8	8
Week 26		4	8	4
Dihydrotestosterone				
Day 1		8	8	8
Week 26		4	8	4

Plasma concentrations of 17β-estradiol were not quantifiable in rats.

Dosing Solution Analysis

Formulations prepared for use on Day 1 and Week 26 of the study were analyzed to determine homogeneity and achieved concentration. The target range for the preparation of the formulations was 90 to 110% of nominal. Results were within the range 86% to 89%. Test article was not detected in the control sample. Formulations were to be considered homogeneous if the coefficient of variation (CV) of the results is ≤ 6.0%. In addition all the homogeneity results should be within ± 10% of the mean. Results were within these criteria.

Testosterone Undecanoate: A 28-Day Oral (Gavage) Toxicity and Toxicokinetic Study in Dogs (Study no. S361.7.012)

TU was administered by oral gavage to male Beagle dogs (3/group) for 28 days at 0, 180, 600, or 1800/1000 mg/kg/day in oleic acid* approximately 45 to 60 minutes after a can of dog food. At the end of the treatment period, all surviving animals were euthanized and necropsied.

Two animals (one each at 0 and 1800 mg/kg/day) were euthanized in moribund condition on Days 6 and 10, respectively, reportedly due to aspiration of the oleic acid formulation.

Microscopic changes were observed in the testes, epididymides and prostate of all treated animals at 180 mg/kg/day and above. Findings in the testes included minimally increased numbers of degenerating germinal cells and slight to moderate Leydig cell atrophy. The epididymides contained minimal to moderate amounts of sloughed germinal cells and germinal cell debris, considered secondary to the degenerative effects on testicular spermatogenesis. The prostate was slightly to markedly enlarged, which correlated with an increase in absolute and relative weights of the prostate. The enlargement of the prostate was attributed to hypertrophy/hyperplasia and increased secretory content. The liver showed a minimal to slight increase in periportal glycogen deposits in most treated animals at 180 mg/kg/day and above, and in the adrenal gland, which had minimal to slight vacuolation in some animals at 180 mg/kg/day and above and minimal cortical apoptosis in treated animals at 600 mg/kg/day and above. The changes in the liver and adrenal gland were independent of dose. There were slight to moderate increases in absolute and relative kidney weights in all treated animals at 180 mg/kg/day and above, with no dose dependency and no histopathologic correlate. A no observed adverse effect level (NOAEL) was not observed.

The toxicokinetics of TU, DHTU, T, DHT and 17β-estradiol appeared to be non-linear on Days 1, 14 and 28 following oral administration of TU. Systemic (AUC) testosterone exposures on Day 1 were 1370, 4910 and 9370 ng•hr/mL at 180, 600 and 1800 mg/kg/day, respectively. On Day 14, the AUC for testosterone was 3170 ng•hr/ml at 1000 mg/kg/day. Overall, no accumulation of TU, DHTU, T and DHT was observed in male dogs after repeated oral (gavage) administration of 180, 600 or 1800/1000 mg/kg/day of TU for 14 or 28 Days. The results suggest an increased capacity for disposition or removal of TU, DHTU, and T in male dogs after repeated oral (gavage) administration of 180, 600 or 1800/1000 mg/kg/day of TU for 28 Days. Some degree of accumulation of 17β-estradiol was observed in male dogs after repeated oral administration of 180, 600 or 1800/1000 mg/kg/day of TU for 14 or 28 Days.

*The dose volume of 3.4 ml/kg/day was decreased to 2 ml/kg/day on Day 8 for the 0, 180 and 600 mg/kg/day groups and to 1.9 mL/kg/day on Day 11 and 2 ml/kg/day on Day 12 for the 1800/1000 mg/kg/day group to reduce exposure to

the oleic acid vehicle. On Days 11 to 29, the dose level for the high-dose group was reduced from 1800 mg/kg/day to 1000 mg/kg/day because of the decrease in dosing volume and the limited solubility of the test article in oleic acid. Animals were not dosed on Day 7 to allow time for preparation of the dosing formulations at new concentrations.

Study title: Testosterone Undecanoate: A 90-Day Oral (Capsule) Toxicity and Toxicokinetic Study in Dogs

Study no.:	(b) (4) (Sponsor Study No. S361.7.014)
Study report location:	(b) (4) (b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	15 April 2011
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	SLV361 (testosterone undecanoate): Lipocine Lot No. TTU10001K from 27 Apr to 5 Jul 11 (Weeks 1 to 10) and (b) (4) Lot No. X1-091001 from 6 to 25 Jul 11 (Weeks 11 to 13). Based on LC with MS/MS detection

Key Study Findings

Androgenic effects on male reproductive tissues observed in all treated groups (at 5- to 29-fold the maximum proposed clinical exposure to testosterone by AUC,) included Leydig cell atrophy, increased sperm cell degeneration, decreased spermatogenesis, and prostate hypertrophy.

At all treated doses (5- to 29-fold), slight to moderate adrenal cortical atrophy, increases in absolute and relative kidney weights, and slight to severe thymic lymphoid depletion were observed. At the high dose of 1000 mg/kg/day (29-fold), slight increases in the absolute and relative weights of thyroid/parathyroid glands and minimal focal hepatocellular degeneration / necrosis, inflammation and periportal acute/subacute inflammatory cell infiltrate was observed (in two animals, one with minimal periportal acute/subacute inflammation and minimal bile duct hyperplasia). Bile duct hyperplasia was also seen in 1 animal at 240 mg/kg/day (20-fold), with minimal severity.

Hematological changes included slight decreases in hemoglobin and red blood and increases in neutrophils and total white blood cells. However, bone marrow cytologic findings showed slight decreases in myeloid to erythroid ratios in two males at 1000 mg/kg/day, correlating with decreases in red cell mass and possibly reflecting slight stimulation of erythropoiesis.

Methods

Doses:	0, 80, 240, and 1000 mg/kg/day
Frequency of dosing:	daily
Route of administration:	Oral capsules
Dose volume:	2 ml/kg
Formulation/Vehicle:	Oleic Acid
Species/Strain:	Beagle dog
Number/Sex/Group:	4 males per group
Age:	9.5 months
Weight:	9.4 (8.4-10.1) kilograms
Satellite groups:	4 males per group for toxicokinetics
Unique study design:	Dogs were fed a can of food (5% fat content) approximately 45-60 minutes prior to dosing and again 60-90 minutes post dosing.
Deviation from study protocol:	None significant. Vomited capsules were readministered on some occasions.

Observations and Results

Mortality

There were no unscheduled deaths in this study.

Clinical Signs

An increase in the incidence of vomiting of dosing capsules was noted in dogs dosed at 240 and 1000 mg/kg/day (vomited capsules were readministered on some occasions.) Additional findings considered to be test article related were excessive salivation and lacrimation which were noted principally at 1000 mg/kg/day. At 240 mg/kg/day, excessive salivation and lacrimation were seen on a few occasions.

incidence/animals	Males (mg/kg/day)			
Testosterone undecanoate (mg/kg/day)	0	80	240	1000
Lacrimation			12/1	24/2
Excessive salivation			2/2	31/2
Vomiting, food	8/4	7/4	10/4	12/4
Vomiting. capsule			6/4	7/4

Body Weights

There was no dose dependent effect of TU administration on absolute body weights or body weight gain, although minimal early increases in mean body weight gain were observed at all doses of TU compared to the control group, highest in the mid and high dose groups, primarily in the first 7 weeks of the study.

Feed Consumption

No treatment related effects were observed.

Ophthalmoscopy

No treatment related effects were observed.

ECG

Nine lead (I, II, III, aVR, aVL, aVF, V2, rV2, V10) electrocardiograms were taken from all animals at pretest and end of dosing. Qualitative assessment was performed on all electrocardiogram intervals. No treatment related effects were observed on Day 85. All recordings were within normal limits.

Hematology

Hematological changes were observed at Week 13 in the high dose group, compared to control: slight decreases in hemoglobin (-11%), red blood cells (-12%), and mean corpuscular hemoglobin concentration (-3%), an increase in red cell distribution width (+8%), and increases in neutrophils (+59%) and total white blood cells (+35%.)

Bone Marrow Evaluations

Bone marrow cytologic findings were limited to slight decreases in myeloid to erythroid ratios in two males at 1000 mg/kg/day, correlating with decreases in red cell mass and possibly reflecting slight stimulation of erythropoiesis.

Clinical Chemistry

At Week 13, moderate decreases in serum cholesterol at all doses and in triglycerides at doses ≥ 240 mg/kg/day were observed. Albumin and A/G ratio were increased at all doses, consistent with predicted increased anabolic activity and protein synthesis. Observed increases in calcium and phosphorus are consistent with testosterone-mediated phosphorus retention and decrease in urinary excretion of calcium. Mean BUN was increased at 1000 mg/kg/day.

	Males (mg/kg/day)			
Testosterone undecanoate (mg/kg/day)	0	80	240	1000
Blood Urea Nitrogen (% change from control)	--	--	--	+24
Cholesterol (% change from control)	--	-38	-51	-50
Triglycerides (% change from control)	--	--	-25	-31
Albumin (% change from control)	--	+19	+23	+23
Albumin/Globulin Ratio (% change from control)	--	+29	+36	+29
Calcium (% change from control)	--	+6	+8	+8
Phosphorus (% change from control)	--	+18	+22	+27

One animal at 1000 mg/kg/day had increases in aspartate aminotransferase (12-fold), alanine aminotransferase (26-fold), alkaline phosphatase (8.4-fold) and total bilirubin (6.2-fold), compared to pretreatment values.

Urinalysis

At Week 13, an increase in urine pH in animals at 1000 mg/kg/day (pH = 7.4) was observed, compared to the control animals (pH = 6.1.)

Gross Pathology

All treated animals had enlarged prostates, and all but one high dose animal had small adrenals. Small testes were observed in all treated groups.

Organ Weights

Test article-related changes in organ weights were observed at terminal necropsy. Increases in mean absolute and relative weights of the prostate were observed at ≥ 80 mg/kg/day, with some dose dependence. Decreases in mean absolute and relative weights of testes were inversely related to dose. Absolute and relative weights of thymus and adrenal glands, without dose dependence, were observed at ≥ 80 mg/kg/day. Minimal to slight increases in levator ani muscle were observed at ≥ 240 mg/kg/day, without dose dependence. No increases were observed in gastrocnemius muscle. Absolute and relative kidney weights were increased at doses ≥ 80 mg/kg/day, and slight increases in the absolute and relative weights of thyroid/parathyroid glands were observed at 1000 mg/kg/day.

	Males (mg/kg/day)			
Testosterone undecanoate (mg/kg/day)	0	80	240	1000
Prostate (change from control)	--	4.1X	4.5X	5.1X
Testes (% change from control)	--	-68%	-56%	-47%
Kidney (% change from control)	--	+35%	+40%	+45%
Adrenal gland (% change from control)	--	-42%	-47%	-47%
Thymus (% change from control)	--	-56%	-41%	-55%
Thyroid/Parathyroid (% change from control)	--	--	--	+21%
Levator Ani (% change from control)	--	--	+44%	+12%

Histopathology

Adequate Battery: yes

Peer Review: yes

Histological Findings

Androgenic effects on male reproductive tissues were observed in all treated groups. In the testes, marked Leydig cell atrophy and hypospermatogenesis was observed in all treated animals. There was minimal to slight germ cell degeneration in one animal at 80 mg/kg/day and all animals at 240 mg/kg/day and above. There was marked to severe germ cell depletion and tubular contraction at 80 mg/kg/day. In the epididymides, there was minimal to slight initial segment epithelial apoptosis in all treated animals. Oligospermia dose relatedly increased from moderate to severe in treated groups. In the prostate, there was slight to severe hypertrophy with increased secretory product in all treated animals, increasing in severity with dose.

In the adrenal, slight to moderate cortical atrophy was observed in all treated animals. In the thymus, a dose dependent increase from slight to severe lymphoid depletion was observed in all treated animals. Minimal focal hepatocellular degeneration / necrosis with hemorrhage, inflammation and periportal acute/subacute inflammatory cell infiltrate was observed in two animals at 1000 mg/kg, and one of these males also had minimal periportal acute/subacute inflammation and minimal bile duct hyperplasia. Bile duct hyperplasia was also seen in 1 animal at 240 mg/kg/day, with minimal severity.

Table 8 Histopathological findings in male dogs administered oral TU for 90 days

		Males			
Testosterone undecanoate (mg/kg/day)		0	80	240	1000
# animals examined		4	4	4	4
Adrenal glands					
Cortical thinning/ atrophy	slight	0	0	1	1
	moderate	0	4	2	1
	marked	0	0	1	2
	incidence total	0	4	4	4
Testes					
Hypospermatogenesis					
	slight	3	0	1	0
	moderate	1	0	1	2
	marked	0	0	2	2
	incidence total	4	0	4	4
Testes					
Germ cell degeneration: increased					
	minimal	0	0	2	1
	slight	0	0	2	3
	moderate	0	1	0	0
	incidence total	0	1	4	4
Testes					
Germ cell depletion: generalized					
	marked	0	1	0	0
	severe	0	3	0	0
	incidence total	0	4	0	0
Testes					
Segmental hypoplasia	slight	0	0	1	1
Testes					
Leydig cell atrophy	marked	0	4	4	4
Testes					
Tubular contraction					
	marked	0	1	0	0
	severe	0	3	0	0
	incidence total	0	4	0	0
Epididymis					
Reduced sperm					
	slight	4	0	0	0
	moderate	0	0	0	1
	marked	0	0	3	1
	severe	0	4	1	2
	incidence total	4	4	4	4
Epididymis					
Epithelial apoptosis: initial segment					

	minimal	0	1	3	1
	slight	0	3	1	3
	incidence total	0	4	4	4
Prostate					
Hypertrophy/hyperplasia w/ increased secretory product					
	slight	0	0	2	2
	moderate	0	3	2	0
	marked	0	1	0	2
	incidence total	0	4	4	4
Prostate					
Subacute/chronic inflammatory cell infiltrate					
	minimal	0	2	1	1
	slight	0	0	1	0
	incidence total	0	2	2	1
Spleen					
Germinal center size/number					
	minimal	1	0	2	1
	slight	0	1	1	2
	incidence total	1	1	3	3
Thymus					
Lymphoid depletion					
	slight	3	1	0	0
	moderate	1	3	3	1
	marked	0	0	0	3
	severe	0	0	1	0
	incidence total	4	4	4	4
Sternal marrow					
Hematopoietic cellularity					
	slight	0	3	0	0
	moderate	4	1	4	3
	marked	0	0	0	1
	incidence total	4	4	4	4
Femoral marrow					
Hematopoietic cellularity					
	slight	2	4	1	0
	moderate	2	0	3	3
	marked	0	0	0	1
	incidence total	4	4	4	4
Liver					
Extramedullary hematopoiesis	slight	1	2	0	2
Focal hepatocellular degen./necr. w/ hemorrhage and/or inflammation	slight	0	0	0	2
Periportal acute/subacute inflammatory cell infiltrate	slight	0	0	0	1
Bile duct hyperplasia	slight	0	0	1	1
Mononuclear inflammatory cell foci	slight	2	3	2	4
Increased periportal glycogenic vacuolation	slight	0	2	0	3
	moderate	0	1	4	1

Toxicokinetics

A reported clinical mean Cav of 6.1 ng/ml testosterone equates approximately to an AUC_{0-24} of about 6.1 ng/ml x 24 hours or about 147 ng•hr/ml, at the maximum recommended human dose. (Although testosterone levels were not measured in the control group in this study, the *normal* testosterone range in male *dogs* is reported to be 1.0 – 9.4ng/ml.)

A reported clinical mean Cavg of 1.2 ng/ml DHT equates approximately to an AUC_{0-24} of about 27.8 ng•hr/ml.

A reported clinical mean Cavg of 160 ng/ml of testosterone undecanoate equates approximately to an AUC_{0-24} of about 3830 ng•hr/ml.

A reported clinical mean Cavg of 75 ng/ml of dihydrotestosterone undecanoate equates approximately to an AUC_{0-24} of about 1799 ng•hr/ml.

A reported clinical mean Cavg of 0.015 ng/ml of estrogen equates approximately to an AUC_{0-24} of about 0.36 ng•hr/ml.

Multiples of exposure to clinical TU at 80, 240, and 1000 mg/kg/day TU are estimated to be about 5X, 16X, and 28X, respectively, in dogs. (TU is not expected to affect androgen sensitive tissues.)

Multiples of exposure to clinical testosterone at 80, 240, and 1000 mg/kg/day TU are estimated to be about 5X, 20X, and 29X, respectively, in dogs.

Multiples of exposure to clinical DHT at 80, 240, and 1000 mg/kg/day TU are estimated to be about 3X, 9X, and 11X, respectively.

Multiples of exposure to clinical DHTU at 80, 240, and 1000 mg/kg/day TU are estimated to be about 0.4X, 1X, and 1X, respectively.

Multiples of exposure to clinical estrogen at 80, 240, and 1000 mg/kg/day TU are estimated to be about 0.7X, 0.8X, and 0.9X, respectively.

Table 9 Mean AUC0-23h values of testosterone undecanoate, dihydrotestosterone undecanoate, testosterone, and dihydrotestosterone in male dogs following oral (capsule) administration of testosterone undecanoate

AUC_{0-23h} (ng•hr/ml)	Males			
TU dose (mg/kg/day)	0	80	240	1000
Testosterone undecanoate				
Day 2	ND	38000	134000	165000
Day 30		25100	67100	71600
Day 90		18300	62500	108000
Dihydrotestosterone undecanoate				
Day 2		811	2730	3360
Day 30		871	1600	1410
Day 90		755	1730	2190
Testosterone				
Day 2		813	2900	4680
Day 30		951	3640	3490
Day 90		709	2970	4220
Dihydrotestosterone				
Day 2		87.3	209	298
Day 30		101	275	255
Day 90		91.6	250	294

A maximum allowable clinical concentration of testosterone was set at 12.55 ng/ml. Multiples of the clinical maximum concentration of testosterone at 80, 240, and 1000 mg/kg/day TU in dogs were 5X, 26X, and 32X, respectively.

Table 10 Mean Cmax values of testosterone undecanoate, dihydrotestosterone undecanoate, testosterone, and dihydrotestosterone in male dogs following oral (capsule) administration of testosterone undecanoate

Cmax (ng/ml)	Males			
TU dose (mg/kg/day)	0	80	240	1000
Testosterone undecanoate				
Day 2	ND	5110	14500	17700
Day 30		2480	7590	6070
Day 90		2350	6910	11600
Dihydrotestosterone undecanoate				
Day 2		71.9	283	262
Day 30		79	143	107
Day 90		63.9	162	173
Testosterone				
Day 2		75.7	332	367
Day 30		87.1	346	297
Day 90		66.2	328	400
Dihydrotestosterone				
Day 2		6.77	19.0	22.9
Day 30		7.78	22.0	18.3
Day 90		6.71	21.7	22.5

Table 11 Mean tmax values of testosterone undecanoate, dihydrotestosterone undecanoate, testosterone, and dihydrotestosterone in male dogs following oral (capsule) administration of testosterone undecanoate

Tmax (h)	Males			
TU dose (mg/kg/day)	0	80	240	1000
Testosterone undecanoate				
Day 2		7	6	3
Day 30		7	6	4
Day 90		4	6	4
Dihydrotestosterone undecanoate				
Day 2		6	7	8
Day 30		7	7	8
Day 90		5	7	6
Testosterone				
Day 2		7	7	8
Day 30		8	7	7
Day 90		7	7	6
Dihydrotestosterone				
Day 2		8	7	8
Day 30		8	7	7
Day 90		7	7	6

Mean values of plasma toxicokinetic parameters of 17β-estradiol in male dogs following oral (capsule) administration of testosterone undecanoate

17β-estradiol	Males			
TU dose (mg/kg/day)	0	80	240	1000
$AUC_{0\text{-}23h}$ (pg•h/ml)				
Day 2		106	167	208
Day 30		239	346	364
Day 90		259	281	309
Cmax (pg/ml)				
Day 2		8.93	12.8	13.8
Day 30		17.7	22.6	21.5
Day 90		19.1	19.1	17.4
Tmax (h)				
Day 2		8.43	9.73	6.73
Day 30		11.9	10.0	9.46
Day 90		11.8	16.7	8.90

Dosing Solution Analysis

Dose formulations of testosterone undecanoate (TU) prepared for both weekly and daily dosing were found to be homogeneous. The test article was stable in the vehicle for at least 8 days when stored at 37 to 40 ºC and when stored at 37 to 40 ºC and reheated to 50 to 60 ºC prior to use. Analyses conducted during the treatment period confirmed that dose solutions of appropriate concentration were administered.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Reverse Mutation in Five Histidine Requiring Strains of *Salmonella typhimurium*

Study no.:	8225660 (S361.7.005)
Study report location:	(b) (4) (b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	13 April 2010
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	(b) (4) Testosterone Undecanoate, batch number ST-090803, 98.2% pure, by HPLC

Key Study Findings

Testosterone undecanoate (SLV361) was not genotoxic in the Ames assay.

Methods

Strains: TA98, TA100, TA1535, TA1537 and TA102 of *Salmonella typhimurium*

Concentrations in definitive study: 0, 1.6, 8, 40, 200, 1000 and 5000 µg/plate in Experiment 1 and 0, 156.3, 312.5, 625, 1250, 2500, 5000 µg/plate (plus a pre-incubation step in the presence of S-9) in Experiment 2

Basis of concentration selection: An initial toxicity experiment was carried out in the absence and in the presence of S-9 (Aroclor 1254-induced rat liver post-mitochondrial fraction) in strain TA100 only at 1.6, 8, 40, 200, 1000 and 5000 µg/plate, plus negative (vehicle) and positive controls. No evidence of toxicity was observed.

Negative control: Dimethylformamide (DMF)

Positive control:

Chemical***	Stock* Concentration (mg/mL)	Final Concentration (µg/plate)	Strain(s)	S-9
2-nitrofluorene (2NF)	50	5.0	TA98	–
Sodium azide (NaN_3)	20	2.0	TA100, TA1535	–
9-aminoacridine (AAC)	500	50.0	TA1537	–
Mitomycin C (MMC)	2	0.2	TA102	–
Benzo[a]pyrene (B[a]P)	100**	10.0	TA98	+
2-aminoanthracene (AAN)	50**	5.0	TA100, TA1535, TA1537	+
	200**	20.0	TA102	+

Formulation/Vehicle: Dimethylformamide (DMF)

Incubation & sampling time: All concentrations were tested by plate incorporation in the absence and presence of S-9, and incubated for three days in triplicate. Negative (vehicle) and positive controls were included in quintuplicate and triplicate respectively, without and with S-9 mix. A pre-incubation step in the presence of S-9 was added in Experiment 2

Study Validity

Negative and positive controls responded as expected. No evidence of toxicity was observed at any dose of testosterone undecanoate (SLV361.) Precipitation of the test item was observed on all test plates treated at 5000 µg/plate in the Range Finder Experiment and Experiment 1, and at 1250 µg/plate and above in Experiment 2.

Results

No increase in revertant frequencies was observed at any dose of SLV361 tested, in the absence or presence of S-9. It was concluded that SLV361 was not genotoxic under the conditions tested.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes

Study no.:	8225661 (S361.7.006)
Study report location:	(b) (4) (b) (4)
Conducting laboratory and location:	[redacted]
Date of study initiation:	15 April 2010
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	(b) (4) Testosterone Undecanoate, batch number ST-090803, 98.2% pure, by HPLC

Key Study Findings

No increased frequency of structural chromosome aberrations, in the absence or presence of S-9 were observed at any concentration of testosterone undecanoate (SLV361) tested. It was concluded that testosterone undecanoate was not genotoxic under the conditions of this assay.

Methods

Cell line:	human lymphocyte cultures from the pooled blood of three male donors
Concentrations in definitive study:	Experiment 1: 0, 50, 100, 150, and 250 µg/ml (3+17 hours -S-9); 0, 100, 150, and 250 µg/ml (3+17 hours +S+9). Experiment 2: 0, 100, 140, and 180 µg/ml (3+17 hours -S-9); 0, 100, 160, 225, and 250 µg/ml (3+17 hours +S+9)
Basis of concentration selection:	The test article concentrations for chromosomal analysis were selected by evaluating the effect of SLV361 on mitotic index.
Negative control:	DMSO
Positive control:	4-Nitroquinoline 1-oxide (NQO)(-S9) and cyclophosphamide (CPA)(+S9)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Two independent experiments were conducted using duplicate cultures for each condition tested. Treatments covered a broad range of concentrations, separated by narrow intervals, in the absence and

presence of metabolic activation (S-9) from Aroclor 1254 induced animals. Incubations were for 3 hours plus 17 hours of recovery time.

Study Validity

Positive and negative controls responded as expected. The proportion of cells with structural aberrations in vehicle control cultures concurred with historical controls. Test cultures used for chromosomal analysis were selected within an acceptable range of mitotic index. Formulation analyses demonstrated achieved concentrations within 100 ± 10% of the nominal test article concentration.

Results

No increased frequency of structural chromosome aberrations, in the absence or presence of S-9 were observed at any concentration of SLV361 tested. It was concluded that SLV361 did not induce chromosome aberrations in cultured human peripheral blood lymphocytes under the conditions of this assay.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Induction of Micronuclei in the Bone Marrow of Treated Rats

Study no:	8225662 (S361.7.007)
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	15 April 2010
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	(b) (4) Testosterone Undecanoate, batch number ST-090803, 98.2% pure, by HPLC

Key Study Findings

SLV361 did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats and was therefore found to be not genotoxic under the conditions of this experiment.

Methods

Doses in definitive study:	0, 500, 1000, 2000 mg/kg/day
Frequency of dosing:	Daily, for 2 days
Route of administration:	Oral, gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	Oleic acid
Species/Strain:	Rat,
Number/Sex/Group:	6
Negative control:	Oleic acid
Positive control:	Cyclophosphamide (CPA 20 mg/kg)
Methods	Bone marrow smears were prepared from sacrificed animals approximately 24 hours following the final administration. Slides were stained and analyzed for the ratio of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE), ratio expressed as % PCE in a total of 1000 cells. Numbers of micronucleated PCE (MN PCE) were counted in a total of 2000 PCE per animal.

Study Validity

Rats treated with SLV361 at all doses exhibited group mean % PCE that were similar to the values for the vehicle control group and within the historical vehicle control (normal) range, confirming there was no evidence of test article related bone marrow toxicity. The positive and negative controls responded as expected.

Results

MN PCE frequencies at all treated doses were similar or lower than in the vehicle control group and consistent with the laboratory's historical data. There were no increases in micronucleus frequency for any treated groups compared to the concurrent vehicle control, and it was concluded that SLV361 did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats under the conditions of this experiment.

8 Carcinogenicity

As replacement products, testosterone and testosterone esters have been approved based on the benefit of replacement level testosterone outweighing the evidence of models of testosterone induced tumorigenesis.

It is generally agreed that sex steroids, including testosterone, may promote growth and differentiation of responsive tissues and may cause hyperplasia and tumors by epigenetic mechanisms[5] in complex tissue patterns dependent on species and study design[11,12]. The general conclusion is that testosterone may act as a target tissue promoter under certain conditions.

The International Agency for Research on Cancer (IARC) concluded that there was “sufficient” evidence for the carcinogenicity of testosterone in experimental animals[8,13] and cited studies using different animal models and test conditions demonstrating the complexity of their conclusions. For example, in C3H mice chronically administered testosterone propionate, the incidence of mammary tumors was *decreased* and was also decreased in mice given concomitant estradiol, compared to controls. In ovariectomized female Wistar rats, testosterone treatment alone did not cause urinary bladder tumors, but was a promoter of tumors in rats when tumorigenesis was initiated using nitrosamine compared to rats given nitrosamine alone.

Neonatal animal models have been used to study testosterone carcinogenesis[13] In a neonatal BALB/C3H mouse model that expresses mouse mammary tumor virus, testosterone treatment during the first 5 days postnatally, increases the incidence of mammary tumors in adult animals. In contrast, testosterone decreases the incidence of mammary tumors in a neonatal Sprague-Dawley rat model in which female rats are injected with a single dose of testosterone (about 300 mg/kg) on the day of birth, and then treated with a carcinogen (DMBA) on Day 50. As adults, testosterone decreased the incidence of DMBA-induced mammary tumors and increased the age of tumor onset.

The Nobel rat was developed as a tool to study the effects of estrogen and testosterone on mammary and prostate cancer. In this strain, testosterone treatment alone can increase the incidence of prostate cancer, and concomitant treatment with estrogen decreases the age of onset of the tumors [11, 13]. In this strain, the combination of testosterone and estrogen increased incidences of mammary tumors[12]. The dose of testosterone affected the time of tumor onset but not the incidence, and is considered to be evidence of testosterone’s role as a tumor promoter.

IARC concluded that the evidence for an association between androgens and cancer is “limited,” and stated that “The evidence that anabolic steroids can cause both benign and malignant liver tumors [in humans] is quite strong. However, because no analytical epidemiological study has been done, the

Working Group felt constrained to classify the evidence for carcinogenicity in humans as “no more than limited”[8]. However, a recent epidemiological study reported a possible association in post-menopausal women between increased risk of breast cancer and the use of methyltestosterone (not testosterone per se)[14].

The FDA label for AVEED® (testosterone undecanoate) injection for intramuscular use indicates that testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

It was proposed that the class labeling used for other testosterone replacement products also be used for this product, based on the submitted references.

1[5] Neumann F. Early indicators for carcinogenesis in sex-hormone-sensitive organs. Mut Res 1991; 248: 341-356.
2[8] International Agency for Research on Cancer (IARC). Overall evaluation of carcinogenicity: an updating of IARC Monographs Volumes 1 to 42. In: IARC Monographs on the Evaluation of the Carcinogenic risk of Chemicals to Humans. Supplement 7;1987: 96-99.
3[11] Bosland M., Dreef-van der Meulen H., Sukumar, S., Ofner, P., Leav, I., Han, X., Liehr, J. Multistage prostate carcinogenesis: the role of hormones. In: C. Harris et. al. (eds.)*Multistage Carcinogenesis*, CRC Press; 1992: 109-123.
4[12] Xei, B., Tsao, S. and Wong Y. Sex hormone-induced mammary carcinogenesis in female Noble rats: the role of androgens. Carcinogenesis. 1999; 20: 1597-1606.
5[13] International Agency for Research on Cancer (IARC). Testosterone, Testosterone Oenanthate and Testosterone Propionate. In: IARC Monographs on the Evaluation of the Carcinogenic risk of Chemicals to Humans. 1979;Vol. 21: 519, 531-547.
6[14] Tamimi R., Hankinson S., Chen W., Rosner B., Colditz, G. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. Arch Intern Med. 2006;166:1483-1489.

9 Reproductive and Developmental Toxicology

No safe level of exposure of a fetus to testosterone undecanoate has been established through clinical or nonclinical reports. Androgens cause a variety of adverse reproductive and developmental effects in male and female animals and humans. High levels of androgens disrupt the estrus cycle of rats[15]. High doses of testosterone

suppress spermatogenesis and cause a variety of effects on reproductive tissues[16]. During critical periods of development, androgens may be embryolethal, and can cause a variety of developmental effects[17, 18, 19], even after a single dose[20].

Effects on male fertility are cited in the label for AVEED® (testosterone undecanoate) injection for intramuscular use, which states that administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

It was proposed that the class labeling used for other testosterone replacement products also be used for this product. The class labeling, which does not cite animal data and which does not report a no effect level for virilization of a fetus exposed to testosterone, is supported by submitted references, which have also been cited by for previously approved testosterone products.

1[15] Rhees R., Kirk B., Sephton S., Lephart E. Effects of prenatal testosterone on sexual behavior, reproductive morphology and LH secretion in the female rat. Dev Neurosci. 1997;19:430-437.
2[16] Ewing L., Schanbacher B., Desjardins C., Chaffee V. The effect of subdermal testosterone filled polydimethylsiloxane implants on spermatogenesis in rhesus monkeys (Macaca mulata). 1976; Contraception 13: 583-596.
3[17] Schardien J. Hormones and hormonal antagonists. In: J. Schardien, Ed.*Chemically Induced Birth Defects*. New York, NY: Marcel Dekker; 1993: 271-339.
4[18] Herman R., Jones B. Mann D., Wallen K. Timing of prenatal androgen exposure: anatomical and endocrine effects on juvenile male and female rhesus monkeys. Hormones Behavior 2000; 38: 52-66.
5[19] Wolf C., Hotchkiss A., Ostby J., LeBlanc G., Gray, L. Effects of prenatal testosterone propionate on the sexual development of male and female rats: a dose-response study. Toxicol Sci. 2002; 65:71-86.
6[20] Tamura N., Kurabayashi T., Nagata H., Matsushita H., Yahata T., Tanaka K. Effects of testosterone on cancellous bone, marrow adipocytes, and ovarian phenotype in a young female rat model of polycystic ovary syndrome. Fertility and Sterility. 2005; 84 Suppl 2: 1277-1284.

11 Integrated Summary and Safety Evaluation

Testosterone undecanoate (TU) is a prodrug being developed for testosterone replacement therapy in hypogonadal men. As an ester of testosterone with undecanoic acid at the C17β-hydroxyl position, TU is subject to intestinal lymphatic absorption and is deesterified to yield testosterone and undecanoic acid. TU has a relatively high

binding affinity for the androgen receptor compared to that of testosterone and thus has little potential for androgenic activity.

In rats and dogs, oral TU was shown to have incomplete bioavailability, with absorption enhanced by dietary fats. Toxicology studies were designed to optimize absorption while minimizing toxic effects of the fatty vehicle, with high doses limited by solubility and dietary requirements for absorption. Testosterone undecanoate (TU), which is incompletely hydrolyzed, was a major component of drug exposure in both rats and dogs. Exposure to testosterone (T), dihydrotestosterone (DHT), and dihydrotestosterone undecanoate (DHTU) were also observed in rats and dogs. Levels of 17β estradiol were measurable in dogs.

In 26-week rat and 90-day dog toxicology studies, the high doses of TU were 150 and 1000 mg/kg/day, respectively, or nominally, 17-fold and 117-fold the maximum recommended human dose (MRHD) for a 70 kg man. The calculated multiples of blood levels (AUCs) for TU (about 48% and 94% of circulating drug in rats and dogs, respectively) were 10-fold and 28-fold the MRHD at the high doses, in the rat and dog studies, respectively. DHTU was also present in animals and humans at high blood percentages, with rat and dog exposures at the high doses of about 23-fold and 1-fold the MRHD, respectively. Testosterone, the active androgen which accounted for only about 1 and 3.7% of circulating drug in rats and dogs, respectively, was present at about 6-fold and 29-fold the MRHD, in rats and dogs. DHT (also an active androgen) was seen at exposures of about 7-fold and 11-fold the MRHD at the high doses in rats and dogs.

Blood levels of 17β-estradiol were below the detection limits in rats, but were detectable in dogs. Multiples of exposure to clinical estrogen at 80, 240, and 1000 mg/kg/day TU are estimated to be about 0.7X, 0.8X, and 0.9X, respectively.

<u>26-Week rat toxicology study</u>
A no observed adverse effect level (NOAEL) for androgenic effects was not observed in rats 20, 50, and 150 mg/kg/day.)

Findings were observed in the testis, epididymis, prostate, seminal vesicle, mammary gland, thyroid gland, adrenal gland, thymus, lacrimal gland, and parotid gland. The changes in male reproductive organs (interstitial cell atrophy in the testes, distension of the seminal vesicles and prostate), along with increased reproductive organ weights, are considered to be expected effects of supraphysiological exogenous testosterone. Levels of active testosterone will be monitored and adjusted during clinical use of TU.

In the testis, germ cell degeneration/depletion, germ cell exfoliation and interstitial cell atrophy were observed in the majority of animals in all dose groups, along with distension of seminal vesicles and distension/hypertrophy of the prostate. Seminology parameters measured at Week 26 showed mean sperm counts at 0.35 fold, 0.09 fold, and 0.66 fold control values at 20, 50, and 150 mg/kg/day, respectively. Mean sperm motility values were 0.14, 0.008, and 0.11 fold, respectively. Mean sperm velocity

values were 0.19, 0.06, 0.21 fold, respectively. Mean percentage of abnormal sperm were increased by 55.5, 231.5, and 10.5 fold, respectively. Testosterone is known to affect testicular function through suppression of hypothalamic-pituitary hormones. Effects on fertility are reflected in the class labeling.

In the mammary gland, minimal to slight ductular dilation was observed in animals at 50 and 150 mg/kg/day, characterized by an increase in the number of distended ducts lined by cuboidal to columnar epithelium, with or without secretion. A minimal increase in follicular cell hypertrophy was observed in the thyroid gland at 150 mg/kg/day.

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. Thymic atrophy and lacrimal gland acinar hypertrophy/hyperplasia were also observed. An increase in fat infiltration of the parotid gland was observed at 50 and 150 mg/kg/day. The relevance of these effects is not known. However, no similar effects were observed in clinical studies of TU at physiological blood levels of T.

90-Day dog toxicology study

A no observed adverse effect level (NOAEL) for androgenic effects was not observed (80, 240, and 1000 mg/kg/day.)

Androgenic effects on male reproductive tissues observed in all treated groups included Leydig cell atrophy, decreased spermatogenesis, and prostate hypertrophy. The changes in male reproductive organs (interstitial cell atrophy in the testes, distension of the seminal vesicles and prostate), along with increased reproductive organ weights, are considered to be expected effects of supraphysiological exogenous testosterone. Levels of active testosterone will be monitored and adjusted during clinical use.

Absolute and relative kidney weights were increased at all doses and slight increases in the absolute and relative weights of thyroid/parathyroid glands were observed at 1000 mg/kg/day. In the adrenal, slight to moderate cortical atrophy was observed in all treated animals, and in the thymus, a dose dependent increase from slight to severe lymphoid depletion was observed in all treated animals. Minimal focal hepatocellular degeneration / necrosis with hemorrhage, inflammation and periportal acute/subacute inflammatory cell infiltrate was observed in two animals at 1000 mg/kg, and one of these males also had minimal periportal acute/subacute inflammation and minimal bile duct hyperplasia. Bile duct hyperplasia was also seen in 1 animal at 240 mg/kg/day, with minimal severity. The relevance of these effects are not known. However, no similar effects were observed in clinical studies of TU at physiological blood levels of T.

Reproductive effects

No reproductive toxicity assays for TU were performed. This product will not be approved for women; however the proposed class labeling reflects the risk of virilization of a fetus by exposure to testosterone. The proposed label does not contain animal

data, but references to published animal data, supporting the risk teratogenicity of testosterone, were submitted by the sponsor.

Class fertility labeling of previously approved products will be used and states that administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, reversible on cessation of the treatment.

Mutagenesis/ Carcinogenicity
TU was negative in a reverse mutation assay in bacteria, a chromosome aberration assay in cultured human peripheral blood lymphocytes, and a micronucleus assay in rats.

No carcinogenicity assay for TU was performed. Instead, the known risk of testosterone induced tumorigenesis will be made available in the class labeling used for previously approved testosterone products.

TU metabolism/elimination
TU related radioactivity was widely distributed among tissues in a rat study. No accumulation or retention was of note in adrenal or other glandular tissue or in any reproductive tissue. TU was among the least polar entities, (with a few less polar unidentified metabolites), and it is reasonable to assume that TU accounted for a large proportion of the observed distribution. By seven days post dose, radioactivity was cleared from most rat tissues. No determination of the subcellular distribution of TU was made, and it possible that TU's subcellular distribution is different from that of testosterone which has very specific binding proteins in animals and humans. AUC comparisons appear to show similar blood levels of TU and T (at the low doses) in rats and dogs compared to humans; however, no NOAEL was observed in rats or in dogs. No adverse effects on the adrenals or other glandular tissue or on reproductive tissues, however, have been identified at physiological blood levels clinically.

12 Appendix/Attachments

Submitted references:

1 Miescher, K., Wettstein, A., and Tschopp, E. CCLXXCII. The activation of the male sex hormones. II. Biochemical Journal. 1936; 30: 1977-1990.
2 Ott, A.C., Kuizenga, M.H., Lyster, S.C., and Johnson, B.A. Testosterone β-cyclopentylpropionate: a new long-acting androgen. J Clinical Endocrinol Metabolism. 1952; 12: 15-27.
3 Winborn, W.B., Sheridan, P.J. and McGill, H.C. Sex steroid receptors in the stomach, liver, pancreas and gastrointestinal tract of the baboon. Gastroenterology. 1987; 92: 23-32.
4 Pelletier, G. Localization of androgen and estrogen receptors in rat and primate tissues. Histo Histopathol. 2000; 15: 1261-1270.
5 Roy, A.K., Lavronvsky, Y., Song, C.S., Chen, S., Jung, M.H., Velu, N.K., Bi, B.Y., Chatterjee, B. Regulation of androgen action. Vitamins and Hormones. 1999; 55: 309-352.
6 Revelli, A., Massobrio, M., and Tesarik, J. Nongenomic actions of steroid hormones in reproductive tissues. Endocrine Reviews. 1998; 19: 3-17.
7 Toth, M, Zakar, T. Classification of anabolic steroids using the method of competitive metabolism. Exp Clin Endocrinol. 1986; 87:125-132.
8 Wilson, J.D. 1996. Androgens. In: Hardman, J.G., Limbard, L.E., Molinoff, P.B., Ruddon, R.W. and Gilman, A.G. (Eds.) Goodman and Gilman's The Pharmacological Basis of Therapeutics (9th Ed.). MacMillan Publishing Co., Inc., New York, NY/Collier MacMillan Canada, Ltd. Toronto, ON. pp/ 1441-1457.
9 Shahidi, N. A review of the chemistry, biological action, and clinical applications of anabolic-androgenic steroids. Clin Therapeutics. 2001; 23: 1355-1390.
10 Mainwaring, W.I.P., Haining, S.A., and Harper, B. 1988. In: Cooke, B.A., King, R.J.B. and van der Molen, H.J. (eds.) Hormones and Their Actions, Part I. Elsevier Science Pub. Chapter 11, pp. 169-196.
11 Mooradian, A.D, Morley, J.E., and Korenman, S.G. Biological Actions of Androgens. Endocrine Reviews. 1987; 8(1); 1-28.
12 Staub, N.L. and De Beer, M. The role of androgens in female vertebrates. Gen Comp Endocrinol. 1997; 108: 1-24.
131313 Rittmaster, R.S. 1997. Peripheral actions of Androgens. In: Azziz, R., Nestler, J.E. and Dewailly, D. (eds.) Androgen Disorders in Women. Lippincott-Raven Pub. Chapter 7, pp. 63-71.
14 Sherwin, B.S. 1996. Androgen Use in Women. In: Bhasin, S., Gabelnick, H.L., Spieler, J.M., Swerdloff, R.S., Wang, C., and Kelly, C. (Eds.) Pharmacology, Biology, and Clinical Applications of Androgens. Wiley-Liss, Inc. New York, NY. pp. 319-332.
15 Sarrel, P.M. Psychosexual effects of menopause: Role of androgens. Amer J Obstet Gynecol. 1999; 180:S319-S324.
16 Borst, S.E., Lee, J.H. and Conover, C.F. Inhibition of 5α-reductase blocks prostate effects of testosterone without blocking anabolic effects. Am J Physiol Endocrinol Metab. 2005; 288:E222-E227.
17 Labrie, F., Belanger, A., Luu-The, V., Labrie, C., Simard, J. Cusan, L., Gomez, J.-L., and Candas, B. DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: Its role during aging. Steroids. 1998; 63: 322-328.

18 Simpson, E.R. Role of aromatase in sex steroid action. J Molecular Endocrinol. 2000; 25: 149-156.
19 Balthazart, J., and Ball, G.F. New insights into the regulation and function of brain estrogen synthase (aromatase). Trends Neurosci. 1998.; 21: 243-249.
20 Garban H, Marquez D, Cai L, Rajfer J, Gonzalez-Cadavid NF. Restoration of normal adult penile erectile response in aged rats by long-term treatment with androgens. Biol Reprod 1995;53:1365-1372.
21 Lindzey J, Kumar MV, Grossman M, Young C, Tindall DJ. Molecular Mechanisms of androgen action. In Steroids, G litwak, ed. Academic Press. Vitamins and Hormones: Advances in Research and Applications, 1994;;49:383-432.
22 Grinspoon, S., Corcoran, C., Askari, H., Schoenfeld, D., Wolf, L., Burrows, B., Walsh, M., Hayden, D., Parlman, K., Anderson, E., Basgoz, N., and Klibanski, A. Effects of Androgen Administration in Men with the AIDS Wasting Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med. 1998; 129(1): 18-26.
23 Kasra, M. and Grynpas, M.D. The effects of androgens on the mechanical properties of primate bone. Bone. 1995; 17: 265-270.
24 Downs, R.W. 1997. Bone mass, osteoporosis and androgen excess. In: Androgen Excess Disorders in Women, Azziz, R., Nestler, J.E. and Dewailly, D., eds. Lippincott-Raven, Philadelphia; Chapter 67, pp, 689-694.
25 Vanderschueren D, Van Herck E, Suiker AMH, Visser WJ. Bone and mineral metabolism in aged male rats: short and long term effects of androgen deficiency. Endocrinology. 1992;120:2906-2916.
26 Azzarolo, A.M., Mircheff, A.K., Kaswan, R.L., Stanczyk, F.Z., Gentschein, E., Becker, L. Nassir, B. and Warren, D.W. Androgen support of Lacrimal Gland Function. Endocrine. 1997; 6:39-45.
27 Sullivan, D.A., Sullivan, B.D., Evans, J.E. et.al. Androgen deficiency, meibomian gland dysfunction, and evaporative dry eye. Ann NY Acad Sci. 2002; 966: 211-222.
28 Isgor, C. and Sengelaub, D.R. Prenatal gonadal steroids affect adult spatial behavior, CA1 and CA3 pyramidal cell morphology in rats. Hormones Behavior. 1998; 34: 183-198.
29 Garcia-Segura, L.M., Chowen, J.A., Parducz, A., and Naftolin, F. Gonadal hormones as promoters of structural synaptic plasticity: cellular mechanisms. Prog Neurobiol. 1994; 44: 279-307.
30 Leranth, C., Roth, R.H., Elswoth, J.D., Naftolin, F., Horvath, T.L., and Redmond, D.E. Estrogen is essential for maintaining nigrostriatal dopamine neurons in primates: implications for Parkinson's Disease and memory. J Neuroscience. 2000; 20: 8604-8609.
31 Keast, J.R. Effects of testosterone on pelvic autonomic pathways: progress and pitfalls. J Autonom Nerv System. 1999; 79: 67-73.
32 Pelletier, G. Localization of androgen and estrogen receptors in rat and primate tissues. Histo Histopathol. 2000; 15: 1261-1270.
33 Adams, L.A., Vician, L., Clifton, D.K., and Steiner, R.A. Testosterone regulates pro-opiomelanocortin gene expression in the primate brain. Endocrinology. 1991; 128: 1881- 1886.

34 Goudsmit, E., Filers, E., Swaab, D.F. Changes in vasopressin neurons and fibers in aging and Alzheimer's Disease: reversibility in the rat. Progress Clin Biol Res. 1989; 317: 1193-1208.
35 Rubinow, D.R. and Schmidt, P.J. Androgens, brain and behavior. Amer J Psychiatry. 1996; 153: 974-984.
36 Papasozomenos, S.C. The heat shock-induced hyperphosphorylation of τ is estrogen-independent and prevented by androgens: implications for Alzheimer disease. Proc Nat Acad Sci. 1997; 94:6612-6617.
37 Rubinow, D.R. and Schmidt, P.J. Androgens, brain and behavior. Amer J Psychiatry. 1996; 153: 974-984.
38 Wallen, K. Nature needs nurture: the interaction of hormonal and social influences on the development of behavioral sex differences in rhesus monkeys. Hormones Behavior. 1996; 30: 364-378.
39 Besa, E.C. Hematologic Effects of Androgens Revisited: An Alternative Therapy in Various Hematologic Conditions. Hematology. 1994; 31(2): 134-145.
40 Fried, W. and Morley, C. Effects of androgenic steroids on erythropoiesis. Steroids. 1985; 46: 799-826.
41 Wunderlich, F., Benten, W.P, Lieberherr, M., Guo, Z., Stamm, O., Wrehlke, C., Sekeris, C.E., Mossmann, H. Testosterone signaling in T cells and macrophages. Steroids. 2002; 67: 535-538.
42 Olsen, N.J. and Kovacs, W.J. Gonadal steroids and immunity. Endocrine Reviews. 1996; 17: 369-384.
43 Somboonporn, W. and Davis, S.R. Testosterone effects on the breast: Implications for testosterone therapy for women. Endocrine Rev. 2004; 25:374-388.
44 Liao, D.J. and Dickson, R.B. Roles of androgens in the development, growth and carcinogenesis of the mammary gland. J Steroid Biochem Molecular Biol. 2002; 80: 175-189.
45 Labrie, F., Luu-The, V., Labrie, C., Belanger, A., Simard, J., Lin, S.X. and Pelletier, G. Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. Endocrine Rev. 2003; 24:152-82.
46 Melchert, R. B. and Welder, A.A. Cardiovascular effects of androgenic-anabolic steroids. Med Sci Sports Exerc. 1995; 27: 1252-1262.
47 Bagatell, C.J. and Bremner, W.J. Androgens in men - uses and abuses. New England J Medicine. 1996; 344: 707-714.
48 Narducci, W.A., Wagner, J.C., Hendrickson, T.P. and Jeffrey, T.P. Anabolic steroids - a review of the clinical toxicology and diagnostic screening. Clin Toxicol. 1990; 28: 287-310.
49 Ashcroft, G.S. and Mills, S.J. Androgen receptor-mediated inhibition of cutaneous wound healing. J Clin Invest. 2002; 110: 615-624.

50 Ishak, K.G. and Zimmerman, H.J. Hepatotoxic effects of the anabolic/ androgenic steroids. Seminars in Liver Disease. 1987; 7: 230-236.
51 Razmara A, Krause D.N. and Duckles S.P. Testosterone augments endotoxin-mediated cerebrovascular inflammation in male rats. Am J Physiol Heart Circ Physiol. 2005; 289: H1843-H1850.
52 Ando, S., De Amicis, F., Rago, V., Carpino, A., Maggiolini, M., Panno, M.L. and Lanzino, M. Breast cancer: from estrogen to androgen receptor. Mol Cell Endocrinol. 2002; 193: 121-128.
53 Mukherjee, T., Dinh, H., Chaudhuri, G. and Nathan, L. Testosterone attenuates expression of vascular cell adhesion molecule-1 by conversion to estradiol by aromatase in endothelial cells: Implications in atherosclerosis. Proc Nat Acad Sci. 2002; 99: 4055-4060.
54 Tep-areenan, P., Kendall, D.A. and Randall, M.D. Testosterone-induced vasorelaxation in the rat mesenteric arterial bed is mediated predominantly via potassium channels. Brit J Pharmacol. 2002; 135: 735-740.
55 Pham, T.V., Sosunov, E.A., Anyukhovsky, E.P., Danilo, P. and Rosen, M.R. Testosterone diminishes the proarrhythmic effects of dofetilide in normal female rabbits. Circulation. 2002; 106: 2132-2136.
56 Carnes C.A. and Dech, S.J. Effects of dihydrotestosterone on cardiac inward rectifier K+ current. Int J Andrology. 2002; 25: 210-214.
57 Nakamura, J. Lu, Q., Aberdeen, G., Albrecht, E. and Brodie, A. The effect of estrogen on aromatase and vascular endothelial growth factor messenger ribonucleic acid in the normal nonhuman primate mammary gland. J Clin Endocinol Metab. 1999; 84: 1432-1437.
58 Tamimi, R.M., Hankinson, S.E., Chen, W.Y., Rosner, B. and Colditz, G.A. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. Arch Intern Med. 2006; 166:1483-1489.
59 Neumann, F. Early indicators for carcinogenesis in sex-hormone-sensitive organs. Mut Res. 1991; 248: 341-356.
60 Xie, B., Tsao, S.W. and Wong, Y.C. Sex hormone-induced mammary carcinogenesis in female nobel rats: Role of androgens. Carcinogenesis. 1999; 20: 1597-1606.

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

/s/

LAURIE L MCLEOD FLYNN
06/01/2016

MUKESH SUMMAN
06/01/2016
Nonclinical Supports AP

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	208088
Drug Name:	TLANDO (Testosterone Undecanoate)
Indication(s):	Oral treatment of adult male hypogonadism
Applicant:	Lipocine Inc.
Date(s):	Submission Date: August 28, 2015; PDUFA Date: June 28, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Weiya Zhang, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Martin Kaufman, M.D., Clinical Reviewer Suresh Kaul, M.D., Clinical Team Leader
Project Manager:	Jeannie Roule

Keywords: Clinical studies, NDA review

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

Study LPCN 1021-13-001 provides evidence demonstrating the efficacy of the twice a day (BID) 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 ($C_{avg0-24h}$) 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 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 C_{oax} less than 1500 ng/ld. 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 $C_{max0-24h}$ was greater than 2500 mg/ld. while it requires no subjects in this category.

From a statistical perspective, the study provides adequate evidence in support of the efficacy of LPCN 1021 oral capsules in the treatment of adult male hypogonadism.

2 INTRODUCTION

2.1 Overview

In this application, Leporine Inc. is seeking approval of LPCN 1021 oral capsules in the treatment of adult male hypogonadism (submission serial#0000, dated 28 August 2015).

The submission consists of one multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group, efficacy and safety study in adult hypo gonadal male subjects. Table 1 presents a brief study summary.

Table 1: Brief Summary of Clinical Study for LPCN 1021

Study Number (Country/#Sites) Date First Subject Enrolled, Date last Subject Completed	Subject Population	Treatment	Safety Population
LPCN 1021-13-001 (US/40) 7 February 2014, 30 April 2015	Male subjects aged 18 to 80 years of age with a BMI less than 38 kg/m^2 and documented onset of hypogonadism before age 65 who had morning serum total testosterone < 300 ng/ld.	LPCN 1021 Androgen 1.62%	210 105

Source: Statistical Reviewer's listing.

The study was designed to demonstrate the efficacy of LPCN 1021 oral capsule for the treatment of adult male hypogonadism.

2.2 Data Sources

The application was submitted electronically. The submitted SAS datasets were completed and well documented. The review items are located in the CDER Electronic Document Room as described below:

- The completed study report is located at \\CDSESUB1\evsprod\NDA208088\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\testostero\5351-stud-rep-contr\1021-13-00 under submission dated 28 August 2015 (eCTD Sequence Number 0000)
- Raw and derived datasets used for analysis and the datasets define files are located at \\CDSESUB1\evsprod\NDA208088\0000\m5\datasets\1021-13-00\tabulations\sdtm and \\CDSESUB1\evsprod\NDA208088\0000\m5\datasets\1021-13-00\analysis\adam under submission dated 28 August 2015 (eCTD Sequence Number 0000)
- SAS program to generate analysis datasets and tables, figures, and listings in the clinical study reports is located at \\CDSESUB1\evsprod\NDA208088\0000\m5\datasets\1021-13-00\analysis\adam\programs under submission dated 28 August 2015 (eCTD Sequence Number 0000).
- Efficacy analysis report using multiple imputations is located at \\CDSESUB1\evsprod\NDA208088\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\testostero\5353-rep-analys-data-more-one-stud\mbi under submission dated 28 August 2015 (eCTD Sequence Number 0000).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets and definition files are accessible. I was able to reproduce the efficacy results as presented in the study report.

3.2 Evaluation of Efficacy

The Applicant has submitted one pivotal clinical study (LPCN 1021-13-001) to demonstrate the efficacy and safety of LPCN 1021 oral capsules for the treatment of adult male hypogonadism.

3.2.1 Study Design and Endpoints

Studies LPCN 1021-13-001 was a multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group, efficacy and safety study in adult hypogonadal male subjects. Eligible subject were adult men between 18 and 80 years of age and a BMI less than 38 $kg/m^2$with documented onset of hypogonadism before age 65 who had morning serum total testosterone < 300 ng/dL based on 2 consecutive blood samples on 2 separate days. Subjects were also to have been naïve to androgen replacement or had discontinued current treatment and completed a washout period.

Approximately 300 subjects were to be enrolled to meet scientific and regulatory objectives. After meeting the selection criteria, the subjects were to be randomly assigned in a 2:1 ratio such that 200 subjects received LPCN 1021 (oral TU) and 100 subjects received AndroGel 1.62% (testosterone topical gel, active control) for 52 weeks. Analysis of efficacy was carried out in subjects receiving LPCN 1021 after 13 weeks of treatment.

All subjects taking LPCN 1021 started at the same dose of 225 mg (2 capsules of 112.5 mg) taken twice daily approximately 12 hours apart (total daily dose of 450 mg) and approximately 30 minutes after morning and evening meals with water. Dose titration was based on an evaluation of the subject's serum total testosterone (T) concentrations obtained after approximately 3 and 7 weeks of treatment. For the Week 3 (-2 to +5 days) and Week 7 (-2 to +5 days) visits, subjects were confined to the clinic for approximately 26 hours to undergo intensive 24-hour PK profile blood sampling. Dose adjustments were implemented approximately 1 week (-2 to +5 days) after the intensive PK sampling performed during the Week 3 and Week 7 visits (i.e., dose changes were made during the Week 4 and Week 8 visits).

Dose titration was based on the maximum measured serum T concentration (C_{max}) and the 24-hour average serum T concentration ($C_{avg0\text{-}24h}$) as follows:

- If $C_{avg0\text{-}24h} < 300$ ng/dL, dose was titrated upward by 75 mg/dose; or
- If $C_{avg0\text{-}24h} > 1140$ ng/dL, dose was titrated downward by 75 mg/dose; or
- If $C_{max} > 1500$ ng/dL, dose was titrated downward by 75 mg/dose regardless of the $C_{avg0\text{-}24h}$; or
- If $C_{avg0\text{-}24h} = 300$ to 1140 ng/dL and $C_{max} \leq 1500$ ng/dL, dose was not changed.

Efficacy Endpoints

The primary efficacy endpoint was 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 secondary efficacy endpoints were 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 C_{max} at 0 to 12 hours, 12 to 24 hours, and 0 to 24 hours ($C_{max0\text{-}12h}$, $C_{max12\text{-}24h}$, and $C_{max0\text{-}24h}$, respectively) were the following:

1. < 1500 ng/dL in $\geq 85\%$ of all subjects
2. between 1800 and 2500 ng/dL in $\leq 5\%$ of subjects
3. ≤ 2500 ng/dL in all subjects treated

Additional endpoints included responses to the Short Form 36 (SF-36), International Prostate Symptom Score (I-PSS), and Psychosexual Daily Questionnaire (PDQ).

3.2.2 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

($C_{avg0-24h}$ or C_{max}). 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. 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.

Assessment of Primary Efficacy Endpoints

The primary endpoint was summarized for LPCN 1021 treatment group. The target minimum acceptable percentage was 75% with the lower bound of the 95% (2-sided) confidence interval of this estimate of 65% or more to conclude that the LPCN 1021 treatment was efficacious. It was pre-specified in the Statistical Analysis Plan (SAP) that Asymptotic (rather than exact) confidence intervals were to be used in all cases unless stated otherwise. The primary efficacy analysis was conducted using the EPS and additional sensitivity analyses were also conducted using FAS, PK set and PPS datasets. Applicant also provided sensitivity analysis from model-based Multiple Imputation (MI) per statistical reviewer's request through phase 3 protocol review (dated 3 April 2015 for IND106476).

Sample Size Calculation

The sample size for this study was based on the primary efficacy parameter: the incidence of and lower bound of the binomial confidence interval for the percentage of subjects achieving serum T concentrations within the normal range. Assuming the primary efficacy endpoint was to achieved (≥ 75% of subjects have normal T concentrations) the sample of 200 subjects exceeded the number needed to result in the lower bound of a 95% two-sided binomial confidence interval being no less than 65%. The additional subjects were included to obtain a reasonable safety profile.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

A total of 315 subjects were randomly assigned to treatment: 210 were assigned to LPCN 1021 and 105 were assigned to AndroGel 1.62%. Subject disposition with reasons for premature study discontinuation is described in Table 2. About 61.9% subjects in the LPCN 1021 completed the 52-week study. High percentage of discontinuations was noted in this study, with approximately

38% and 32% in LPCN 1021 and AndroGel treated subjects, respectively. About 75% subjects in the LPCN 1021 group had week 13 efficacy assessment. The most common reasons for premature discontinuation in the LPCN 1021 were withdrawal of consent (13.8%), "Other" reasons (8.6%), and lost to follow-up (6.2%).

Table 2: Subject Disposition (All Enrolled Subjects)

Status	LPCN 1021 n (%)	AndroGel 1.62% n (%)	Total n (%)
Randomly assigned to treatment	210	105	315
Received treatment	210 (100)	104 (99.0)	314 (99.7)
Completed 52-week study	130 (61.9)	71 (67.6)	201 (63.8)
Subjects with week 13 efficacy assessment[a]	157 (74.8)	NA	NA
Discontinued during 52-week study	80 (38.1)	34 (32.4)	114 (36.2)
Consent withdrawn	29 (13.8)	9 (8.6)	38 (12.1)
Lost to follow-up	13 (6.2)	12 (11.4)	25 (7.9)
C_{max} > 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/dL or with CfB > 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	3 (1.4)	0	3 (1.0)
Heath risk to subject with continued participation (including adverse events)	3 (1.4)	1 (1.0)	4 (1.3)
Other reasons	18 (8.6)	8 (7.6)	26 (8.3)

Source: Table 13 in clinical study report.
[a] Reviewer's analysis.

The number of subject in the analysis datasets are summarized in Table 3. There were 151 subjects were available in the EPS dataset.

Table 3: Datasets for Analysis

Status	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)

Source: Table 17 in clinical study report.

Demographic data and baseline characteristics of all subjects randomly assigned presented by treatment were summarized in Appendix Table 10. The mean age at baseline was 53.1 years, with about 10% 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 LPCN 1021 and AndroGel 1.62% were similar, although a slightly larger percentage of subjects randomly assigned to AndroGel 1.62% than LPCN 1021 were considered obese (BMI ≥ 30 kg/ m^2: 63.8% vs 56.2%).

Reviewer's Comment

Note that no efficacy comparison was planned between Lipocine and Androgel 1.62% gel, the latter was included for safety evaluation only. Effect of high discontinuation rate on efficacy will be one of the focuses of this review.

3.2.4 Results and Conclusions

Primary efficacy Endpoint

As pre-specified in the protocol, the success criteria were that at least 75% percent of subjects achieve T in the normal range. Table 4 shows the efficacy results using EPS as the efficacy analysis dataset. It was specified in the SAP that asymptotic confidence intervals were to be used for the efficacy analysis, but instead, exact confident interval was provided in the clinical study report (CSR). The difference is minimal and did not affect the study result.

87.4% of subjects achieved a 24-hour average serum T concentration within the normal range at Week 13 with the lower bound of the 95% CI of 81.1% (Table 4), which met the criterion of demonstrating efficacy.

Table 4: Primary Efficacy Endpoint Analysis: Proportion of LPCN 1021-Treated Subjects Achieving 24-hour Average Serum T Concentration within Normal Range at Week 13 (EPS)

Measure	Target	EPS N=151[a]
Subjects achieving 24-hour average serum T concentration within normal range[b], n (%)	≥ 75%	132 (87.4)
95% CI[c]	≥ 65% (Lower Bound)	81.1, 92.3[d]

Source: Tables 21 in the Clinical Study Report and reviewer's analysis.
[a] Subject LPCN 1021-13-001-(b) (6) did not have a 24-hour average serum T concentration.
[b] Normal Range: 300-1140 ng/dL.
[c] A 95%, 2-sided, binomial CI surrounding the point estimate was calculated.
[d] This CI is from reviewer's analysis that is slightly different from CSR. The calculation of CI in the CSR did not include the subject LPCN 1021-13-001-(b) (6) in EPS. This subject should be included following the EPS definition although he had only post-baseline C_{max} and no C_{avg}.

As noted earlier, to investigate the potential impact of protocol deviations and the high discontinuation rate on efficacy , sensitivity analyses were performed for the primary endpoint using the safety set, FAS, and PPS, and model-based multiple imputation based on safety set (Table 5). Results from the sensitivity analyses were similar to those obtained using the EPS dataset, that is, the proportion of subjects who achieved a 24-hour average serum T concentration within the normal range was greater than 75% target, and the lower bound of the CI was also greater than 65% from all the sensitivity analyses.

Table 5: n (%) of Subjects achieving 24-hour average serum T concentration within normal range [300, 1140] ng/dL

Analysis dataset	N	Respond rate n (%)	95% CI (%)
Safety Set	210	168 (80.0)	(73.9, 85.2)
Full Analysis Set	193	168 (87.0)	(81.5, 91.4)[a]
Efficacy Population Set	151	132 (87.4)	(81.1, 92.3) [a]
Per-Protocol Set	130	114 (87.4)	(80.8, 92.8)
Multiple Imputation based on safety set	210	87.3	(81.4, 91.5)

Source: Tables 21, 22, 14.2.3.2, 14.2.3.5 in the clinical study report, Statistical Analysis Plan for Primary Endpoint Utilizing Model-Based Multiple Imputation Approach, and reviewer's analysis.
[a] This CI is from reviewer's analysis that is slightly different from CSR. The calculation of CI in the CSR did not include the subject LPCN 1021-13-001-(b) (6) in EPS. This subject should be included following the EPS definition although he had only post-baseline Cmax and no Cavg.

Secondary efficacy Endpoint

The results for LPCN 1021-treated subjects who achieved C_{max} values within the predetermined limits are displayed in Table 6. The target for the proportion of subjects with C_{max} < 1500 ng/dL (≥ 85%) was not met in general for LPCN 1021 for $C_{max0\text{-}24h}$, there were 82.8% subjects with C_{max} less than 1500 ng/dL while it was met for $C_{max0\text{-}12h}$, $C_{max12\text{-}24h}$. The proportion of subjects with C_{max} between 1800 and 2500 ng/dL met the target of ≤ 5% for all 3 measures (range: 2.0%-4.6%). There were 3 (2.0%) subjects whose $C_{max0\text{-}24h}$ greater than 2500 mg/dL. These 3 subjects were LPCN 1021-13-001-(b) (6) LPCN 1021-13-001-(b) (6) and LPCN 1021-13-001-(b) (6) The clinical assessment to evaluate the safety aspect of these 3 subjects can be found in Clinical Reviewer's report.

Table 6. Proportion of LPCN 1021-Treated Subjects Achieving Maximum Serum Total T Concentrations within Predetermined Limits at Week 13 (Efficacy Population Set)

Measure	Target	$C_{max0\text{-}24h}$ N = 151	$C_{max0\text{-}12h}$ N = 151	$C_{max\ 12\text{-}24h}$ N = 151
C_{max} <1500 ng/dL, n (%) 95% CI[a]	≥ 85%	125 (82.8) (75.8, 88.4)	135 (89.4) (83.4, 93.8)	135 (89.4) (83.4, 93.8)
1800 ≤ C_{max} ≤ 2500 ng/dL, n (%) 95% CI[a]	≤ 5%	7 (4.6) (1.9, 9.3)	4 (2.6) (0.7, 6.6)	3 (2.0) (0.4, 5.7)
C_{max} > 2500 ng/dL,n (%) 95% CI[a]	0%	3 (2.0) (0.4, 5.7)	3 (2.0) (0.4, 5.7)	1 (0.7) (0.0, 3.6)

Key: CI = confidence interval; C_{max} = maximum observed serum concentration; T = testosterone.
[a] A 95%, 2-sided, binomial CI surrounding the point estimate was calculated.
Source: Table 14.2.4.5, Table 14.2.4.13, Table 14.2.4.17 in the clinical study report.

3.3 Other Special/Subgroup Populations

Subgroup analyses were also conducted on the primary efficacy endpoint to evaluate inference sensitivity. The proportion of LPCN 1021-treated subjects grouped by BMI category achieving a $C_{avg0\text{-}24h}$ within the normal range up to Week 13 are presented for the EPS and FAS in Table 7 . Overall, 92.2% of non-obese subjects (BMI < 30 kg/ m^2) and 83.9% of obese subjects (BMI ≥ 30 kg/ m^2) achieved C_{avg} within the normal range. The same data are presented for the FAS in the

Table 7. Proportion of subjects with T within normal range was numerically higher in the non-obese subjects than the obese subjects.

Table 7. Proportion of LPCN 1021-treated Subjects Achieving 24-Hour Average Serum Total Testosterone Concentrations within Normal Range up to Week 13 by BMI Category (EPS and FAS)

BMI Category	Statistic	EPS	FAS
	N	**64**	**82**
< 30 kg/m^2	n (%)	59 (92.2)	73 (89.0)
	95% CI	(82.7, 97.4)	(80.2, 94.9)
	N	**87**	**111**
≥ 30 kg/ m^2	n (%)	73 (83.9)	95 (85.6)
	95% CI	(74.5, 90.9)[a]	(77.6, 91.5)[a]

Source: Table 14.2.3.6, and Table 14.2.3.7 in the clinical study report and reviewer's analysis
[a] This CI is from reviewer's analysis that is slightly different from CSR. The calculation of CI in the CSR did not include the subject LPCN 1021-13-001-(b) (6) in EPS. This subject should be included following the EPS definition although he had only post-baseline Cmax and no Cavg. .

Clinical reviewer noted that the normal range for testosterone level baseline level in the ADLB analysis dataset was [241, 827] ng/dL other than [300, 1140] ng/dL. If we use the laboratory normal range to identify the subjects who were hypogonadal (baseline T less than 241 ng/dL) at baseline, the proportion of LPCN 1021-Treated subjects achieving 24-hour average serum testosterone concentration within normal range of [300, 1140] ng./dL at Week 13 is listed in Table 8. The response rate is greater than 75% with lower 95% confidence level greater than 65% for all analysis datasets.

Table 8: Proportion of subjects achieving 24-hour average serum T concentration within normal range [300, 1140]ng/dL for subjects whose baseline T level less than 241 ng/dL

		Respond rate	
Analysis dataset	**N**	**n (%)**	**95% CI (%)**
Safety Set	138	108 (78.3)	(70.4, 80.8)
Full Analysis Set	126	108 (85.7)	(78.4, 91.3)
Efficacy Population Set	97	84 (86.6)	(78.2, 92.7)
Per-Protocol Set	82	71 (86.6)	(77.3, 93.1)

Source: reviewer's analysis.

During review, the Clinical Pharmacology Reviewer and the Statistical Reviewer noted the baseline T values were different between ADLB and ADPC datasets. An IR letter was sent to Applicant on 18 May 2016 for clarification. Applicant responded on 20 May 2016:

(b) (4)

(b) (4)

A sensitivity analysis was conducted using the baseline T values from ADPC dataset; there would be 102 subjects in the EPS and 132 in FAS. The efficacy results are shown in Table 9. The response rate is greater than 75% with lower 95% confidence level greater than 65% for both analysis datasets.

Table 9: Primary Efficacy Endpoint Analysis: Proportion of LPCN 1021-Treated Subjects Achieving 24-hour Average Serum T Concentration within Normal Range at Week 13 – Baseline from ADPC dataset

Measure	Target	EPS N=102	FAS N=132
Subjects achieving 24-hour average serum T concentration within normal range, n (%)	≥ 75%	86 (84.3)	111 (84.1)
95% CI	≥ 65% (Lower Bound)	75.8, 90.8	76.7, 89.9

Source: reviewer's analysis.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

One minor statistical issue was identified in the NDA review. It was specified in the SAP that Asymptotic (rather than exact) confidence intervals were to be used in the efficacy analysis. Actually the exact confidence interval was provided in the CSR. However, the difference was minimal and had no effect on the study results.

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

4.2 Collective Evidence

Study LPCN 1021-13-001 provides evidence demonstrating the efficacy of the twice a day (BID) 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 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.

4.3 Conclusions and Recommendations

From a statistical perspective, the study provided evidence in support of the efficacy of LPCN 1021 oral capsules in treatment of adult male hypogonadism.

APPENDIX

Table 10. Demographic and Baseline Characteristics (Randomly Assigned Subjects)

Characteristic	LPCN 1021 N = 210	AndroGel 1.62% N = 105	Overall N = 315
Sex			
Male, n (%)	210 (100)	105 (100)	315 (100)
Age (years)a			
Mean (SD)	52.6 (10.24)	54.2 (9.39)	53.1 (9.98)
≤ 65, n (%)	190 (90.5)	96 (91.4)	286 (90.8)
> 65, n (%)	20 (9.5)	9 (8.6)	29 (9.2)
Weight (kg)			
Mean (SD)	97.1 (14.96)	99.2 (14.78)	97.8 (14.91)
Median	96.2	99.3	97.5
Range	54.7-151.0	43.7-126.1	43.7-151.0
BMI (kg/m2)b			
Mean (SD)	30.8 (3.88)	31.0 (3.88)	30.9 (3.87)
Median	30.7	31.1	30.9
Range	20.8-37.8	15.6-37.9	15.6-37.9
< 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)
Race n (%)			
Asian	3 (1.4)	3 (2.9)	6 (1.9)
Black or African American	32 (15.2)	10 (9.5)	42 (13.3)
White	172 (81.9)	92 (87.6)	264 (83.8)
Other	3 (1.4)	0	3 (1.0)

Key: BMI = body mass index; SD = standard deviation.
Note: Percentages were based on N.
a Age was calculated as the difference between date of birth and date of informed consent, in years.
b BMI was calculated as weight (kg) / height (m)2 at screening.
Source: Table 14.1.2.1.

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

/s/

WEIYA ZHANG
06/01/2016

MAHBOOB SOBHAN
06/01/2016