TLANDO™ (ORAL TESTOSTERONE UNDECANOATE CAPSULES) FOR TESTOSTERONE REPLACEMENT THERAPY IN HYPOGONADAL MEN

NDA 208088

BRIEFING DOCUMENT FOR

BONE, REPRODUCTIVE, AND UROLOGIC ADVISORY COMMITTEE MEETING

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADME	Absorption, distribution, metabolism, and excretion
ALT	Alanine transaminase (SGPT)
AR	Androgen receptor
AST	Aspartate transaminase (SGOT)
AUC	Area under the serum concentration-time curve
BID	Twice daily
BLOCF	Last observation carried forward including baseline
BMI	Body mass index
Cavg	Average serum concentration
CBL	Change from baseline
CI	Confidence interval
Cmax	Maximum observed serum concentration
CRL	Complete response letter
CRP	C-reactive protein
Hs-CRP	High sensitive C-reactive protein
CV	Coefficient of variation
DHT	Dihydrotestosterone
DHTU	Dihydrotestosterone undecanoate
E2	Estradiol
ECG	Electrocardiogram
EOS	End of study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GGT	Gamma glutamyl transferase
GPRD	General Practice Research Database
HCT	Hematocrit
HDL	High density lipoprotein
Hgb	Hemoglobin
HPA	Hypothalamus pituitary axis
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational new drug application
I-PSS	International Prostate Symptom Score
ISS	Integrated safety summary
LC-MS	Liquid chromatography tandem mass spectrometry
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone

LOCF	Last observation carried forward
MACE	Major adverse cardiac event
Max	Maximum value
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum value
NDA	New Drug Application
PDQ	Psychosexual Daily Questionnaire
PK	Pharmacokinetic
POME	Pulmonary oil micro-embolism
PSA	Prostate specific antigen
SAE	Serious adverse event
SD	Standard deviation
SF-36	Short Form-36
SHBG	Sex hormone binding globulin
SOC	System organ class
SS	Safety set
T	Total testosterone (when referring to testosterone concentration)
TEAE	Treatment emergent adverse event
TID	Three times a day
Tmax	Time to maximum observed serum concentration
TRT	Testosterone replacement therapy
TU	Testosterone undecanoate
US	United States

1. EXECUTIVE SUMMARY

1.1 Background

TLANDO™ is an oral capsule containing testosterone undecanoate (TU) and has been developed for the treatment of hypogonadism in adult males. TLANDO is proposed as testosterone replacement therapy (TRT) for the treatment of conditions associated with a deficiency or absence of endogenous testosterone (T) due to primary or hypogonadotropic hypogonadism, as per standard class TRT labeling.

There are various testosterone preparations with different routes of administration available in the United States (US). Each TRT therapy is approved to provide testosterone replacement therapy, but the various TRT agents have unique pharmacokinetic (PK) properties, limitations, risks, and safety concerns. The only oral preparation approved for use in the US are 17-alpha-alkylated drugs that undergo first pass metabolism and thus pose the risk of hepatotoxicity.

There are several challenges to developing a non-17-alpha alkylated oral testosterone formulation with an adequate PK profile, including providing adequate bioavailability, minimizing food effects, and having low variability in serum concentrations. TLANDO is an oral capsule product containing 112.5 mg of TU and a proprietary formulation composed primarily of non-triglyceride based lipids. TLANDO is designed to enable absorption of TU predominantly via the intestinal lymphatic pathway. Testosterone undecanoate is a prodrug delivered as a straight chain fatty acid ester of testosterone, which is not alkylated at the 17-alpha position. After being absorbed via the lymphatics, TU is converted to active testosterone by non-specific esterases.

Currently, TU is available as an injectable product in the US (brand name, Aveed®). Oral TU (Andriol®) is not approved in the US, but has been marketed for more than 20 years outside of the US in more than 80 countries, including Canada, for the treatment of male hypogonadism.[4]

1.2 Original NDA Development Program

Lipocine developed TLANDO for the US market under US IND # 106,476. The TLANDO clinical development program includes 12 clinical trials. A total of 525 hypogonadal men across eight clinical studies, and 66 postmenopausal women across four clinical studies were treated to date with TLANDO. In the original NDA submission (28 August 2015), 10 clinical studies evaluating TLANDO were presented. These studies included:

- Four exploratory single dose clinical studies in 66 postmenopausal women (1021-15-001, S361.1.002, M12-868, and LPCN 1111-15-001)
- Six clinical studies in the target population, 381 hypogonadal men, including a food/fat effect study (14-001), a Phase 2 dose-finding study (M12-778), and a Phase 3 safety and efficacy study (13-001).

The food/fat effect study (14-001, Section 7.2) showed that similar T exposures were observed in each fed/fat condition. Under fasting conditions there was only a small increase in T concentrations. The data demonstrated that TU absorption and subsequent increases in T concentrations were not dependent on the type of meal provided. Meals containing low, medium (standard), and high fat content resulted in consistent and predictable therapeutic levels of T with little variability in relation to food fat content.

In efficacy trials of testosterone replacement products, the traditional efficacy endpoints developed and relied upon for transdermal gels or injectables are pharmacokinetic measures of testosterone and are described below:

- Primary Endpoint:
  - At least 75% of subjects to achieve an average serum T concentration (Cavg) within the normal range with the lower bound of the associated 95% confidence interval (CI) at least 65%.
- Secondary Endpoints:
  - The maximum serum T concentration (Cmax) ≤ 1500 ng/dL in at least 85% of subjects
  - Testosterone Cmax between 1800 and 2500 ng/dL in not more than 5% of subjects
  - Testosterone Cmax > 2500 ng/dL in no subject

A Phase 2 dose-ranging study (M12-778, Section 7.3) demonstrated that 225 mg TLANDO administered twice daily (BID) with a standard meal provided the best overall efficacy profile. No unexpected safety concerns were identified. In this study, twice daily fixed doses of 75 mg, 150 mg, 225 mg and 300 mg were administered over a minimum of 15 days. The study results supported the 225 mg BID dose as optimal:

225 mg BID: 83% of subjects met Cavg targets and the lower bound of the 95% CI for this proportion was 69% (primary endpoint); 88% of subjects had Cmax ≤ 1500 ng/dL; and no subject had Cmax > 1800 ng/dL (secondary endpoint).

75 mg BID and 150 mg BID: did not meet the Cavg targets (only 44% and 47% of subjects, respectively, met Cavg targets).

300 mg BID: met the Cavg efficacy targets (100%) and the lower bound of the 95% CI for this proportion was 79%, but exceeded the allowable Cmax targets (44% of subjects had Cmax >1800 ng/dL).

The original Phase 3 study (13-001, Section 7.4) was a randomized, open-label, active controlled, dose-titration study that randomized 210 subjects to TLANDO treatment and 105 subjects to transdermal Androgel® 1.62% treatment, which was used according to its product label and was included primarily as a safety comparator. TLANDO had a starting fixed dose of 225 mg twice daily with a standard meal. Dose titration of TLANDO was allowed twice, at Week 4 and Week 8 based on average (Cavg) and maximal (Cmax) serum testosterone concentrations determined from 24-hour PK profiles at Week 3 and Week 7. The dose could be titrated up to 300 mg BID, down to 150 mg BID, or remain the same.

From Week 8 onward, all subjects remained on the same dose for the remainder of the study. The primary efficacy endpoint was at Week 13 with therapy to continue for 52 weeks to collect long term safety and patient reported outcome data. Key findings:

- Study 13-001 confirmed the efficacy findings of Study M12-778 for the primary endpoint. Cavg at both Week 3 pre-titration (225 mg BID fixed dosing) and at the primary endpoint at Week 13 post titration (all TLANDO dose groups) resulted in 86% and 88% of subjects, respectively, within the normal range.
- The lower bound of the Cavg 95% CI exceeded the pre-defined limits at both Week 3 (225 mg BID fixed dosing) and Week 13 (post-titration), 81% and 82%, respectively.
- At Week 13, 11.4% of subjects had Cmax between 1800-2500 ng/dL and 4.1% of subjects had Cmax greater than the 2500 ng/dL threshold. A similar result was observed with the Week 3 pre-titration results (11.4% and 4.7% respectively).
- Titration did not improve Cavg or Cmax efficacy outcomes.
- TLANDO was well tolerated and the safety findings were consistent with those observed with AndroGel.

Lipocine performed additional analyses of Study 13-001 to develop an algorithm of titrating subjects in clinical practice based on a single blood draw after the morning dose. This algorithm was submitted in the original New Drug Application (NDA) on 28 August 2015.

1.3 Complete Response Letter and Resubmission Development Program

Following the review of the original NDA, the FDA issued a Complete Response Letter (CRL) on 28 June 2016 (Section 7.5). In the CRL, the FDA identified the generalizability of the titration scheme as the deficiency, and recommended that Lipocine validate the proposed dosing regimen and titration algorithm for real-world use in a clinical study. As per the CRL, the FDA advised:

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

In response to the CRL, additional analyses and modeling and simulations based on Study 13-001 were performed by Lipocine (Section 7.6). These extensive analyses showed that titration based on one or two testosterone samples would have little to no effect on the percentage of Cavg responders or Cmax excursions above the target ranges. A fixed dose regimen would result in similar outcomes in terms of Cavg responders and Cmax outliers versus titration. Additionally, if proven successful in a prospective study, a fixed dose regimen would readily extrapolate to real-world use and avoid issues associated with titration. This conclusion was further supported by the results of Study 13-001 where little difference was observed with the efficacy parameters after a fixed dose period of TLANDO and after a period where TLANDO was titrated.

Based on these analyses and with feedback from the FDA, two fixed dose regimens for TLANDO were proposed for evaluation in two additional pivotal Phase 3 trials: 225 mg BID

and 150 three times daily (TID), each providing the same 450 mg daily dose. These fixed dose regimens were then evaluated in separate prospectively designed, open-label clinical trials (Study 16-002 and Study 16-003). In the Post-Action Meeting Minutes, the Division noted that "*the Sponsor should be able to leverage data from the existing trials to help support safety."* Therefore, the focus of these studies was to evaluate the efficacy of the respective dose regimens.

Study 16-002 (Section 7.7) was an open-label, Phase 3 study, single arm study that used a fixed dose treatment regimen of TLANDO 225 mg BID with meals. The study was designed with inclusion and exclusion criteria that is generally accepted for TRT trials. Patients were not excluded from the study based on body mass index (BMI) status, blood pressure or use of antihypertensive medication. The study enrolled 95 hypogonadal men. Efficacy was demonstrated on the primary endpoint, achieving average T concentrations within the normal range for 80% of subjects. The lower bound of the 95% CI for this endpoint exceeded the predefined limits (72%). The mean (SD) T Cavg was 476 (174) ng/dL, which is within the normal range for Cavg. Efficacy was demonstrated in both obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) patients. For the secondary endpoints, there were a small number of Cmax excursions above the pre-defined thresholds. The exposure to elevated T levels occurred in a small proportion of subjects, were transient, and showed no sign of repeatability. Those subjects with Cmax elevations above the predefined limits did not have an increased risk of adverse events or changes in vital signs or key laboratory parameters based on up to 52 weeks of exposure.

Study 16-003 (Section 7.8) of TLANDO at a fixed dose of 150 mg TID did not meet the primary endpoint with an insufficient percentage of subjects (69%) reaching the normal therapeutic range; thus, supporting the conclusion that 225 mg BID was the correct dose. TLANDO has been extensively studied for its most appropriate regimen, with 225 mg BID dosing found to be optimal.

Multiple studies were cohesive in support of the 225 mg BID fixed dose as the appropriate dosing regimen for effective T repletion in hypogonadal patients. The percentage of subjects (lower limit of 95% CI) on the 225-mg fixed dose who met T Cavg targets was 83% (69%), 86% (81%), and 80% (72%) in Studies M12-778, 13-001, and 16-002, respectively. The Cavg results from Studies 13-001 and 16-002 are consistent with a mean (SD) daily T Cavg of 471 ng/dl (192) and 476 ng/dl (174), respectively.

TLANDO was generally safe and well tolerated in the clinical studies. The commonly reported adverse events were consistent with those reported for AndroGel, the active control in Study 13-001, and expected with TRT products. Adverse events reported with either TLANDO or AndroGel were mainly mild or moderate in severity. Serious adverse were uncommon, diverse in nature, and not attributed to study drug.

Most laboratory results showed no clinically significant changes or when changes were observed, they were generally consistent with AndroGel. Most notably were declines in high density lipoprotein (HDL) and sex hormone binding globulin (SHBG) with TLANDO that were slightly more common that what was observed with AndroGel. These findings were

not correlated with increased cardiovascular risk or signs of excessive androgen activity. There was no evidence of hepatic or gastro-intestinal toxicity and no significant effect on prostate health as measured by prostate specific antigen (PSA), and International Prostate Symptoms Scores (I-PSS).

1.4 Topics of Interest

The FDA has shared some topics of interest for advisory panel input and discussion regarding TLANDO that are described in detail in Section 9 of this briefing document. In addition to presenting the overall safety and efficacy supporting TLANDO dosing of 225 mg BID, the Division has asked Lipocine to focus its discussion on the following items:

Ex-Vivo Conversion of TU to T (Section 9.1).

- Based on an ex-vivo experiment evaluating potential conversion of TU to T, it was determined that conversion of TU to T does not occur during sample processing through serum harvesting when using the recommended sampling collection and handling procedures used in TLANDO clinical trials.

The effect of food on TU absorption (Sections 7.2 and 9.2).

- The effect of food on drug absorption is a key area of interest for lipophilic products administered via the oral route. Study 14-001 demonstrated that while TLANDO needs to be taken with food, it does not require any specific type of meal to be absorbed.

Cardiovascular Risk (Section 9.3)

- There remain unanswered questions about the long-term cardiovascular risk of testosterone replacement therapies; therefore, as with all TRT products, a careful assessment of cardiovascular risk was performed for TLANDO. There were no serious cardiovascular events (including major adverse cardiac events [MACE]) that occurred in the TLANDO clinical program. The FDA has mandated a cardiovascular safety study of approved testosterone products that is currently being planned. This study will help to clarify the impact of TRT on cardiovascular disease.
- A careful assessment of blood pressure was done at FDA's request, and heart rate, lipids, ECGs, and C-reactive protein levels were also assessed. Mean blood pressure over the course of the 52-week Study 13-001 was similar in TLANDO and AndroGel treatment arms and at end of study were slightly lower than baseline in both treatment arms. Hypertension and blood pressure-related adverse events occurred in fewer TLANDO-treated subjects (1.6% and 0.8%, respectively) than AndroGel-treated subjects (4.8% and 1.9%, respectively). A thorough evaluation of systolic and diastolic blood pressures, pulse rate, lipid parameters, ECG findings, and C-reactive protein levels revealed no clinically meaningful or statistically significant differences ($p > 0.05$) between TLANDO and AndroGel.
- Greater reductions in HDL were observed with TLANDO when compared with AndroGel. Other lipid parameters remained practically unchanged. Androgens, particularly T, have been shown to lower HDL levels and this effect is reflected by

cautionary language in the labels of approved T replacement products. The relevance of HDL as a sole surrogate predictor for cardiovascular risk, however remains unclear.

- To further ascertain any increased cardiovascular risk, Lipocine utilized two different risk scores that have been developed to estimate individual 10-year cardiovascular risk, the Framingham Risk Score and the Reynolds Risk Score. These scores take into consideration blood pressure, lipid values, and C-reactive protein (Reynolds). A post-hoc analyses of data from Study 13-001 was performed for each individual subject using both risk calculators at baseline and end of study. The values of the individual scores were used to calculate the mean and 95% CI for the overall study population to assess overall cardiovascular risk. The Framingham Risk Score mean baseline score and change from baseline to the end of study was 16.0 and 0.36 for TLANDO-treated subjects and 19.3 and 0.03 for AndroGel-treated subjects. The Reynolds Risk Score mean baseline score and change from baseline to the end of study was 5.9 and 0.09 for TLANDO-treated subjects and 6.8 and 0.04 for AndroGel-treated subjects. The results of this post-hoc cardiovascular risk assessment indicate that there is no meaningful impact on overall cardiovascular risk with the use of TLANDO over the periods of time available for evaluation.
- Clinical relevance of increases in concentrations of dihydrotestosterone (DHT) and estradiol (E2) observed in some subjects were evaluated (Section 9.4).
- Changes in DHT and E2 from baseline to end of study were either similar to AndroGel or were within the range observed with other TRT products. An analysis of DHT or E2 concentrations and their impact on lipid parameters (including HDL), blood pressure, hemoglobin/hematocrit, SHBG and C-reactive protein revealed no correlation.

Patient monitoring and TLANDO discontinuation guidelines (Section 9.5)

- Appropriate patient monitoring guidelines should be provided to health care practitioners to identify patients who are receiving sub- or supra-therapeutic doses of T and to provide guidance on how to most appropriately treat these patients, including the possibility of discontinuing treatment. Lipocine tested a variety of monitoring approaches based on the results of Study 16-002 and found that a testosterone level measurement performed between 7 to 9 hours after the morning dose correlated best with predicting nonacceptable Cavg exposure. This approach was then applied to Study 13-001, which confirmed its reliability.
- Labeling for TLANDO will therefore advise: “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.”

1.5 Summary

In summary, TLANDO was effective in restoring T levels in hypogonadal men. TLANDO will avoid many of the limitations of current marketed products due to formulation-specific issues such as accidental secondary T topical transference risk observed with transdermal

gels and solutions, or anaphylactic or pulmonary micro-embolism risk associated with injectables. TLANDO will provide clinicians and patients with a fixed-dose oral TRT dosage form that will be familiar, convenient, easy to use, and reliable if taken with any type of meal. TLANDO does not require titration. Monitoring within the first three months can detect the small number of patients who will have subtherapeutic or supratherapeutic T levels. The data will support that overall, approximately 80-85% of patients treated with TLANDO 225 mg BID will be adequately treated, while approximately 10-15%may be subtherapeutic and less than 5% will be supratherapeutic.

The observed safety profile of TLANDO in clinical studies was consistent with the active control and is similar to other approved T replacement products. No unexpected risks specific to TLANDO were observed during the clinical program. TLANDO was not shown to increase blood pressure or cardiovascular risk, and no hepatic safety signals were observed.

In conclusion, Lipocine believes that there is an unmet need for a safe, effective, and convenient oral dosage form of TRT. TLANDO can provide the option for the treatment of hypogonadal men.

2. HYPOGONADISM AND UNMET MEDICAL NEED

2.1 Male Hypogonadism

The Endocrine Society defines hypogonadism in men as "a clinical syndrome that results from failure of the testis to produce physiological levels of T (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic pituitary-testicular axis" (Bhasin 2010). Male hypogonadism, a clinical syndrome resulting from insufficient secretion of T, 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]). Lipocine seeks approval of TLANDO for the treatment of men with classical causes of hypogonadism as per approved class TRT labels.

The Endocrine Society recommends T therapy for men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, muscle mass and strength, and bone mineral density. The Endocrine Society Guidelines recommend that physicians evaluate patients on testosterone replacement (TRT) 3 to 6 months after treatment initiation and then annually thereafter to assess whether symptoms have responded to treatment, and whether the patient is experiencing any adverse effects.

2.2 Testosterone Replacement Therapies

The therapeutic goal of treating hypogonadism is to attain an average serum testosterone concentration over the dosing interval in the normal physiological range. Each of the routes of delivery and formulations that are approved to provide testosterone replacement therapy, have unique pharmacokinetic properties, limitations, risks, and safety concerns. Formulations available in the US include transdermal (gels, solutions, or patches), intramuscular injection, buccal tablets, intranasal, and pellets for implantation (Appendix 1). The most commonly used formulations are gels, and depot T injection products, as evidenced by prescription volume of these products.

Gels are applied with the hands to the shoulders and upper arms and/or abdomen and require daily application and adequate product drying time (2.5 to 5 minutes) prior to getting dressed. In addition, these products can cause skin reactions, and all have the potential for causing secondary exposure to women or children. The latter safety issue has resulted in the inclusion of a black box warning on their labels regarding the risk of transference.

Depot T injection products are formulated in an oil-based vehicle. These formulations do not have the risk of transference, but carry the risk of immediate post-injection reactions such as cough, respiratory distress, and anaphylaxis. The recently approved long-acting depot formulation (AVEED) has a black box warning on its label regarding the immediate post-injection risk of pulmonary oil micro-embolism (POME) and anaphylaxis. The short-acting depot injectable products have the potential to cause sustained supra-physiologic levels of T.

The only oral product currently used in the United States is a 17-alpha-alkyl androgen (methyl testosterone, brand names include: Android®, Methitest®, Testred®). Prolonged use of high doses of these orally active 17-alpha-alkyl androgens has been associated with serious hepatic adverse effects (eg, peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Due to hepatotoxicity and its poor oral bioavailability, methyl testosterone is not widely used.

Other dosage forms and routes of administration also have limitations. Intranasal gel (Natesto®) must be applied to the nostrils three times per day. Buccal tablets have been associated with alterations in taste and gum-related adverse events including irritation, inflammation, and gingivitis. Pellet implants require surgical insertion, which can be painful, introduce risk of scarring and infection, and the pellets may spontaneously extrude (Conway 1988).

2.3 Unmet Medical Need

To date, there is no FDA approved oral TRT product that is not 17-alpha-alkylated. The availability of such an oral product may confer multiple benefits over existing T replacement products including absence of transfer risk, inconvenience for transdermal application, and application site reactions; need for self-injections/doctor's office visit for injections; and a potentially improved safety profile compared with 17-alpha-alkylated androgens (Conway 1998).

Many forms of TRT are available, but compliance is poor. A study by Schoenfeld showed that by six months, only 35 percent of patients were maintained on their transdermal product, and by one year, compliance was down to 13 percent (Schoenfeld 2013). In the case of short lasting injections, a study by Donatucci et al. showed that by 3 months, only 31% of short lasting T injection users were still on therapy (Donatucci 2014).

TLANDO was developed to provide for an effective and safe oral TRT product that could be an attractive therapeutic option for hypogonadal men. A dosage form familiar to patients and easy to use may improve compliance and improve treatment outcomes.

3. PROPOSED INDICATION

TLANDO is proposed for the same indication as other approved TRT products:

TLANDO is indicated for replacement therapy in adult 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 [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) 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.

Limitations of use:

- Safety and efficacy of TLANDO in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.
- Safety and efficacy of TLANDO in males less than 18 years old have not been established.

4. PHARMACEUTICAL DEVELOPMENT

Oral administration of native T generally results in low bioavailability as it is extensively metabolized through pre-systemic first-pass metabolism (Dagget 1978). TLANDO was developed to avoid this first pass metabolism and provide therapeutic levels of T.

TLANDO is an oral capsule product containing 112.5 mg TU employing a proprietary formulation composed of lipids. Testosterone undecanoate is an esterified T derivative that does not undergo extensive first pass metabolism and is orally bioavailable. After oral administration, TU is absorbed into systemic circulation primarily via the lymphatic system following incorporation into chylomicrons (Shackleford 2003). Once within the systemic circulation TU is de-esterified by plasma esterases to T, which becomes available for binding to systemic target tissues.

5. REGULATORY HISTORY

Lipocine developed TLANDO under US Investigational New Drug (IND) application #106,476 filed on 01 April 2010. During the development program, a pre-IND meeting was held on 11 January 2010, a development meeting was held on 15 November 2012, and a pre-NDA meeting was held on 19 March 2015. During these meetings, Lipocine and FDA agreed on a developmental plan for the proposed NDA. In line with the agreements, the proposed nonclinical studies, bioavailability studies, a definitive food effect study, and the pivotal Phase 3 Study 13-001 were completed.

Lipocine Inc., submitted a 505b(2) NDA 208088, to the FDA on 28 August 2015. Subsequently, on 28 June 2016, the FDA issued a Complete Response Letter (CRL). The FDA cited a titration and dosing algorithm related label deficiency. Dose titration in Study 13-001 was based on intensive PK sampling (i.e., 15 blood samples over a 24-hour period). As intensive PK sampling is not a practical titration methodology for real-world use, Lipocine performed analyses of Study 13-001 data to develop a suitable algorithm to titrate subjects in clinical practice based on a single blood draw after the morning dose, and this algorithm was submitted in the original NDA. The FDA recommended that Lipocine validate the proposed dosing regimen and titration scheme for real-world use in a clinical study:

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

In response to the CRL, additional modeling and simulations based on Study 13-001 clinical data were performed. The findings of these analyses were presented and discussed with the FDA on 06 October 2016. Based on these analyses and feedback from the FDA, Lipocine identified a "no titration" fixed dose of 225 mg twice daily with food for further study.

Lipocine conducted two new Phase 3 clinical studies; Study 16-002 evaluated a 225 mg fixed dose two times daily regimen and Study 16-003 evaluated a 150 mg fixed dose three times daily regimen. Both studies provided a total daily dose of 450 mg.

The clinical study protocol (16-002) was submitted to the FDA who provided agreement on the general design and provided some minor recommendations. Lipocine submitted protocol amendments for Study 16-002 to address all FDA comments. These same comments were incorporated into the protocol for Study 16-003 that tested the 150 mg TID regimen.

The updated NDA that included results from the two additional Phase 3 studies (16-002 and 16-003) addressed the items cited in the CRL was submitted to the FDA on 08 August 2017 and is currently under review. The proposed product label submitted in the NDA describes safety findings from Study 13-001 and efficacy findings from Study 16-002. Lipocine is requesting approval of TLANDO with a 225 mg twice daily fixed dosage regimen.

6. NONCLINICAL STUDIES

The safety of TU has been well characterized in a comprehensive battery of nonclinical studies. Lipocine conducted absorption, distribution, metabolism, and excretion (ADME) and toxicology studies including both rat and dog repeat-dose studies as well as ICH-compliant genotoxicity studies. A study to examine the effects of TU on the human androgen receptor (AR) binding assay was also performed.

It has been determined that T is the primary active metabolite derived from orally-administered TU and that dihydrotestosterone (DHT) is the primary metabolite of T. The primary actions of T have been described in the literature. The human AR binding assay indicated that TU affinity to bind to the human AR receptor is several-fold lower than that of T. In addition, the nonclinical pharmacology and safety studies of orally-administered TU in rat and dogs indicate that TU and subsequent metabolites (e.g., DHTU) does not present a safety concern over and beyond the effects of testosterone.

7. CLINICAL STUDIES

7.1 Clinical Development Strategies and Efficacy Endpoints

Traditionally, clinical efficacy and safety studies of hypogonadism therapy enroll men with a previous diagnosis of hypogonadism and confirmed morning serum T concentrations below 300 ng/dL. The pivotal trials can be conducted with or without a comparator and are designed to show that administration of the investigational TRT product meets the pharmacokinetic endpoints that were defined by the FDA, over time, based on their evolving understanding of the performance of injectable and transdermal products. Validated bioanalytical methodology was used for the PK analyses. Serum samples were used as the biological matrix. Testosterone was measured using LC-MS/MS. The efficacy endpoints are as follows:

- Primary Endpoint:
  - At least 75% of subjects are to achieve an average serum T concentration (Cavg) within the normal range with the lower bound of the associated 95% CI at least 65%.
- Secondary Endpoints:
  - The maximum serum T concentration (Cmax) is to be ≤1500 ng/dL in at least 85% of subjects
  - Testosterone Cmax is to be between 1800 and 2500 ng/dL in not more than 5% of subjects
  - Testosterone Cmax is to be >2500 ng/dL in no subject

Lipocine defined several population analyses sets for analyzing and summarizing data. The analyses sets are defined as follows:

Safety Set (SS): The safety set includes all subjects who were randomized and received a dose of study drug.

Full Analysis Set (FAS): The FAS consists of all subjects enrolled into the study with at least one post baseline efficacy variable data point (Cmax or Cavg).

Efficacy Population Set (EPS): The EPS included all FAS subjects who did not have major protocol deviations.

Pharmacokinetic Set (PK Set): The PK set consists of subjects in FAS who complete the study without major protocol deviations.

Per-Protocol Set (PPS): The PPS included all subjects who completed the study without major protocol deviations.

7.2 Food-Fat Study 14-001

7.2.1 Overview

The effect of food and fat content was evaluated in Study 14-001. The PK objective of this study was:

- To compare serum concentrations of T, DHT, TU, and DHTU following administration of a single oral dose of TLANDO (final formulation) as 2 x 112.5 mg capsules under various food and fat content conditions (low, medium, and high) in hypogonadal males.

This food effect study was a single-center, open-label, randomized, single-dose, 4-period, 4-way crossover study. Fourteen hypogonadal subjects were enrolled into the study and received a single dose of TLANDO, 225 mg oral dose (2 x 112.5 mg capsules) of TU under fasting and fed conditions with different fat content. Fourteen subjects were enrolled and 13 completed the study.

Meal composition is summarized in Table 1.

Table 1. Description of Meals

Meal Description	Total Energy	Carbohydrate	Protein	Fat
	Calories	Quantity in grams (% Total Calories)		
Standard (medium) 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%)

7.2.2 Pharmacokinetic Results

7.2.2.1 Observed Testosterone

Results for T PK parameters, including the area under the serum concentration curve (AUC) and Cmax following fasted and fed/fat conditions are shown in Table 2 and corresponding ratios and 90% geometric mean CIs are provided in Table 3.

Table 2. Pharmacokinetic Parameters for Serum Total Testosterone under Fasted vs Fed Conditions

Parameter	Statistic	Treatment			
		A Standard-Fat Meal	B Low-Fat Meal	C High-Fat Meal	D Fasting Conditions
Cmax (ng/dL)	N	13	13	13	14
	Mean	1560	1570	1680	562
	SD	476	556	738	146
AUC0-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

Table 3. Ratios and 90% Geometric Confidence Intervals for AUC_{0-t} and C_{max} for Observed Total Testosterone

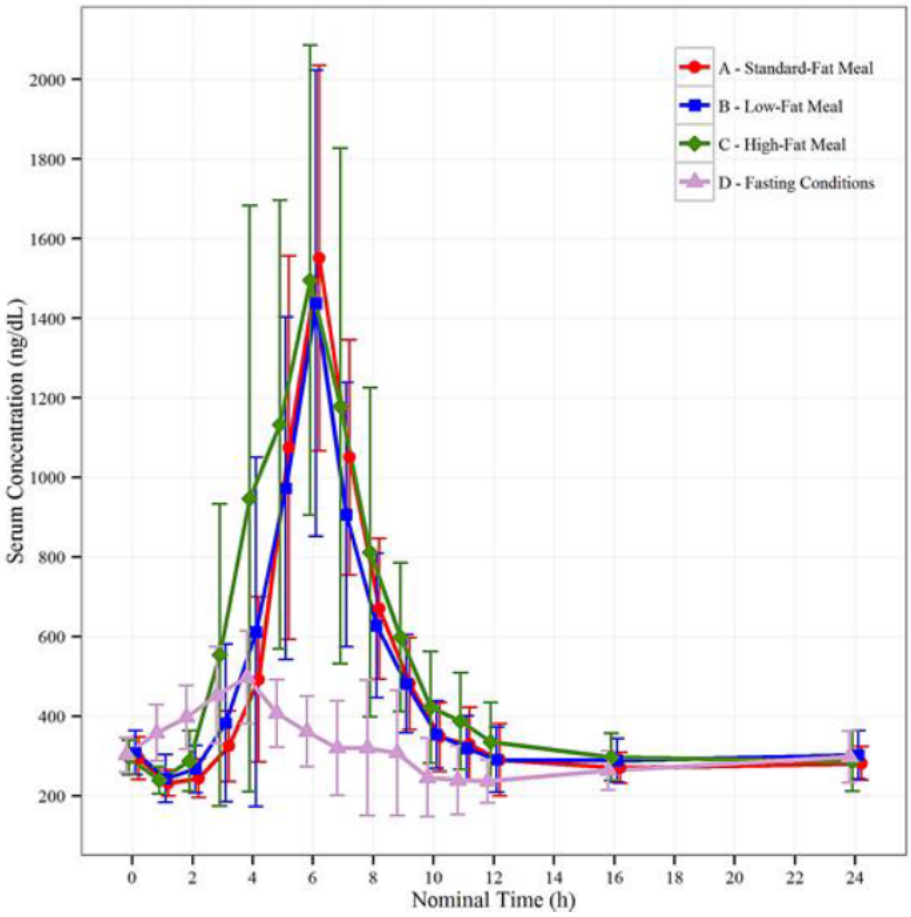
Parameter	Treatment Comparisons[3]	Geo. LSM Ratio[1]	90% Geometric CI[2]	
			Lower	Upper
AUC0-t	Low-fat meal vs. standard-fat meal	98.86%	90.99%	107.42%
	High-fat meal vs. standard-fat meal	114.06%	104.98%	123.93%
	High-fat meal vs. overnight fasting	160.55%	147.76%	174.44%
	Low-fat meal vs. High-fat meal	86.67%	79.77%	94.17%
Cmax	Low-fat meal vs. standard-fat meal	98.26%	82.18%	117.48%
	High-fat meal vs. standard-fat meal	102.72%	85.92%	122.82%
	High-fat meal vs. overnight fasting	282.76%	236.49%	338.07%
	Low-fat meal vs. High-fat meal	95.65%	80.00%	114.36%

Geo=Geometric; LSM=lest square means
1 Calculated using least-squares means according to the formula: e(DIFFERENCE) X 100.
2 90% Geometric Confidence Interval using ln-transformed data.
3A : Standard-fat meal; B : Low-fat meal; C : High-fat meal; D : Fasting conditions.

Similar T exposures were observed in each fed/fat condition. Under fasting conditions there was only a small increase in T concentrations. With food, total T exposure was notably increased under the fed state compared with the fasted state. A key comparison shown in Table 3 is the comparison of TLANDO exposures with a low-fat meal to TLANDO with a high-fat meal. For this comparison, TLANDO exposure for both AUC and Cmax were numerically lower with the low-fat versus high-fat diets, but importantly the lower 90% geometric CIs for these comparisons were 80%, meeting the lower limit of acceptability for bioequivalence.

Figure 1 shows the pharmacokinetic profile of the four dietary conditions.

Figure 1. Mean (±SD) Observed Total Testosterone Serum Concentration-Time Profiles



7.2.2.2 Observed Dihydrotestosterone

Results for the active metabolite DHT PK parameters, including AUC0-t and Cmax following fasted and fed/fat conditions are shown in Table 4. DHT concentrations were similar across each of the fed/fat conditions and lower under fasting conditions.

Table 4. Pharmacokinetic Parameters for Serum DHT under Fasted vs Fed Conditions

Parameter	Statistic	Treatment			
		A Standard-Fat Meal	B Low-Fat Meal	C High-Fat Meal	D Fasting Conditions
Cmax (ng/dL)	N	13	13	13	14
	Mean	169	158	191	69.3
	SD	33.0	43.3	50.2	38.0
AUC0-t (ng*h/dL)	N	13	13	13	13
	Mean	1625.2	1526.0	1972.1	866.01
	SD	346.98	446.70	474.82	401.17

7.2.3 Conclusions

TLANDO when administered under a fed state gives consistent and predictable therapeutic levels of T and DHT with no significant sensitivity to food fat content. Administration of TLANDO under fasted conditions does not appear to be a viable option for dosing as there is a significant reduction in T levels.

The recommended dosage instructions should state that TLANDO should be taken with food.

7.3 Dose Finding Study M12-778

7.3.1 Overview

Dose finding 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).

The study consisted of 5 treatment groups, 75 mg, 150 mg, 225 mg, 300 mg TLANDO, or placebo administered two times daily with a standard meal for 15 or 29 days. Blood sampling was performed on Day 15 to obtain a PK profile and assess efficacy.

A total of 84 healthy adult hypogonadal male subjects were enrolled with 81 subjects completing the study. Subject disposition by dosing regimen and dose group is shown in Table 5.

Table 5. Subject Disposition by Dosing Regimen and Dose Group

	TLANDO or Placebo				
	15 Days of Dosing			29 Days of Dosing	
	Group 1	Group 2	Group 3	Group 4	Group 5
Subject Disposition Category	75 mg	150 mg	225 mg	300 mg	225 mg
No. Subjects Planned	20	20	20	12	12
All Subjects Randomized[a]	20	20	20	12	12
Subjects Completing	19	19	19	12	12
Subjects Terminating	1[b]	1[c]	1[c]	0	0

[a] Subject count include those randomized to TLANDO and placebo
[b] Subject who terminated was randomized to placebo;
[c] Subject who terminated was randomized to TLANDO

7.3.2 Efficacy Results

The mean (SD) PK parameters on Day 15 are shown in Table 6.

Table 6. Pharmacokinetic Parameters Dose Finding Study from M12-778

PK Parameters	Units	75mg TU Twice Daily	150mg TU Twice Daily	225mg TU Twice Daily	300mg TU Twice Daily
Number of subjects		16	15	16	9
Tmax	h	7.8 ± 4.8	8.7 ± 6.3	8.7 ± 4.7	8.2 ± 5.6
Cavg	ng/dL	270 ± 94.4	319 ± 77	446 ± 162	644 ± 215
Cmax	ng/dL	544 ± 169	792 ± 276	1169 ± 356	1923 ± 835
AUC0-t	ng*h/dL	6488 ± 2265	7652 ± 1839	10693 ± 3872	15466 ± 5163

Average T concentrations did not reach the normal range with the 75 mg dose and the Cavg was at the lower end of the normal range for the 150 mg dose. The 225 mg dose provided mean Cavg value within the normal range and Cmax values that were near the upper limit of the normal range (1140 ng/dL). The 300-mg dose group had a Cavg within the normal range; however, the average Cmax was above 1800 ng/dL.

The proportion of subjects with T Cavg in the normal range and the proportion of subjects with T Cmax in different Cmax categories are presented in Table 7.

Table 7. Efficacy Analysis from Dose Finding Study M12-778

	% of Subjects meeting the criteria post steady state (Day 15)				
PK Parameters	**Criteria / Target**	**75mg TU Twice Daily**	**150mg TU Twice Daily**	**225mg TU Twice Daily**	**300mg TU Twice Daily**
Number of subjects		16	15	24	9
Primary End Points					
Cavg 300-1140[#] ng/dL	≥ 75%	44	47	83	100
Lower Bound 95% CI	≥ 65%	27	35	69	79
Secondary End Points					
Cmax ≤ 1500 ng/dL	≥ 85%	100	100	88	44
Cmax 1800-2500 ng/dL	≤ 5%	0	0	0	11
Cmax > 2500 ng/dL	0	0	0	0	33

With the 225 mg twice daily dose, 83% of subjects reached the eugonadal range (300 – 1140 ng/dL), with a 95% CI of 69%; 88% of subjects had a Cmax ≤ 1500 ng/dL, and no subjects had Cmax between 1800 – 2500 ng/dL, or > 2500 ng/dL. The 75 mg and 150 mg dose groups did not meet the Cavg efficacy targets. The 300 mg dose met the Cavg efficacy targets, but exceeded the allowable Cmax targets in more than 10% of subjects.

7.3.3 Conclusions

From the results of this Phase 2 dose-finding study, it was concluded that the 225 mg twice daily dose provided the best overall efficacy profile.

7.4 Phase 3 Dose Titration Study 13-001

7.4.1 Overview

Study 13-001 was a multicenter, Phase 3, randomized (2:1), open-label, active controlled, parallel-group study evaluating the efficacy and safety of TLANDO for TRT.

This study enrolled 18 to 80-year-old male subjects with a diagnosis of hypogonadism (primary or secondary), who had confirmed low serum total T concentrations (< 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. Subjects older than 65 years of age required a documented diagnosis or onset of hypogonadism prior to age 65.

Subjects were randomized to receive either orally administered TLANDO capsules or topically applied AndroGel 1.62%, an FDA approved transdermal gel TRT product. Subjects were randomized in a 2:1 ratio such that 210 subjects were assigned to the TLANDO treatment group and 105 subjects were assigned to the AndroGel treatment group. The sample size for this study was based on the primary efficacy parameter: the incidence and lower bound of the 95% CI for the percentage of subjects achieving serum T concentrations within the normal range. Assuming the primary efficacy endpoint is achieved (≥ 75% of

subjects have normal T concentrations) the sample of 200 subjects exceeded the number required to result in the lower bound of a 95% two-sided CI being no less than 65%.

7.4.2 Dosing and Administration

In the TLANDO treatment group, all subjects started at a dose of 225 mg taken two times a day, approximately 12 hours apart. As this study was conducted concurrent to the pivotal food/fat effect Study 14-001, the study specified administration with a standard meal consisting of 800 to 1400 calories per meal with ~20 to 35% fat content. The study involved up to two dose titration steps aimed at reliably restoring serum T levels based on individual subject response.

At Week 3 and Week 7, subjects underwent a 24-hour intensive blood sampling period to evaluate serum T PK. Based on the 24-hour T Cavg and T Cmax, subjects were assessed for possible dose adjustment (implemented at Weeks 4 and 8) based on the T PK parameters of the previous week. Possible dose titration at Weeks 4 and 8 was based on the 24-hour T Cavg and the T Cmax as follows:

- If Cavg < 300 ng/dL, dose was titrated upward by 75 mg/dose; or
- If Cavg > 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 Cavg; or
- If Cavg = 300 to 1140 ng/dL and Cmax ≤ 1500 ng/dL, dose was not changed.

The final allowed dose regimens were 150 mg, 225 mg, and 300 mg twice daily.

In accordance with the dosing instructions in the AndroGel 1.62% package insert, the starting dose 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 (± 2 days) and Day 28 (± 2 days) in accordance with the approved package insert. Dose adjustments were made based on the serum T concentration as follows:

- Serum T > 750 ng/dL: daily decreased by 1 pump actuation (equivalent of 20.25 mg)
- Serum T ≥ 350 and ≤ 750 ng/dL: no change
- Serum T < 350 ng/dL: dose increased by 1 pump actuation (equivalent of 20.25 mg)

The AndroGel 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).

Subjects in both treatment groups were to remain on therapy for 52 weeks. Subjects in the TLANDO arm remained on their final dose from Week 8 onwards and subjects in the AndroGel arm remained on their final dose from Week 5 onwards. Full 24-hour testosterone profiles were obtained for only the TLANDO group at Weeks 3, 7, and 13 with the Week 13 values being the primary efficacy endpoint, AndroGel was included in the study for primarily safety purposes so only single T measurements for monitoring were performed.

7.4.3 Subject Demographics

The subject demographic profile is shown in Table 8. Demographics and baseline characteristics were similar between treatment groups.

Table 8. Demographic and Baseline Characteristics-Randomized Subjects (N = 315)

Characteristic	TLANDO N=210	AndroGel 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[1], 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)

Mean baseline T concentrations were 209 ng/dL and 200 ng/dL for the TLANDO and AndroGel, respectively.
Key: SD = standard deviation
[1]Calculated as weight (kg) / height (m)²

AndroGel-treatment groups, respectively. Prior androgen therapy was reported by 51.4% of subjects in the TLANDO group and 55.2% of subjects in the AndroGel 1.62% group. All subjects completed the protocol-specified washout period before screening.

7.4.4 Subject Disposition

A total of 315 subjects were randomized to study treatment of which 210 were assigned to TLANDO and 105 were assigned to AndroGel. Overall, 61.9% of subjects in the TLANDO group and 67.6% of subjects in the AndroGel group completed the study.

Table 9 provides a summary of the subject disposition.

Table 9. Subject Disposition

Status	TLANDO n (%)	AndroGel n (%)
Subjects Randomized	210	105
Subjects who Received Treatment	210 (100)	104 (99.0)
Subjects who Completed the Study	130 (61.9)	71 (67.6)
Subjects who Discontinued Early from the Study	80 (38.1)	34 (32.4)
Reason for Early Discontinuation		
Consent Withdrawn due to		
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)
Abnormal lab parameters, adverse events, or lack of efficacy based on symptoms*		
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
Lack of Efficacy	5 (2.4)	4 (3.8)
Other		
Cmax or Cavg not Achieved; Met the Stopping Criteria	9 (4.3)	NA
Duplicate Subject[1]	4 (1.9)	3 (2.9)

[1]Subjects who enrolled and/or screened at more than one site. In cases where this occurred, subjects were withdrawn at both study sites.

The most common reasons for study discontinuation were withdrawal of consent either due to confinement or schedule conflicts or other reasons; abnormal lab parameters, adverse events or lack of efficacy; and lost to follow-up.

7.4.5 Dose Distribution and Treatment Compliance

The dose distribution of TLANDO by study week and dose is shown in Table 10.

Table 10. Dose Distribution of TLANDO

Visit	Number of Subjects			
	150 mg TU twice daily	225 mg TU twice daily	300 mg TU twice daily	Total
Week 3	0	193	0	193
Week 7	51	105	26	182
Week 13	50	82	25	157

Subjects randomized to AndroGel started on the 40.5 mg dose and underwent two titration steps one at Week 3 and another at Week 5. There were four dose options, 20.25 mg, 40.5 mg, 60.75 mg and 81 mg. The final dose distribution of AndroGel at Week 5 is shown in Table 11.

Table 11. Final Dose Distribution of AndroGel

Visit	Number of Subjects			
	20.25 mg	40.5 mg	60.75 mg	81 mg
Week 5	1	10	33	53

Treatment compliance is shown in Table 12. Compliance was calculated as the total quantity dispensed minus returned/expected quantity to be used *100. Treatment compliance was similar between treatment groups. In some cases, bottles were not returned, and the apparent compliance exceeded 100%.

Table 12. Treatment Compliance

Percent Compliance [a]	TLANDO	Androgel
n	207	101
Mean (SD)	88.5 (22.23)	90.5 (21.47)
Median (Min-Max)	94.3 (0-198)	94.1 (24-169)

Key: Min=minimum; Max=maximum; SD=standard deviation.
[a] Treatment compliance was computed as (total quantity dispensed minus returned)/expected quantity*100

The overall compliance in both treatment groups were similar.

7.4.6 Primary Efficacy Endpoint – T Cavg

Responder analysis results for the Cavg primary endpoint at Week 13 from the Full Analysis Set (FAS) using a last observation carried forward (LOCF) approach are shown in Table 13. The FAS included all subjects randomly assigned to treatment in the study who had at least one post-baseline efficacy variable response (Cavg or Cmax). Also shown are results from the Week 3 PK sampling performed prior to titration.

Table 13. Proportion of TLANDO-Treated Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range on Efficacy Day – FAS LOCF (N=192*)

Measure	Targets	FAS (LOCF)	FAS (LOCF)
Time Point		Week 3 Pre-Titration	Week 13 Post-Titration
Primary Efficacy Endpoint		n=192*	n=192*
% subjects with Cavg in the normal range[1]	≥75%	86%	88%
95% CI[2] lower bound	≥65%	81%	83%

Key: Cavg = average serum concentration
[1]Normal Range: 300 to 1140 ng/dL
[2]A 95%, 2-sided, binomial confidence interval surrounding the point estimate was calculated.
*FAS has 193 subjects with one subject missing 24-hour Cavg data, therefore N is 192 for Cavg.

Efficacy was demonstrated for Cavg at both Week 3 pre-titration when all subjects were on the 225 mg BID dose and at the primary endpoint at Week 13 post titration with 86% and 88% of subjects, respectively, within the normal range. The lower bound of the 95% CI for that proportion exceeded the pre-defined lower limit of acceptability. At Week 3 with the 225 mg BID fixed dose, there were 27 subjects whose Cavg was outside the normal range. Of these, the large majority 24 of 192 (12.5%) subjects had Cavg below the normal range and 3 of 192 (1.6%) had a Cavg above the normal range.

7.4.7 Secondary Endpoints – T Cmax

The Cmax responder analysis is shown in Table 14. Both Week 3 and Week 13 data are provided.

Table 14. Proportion of Subjects in T Cmax Categories

		Week 3 Pre-Titration	Week 13 Post-Titration
	Targets % Subjects	All Available Data N = 193	FAS (LOCF) N = 193
Cmax <1500 ng/dL	≥85	67.9%	72.0%
Cmax 1800-2500 ng/dL	≤5	10.9%	11.4%
Cmax > 2500 ng/dL	0	4.7%	4.1%

Key: Cmax = maximum observed serum concentration

At Week 13, 11.4% of subjects had a Cmax value between 1800-2500 and 4.1% of subjects exceeded the 2500 ng/dL threshold. A similar result was observed with the Week 3 pre-titration data.

7.4.8 Patient Reported Outcomes

To complement the PK findings, patient reported outcome (PRO) questionnaires were used to assess symptomatic improvement and were completed by all subjects for both treatment groups. The validated PRO instruments that were used were the Psychosexual Daily Questionnaire and the Short Form-36 questionnaire. While there are limitations of PRO data

obtained from open-label studies, the results provide additional support for the efficacy of TLANDO, and provide for comparisons to AndroGel.

The instruments were administered at baseline and at Week 52 or at Early Termination and change from baseline was analyzed. The Safety Set (all subjects who received at least one dose of drug) was used for analysis of these endpoints.

7.4.8.1 Short Form-36

The SF-36 questionnaire 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. SF-36 results are shown in Table 15. Scores for each subscale range from 0 to 100 with higher scores representing a more favorable health state.

Table 15. Mean (SD) Change from Baseline to End of Study/Early Termination by Treatment for SF-36 Assessment – Safety Set

	TLANDO (N = 210)			AndroGel (N = 104)		
SF-36 Assessment Subscale	Change from Baseline to EOS		EOS vs Baseline	Change from Baseline to EOS		EOS vs Baseline
	N	Mean (SD)	p-value[1]	N	Mean (SD)	p-value[2]
Physical Functioning	174	0.95 (9.54)	0.1898	85	1.49 (8.56)	0.1127
Bodily Pain	173	-0.03 (9.63)	0.9628	85	-0.16 (10.63)	0.8906
General Health Perceptions	172	0.46 (7.25)	0.4095	85	0.93 (6.98)	0.2247
Vitality	173	6.89 (14.05)	<.0001*	85	3.82 (12.00)	0.0043*
Physical Role Functioning	167	0.85 (3.81)	0.0044*	82	0.24 (3.19)	0.4992
Emotional Role Functioning	167	0.65 (4.65)	0.0718	82	0.38 (4.08)	0.4024
Social Role Functioning	171	2.17 (9.68)	0.0038*	85	0.64 (9.27)	0.5252
Mental Health	173	2.91 (11.89)	0.0015*	85	-0.10 (10.06)	0.9277
Physical Component Summary	165	0.07 (7.02)	0.9003	82	1.03 (6.92)	0.1808
Mental Component Summary	165	3.82 (10.00)	<.0001*	82	0.55 (8.72)	0.5701

Key: EOS = end of study; SD = standard deviation
[1] p-value calculated using paired t-test comparing Baseline versus End of Study/Early Termination for TLANDO subjects.
[2]p-value calculated using paired t-test comparing Change from Baseline to End of Study for AndroGel subjects.
*Statistically significant (p-value < 0.01)

For the SF-36 Health Survey, subscales that would expect to show improvement with TRT showed statistically significant increases from baseline to end of study with TLANDO.

7.4.8.2 Psychosexual Daily Questionnaire

The Psychosexual Daily Questionnaire (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 Week 52 (or early termination).

During each of these assessments, subjects completed the PDQ over a 7-day period. The PDQ results are shown in Table 16.

Table 16. Change from Baseline to End of Study/Early Termination by Treatment for Psychosexual Daily Questionnaire – Safety Set

	TLANDO (N=210)			AndroGel (N=104)		
Psychosexual Daily Questionnaire Subscale	Change from Baseline to EOS		EOS vs Baseline	Change from Baseline to EOS		EOS vs Baseline
	N	Mean (SD)	p-value[5]	N	Mean (SD)	p-value[6]
Weekly Overall Sexual Desire[1]	163	1.38 (1.69)	<.0001*	82	1.35 (1.81)	<.0001*
Weekly Highest Pleasure without Partner [1]	159	0.85 (1.96)	<.0001*	82	0.65 (1.56)	0.0003*
Weekly Highest Pleasure with Partner[1]	159	0.78 (2.15)	<.0001*	79	1.06 (1.95)	<.0001*
Weekly Positive Mood[2]	161	0.60 (1.39)	<.0001*	82	0.74 (1.19)	<.0001*
Weekly Negative Mood[2]	162	-0.57 (1.20)	<.0001*	82	-0.20 (1.15)	0.1262
Weekly Sexual Activity[3]	163	1.72 (2.72)	<.0001*	82	1.710 (2.64)	<.0001*
Weekly Full Erection, 0% to 100%	108	19.62 (26.66)	<.0001*	55	12.93 (23.29)	.0001*
Weekly Maintained Satisfactory Erection[4]	107	1.591 (1.85)	<.0001*	55	1.09 (1.80)	<.0001*

Key: EOS = end of study; SD = standard deviation
[1]Recorded on an ordinal scale from 0 to 7 where 0 = none and 7 = very high.
[2]Individual mood variables are rated on an ordinal scale from 0 to 7 where 0 = Not at all true and 7 = Very true. Positive mood is the sum of the 4 positive mood variables-alert, full of pep/energetic, friendly, and well/good. Negative mood is the sum of the 5 negative mood variables angry, irritable, sad or blue, tired, and nervous.
[3]Weekly sexual activity comprises a 12-item checklist with average number of items experienced each day.
[4]Recorded on an ordinal scale from 0 to 7 where 0 = Not satisfactory and 7 = Very Satisfactory.
[5]p-value calculated using paired t-test comparing Baseline versus End of Study/Early Termination for TLANDO subjects.
[6]p-value calculated using paired t-test comparing Change from Baseline to End of Study for AndroGel subjects.
*Statistically significant (p-value < 0.01)

Statistically significant improvements were observed from baseline to end of study for all domains of the PDQ for the TLANDO-treatment group.

7.4.9 Conclusions

The efficacy analyses from Study 13-001 demonstrated that when the dose was titrated based on 24-hour PK sampling, at the primary endpoint 88% of subjects reached the eugonadal range (300 – 1140 ng/dL). The lower bound of the 95% CI was within the pre-defined limits. At Week 3, prior to titration with all subjects receiving the 225 mg twice daily dose, 86% of subjects reached the eugonadal range. At Week 3, the lower bound of the 95% CI was within the pre-defined limits. At Week 13, 72.0% of subjects had a Cmax < 1500 ng/dL, and 11.4% between 1800 – 2500 ng/dL, and 4.1% > 2500 ng/dL; similar results were observed without titration at Week 3.

These results for the primary and secondary endpoints at Week 3 (pre-titration) are almost the same as those observed at Week 13 after dose titration and indicate that titration had

minimal effect on gaining additional Cavg responders or reducing Cmax events outside of the target range.

An NDA was submitted on 28 August 2015, with a proposal to assess T levels at only one timepoint to monitor the success to therapy. This approach was supported by the data from Study 13-001, however it had not prospectively evaluated in a clinical study.

7.5 FDA Complete Response Letter

On 28 June 2016, the FDA issued a Complete Response Letter (CRL) for NDA 208088 and described one deficiency related to dosing and requested information to resolve the deficiency.

Deficiency per FDA:

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

Information identified by FDA needed to resolve the deficiency was per FDA:

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

In response to the CRL, additional modeling and simulations based on Study 13-001 clinical data were performed.

7.6 Modeling and Simulation

Extensive analyses, modeling and simulations were performed to address the CRL deficiency. A population PK model for T concentration using data from Study 13-001 was developed and the model was used to derive dosing strategies. Variations involving one or two blood sample draws and one or two titration visits were evaluated using the model; however, based on the results, a single point titration offered no real advantage over a fixed dose regimen (Table 17).

Table 17. Modeling and Simulation: Summary Cavg Responders and Cmax Targets for No Titration and Single-Point Titration Schemes

Dosing Strategy	Cavg (300-1140 ng/dL)	Cmax(0-24) (< 1500 ng/dL)	Cmax(0-24) (1800-2500 ng/dL)	Cmax(0-24) (> 2500 ng/dL)
Final Simulations (Target Concentrations: 300-1200 ng/dL; Time Window: 3 hr to 7 hr)				
Median % (95% Lower Bound, 95% Upper Bound)				
No Titration	89.2 (84.7, 93.0)	69.4 (63.0, 76.1)	11.8 (8.0, 16.6)	5.4 (2.9, 8.6)
Single sample, one titration visit	89.8 (85.0, 93.6)	71.7 (64.7, 78.1)	11.2 (7.0, 15.5)	4.5 (2.1, 8.0)
Single sample, two titration visits	90.4 (86.1, 94.1)	71.7 (65.2, 78.1)	11.2 (7.0, 16.0)	4.3 (1.6, 7.5)

The findings of these analyses were presented and discussed with the FDA on 06 October 2016. Based on these analyses and feedback from the FDA, two viable 'no titration' fixed dose regimens for TLANDO were identified: 225 mg twice daily dose and 150 mg three times daily dose. These fixed dose regimens were evaluated in two separate prospectively designed, open-label clinical trials. Study 16-002 was conducted to evaluate a daily dose of 450 mg, administered as two equal doses of 225 mg. Study 16-003 was conducted to evaluate the same total daily dose 450 mg, administered as three equal doses of 150 mg, and shared the same design elements as Study 16-002. In the Post-Action Meeting Minutes, the Division noted that "*the Sponsor should be able to leverage data from the existing trials to help support safety.*" Therefore, the focus of these studies was to evaluate the efficacy of the respective dose regimens.

7.7 Phase 3 Fixed Dose Study 16-002

7.7.1 Overview

Study 16-002 was a multicenter, open-label, single-treatment study evaluating the efficacy of 225 mg twice daily administration (approximately every 12 hours) of T replacement in hypogonadal men. 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 (efficacy visit, Day 24) was for confinement of subjects and intensive PK sampling.

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 was used to meet eligibility criteria.

Subjects were dosed with 225 mg of TLANDO two times a day with a meal for about 24 days (window of 20 to 28 days). Since this study was conducted after the definitive food/fat effect Study 14-001, there were no fat requirements restriction for the meal. Pharmacokinetic efficacy assessments were carried out at Visit 4, Day 24 (-4 to +4 days). On Day 24, subjects were confined for about 38 hours. Subjects received two doses spaced every 12 hours apart and intensive PK sampling was carried out for 24 hours. Blood samples were

obtained at 0 (pre-dose), 2, 3, 4, 5, 6, 8, 12 hours after the morning dose, and 2, 3, 4, 5, 6, 8, 12 hours after the evening dose for a total of 15 samples over a 24-hour period.

7.7.2 Analyses of Results

7.7.2.1 Study Populations

The study enrolled hypogonadal men, 18 to 80 years-of-age with a documented diagnosis of hypogonadism prior to age 65. One of the changes for this study from prior Study 13-001 is that a BMI restriction was removed at the recommendation of the FDA.

Study eligibility criteria allowed enrollment of subjects who were naïve (subjects with no documented prior history of androgen therapy) to T treatment or who had stopped their current treatment and completed an adequate washout period. At the time of study enrollment, prior androgen therapy was reported by 68.4% of subjects. All subjects completed the protocol-specified washout period before screening for T levels as an entry criterion into the study.

7.7.2.2 Subject Demographics

A total of 95 subjects were enrolled into the study and received the study treatment. Key demographic information is provided in Table 18.

Table 18. Demographic Characteristics – Safety Set

Characteristic	Value
Age, Mean Years (SD)	56.0 (8.9)
≤ 65, n (%)	79 (83.2)
> 65, n (%)	16 (16.8)
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[1], 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)

Key: SD = standard deviation
[1]Calculated as weight (kg) / height (m)²

The mean (SD) baseline T levels were 202 (74) ng/dL. Baseline serum T, dihydrotestosterone (DHT) and estradiol (E2) levels are presented in Table 19. Mean baseline DHT and E2 concentrations were within the normal range.

Table 19. Baseline (Screening) Hormone Levels – Safety Set

Characteristic	Value
Baseline T value (ng/dL)[1]	
N	95
Mean (SD), First Measurement (ng/dL)	200 (76.6)
Mean (SD), Second Measurement (ng/dL)	203 (72.7)
Mean (SD), Overall of both measurements (ng/dL)	202 (74.5)
Minimum, Maximum	18.0, 299.0
Baseline DHT value (ng/dL)[2]	
N	95
Mean (SD)	18.1 (13.8)
Minimum, Maximum	1.3, 126.0
Baseline E2 value (pg/mL)[3]	
N	94
Mean (SD)	18.0 (10.2)
Minimum, Maximum	3.2, 69.5

Key: SD = standard deviation
[1] Normal range for healthy young adult male for T is 300 to 1080 ng/dL.
[2] Normal range for healthy young adult male for DHT is 10.6 to 71 ng/dL.
[3] Normal range for healthy young adult male for E2 is 10.0 to 42.0 pg/mL.

7.7.2.3 Subject Disposition

Ninety-four (98.9 %) of 95 subjects completed the study. One subject discontinued prior to completion of Visit 4 (PK visit). Table 20 provides a summary of the subject disposition for Study 16-002.

The one subject who discontinued was withdrawn from the study due to a serious adverse event of gastric ulcer related hemorrhage, which was classified by the investigator as not related to study drug.

Table 20. Subject Discontinuation – Safety Set

Status	n (%)
Subjects enrolled in the trial	95
Subjects in safety set (who received at least one dose study treatment)	95 (100)
Total subjects who completed the study	94 (98.9)
Total subjects who discontinued early from the study	1 (1.1)
Reason for early discontinuation[1]	
Adverse event	1 (1.1)

[1] One subject discontinued to an SAE of a gastric ulcer related hemorrhage.

7.7.2.4 Treatment Compliance:

The mean (SD) treatment compliance for the FAS (n=94) was 99.7 (4.9) %.

7.7.2.5 Primary Analysis Datasets:

The Safety Set (SS) was the primary dataset for the efficacy analysis. The SS included all subjects who received at least one dose of study drug.

Handling of Missing Data:

The following imputation methods were used for missing values comprising the primary and secondary endpoints:

For the Cavg primary endpoint baseline observation carried forward (BLOCF) was the imputation method used for the primary efficacy analysis.

For the Cmax secondary endpoints, model based multiple imputation was the imputation method used for the secondary efficacy analysis. The Model-Based Multiple Imputation approach was used to impute missing data from the confinement visit using baseline covariates BMI, Race, Age, and Baseline T.

With only one post baseline PK sampling period, the BLOCF imputation is a worst-case analysis with values less than 300 ng/dL carried forward. BLOCF imputation results in any subject without Day 24 Cavg data to be considered a treatment failure.

7.7.3 Efficacy Results

7.7.3.1 Primary Efficacy Endpoint – T Cavg

The primary analysis results for the primary endpoint are displayed in Table 21.

Table 21. Proportion of Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range – Safety Set

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 bound %)[2]	≥ 65%	72%

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.

Efficacy was demonstrated by the achievement of average T concentrations within the normal range for 80% of subjects. The lower bound of the 95% CI also exceeded the pre-defined limits. None of the subjects had Cavg greater than 1080 ng/dL. The mean (SD) T Cavg was 476 (174) ng/dL.

7.7.3.2 Secondary Efficacy Endpoints –– T Cmax

The proportion of subjects in the defined Cmax categories per day are shown in Table 22.

Table 22. Proportion of Subjects for the T Cmax Secondary Endpoint on Efficacy Day – Safety Set

Measure	Target	T Cmax (0-24)
Number of Subjects		95
T Cmax < 1500 ng/dL, %	≥ 85%	74%
1800 - 2500 ng/dL, %	≤ 5%	14%
T Cmax > 2500 ng/dL (n)	No subject	One subject

One subject (#207-0014) had a Cmax value that exceeded 2500 ng/dL with one single measurement of 2730 ng/dL 4 hours after the evening dose. The Cmax after the morning dose was 1130 ng/dL, observed 2 hours post morning dose. The subject experienced one treatment emergent adverse event (TEAE), headache, that was considered mild in severity.

7.7.3.3 Impact of Body Mass Index on Efficacy

A subgroup analysis was performed to evaluate the effect of body mass index (BMI) (obese vs non-obese) on the primary endpoint of the study (i.e., the proportion of subjects who achieved a T Cavg within the normal range on Day 24).

Of the 95 subjects about 70% subjects had a BMI ≥30 kg/m^2, which meets the criteria for obesity. Mean T Cavg for the 29 non-obese subjects and the 65 obese subjects was 557 ng/dL and 437 ng/dL, respectively. Mean T Cmax values were 1382 ng/dL and 1090 ng/dL in non-obese and obese subjects, respectively.

At Day 24, 93% of non-obese subjects and 75% of obese subjects achieved T Cavg between 300 to 1080 ng/dL with corresponding lower bound 95% confidence intervals of 84% and 65%, respectively.

TLANDO was effective in restoring T levels in both obese and non-obese subgroups. The differences observed between BMI categories are not considered clinically meaningful.

7.7.3.4 Conclusions

Study 16-002 confirmed that TLANDO at a fixed dose of 225 mg twice daily was effective in restoring testosterone to acceptable levels in hypogonadal men with 80% of subjects achieving therapeutic T concentrations in the normal range. Efficacy was also demonstrated in both obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) patients implying no need for dose adjustment needed based on the degree of adiposity.

The findings of efficacy in Study 16-002 using the 225 mg BID dosing is supported by the consistent findings observed across multiple studies (Table 23) and provides the key efficacy data for the product label.

Table 23. Consistent Efficacy of 225 mg Twice Daily Fixed Dose Across Studies

	225 mg Twice Daily Fixed Dose		
Measure	**Study M12-778**	**Study 13-001 (Week 3)**	**Study 16-002**
	N=24	**N=192**	**N=95**
Primary Efficacy Endpoint (% Subjects)			
T Cavg in normal range	83%	86%	80%
95% CI Lower Bound	69%	81%	72%
Mean (SD) T Cavg	446 (162)*	494 (193)*	476 (174)

*225 mg dose group

7.8 Phase 3 Fixed Dose Study 16-003

7.8.1 Overview

Study 16-003 was a multicenter, open-label, single-treatment study evaluating the efficacy of 150 mg three times daily administration (approximately every 8 hours) of TLANDO for TRT in hypogonadal men. The study design was the same as Study 16-002, which is described above. The study enrolled 100 subjects. Demographics and baseline characteristics were similar to Study 16-002. Two subjects discontinued early from the study.

7.8.2 Efficacy Results

7.8.2.1 Primary Efficacy Endpoint - Cavg

The primary analysis results for the primary endpoint are displayed in Table 24. The Safety Set was used for the analysis with baseline values carried forward for missing data.

Table 24. Proportion of Subjects Achieving 24-hour Average Serum Testosterone Concentration within Normal Range – Safety Set

Parameter	Target	Safety Set, BLOCF N=100
Percentage subjects achieving 24-hour average serum T concentration within normal range[1]	≥ 75%	69%
95% Confidence interval (lower bound %)[2]	≥ 65%	60%

Key: T = total testosterone; BLOCF = baseline observation carried forward.
[1]Normal Range: 300 to 1080 ng/dL
[2]A 95%, 2-sided, binomial confidence interval surrounding the point estimate was calculated.

The efficacy targets were not met in this study with only 69% of subjects having T Cavg within the normal range. The lower bound of the 95% CI was 60%.

7.8.2.2 Secondary Efficacy Endpoints - Cmax

The proportion of subjects in the defined Cmax categories are shown in Table 25.

Table 25. Proportion of Subjects for the T Cmax Secondary Endpoint on Efficacy Day – Safety Set

Measure	Target	T Cmax (0-24)
Number of Subjects		100
Number of Cmax observations		100
T Cmax ≤ 1500 ng/dL, %	≥ 85%	95%
T Cmax 1800 - 2500 ng/dL, %	≤ 5%	1%
T Cmax > 2500 ng/dL (n)	No subject	None

The Cmax targets were met in this study. Only one subject had a Cmax value above 1800 ng/dL

7.8.2.3 Conclusions

The results of this study demonstrated that 150 mg TID was not effective and provides additional support for the 225 mg BID dose as the optimum dose. Although secondary Cmax targets were met, the primary efficacy endpoint was not met with only 69% of subjects having a T Cavg within the normal range.

7.9 Transient and Isolated Cmax Excursions

Data from Study 16-002 were analyzed for the time during which the T concentration was >1500 ng/dL and >1800 ng/dL in subjects who had Cmax exceed these values. The mean time spent above 1500 ng/dL for subjects with Cmax >1500 was 1.7 hours. Time spent above 1800 ng/dL for subjects with Cmax >1800 ng/dL was 1.0 hours.

Analyses were performed to determine if Cmax excursions outside of the pre-determined limits are repeated with the next dose, or if they are isolated events. In Study 16-002, 13 subjects (14%) had a Cmax value that exceeded 1800 ng/dL. None of these subjects had a Cmax value >1800 ng/dL in both the morning and evening dosing periods. Using a cutoff of >1500 ng/dL, in Study 16-002, four (4.3%) of subjects exceeded this value with both morning and evening doses. None of these four subjects had a Cavg above the normal range.

In Study 13-001, the percentage of subjects who had repeat excursions above 1500 ng/dL for both morning and evening dosing periods was 8.8% (17 out of 193) and 3.2% (5 out of 157) for Weeks 3 and 13, respectively. Among these subjects, two subjects had Cavg above the normal range at Week 3 and one subject had Cavg above the normal range at Week 13.

In Study 13-001, using a cutoff of >1800 ng/dL, 5.2% (10 out of 193) and 0.6% (1 out of 157) of subjects exceeded 1800 ng/dL for Weeks 3 and 13, respectively. Among these subjects, only one subject had a Cavg above the normal range at Week 3.

These results indicate that Cmax excursions are generally transient and isolated events in any given patient that usually do not predict any overall high Cavg exposure.

7.10 Efficacy Conclusions

Consistent and predictable therapeutic levels of T was demonstrated for TLANDO when administered with food containing varying amounts of fat. Although TLANDO should be administered with food, the patient will have flexibility in dietary choices. Consistent failure to take the product with food would lead to a suboptimal treatment response, but would not pose a safety risk.

Efficacy was demonstrated in Study 16-002 by the achievement of average T concentrations within the normal range for 80% of subjects. The lower bound of the 95% CI also exceeded the pre-defined limits. None of the subjects had a Cavg greater than 1080 ng/dL. The mean (SD) T Cavg was 476 (174) ng/dL. Efficacy was also demonstrated in both obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) patients thus allowing this product to be used in a broad hypogonadal population without the need for dose adjustment based on degree of adiposity.

7.11 Clinical Pharmacology

7.11.1 Testosterone Undecanoate and Dihydrotestosterone Undecanoate

While TU and DHTU are not considered to provide any biologic activity, the pharmacokinetic parameters by for TU and DHTU on Day 24 are shown in Table 26 and Table 27.

Table 26. Serum PK Parameters of TU (ng/mL) on Day 24 – PK Set (N = 90)

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg, ng/mL	Mean (SD)	111 (50.4)		
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)

Key: Cavg = average serum concentration from 0 to 24 hours (area under the curve /24); Cmax = maximum observed serum concentration post dose; SD = standard deviation; Tmax = time to maximum observed serum concentration.

Table 27. Serum PK Parameters of DHTU (ng/mL) on Day 24 – PK Set (N = 90)

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg, 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)

Key: Cavg = average serum concentration from 0 to 24 hours (area under the curve /24); Cmax = maximum observed serum concentration post dose; SD = standard deviation; Tmax = time to maximum observed serum concentration.

Figure 2 and Figure 3 display serum TU and DHTU concentrations, respectively, at Day 24 from Study 16-002.

Figure 2. Mean (SD) Serum Testosterone Undecanoate (ng/mL) Concentration over Time on Day 24 – PK Set (N = 90)

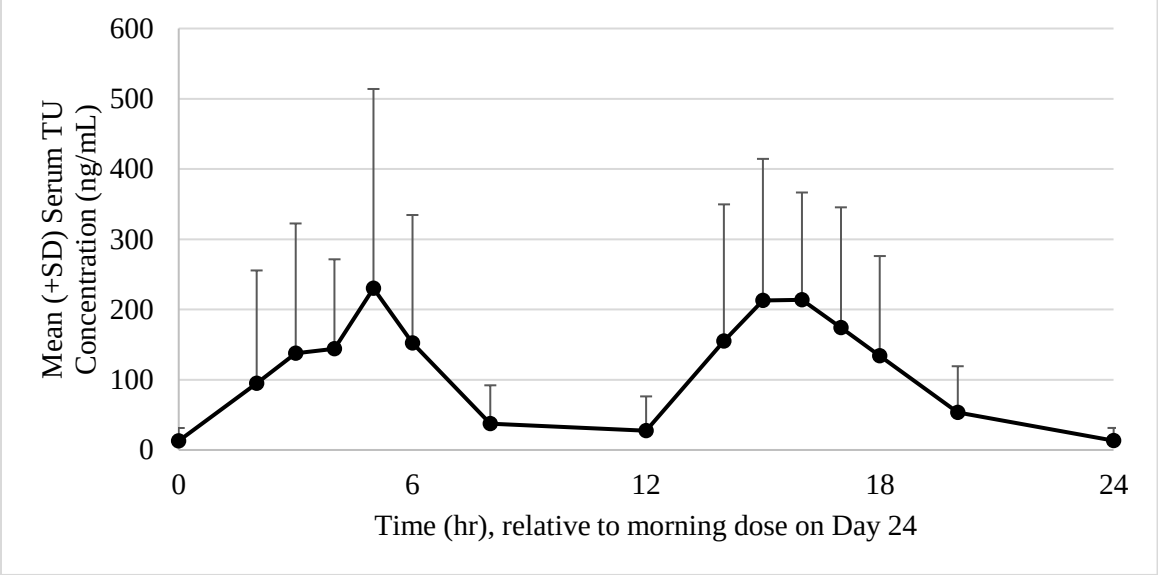
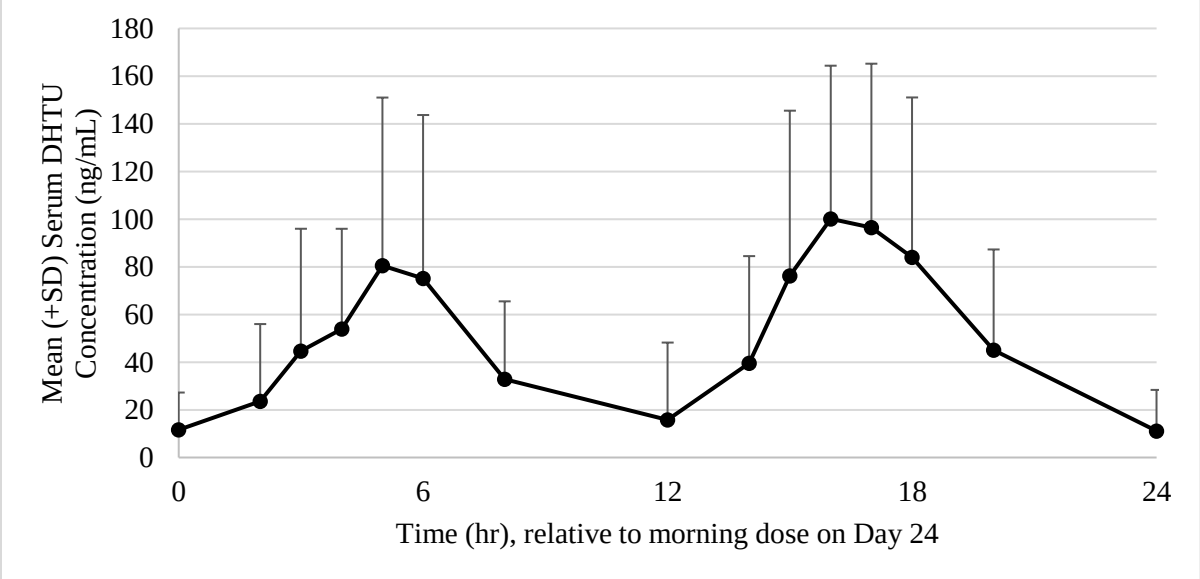


Figure 3. Mean (SD) Serum DHTU Concentration (ng/mL) over Time on Day 24 – PK Set (N = 90)



The conversions of TU to T 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).

7.11.2 Total Testosterone

The mean (SD) serum T pharmacokinetic parameters are shown in Table 28. The mean T Cavg concentrations and Cmax values are within the normal range.

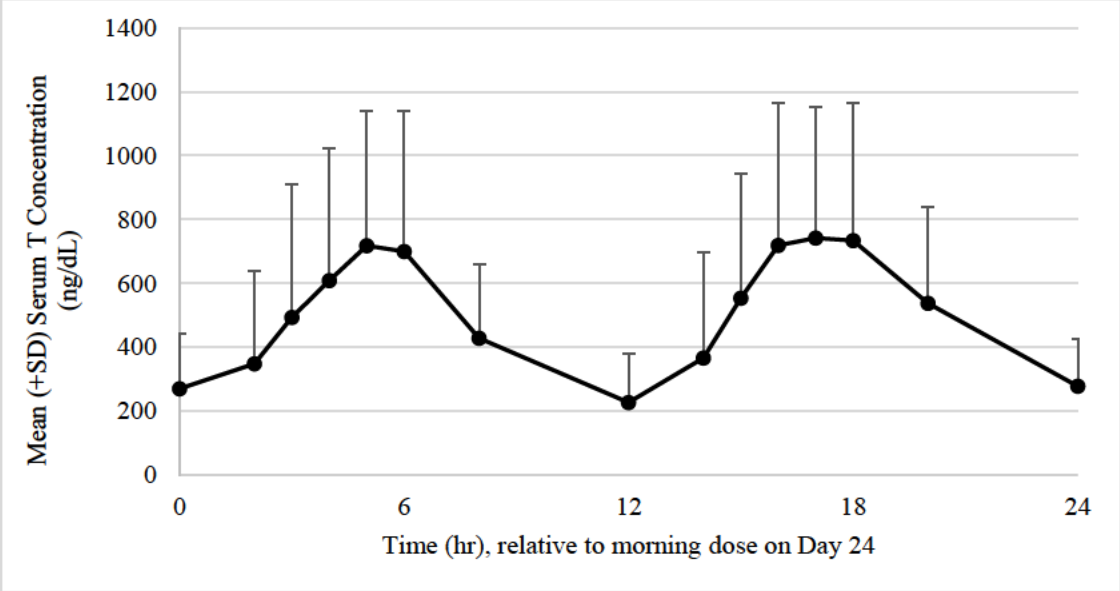
Table 28. Serum PK Parameters of Serum Testosterone on Day 24 – PK Set (N=90)

Parameter	Statistic	24-hour post morning dose
T Cavg, ng/dL	Mean (SD)	476 (174)
T Cmax, ng/dL	Mean (SD)	1178 (484)
Tmax, h	Median (Min, Max)	14.8 (2.0, 24.0)

Key: Cavg = average serum concentration from 0 to 24 hours (area under the curve /24); Cmax = maximum observed serum concentration post dose; SD = standard deviation; Tmax = time to maximum observed serum concentration.

Figure 4 displays serum T concentrations at Day 24 from Study 16-002.

Figure 4. Mean (SD) Serum T Concentration (ng/mL) over Time on Day 24 – PK Set (N = 90)



The mean serum T concentrations produced by TLANDO are similar or slightly lower than other approved TRT products.

7.11.3 Sex Hormone Binding Globulin

In Study 13-001 the mean values at baseline sex hormone binding globulin (SHBG), were similar between both treatment groups; however, SHBG concentrations decreased in the TLANDO group and generally increased in the AndroGel group, (Table 29).

Table 29. Mean Baseline and Mean Change from Baseline Values of SHBG in TLANDO- and AndroGel-Treated Subjects (Study 13-001)

	TLANDO					AndroGel				
		SHBG Value (nmol/L)		Change from Baseline (nmol/L)			SHBG Value (nmol/L)		Change from Baseline (nmol/L)	
Visit	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	204	30.34	15.01			99	30.35	11.79		
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

Key: SHBG = sex hormone binding globulin; SD = standard deviation.

In Study 16-002, SHBG concentrations decreased form baseline to Day 24 (Table 30).

Table 30. Mean Baseline and Mean Change from Baseline Values of SHBG in Study 16-002

		SHBG Value (nmol/L)	Change from Baseline (nmol/L)
Visit	N	Mean (SD)	Mean (SD)
Baseline	95	29.53 (11.59)	
Exit	93	18.72 (9.50)	-10.81 (7.52)

Key: SHBG = sex hormone binding globulin; SD = standard deviation.

7.11.4 Free Testosterone

Testosterone circulates almost entirely bound to transport proteins. Most is bound to SHBG and lesser amounts are bound to albumin. Normally less than 1% is free. Free T values were estimated for Study 16-002 using a technique based on the Vermullian method. The calculated mean (SD) free T Cavg was 13 (4.4) ng/dL at Day 24, which is within the normal range of T, 9 to 30 ng/dL (Mayo Clinic). Mean baseline values prior to initiation of treatment was 4.7 (1.8) ng/dL

Although reduced SHBG levels were observed following TLANDO administration, excessive free T levels were not observed.

7.11.5 Luteinizing Hormone and Follicle Stimulating Hormone

In Study 13-001, mean concentrations of LH were similar between the two treatment groups at baseline (Table 31). As anticipated, both treatment groups showed generally similar decreases at each time point. In Study 16-002, LH concentrations also decreased from baseline (Table 32).

Table 31. Mean Baseline and Mean Change from Baseline Values of LH in TLANDO- and AndroGel-Treated Subjects in Study 13-001

	TLANDO					AndroGel				
		LH Value (IU/L)		Change from Baseline (IU/L)			LH Value (IU/L)		Change from Baseline (IU/L)	
Visit	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	5.75	7.34			104	4.75	4.40		
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

Key:LH = luteinizing hormone; SD = standard deviation.

Table 32. Mean Baseline and Mean Change from Baseline Values of LH in TLANDO-Treated Subjects in Study 16-002

Visit		LH Value (IU/L)	Change from Baseline (IU/L)
	n	Mean (SD)	Mean (SD)
Baseline	93	6.17 (5.56)	
Exit	62	2.17 (3.34)	-4.74 (4.92)

Key:LH = luteinizing hormone; SD = standard deviation.

In Study 13-001, mean concentrations of FSH were similar between the two treatment groups at baseline (Table 33). Both treatment groups showed generally similar decreases at each time point. In Study 16-002, FSH concentrations also decreased from baseline (Table 34).

Table 33. Mean Baseline and Mean Change from Baseline Values of FSH in TLANDO- and AndroGel-Treated Subjects in Study 13-001

	TLANDO					AndroGel				
		FSH Value (IU/L)		Change from Baseline (IU/L)			FSH Value (IU/L)		Change from Baseline (IU/L)	
Visit	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	8.43	10.30			104	7.20	7.61		
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

Key:FSH = follicle-stimulating hormone; SD = standard deviation.

Table 34. Mean Baseline and Mean Change from Baseline Values of FSH in TLANDO-Treated Subjects in Study 16-002

		FSH Value (IU/L)	Change from Baseline (IU/L)
Visit	n	Mean (SD)	Mean (SD)
Baseline	95	7.06 (6.30)	
Exit	92	2.23 (3.56)	-4.91 (4.88)

In Study 13-001, LH and FSH reductions were similar between both treatment groups, which suggests a similar degree of pituitary hormone suppression with TLANDO and AndroGel, consistent with testosterone supplementation and negative feedback.

7.11.6 Cosyntropin Stimulation Testing

In Studies 16-002 and 16-003, a subset of subjects had cosyntropin stimulation testing done at screening and end of study to assess any possible adverse effects on the hypothalamic-pituitary-adrenal (HPA) axis. The cosyntropin stimulation test was administered as a 60-minute test as recommended by the product label; with the 60-minute interval, at least approximately doubling of the basal plasma cortisol value is the criterion for a normal response.

In Study 16-002, testing was performed on 39 subjects at baseline and 37 subjects at study exit. At baseline, the mean cortisol at 0 minutes was 13.8 µg/dL, and the mean cortisol at 60 minutes was 32.1 µg/dL (153.9% increase). At study exit, the mean cortisol at 0 minutes was 14.4 µg/dL and the mean cortisol at 60 minutes was 30.0 µg/dL (143.6% increase)._

In Study 16-003, testing was performed on 59 subjects at baseline and 54 subjects at study exit. At baseline, the mean cortisol at 0 minutes was 13.6 µg/dL, and the mean cortisol at 60 minutes was 30.0 µg/dL (160% increase). At study exit, the mean cortisol at 0 minutes was 13.3 µg/dL and the mean cortisol at 60 minutes was 26.5 µg/dL (139% increase)._

The results of the cosyntropin stimulation tests were similar between baseline and end of study for both studies and demonstrate that the HPA axis is not being suppressed by TLANDO administration.

8. SAFETY EVALUATION

8.1 Overall Safety Database

For the pivotal 52-week safety study, 13-001, 210 subjects received TLANDO treatment and 105 subjects received AndroGel. Seven clinical studies in hypogonadal men (16-002, 16-003, 14-001, 1021-09-001, S361.1.001, M12-778, and M13-298) provide supportive safety data.

Table 35 displays the number of subjects receiving study drug by study for the pivotal safety and supportive clinical studies.

Table 35. Summary of Safety Populations by Study for Pivotal Safety and Supportive Clinical Studies

Study ID	TLANDO	AndroGel	Andriol	Placebo
Studies in Hypogonadal Men				
Total- ISS	**525**	**104**	**34**	**18**
13-001	210	104	0	0
09-001	35	0	34	0
S361.1.001	24	0	0	0
M12-778	66	0	0	18
M13-298	32	0	0	0
14-001	14	0	0	0
16-002	95	0	0	0
16-003 (total subjects[2])	100	0	0	0
16-003 (unique subjects)	49	0	0	0
Studies in Postmenopausal Women (not included in ISS)				
Total	**66**	**0**	**24**	**0**
05-001	24	0	24	0
S361.1.002	20	0	0	0
M12-868	12	0	0	0
LPCN 1111-15-001	*10*	*0*	*0*	*0*

[1] Subjects could be exposed to more than one treatment/dose. Thus the overall count may be different from the sum of counts of all treatment/dose columns.
[2] Subjects from the 16-002 study were allowed to rollover into the 16-003 study

8.2 Extent of Exposure

The extent of exposure to TLANDO is summarized in Table 36. The most commonly used TLANDO dose in these studies was 225 mg twice daily (265 subjects), which had a median exposure of 119 days (ranging from 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 36. Exposure of Subjects by Duration (All Doses)

Subjects Exposed At Least	n (%)
1 day[1]	591 (100%)
≥ 90 days[2]	157 (35.9%)
6 months[2]	145 (33.2%)
1 year[2]	121 (27.7%)

[1] All subjects exposed to at least one dose of TLANDO are included and is derived from all studies completed to date (05-001, 09-001, S361.1.001, S361.1.002, M12-778, M12-868, M13-298, 13-001, 14-001, 16-002, 16-003)
[2] 13-001 is the only study with subject exposure > 90 days.

For 6 months, cutoff calculated as 180 days along with protocol defined windows of -2 to +5 days, likewise, 1 year cutoff calculated as 365 days with protocol defined window of -2 to +5 days.

The extent of exposure to study drug in the pivotal safety study 13-001 is shown in Table 37.

Table 37. Exposure to Study Drug (Safety Set) for Study 13-001

Parameter Statistic	TLANDO N = 210	AndroGel N = 104
Total Number of Days on Study[a]		
Mean (SD)	273.8 (134.88)	308.5 (109.9)
Median	364.0	364.0
Min-Max	1–391	1–421
Duration of Exposure (weeks)		
Mean (SD)	37.22 (20.66)	41.5 (17.66)
Median	52.0	52.00
Min-Max	0.1–54.6	0.1–54.6

Key: Min = minimum; Max = maximum; SD = standard deviation.
Note: Total number of days on study includes subject participation from the time of randomization until termination from or completion of the study. Duration of exposure only includes the time subjects were receiving study drug (i.e., [date of last dose – date of first dose + 1]/7).
[a] Total number of days on study is defined as the number of days from date of randomization to date of discontinuation or Week 52 visit.

The extent of exposure to TLANDO for Study 16-002 is shown in Table 38.

Table 38. Exposure to Study Drug, (Safety Set) for Study 16-002

Parameter Statistic	TLANDO N = 95
Total Number of Days on Study[a]	
Mean (SD)	26.0 (2.55)
Median	26.0
Min-Max	21-33
Duration of Exposure (days)	
Mean (SD)	24.6 (2.66)
Median	24.0
Min-Max	12-31

8.3 Adverse Events for Studies 13-001 and 16-002

8.3.1 Overall Incidence of Adverse Events

The overall incidence of adverse events (AEs) in Study 13-001 is presented in Table 39. The incidence of treatment-emergent AEs (TEAEs) between the TLANDO and AndroGel groups was similar, 67.6% vs 65.4%. Nineteen subjects in the TLANDO group (9.0%) experienced TEAEs that led to study discontinuation compared with 5 subjects (4.8%) in the AndroGel group.

Table 39. Overall Incidence of Adverse Events for Study 13-001 (Safety Set)

Parameter	TLANDO (N = 210)		AndroGel (N = 104)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Any TEAE	142 (67.6)	380	68 (65.4)	195
Any treatment-related TEAE[a]	51 (24.3)	79	23 (22.1)	43
Any treatment-related and severe TEAE	0	0	0	0
Any TEAE leading to discontinuation	19 (9.0)	33	5 (4.8)	6
Any treatment-emergent SAE	12 (5.7)	15	2 (1.9)	4
Any treatment-related, treatment-emergent SAE	0	0	0	0
Any TEAE resulting in death	0	0	0	0

Key: SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Percentages are based on N.
[a] Adverse events were considered treatment-related if the relationship to study drug was related.

The overall incidence of adverse events (AEs) in Study 16-002 is presented in Table 40. Overall, 21.1% (20/95) of subjects experienced at least one TEAE. One subject experienced one serious adverse event (SAE), bleeding gastric ulcer, that led to study discontinuation.

Table 40. Overall Incidence of Adverse Events for Study 16-002 (Safety Set)

Preferred Term	TLANDO (N = 95)	
	Subjects n (%)	Events (n)
Any TEAE	20 (21.1)	33
Any treatment-related TEAE	6 (6.3)	9
Any treatment-related and severe TEAE	0	0
Any TEAE leading to discontinuation	1 (1.1)	1
Any treatment-emergent SAE	1 (1.1)	1
Any treatment-related, treatment-emergent SAE	0	0
Any TEAE resulting in death	0	0

Notes: Adverse events were classified into system organ class and preferred term by using Medical Dictionary for Regulatory Activities Version 17.1.
Adverse events were considered as drug reactions if the relationship to study drug was related.
Subjects were counted only once per system organ class and per preferred term.
Percentages are based on N.

8.3.2 Adverse Event Summary for Studies 13-001 and 16-002

A summary if TEAEs reported in 2% or more of subjects for Study 13-001 is presented in Table 41.

Table 41. Treatment-emergent Adverse Events Reported in at Least 2% of Subjects in Either Treatment Arm in Study 13-001 (Safety Set)

Preferred Term	TLANDO (N = 210)		AndroGel (N = 104)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
Upper respiratory tract infection	11 (5.2)	12	6 (5.8)	6
Headache	10 (4.8)	10	5 (4.8)	6
Nasopharyngitis	8 (3.8)	8	5 (4.8)	5
Fatigue	5 (2.4)	5	7 (6.7)	8
Hypertension	6 (2.9)	6	5 (4.8)	5
Weight increased	10 (4.8)	10	1 (1.0)	1
Acne	7 (3.3)	7	3 (2.9)	3
Back pain	6 (2.9)	6	3 (2.9)	3
Arthralgia	3 (1.4)	5	4 (3.8)	4
Diarrhoea	6 (2.9)	6	1 (1.0)	1
Bronchitis	3 (1.4)	3	3 (2.9)	3
Sinusitis	5 (2.4)	5	1 (1.0)	2

Notes: Adverse events were classified into system organ class and preferred term by using Medical Dictionary for Regulatory Activities Version 16.1.
Subjects were counted only once per system organ class and per preferred term.
Percentages are based on N.

A summary if TEAEs reported in 2% or more of subjects for Study 16-002 is presented in Table 42.

Table 42. Treatment-Emergent Adverse Events Reported in at Least 2% of Subjects in Study 16-002 (Safety Set)

Preferred Term	TLANDO (N = 95)	
	Subjects n (%)	Events n
Blood prolactin increased	6 (6.3)	6
Weight increased	2 (2.1)	2
Headache	2 (2.1)	2
Musculoskeletal pain	2 (2.1)	2

Notes: Adverse events were classified into system organ class and preferred term by using Medical Dictionary for Regulatory Activities Version 17.1.
Adverse events were considered as drug reactions if the relationship to study drug was related.
Subjects were counted only once per system organ class and per preferred term.
Percentages are based on N

Androgenic adverse events in Study 13-001 are shown in Table 43. The frequencies were low and similar between treatment groups.

Table 43. Androgenic Adverse Events (Study 13-001)

Preferred Term	TLANDO N=210 n (%)	AndroGel N=104 n (%)
Sleep apnea syndrome	3 (1.4)	1 (1.0)
Peripheral edema	3 (1.4)	1 (1.0)
Prostatic symptoms	3 (1.4)	1 (1.0)
Polycythemia	1 (0.5)	1 (1.0)
Acne	7 (3.3)	3 (2.9)

8.3.3 Discontinuations due to Abnormal Lab Parameters, Adverse Events, or Lack of Efficacy

In Study 13-001, 22 (10.5%) subjects in the TLANDO treatment group discontinued the study due to abnormal laboratory parameters, adverse events, or lack of efficacy. Eleven (10.5%) subjects in the AndroGel group discontinued for the same reasons. A further breakdown of the discontinuations is shown in Table 44.

Table 44. Discontinuation Due to Abnormal Lab Parameters, any AEs & Lack of Efficacy (Study 13-001)

Parameter	TLANDO (N=210) n (%)	AndroGel (N=105) n (%)
Discontinued due to abnormal lab parameters, any AEs & lack of efficacy	22 (10.5)	11 (10.5)
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
Other adverse events	7 (3.3)	5 (4.8)
Decreased sex drive	1 (0.5)	-
Insomnia		1 (1.0)
Prostate Cancer		1 (1.0)
Others (Investigator / patient discretion)	6 (2.9)	3 (2.9)
Serious adverse events	3 (1.4)	0
Lack of efficacy (symptomatic)	5 (2.4)	4 (3.8)

In Study 16-002 only one subject discontinued due to an adverse event (bleeding gastric ulcer).

8.3.4 Deaths and Serious Adverse Events

There were no deaths in any clinical studies of TLANDO. In Study 13-001, 12 subjects (5.7%) in the TLANDO group experienced treatment-emergent SAEs compared with 2 subjects (1.9%) in the AndroGel group. In Study 16-002, one subject experienced one treatment-emergent SAE. No SAEs were considered related to study drug in either study.

A summary of SAEs for Study 13-001 are shown in Table 45. Of note, the events were varied and not driven by any particular body system.

Table 45. Summary of Treatment-Emergent SAEs for Study 13-001 (Safety Set)

System Organ Class Preferred Term	TLANDO (N = 210) n (%)	AndroGel (N = 104) n (%)
Any treatment-emergent SAE	**12 (5.7)**	**2 (1.9)**
Infections and infestations	**3 (1.4)**	**1 (1.0)**
Sepsis	1 (0.5)	1 (1.0)
Cholecystitis infective	0	1 (1.0)
Osteomyelitis	1 (0.5)	0
Pneumonia	0	1 (1.0)
Pneumonia streptococcal	1 (0.5)	0
Staphylococcal bacteraemia	1 (0.5)	0
Musculoskeletal and connective tissue disorders	**3 (1.4)**	**0**
Arthritis	1 (0.5)	0
Osteonecrosis	1 (0.5)	0
Spinal osteoarthritis	1 (0.5)	0
Gastrointestinal disorders	**2 (1.0)**	**0**
Abdominal pain	1 (0.5)	0
Gastrooesophageal reflux disease	1 (0.5)	0
General disorders and administration site conditions	**1 (0.5)**	**1 (1.0)**
Chest pain	0	1 (1.0)
Non-cardiac chest pain	1 (0.5)	0
Injury, poisoning and procedural complications	**2 (1.0)**	**0**
Cervical vertebral fracture	1 (0.5)	0
Face injury	1 (0.5)	0
Nervous system disorders	**2 (1.0)**	**0**
Ataxia	1 (0.5)	0
Balance disorder	1 (0.5)	0
Syncope	1 (0.5)	0

Key: SAE = serious adverse event.
Notes: Adverse events were classified into system organ class and preferred term by using Medical Dictionary for Regulatory Activities Version 16.1.
Subjects were counted only once per system organ class and per preferred term.
Percentages are based on N.

8.3.5 Hematology and Clinical Chemistry

Select clinical laboratory mean value results by visit for Study 13-001 are shown in Table 46. Results for hematocrit, hemoglobin, total cholesterol, low-density lipoproteins, high-density lipoproteins, prostate specific antigen, and C-reactive protein are also discussed in Section 9. Study 16-002 was of shorter duration and the results observed were similar to Study 13-001; therefore, laboratory results from Study 16-002 are not presented.

Table 46. Clinical Laboratory Results for Study 13-001 – Mean (SD)

Test (Unit)	Normal Range#	Treatment Group	Baseline	Week 7	Week 13	Week 26	Week 39	Week 52	Early Term
Hematocrit (%)	37.0 to 51.0	TLANDO	43 (3.2)	44 (3.7)	45 (3.9)	46 (3.6)	46 (4)	46 (3.8)	45 (4.4)
		AndroGel	44 (3.4)	45 (3.3)	46 (3.8)	47 (3.8)	46 (3.7)	46 (3.5)	46 (3.6)
Hemoglobin (g/dL)	12.5 – 17.0	TLANDO	14.4 (1.1)	14.4 (1.2)	14.5 (1.3)	14.7 (1.2)	14.9 (1.3)	15.2 (1.3)	14.7 (1.4)
		AndroGel	14.6 (1.1)	14.7 (1.0)	14.8 (1.2)	15.1 (1.1)	15.1 (1.2)	15.3 (1.2)	15.1 (1.2)
Hemoglobin A1C (%)	4.0 to 6.0	TLANDO	6 (1.3)	5.9 (1.4)	6.1 (1.5)	6.2 (1.7)	6.2 (1.6)	6 (1.5)	6.1 (1.3)
		AndroGel	6.2 (1.5)	6 (1.4)	6.1 (1.5)	6.3 (1.7)	6.4 (1.6)	6.2 (1.5)	6.3 (1.3)
Alkaline Phosphatase (IU/L)	43 to 115	TLANDO	72 (19)	66 (19)	65 (18)	67 (20)	68 (21)	67 (21)	70 (20)
		AndroGel	73 (31)	75 (29)	74 (29)	70 (20)	71 (23)	70 (21)	93 (57)
Albumin (g/L)	35 to 55	TLANDO	45 (2.7)	43 (2.9)	43 (2.8)	44 (2.8)	45 (2.9)	45 (2.9)	45 (2.9)
		AndroGel	45 (2.6)	44 (2.5)	44 (2.5)	44 (2.1)	45 (2.4)	45 (2.4)	44 (1.9)
Blood Urea Nitrogen (mg/dL)	5 to 20	TLANDO	16.6 (4.7)	14.5 (4.2)	14.6 (4.8)	14.5 (4.3)	14.9 (4.4)	15.1 (4.7)	16.0 (4.6)
		AndroGel	16.3 (4.1)	16.1 (4.9)	15.5 (14.2)	15.2 (3.7)	15.9 (5.3)	15.4 (4.1)	16.1 (3.6)
C Reactive Protein* (mg/L)	5 mg/L	TLANDO	2.5 (2.0)	2.7 (2.0)	2.7 (2.1)	2.6 (2.1)	2.5 (1.9)	2.4 (1.9)	2.6 (2.1)
		AndroGel	2.2 (2.0)	2.1 (1.6)	2.1 (1.9)	2.2 (2.0)	2.5 (2.1)	2.4 (2.1)	2.4 (2.1)
Alanine Aminotransferase (IU/L)	10 to 40	TLANDO	30 (14)	25 (12)	24 (10)	24 (10)	27 (13)	26 (11)	29 (12)
		AndroGel	30 (14)	28 (12)	26 (11)	27 (13)	29 (12)	28 (12)	29 (18)
Aspartate Aminotransferase (IU/L)	10 to 43	TLANDO	24 (8.7)	23 (10)	23 (8.2)	21 (6.5)	22 (6.8)	22 (7.1)	24 (7.9)
		AndroGel	25 (9)	23 (7.6)	23 (8.6)	23 (7.5)	25 (8.7)	23 (9.3)	22 (9.2)
Gamma Glutamyl Transferase (IU/L)	10 to 49	TLANDO	36 (33)	30 (25)	30 (28)	35 (41)	37 (46)	34 (31)	37 (25)
		AndroGel	35 (32)	34 (27)	32 (24)	33 (20)	36 (22)	33 (20)	25 (11)
Bilirubin (mg/dL)	0.1 to 1.10	TLANDO	0.5 (0.2)	0.3 (0.2)	0.3 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
		AndroGel	0.5 (0.3)	0.4 (0.2)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)

Test (Unit)	Normal Range#	Treatment Group	Baseline	Week 7	Week 13	Week 26	Week 39	Week 52	Early Term
Lipoprotein-Associated Phospholipase A2 (ng/mL)	< 235	TLANDO	192 (48)	186 (55)	195 (55)	196 (55)	189 (63)	179 (43)	210 (53)
		AndroGel	192 (48)	191 (47)	200 (49)	202 (52)	191 (50)	178 (42)	225 (50)
HDL Cholesterol (mg/dL)	40 to 60	TLANDO	48.5 (12.7)	39.3 (9.9)	39.9 (9.5)	41.6 (9.8)	4.7 (9.9)	43.3 (10.3)	43.6 (11.4)
		AndroGel	46.5 (10.6)	44.1 (10.0)	43.9 (9.5)	43.3 (10.3)	44.7 (10.5)	44.8 (9.8)	38.4 (9.1)
LDL Cholesterol (mg/dL)	50 to 160	TLANDO	114 (30.9)	109 (35.5)	110 (36.2)	113 (37.2)	113 (36.8)	113 (37.4)	114 (32.3)
		AndroGel	110 (36.4)	101 (29.3)	99.6 (32.6)	99.7 (28.0)	106 (31.4)	103 (35.8)	96.2 (23.9)
Triglycerides (mg/dL)	45 to 200	TLANDO	192 (142.5)	180 (113.7)	171 (96.4)	170 (130)	163 (98.4)	159 (103.8)	215 (145)
		AndroGel	186 (113.9)	197 (112)	208 (141)	221 (237)	200 (149)	179 (131)	282 (273)
Cholesterol (mg/dL)	125 to 200	TLANDO	198 (37.4)	183 (41.0)	183 (40.8)	187 (41.7)	185 (40.2)	185 (41.3)	199 (42.7)
		AndroGel	192 (43.2)	183 (37.1)	183 (43.4)	185 (41.0)	190 (44.3)	182 (43.3)	185 (34.9)
Prolactin (ng/mL)	2.1 to 17.7	TLANDO	6.5 (3.7)	8.3 (4.1)	8.4 (4.2)	7.9 (3.8)	7.4 (4.2)	7.4 (3.5)	8.2 (4.2)
		AndroGel	6.3 (2.7)	7.8 (3.6)	8.5 (5.4)	8.3 (4.4)	7.5 (3.3)	7.4 (3.6)	7.2 (2.1)
Prostate Specific Antigen (µG/L)	< 4.0	TLANDO	0.7 (0.5)	0.9 (0.7)	0.8 (0.6)	0.9 (0.7)	0.9 (0.6)	1 (0.7)	1.1 (1.7)
		AndroGel	0.6 (0.4)	0.7 (0.5)	0.7 (0.5)	0.7 (0.4)	0.7 (0.4)	0.7 (0.4)	0.9 (0.6)

Normal value based on the central laboratory used for the study
* Based on Centers for Disease Control and American Heart Association recommendations, CRP values > 10.0 mg/L were excluded, as such a high CRP level is possibly related to acute inflammation.

8.3.6 Urinalysis

In Study 13-001, for the analytes of specific gravity, pH, and urobilinogen, there were no notable differences between the TLANDO and AndroGel groups at baseline or at other time points. Mean changes from baseline were generally not clinically meaningful, and there were no remarkable trends. While there were outliers for various analytes, mean values remained within normal limits. There were no remarkable findings from Study 16-002.

8.3.7 Hepatic Safety

Results of liver function tests as presented in Table 46, show no meaningful changes from baseline and indicate that there is no detrimental effect to liver function.

8.4 Safety Relevance of Cmax Excursions

There were a small number of Cmax excursions (secondary endpoints) above the defined thresholds. The exposure of these patients to elevated T levels were minimal, transient, showed no consistent repeatability or escalation over time, and were quickly reversible. The Cmax excursions did not correlate with high Cavg concentrations. The Cmax elevations were also not associated with changes in vital signs or key laboratory parameters based on up to 52 weeks of treatment.

Lipocine evaluated the safety relevance of observed T Cmax excursions outside of the conventional transdermal endpoint of Cmax greater than 1500 ng/dL in Study 13-001 by looking for any apparent trends in the frequency of AEs and changes in laboratory parameters of special interest in subjects with Cmax >1500 ng/dL compared with those with Cmax <1500 ng/dL. Since there were no dose changes following Week 8, subjects' Week 13 Cmax events were used in these analyses of AEs with onset after Week 13. These adverse event summaries are provided in Appendix 2.

No apparent trends were evident with respect to the frequency of AEs or AEs of special interest in subjects with T Cmax events greater than 1500 ng/dL, compared with subjects with T Cmax events less than 1500 ng/dL.

Smaller changes from baseline to end of study were observed for Hgb and Hct in subjects who had a T Cmax events greater than 1500 ng/dL compared to subjects who had a T Cmax events below 1500 ng/dL. The change from baseline to end of study in HDL and PSA levels was not different for subjects with T Cmax greater than 1500 ng/dL compared to subjects with T Cmax below 1500 ng/dL.

9. TOPICS OF SPECIAL INTEREST

9.1 Testosterone Undecanoate to Testosterone Conversion Ex-Vivo

The biological matrix used for the bioanalysis of clinical samples in the TLANDO program was serum. For the pivotal Studies 13-001, 16-002 and 16-003, bioanalytical testing and method validation were performed by PPD® Laboratories. It has been reported in the literature that the TU to T conversion due to esterase activity may continue ex-vivo unless appropriate steps and procedures are in place to control for it. The possible conversion of TU to T ex-vivo was evaluated, to ascertain if the sample collection and processing steps in place during TLANDO clinical studies were adequate to ensure the conversion of TU to T was controlled. The experiments conducted in this evaluation are discussed in Appendix 4, and show that sufficient controls were in place during sample collection and processing for TLANDO clinical studies, and that PK data from the respective studies are accurate and validated with respect to TU to T ex-vivo conversion.

9.2 Dietary Considerations: Effect of Food and Fat

A single-dose pilot food effect study (S361.1.002) was conducted in post-menopausal women with preliminary formulations of TU to provide an initial assessment of the effect of food-fat on drug bioavailability. Both food with no fat and food with fat, increased the bioavailability over fasting conditions. With these initial formulations, normal and high fat conditions increased T concentrations more than the fed/no fat and fed/low fat conditions.

The Phase 2 dose ranging study (M12-778) and the Phase 3 study (13-001) were initiated before the definitive food/fat effect study (14-001) was conducted. Therefore, the protocols prescribed dosing to be done approximately 30 minutes after a standard meal containing moderate amounts of fat.

The definitive food/fat effect study (14-001) showed that TU administered under a fed state gave consistent and predictable therapeutic levels of T and DHT with no significant sensitivity to food fat content. Based on these findings, the fixed dose Phase 3 studies (16-002, 16-003) did not have strict dietary fat requirements but only required that each dose be taken after / with a meal.

Lipocine also evaluated the effect of co-administration of the TLANDO capsules with ethanol and possible dose dumping using *in vitro* dissolution testing. The results of the dissolution test indicated that dose dumping would not occur with co-administration of ethanol.

9.3 Cardiovascular Risk

Cardiovascular adverse effects attributed to TRT have been the subject of recent meta-analyses (Fernández-Balsells 2010), (Haddad 2007) (Xu 2013); however, these studies have produced controversial and conflicting results. The information in the following sections reviews the cardiovascular safety data related to TLANDO.

9.3.1 Cardiovascular Adverse Events

Treatment-emergent adverse events for Study 13-001 from the Cardiac Disorders System Organ Class (SOC) are provided in Table 47. These AEs were mild or moderate in severity, and were balanced between the two treatment arms.

Table 47. Treatment-Emergent Adverse Events from Cardiac Disorder SOC in both Treatment Arms for Study 13-001 (Safety Set)

System Organ Class Preferred Term	TLANDO N=210		AndroGel N=104	
	Subjects n (%)	Events n	Subjects n (%)	Events n
CARDIAC DISORDERS	7 (3.3)	9	6 (5.8)	8
Atrial fibrillation	1 (0.5)	1	2 (1.9)	2
Tachycardia	2 (1.0)	2	1 (1.0)	1
Palpitations	2 (1.0)	2	0	0
Bradycardia	0	0	1 (1.0)	1
Bundle branch block bilateral	0	0	1 (1.0)	1
Cardiac flutter	1 (0.5)	1	0	0
Left atrial dilatation	0	0	1 (1.0)	1
Mitral valve incompetence	1 (0.5)	1	0	0
Sinus tachycardia	0	0	1 (1.0)	1
Tricuspid valve incompetence	1 (0.5)	1	0	0
Ventricular extrasystoles	0	0	1 (1.0)	1
Ventricular hypertrophy	1 (0.5)	1	0	0

Notes: Adverse events were classified into system organ class and preferred term by using Medical Dictionary for Regulatory Activities Version 16.1.
Subjects were counted only once per system organ class and per preferred term.
Percentages are based on N.

Adverse events associated with the vascular disorder SOC for Study 13-001 are presented in Table 48.

Table 48. Summary of Treatment-Emergent Adverse Events from Vascular Disorder SOC in both Treatment Arms for Study 13-001 (Safety Set)

System Organ Class Preferred Term	TLANDO N=210		AndroGel N=104	
	Subjects n (%)	Events n	Subjects n (%)	Events n
VASCULAR DISORDERS	9 (4.3)	9	6 (5.8)	6
Hypertension	6 (2.3)	6	5 (5.8)	5
Flushing	2 (1.0)	2	1 (1.0)	1
Hot Flush	1 (0.5)	1	0	0

Notes: Adverse events were classified into system organ class and preferred term by using Medical Dictionary for Regulatory Activities Version 16.1.
Subjects were counted only once per system organ class and per preferred term.
Percentages are based on N.

Of all the subjects who had an AE classified as Cardiovascular or Vascular Disorders SOC, only one subject had study drug discontinued, and this arose in the AndroGel arm. No subjects in the TLANDO arm discontinued from study drug due to a cardiovascular AE related.

9.3.2 Blood Pressure and Pulse Rate

In clinical studies, 13-001, 16-002, and 16-003, vital signs (blood pressure and heart rate) were taken during each visit. For Studies 16-002 and 16-003 vital sign measurements were taken at screening, at the confinement visit (time 0 of the pharmacokinetic sampling, Day 24), and at the end of the study. For Study 13-001 subjects who received TLANDO had vital sign measurements at screening and Weeks 3, 7, 13, 26, 39, and 52 (or early term). Subjects who received AndroGel had vital signs measurements at screening and Weeks 2, 4, 7, 13, 26, 39, and 52 (or early term).

Blood pressure was measured after the subject was sitting at rest for at least 5 minutes. Each clinical site used automated blood pressure devices; however, the device type and methodology were not specifically standardized across study sites.

The vital sign data in the following sections will primarily focus on measurements obtained from Study 13-001 due to the longer duration of the study and larger number of blood pressure and pulse measurements.

9.3.2.1 Vital Sign Measurements

Mean (SD) systolic and diastolic blood pressures and heart rate by visit are presented in Table 49. Mean vital sign values were consistent across all visits and were similar between treatment groups. Mean values at end of study were similar to baseline.

Table 49. Mean (SD) Blood Pressures and Pulse Rate for Study 13-001

Visit	Measurement	TLANDO (N=210) Mean (SD)	AndroGel (N=104) Mean (SD)
Baseline	SBP	132.6 (14.50)	132.6 (14.14)
	DBP	82.9 (8.58)	82.4 (8.61)
	PR	70.7 (10.12)	69.1 (11.10)
Week 2	SBP	---	131.9 (14.76)
	DBP	---	81.5 (9.30)
	PR	---	72.9 (10.95)
Week 3	SBP	132.6 (16.11)	---
	DBP	81.2 (9.15)	---
	PR	72.2 (10.44)	---
Week 4	SBP	---	132.3 (13.94)
	DBP	---	82.6 (8.90)
	PR	---	73.0 (10.73)
Week 7	SBP	131.4 (14.33)	129.9 (12.56)
	DBP	79.7 (8.93)	81.7 (8.02)
	PR	72.7 (11.60)	72.3 (10.50)
Week 13	SBP	131.3 (12.65)	130.7 (12.47)
	DBP	80.6 (8.46)	82.6 (9.37)
	PR	73.0 (11.63)	73.3 (11.34)
Week 26	SBP	130.7 (13.28)	131.0 (13.82)
	DBP	81.1 (9.32)	82.1 (8.95)
	PR	72.8 (10.91)	71.6 (10.60
Week 39	SBP	131.0 (13.71)	132.8 (13.86)
	DBP	82.1 (8.27)	83.6 (8.07)
	PR	73.5 (10.55)	71.3 (11.06)
Week 52	SBP	131.2 (14.70)	133.5 (13.76)
	DBP	81.4 (9.18)	83.0 (9.11)
	PR	72.5 (10.66)	70.0 (9.06)
Early Term	SBP	130.2 (11.17)	131.1 (12.06)
	DBP	81.3 (7.85)	80.1 (9.41)
	PR	74.2 (9.43)	72.4 (15.37)

SBP = systolic blood pressure; DBP = diastolic blood pressure; PR = pulse rate; SD = standard deviation.

Figure 5, Figure 6, Figure 7, present systolic blood pressures, diastolic blood pressures and pulse rate for Study13-001 as cumulative function curves as the percentage of subjects meeting their maximal systolic and diastolic blood pressure and pulse rate value at baseline and at any successive visit for both TLANDO and AndroGel.

Figure 5. Cumulative Function Curve of the On-treatment Maximal Systolic Blood Pressure in TLANDO- and AndroGel-Treated Subjects (13-001)

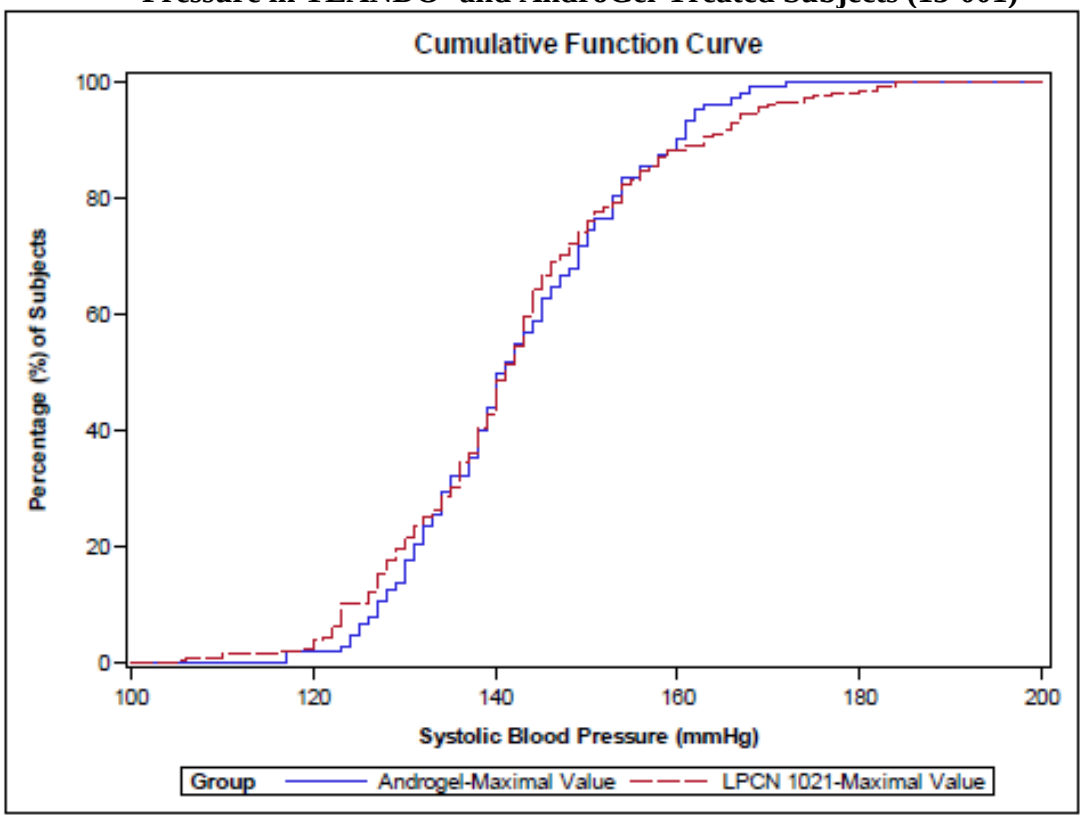


Figure 6. Cumulative Function Curve of the On-treatment Maximal Diastolic Blood Pressure in TLANDO- and AndroGel-Treated Subjects (13-001)

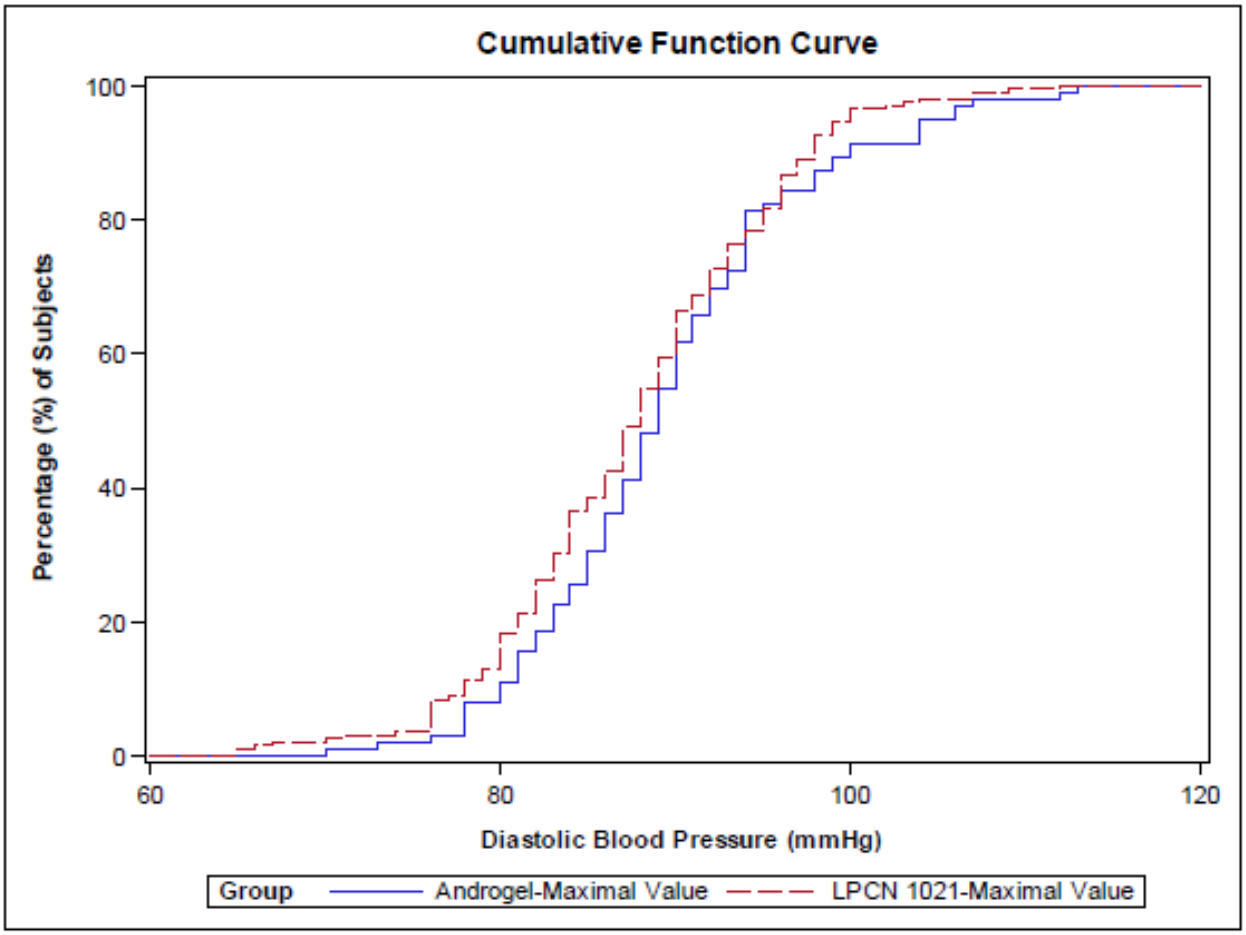
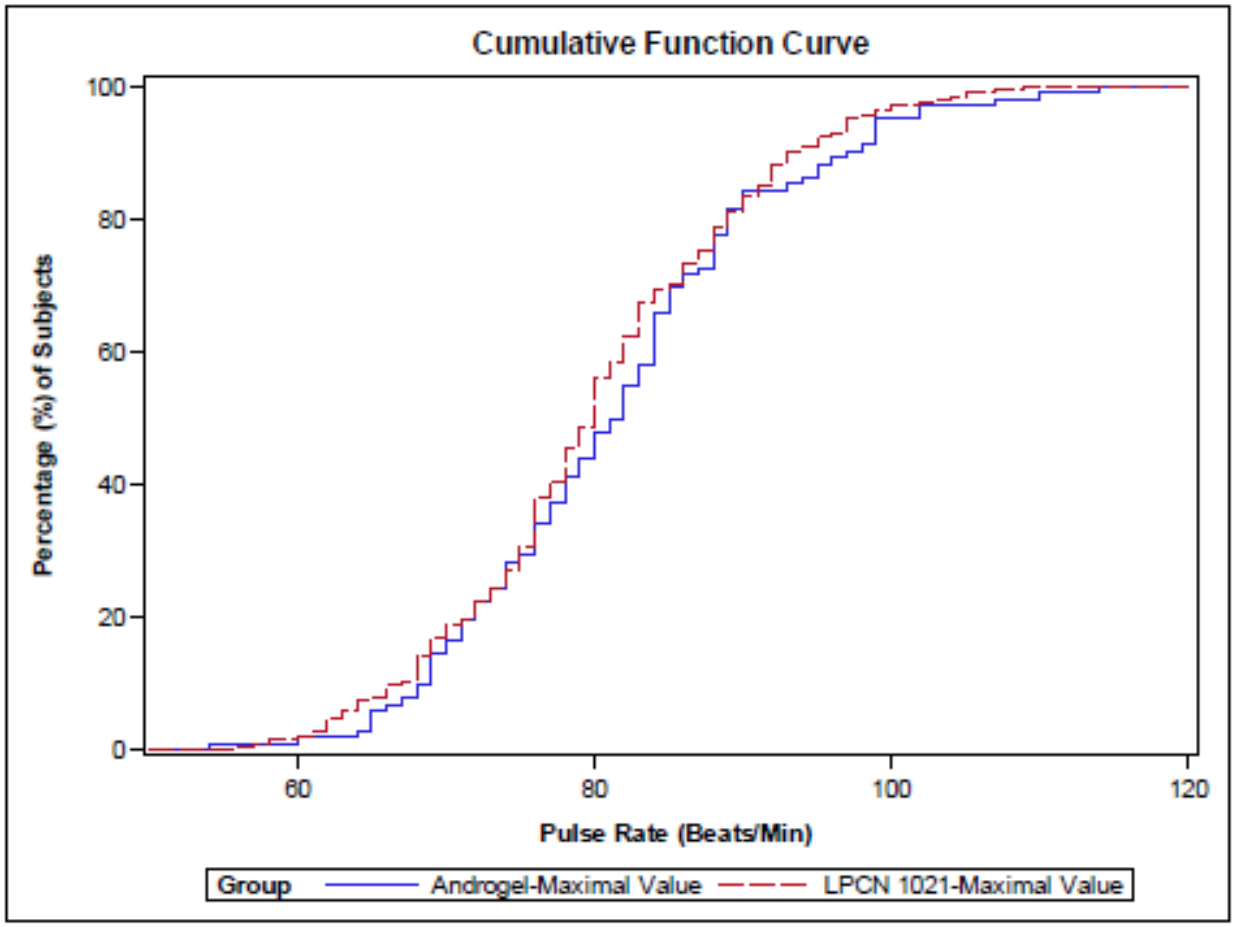


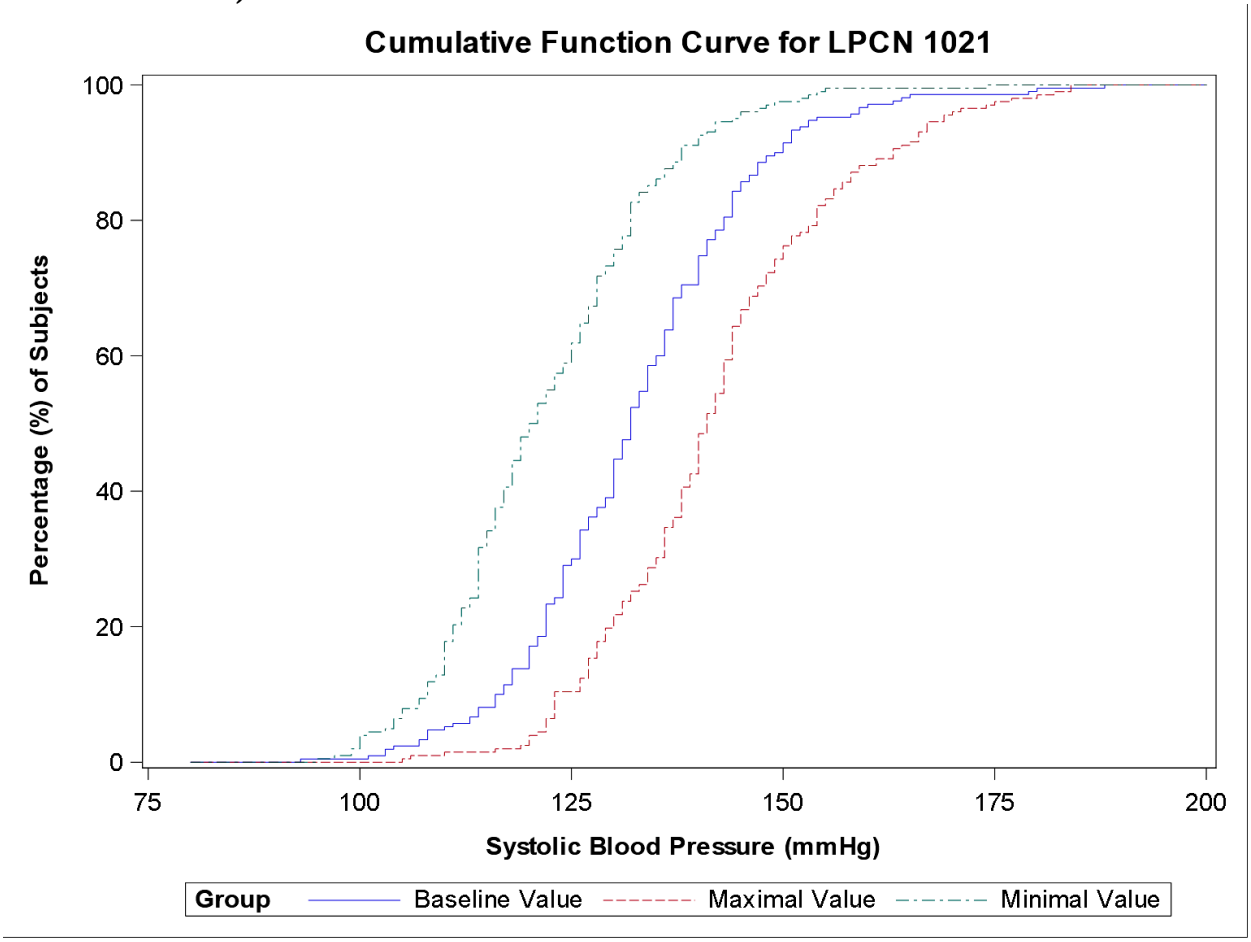
Figure 7. Cumulative Function Curve of the On-treatment Maximum Pulse Rate in TLANDO- and AndroGel-Treated Subjects (13-001)



The cumulative function curves of maximal systolic and diastolic blood pressure and pulse rate were similar between treatment groups.

Figure 8 shows the cumulative function curves for baseline systolic blood pressure as well as maximal and minimal systolic blood pressure curves (based on maximal or minimal blood pressure recorded at baseline and at any successive visit 6 visits) TLANDO-treated subjects in Study 13-001.

Figure 8. Cumulative Function Curve of the Baseline and On-treatment Minimum and Maximum Systolic Blood Pressure Values in TLANDO-Treated Subjects (Study 13-001)



The minimum and maximum function curves are approximately equidistant from the baseline systolic blood pressure curve and do not show a shift in either direction. The results of Study 13-001 therefore support that TLANDO therapy did not cause a significant shift in blood pressure either upward or downward. Rather, patients moved equally from baseline (upwards or downwards) if a maximal change in either direction were considered. This is consistent with normal variability.

Mean blood pressure data and cumulative functions curves do not suggest that TLANDO elevated blood pressure or increased pulse rate. TLANDO has similar effects on blood pressure and pulse rate as AndroGel.

9.3.2.2 Hypertension and Blood Pressure Adverse Events

Studies 13-001, 16-002, and 16-003 did not restrict inclusion of subjects with pre-existing hypertension from participating in the study. At baseline in Study 13-001 46% of subjects in the TLANDO group and 45% of subjects in the AndroGel group had pre-existing hypertension. In Studies 16-002 and 16-003, 49.5% and 49.0% of subjects, respectively, had pre-existing

hypertension. The estimated overall incidence of hypertension in the overall adult population is approximately 33.5% (CDC 2013-2014).

No subject discontinued in Studies 13-001, 16-002, or 16-003 due to reasons related to blood pressure management. No subject reported AEs related to blood pressure or hypertension in Studies 16-002 or 16-003. In Study 13-001, 15 AEs related to blood pressure/hypertension were reported by both TLANDO and AndroGel subjects. As these were not serious, no further details are available. There were 2 subjects (1%) in TLANDO and 2 subjects (2%) in AndroGel who had changes to their antihypertensive regimen (increase in dose) during the Study 13-001.

Table 50 summarizes the adverse events of hypertension of blood pressure increased reported.

Table 50. Blood Pressure Adverse Events for Study 13-001

System Organ Class Preferred Term	TLANDO (N=210)		AndroGel (N=104)	
	Subjects n (%)	Events (n)	Subjects n (%)	Events (n)
INVESTIGATIONS				
Blood Pressure Increased	2 (1.9)	3	1 (0.5)	1
VASCULAR DISORDERS				
Hypertension	5 (2.3)	5	6 (5.9)	6

SOC=System Organ Classification

No subjects in Studies 16-002 or 16-003 had changes in their antihypertensive regimen.

9.3.3 Laboratory Parameters Related to Cardiovascular Safety

9.3.3.1 Hematocrit

Stimulation of erythropoiesis and increase in hematocrit (HCT) are known androgenic effects of testosterone. Hematocrit increased in both treatment groups; however, the mean changes were minor and similar in both treatment groups. Results are summarized in Table 51. The study had a discontinuation criterion for subjects whose HCT exceeded 54%; details on subjects with HCT above 54% are provided in Appendix 3. Three subjects were discontinued for having met this criterion; two subjects in the TLANDO group and one subject in the AndroGel group.

Table 51. Mean Baseline and Mean Change from Baseline Values of Hematocrit in TLANDO- and AndroGel-Treated Subjects (Study 13-001)

	TLANDO					AndroGel				
		HCT Value (%)		Change from Baseline (%)			HCT Value (%)		Change from Baseline (%)	
Visit	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	206	43.48	3.20			103	44.03	3.36		
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

Key:HCT = hematocrit; SD = standard deviation; Term = termination.
Note: The last no missing measurement at screening served as the baseline.

9.3.3.2 Hemoglobin

Results for hemoglobin (Hgb) are summarized in Table 52.

Table 52. Mean Baseline and Mean Change from Baseline Values of Hemoglobin in TLANDO- and AndroGel-Treated Subjects (Study 13-001)

	TLANDO					AndroGel				
Visit		Hgb Value (g/dL)		Change from Baseline (g/dL)			Hgb Value (g/dL)		Change from Baseline (g/dL)	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	206	14.4	1.1			103	14.6	1.1		
Week 52	128	15.2	1.3	0.9	1.1	67	15.3	1.2	0.7	1.1
Early Term	50	14.7	1.4	0.2	0.9	14	15.1	1.2	0.2	0.8

Key: Hgb = hemoglobin; SD = standard deviation; Term = termination.
Note: The last nonmissing measurement at screening served as the baseline.

Hemoglobin increased from baseline in both treatment groups to a small degree. Increased erythropoiesis is a known pharmacological effect of testosterone.

9.3.3.3 Serum Lipids

The mean values of total cholesterol and mean changes from baseline are summarized for Study 13-001 in Table 53 and for Study 16-002 in Table 54. A small decrease for total cholesterol was observed in both treatment groups.

Table 53. Mean Baseline and Mean Change from Baseline Values of Total Cholesterol in TLANDO- and AndroGel-Treated Subjects (Study 13-001)

	TLANDO					AndroGel				
		TC Value (mg/dL)		Change from Baseline (mg/dL)			TC Value (mg/dL)		Change from Baseline (mg/dL)	
Visit	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	207	197.6	37.4			104	192	43.2		
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

Key: SD = standard deviation; TC = total cholesterol; Term = termination.
Note: The last nonmissing measurement at screening served as the baseline.

Table 54. Mean Baseline and Mean Change from Baseline Values of Total Cholesterol in TLANDO-Treated Subjects (Study 16-002))

		Total Cholesterol (mg/dL)	Change from Baseline (mg/dL)
Visit	n	Mean (SD)	Mean (SD)
Baseline	95	192.0 (42.42)	
Exit	93	181.8 (45.51)	-10.6 (33.11)

Key: SD = standard deviation.

The mean values of high density lipoprotein (HDL) and mean changes from baseline are summarized for Study 13-001 in Table 55. and for Study 16-002 in Table 56. A decrease in HDL was observed in both treatment groups, but to a somewhat greater degree in the TLANDO group. Following an initial decrease observed at Week 7, HDL levels plateaued and remained relatively constant for the remainder of the study.

Table 55. Mean Baseline and Mean Change from Baseline Values of HDL in TLANDO- and AndroGel-Treated Subjects (Study 13-001)

	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)	
Visit	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

Note: The last nonmissing measurement at screening served as the baseline.

Table 56. Mean Baseline and Mean Change from Baseline Values of HDL in TLANDO-Treated Subjects (Study 16-002)

		HDL Value (mg/dL)	Change from Baseline (mg/dL)
Visit	n	Mean (SD)	Mean (SD)
Baseline	95	40.4 (10.26)	
Exit	93	33.5 (9.45)	-6.9 (7.30)

HDL values in subjects were further evaluated in terms of shift of subjects from normal to outside of normal to understand the effect of HDL lowering. Table 57 presents a summary of shifts in HDL values in subjects from baseline to end of study (Week 52 or exit visit of early term subjects). In summary, about 19% of subjects shifted from normal to outside of normal to low in the TLANDO arm and about 15% subjects in the AndroGel arm by the end of the study.

Table 57. Baseline to End of Study (Week 52 + Early term) shift in HDL category in TLANDO- and AndroGel-Treated Subjects (Study 13-001)

		Baseline		
	Assessment	Low n (%)	Normal n (%)	High n (%)
TLANDO (N=179)	Low	31 (17.3)	34 (19.0)	1 (0.6)
	Normal	7 (3.9)	70 (39.1)	20 (11.2)
	High	0 (0.0)	3 (1.7)	10 (5.6)
AndroGel (N=83)	Low	17 (20.5)	12 (14.5)	0 (0.0)
	Normal	8 (9.6)	32 (38.6)	6 (7.2)
	High	0 (0.0)	4 (4.8)	3 (3.6)

The mean values of calculated low density lipoprotein (LDL-C) and mean changes from baseline are summarized for Study 13-001 in Table 58 and for Study 16-002 in Table 59. There were minimal LDL changes in both treatment groups throughout the duration of the study

Table 58. Mean Baseline and Mean Change from Baseline Values of LDL-C in TLANDO- and AndroGel-Treated Subjects (Study 13-001)

	TLANDO					AndroGel				
		LDL-C Value (mg/dL)		Change from Baseline (mg/dL)			LDL-C Value (mg/dL)		Change from Baseline (mg/dL)	
Visit	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	194	113.6	30.9			97	109.9	36.4		
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

Note: The last nonmissing measurement at screening served as the baseline.

Table 59. Mean Baseline and Mean Change from Baseline Values of LDL-C in TLANDO-Treated Subjects (Study 16-002)

		LDL-C Value (mg/dL)	Change from Baseline (mg/dL)
Visit	n	Mean (SD)	Mean (SD)
Baseline	95	115.4 (32.97)	
Exit	93	113.8 (39.03)	-1.5 (26.17)

Testosterone has been shown to affect serum lipid concentrations and this is reflected in the approved TRT product labels, which caution physicians to monitor serum lipid levels. HDL levels were decreased to a greater degree with TLANDO than with AndroGel; however, the relevance of decreases in HDL as a sole surrogate predictor for cardiovascular risk remains unclear.

9.3.3.4 C-Reactive Protein

C-reactive protein (CRP) is a substance produced by the liver in response to inflammation. A high level of CRP in the blood is a marker of inflammation. It can be caused by a wide variety of conditions, from infection to cancer. High CRP levels can also indicate that there is inflammation in the arteries of the heart, which can mean a higher risk for heart attack. However, the CRP test is an extremely nonspecific test, and CRP levels can be elevated in any inflammatory condition.

Results for serum CRP assays are summarized in Table 60. Reductions in serum CRP were observed in both treatment groups and would suggest no inflammatory process is occurring.

Table 60. Mean Baseline and Mean Change from Baseline Values of CRP in TLANDO- and AndroGel-Treated Subjects (Study 13-001)

	TLANDO					AndroGel				
		CRP Value (mg/L)		Change from Baseline (mg/L)			CRP Value (mg/L)		Change from Baseline (mg/L)	
Visit	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	196	2.5	2.0			99	2.2	2.0		
Week 52	120	2.4	1.9	-0.4	2.4	68	2.4	2.1	-0.4	4.1
Early Term	48	2.6	2.1	-0.6	4.8	14	2.4	2.1	-2.8	10.8

Key: CRP = C-reactive protein; SD = standard deviation; Term = termination.
Note: The last nonmissing measurement at screening served as the baseline.
Based on Centers for Disease Control and American Heart Association recommendations, CRP values > 10.0 mg/L were excluded, as such a high CRP level is possibly related to acute inflammation.

9.3.3.5 Cardiovascular Risk Scores

Given the influence of various demographic, vital sign and lipid parameters on the overall cardiovascular health in subjects, post-hoc analyses of data from the 52 week Study 13-001 were carried out. Individual cardiovascular risk factors were assessed by two different algorithms that have been developed based on large studies conducted to estimate CV risk. The algorithms are described below along with the results from the analyses.

The Framingham Risk Score (Wilson 1998) is a gender-specific algorithm that estimates the 10-year cardiovascular risk of an individual. The Framingham Risk Score was first developed based on data obtained from the Framingham Heart Study. This study was designed to examine the association of Joint National Committee (JNC-V) blood pressure and National Cholesterol Education Program (NCEP) cholesterol categories with coronary heart disease (CHD) risk, to incorporate them into coronary prediction algorithms, and to compare the discrimination properties of this approach with other noncategorical prediction functions. The study evaluated 2489 men and 2856 women aged 30 to 74 years at baseline with 12 years follow up. Based on the observations, guidelines of blood pressure, total cholesterol, and LDL cholesterol effectively predict CHD risk was developed. A simple coronary disease prediction algorithm was developed using categorical variables, which allows physicians to predict multivariate CHD risk in patients without overt CHD.

The Reynolds risk score (Ridker 2008) was developed based on 10,724 initially healthy American non-diabetic men who were followed prospectively over a median period of 10.8 years. The model developed comparing the test characteristics of global model fit, discrimination, calibration, and reclassification in two prediction models for incident cardiovascular events, one based on age, blood pressure, smoking status, total cholesterol, and high density lipoprotein cholesterol (traditional model), and the other based on these risk factors as well as CRP and parental history of myocardial infarction before age 60 years (Reynolds Risk Score for men).

The values of the individual scores were used to calculate the mean and 95% CI for the overall study population to assess overall cardiovascular risk. The Framingham and Reynolds Risk scores for all subjects at baseline and end of study (Week 52 plus exit visit) are presented in Table 61 and Table 62, respectively.

Table 61. Mean (SD) and confidence interval of Framingham Risk Score at Baseline and End of Study in TLANDO and AndroGel treated subjects

	TLANDO				AndroGel		
Statistic	Baseline	End of Study	Change from baseline to end of study		Baseline	End of Study	Change from baseline to end of study
N	207	177	175		104	82	82
Median	13.4	13.8	0.3		16.1	18.3	-0.2
Mean	15.3	16.0	0.3		18.2	19.4	-0.1
SD	10.4	10.6	4.5		12.4	12.5	6.1
95 % LB	13.9	14.4	-0.4		15.8	16.7	-1.4
95 % UB	16.8	17.5	1.0		20.5	22.1	1.2

Change from baseline calculated for subjects who had data on all parameters required to calculate risk score at both baseline and end of study

Table 62. Mean (SD) and confidence interval of Reynolds Risk Score at Baseline and End of Study in TLANDO and AndroGel treated subjects

	TLANDO				AndroGel		
Statistic	Baseline	End of Study	Change from baseline to end of study		Baseline	End of Study	Change from baseline to end of study
N	207	176	174		104	81	81
Median	5.3	5.4	0.0		5.6	5.6	0.0
Mean	5.8	6.0	0.1		6.6	7.0	-0.1
SD	4.5	4.4	2.4		5.2	5.2	2.8
95 % LB	5.2	5.4	-0.3		5.6	5.9	-0.7
95 % UB	6.4	6.7	0.4		7.6	8.1	0.5

Change from baseline calculated for subjects who had data on all parameters required to calculate risk score at both baseline and end of study

Mean scores of the Framingham and Reynolds Risk Scores are virtually unchanged from baseline to end of study for both the TLANDO and AndroGel arms. The results of the

cardiovascular risk assessment indicate that TLANDO has no impact on overall cardiovascular risk, and the means scores were consistent with the approved TRT product AndroGel.

9.3.4 Cardiovascular Risk Conclusion

A review of the results from Studies 13-001, 16-002 and 16-003 did not identify any significant cardiovascular risk. There was little change in mean blood pressures or pulse rate from baseline to end of study in the TLANDO treatment group. There were only a few adverse events of hypertension and no subject was discontinued from study participation because of hypertension. Small and similar increases in mean hematocrit was observed in both treatment groups. Few subjects were discontinued from study participation due to elevated hematocrit. A decrease in HDL was observed with TLANDO and with AndroGel, but to a slightly greater degree with TLANDO. The relevance of this change as a sole indicator of cardiovascular risk is unknown. The cardiovascular risk calculator, which assess many cardiovascular risk factors, indicate that there was no change in cardiovascular risk detected for TLANDO or AndroGel over the treatment period.

9.4 Dihydrotestosterone and Estradiol

9.4.1 Dihydrotestosterone

9.4.1.1 Dihydrotestosterone Levels in TLANDO-Treated Subjects

Dihydrotestosterone is the primary androgenic active metabolite of T and DHTU. The established laboratory normal range for DHT is 10.6 to 71.9 ng/dL. Levels of DHT are known to rise with all TRT. It is the result of metabolic reduction by a series of 5-alpha reductases existing in numerous tissues, including the skin and the gastrointestinal tract.

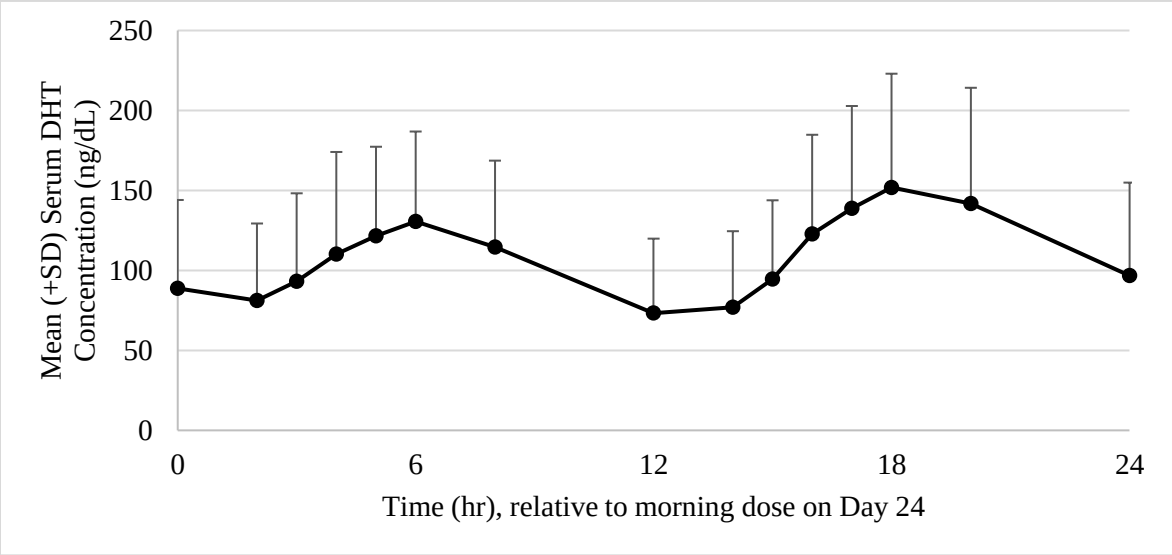
The arithmetic mean baseline DHT concentrations was 18.1 ng/dL (N=95) for Study 16-002. Pharmacokinetic parameters for DHT at Day 24 in the PK set is shown in Table 63. Measured DHT concentrations increased as T concentrations increased, indicating that the DHT PK mirrored those of T. The mean (SD) ratio of AUC DHT/T at Day 24 was 0.23 (0.06) and was within normal range for the DHT/T ratio of 0.05 to 0.33 (Wang 1999).

Table 63. Serum PK Parameters for Dihydrotestosterone) on Day 24 – PK Set for Study 16-002 (N = 90)

PK Parameter	n	Mean	SD	Median	Min, Max	Geo Mean	CV %
Cavg (ng/dL)	90	108	46.4	101	32, 280	99	42.8
Cmax (ng/dL)	90	179	71.8	170	40, 436	165	40.0

Figure 9 displays serum DHT concentrations at Day 24. The DHT concentration profile peaks around 6 hours post dose and the morning and evening dose profiles were similar.

Figure 9. Mean (+SD) Serum Dihydrotestosterone Concentrations over Time on Day 24 – PK Set (N = 90)



On Day 24, mean DHT levels were above the normal range of DHT (71.9 ng/dL); however, these levels were within a range seen with other TRT products.

Like with other TRT products, DHT concentrations increase as a result of TLANDO administration. DHT/T ratios also increase after T supplementation. A recent review of 52 clinical studies using intramuscular, transdermal gel and patches, and oral testosterone products reported that the pre- to post- treatment fold increase in DHT ranges from 1.8 to 14.2 fold (Borst 2014). In Study 16-002, the mean DHT Cavg at baseline was 18.1 ng/dL and increased to 108 ng/dL, representing approximately a 6-fold increase.

Analyses were performed to evaluate the proportion of TLANDO-treated subjects with DHT Cavg and Cmax above the normal range. Table 64 below summarizes Cavg and Cmax data for Week 3, 7 and 13 for TLANDO and single point serum DHT based analysis for Weeks 26, 39 and 52 for both TLANDO and AndroGel, with subjects subgrouped by DHT levels above the upper limit of normal (ULN), 2 times ULN, 3 times ULN and 5 times ULN in Study 13-001.

Table 64. Proportion of Subjects with DHT Cavg and Cmax in the Normal Range, and ≥ ULN, ≥ 2X ULN, ≥ 3X ULN, and ≥ 5X ULN (Study 13-001)

Visit	Treatment	Parameter	% of Subjects Above				
			Normal	ULN	2 ULN	3 ULN	5 ULN
Week 03	TLANDO	Cavg	12.3	87.7	18.5	2.3	0
Pharmacokinetic Set		Cmax0-24	0.8	99.2	77.7	33.1	3.1
Week 07	TLANDO	Cavg	15.4	84.6	17.7	0.8	0.8
Pharmacokinetic Set		Cmax0-24	0.8	99.2	74.6	23.8	1.5
Week 13	TLANDO	Cavg	19.2	80.8	20.8	0.8	0
Pharmacokinetic Set		Cmax0-24	0.8	99.2	69.2	32.3	1.5
Week 26	TLANDO	Concentration	55.7	44.3	7.6	1.0	0
Safety Set	AndroGel		56.7	43.3	17.3	4.8	1.0
Week 39	TLANDO	Concentration	61.4	38.6	7.6	0.5	0
Safety Set	AndroGel		64.4	35.6	8.7	1.9	0
Week 52	TLANDO	Concentration	60.5	39.5	11.9	1.9	0
Safety Set	AndroGel		63.5	36.5	9.6	1.0	0

* Proportion of subjects calculated using lab normal for DHT Study 16-002: 10.6 to 71.9 ng/dL

As shown in Table 64, the majority of TLANDO-treated subjects had a DHT Cavg above the ULN, as anticipated. The number of TLANDO treated subjects who fell 2-fold or more above the upper limit of normal for Cavg were approximately 20%, while very few subjects (1-2%) had their Cavg for DHT rise to 3-fold or more. The data from Weeks 26, 39 and 52 reassuringly also reveal that the TLANDO arm DHT values were comparable to those observed in the AndroGel arm.

Review of AEs was carried out for the subjects who had DHT values above 3 times the ULN at the end of the study (Week 52). The four subjects in TLANDO arm reported AEs of common cold, sore throat, anemia and sinus infection (one each). All the AEs were mild in severity and classified as not related to study drug. Of the two subjects in AndroGel arm, one subject reported cholecystectomy, pneumonia and septicemia as AE which were classified as severe but not related to study drug. The second subject reported elevated bilirubin as an AE that was classified as mild in severity and not related to the study drug. The clinical relevance of the DHT values is discussed further in Section 9.4.1.3.

The same analysis was also performed for Study 16-002. Table 65 below provides the proportion of subjects with DHT Cavg and Cmax values above the ULN, 2 times ULN, 3 times ULN and 5 times ULN in Study 16-002.

Table 65. Proportion of Subjects with DHT Cavg and Cmax in the Normal Range, and ≥ ULN, ≥ 2X ULN, ≥ 3X ULN, and ≥ 5X ULN, PK Set (Study 16-002))

Parameter	N	% of Subjects Above				
		Normal	ULN	2 ULN	3 ULN	5 ULN
Cavg (ng/dL)	90	21.1	78.9	18.9	2.2	0
Cmax0-24 (ng/dL)	90	3.3	96.7	66.7	28.9	2.2

* The lab normal value for DHT for Study 16-002 was 10.6 to 71.9 ng/dL.

As shown in Table 65, the majority of TLANDO-treated subjects had DHT levels above the upper limit of normal in Study 16-002, but relatively few had elevations beyond 3-fold or more. This finding is consistent with the findings in Study 13-001. This finding is also consistent with other TRT products; the reported DHT levels of other TRT products are provided in Section 9.4.1.2. The clinical relevance of DHT levels above the normal limit is evaluated in Section 9.4.1.3.

9.4.1.2 Dihydrotestosterone Concentrations Reported for Androgel and Other TRT Products

The summary basis of approval documents (medical and clinical pharmacology review) of three marketed products, Axiron® (NDA #022504), AndroGel® (NDA #022309) and Natesto® (NDA #205488), report the DHT/T ratio is in the range of 0.05 to 0.33. The observed DHT/T ratios following treatment with TLANDO showed a reasonably constant arithmetic mean with the AUC DHT/T ratio of 0.23.

In Study 16-002, TLANDO-treated subjects showed a 24-hour average DHT mean (SD) values of 108 (46) with 95 % CIs ranging from 98.5 to 117.5 ng/dL. These values are about 1.5 times the upper limit of the normal range. The established laboratory normal range for DHT is 10.6 to 71.9 ng/dL. In Study 13-001, the levels of DHT observed with TLANDO were comparable to the levels seen with the AndroGel active control arm. The DHT results from Study 13-001 are summarized in Table 66 and reveal comparable changes between treatment arms from Week 13 onwards.

Table 66. Mean (SD) Serum DHT Cavg at Week 13 and single point DHT value at Weeks 26, 39, and 52

		Week 3	Week 7	Week 13	Week 26	Week 39	Week 52
	Parameter	Mean (SD)					
TLANDO	Cavg DHT (ng/dL)	116 (42)	114 (49)	112 (36)	91 (49)	93 (44)	92 (58)
	DHT/T Ratio	0.24 (0.06)	0.26 (0.07)	0.26 (0.07)	0.23 (0.11)	0.22 (0.12)	0.23 (0.12)
AndroGel	Cavg DHT (ng/dL)			99 (56)	102 (70)	86 (51)	87 (49)
	DHT/T Ratio			0.20 (0.06)	0.19 (0.06)	0.19 (0.08)	0.20 (0.07)

The DHT levels observed in Study 13-001 are comparable to the reported DHT levels and ratios for other TRT products. Examples of reported DHT concentrations for other TRT products based on published literature or FDA summary basis of approval documents are presented in Table 67, Table 68, and Table 69.

Table 67. DHT Concentrations reported with AndroGel 1%

	Reported DHT:T Ratio	Reported T at Day 180 Cavg, ng/dL	Calculated DHT Cavg, ng/dL
Dose	Range	Mean (SD)	Range
100 mg T (N=48)	0.27 - 0.33	713 (209)	193 – 235
50 mg T (N=44)	0.23 - 0.29	555 (225)	128 – 161

Source: AndroGel 1% label (NDA 021015, approved 02/28/2000). Dihydrotestosterone Cavg calculated based on reported T concentration and DHT:T ratio.

Table 68. DHT Concentrations reported with AndroGel 1.62%

	Calculated DHT:T Ratio	Reported T at Day 182 Cavg, ng/dL	Reported DHT at Day 182 Cavg , ng/dL (n=12)
Dose	Mean	Mean (SD)	Mean (SD)
20.25 mg T	0.19	524 (228)	81.2 (44.9)
81 mg T	0.15	537 (240)	82.3 (46.2)

Source: AndroGel (NDA 022309, approved 04/29/2011) Clinical Review, page 66, Clinical Pharmacology Review page 48.

Table 69. DHT Concentrations reported with Axiron

	Calculated DHT:T Ratio	Reported T Cavg, ng/dL	Reported DHT, ng/dL
Dose		Mean (SD)	Mean (SD)
30 mg T, Day 60 (N=136)	0.20	487 (104)	96.2 (40.2)
30 mg T, Day 120 (N=135)	0.21	480 (177)	98.7 (41.2)

Source: Axiron (NDA 022504, approved 11/23/2010) Clinical Pharmacology and Biopharmaceutics Reviews, page 14.

9.4.1.3 Clinical Relevance of Elevated Dihydrotestosterone Concentrations

Analyses of Influence of Elevated Dihydrotestosterone Concentrations on Lab Parameters and Blood Pressure

Lipocine has evaluated the influence of elevated DHT concentrations by looking at correlations of DHT levels on various laboratory and safety parameters to determine if DHT has a significant role in the safety profile of TLANDO. Various measurements and laboratory parameters were evaluated for correlations between the shift from baseline to last visit and DHT concentration. The results of these correlations for both TLANDO and AndroGel are shown in Table 70. The Pearson Correlation Coefficient values represent the degree of correlation from 0 to 1, with a value of 1 representing the highest degree of correlation. The slope represents the least squares line of the scatter plots best fit where the measurement of interest is plotted on the y-axis and DHT concentration is plotted on the x-axis. A flat line would show that there is there is no

correlation of the parameter of interest with increasing DHT concentrations. No correlations between TLANDO DHT concentrations or AndroGel DHT concentrations for and these parameters were observed.

Table 70. DHT Cavg at Week 13 vs. Lab Parameters Shift from Baseline to Last Visit

Lab Parameters	TLANDO DHT Cavg at Week 13		AndroGel DHT Conc. at Week 13	
	Slope	Pearson Correlation Coefficient	Slope	Pearson Correlation Coefficient
SBP (mmHg)	0.0058	0.01658	-0.0061	-0.02404
HDL (mg/dL)	0.0104	0.05548	0.0184	0.11916
LDL (mg/dL)	0.0565	0.09122	0.0433	0.08916
Total Cholesterol (mg/dL)	0.0938	0.12177	0.0593	0.09675
SHBG (nmol/L)	0.0562	0.02550	-0.0480	-0.03734
LH (IU/L)	-0.0086	-0.05230	-0.0143	-0.30350
FSH (IU/L)	-0.0270	-0.12518	-0.0113	-0.11898
Hematocrit (%)	0.0011	0.01325	0.0151	0.25337
Hemoglobin (mg/dL)	0.0025	0.01000	0.0461	0.22551
PSA (ng/mL)	0.0009	0.09381	-0.0002	-0.04320
CRP (mcg/mL)	-0.0213	-0.10483	0.0065	0.05899

Scatter plots of DHT versus systolic blood pressure, HDL, SHBG, and HCT are shown in Figure 10, Figure 11, Figure 12, and Figure 13. No correlations between TLANDO DHT concentrations and these parameters were observed. No correlations were observed.

Figure 10. Correlation of DHT Concentration with Systolic Blood Pressure (Study 13-001)

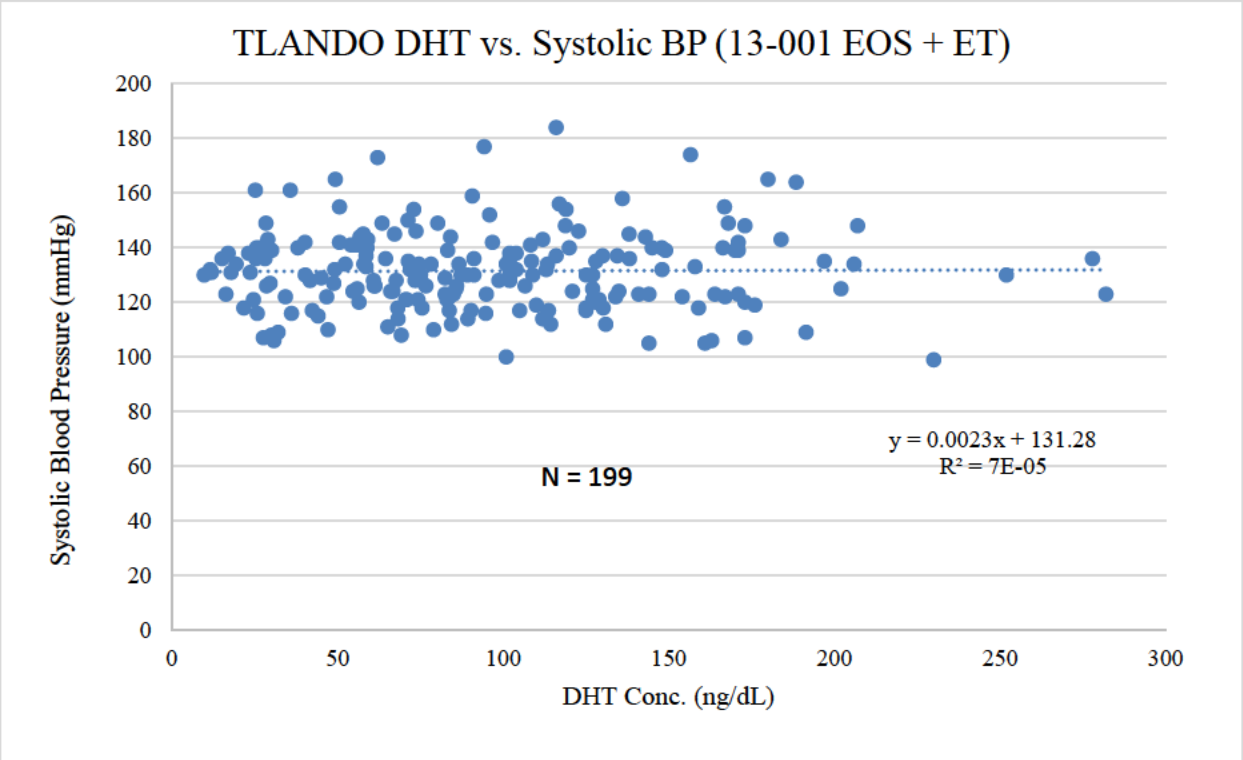


Figure 11. Correlation of DHT Concentration with HDL (Study 13-001)

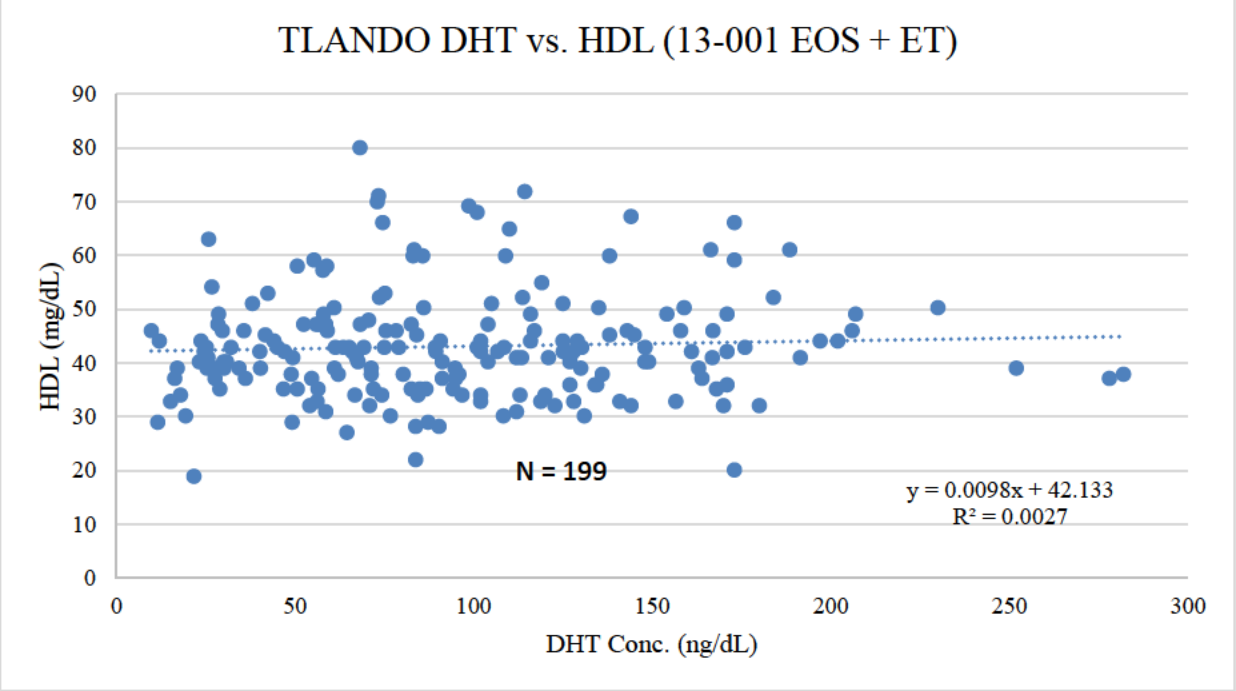


Figure 12. Correlation of DHT Concentration with SHBG (Study 13-001)

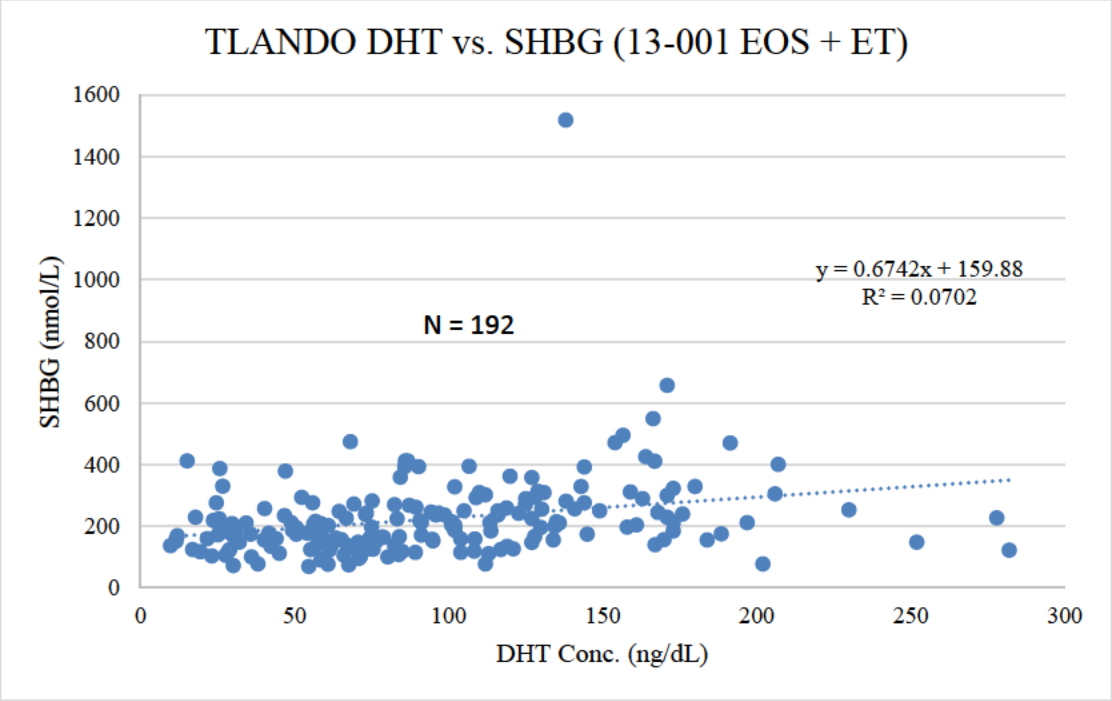
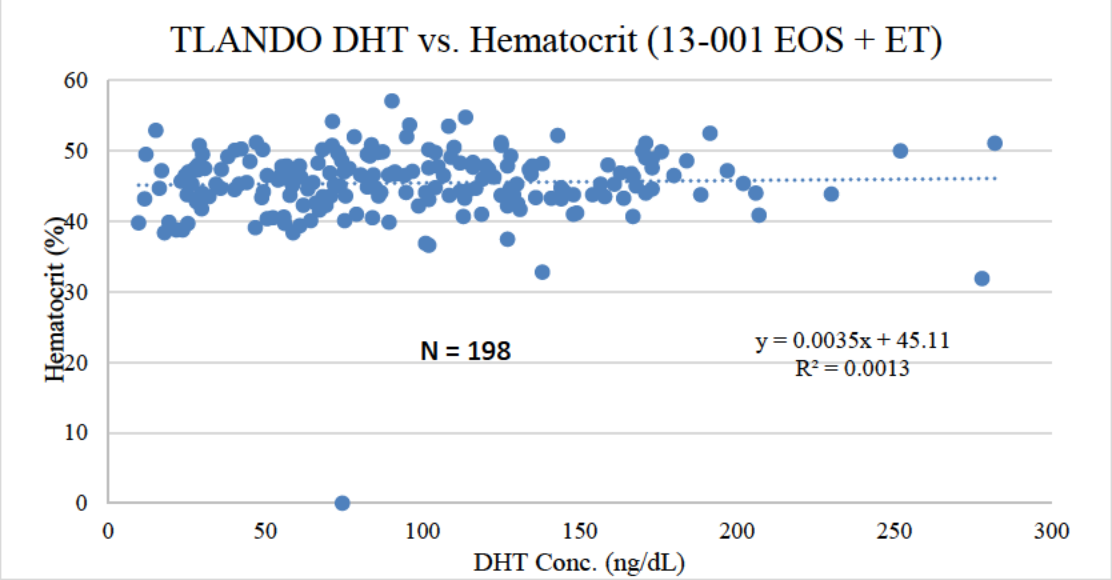


Figure 13. Correlation of DHT Concentration with HCT (Study 13-001)



Analyses of Influence of Elevated Dihydrotestosterone Concentrations on TEAEs

The safety of TLANDO was evaluated by summarizing TEAEs by subjects who had DHT Cavg above or below 2 x ULN and the results are shown in Table 71. The Week 13 DHT Cavg values were used in these analyses as overall DHT exposure is more likely to be clinically relevant, along with the TEAEs with onset from Week 13 to end of study as there were no dose changes during this period.

Table 71. Treatment-Emergent Adverse Events in >2% of TLANDO-treated Subjects in Study 13-001 Based on DHT Cavg Greater or Lower than 2 x ULN

System Organ Class Preferred Term	<= 2 x ULN (N=126) n (%)	> 2 x ULN (N=31) n (%)
GASTROINTESTINAL DISORDERS		
Diarrhoea	3 (3.00)	1 (3.23)
Nausea	2 (2.00)	2 (6.45)
INFECTIONS AND INFESTATIONS		
Influenza	4 (3.17)	0
Nasopharyngitis	3 (3.00)	2 (6.45)
Upper respiratory tract infection	6 (4.76)	2 (6.45)
INVESTIGATIONS		
Enzyme level increased	4 (3.17)	0
Weight increased	5 (5.00)	2 (6.45)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	3 (2.38)	1 (3.23)
NERVOUS SYSTEM DISORDERS		
Headache	3 (3.00)	1 (3.23)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Acne	4 (4.00)	1 (3.23)
VASCULAR DISORDERS		
Hypertension	4 (3.17)	0

The TEAEs were varied and there was no trend for higher TEAEs associated with higher DHT levels.

9.4.1.4 Clinical Studies Evaluating Dihydrotestosterone

A recent review on the clinical implications of serum DHT concentrations by Swerdloff et al (Swerdloff 2017) found that modest increases observed in serum DHT and in the DHT/T ratio observed after TRT are unlikely to be a cause of clinical concern:

- Circulating levels of DHT in response to TRT do not correlate with those found in androgen sensitive tissue (e.g., prostate, adipose, muscle) due to tight control of intracellular androgen homeostasis.
- The current body of knowledge provides some assurance that circulating levels of androgens (or changes in levels) do not play as pivotal a role as once thought in the development of prostate disease.
- Dihydrotestosterone does not play a substantive role in body composition compared to T under normal conditions.

Dihydrotestosterone has been evaluated as a treatment modality for hypogonadism and has been approved in some European countries. Double-blind, placebo-controlled trials in which hypogonadal men were treated with a DHT gel data are summarized in Table 72, and provide support that DHT levels higher than those observed in TLANDO clinical studies did not result in safety signals.

Table 72. Literature Summary of Randomized Placebo-Controlled Studies of Transdermal DHT-Gel

Duration of Dosing (Month)	Subject	DHT Gel Dose	Serum level in the DHT group**			Safety	Reference
			DHT (ng/dL)	Testosterone (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 2011
3	Healthy male >60 yrs; N=l8D N=l 9P	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 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 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	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 2010

D: DHT Gel; P: Placebo; **Serum DHT and T were stable over the course of treatment; Base: baseline; NA: not available

9.4.1.5 Dihydrotestosterone and Prostate Health

Prostate health was monitored using the International Prostate Symptom Questionnaire (I-PSS) and prostate specific antigen (PSA) concentration measurements. There were no significant findings with these measures as summarized in the following sections.

International Prostate Symptom Questionnaire

Prostate-related symptoms associated with benign prostatic hyperplasia (BPH) were assessed using the I-PSS. The I-PSS is a validated questionnaire used to assess the severity and impact of urinary symptoms and was used at screening to exclude men with moderate to severe symptoms of BPH. The I-PSS is comprised of 7 questions regarding urinary symptoms that are rated by the patient using a score ranging from 0 = not at all (or none) to 5 = almost always (or 5 or more times). Total scores could range from 0 to 35 with higher scores representing higher severity and impact of urinary symptoms. The screening I-PSS score must have been ≤ 19 to meet eligibility requirements. Subjects also completed the I-PSS at Week 52 or end of study. The I-PSS total score and change from baseline is shown in Table 73.

Table 73. Summary of I-PSS Total Score and Change from Baseline (Study 13-001)

Visit	TLANDO (N=210) Mean (SD)	AndroGel (N=104) Mean (SD)
I-PSS Total Score		
Baseline	5.6 (4.83)	4.6 (3.93)
EOS/Early termination	6.9 (5.85)	7.0 (6.31)
Change from Baseline	1.0 (4.22)	2.3 (5.07)

EOS=end of study

A slight increase in the mean I-PSS total symptom score was noted at end of study, but these changes were not considered clinically meaningful.

Nine subjects (4.3%) who received TLANDO and 3 subjects (2.9%) who received AndroGel 1.62% had an increase in I-PSS total score ≥ 19 at the end of the study (or early termination). The baseline I-PSS total score for these subjects was higher than the population mean. Subjects who received TLANDO had mean baseline I-PSS total scores of 15 (range 9-18) and subjects who received AndroGel had mean baseline I-PSS total scores of 8.7 (range 7-11).

Prostate Specific antigen

The PSA results for Study 13-001 are summarized in Table 74. Small and similar increases were observed for PSA in both the TLANDO and AndroGel treatment groups.

Table 74. PSA: Mean Baseline and Mean Change from Baseline Values of PSA in TLANDO- and AndroGel-Treated Subjects in Study 13-001

	TLANDO					AndroGel				
		PSA Value (µg/L)		Change from Baseline (µg/L)			PSA Value (µg/L)		Change from Baseline (µg/L)	
Visit	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	208	0.70	0.47			104	0.62	0.40		
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

Key: PSA = prostate-specific antigen; SD = standard deviation.
Note: The last nonmissing measurement at screening served as the baseline

Elevated PSA values > 4 ng/mL were seen in 5 subjects: 3 subjects in the TLANDO group and 2 subjects in the AndroGel group; details on subjects with elevated PSA are provided in Appendix 3. One subject in the TLANDO group and one subject in the AndroGel group discontinued because of the elevated PSA

9.4.1.6 Dihydrotestosterone Safety Summary

Lipocine finds that the DHT levels and DHT/T ratios are at acceptable levels for the following reasons:

- TLANDO DHT/T ratios are in within the normal range of 0.05 to 0.33.
- The levels of DHT levels observed in Study 13-001 were generally comparable between TLANDO and the AndroGel active control arm.
- The DHT levels observed with TLANDO are comparable to the reported DHT levels and DHT:T ratios for other TRT products.
- There were no trends for more AEs or higher PSA scores with higher DHT concentrations.

DHT concentrations demonstrated a lack of correlation with various measurements and laboratory parameters including, systolic blood pressure, HDL, SHBG, PSA and HCT. No findings have been observed to show that DHT levels adversely affect the overall safety profile of TLANDO.

9.4.2 Estradiol

9.4.2.1 Estradiol levels

Estradiol (E2) is an active metabolite of T. A single blood sample was collected from each subject during the screening visit for an assessment of baseline E2 concentration. The established laboratory normal value for E2 is 10.0 to 42.0 pg/mL. The arithmetic mean baseline E2 concentrations Study 16-002 (N=95) was 18.0 pg/mL and within the normal range. Table 75 displays PK parameters for E2 after TLANDO administration at Day 24 for the PK set. Following treatment with TLANDO, the mean estradiol Cavg value was 29 pg/mL, which is within the normal range.

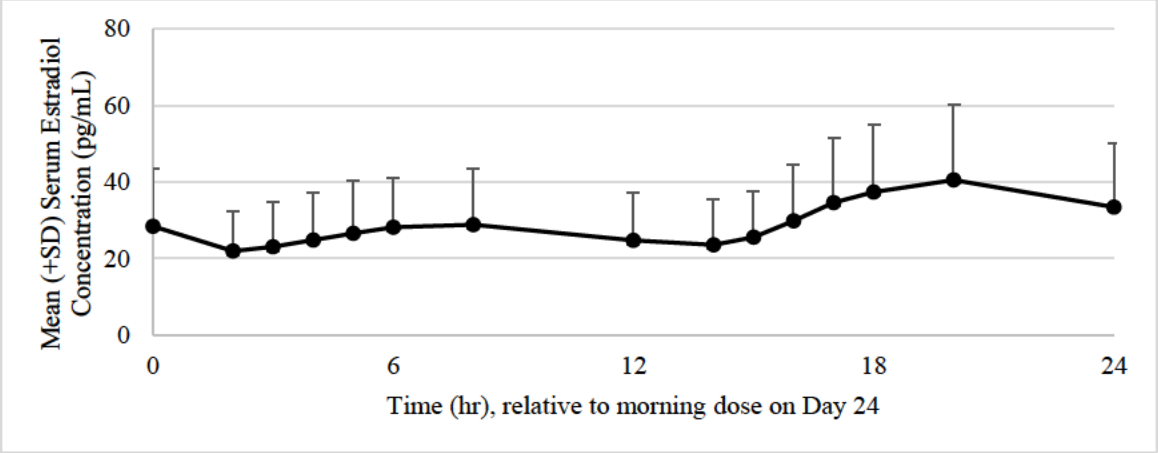
Table 75. Serum Estradiol PK (Cavg and Cmax) on Day 24 – PK Set (N = 90)

Parameter	Statistic	24-hour post morning dose	12-hour post morning dose	12-hour post evening dose
Cavg, 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)

Key: Cavg = average serum concentration; Cmax = maximum observed serum concentration; SD = standard deviation.

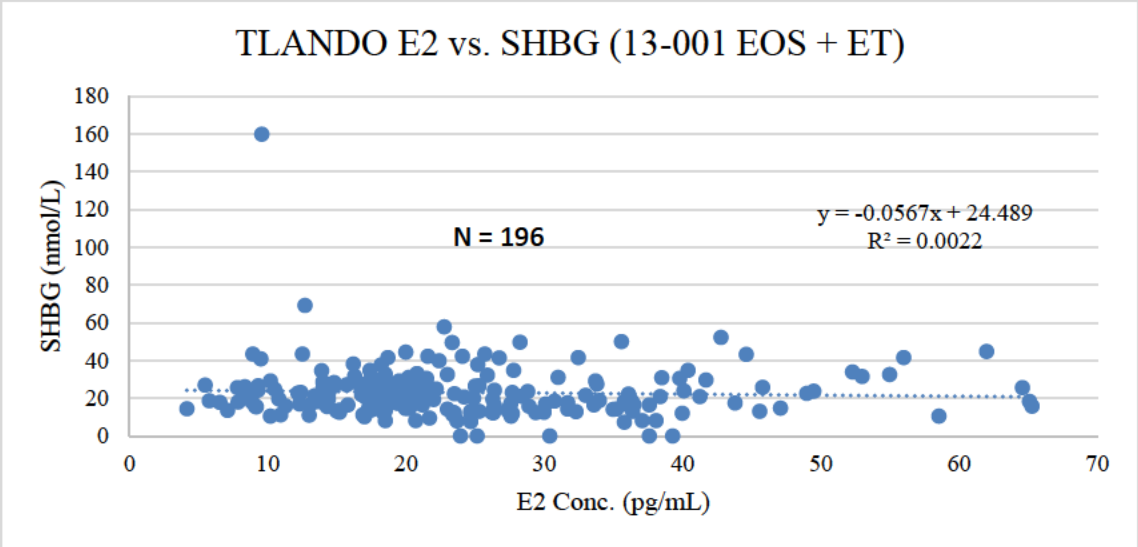
Figure 14 displays serum E2 concentrations. Serum E2 concentrations reached a peak concentration about 6 to 8 hours after dosing.

Figure 14. Mean (+ SD) Serum Estradiol Concentrations vs Time Curve on Day 24 – PK Set (N = 90)



The established laboratory normal range for E2 is 10.0 to 42.0 pg/mL. In Study 16-002, the baseline mean E2 concentration of 18.0 pg/mL increased to 29 pg/mL at end of treatment. This value is within the normal E2 range. No reports of gynecomastia, an adverse effect of excessive E2, was reported in any clinical study. Like the analyses of DHT, various measurements and laboratory parameters were evaluated for correlations to E2 concentration. No correlations of E2 concentration with either systolic blood pressure or laboratory parameters were observed. Importantly, E2 was not correlated with changes in SHBG, which can be observed in conditions of E2 excess (Figure 15).

Figure 15. Correlation of E2 Concentration with SHBG (Study 13-001)



Analyses were performed to evaluate the proportion of TLANDO-treated subjects with E2 Cavg and Cmax above the normal range. Table 76 below summarizes Cavg and Cmax data for Week 3, 7 and 13 for TLANDO and single point serum E2 based analysis for Weeks 26, 39 and 52 for both TLANDO and AndroGel, with subjects subgrouped by E2T levels above the upper limit of normal (ULN), 2 times ULN, 3 times ULN and 5 times ULN in Study 13-001.

Table 76. Proportion of subjects with E2 Cavg and Cmax in the normal range, and ≥ ULN, ≥ 2X ULN, ≥ 3X ULN, and ≥ 5X ULN (Study 13-001)

Visit	Treatment	Parameter	% of Subjects Above			
			ULN	2 ULN	3 ULN	5 ULN
Week 03 Pharmacokinetic Set	TLANDO	Cavg	12.3	0.8	0	0
		Cmax	46.9	3.1	0	0
Week 07 Pharmacokinetic Set	TLANDO	Cavg	14.6	0.8	0	0
		Cmax	46.9	4.6	0.8	0.8
Week 13 Pharmacokinetic Set	TLANDO	Cavg	12.3	0.8	0	0
		Cmax	44.6	3.1	0.8	0
Week 26 Safety Set	TLANDO	Concentration	6.7	0	0	0
	AndroGel		11.5	1.0	0	0
Week 39 Safety Set	TLANDO	Concentration	3.8	0	0	0
	AndroGel		8.7	1.0	0	0
Week 52 Safety Set	TLANDO	Concentration	5.7	0	0	0
	AndroGel		13.5	1.0	0	0

* Proportion of subjects calculated using lab normal for estradiol from LPCN 1021-16-002 study: 10 to 42 pg/mL.

The same analysis was also performed for Study 16-002. Table 77 below provides the proportion of subjects with DHT Cavg and Cmax values above the ULN, 2 times ULN, 3 times ULN and 5 times ULN in Study 16-002.

Table 77. Proportion of subjects with estradiol Cavg and Cmax in the normal range, and at various levels above the ULN, Pharmacokinetic Set (Study 16-002)

Parameter	N	n (%) of Subjects Above			
		ULN	2 ULN	3 ULN	5 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)

* The lab normal value for estradiol for Study LPCN 1021-16-002 was 10 to 42 pg/mL.

As can be seen in Table 76 and Table 77, most subjects in Study 13-001 and Study 16-002 were in the normal range for E2, and the proportions of subjects above the normal range were consistent across both studies. The clinical relevance of E2 levels above the normal range is discussed in the next section.

9.4.2.2 Analyses of Influence Elevated E2 Concentrations on TEAEs

The safety of TLANDO was evaluated by summarizing TEAEs by subject who had E2 Cavg above or below the ULN and the results are shown in Table 78. The Week 13 E2 Cavg values were used in these analyses were used in these analyses as overall E2 exposure was considered more likely to be clinically relevant, along with the TEAEs with onset from Week 13 to end of study, as there were no dose changes during this period.

Table 78. Treatment-emergent Adverse Events Observed in > 2% of TLANDO-Treated Subjects in Study 13-001 Categorized Based on E2 Cavg Greater and Lower than the ULN

System Organ Class Preferred Term	Below the ULN (N=137) n (%)	Above the ULN (N=20) n (%)
GASTROINTESTINAL DISORDERS		
Diarrhoea	4 (2.92)	0
Nausea	4 (2.92)	0
INFECTIONS AND INFESTATIONS		
Influenza	4 (2.92)	0
Nasopharyngitis	4 (2.92)	1 (5.00)
Upper respiratory tract infection	6 (4.38)	2 (10.00)
INVESTIGATIONS		
Enzyme level increased	4 (2.92)	0
Weight increased	5 (3.65)	2 (10.00)
METABOLISM AND NUTRITION DISORDERS		
Back pain	3 (2.19)	1 (5.00)
Nervous system disorders		
Headache	3 (2.19)	1 (5.00)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Acne	3 (2.19)	2 (10.00)
VASCULAR DISORDERS		
Hypertension	3 (2.19)	1 (5.00)

The TEAEs were varied and there was no trend for higher AEs associated with higher E2 levels.

9.5 Patient Monitoring in Clinical Practice and for TLANDO

For general monitoring of hypogonadal patients who are being treated with testosterone replacement therapy, the Endocrine Society Clinical Practice Guidelines recommend evaluating the patient 3 to 6 months after initiation of therapy to assess response to treatment, adverse effects, and compliance with the treatment regimen. Annual visits are recommended thereafter. It is recommended that at baseline and at each of these visits, HCT levels be determined. If HCT is above 54%, T therapy should be stopped until HCT decreases to a safe level. The patient should also be evaluated for hypoxia or sleep apnea to assess any impact on HCT levels.

The Endocrine Society recommends monitoring of the prostate. In men 40 years of age or older who have a baseline PSA greater than 0.6 ng/mL, a digital examination of the prostate should be performed, and a PSA measurement should be obtained before initiating T treatment. Evidence-based guidelines for prostate cancer screening depending the age and race of the patient should be followed. The Endocrine Society recommends a urological consult if 1) there is an increase in PSA concentration greater than 1.4 ng/mL within any 12-month period, 2) there is a PSA velocity of more than 0.4 ng/mL·year after 6 months of T therapy, 3) a prostate abnormality is detected with a digital rectal examination, and 4) there is an IPSS score greater than 19.

Lipocine has evaluated TLANDO stopping criteria for patients who do not achieve testosterone concentrations within the target therapeutic range. The following stopping criteria instructions are proposed for the product label:

To evaluate 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 in the first 3 months of therapy with TLANDO should be discontinued.

The stopping criteria utilize the normal range for testosterone of 300 to 1080 ng/dL established by the bioanalytical laboratory that performed the bioanalytical testing for Study 16-002. 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 16-002. This analysis showed that evaluating testosterone concentration in this time window would identify most subjects who had a Cavg below the normal range at the efficacy assessment of the study (14 out of 18 subjects with Cavg <300 ng/dL). There were no subjects with Cavg above the normal range in the study. Other time windows were examined; however, the 7 to 9 hour window was most effective in identifying subjects with T levels above or below the target range.

The criteria identified in Study 16-002 were subsequently tested in an analysis using the Week 3 PK data from Study 13-001. The analysis showed that applying these criteria to the Week 3 PK profile data would identified most of the subjects with a Cavg below the normal range (20 out of 24 subjects with Cavg <300 ng/dL), and that the criteria identified all

subjects with a Cavg above the normal range at Week 3 (4 out of 4 subjects with Cavg >1080 ng/dL). The analyses from both studies are summarized in Table 79 below.

Table 79. Discontinuation Criteria Applied to Study 16-002 and Study 13-001

	Criteria: 300 – 1080 ng/dL Between 7 and 9 Hrs Post AM Dosing*	
	Study 16-002 Efficacy assessment (225 mg twice daily)	Study 13-001 Week 3 PK data (225 mg twice daily)
Total N	94	193
Total number of subjects with Cavg< 300 ng/dL	18	24
Subjects with Cavg < 300 ng/dL who are identified using proposed criteria	14	20
Total number of subjects with Cavg> 1080 ng/dL	0	4
Subjects with Cavg > 1080 ng/dL who are identified using proposed criteria	-	4

* Results based on 8 hours post AM dosing data.

Lipocine proposes that the TLANDO stopping criteria, in conjunction with Endocrine Society Clinical Practice Guidelines for testosterone therapy, provide for the safe and effective use of TLANDO.

10.SAFETY CONCLUSIONS

TLANDO was generally well tolerated and the safety findings were consistent with those observed with other TRT products. Gastrointestinal adverse events were of low frequency. Most adverse events that occurred were mild or moderate in severity. No severe cardiac or hepatic disorders occurred during any clinical studies. No deaths were reported. A total of 16 treatment-emergent SAEs were reported for 12 TLANDO-treated subjects (5.7%) during the 52-week pivotal safety study. The SAEs were varied in nature and none were considered by the investigator to be related to study drug.For the combined clinical studies, 525 hypogonadal men received TLANDO for a mean 115 days. One hundred thirty subjects receiving TLANDO completed the 52-week duration pivotal safety study, providing adequate long-term safety data to meet the requirement of the International Conference on Harmonisation (ICH) E1A Guidance.

Overall, key laboratory parameters and other biomarkers were mostly within reference ranges and/or were consistent with levels observed for other approved T replacement products. Increased hematocrit is a known androgenic effect of T administration and mean increases observed were minor and similar in both treatment groups. Liver and renal function tests did not reveal any safety concerns with respect to TLANDO. Greater reductions in HDL and SHBG were observed for TLANDO when compared with AndroGel. The relevancy of HDL as a sole surrogate predictor for cardiovascular risk, however remains unclear. When considered in multivariate cardiovascular risk scores, these changes did not influence overall estimated cardiovascular risk. Androgens, particularly T, have been shown to lower HDL levels and this effect is reflected by cautionary language in the labels of approved T replacement products. Despite reduced SHBG levels, estimated free T concentrations based on total T calculations remained within normal ranges.

DHT concentrations increased on average to about 1.5 times the upper limit of normal following TLANDO treatment. However, the mean DHT values were less than what has been reported in clinical studies with other agents where the DHT elevation was not associated with increased adverse events. The increases in DHT and DHT/T ratios associated with TLANDO treatment are like those observed with other approved TRT products. A correlation analysis of DHT concentrations to HDL, blood pressure, SHBG and other parameters did not show a correlation with elevated DHT concentrations. A similar correlation analysis with E2 and T concentrations also did not show a correlation with blood pressure or other laboratory parameters.

There were no significant changes in blood pressure nor was there an excess in hypertension-associated adverse events with TLANDO (1.6% and 0.8%, respectively) as compared to AndroGel (4.8% and 1.9%, respectively). A post-hoc analyses of data from Study 13-001 using two different algorithms that have been developed to estimate individual 10-year cardiovascular risk, the Framingham Risk Score and the Reynolds Risk Score indicate that there is no impact on overall cardiovascular risk. These risk scores take into consideration changes in blood pressure, total cholesterol, LDL-C, HDL, and CRP (Reynolds).

In summary, the overall safety results demonstrate that TLANDO has an acceptable safety profile.

11.BENEFITS AND RISKS CONCLUSIONS

The development program has demonstrated that TLANDO 225 mg BID with food is safe and effective in providing testosterone replacement therapy in hypogonadal men. TLANDO will provide clinicians and patients with a new oral dosage form that will be familiar to patients, convenient, easy to use, and may improve patient compliance. TLANDO does not require titration.

TLANDO will avoid many of the limitations of current products due to formulation-specific issues. TLANDO will eliminate the risk of T transference from gels, avoid application site reactions, eliminate the inconvenience of waiting for a transdermal gel to dry or delay contact, and requires no deliberate clean-up. TLANDO will eliminate the specific risks associated with injectable products including pain at the injection site and post-injection reactions such as cough, respiratory distress, pulmonary oil micro-embolism, and anaphylaxis. TLANDO will confer advantages over alternative dosage forms and administration routes such as intranasal, buccal, and pellet implantation by the elimination of administration site adverse effects such as nasal irritation, gum-related adverse events, and potential scarring and infection.

TLANDO is not a 17-alpha-alkylated T and has shown no evidence of hepatic toxicity in subjects studied to date. Currently, the only oral T product currently available is a 17-alpha-alkyl androgen (methyltestosterone) which has been associated with serious hepatic adverse effects (e.g., peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) (Android label).

Consistent and predictable therapeutic levels of T was demonstrated for TLANDO when administered with food containing varying amounts of fat. Although TLANDO should be administered with food, the patient will have flexibility in dietary choices. Consistent failure to take the product with food would lead to a suboptimal treatment response, but would not pose a safety risk.

Several studies conclusively demonstrated that 225 mg twice daily is the optimum dose. Efficacy of TLANDO was demonstrated in Study 16-002 with 80% of subjects achieving therapeutic T concentrations in the normal range. Efficacy was also demonstrated in both obese (BMI $\geq$ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) patients thus allowing this product to be used in a broad hypogonadal population without the need for dose adjustment based on degree of adiposity.

Despite limitations of patient reported outcome data from open-label trials (13-001), the changes observed in the SF-36 and PDQ showed improvement in the domains and subscales one would expect from testosterone replacement and further supports the efficacy of TLANDO.

TLANDO was generally safe and well tolerated in the clinical studies. The commonly reported adverse events were consistent with those reported for AndroGel and those expected

with T containing products. There were no drug-related serious or severe adverse events in the clinical trials. Among all the adverse events, most were mild or moderate in severity.

Most laboratory results showed no clinically significant changes or when changes were observed, they were generally similar to AndroGel. There was no evidence of hepatic toxicity and no significant effect on the prostate was observed.

There were however, some differences from AndroGel that were observed with TLANDO therapy. Greater reductions in HDL and SHBG were observed when compared with AndroGel. The relevancy of HDL as a sole surrogate predictor for cardiovascular risk, however remains unclear. Androgens, particularly T, have been shown to lower HDL levels and this effect is reflected by cautionary language in the labels of approved T replacement products. Despite reduced SHBG levels, estimated free T concentrations based on total T remained within normal ranges. DHT, a potent metabolite of T was elevated; however, the changes were similar to AndroGel and other T products. A correlation analysis of DHT concentrations to HDL, blood pressure, SHBG and other parameters did not show a correlation with elevated DHT concentrations.

There remain unanswered questions about the long-term cardiovascular risk of currently approved testosterone replacement therapies. However, TLANDO did not demonstrate an increased cardiovascular risk and had little impact on blood pressure. Although infrequent, hypertension and blood pressure increases were reported at a lower rate in subjects treated with TLANDO (1.6% and 0.8%, respectively) as compared to AndroGel (4.8% and 1.9%, respectively). The FDA has mandated a cardiovascular safety study of approved testosterone products that is currently being planned and may help clarify the impact of testosterone products on cardiovascular disease and the risk of stroke. Lipocine believes that TLANDO has not been shown to increase cardiovascular risk in studies to date.

To further ascertain cardiovascular risk, Lipocine utilized two different algorithms that have been developed to estimate individual 10-year cardiovascular risk, the Framingham Risk Score and the Reynolds Risk Score. These scores take into consideration blood pressure, lipid values, and CRP (Reynolds). A post-hoc analyses of data from Study 13-001 was performed for each individual subject using both risk calculators at baseline and end of study. The values of the individual scores were used to calculate the mean and 95% CI for the overall study population to assess overall cardiovascular risk. The results of the cardiovascular risk assessment indicate that there is no/little impact on overall cardiovascular risk over the treatment periods with TLANDO.

In conclusion, TLANDO 225 mg BID with food was effective in restoring T levels in hypogonadal men. The observed safety profile of TLANDO in clinical studies conducted was consistent with the active control and is expected to be similar to other approved T replacement products. There were no unexpected risks specific to TLANDO identified during the clinical program. Lipocine believes that there is an unmet need for a safe and convenient oral dosage form and believes the risk/ benefit supports the approval of this new novel agent.

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APPENDIX 1. TESTOSTERONE PREPARATIONS IN THE UNITED STATES

Testosterone Preparations available in the United States

Proprietary Name	Dosage form/ Route	Applicant Holder	Approval Date
METHYL TESTOSTERONE			
Methyltestosterone	Oral Capsule	Impax	21-Sep-15
Methyltestosterone	Oral Tablet	Impax	Prior to Jan 1, 1982
Testred	Oral Capsule	Valeant	Prior to Jan 1, 1982
Android 25	Oral Tablet	Valeant	Prior to Jan 1, 1982
TESTOSTERONE			
AndroGel	Transdermal Gel	Abbvie	28-Feb-00
Testim	Transdermal Gel	Auxilium	31-Oct-02
Striant	Buccal Tablet, ER	Auxilium	19-Jun-03
Testosterone	Transdermal Gel	Actavis	27-Jan-06
Testosterone	Transdermal Gel	Par Pharmaceutical	23-May-07
Axiron	Transdermal Solution, Metered	Eli Lilly	23-Nov-10
Fortesta	Transdermal Gel, Metered	Endo Pharmaceuticals	29-Dec-10
AndroGel	Transdermal Gel, Metered	Abbvie inc	29-Apr-11
Androderm	Transdermal Film, ER	Allergan	20-Oct-11
Testosterone	Transdermal Gel	ANI Pharmaceuticals	14-Feb-12
AndroGel	Transdermal Gel	Abbvie	7-Sep-12
Testosterone	Transdermal Gel, Metered	Perrigo Israel	31-Jan-13
Natesto	Nasal Gel, Metered	Aytu bioscience inc	28-May-14
Vogelxo	Transdermal Gel	Upsher-Smith	4-Jun-14
Vogelxo	Transdermal Gel, Metered	Upsher-Smith	4-Jun-14
Testosterone	Transdermal Gel, Metered	Perrigo Israel	4-Aug-15
Testosterone	Transdermal Gel, Metered	Actavis / Teva	5-Aug-15
Testosterone	Transdermal Solution, Metered	Perrigo Israel	28-Feb-17
Testosterone	Transdermal Gel	Perrigo UK	12-Jul-17
Testosterone	Transdermal Solution, Metered	Actavis	7-Aug-17
Testosterone	Transdermal Gel	Actavis	18-Sep-17
Testopel	Implantation Pellet	Auxilium	Prior to Jan 1, 1982
TESTOSTERONE CYPIONATE			

Proprietary Name	Dosage form/ Route	Applicant Holder	Approval Date
Testosterone Cypionate	Injection Injectable	Paddock	31-Jan-05
Testosterone Cypionate	Injection Injectable	Sandoz	10-Aug-06
Testosterone Cypionate	Injection Injectable	Mylan	11-Dec-06
Testosterone Cypionate	Injection Injectable	West-ward	15-Jul-10
Testosterone Cypionate	Injection Injectable		1-May-12
Testosterone Cypionate	Injection Injectable	Sun	3-Jun-13
Testosterone Cypionate	Injection Injectable	Luitpold	16-Jun-17
Depo-testosterone	Injection Injectable	Pharmacia and Upjohn	Prior to Jan 1, 1982
Testosterone Cypionate	Injection Injectable	Watson	Prior to Jan 1, 1982
TESTOSTERONE ENANTHATE			
Testosterone Enanthate	Injection Injectable	Paddock	14-Jun-06
Testosterone Enanthate	Injection Injectable	Mylan	5-Oct-09
Testosterone Enanthate	Injection Injectable	Hikma Farmaceutica	18-Sep-12
Testosterone Enanthate	Injection Injectable	Watson	Prior to Jan 1, 1982
Delatestryl	Injection Injectable	Endo	Prior to Jan 1, 1982
TESTOSTERONE UNDECANOATE			
Aveed	Intramuscular Injectable	Endo	5-Mar-14
DISCONTINUED PRODUCTS			
Testosterone Cypionate	Injection Injectable	Multiple	Prior to Jan 1, 1982
Testosterone Enanthate	Injection Injectable	Multiple	Prior to Jan 1, 1982
Testosterone Propionate	Injection Injectable	Multiple	Prior to Jan 1, 1982
Methyltestosterone	Oral Tablet, Capsule	Multiple (41 products)	Prior to Jan 1, 1982
Testosterone			
Testosterone	Injection Injectable	Multiple	7-Jul-83
Testoderm	Transdermal Film, Extended Release	Alza Corp	12-Oct-93
Androderm	Transdermal Film, Extended Release	Allergan Sales LLC	29-Sep-95
Testoderm TTS	Transdermal Film, Extended Release	Alza Corp	18-Dec-97

APPENDIX 2. ADVERSE EVENTS BY CMAX THRESHOLD

Adverse Events Subgrouped by Cmax Greater and Less than 1500 ng/dL (Study 13-001)

	Treatment-Related TEAEs from Week 13 to End of Study Categorized by Subject Week 13 Cmax	
System Organ Class Preferred Term	**Cmax < 1500 ng/dL (N=118) N (%)**	**Cmax > 1500ng/dL (N=39) N (%)**
Blood and lymphatic system disorders	**1 (0.85)**	**0**
Polycythaemia	1 (0.85)	0
Cardiac disorders	1 (0.85)	0
Cardiac flutter	1 (0.85))	0
Gastrointestinal disorders	1 (0.85)	0
Gastritis	1 (0.85)	0
General disorders and administration site conditions	**1 (0.85)**	**0**
Fatigue	1 (0.85)	0
Investigations	**9 (7.63)**	**1 (2.56)**
Blood pressure increased	1 (0.85)	0
Enzyme level increased	2 (1.69)	0
Haematocrit increased	1 (0.85)	1 (2.56)
Haemoglobin increased	0	1 (2.56)
High density lipoprotein decreased	1 (0.85)	0
Lipids increased	1 (0.85)	0
Prostatic specific antigen increased	1 (0.85)	0
Weight decreased	1 (0.85)	0
Weight increased	2 (1.69)	1 (2.56)
Metabolism and nutrition disorders	**1 (0.85)**	**0**
Diabetes mellitus	1 (0.85)	0
Musculoskeletal and connective tissue disorders	**1 (0.85)**	**0**
Flank pain	1 (0.85)	0
Psychiatric disorders	**1 (0.85)**	**0**
Anxiety	1 (0.85)	0
Renal and urinary disorders	**2 (1.69)**	**0**
Pollakiuria	1 (0.85)	0
Urinary retention	1 (0.85)	0
Reproductive system and breast disorders	**2 (1.69)**	**0**
Prostatomegaly	2 (1.69)	0
Respiratory, thoracic and mediastinal disorders	**0**	**1 (2.56)**
Dyspnoea	0	1 (2.56)
Skin and subcutaneous tissue disorders	**2 (1.69)**	**1 (2.56)**
Acne	1 (0.85)	1 (2.56)
Hair growth abnormal	1 (0.85)	0
Vascular disorders	**1 (0.85)**	**0**
Hypertension	1 (0.85)	0

Adverse Events of Special Interest Subgrouped by Cmax <1500 ng/dL and >1500 ng/dL (Study 13-001)

System Organ Class Preferred Term	Adverse Events of Special Interest from Week 13 to End of Study Categorized by Subject Week 13 Cmax)	
	Cmax < 1500 ng/dL (N=118) N (%)	Cmax > 1500 ng/dL (N=39) N (%)
Blood and lymphatic system disorders	**2 (1.69)**	**0**
Anaemia	1 (0.85)	0
Polycythaemia	1 (0.85)	0
Cardiac disorders	**3 (2.54)**	**1 (2.56)**
Atrial fibrillation	1 (0.85)	0
Cardiac flutter	1 (0.85)	0
Palpitations	1 (0.85)	0
Tachycardia	0	1 (2.56)
General disorders and administration site conditions	**1 (0.85)**	**0**
Oedema	1 (0.85)	0
Investigations	**9 (7.63)**	**3 (7.69)**
Blood creatine phosphokinase increased	0	1 (2.56)
Blood pressure increased	1 (0.85)	0
Blood triglycerides increased	2 (1.69)	1 (2.56)
Enzyme level increased	2 (1.69)	0
Haematocrit increased	1 (0.85)	1 (2.56)
Haemoglobin increased	0	1 (2.56)
High density lipoprotein decreased	1 (0.85)	0
Lipids increased	1 (0.85)	0
Prostatic specific antigen increased	1 (0.85)	0
Red blood cell count increased	1 (0.85)	0
Metabolism and nutrition disorders	**2 (1.69)**	**0**
Hypercholesterolaemia	2 (1.69)	
Nervous system disorders	**2 (1.69)**	**0**
Dizziness	1 (0.85)	0
Headache	1 (0.85)	0
Transient ischaemic attack	1 (0.85)	0
Psychiatric disorders	**2 (1.69)**	**0**
Anxiety	1 (0.85)	0
Insomnia	1 (0.85)	0
Renal and urinary disorders	**1 (0.85)**	**0**
Urinary retention	1 (0.85)	0
Reproductive system and breast disorders	**2 (1.69)**	**1 (2.56)**
Prostatitis	0	1 (2.56)
Prostatomegaly	2 (1.69)	0
Respiratory, thoracic and mediastinal disorders	**1 (0.85)**	**1 (2.56)**
Sleep apnoea syndrome	1 (0.85)	1 (2.56)
Skin and subcutaneous tissue disorders	**1 (0.85)**	**1 (2.56)**
Acne	1 (0.85)	1 (2.56)
Vascular disorders	**3 (2.54)**	**1 (2.56)**
Hypertension	3 (2.54)	1 (2.56)

Lab Parameters of Interest Categorized <1500 and >1500 ng/dL (Study 13-001)

	Change from Baseline to End of Study			
Subject T Cmax at Week 13	**High Density Lipoprotein (mmol/L)**	**Hematocrit (%)**	**Hemoglobin (g/dL)**	**Prostate Specific Antigen (ng/mL)**
T Cmax<1500 ng/dL (N=118)	-0.13 (0.21)	3.0 (3.4)	0.83 (1.07)	0.24 (0.47)
T Cmax>1500 ng/dL (N=39)	-0.19 (0.19)	1.2 (3.2)	0.37 (0.94)	0.15 (0.38)
p value for Mean	0.109	0.05	0.014	0.211

APPENDIX 3. SUBJECTS WITH ELEVATED HCT AND PSA

Subjects with Elevated > 54%Hematocrit

Subject Number (Study Disposition)	Age (years)	Visit	HCT Result[a] (%)	Total Dose Taken	Adverse Event[b] (Severity/Relationship/ Action Taken/ Resolution)
TLANDO					
106-0020 (ET due to HCT > 54%)	55	Screening	46	43088 mg	Polycythemia (Mild/Related/Drug withdrawn/Not resolved)
		Week 7	49.7		
		Week 13	54.6		
		ET	52.9		
109-0007 (completed study)	51	Screening	46.9	130050 mg	None recorded due to lab value.
		Week 7	51.3		
		Week 13	55.3		
		Unsch	50.8		
		Week 26	51.1		
		Week 39	48.8		
		Week 52	52.1		
112-0005 (completed study)	57	Screening	47.4	167850 mg	None recorded due to lab value.
		Week 7	54.4		
		Unsch	48.9		
		Week 13	48		
		Week 26	53.5		
		Week 39	53.3		
		Week 52	53.1		
117-0008 (ET due to Other, decreased sex drive)	54	Screening	45.3	24300 mg	None recorded due to lab value.
		ET	54.2		
126-0016 (completed study)	53	Unsch	45	153900 mg	None recorded due to lab value.
		Week 7	43.8		
		Week 13	ND		
		Week 26	50.5		
		Week 39	52.3		
		Week 52	54.5		
139-0034 (ET due to any event leading to subject health risk)	68	Screening	49.5	91275 mg	Red blood cell count increased (Mild/Not related/Drug withdrawn/ Resolved)
		Unsch	46.1		
		Week 7	53.1		
		Week 13	55		
		Unsch	54.9		
		Week 26	52.5		
		Week 39	55		
		Unsch	57.1		
		ET	53.6		
154-0012 (ET due to protocol violation)	57	Screening	47.4	32175 mg	HCT increased (Mild/Related/Dose not changed/Resolved)
		Week 7	49.5		
		Week 13	54.1		
		Unsch	54.8		
		ET	51		
156-0015 (ET due to HCT > 54%)	54	Screening	47.1	24300 mg	HCT increased (Mild/Related/Drug withdrawn/Not resolved)
		Week 7	54.3		
		ET	53.5		
AndroGel					
106-0001 (ET due to HCT > 54%)	57	Screening	43.6	909 g	Polycythemia (Mild/Related/Drug withdrawn/Resolved)
		Week 7	45.7		
		Week 13	49.1		
		Week 26	50		
		Week 39	55.8		
		ET	51.3		

Key: ET = early termination; HCT = hematocrit; ND = not done; Unsch = unscheduled.

[a] Reference range for HCT was 37%-51%.

[b] Any adverse event(s) associated with the abnormal laboratory value.

Subjects with Elevated PSA > 4 ng/mL

Subject Number (Study Disposition)	Age (years)	Visit	PSA Result (ng/mL)	Total Dose Taken	Adverse Event[a] (Severity/Relationship/ Action Taken/ Resolution)
TLANDO					
112-0009 (completed study)	64	Screening	2.0	161325 mg	Prostatic specific antigen increased (Mild/Not related/Dose not changed/Resolved)
		Week 7	2.2		
		Week 13	2.1		
		Week 26	4.2		
		Unsch	3.2		
		Week 39	2.5		
		Week 52	2.7		
124-0004 (completed study)	62	Screening	1.9	158850 mg	None recorded due to lab value.
		Week 7	1.6		
		Week 13	1.6		
		Week 26	5.1		
		Unsch	3.8		
		Week 39	2.2		
		Week 52	2.5		
143-0026 (ET due to PSA > 4 ng/mL)	46	Screening	0.5	22575 mg	Prostatic specific antigen increased (Moderate/Related/ Drug withdrawn/Not resolved)
		Week 7	4.1		
		Unsch	5.1		
		ET	12.2		
		Unsch	7.8		
AndroGel					
108-0016 (ET due to PSA > 4 ng/mL)	59	Screening	1.4	245 g	None recorded due to lab value.
		Week 7	3.2		
		Unsch	4.1		
		Unsch	0.7		
146-0012 (ET due to AE of prostate cancer)	66	Screening	1.8	758 g	Prostate cancer (Moderate/Not related/Drug withdrawn/Resolved)
		Week 7	1.8		
		Week 13	4.4		
		Unsch	2.3		
		ET	2.2		

Key: ET = early termination; PSA = prostate-specific antigen; Unsch = unscheduled.
[a] Any adverse event(s) associated with the abnormal laboratory value.

APPENDIX 4. EX-VIVO CONVERSION

Title: Evaluation of Potential Ex-Vivo TU to T Conversion.

Objective: The objective of the study was to evaluate potential conversion of testosterone undecanoate (TU) to testosterone (T) during sample collection and processing method through serum harvesting that is consistent and closely replicates the collection and processing recommendations provided to clinical sites in the Phase 3 clinical study.

Background:

As a part of sample processing for Phase 3 clinical study, sites were instructed to collect whole blood samples into a vacutainer without an enzyme inhibitor, the samples are allowed to clot for 30 minutes at ambient temperature and centrifuge for 10-15 minutes for harvesting of serum for bioanalysis. Following serum harvesting, aliquots of samples are transferred to storage tubes and stored at -20°C (-15°C to -25°C) or shipped on dry ice. Stability of T levels in serum containing other analytes (dihydrotestosterone [DHT], TU and dihydrotestosterone undecanoate [DHTU]) was well established via bench top ambient temperature stability studies, short term and long term low temperature stability studies, incurred sample reanalysis (ISR) samples testing studies and submitted as part of the method validation package in the NDA.

Previous ex-vivo potential TU to T conversion assessment conducted during bioanalytical method development did not closely mimic the sample processing conditions as the blood collection tubes contained heparin, whole blood / plasma, and 100% acetonitrile (a less-polar solvent) as the TU spiking solvent (Information Request Response dated 27 November 2017).

Therefore, this experiment is aimed at addressing the ex-vivo potential for conversion of TU to T under sample processing conditions that closely mimic clinical trial recommendations using biocompatible spiking solvent system.

Materials and Methods:

- Donors: Blood samples from up to four normal healthy male donors were utilized to evaluate any potential ex-vivo TU to T conversion,
- TU solutions:
    - Spiking solvent: to mimic a biocompatible solvent system that has adequate solubility at room temperature to cover the range of spiking concentrations, 95 % phosphate-buffered saline (PBS) with 5% ethanol was used.
    - Stock and working solutions: A 1.00 mg/mL stock solution of TU was prepared in ethanol. Working solutions were prepared by dilution of stock solution with 95% phosphate-buffered saline (1X PBS)/ 5% ethanol.
    - Concentrations: final working solution concentrations targeted were approximately 8500 ng/mL, ~3333 ng/mL, ~1000 ng/mL and ~100 ng/mL and 0 ng/ml (control).

  - Solubility and stability of working solutions: solutions of TU at concentrations up to ~8500 ng/mL were evaluated for solubility of TU and stability for up to 5 hours at room temperature. Solutions of TU in 95 % PBS/5% ethanol was evaluated by HPLC for recovery of TU at T=0 and T=5 hours. Based on the results of the analysis, TU recovery was within 90 to 110 % of target concentration both at T=0 and 5 hours.

- Blood collection: Blood samples were collected from each donor by a professional phlebotomist into five sequential tubes without enzyme inhibitor.
  - 200 µL of TU working solutions in 5% ethanol / 95% PBS with concentrations of 0 (control) to 8,500 ng/mL were spiked into the freshly collected blood using a 0.5 cc syringe.
- Blood collection tube processing: Immediately after spiking the TU solutions, the tube was mixed by gently inverting it 5-10 times, and the blood was allowed to clot in the upright position for 30 minutes at ambient temperature. The tube was then centrifuged for 10-15 min (RCF 650-1400g), and the serum was transferred to a labeled polypropylene storage tube.
- Serum samples collected were stored at -20°C prior to analysis.
- Testosterone analysis:
  - Serum sample analysis: Each serum sample collected per donor were thawed to room temperature and analyzed in triplicates (three separate serum sample were prepared and analyzed per donor per concentration spiked) for T in a standard analytical run containing calibrators and QCs.
  - Method: The samples were analyzed for T according to PPD Method LCMSC 260.10 V 1.00, entitled "Quantitation of Testosterone and Dihydrotestosterone in Human Serum via HPLC with MS/MS Detection," which was validated under Project Code "RBJE2", the same analytical method utilized for study LPCN 1021-16-002 and LPCN 1021-13-001.
- Testosterone undecanoate analysis:
  - Serum sample at each concentration including control per donor were analyzed for TU using standard analytical run containing calibrators and QCs.
  - The samples were analyzed according to PPD Method LCMSC 521.1, entitled "Quantitation of Testosterone Undecanoate and 5α-Dihydrotestosterone Undecanoate in Human Serum via HPLC with MS/MS Detection," which was validated under Project Code "RBJF2", the same analytical method utilized for study LPCN 1021-16-002 and LPCN 1021-13-001.

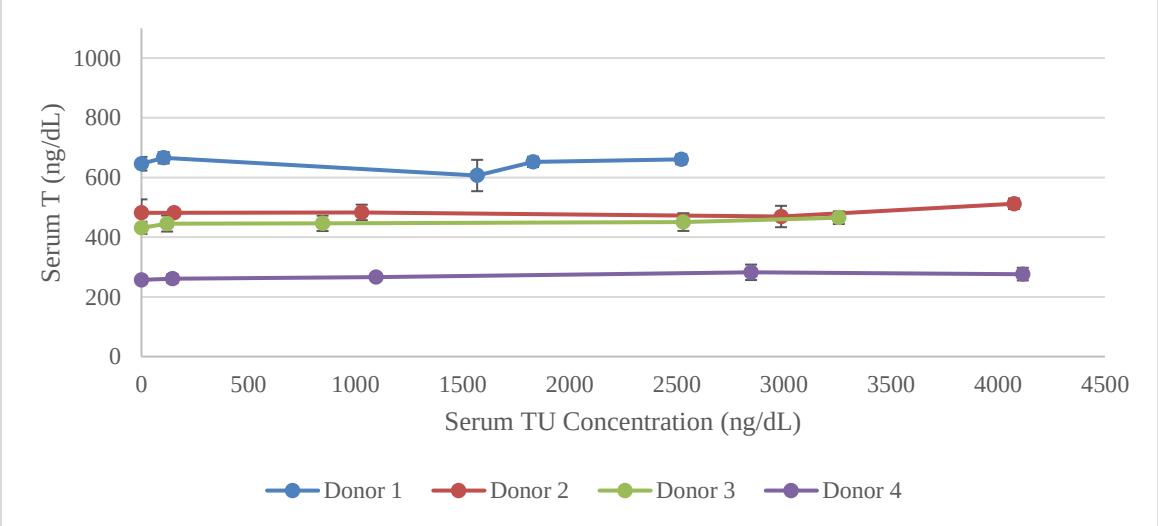
Results: Whole blood in serum tubes with no enzyme inhibitor were spiked with TU working solutions with levels of up to 8500 ng/mL. The samples were processed, and the serum was harvested using procedures similar to those used in LPCN 1021 clinical trials during sample processing. Under these conditions, the mean measured T values (n=3) for the TU fortified samples (four levels per donor) were compared to the control sample without any TU fortification for each respective donor. Results are summarized in Table 80.

Table 80. Measured Serum TU and T (ng/dL) in Individual Donors

Donor	Measured TU Level (ng/dL)	Measured T Level (ng/dL) Mean (%CV)
Donor 1	0	646 (3.5%)
	104	666 (2.8%)
	1568	607 (8.7%)
	1829	652 (2.6%)
	2521	661 (2.5%)
Donor 2	0	482 (9.4%)
	152	481(2.4%)
	1029	483 (5.4%)
	2987	469 (7.6%)
	4075	512 (3.4%)
Donor 3	0	431 (4.7%)
	120	446 (6.0%)
	846	446 (5.8%)
	2531	451 (6.6%)
	3257	465 (4.5%)
Donor 4	0	257 (4.4%)
	145	261 (5.7%)
	1096	266 (3.8%)
	2847	282 (9.2%)
	4116	276 (7.6%)

As shown in Table 80, the measured T levels in TU fortified samples are not changing with increasing measured serum TU levels (amount of TU that could be available for conversion), an indicator for TU toT conversion, suggesting no TU to T conversion. The measured T levels and corresponding TU levels are shown graphically in Figure 16 below.

Figure 16. Measured Serum T levels (ng/dL) as Function of Increasing TU Levels (ng/dL)

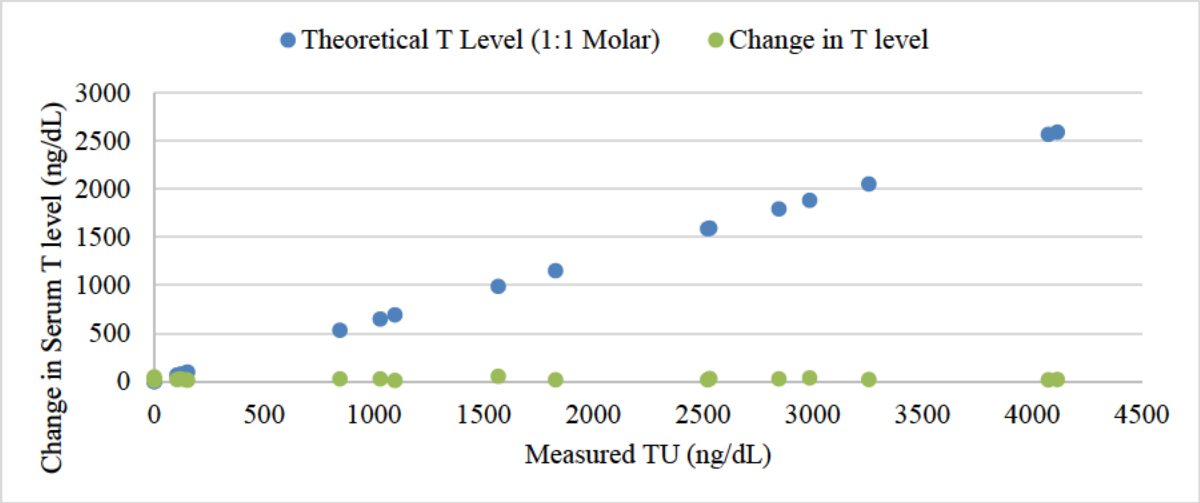


Both Table 80 and Figure 16 show that in donors with a range of baseline measured T (unfortified samples ranging from 257 to 646 ng/dL), no increases in the measured T levels of fortified samples relative to control (unfortified samples) were observed, despite the presence of increasingly appreciable levels of TU, as measured in serum. These data suggest no ex-vivo conversion of T from TU in serum.

Figure 17 presents the change in measured mean T (represented by grey dots in the graph below), and the calculated potential change in T levels that would be observed if all of the measured TU, (minimal amount of TU that could be available for conversion), were to convert to T (represented by the blue dots in the graph below). In this figure, the calculated potential change in serum T levels from TU were projected based on the following:

- The measured TU level, conservatively assumed to be the least amount of TU available for conversion during sample processing.
- The T:TU molecular weight ratio (0.63), with the assumption that if TU to T conversion is occurring, one molecule of TU converts to one molecule of T.

Figure 17. Measured and Theoretical Change in Serum T Levels (ng/dL) as a Function of Increasing TU Levels (ng/dL) (1:1 Molar TU to T)



If TU to T conversion were occurring, it would be expected that T levels would increase with increasing TU levels, similar to the theoretical T levels depicted by the blue dots in Figure 17. Instead, the measured serum T levels showed no change with increasing TU levels, further confirming that interference in serum T levels due to ex-vivo hydrolysis of the TU did not occur during blood collection and serum harvesting in LPCN 1021 clinical studies.

Conclusion:

In sample processing conditions similar to the recommendations and controls used in LPCN 1021 clinical studies, no ex-vivo TU to T conversion occurred. Given that there was no ex-vivo conversion, the generated serum testosterone data in clinical studies should not be impacted.

Title: Ex-Vivo TU to T Conversion Evaluation During Sample Preparation

Executive Summary:

Testosterone undecanoate, a prodrug of T, is converted by nonspecific esterases in blood to T. The impact of sample processing conditions on ex-vivo TU to T conversion have been assessed by various groups in the literature, and by the Sponsor. Considering the literature reports of ex-vivo testosterone undecanoate (TU) to testosterone (T) conversion, it is the objective of this report to identify and resolve any potential discrepancies in assessment of any ex-vivo TU to T conversion. In summary, the following data are discussed in this document:

- Clinical Study:
  - LaChance et al. (Lachance 2015) conducted a clinical study in which T levels were measured using serum and enzyme inhibited plasma samples. The authors noted PK parameters were 30% higher in terms of T when using serum prepared without an enzyme inhibitor compare to plasma with an enzyme inhibitor, however, reportedly, there is a known underestimation of T (15 - 20%) when using assay matrix with enzyme inhibitors. Therefore, considering the known negative T measurement bias associated with the enzyme inhibited assay method, the Sponsor's analysis of the results from the study suggest no clinically meaningful conversion of TU to T.
- Ex-Vivo Studies:
  - LaChance et al. found that there is a 243% overestimation of T levels when using serum without an enzyme inhibitor. This high overestimation finding does not align with the LaChance et al. clinical study results. The overestimation of ex-vivo TU to T conversion may be a result of the study's use of non-biocompatible, 100% methanol less polar, TU spiking solvent. Similar excessive overestimation results were observed by the Sponsor when a less-polar non-biocompatible solvent, 100% acetonitrile, was used as TU spiking solvent (Information Request Response dated 27 November 2017).
  - Wang et al. (Wang 2008) conducted an ex-vivo experiment and demonstrated no TU to T conversion when using biocompatible ethanolic phosphate buffered saline (PBS) as TU spiking solvent.
  - Therefore, use of an appropriate, biocompatible solvent appears to be critical in ex-vivo experiments.
  - The Sponsor conducted a new ex-vivo study evaluating serum T levels following spiking of varying TU concentrations in ethanolic PBS (5%:95%, pH: 7.4) in freshly collected whole blood. The study demonstrated no conversion of T from appreciable measured amounts of TU.
  - Based on totality of data from multiple sources (Sponsor studies, Wang et al., and LaChance et al.), no ex-vivo TU to T conversion is seen with serum assay without inclusion of an enzyme inhibitor in conditions similar in blood collection and sample processing through serum harvesting that was adopted in clinical trials.

Background:

Testosterone undecanoate, a prodrug of T, is converted by nonspecific esterases in blood to T. Typical clinical practice is to analyze T in human serum. The impact of sample processing conditions on ex-vivo TU to T conversion have been assessed by the Sponsor, and reported in literature. The findings are summarized below.

LACHANCE ET AL. CLINICAL STUDY EVALUATING TU TO T CONVERSION

LaChance et al. reported conversion of TU to T based on T concentrations obtained in a clinical study in which a cohort of 15 subjects were administered an oral dose of TU twice daily and then had their T levels measured using serum without inclusion of an enzyme inhibitor and plasma with enzyme inhibitors. The authors concluded that the pharmacokinetic (PK) parameters for plasma and serum were not bioequivalent. However, the following points show that no clinically meaningful conversion of TU to T occurred when using serum without inclusion of an enzyme inhibitor:

- The PK study results presented by the authors (Table 5 of the publication) suggested an apparent positive bias for serum-based T results (~30%) compared to the author's recommended enzyme-inhibited plasma assay (blood was collected in NaF-Na_2 EDTA collection tubes).
- LaChance et al. reported a unidirectional negative bias ranging from 8.6% to 15.4 % (Table 3 of the publication) in endogenous testosterone measurements from different donors when samples were analyzed using enzyme inhibited plasma with NaF/ Na_2EDTA collection tubes, compared to serum. In addition to the findings of LaChance et al., a similar negative bias (~20%) in T results was reported by Wang et al. when using sample matrix containing an enzyme inhibitor.
- In totality, LaChance et al. clinical data, considering the negative T measurement bias by enzyme inhibited plasma assay, suggest no clinically meaningful conversion of TU to T occurred when using serum without inclusion of an enzyme inhibitor, as the expected results would be bioequivalent in presence of up to 20% negative bias observed with enzyme inhibited plasma.

EX-VIVO STUDIES

Wang et al. Ex-Vivo:

Wang et al. demonstrated that there is no ex-vivo TU to T conversion. In an experiment where high levels of TU (up to 1000 ng/ml) in ethanolic PBS were added to whole blood collected in plain tubes with no enzyme inhibitor, and subsequently harvested for serum, T levels were not significantly increased in samples spiked with TU. In contrast, the addition of testosterone enanthate (TE) with identical sample preparation methodology resulted in a dose related increase in serum T due to the action of non- specific esterase in red blood cells. The positive interference results with TE represent a positive control with respect to appropriateness of the methodology utilized by Wang et al. in assessing ex-vivo conversion of TU to T.

LaChance et al. Ex-Vivo:

LaChance et al. reported that TU converts extensively ex-vivo into T in human blood under certain conditions of serum harvesting, causing overestimation of T concentration. The authors suggest that T must be analyzed in enzyme inhibited plasma when TU is the administered medication. Their ex-vivo simulations methodology entailed spiking 100% methanol-solubilized TU in whole blood using at concentrations of 160,000 ng/dl, and thereby showed an increase in T levels of up to 243% (Table 2 of the publication) in serum without anticoagulant, relative to unfortified serum without anticoagulant. Such extensive ex-vivo conversion and potential for overestimation is not corroborated by the clinical study results described earlier (Table 5 of the publication).

This reported 243% overestimation in serum contrasts with independent reports of Wang et al. and a study by the Sponsor in which ethanolic PBS solution was the TU spiking solvent, suggesting that the observed results by LaChance et al. are most likely due to the adopted simulation conditions, particularly the use of 100% methanol as the TU spiking solvent.

LaChance et al. performed an experiment in which blood collection was performed separately in conventional serum tubes and in NaF-Na_2 $K_2C_2O_4$ collection tubes, followed by fortification with TU at a final concentration of 60,000 ng/dl with 100% undiluted methanol as TU spiking solvent, and the following observations can be made based on the reported data:

- Mean T concentrations in serum from blood spiked with TU solution in methanol showed a 335% increase (Table 4 of the publication) in T levels at 30 min serum RT.
- LaChance et al. claimed that enzyme inhibited plasma minimized conversion of TU to T, but the reported mean T concentrations in plasma spiked with TU in methanol at 4^0C at 30 min resulted in a ~50% increase (Table 4) in T concentrations, suggesting an increased esterase activity when less-polar organic solvents are used, even in presence of an enzyme inhibitor.

This finding is confirmed by a study conducted by the Sponsor in which the use of TU solution in acetonitrile, a relatively less-polar spiking solvent, also resulted in an increased T concentration in plasma without an enzyme inhibitor (Information Request Response dated 27 November 2017).

Review of LaChance et al. and Sponsor's data strongly suggest that the choice of TU spiking solvent into blood has a significant impact on the assessment of ex-vivo TU to T conversion. Although good for TU solubilization, use of straight undiluted, relatively less-polar (Reichardt 2003), organic spiking solvents such as methanol (relative polarity of 0.762 to water) or acetonitrile (relative polarity of 0.46 to water) could have an adverse effect on various components of blood, including red blood cells and potentially activate additional esterases relative to the esterases ordinarily available for action during normal blood clotting process.

This suggests that the choice of solvent used in these experiments is critical and an appropriate solvent to use to spike TU in ex-vivo experiments should have following characteristics:

- Able to fully solubilize the amount of TU to be spiked; and
- Compatible with blood in terms of being aqueous, having a similar pH to blood (pH7.4), and maintain osmolality.

Both 100% methanol and 100% acetonitrile have adequate TU solubility but are not aqueous, suggesting they may perturb or alter the actual clotting and/ or esterase activity in the blood sample.

Given the aqueous nature of whole blood with pH of ~7.4, TU spiked in aqueous solvent such as PBS with small amounts of organic solvent such as ethanol to maintain TU fully solubilized, would be blood compatible spiking solvent that is expected to induce least perturbation in sample preparation through serum or plasma harvesting.

New Ex-Vivo Study:

The Sponsor have independently confirmed that TU in working solution containing 5% ethanol and 95% PBS was fully solubilized (summarized in experimental data document). Using this solvent system, the Sponsor conducted an ex-vivo study to evaluate the potential of ex-vivo TU to T conversion when blood is collected in plain serum tubes with no enzyme inhibitor. The study clearly demonstrated that no conversion of TU to T was observed when using spiking solutions of TU solubilized in blood-compatible ethanolic aqueous PBS solutions are spiked in whole blood and processed under typical serum harvesting conditions. Further, the TU concentrations in the samples were measured, and show that significant TU levels were present.

Conclusion:

The Sponsor's ex-vivo study evaluating serum T levels following spiking of varying TU concentrations in biocompatible spiking solvent in whole blood demonstrated no conversion of TU to T. This observation was similar to the one determined using LaChance et al clinical data, suggesting no TU to T conversion, taking into account the negative T measurement bias by enzyme inhibited plasma assay.

Based on totality of data from multiple sources (Sponsor studies, Wang et al., and LaChance et al.), no ex-vivo TU to T conversion is seen with serum assay without inclusion of an enzyme inhibitor in conditions similar in blood collection and sample processing through serum harvesting that was adopted in clinical trials.

APPENDIX 5. DESCRIPTION OF CLINICAL STUDIES

A summary of the 12 clinical studies conducted for the TLANDO clinical development program are presented below, with links to the clinical study synopses of pivotal studies supporting the safety and efficacy of TLANDO (Studies 13-001 and 16-002).

Table 81. TLANDO Clinical Studies

Study ID (Study Period; Location)	Design; Control Type	# Subjects by Arm; Planned/ Enrolled	Population Studied	Duration	Study and Control Drugs Dose, Route, Regimen
Pivotal Studies					
13-001 (February 2014 to April 2015: United States)	Multicenter, randomized, open-label, active-control, parallel-group, efficacy and safety study or oral TU	TLANDO: 200/210 AndroGel 1.62%: 100/105	Hypogonadal men	Multiple dose (52 weeks)	TLANDO To-be-Marketed Formulation 225 mg TU titrated to 150 mg or 300 mg oral TU twice daily, as needed Active Control: AndroGel 1.62%; transdermal
16-002 (December 2016 to February 2017, United States) New clinical study to address CRL	Multicenter, open-label, one treatment study evaluating the efficacy of TLANDO in adult hypogonadal male subjects.	100/95	Hypogonadal men	Multiple doses (24 days)	TLANDO To-be-Marketed Formulation 225 mg TU twice daily
16-003 (January 2017 to May 2017, United States) New clinical study to address CRL	Multicenter, open-label, one treatment study evaluating the efficacy of TLANDO in adult hypogonadal male subjects.	100/100	Hypogonadal men	Multiple doses (24 days)	TLANDO To-be-Marketed Formulation 150 mg TU three times daily
Phase 1 Studies in Target Population					
09-001 (October 2009 to February 2010; Canada)	Randomized, open-label, single and multiple dose pilot bioavailability and pharmacokinetic (PK) study of two oral TU capsule formulations	TLANDO: 36/36 Andriol (commercial Canadian oral product) 36/36	Hypogonadal men	Single and multiple dose (5 days)	LPCN 1021-07[1] LPCN 1021-08 50 and 100 mg oral TU (QD on Day 1 and 8; twice daily on Day 3-7) Active Control: Andriol; oral
S361.1.001 (June 2010 to August 2010; United States)	Open-label, single dose bioavailability and PK study of two oral TU capsule formulations	24/24	Hypogonadal men	Single dose	LPCN 1021-07[1] LPCN 1021-10 75, 150, and 225 mg oral TU
M12-778	Randomized double-blind, placebo-controlled dose escalating study of	84/84	Hypogonadal men	Multiple dose (14	LPCN 1021-07[1] 75, 150, 225 and 300 mg oral TU twice daily

Study ID (Study Period; Location)	Design; Control Type	# Subjects by Arm; Planned/ Enrolled	Population Studied	Duration	Study and Control Drugs Dose, Route, Regimen
(March 2011 to September 2011; United States)	safety, tolerability and PK of oral TU			to 28 days)	Placebo
M13-298 (October 2011 to January 2012; United States	Single and multiple dose relative bioavailability study of four TU capsule formulations	32/32	Hypogonadal men	Multiple doses (14 days)	LPCN 1021-11 LPCN 1021-12 LPCN 1021-13 LPCN 1021-14 225 mg oral TU twice daily
1021-14-001 (March 2015 to April 2015; Canada)	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	16/14	Hypogonadal men	Single dose	TLANDO Registration Lot 225 mg oral TU
Exploratory Studies in Postmenopausal Women					
1021-05-001 (February 2006 to March 2006; Canada)	Bioavailability and PK of four oral TU capsule formulations	24/24 Andriol: 24/24	Postmenopausal women	Single dose	LPCN 1021-01[2] LPCN 1021-02 LPCN 1021-05 LPCN 1021-06 120 mg oral TU Active Control: Andriol; oral
S361.1.002 (June 2010 to July 2010; United States)	Open-label, single dose, pilot food effect study on the bioavailability and PK of two oral TU capsule formulations	20/20	Postmenopausal women	Single dose	LPCN 1021-07[1] LPCN 1021-10 75 mg oral TU
M12-868 (April 2011 to May 2011; United States)	Open-label, crossover study to compare relative bioavailability of 2 lots of TU capsules	12/12	Postmenopausal women	Single dose	LPCN 1021-07[1] 75 mg oral TU
1111-15-001 (March 2015 to May 2015; United States)	Open-Label, Randomized, Cross-Over, Single-Dose, Pilot, Four-Treatment, Four-Period Study to Evaluate Pharmacokinetics of LPCN 1111 and TU Formulations in Healthy Postmenopausal Women	10/10	Postmenopausal women	Single dose	TLANDO Registration Lot LPCN 1021-17[3] 225 mg oral TU

[1] LPCN 1021-07 formulation is similar to Registration lot.
[2] LPCN 1021-01 formulation is the same as the LPCN 1021-07 formulation except for the strength.
[3] LPCN 1021-17 is a novel formulation under development and data from this study is not presented in the NDA.

NAME OF SPONSOR/COMPANY: Lipocine, Inc NAME OF FINISHED PRODUCT: Testosterone Undecanoate (TU; LPCN 1021) NAME OF ACTIVE INGREDIENT(S): Testosterone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: LPCN 1021-13-001

Title of Study: Phase 3, Active-Controlled, Safety and Efficacy Trial of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men

Investigators: Multicenter

Study Center(s): Multicenter – 40 sites in the United States

Publications (References): Wang C, DelConte A, Kaminetsky JC, et al. Efficacy and Pharmacokinetics of LPCN 1021, a Novel Oral Testosterone Replacement Therapy (TRT), in Hypogonadal Men: Study of Androgen Replacement (SOAR). Oral presentation at the Endocrine Society's 97th Annual Meeting & Expo, 07 March 2015, San Diego, CA.

Kaminetsky JC, DelConte A, Dobs AS, et al. Efficacy and Pharmacokinetics of LPCN 1021, a Novel Oral Testosterone Replacement Therapy (TRT), in Hypogonadal Men: Study of Androgen Replacement (SOAR). Oral presentation at the American Urological Association Annual Meeting, 18 May 2015, New Orleans, LA.

Dobs A, Kaminetsky J, Miner M, et al. Efficacy and Pharmacokinetics of LPCN 1021, a Novel Oral Testosterone Replacement Therapy (TRT) in Obese And Non-Obese Hypogonadal Men: Study Of Androgen Replacement (SOAR). Oral and poster presentation at the American Society of Andrology 40th Annual Conference, 19 April 2015, Salt Lake City, UT.

Study Period: 07 February 2014 (first subject enrolled) to 30 April 2015 (last subject completed)	**Phase of Development:** 3

Objectives: The primary objective was to determine 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 study treatment. The normal range for serum total T (Cavg0-24h) was defined as 300 to 1140 ng/dL.

The following were the secondary objectives of the study:

- To determine the percentage of LPCN 1021-treated subjects who had serum total 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.
- To assess change from baseline in safety parameters for the LPCN 1021 and active control, AndroGel 1.62%, groups over the course of treatment. Key safety parameters included adverse events (AEs), physical examinations, clinical laboratory tests, changes in hematocrit (HCT), lipids (low-density lipoprotein [LDL], high-density lipoprotein [HDL]), serum transaminases, and prostate-specific antigen (PSA).
- To evaluate change from baseline to endpoint in the International Prostate Symptom Score (I-PSS), the Short Form-36v2® Health Survey Version 2.0 (SF-36) quality-of-life questionnaire, and the Psychosexual Daily Questionnaire (PDQ) for the LPCN 1021 and AndroGel 1.62% groups.

Methodology: This was a multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group, efficacy and safety study in adult hypogonadal male subjects. Subjects were enrolled in the study based on selection criteria designed to represent the general population of hypogonadal men while minimizing risk to study participants. 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 testosterone undecanoate [TU]) and 100 subjects received AndroGel 1.62% (testosterone topical gel, active control) for 52 weeks. Subjects could have been naïve to testosterone treatment or could have been enrolled after stopping current treatment and completing an adequate washout period as described in Inclusion Criterion 5.

Analysis of efficacy was carried out in subjects receiving LPCN 1021 after 13 weeks of treatment. Final safety analysis was carried out in all subjects receiving LPCN 1021 and AndroGel 1.62% after 52 weeks of treatment.

Number of Subjects (planned and analyzed): Approximately 300 subjects were planned for the study. A total of 315 subjects were randomly assigned to treatment: 210 were assigned to LPCN 1021 and 105 were assigned to AndroGel 1.62%. The Safety Set included all subjects who received at least 1 dose of study drug (N = 314). Efficacy analyses were performed only on subjects who received LPCN 1021. The Full Analysis Set (FAS) included all subjects with

NAME OF SPONSOR/COMPANY: Lipocine, Inc NAME OF FINISHED PRODUCT: Testosterone Undecanoate (TU; LPCN 1021) NAME OF ACTIVE INGREDIENT(S): Testosterone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

at least 1 postbaseline efficacy variable response (Cavg0-24h or Cmax) (N = 193). The Efficacy Population Set (EPS) included all subjects in the FAS who did not have a major protocol deviation (N = 151). The Per-Protocol Set (PPS) included all subjects who completed the study without a major protocol deviation (N = 130). 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 (N = 130; identical to the PPS).

Diagnosis and Main Criteria for Inclusion: A subject was eligible for study participation if he met all of the following:

1. 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.
2. Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism before age 65.
3. Documented diagnosis of primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired).
4. 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.
5. Naïve 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.
6. 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.

Test Product, Dose, Mode of Administration, and Batch No.: LPCN 1021 (TU) capsules, administered orally. Batch numbers used were as follows: 3310J13A (75-mg capsules); 3314J13A and 3316K13A (112.5-mg capsules).

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 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 (-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 (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.

Dose at Time of PK Analysis	**If titrated upward, the new dose was:**	**If titrated downward, the new dose was:**
225 mg BID (450 mg total daily)	300 mg BID (600 mg total daily)	150 mg BID (300 mg total daily)
150 mg BID (300 mg total daily)	225 mg BID (450 mg total daily)	—[a]
300 mg BID (600 mg total daily)	No dose adjustment	225 mg BID (450 mg total daily)

Key: BID = twice per day; Cmax = maximum observed serum concentration; PK = pharmacokinetic.
[a] Stopping criteria: Any subject with Cmax > 1500 ng/dL even after lowering the dose of LPCN 1021 to 150 mg.

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Reference Product, Dose, Mode of Administration, and Batch No.: AndroGel 1.62% gel, administered topically. Batch numbers used were 82251A0 and 82251B0.

Subjects who were assigned to the AndroGel 1.62% treatment arm received treatment according to the approved package insert for the product. In accordance with the dosing instructions in the package insert, 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 (± 2 days) and Day 28 (± 2 days) 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).

Duration of Treatment: Analysis of efficacy was carried out in subjects receiving LPCN 1021 after 13 weeks of treatment. Final safety analysis was carried out in all subjects receiving LPCN 1021 and AndroGel 1.62% after 52 weeks of treatment.

Criteria for Evaluation:

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

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 Cmax at 0 to 12 hours, 12 to 24 hours, and 0 to 24 hours (Cmax0-12h, Cmax12-24h, and Cmax0-24h, respectively) 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 SF-36, I-PSS, and PDQ.

Pharmacokinetic: Pharmacokinetic parameters calculated for LPCN 1021 (TU), T, dihydrotestosterone undecanoate (DHTU), dihydrotestosterone (DHT), and estradiol (E2) included:

- Cmax0-12h, Cmax12-24h, and Cmax0-24h
- Time to maximum observed serum concentration (Tmax)
- Cavg0-24h
- Area under the serum concentration-time curve from 0 to 24 hours (AUC0-24h)

Additional parameters were to be calculated if determined to be useful in the interpretation of the data. The AUC0-24h ratio of serum T to DHT was also calculated.

Safety: Key safety endpoints included incidence of AEs; physical examination results; clinical laboratory test results; and changes in HCT, lipids (LDL and HDL), serum transaminases, and PSA. Safety assessments also included vital sign measurements and ECG results.

Pharmacodynamic: Pharmacodynamic variables included change from baseline in sex hormone binding globulin (SHBG), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Additional parameters were to be calculated if determined to be useful in the interpretation of the data.

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Statistical Methods: All efficacy analyses were performed for the LPCN 1021 treatment arm only.

The primary endpoint was the percentage of LPCN 1021-treated subjects who achieved a Cavg0-24h within the normal range of 300 to 1140 ng/dL upon completion of 13 weeks of treatment. The target minimum acceptable percentage was 75%. A 95%, 2-sided, binomial CI surrounding the point estimate had to have a lower bound of 65% or more to conclude that the LPCN 1021 treatment was efficacious. Asymptotic (rather than exact) CIs were used in all cases unless stated otherwise. The primary analysis was done by using the EPS. Additional analyses were done for the FAS, PPS, and PK Set.

Missing data were imputed by using the last observation carried forward method for the FAS and EPS.

The secondary efficacy endpoints included the percentage of subjects in the EPS who exhibited maximum serum total T concentrations within predetermined limits upon completion of 13 weeks on TU treatment as described previously. Values for Cmax0-12h, Cmax12-24h, and Cmax0-24h were analyzed separately. The primary analysis was done for the EPS. Additional analysis was done for the FAS, PPS, and PK Set. Missing values were handled as specified for the primary efficacy endpoint.

The SF-36, I-PSS, and PDQ scores at baseline and study exit or early termination visits were analyzed by using descriptive statistics for each group. Specific details as to how each of these questionnaires was scored and rules for handling missing data are provided in the SAP.

All PK analyses were performed for the LPCN 1021 treatment arm only. A comprehensive listing and model-independent analysis of the serum hormone concentrations measured during the study confinement periods were performed. Individual and group average values, by dose and treatment overall, were presented.

One of the exploratory analyses performed was to evaluate the use of the single-point serum T concentration measurement for dose adjustment. The goal of the exploratory analysis was to develop single-point titration criteria for the clinical label based on the Phase 3 study criteria. Available data for subjects from Weeks 13, 26, 39, and 52 were used in the analysis.

Safety analysis was carried out throughout the study on all subjects receiving LPCN 1021 and AndroGel 1.62%. The final safety data collection was after 52 weeks of treatment. The population used for safety analyses was the Safety Set. Safety was assessed on the basis of AE reports, clinical laboratory data, ECG parameters, physical examinations, and vital sign measurements.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: The design of this Phase 3 LPCN 1021-13-001 study and the efficacy criteria for success was consistent with studies conducted for other testosterone replacement therapy (TRT) products. The study enrolled subjects with a diagnosis of hypogonadism (primary or secondary) who had confirmed low serum T concentrations (< 300 ng/dL) based on 2 consecutive blood samples, obtained between 6 and 10 AM, on 2 separate days approximately at the same time of day. The study was designed to assess whether LPCN 1021 would reliably restore serum T concentrations in these subjects within the normal range for healthy, eugonadal men (T Cavg0-24h of 300-1140 ng/dL).

Results of the primary efficacy analysis showed that LPCN 1021 treatment met the ≥ 75% target described in the SAP. For the EPS, 87.4% of subjects achieved a Cavg0-24h value within the normal range. Sensitivity analyses on the FAS and PK Set supported this finding.

The Week 13 serum testosterone PK parameters were mostly similar across all populations, with slightly higher values at Week 3 compared with subsequent visits. The average serum T levels were similar across all dose levels throughout the study. Peak serum T levels increased with increase in dose, achieving Tmax at approximately 6 hours for all dose levels. Overall, the peak serum testosterone levels were higher after morning dosing compared with evening dosing throughout the study.

Results of both the SF-36 and PDQ supported the therapeutic benefit of LPCN 1021.

SAFETY RESULTS:

- The incidence of treatment-emergent adverse events (TEAEs) between groups was similar: 67.6% vs 65.4% for subjects receiving LPCN 1021 and AndroGel 1.62%, respectively.
- While 16 subjects experienced 27 severe TEAEs, none of the events were considered related to study drug by the investigator.
- Overall, 23.6% of subjects (74/314) experienced 122 treatment-related AEs, and the incidence of treatment-related

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AEs between groups was similar.

- Of all subjects, 24 (7.6%) discontinued because of TEAEs. The percentage of subjects who discontinued from the LPCN 1021 group was almost twice that of subjects who discontinued from the AndroGel 1.62% group.
- A total of 14 subjects reported 19 treatment-emergent serious AEs, none of which were considered related to study drug.
- No deaths were reported during the course of the study.
- Elevated HCT and PSA values were seen in subjects in both treatment groups and were consistent with the pharmacologic effects of androgen treatment.
- In general, clinical laboratory values and changes from baseline were consistent among LPCN 1021- and AndroGel 1.62%-treated subjects through Week 52. The data demonstrate that key laboratory parameters and other biomarkers are mostly within reference ranges and/or are consistent with levels observed for other approved TRT products. Further, the clinical relevance of changes in these biomarkers is not well understood.
- Results of vital sign measurements, physical examinations, and ECGs were also consistent with androgen treatment and the patient population.

In summary, the safety results of this study demonstrate that LPCN 1021 has an acceptable safety profile:

- Treatment with LPCN 1021 generally met the prespecified secondary endpoint targets.
- Safety laboratory parameters and AE reports were consistent with other TRT products; particularly for AEs that are known to be androgenic mediated (e.g., increased HCT, changes in PSA, and changes in lipid parameters).

Based on the results of this study, LPCN 1021 appears to have a safety profile that is not meaningfully different from existing TRT products.

CONCLUSIONS: LPCN 1021 is an orally administered TRT product that successfully attained serum T levels, in both obese and nonobese hypogonadal men, that met United States Food and Drug Administration targets.

Date of the report: 11 August 2015

2 SYNOPSIS

NAME OF SPONSOR/COMPANY: Lipocine, Inc NAME OF FINISHED PRODUCT: Testosterone Undecanoate (TU; LPCN 1021) NAME OF DRUG SUBSTANCE: Testosterone Undecanoate	Synopsis Page **2** of **87**	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: LPCN 1021-16-002		
Title of Study: Validation of Dosing Regimen of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men.		
Investigators: Multicenter		
Study Center(s): Multicenter – 12 sites in the United States		
Publications (References): N/A		
Study Period: 12 January 2017 (first subject enrolled) to 06 April 2017 (last subject completed)		**Phase of Development:** 1

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

The secondary efficacy endpoints were based on the proportion of T Cmax and T Cmax (0-24) within three predetermined limits in subjects treated with LPCN 1021 for about 24 days. The predetermined limits are:

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

Methodology: This was a multicenter, open-label, single treatment study evaluating the efficacy of LPCN 1021 in adult hypogonadal male subjects. Subjects could be naive to T treatment or could enroll after stopping current treatment and completing an adequate washout period.

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 was used for screening T levels.

Visit 3: A total of 95 hypogonadal men meeting inclusion criteria and none of the exclusion criteria were enrolled to the study and assigned to receive 225 mg of LPCN 1021 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 on Day 24 morning) and remained confined until the 24-hour blood draw on Day 25 was completed. Subjects exited from 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 (refer to Section 8.4.1.7) 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 resulting in a total of 15 blood samples collected per subject with 12 mL of whole blood collected for each sample. A total of 180 mL of whole blood was collected per subject for PK analysis.

Number of Subjects (planned and analyzed): Approximately 100 subjects were planned for the study. A total of 95 subjects were enrolled in the study and received LPCN 1021. The Safety Set included all subjects who received at least one dose of study drug (N = 95). The Full Analysis Set (FAS) included all subjects with at least 1 postbaseline efficacy variable response (Cavg0-24h or Cmax) (N = 94). The Pharmacokinetic (PK) Set included all subjects in FAS who complete the study without major protocol deviations (N = 90).

Diagnosis and Main Criteria for Inclusion: A subject was eligible for study participation if he met all of the following:

1. Voluntarily sign and date the study consent form(s) which have been approved by an Institutional Review Board (IRB). Written consent must be obtained prior to the initiation of any study procedures.
2. Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism prior to age 65.

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3. Subjects should be diagnosed to be primary (congenital or acquired) or secondary hypogonadal (congenital or acquired).
4. 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.
5. Naïve 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.
6. Judged to be in good general health as determined by the investigator at screening.

Test Product, Dose, Mode of Administration, and Batch No.: LPCN 1021 (TU) capsules, administered orally. Batch numbers used was as follows: 3315J13A (112.5-mg capsules).

All subjects received LPCN 1021 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.

Duration of Treatment: Analyses were carried out after subjects had received LPCN 1021 for about 24 days (window of 20 to 28 days).

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint and analysis for this study was the percentage of LPCN 1021 treated subjects who had achieved a 24-hour average serum T concentration within the normal range of 300 to 1080 ng/dL at Visit 4 (Day 24 ± 4 days). For the primary efficacy endpoint of the study to be met, the target minimum acceptable 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 LPCN 1021 treatment was efficacious.

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:

T Cmax ≤ 1500 ng/dL (targeted to be ≥ 85%)

T Cmax between 1800 and 2500 ng/dL (targeted to be ≤ 5%)

T Cmax > 2500 ng/dL (targeted to be no subjects (0%))

The secondary endpoints were based on the proportion of T Cmax and T 24-hour Cmax in subjects treated with LPCN 1021 for about 24 days. The following sections explain the computation of these two Cmax values (T Cmax and T Cmax (0-24)).

T Cmax is defined as the maximum serum concentrations of T following administration of a dose and prior to the next dose. In the LPCN 1021-16-002 study, LPCN 1021 was administered BID and was expected to have one T Cmax after each dose administration. Therefore, on Day 24 when full day PK values were obtained and dosing occurred every 12 hours, two T Cmax values were observed: the first Cmax that occurs in the 12 hour interval post morning dose (T Cmax0 12h) and the second Cmax that occurs in the 12 hour interval post evening dose (T Cmax12 24h). For the computation of the proportions within the pre-defined limits, both Cmax values observed in each subject were used to compute the proportions (hereafter referred to as T Cmax or Cmax per dose). This results in a total of 190 Cmax values observed in the 95 subjects used to compute the proportions.

T Cmax (0-24), defined as maximum serum concentration of Total T that occurred in the 24-hour interval post morning dose on Day 24. This results in a total of 95 Cmax values that were observed over the 24-hour period covering both the doses administered on Day 24 (the highest of the values seen in two peaks in a day, hereafter referred to as T Cmax (0-24) or Cmax per day).

Pharmacokinetic: Pharmacokinetic parameters calculated for LPCN 1021 (TU), T, dihydrotestosterone undecanoate (DHTU), dihydrotestosterone (DHT), and estradiol (E2) included:

- Cmax0-12h, Cmax12-24h, and Cmax0-24h
- Time to maximum observed serum concentration (Tmax)
- Cavg0-24h
- Area under the serum concentration-time curve from 0 to 24 hours (AUC0-24h)

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Safety: Key safety endpoints included incidence of AEs; physical examination results; clinical laboratory test results; and changes in HCT, lipids (LDL and HDL), serum transaminases, PSA, sex hormone binding globulin (SHBG), follicle stimulating hormone (FSH), and luteinizing hormone (LH. Safety assessments also included vital sign measurements and ECG results.

Statistical Methods: Complete information on statistical approach used in this study can be found in the SAP.

The primary endpoint was the percentage of LPCN 1021-treated subjects who achieved a Cavg0-24h within the normal range of 300 to 1080 ng/dL upon completion of 24 days of treatment. The target minimum acceptable percentage was 75%. A 95%, 2-sided, binomial CI surrounding the point estimate had to have a lower bound of 65% or more to conclude that the LPCN 1021 treatment was efficacious.

The primary endpoint analysis used the SS with a last observation carried forward including baseline (BLOCF) approach for missing PK data. Additional sensitivity analyses were performed using the SS with a Model-Based Multiple Imputation approach for missing data, and using the FAS, and PK Sets.

The secondary endpoints were based on the proportion of T Cmax and T 24-hour Cmax within predetermined limits in subjects treated with LPCN 1021 for about 24 days. The secondary endpoint analysis used the SS as primary dataset for with model based multiple imputation approach used to impute missing T Cmax and T 24-hour Cmax.

The PK set was used for the pharmacokinetic analysis. Data from subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantified) was considered as missing and the subject's data was used if the primary PK parameters can be estimated using available data points. Otherwise relevant data from these subjects were excluded from the final analysis.

Safety analysis was carried out throughout the study on all subjects receiving LPCN 1021. The population used for safety analyses was the Safety Set. Safety was assessed on the basis of AE reports, clinical laboratory data, ECG parameters, physical examinations, and vital sign measurements.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: The design of this study and the efficacy criteria were consistent with studies conducted for other testosterone replacement therapy (TRT) products. The study enrolled subjects with a diagnosis of hypogonadism (primary or secondary) who had confirmed low serum T concentrations (< 300 ng/dL) based on 2 consecutive blood samples, obtained between 6 and 10 AM, on 2 separate days approximately at the same time of day. The study was designed to assess whether LPCN 1021 would reliably restore serum T concentrations in these subjects within the normal range for healthy, eugonadal men (T Cavg0-24h of 300-1080 ng/dL).

Results of the primary efficacy analysis showed that LPCN 1021 treatment met the ≥ 75% target described in the SAP. For the SS, 80% of subjects achieved a Cavg0-24h value within the normal range. The lower bound of the CI was 72%, which also met the ≥ 65% target defined in the SAP. Sensitivity analyses on the SS, FAS, and PK Set supported this finding.

Results for the secondary endpoint were generally within the predetermined limits for the T Cmax analysis. One patient had a Cmax value >2500 ng/dL. This patient was admitted to study despite being in violation of the exclusion criteria. The Day 24 serum testosterone PK assessment yielded a Cavg of 476 ng/dL and a Tmax of 4-6 hours.

SAFETY RESULTS:

- The incidence of TEAEs for subjects receiving LPCN 1021 was similar to previous studies (21.1%).
- One subject experienced a severe TEAEs that was not considered related to study drug by the investigator.
- Overall, 6.3% of subjects (6/95) experienced 9 treatment related AEs
- One subject discontinued because of TEAEs.
- One subject reported a treatment emergent SAEs which was not considered related to study drug by the investigator.
- No deaths were reported during the study.
- Changes in HCT, PSA, and cholesterol values were similar to those observed in previous LPCN 1021 clinical studies and were consistent with the pharmacologic effects of androgen treatment.
- Results of vital sign measurements and clinical laboratory values were also consistent with androgen treatment and the patient population. The clinical relevance of changes in these biomarkers is not well understood.

In summary, the safety results of this study demonstrate that LPCN 1021 has an acceptable safety profile:

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- Treatment with a twice daily, fixed-dose of LPCN 1021 (450 mg total daily dose) produced a safety profile consistent with other TRT products.

CONCLUSIONS: A twice-daily, fixed-dose of LPCN 1021 (450 mg total daily dose) successfully attained serum T levels that met US FDA targets with a safety profile comparable to what has been observed with other TRTs

Date of the report: July 24, 2017