CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206089Orig1s000

NON-CLINICAL REVIEW(S)

PHARMACOLOGY/TOXICOLOGY MEMORANDUM

CDER Stamp Date:	September 27, 2018
NDA:	206089
Sponsor:	Clarus Therapeutics, Inc.
Drug:	Testosterone undecanoate (JATENZO)
Indication:	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone due to primary or hypogonadotropic hypogonadism
Subject:	Final Labeling Review
Reviewer:	Yangmee Shin, PhD

Background: Clarus Therapeutics resubmitted NDA 206089 under a 505(b)(2) regulatory pathway following a 2nd Complete Response (CR) letter issued on March 22, 2018. NDA 206089 was first submitted on January 3, 2014 as a 505(b)(2) application. To support the nonclinical requirements of NDA via a 505(b)(2) pathway, the sponsor submitted published literature along with the findings of a 3-month oral toxicology study of Clarus' oral testosterone undecanoate (TU) formulation in dogs. The sponsor also provided literature references to address ADME of TU by the oral route. The 3-month oral toxicology study in male dogs and relevant published literature were provided to support the use of borage oil as a novel excipient. The sponsor also supplied published literature regarding the fertility, pregnancy, and carcinogenicity of testosterone (T). Pharmacology and Toxicology recommended approval of the initial submission of NDA 206089 during the first cycle review.

In the 1st resubmission to NDA 206089 on June 22, 2017, Clarus refiled the NDA as a 505(b)(1) application and provided nonclinical studies of oral TU including a 9-month oral toxicology study in male dogs, a battery of genotoxicity tests, a 6-month carcinogenicity study in Tg·rasH2 male mice, and a fertility study in male rats, upon agreement with the Division on November 19, 2015. This resubmission received a 2nd CR letter. Pharmacology and Toxicology recommended a CR action for the resubmission of the NDA based on inadequate doses tested that did not permit adequate characterization of the potential effect of the oral TU product following chronic treatment, particularly, for male fertility (integrated with a micronucleus test) and carcinogenicity assessments.

In the 2nd CR resubmission filed on September 27, 2018, the sponsor proposed to reclassify the NDA as a 505(b)(2) application and to address the nonclinical deficiencies noted in the CR letter, referencing the information provided in the original NDA submission. The sponsor submitted 3 additional published articles in support of labeling statements regarding the effect of T on male fertility and spermatogenesis. The

sponsor's proposal was acceptable from the Pharmacology and Toxicology perspective and approval of NDA 206089 was recommended on March 1, 2019 (see previous NDA reviews submitted to DARRTS on August 4, 2014; February 27, 2018; and March 1, 2019 for details).

Summary of Nonclinical Studies relevant to Labeling: The sponsor conducted 3- and 9-month oral toxicology studies of Clarus' oral TU formulation in male dogs. The sponsor proposes to rely on published literature to support 'class labeling' for its T replacement product as it relates to carcinogenicity and reproductive toxicity assessments. Additional published journal articles were submitted in support of labeling statements regarding the effect of T on male fertility and spermatogenesis in Module 4.3 within the current resubmission.

The major findings in the 3-month study in eugonadal male dogs at 38 mg/kg BID (76 mg/day) and 126 mg/kg BID (252 mg/day) were moderate to marked adrenal cortex atrophy, minimal to marked atrophy of the testes, moderate to severely reduced sperm production in the epididymides, and marked hypertrophy of the prostate correlated with altered organ weights in all treated groups. Serum cholesterol was suppressed in all treated groups (up to ~48%) compared to control animals but resolved after drug withdrawal. A two-fold increase (~93%) in ALT (not statistically significant) without a histopathology correlate was noted at 126 mg/kg BID, which resolved after drug withdrawal. The histopathological findings in the adrenal cortex, epididymides, and testes were not completely reversed at the end of the 4-week recovery period. The severity at the high-dose was reduced (adrenal) or increased (epididymides, testes) after the 4-week recovery period. Based on AUC comparisons, exposure to T or TU in dogs at 76 and 252 mg/kg/day resulted in approximately 2-fold and 5-fold, respectively, the human T or TU exposure following a single dose of TU at 475 mg and a high fat meal (see original NDA review by Drs. Eric Andreasen and Lynnda Reid).

In the 9-month toxicology study in eugonadal male dogs, the major findings included: dose-related increases in reticulocytes, dose-related decreases in cholesterol in all treated groups at ≥7.5 mg/kg BID (15 mg/kg/day), dose-related decreases in adrenal weights at ≥7.5 mg/kg BID associated with moderate adrenal vacuolation in one dog at high dose (30 mg/kg BID), increased incidence of minimal renal papillary mineralization associated with increased creatinine and increased kidney weights at the high dose, dose-related increase in enlarged prostate at ≥7.5 mg/kg BID, and severe diffuse testicular atrophy/degeneration and correlative changes of severe hypospermia in the epididymis associated with small testes and decreased testis weights at ≥7.5 mg/kg BID. The findings in the reproductive system persisted following an 8-week treatment-free period. The exposure to TU-related compounds including TU and T at the high-dose corresponded to approximately 2- and 1-fold, respectively, the maximum anticipated human exposure at the MRHD.

Label: The following annotated labeling contains DBRUP recommendations to the sponsor's proposed labeling relevant to nonclinical sections. The recommended PLLR label in Section 8 is adopted from the previously approved and labeled T products, XYOSTED®, AndroGel® 1.62% and AndroGel 1%. The revisions are limited to sections where the text has been altered (italicized in red) or deleted (strikethrough).

HIGHLIGHTS OF PRESCRIBING INFORMATION

CONTRAINDICATIONS

- Women who are pregnant. Testosterone may cause fetal harm. (4, 5.7, 8.1, 8.2, (b) (4)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

JATENZO (b) (4) is contraindicated in pregnant women. (b) (4)

Testosterone is teratogenic and may cause fetal harm based on data from animal studies and its mechanism of action *[see Contraindications (4) and Clinical Pharmacology (12.1)]*. Exposure of a female fetus to androgens may result in varying degrees of virilization. In animal developmental studies, exposure to testosterone in utero resulted in hormonal and behavioral changes in offspring and structural impairments of reproductive tissues in female and male offspring. These studies did not meet current standards for nonclinical development toxicity studies.

Data

(b) (4)

[redacted] *Animal Data:*

[redacted]

In developmental studies conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used for testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased anogenital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes.

Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant female rats and their offspring exposed to doses approximately twice those used for testosterone replacement therapy.

8.2 Lactation

Risk Summary

JATENZO is not indicated for use in women [redacted]

[redacted]

8.3 Females and Males of Reproductive Potential

[redacted]

Infertility

[redacted]

During treatment with large doses of [redacted] exogenous androgens, including JATENZO, spermatogenesis may be suppressed [redacted] through feedback inhibition of the hypothalamic-pituitary-testicular axis *[see Warnings and Precautions (5.8)],* [redacted] possibly leading to adverse effects on semen parameters including sperm count. Reduced fertility is observed in some men taking testosterone replacement therapy. Testicular atrophy, subfertility, and infertility have been reported in men who abuse

anabolic androgenic steroids *[see Drug Abuse and Dependence (9.2)]*. With either type of use, the impact on fertility may be irreversible.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution. (b) (4)

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, whereas secondary hypogonadism (also known as hypogonadotropic hypogonadism) is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Mutagenesis
Testosterone (b) (4) was (b) (4) negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. (b) (4)

Impairment of Fertility
The administration of exogenous testosterone suppresses spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

13.2 (b) (4) Animal Toxicology and/or Pharmacology

JATENZO has been evaluated in 3- and 9-month- (b) (4) repeat-dose oral toxicity studies in male eugonadal dogs. (b) (4)

(b) (4)

JATENZO caused exaggerated pharmacological effects on androgen (b) (4) responsive tissues (b) (4) including testes, epididym (b) (4) s, prostate and adrenals at exposures to testosterone or testosterone undecanoate, comparable to the maximum human exposure based on AUC comparisons. Following a 4-week drug-free period, a reduced severity of these findings was observed, suggesting partial reversibility.

In adrenal glands, moderate to severe atrophy, characterized as thinning of the zona fasciculata, was observed with reduced adrenal weights and (b) (4) reduced circulating levels of cortisol in testosterone undecanoate-treated dogs after 3 months of treatment (b) (4) Following 9-month treatment, there were dose-related decreases in adrenal weights in testosterone undecanoate-treated male dogs and moderate adrenal vacuolation in one testosterone undecanoate-treated male dog. The clinical significance of these adrenal and cortisol findings is unknown.

(b) (4)

(b) (4)

Outstanding Nonclinical Issue: None

Summary and conclusion: All nonclinical revisions to the sponsor's proposed labeling were accepted by the sponsor. The sponsor's revised labeling submitted on March 21, 2019 is acceptable from a Pharmacology and Toxicology perspective. There are no further recommendations at this time.

Recommendation: Pharmacology and Toxicology recommends approval of the sponsor's final labeling revisions.

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

/s/

YANGMEE SHIN
03/25/2019 04:14:51 PM

KIMBERLY P HATFIELD
03/25/2019 04:35:30 PM

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206089
Supporting document/s:	SDN-61
Applicant's letter date:	9/27/2018
CDER stamp date:	9/27/2018
Product:	Testosterone undecanoate (JATENZO)
Indication:	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone due to primary or hypogonadotropic hypogonadism
Applicant:	Clarus Therapeutics, Inc.
Review Division:	Division of Bone, Reproductive, and Urologic Products
Reviewer:	Yangmee Shin, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Jeannie Roule

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206089 are owned by Clarus Therapeutics or are data for which Clarus Therapeutics has obtained a written right of reference.

Any information or data necessary for approval of NDA 206089 that Clarus Therapeutics does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206089.

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1 Executive Summary

1.1 Introduction

This Class 2 NDA resubmission constitutes a Complete Response (CR) to three major deficiencies outlined in the 2nd CR letter issued on March 22, 2018. In the CR letter, the Division requested that Clarus Therapeutics (1) ensure safe use of the oral testosterone undecanoate (TU) together with an assessment to mitigate risks related to the increased ambulatory blood pressure observed with TU use in the sponsor's phase 3 clinical trial and (2) ensure accurate and reliable test for testosterone (T) concentrations due to a concern for TU to testosterone (T) *ex vivo* conversion relative to the use of sodium fluoride (NaF)/ethylenediaminetetraacetic acid (EDTA) tubes, such that it may lead to an overestimation of circulating T concentrations. (3) A Pharmacology and Toxicology deficiency included unacceptable nonclinical studies submitted to support approval of the NDA through a 505(b)(1) pathway.

The proposed oral TU (JATENZO) is a self-emulsifying drug delivery system (SEDDS) containing a T ester prodrug, indicated for replacement therapy in adult males with a deficiency or absence of endogenous T: primary and hypogonadotropic hypogonadism at the starting dose of 237 mg, taken orally twice daily (BID)- once in the morning with food and once in the evening with food. The dose can be decreased to (b) (4) mg BID or increased to (b) (4) mg BID, based on serum T concentrations from a sample drawn 6 hours after the morning dose.

In the current resubmission, the sponsor intends to reclassify NDA as a 505(b)(2) application and to address the nonclinical deficiencies noted in the CR letter, referencing the information provided in the original NDA submission. Pharmacology and Toxicology recommended approval of the initial submission of the NDA on August 4, 2014 during the first cycle review. The initial NDA provided literature references to address ADME of TU by the oral route. The sponsor conducted a 3-month oral toxicology study of the oral TU formulation in male dogs and included published literature to support the use of borage oil as a novel excipient. The sponsor also supplied published literature to support the safety and labeling on fertility, pregnancy, and carcinogenicity. Within the resubmission, the sponsor submitted 3 additional published articles in support of labeling statements regarding the effect of T on male fertility and spermatogenesis.

1.2 Brief Discussion of Nonclinical Findings

Reference is made to the Pharmacology and Toxicology review, filed in DARRTS on February 27, 2018. Pharmacology and Toxicology recommended a CR action for the 1st resubmitted NDA via a 505(b)(1) pathway based on inadequate doses tested that did not permit adequate characterization of the potential effect of the oral TU product following chronic treatment, particularly, to support male fertility (combined with an in vivo genotoxicity test) and carcinogenicity assessments.

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The sponsor's nonclinical studies to support the 505(b)(1) NDA of oral TU included a 9-month oral toxicology study in male dogs, a battery of genotoxicity tests, a 6-month carcinogenicity study in Tg·rasH2 male mice (with a 28-day dose range finding study in male CByB6F1-Tg (HRAS) 2Jic mice), and a fertility study in male rats.

In the 9-month toxicology study in male eugonadal dogs, there were no new or significant findings other than the expected androgenic effects up to the doses, which produced 1-2 times the AUC exposure to TU or T relative to the maximum human AUC exposure.

TU was negative in a battery of genotoxicity tests. The in vivo micronucleus study was incorporated into the male fertility study; however, no criteria were provided for the selection of the top dose.

In the fertility study, the tested doses did not produce the anticipated effects on spermatogenesis and/or fertility, which may reflect insufficient exposure to T and/or TU. In addition, there were no toxicokinetic data to evaluate drug exposure. Consequently, this study was considered inadequate.

In the 6-month carcinogenicity study in male Tg·rasH2 mice, no basis of dose selection was provided: the maximally tolerated dose, maximum feasible dose or limit dose was not identified in the 28-day dose range finding study or in the main study. The use of 25 males/group due to "gender specific effects" was not a valid evaluation, as the study remained insufficiently powered for one sex. The sponsor's additional information submitted on November 30, 2017, including the basis of appeal to then the Acting Director in Office of New Drugs, Dr. Janet Woodcock and an amended report for the 6-month study in Tg·rasH2 mice that contains the sponsor's justification for dose selection was not considered adequate to address the deficiency.

This resubmission contains no nonclinical studies. The sponsor's proposal to reference the original submission of this NDA with additional published literature is acceptable. There are no additional pharmacology and toxicology data and information required to fulfill the nonclinical requirement to support the NDA via the 505(b)(2) pathway.

1.3 Recommendations

1.3.1 Approvability

From a Pharmacology and Toxicology, the current submission, along with the initial NDA submission, contains adequate information to support approval of NDA 206089 via a 505(b)(2) pathway.

1.3.2 Additional Non-Clinical Recommendations

Additional nonclinical studies are not requested at this time.

1.3.3 Labeling

The sponsor submitted an updated labeling for conformance with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements, including 3 additional

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literature references regarding the effect of T on male fertility and spermatogenesis in Module 4.3.

The following annotated labeling is the DBRUP recommendations to the sponsor's proposed labeling relevant to nonclinical sections. The recommended label in Section 8 is adopted from the previously approved and labeled T products, XYOSTED® and AndroGel®. The revisions are limited to sections where the context has been altered (italicized in red) or deleted (strikethrough). Any additional label changes will be addressed in an addendum review.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

JATENZO, (b) (4) is contraindicated in wome (b) (4) Testosterone is teratogenic and may cause fetal harm based on data from animal studies and its mechanism of action *[see Contraindications (4) and Clinical Pharmacology (12.1)]*. Exposure of a female fetus to androgens may result in varying degrees of virilization. In animal developmental studies, exposure to testosterone in utero resulted in hormonal and behavioral changes in offspring and structural impairments of reproductive tissues in female and male offspring. These studies did not meet current standards for nonclinical development toxicity studies.

Data

(b) (4)

(b) (4)

(b) (4) *Animal Data:*

(b) (4)

In developmental studies conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used for testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased anogenital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes.

Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant female rats and their offspring exposed to doses approximately twice those used for testosterone replacement therapy.

8.2 Lactation

Risk Summary

JATENZO is not indicated for use in women (b) (4)

(b) (4)

8.3 Females and Males of Reproductive Potential

(b) (4)

Infertility

(b) (4)

During treatment with large doses of (b) (4) exogenous androgens, including JATENZO, spermatogenesis may be suppressed (b) (4) through feedback inhibition of the hypothalamic-pituitary-testicular axis (b) (4) possibly leading to adverse effects on semen parameters including sperm count *[see Warnings and Precautions (5.8)]*. Reduced fertility is observed in some men taking testosterone replacement therapy. Testicular atrophy, subfertility, and infertility have been reported in men who abuse anabolic androgenic steroids *[see Drug Abuse and Dependence (9.2)]*. With either type of use, the impact on fertility may be irreversible.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution. (b) (4)

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, whereas secondary hypogonadism (also known as hypogonadotropic hypogonadism) is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Mutagenesis

Testosterone [redacted] was [redacted] negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. [redacted]

Impairment of Fertility

The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

13.2 [redacted] Animal Toxicology and/or Pharmacology

JATENZO has been evaluated in 3- and 9-month [redacted] repeat-dose oral toxicity studies in male eugonadal dogs. [redacted] JATENZO caused exaggerated pharmacological effects on androgen [redacted] responsive tissues [redacted], including testes, epididymis, prostate and adrenals at exposures to testosterone or testosterone undecanoate, comparable to the maximum human exposure based on AUC comparisons. Following a 4-week drug-free period, a reduced severity of these findings was observed, suggesting partial reversibility.

In adrenal glands, moderate to severe atrophy, characterized as thinning of the zona fasciculata, was observed with reduced adrenal weights and [redacted] reduced circulating levels of cortisol were observed in testosterone undecanoate-treated dogs after 3-month treatment. Following 9-month treatment, there were dose-related decreases in adrenal weights in testosterone undecanoate-treated male dogs and moderate adrenal vacuolation in one testosterone undecanoate-treated male dog. The clinical significance of these adrenal and cortisol findings is unknown.

[redacted]

[redacted]

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2 Drug Information

2.1 Drug

CAS Registry Number: 5949-44-0

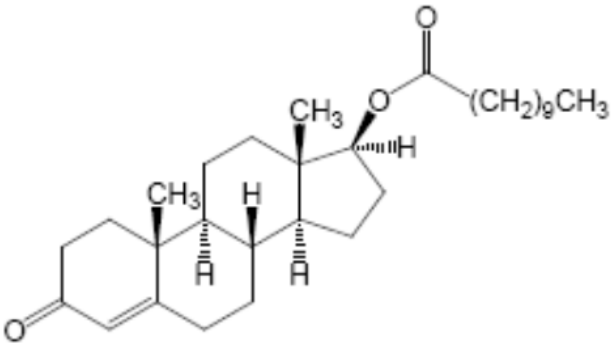
Generic Name: Testosterone undecanoate

Code Name: N/A

Chemical Name: 17β-Hydroxyandrost-4-en-3-one undecanoate

Molecular Formula/Molecular Weight: $C_{30}H_{48}O_3$/456.7

Structure or Biochemical Description:



Pharmacologic Class: Androgen

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 078104
- NDA 209863 (Xyosted®, TE injection); NDA 205488 (Natesto®, nasal T gel); NDA 204399 (Vogelxo®, transdermal T gel 1%); NDA 203098 (transdermal T gel 1%); NDA 202763 (T Gel 1%); NDA 022504 (Axiron®, topical T solution); NDA 022309 (AndroGel® 1.62%, transdermal); NDA 022219 (Aveed®, TU injection); NDA 021543 (Striant®, buccal T tablet); NDA 021463 (Fortesta®, T gel); NDA 021454 (Testim®, 1% T gel); NDA 021015 (AndroGel 1%, transdermal T); NDA 020791 (Testoderm® TTS, transdermal T); NDA 020489 (Androderm®, transdermal T patch); NDA 019762 (Testoderm®, transdermal T); NDA 004652 (Oreton®, T pellet)
- [redacted] (b) (4)

2.3 Drug Formulation

Immediate release, soft gelatin capsules containing 158.3 mg, 197.9 mg, and 237.5 mg TU in a self-emulsifying drug delivery system (SEDDS) formulation.

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The following sponsor's table describes the unit composition of the TU capsules.

Components	Function	TU Capsule (mg/capsule)		
		100 mg[aa)]	125 mg[a]	150 mg[a]
Testosterone undecanoate (DMF (b) (4) and DMF (b) (4))	Active Pharmaceutical Ingredient (API)	158.3	197.9	237.5
Oleic acid	(b) (4)			
Cremophor® RH40 (DMF # (b) (4))				
Borage seed oil				
Peppermint oil				
BHT				

Cremophor® RH40=polyoxyl 40 hydrogenated castor oil NF; BHT=butylated hydroxytoluene; TU=testosterone undecanoate; a) and aa)=Testosterone equivalent

2.4 Comments on Novel Excipients

All inactive ingredients are considered qualified. The product contains one novel excipient borage seed oil and (b) (4) 3 excipients (oleic acid, butylated hydroxytoluene, and polyoxyl 40 hydrogenated castor oil) (b) (4) Safety of the excipients was assessed in the 13-week and 9-month toxicology studies in male dogs. The sponsor also provided safety assessments of borage seed oil based on literature references in the original NDA submission, which were considered adequate. Oleic acid, butylated hydroxytoluene, and polyoxyl 40 hydrogenated castor oil were considered safe to use, given that the excipients are generally regarded as safe (GRAS) and do not exceed the food content or maximum daily intake level (not specified for oleic acid) (see original NDA Review by Drs. Eric Andreasen and Lynnda Reid for details).

2.5 Comments on Impurities/Degradants of Concern

There are no leachable/extractable or other impurity issues. Justification of specifications for individual impurities for the drug substance and the drug product is acceptable (see CMC Review for details).

2.6 Proposed Clinical Population and Dosing Regimen

Treatment of male primary and hypogonadotropic hypogonadism associated with a deficiency or absence of endogenous T at the starting dose of 237 mg of TU, taken orally twice daily- once in the morning with food and once in the evening with food to deliver T concentrations in serum of 425-970 ng/dL. Dose can be adjusted to a minimum of (b) (4) mg BID and a maximum of (b) (4) mg BID based on total T concentration in serum from blood collected in plain (red top) tubes drawn 6 hours after the morning dose and at least 7 days after starting treatment or following dose adjustment. Additionally, serum T concentrations should be assessed periodically thereafter.

The following sponsor's table shows the dose adjustment scheme that is based on serum T concentration from a sample drawn 6 hours after the morning dose.

Testosterone Concentration in Serum From Plain (Red-Top) Tube Drawn 6 hours After Dose	Current JATENZO Dose (mg, BID)	New JATENZO Dose (mg, BID)
<425 ng/dL	158	198
	198	237
	237	316
	316	(b) (4)
425 – 970 ng/dL	No Dose Change	
>970 ng/dL	396	316
	316	237
	237	198
	198	158
	158	Discontinue Treatment

BID = twice daily

2.7 Regulatory Background

The current NDA submission is a Class 2 resubmission following a CR letter issued on November 3, 2014 and March 22, 2018. The Division issued the 1st CR letter due to safety concerns including: 1) lack of sufficient evidence for efficacy, 2) unknown potential risks associated with very high TU and dihydrotestosterone undecanoate (DHTU) exposures and significantly decreased sex hormone binding globulin (SHBG), 2) known potential risks, such as increased blood pressure and increased hematocrit, associated with dihydrotestosterone (DHT) concentrations and DHT/T ratios above the normal range, and 3) an unmanageable effect of food on T exposure, with severe impact on variations in PK parameters for T, resulting in an inability to write labeling that will provide reliable guidance for dosing. In addition, the sponsor was requested to address the effect of oral TU on the human hypothalamic-pituitary-adrenal (HPA) axis based on the adrenal findings in dogs (i.e., moderate to marked atrophy of the adrenal cortex with an accompanying reduction in serum cortisol) that may lead to secondary adrenal insufficiency.

Subsequently, the sponsor made a strategic regulatory decision to pursue resubmission of NDA using a 505(b)(1) pathway and conducted a series of nonclinical studies of oral TU including a 9-month oral toxicology study in male dogs, a battery of genotoxicity tests, a 6-month carcinogenicity study in Tg·rasH2 male mice, and a fertility study in male rats upon agreement with the Division on November 19, 2015. The sponsor received a 2nd CR on March 22, 2018 due to Clinical, Clinical Pharmacology, and Pharmacology and Toxicology deficiencies. These included the potential for an associated increased risk of major adverse cardiovascular events related to the increased mean blood pressure; and sample collection and post-collection processing factors contributing to the observed differences in T concentrations between serum from plain test tubes *versus* T concentrations in plasma from NaF-EDTA test tubes due to *ex*

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vivo conversion of TU to T, and handling conditions of samples such as temperature and time, *etc*.

Pharmacology and Toxicology recommended a CR action for the 2nd resubmission of NDA based on inadequate doses tested that did not permit adequate characterization of the potential effect of the oral TU product following chronic treatment, particularly, for male fertility (integrated with a micronucleus test) and carcinogenicity assessments (see previous NDA review for details).

In the current resubmission, the sponsor intends to identify the application as a 505(b)(2) application to address the nonclinical deficiencies noted in the CR letter, referring to the information and data submitted to the original NDA.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical studies were submitted.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

IND 078104 and previous NDA 206089 Reviews

11 Integrated Summary and Safety Evaluation

The 1st resubmission of the NDA included a 9-month oral toxicology study in male dogs, a battery of genotoxicity tests, a 6-month carcinogenicity study in Tg·rasH2 male mice (with a 28-day dose range finding study in male CByB6F1-Tg (HRAS) 2Jic mice), and a fertility study in male rats with oral TU, as agreed by the Division to support the NDA 206089 resubmission via a 505(b)(1) application. However, submitted nonclinical studies were unacceptable to support the 505(b)(1) application of the NDA from the Pharmacology and Toxicology perspective.

Specifically, the 6-month carcinogenicity study in male Tg·rasH2 mice and the male fertility study in rats were tested up to 80 mg/kg/day, which did not produce expected androgenic effects, reflecting insufficient exposure to T and/or TU. TU was negative in a bone marrow micronucleus test, integrated into the male fertility study. However, there were no criteria provided for the selection of the top dose (80 mg/kg/day). The high dose of TU in the 9-month toxicology study in dogs was ~1-2 times the maximum human dose based on AUC exposures to TU or T.

The following comments were provided in the 2nd CR letter issued on March 22, 2018.

Nonclinical deficiency:
The submitted nonclinical studies are unacceptable to support approval of your NDA through the 505(b)(1) pathway. Specifically, your TU doses were inadequate to

Reference ID: 4397737

characterize and provide a meaningful and valid evaluation of the chronic effects of your product on male fertility and carcinogenicity. In the fertility study, the tested doses did not produce the anticipated effects on spermatogenesis and/or fertility, which may reflect insufficient exposure to T and/or TU. You did not submit toxicokinetic data to evaluate drug exposure. With regards to your 6-month carcinogenicity study in male Tg·rasH2 mice, the rationale provided in your November 30, 2017, letter does not satisfactorily address the nonclinical deficiency communicated in our letter dated October 4, 2017. Specifically, per International Conference on Harmonization (ICH) guidance S1C(R2) Dose Selection for Carcinogenicity Studies (2008), the maximally tolerated dose (MTD), maximum feasible dose or limit dose was not identified in your 28-day dose range finding study or in your 6-month carcinogenicity study. The use of 25 males/group due to "gender specific effects" is not a valid evaluation in your 6-month carcinogenicity study, as the study remains insufficiently powered for one sex.

Information needed to resolve the deficiency:
Provide justification for dose selection for the fertility study combined with the in vivo micronucleus test, and conduct a new, adequately designed carcinogenicity study. Submit the carcinogenicity study protocol for review by the Division and the Executive Carcinogenicity Assessment Committee per the guidance "Guidance for Industry Carcinogenicity Study Protocol Submissions" found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078924.pdf.

Alternatively, you may classify your NDA as a 505(b)(2) application without submitting additional nonclinical studies if you provide appropriate nonclinical published literature references to address the nonclinical deficiencies above. If you proceed with a 505(b)(2) NDA, the results from your completed fertility and carcinogenicity studies will not be included in the product labeling.

In this 2nd resubmission of NDA, the sponsor proposes to use a 505(b)(2) pathway, reclassifying the NDA with appropriate nonclinical published literature references to address the nonclinical deficiencies noted in the CR letter. This NDA resubmission contains one Phase 1 study (CLAR-18019), two bioanalytical studies (CLAR-18016 and CLAR-18021) and two assay validation studies (CLAR-18018 and CLAR-18020) to address the bioanalytical issues including the post-collection conversion of TU to T collected into different types of sample tubes. The sponsor proposed to address the potential risks of adrenal insufficiency and high systemic TU concentrations with chronic dosing of oral TU in post-marketing studies. To mitigate the risk of increases in blood pressure with chronic administration of oral TU, the sponsor proposed detailed strategies in labeling as directed by the Division (see Clinical and Clinical Pharmacology reviews for details).

This resubmission contains no additional nonclinical studies. The sponsor intends to reference the original NDA submission containing published literature along with the findings of a 3-month oral toxicity study of Clarus' oral TU formulation in male dogs. The sponsor proposes to rely on published literature to support 'class labeling' for its T

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replacement product as it relates to carcinogenicity and fertility assessments. Additional published journal articles were submitted in support of labeling statements regarding the effect of T on male fertility and spermatogenesis in Module 4.3.

Pharmacology and Toxicology considers that the sponsor has fulfilled the nonclinical request to resolve deficiency in the CR letter. The current submission, along with the initial NDA submission, contains adequate information to support approval of NDA 206089.

12 Appendix/Attachments

12.1 References

The following references were provided within the resubmission in support of the nonclinical sections of the proposed oral TU labeling.

England GCW. Effect of Progestogens and Androgens upon Spermatogenesis and Steroidogenesis in Dogs. J Reprod Fertil Suppl 51:123-138, 1997.

Glaser RL, Newman M, Parsons M, Zava D, and Glaser-Garbrick D. Safety of Maternal Testosterone Therapy during Breast Feeding. Int J Pharm Compd 2009; 13(4): 314-317.

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Testosterone, Testosterone Oenanthate and Testosterone Propionate. 21:519, 1979.

Mclachlan RI, Wreford NG, Meachem SJ, De Kretser DM, and Robertson DM. Effects of Testosterone on Spermatogenic Cell Populations in the Adult Rat. Biol Reprod 51:945, 1994.

Poswillo DE. Tridione and Paradione as Suspected Teratogens. Ann Roy Coll Surg Engl 50:367, 1972.

Reuber MD. Effect of Age and Testosterone on the Induction of Hyperplastic Nodules, Carcinomas, and Cirrhosis of the Liver in Rats Ingesting N-2-fluorenyldiacetamide. Eur J Cancer 12:137, 1976.

Reuber MD. Influence of Sex and Sex Hormones on Transplantable Hepatocellular Carcinoma in the Rat. Pathol Microbiol (Basel) 42:59, 1975.

Schenken JR and Burns EL. Spontaneous Primary Hepatomas in Mice of Strain C3H. III. The Effect of Estrogens and Testosterone Propionate on Their Incidence. Cancer Res 3:693, 1943.

Schnabel PG, Bagchus W, Lass H, Thom T, Geurts TBP. The effect of food composition on serum testosterone levels after oral administration of Andriol Testocaps. Clin Endocrinol (Oxf) 66 (4):579, 2007.

Van Nie R, Smit GMJ, and Mühlbock O. The Induction of Uterine Tumours in Mice Treated with Testosterone. Acta Un Int Cancer 18:194, 1962.

Van Nie R. Biological Aspects of the Genesis of Uterine Tumours Induced in Mice by Testosterone. Jaarb Kankeronderz Kankerbestrijd Ned 14:247, 1964.

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Weinbauer GF, Schlatt S, Walter V, and Nieschlag E. Testosterone-Induced Inhibition of Spermatogenesis is More Closely Related to Suppression of FSH than to Testicular Androgen Levels in the Cynomolgus Monkey Model (*Macaca fascicularis*). J Endocrinol 168:25, 2001.

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/s/

YANGMEE SHIN
03/01/2019 11:05:31 AM

MUKESH SUMMAN
03/01/2019 12:00:06 PM
Nonclinical supports AP

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206089
Supporting document/s:	SDN-31; SDN-49
Applicant's letter date:	6/22/2017; 11/30/2017
CDER stamp date:	6/22/2017; 11/30/2017
Product:	Testosterone undecanoate (JATENZO)
Indication:	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone due to primary or hypogonadotropic hypogonadism
Applicant:	Clarus Therapeutics, Inc.
Review Division:	Division of Bone, Reproductive, and Urologic Products
Reviewer:	Yangmee Shin, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Jeannie Roule

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206089 are owned by Clarus Therapeutics or are data for which Clarus Therapeutics has obtained a written right of reference.

Any information or data necessary for approval of NDA 206089 that Clarus Therapeutics does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206089.

Reference ID: 4227239

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1 Executive Summary

1.1 Introduction

Clarus Therapeutics, Inc., has resubmitted the oral testosterone undecanoate (TU) NDA following a Complete Response (CR) letter issued on November 3, 2014. Based on the proposed label, the oral TU (JATENZO) capsules are indicated for replacement therapy in adult males with a deficiency or absence of endogenous testosterone: primary and hypogonadotropic hypogonadism at the starting dose of 237 mg, taken orally twice daily (BID)- once in the morning with food and once in the evening with food. The dose can be decreased to (b) (4) mg BID or increased up to 396 mg BID, based on plasma T concentrations collected in a sodium fluoride (NaF)-EDTA tube drawn 3-5 hours after the morning dose and at least 7 days after starting treatment and following dose adjustment.

To enable re-classification of the NDA 206089 submission from a 505(b)(2) to a 505(b)(1) application, the sponsor conducted a 9-month oral toxicology study in male dogs, a battery of genotoxicity tests, a 6-month carcinogenicity study in Tg·rasH2 male mice (with a 28-day dose range finding study in male CByB6F1-Tg (HRAS) 2Jic mice), and a fertility study in male rats.

1.2 Brief Discussion of Nonclinical Findings

TU (Ki=1.20 μM, IC_{50}=2.04 μM) itself has approximately 1000 times less binding affinity of testosterone (T) (Ki= 1.12 nM, IC_{50}=1.91 nM), suggesting that TU possesses low potential for androgenic activity without being metabolized to T.

Undecanoic acid is a medium chain length (11 carbon) fatty acid that is incorporated into glycerides and phospholipids, and metabolized by β-oxidation and the tricarboxylic acid pathways. Undecanoic acid is identified as a food additive. However, the extent of exposure to undecanoic acid administered via TU in men is unknown.

TU is highly lipophilic compared to T and may accumulate in lipid-rich and/or well-perfused tissues and organs such as the adrenal gland, liver, kidney, fat, and heart following repeated administration. The proposed oral TU product contains other lipophilic substances, formulated in a self-emulsifying drug delivery system (SEDDS) that was designed to promote TU absorption into the intestinal lymphatics and subsequent metabolism to T and undecanoic acid by non-specific esterases.

In the 9-month toxicology study in male dogs, the major findings included: dose-related increases in reticulocytes, dose-related decreases in cholesterol in all treated groups at ≥7.5 mg/kg BID (15 mg/kg/day), dose-related decreases in adrenal weights at ≥7.5 mg/kg BID associated with moderate adrenal vacuolation in one dog at high dose (30 mg/kg BID), increased incidence of minimal renal papillary mineralization associated with increased creatinine and increased kidney weights at the high dose, dose-related increase in enlarged prostate at ≥7.5 mg/kg BID, and severe diffuse testicular atrophy/degeneration and correlative changes of severe hypospermia in the epididymis

associated with small testes and decreased testis weights at ≥7.5 mg/kg BID, which persisted during an 8-week treatment-free period. The exposure to TU ($AUC_{0\text{-last}}$~4000 ng·hr/mL), DHTU ($AUC_{0\text{-last}}$~130 ng·hr/mL), T ($AUC_{0\text{-last}}$~170 ng·hr/mL), or DHT ($AUC_{0\text{-last}}$~20 ng·hr/mL) at the high-dose (30 mg/kg BID) corresponded to approximately 2-, <1-, 1, and 1-fold, respectively, the maximum anticipated human exposure at the MRHD of 396 mg BID ($AUC_{0\text{-24h}}$~1900 ng·hr/mL for TU, $AUC_{0\text{-24h}}$~600 ng·hr/mL for DHTU, $AUC_{0\text{-24h}}$~150 ng·hr/mL for T, $AUC_{0\text{-24h}}$~20 ng·hr/mL for DHT).

TU was negative in a battery of genotoxicity tests. The in vivo micronucleus study was incorporated into the male fertility study; however, no criteria were provided for the selection of the top dose.

In the male fertility study in rats administered up to 80 mg/kg/day, small testes and epididymides associated with dose-related reduction of testis weights were observed at ≥40 mg/kg/day. There were no effects on the sperm analysis and/or fertility parameters up to the high dose tested, which was comparable to the maximum recommended human dose based on body surface area.

In the 6-month carcinogenicity study in male Tg·rasH2 mice, there were no tumor findings up to the doses tested at 20, 40, and 80 mg/kg/day. The doses were selected based on the minimal testicular degeneration observed in 9 out of 10 mice at 80 mg/kg compared to 1 out of 10 in vehicle-treated mice in the 1-month dose range-finding study. The carcinogenicity study was conducted without Executive Carcinogenicity Assessment Committee (Exec CAC) review for pre-study protocol and dose selection. The Committee concurred with the Division that the study was inadequate to assess the risk of carcinogenicity because it did not reach a maximum tolerated dose (MTD); no basis of dose selection was provided by the applicant; and the study was insufficiently powered for one sex. Based on the Exec CAC recommendations, the Division requested that the sponsor provide clarification how this nonclinical deficiency would be addressed for filing of a 505(b)(1) NDA. The sponsor submitted their response on November 30, 2017, including the basis of appeal to Acting Director in Office of New Drugs, Dr. Janet Woodcock to rescind the Exec CAC decision and to affirm the 505(b)(1) status of the NDA. The sponsor also submitted an amended report for the 6-month study in Tg·rasH2 mice that contains the sponsor's justification for dose selection and number of animals per group in further support of the conclusion that oral TU was not carcinogenic in this model. However, the sponsor's response is not considered adequate to address the deficiency (see **Integrated Summary and Safety Evaluation** for details).

Overall there were no new or significant findings were observed in eugonadal male dogs in the 9-month toxicology study up to the oral TU doses tested, which produced 1-2 times the AUC exposure to TU or T relative to the maximum anticipated human AUC exposure. The findings in the reproductive organs (i.e., prostate, epididymis, and testis) in male eugonadal dogs at T levels above the baseline AUC (~2-9 times) and C_{max} (~4-20 times) are expected androgenic effects that would likely not occur in hypogonadal men exposed to T in the eugonadal range. The negative results from the carcinogenicity

and male fertility studies may reflect insufficient exposure to T and/or TU. From the Pharmacology and Toxicology perspective, the submitted nonclinical studies are not considered adequate to characterize the potential effect of oral TU following chronic treatment.

1.3 Recommendations

1.3.1 Approvability

Pharmacology and Toxicology recommends a Complete Response action for this NDA. The submitted nonclinical studies are unacceptable to support the 505(b)(1) application of the NDA based on the doses tested that would not permit adequate characterization of the potential effect of the oral TU product following chronic treatment.

Nonclinical deficiencies:
Inadequate doses were used to allow adequate characterization of male fertility and carcinogenicity, which would preclude a meaningful and valid evaluation of the potential chronic effect of the oral TU product.

Information needed to resolve the deficiencies:

- The doses tested for the fertility study in male rats did not produce anticipated effects on the spermatogenesis and/or fertility that may reflect insufficient exposure to T and/or TU. No toxicokinetic data have been submitted to evaluate drug exposure. Provide a justification for dose selection for the fertility study combined with the in vivo micronucleus test.
- Your rationale for adequacy of the 6-month carcinogenicity study in male Tg·rasH2 mice provided in the letter on November 30, 2017 is not satisfactory to address the nonclinical deficiency communicated in the letter dated October 4, 2017. Conduct a new, adequately designed carcinogenicity study. Submit the carcinogenicity study protocol for review by the Division and the Executive Carcinogenicity Assessment committee (CAC) per the following guidance "Guidance for Industry Carcinogenicity Study Protocol Submissions" found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078924.pdf.
- Alternatively, you may classify your NDA as a 505(b)(2) application without submitting additional nonclinical studies if you have provided appropriate nonclinical published literature references to address the nonclinical deficiencies above. The Division, however, advises that results from the completed studies will not be included in the product labeling.

1.3.2 Additional Non Clinical Recommendations

None (see above)

1.3.3 Labeling

Labeling review will be conducted under separate review. The sponsor has submitted revised label on October 3, 2017 including 2 literature references in response to the Division request to submit the labeling in PLLR format in a 74-day letter.

2 Drug Information

2.1 Drug

CAS Registry Number: 5949-44-0

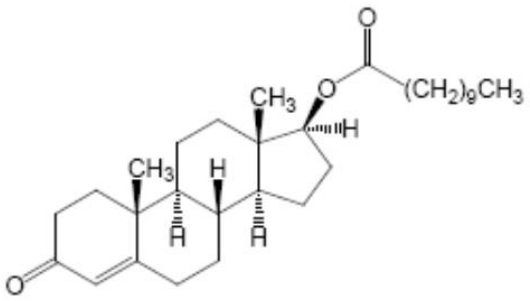
Generic Name: Testosterone undecanoate

Code Name: N/A

Chemical Name: 17β-Hydroxyandrost-4-en-3-one undecanoate

Molecular Formula/Molecular Weight: $C_{30}H_{48}O_3$/456.7

Structure or Biochemical Description:



Pharmacologic Class: Androgen

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 078104; NDA 205488 (Natesto®, nasal T gel); NDA 204399 (Vogelxo®, transdermal T gel 1%); NDA 203098 (transdermal T gel 1%); NDA 202763 (T Gel 1%); NDA 022504 (Axiron®, topical T solution); NDA 022309 (AndroGel® 1.62%, transdermal); NDA 022219 (Aveed®, TU injection); NDA 021543 (Striant®, buccal T tablet); NDA 021463 (Fortesta®, T gel); NDA 021454 (Testim®, 1% T gel); NDA 021015 (AndroGel 1%, transdermal T); NDA 020791 (Testoderm® TTS, transdermal T); NDA 020489 (Androderm®, transdermal T patch); NDA 019762 (Testoderm®, transdermal T); NDA 004652 (Oreton®, T pellet); DMF (b) (4) ; DMF (b) (4) ; DMF (b) (4) ; DMF (b) (4)

2.3 Drug Formulation

Immediate release, soft gelatin capsules containing 158.3 mg, 197.9 mg, and 237.5 mg TU in a self-emulsifying drug delivery system (SEDDS) formulation.

The following sponsor's table describes the unit composition of the TU capsules.

Components	Function	TU Capsule (mg/capsule)		
		100 mg[aa)]	125 mg[a]	150 mg[a]
Testosterone undecanoate (DMF # (b) (4) and DMF # (b) (4))	Active Pharmaceutical Ingredient (API)	158.3	197.9	237.5
Oleic acid	(b) (4)			(b) (4)
Cremophor® RH40 (DMF # (b) (4))				
Borage seed oil				
Peppermint oil				
BHT				
	Total:			

Cremophor® RH40=polyoxyl 40 hydrogenated castor oil NF; BHT=butylated hydroxytoluene; TU=testosterone undecanoate; a) and aa)=Testosterone equivalent

2.4 Comments on Novel Excipients

All inactive ingredients are considered qualified. The product contains one novel excipient, borage seed oil, (b) (4) 3 excipients (oleic acid, butylated hydroxytoluene, and polyoxyl 40 hydrogenated castor oil) (b) (4) The safety of the formulation was assessed in the 13-week and 9-month toxicology studies in dogs. In addition, oleic acid, butylated hydroxytoluene, and polyoxyl 40 hydrogenated castor oil are considered generally regarded as safe (GRAS) that do not exceed the food content or maximum daily intake level (not specified for oleic acid). Safety assessment of borage seed oil had been submitted in the original NDA submission (see original NDA Review by Dr. Eric Andreasen for details).

2.5 Comments on Impurities/Degradants of Concern

There are no impurity issues. The justification of specifications for individual impurities for the drug substance and the drug product is acceptable (see CMC Review for details).

2.6 Proposed Clinical Population and Dosing Regimen

Treatment of male primary and hypogonadotropic hypogonadism associated with a deficiency or absence of endogenous testosterone at the starting dose of 237 mg of TU, taken orally twice daily- once in the morning with food and once in the evening with food to deliver T concentrations in plasma of 252-907 ng/dL. Dose can be adjusted to a minimum of 158 mg twice daily and a maximum of 396 mg twice daily based on total T concentration in plasma from blood collected in NaF-EDTA tubes drawn 3-5 hours after the morning dose and at least 7 days after starting treatment or following dose adjustment. Additionally, T concentration in plasma from blood drawn in tubes containing NaF-EDTA should be assessed periodically thereafter.

2.7 Regulatory Background

The enanthate, cypionate, and undecanoate esters of T are approved in the United States as intramuscular injections for use in T replacement therapy in adults. Oral TU is available in Canada as Andriol® (TU dissolved in a mixture of castor oil and propylene

glycol monolaurate) and in many other countries as Andriol® Testocap®, Androxon®, Taro-Testosterone, and pms-Testosterone. However, no oral testosterone replacement therapy using TU is approved for adult men in the United States.

The current NDA submission is a Class 2 resubmission following a CR letter issued on November 3, 2014. The Division issued the CR letter due to safety concerns related to food effect and significantly altered steroid hormone levels such as TU, dihydrotestosterone (DHT), dihydrotestosterone undecanoate (DHTU), sex hormone binding globulin (SHBG) that may lead to adverse effects. Additional clinical studies were requested to support the safety of the product including efficacy and safety and the effect of food.

To enable re-classification of the NDA from a 505(b)(2) to a 505(b)(1) application, the sponsor conducted a series of nonclinical studies upon agreement with the Division on November 19, 2015.

On October 4, 2017, the Division sent an Information Request letter regarding the Executive (Exec) Carcinogenicity Assessment Committee (CAC) decision on the adequacy of the 6-month carcinogenicity study in Tg·rasH2 mice. The Exec CAC noted that the carcinogenicity study in male Tg·rasH2 mice was not conducted adequately to assess the risk of carcinogenicity because the maximum tolerated dose (MTD) was not reached; no basis of dose selection was provided; and the study was insufficiently powered for one sex. The Exec CAC also noted the lack of prior FDA concurrence with the protocol or dose selection. The Division requested that the sponsor address the nonclinical requirement of a 505(b)(1) NDA by conducting a new, adequately designed carcinogenicity study unless the sponsor intends to identify the application as a 505(b)(2).

In a response letter sent on November 30, 2017, the sponsor disagreed with reasons proffered by the Division and Exec CAC and included a letter to Acting Director in Office of New Drugs, Dr. Janet Woodcock to repeal the Exec CAC decision and affirm the 505(b)(1) status of the NDA. The sponsor also submitted an amended report for the 6-month study in Tg·rasH2 mice that contains the sponsor's justification for dose selection and number of animals per group in further support of the conclusion that oral TU was not carcinogenic in this model.

3 Studies Submitted

3.1 Studies Reviewed

- (b) (4) T Safety Screen (Study No. AB23843-1180936)
- TU Safety Screen (Study No. AB23843-1180937)
- DHTU Safety Screen (Study No. AB25004)
- TU IC50 Androgen Receptor (Study No. AB26675)
- TU and DHTU Aldosterone Receptor Binding Study (Study No. AB76962)

- 9-Month Oral (Capsule) Toxicity Study of Testosterone Undecanoate in Male Beagles Dogs with an 8-Week Recovery Period (Study No. 16-845)
- Bacterial Reverse Mutation Assay (Study No. AE50JJ.502ICH.BTL)
- In Vitro Mammalian Chromosomal Aberration Assay in Chinese Hamster Ovary Cells (Study No. AE50JJ.331ICH.BTL)
- Bone Marrow Micronucleus Evaluation (Study No. AE50JJ.129GLP.BTL)
- 28-Day Range-Finding Oral Toxicity and Toxicokinetic Study of Testosterone Undecanoate in Male CByB6F1-Tg (HRAS) 2Jic (Wild Type) Mice (Study No. 16-856)
- 26-Week Oral Carcinogenicity Study of Testosterone Undecanoate in Male CByB6F1-Tg(HRAS)2Jic (tg/wt) Mice (Study No. 16-877]
- Oral Reproductive Toxicity Study (Segment I) of Testosterone Undecanoate in Rats (Study No. 16-881)

3.2 Studies Not Reviewed

The following studies were submitted with the original IND and NDA submission, and reviewed by Drs. Eric Andreasen and Jeffrey Bray.

- Effect of Different Testosterone Esters on Androgen Receptor Binding Using Invitrogen's PolarScreen^{TM} AR Fluorescence Polarization Assay (Study No. 013325-02)
- Absorption, Distribution, and Elimination (ADE) of Testosterone Undecanoate, a Prodrug of Testosterone (Applicant's Position Paper based on literature references)
- 13-Week Oral (Capsule) Toxicity Study of Testosterone Undecanoate in Male Beagle Dogs (Study No. CLAR-PC-11001)
- Safety Assessment of Borage Oil as an Excipient in Oral Testosterone Formulations (Applicant's Position Paper based on literature references)

3.3 Previous Reviews Referenced

IND 078104 and NDA 206089 Reviews

4 Pharmacology

4.1 Primary Pharmacology

- ~76% and ~29% inhibition of androgen (T) receptor (human LNCaP clone FGC cells) binding for TU and dihydrotestosterone undecanoate (DHTU), respectively, at 10 µM with ~1000 times less binding affinity of TU (Ki=1.20 µM, IC_{50}=2.04 µM) than T itself (Ki= 1.12 nM, IC_{50}=1.91 nM)
- ~101%, ~43%, ~75%, ~98%, and ~51% inhibition of androgen- (human LNCaP clone FGC cells), estrogen ERα- (human recombinant insect Sf9 cells),

glucocorticoid- (human recombinant insect cells), progesterone PR-B- (human recombinant insect Sf9 cells) receptors, and Site 2 sodium channel (Wistar rat brain) binding for T, respectively, at 10 µM

- ~8% and ~4% inhibition of estrogen receptor ERα (human recombinant insect Sf9 cells) binding for TU and DHTU, respectively, at 10 µM
- ~46% and ~2% inhibition of progesterone PR-B receptor (human recombinant insect Sf9 cells) binding for TU and DHTU, respectively, at 10 µM
- ~11% and ~1% inhibition of glucocorticoid receptor (human recombinant insect cells) binding for TU and DHTU, respectively at 10 µM
- ~3% and ~1% inhibition of mineralocorticoid (aldosterone) receptor (Wistar rat kidney) binding for TU and DHTU, respectively, at 10 µM

Table 1. Inhibitory Effects of TU, DHTU, T, and Dihydrotestosterone (DHT) on Steroid Receptors at 10 µM

Compound / Type	TU	DHTU	T	DHT
Androgen	~76% (IC_{50}~2 µM)	~29%	~101% (IC_{50}~1.9 nM)	-
Estrogen	~8%	~4%	~43%	-
Progesterone	~46%	~2%	~98%	-
Glucocorticoid	~11%	~1%	~75%	-
Mineralocorticoid	~3%	~1%	-	-

-: Not available

4.2 Secondary Pharmacology

Not provided

4.3 Safety Pharmacology

Not provided

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

- Increased systemic exposure of T in animals (lymph duct-cannulated rats and dogs) (J Pharmacol Exp Ther 306:925, 2003; Int J Pharmaceut 24:173, 1985; Acta Endocrinol 79:789, 1975) and thoracic duct-cannulated oral cancer patients (Klin Wochenschr 54:874, 1976) via intestinal lymphatic transport of TU by avoiding the extensive first-pass effect responsible for the inactivation of T after oral administration
- Higher AUC for TU (~4050 *vs* ~1770 nmol·h/L), longer residence time (~41 *vs* ~12 days), longer terminal half-life (~26 *vs* ~10 days), and lower maximal T concentration than testosterone enanthate (TE) following 10 mg/kg intramuscular injection of TU in cynomolgus monkeys (Eur J Endocrinol 132:514, 1995)
- Mean oral bioavailability of T and TU was 3.56% and 6.83%, respectively, in 12 women who received a single 25 mg oral dose of T delivered in miglyol 810 or a

single 40 mg oral TU dose in miglyol 810 (Eur J Drug Metab Pharmacokinet 11:145, 1986)
- Significant increase in oral absorption for TU, T, and dihydrotestosterone (DHT) with a fat-free, low, standard fat, or fatty diet compared to fasting in humans (Clin Endocrinol 66:579, 2007; Pharmacotherapy 23:319, 2003)

Metabolism
- Major metabolites of T, DHT, DHT-TU, 3β-diol, 3α-diol, epiandrosterone, androsterone, 4-androstenedione, and 5α-androstenedione were observed in castrated rats dosed with ^{3}H-TU in arachis oil with higher levels of undecanoate-bound androgens (TU and DHTU) which dominated over undecanoate-free metabolites (T, DHT, and others) in plasma. In contrast, metabolites free of the undecanoate side chain dominated over undecanoate bound androgens in target tissues such as prostate, seminal vesicle, bulbocavernosus muscle, and skeletal muscle (Horm Metab Res 12:541, 1980)
- Additional urinary metabolites including androsta-4,6-dien-3,17-dione, androsta-1,4-dien-3,17-dione, 17-hydroxy-androsta-4,6-dien-3-one, and 15-androsten-3, 17-dione following a single oral TU (120 mg) administration to healthy males (Steroids 76:1367, 2011; Anal Bioanal Chem 398:1759, 2010)

Excretion
- ~44% of the administered dose recovered in urine as glucuronide conjugates within 24 hours, with the primary metabolites of androsterone glucuronide and epitestosterone glucuronide in six men after a single 120 mg oral TU dose (Steroids 67:39, 2002)

5.2 Toxicokinetics

- Increased plasma concentrations of TU and its metabolites in all treated groups with maximum concentrations occurring typically 1-4 hours post-dose and no apparent accumulation upon repeated dosing following 9-month daily doses of 0, 7.5, 15, 30 mg/kg BID in dogs (see study report below)

6 General Toxicology

6.1 Single-Dose Toxicity

Nor provided

6.2 Repeat-Dose Toxicity

Study title: 13-Week Oral (Capsule) Toxicity Study of Testosterone Undecanoate in Male Beagle Dogs with a 4-Week Recovery Period

Key Study Findings (based on the previous NDA review by Dr. Eric Andreasen)

- Clinical pathology:
  - Dose-related decrease (~45-48%) in serum cholesterol in all treated groups (38 mg/kg BID and 126 mg/kg BID) groups which resolved after drug withdrawal
  - Increase (~93%) in ALT (non-statistically significant) at 126 mg/kg BID, which resolved after drug withdrawal
- Adrenal cortex: moderate to marked severity of atrophy (partially reversible at the end of 4-week recovery period) correlated with a ≥30% decrease in adrenal weights in all TU-dosed animals and cortisol levels below the lower limit of quantitation (LLOQ) (10 ng/mL) at the HD
- Epididymides: moderate to severe hypospermia in all treated groups which persisted at HD during the drug-free period
- Prostate: marked hypertrophy in all dogs in all treated groups correlated with increased weights that were reversible after the recovery period
- Testes: non-reversible atrophy/degeneration in all dogs with minimal to severe severity correlated with the testicular weight loss
- TK: dose-proportional increase in TU, DHTU, T, and DHT with no apparent accumulation upon repeat-dosing, with ~7-10 times greater exposure to TU than T based on AUC
- Exposure Multiple:
  - TU: ~3 and ~7 times the C_{max} and ~2 and ~5 times the AUC at 38 and 126 mg/kg BID, respectively, compared to the exposure in men after a 475 mg TU dose
  - DHTU: <1 and 1 times the C_{max} and <1 times and <1 times the AUC at 38 and 126 mg/kg BID compared to the exposure in men after a 475 mg TU dose
  - T: ~6 and 12 times the C_{max} and ~2 and 5 times the AUC at 38 and 126 mg/kg BID, respectively, compared to the exposure in men after a 475 mg TU dose
  - DHT: ~3 and 5 times the C_{max} and ~1 and 2 times the AUC at 38 and 126 mg/kg BID, respectively, compared to the exposure in men after a 475 mg TU dose

Study title: 9-Month Oral (Capsule) Toxicity Study of Testosterone Undecanoate (TU) in Male Beagles Dogs with an 8-Week Recovery Period

Study no.:	16-845
Study report location:	Module 4.2.3.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	2/23/2016 (initiation of dosing)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TU, #PD-16-013, #PD-16-078, #PD-16-130, 99.54%

Key Study Findings

- Clinical pathology:
  - Dose-related increased (up to ~77%) reticulocytes in all treated groups compared to controls
  - Dose-related decreased (up to ~38%) cholesterol in all treated groups compared to controls
- Prostate: dose-related increased (up to ~297%) absolute weights and enlarged prostate in all treated groups
- Adrenal: moderate diffuse adrenal cortex vacuolation in one dog at 60 mg/kg/day associated with small adrenals (bilateral) and dose-related decreased (up to 42%) absolute adrenal weights, but no effect on cortisol levels
- Kidney: increased incidence of minimal renal papillary mineralization associated with increased creatinine (~26%) and increased (~25%) kidney weights at HD
- Testis/epididymis: severe diffuse testicular atrophy/degeneration and correlative changes of severe hypospermia in the epididymis associated with small testes (bilateral) and decreased (up to ~78%) absolute testis weights in all treated animals which persisted during an 8-week treatment-free period
- TK:
  - TU and DHTU: Greater than dose-proportional increase at LD and MD, but comparable for MD and HD with no apparent accumulation
  - DHT/T ratios: rapid rise in plasma T occurring shortly after TU administration, followed by the metabolism of T to form DHT
- Exposure Multiple:
  - TU: ≤1 and ~4 times the C_{max} and ≤1 and ~2 times the AUC at LD and HD, respectively, compared to the exposure in men at the maximum anticipated exposure
  - DHTU: <1 and <1 times the C_{max} and <1 and <1 times the AUC at LD and HD, respectively, compared to the exposure in men at the maximum anticipated exposure

- T: <1 and ~3 times the C_{max} and <1 and ~1 times the AUC at LD and HD, respectively, compared to the exposure in men at the maximum anticipated exposure
- DHT: ~1 and ~4 times the C_{max} and <1 and ~1 times the AUC at LD and HD, respectively, compared to the exposure in men at the maximum anticipated exposure

Methods

Doses:	0, 7.5, 15, 30 mg/kg BID
Frequency of dosing:	Twice daily
Route of administration:	Oral capsule
Dose volume:	0.16, 0.04, 0.08, and 0.16 mL/kg/dose for 0, 7.5, 15, and 30 mg/kg
Formulation/Vehicle:	Gelatin capsule
Species/Strain:	Male beagle dogs ([redacted] (b) (4))
Number/Sex/Group:	6/groups
Age:	8-9 months
Weight:	9-12 kg
Satellite groups:	2/group for recovery groups
Unique study design:	Animals were dosed orally twice daily (BID) approximately 8 hours apart
Deviation from study protocol:	Not significant

Observations and Results

Mortality: Twice daily

- None

Clinical Signs: Pre-study and twice daily

- Unremarkable

Body Weights: Pre-study and weekly for the 1st 13 weeks & every 2 weeks thereafter

- Unremarkable

Feed Consumption: Not determined

Ophthalmoscopy: Indirect funduscopic ophthalmic examinations prior to treatment initiation & prior to scheduled termination (after ~8½ -9 months)

- Unremarkable

ECG: Prior to treatment initiation, on Day 135 (±2 days) & during the week prior to the scheduled termination & prior to and end of the recovery necropsy

- Unremarkable

Hematology: Prior to treatment initiation (baseline), during week 17-18 & prior to the scheduled necropsy (Days 274 & 330) collected from the jugular vein

- Dose-related increased (up to ~77%) reticulocytes in all treated groups compared to controls

Clinical Chemistry: Prior to treatment initiation (baseline), during Week 17/18 & prior to the scheduled necropsy (Days 274 & 330), collected from the jugular vein

- Dose-related decreased (up to ~38%) cholesterol in all treated groups compared to controls
- Dose-related increased creatinine (up to ~26%) in all treated groups compared to controls

Urinalysis: At the end of the treatment & recovery periods (Days 275/276 & Day 332) directly from the bladder

- Absent sperm in all treated animals

Gross Pathology: Days 275/276 & Day 332

- Small adrenals (bilateral) at HD
- Small testes (bilateral) in all treated animals (noted in 1 MD animal at recovery necropsy)
- Enlarged prostate in all treated groups

Organ Weights: Days 275/276 & Day 332 (adrenals, brain, heart, kidneys, liver, prostate, spleen, testes, thyroid with parathyroids)

- Dose-related decreased (up to 42%) absolute adrenal weights in all treated groups compared to controls
- Decreased (up to ~78%) absolute testis weights in all treated groups compared to controls (partially/non-reversible at the end of recovery period)
- Dose-related increased (up to ~297%) absolute prostate weights in all treated groups compared to controls
- Increased (~25%) absolute kidney weights at HD compared to controls

Histopathology: Days 275/276 & Day 332 (only those tissues with compound-related lesions identified in the terminal sacrifice groups were examined from the core low, mid and recovery groups)

Adequate Battery: Yes

Peer Review: No

Histological Findings:

- Moderate diffuse adrenal cortex vacuolation in 1 HD animal
- Increased incidence of renal papillary mineralization with minimal severity at HD
- Severe diffuse testicular atrophy/degeneration and correlative changes of severe hypospermia in the epididymis of all TU-treated animals which persisted after an 8-week treatment-free period with mild to severe severity

Special Evaluation: N/A

Toxicokinetics: Prior to treatment (0) & 0.5, 1, 2, 4, 6, & 8 hours following the 1st dose of the day on Days 1, 135 (±2), and 270 (±2) for plasma T, DHT, TU & DHTU in plasma containing NaF/EDTA gray-top vacutainer tubes

- Increased plasma concentrations of both TU and T in all treated groups as early as 30-minute post-dose, with maximum concentrations occurring typically 1 to 2-hour post-dose, and returning to pre-dose levels in most cases by 8 hours, prior to the second daily dose
- Greater than dose-proportional increase in TU and DHTU at LD and MD, but comparable for MD and HD with no apparent accumulation
- Greater than dose-proportional increase in T and DHT with no accumulation
- Decrease of plasma T for 2 to 4-hour post-dose followed by an increase through the final time point of 8-hour post-dose, suggesting a rapid rise in plasma T occurring shortly after TU administration

Dosing Solution Analysis: A fresh stock of the active TU manufactured every 3 months

- 98.3%, 99.1%, and 100% of target for Lot #PD-16-013, #PD-16-078, and #PD-16-130, respectively

The following table summarizes noteworthy observations made in the 9-month study in male beagle dogs.

Dose, mg/kg/day **Observations**	**0** 8♂	**15** 8♂	**30** 8♂	**60** 8♂
Hematology, Day 274	n=7	n=7	n=7	n=7
Reticulocytes, 10^9/µL, absolute	35.8	**52.5**	**52.4**	**63.4**
%	0.49	**0.73**	**0.73**	**0.93**
Clinical chemistry, Week 39				
Cholesterol, mg/dL	173	**126***	**107***	**107***
Creatinine, mg/dL	0.69	**0.81**	**0.83**	**0.87***
Organ weights[a], absolute, g, Days 275/276 (Day 332)	n=6(2)	n=6(2)	n=6(2)	n=6(2)
Adrenal	1.50	**1.13***	**0.96***	**0.87***
Kidney	59.7	**65.8**	**64.6**	**74.5***
Testis	14.3(14.1)	**3.2*(8.4*)**	**3.8*(6.5*)**	**3.8*(8.3*)**
Prostate	9.33	**9.81**	**16.86***	**39.08***
Gross pathology[a], Days 275/276 (Day 332)	n=6(2)	n=6(2)	n=6(2)	n=6(2)
Adrenals, small, bilateral				1
Testes, small, bilateral		6	6(1)	6
Prostate, enlarged		1	4	6
Histopathology[a,b], Days 275/276 (Day 332)	n=6(2)	n=6 (2)	n=6 (2)	n=6(2)
Adrenal cortex, vacuolation				1^3
Epididymides, infiltrate, mononuclear cells				1^2
hypospermia		$6^5(2^{4/5})$	$6^5(2^5)$	$6^5(2^5)$
Kidneys, mineralization, papillary	2			5^1
Testes, atrophy/degeneration		$6^5(2^{2/5})$	$6^5(2^{2/5})$	$6^5(1^4)$

Toxicokinetics, 8/timepoint					
TU					
$AUC_{0\text{-}8hr}$, ng·hr/mL,	Day 1	0	445[c]	4500	4670
	Day 135	0	1310	4640	3370
	Day 270	0	1290	3210	4040
C_{max}, ng/mL,	Day 1	0	332	2990	2690
	Day 135	0	654	3080	1860
	Day 270	0	692	1500	2130
T_{max}, hr,	Day 1	0	1.5	1.4	1.7
	Day 135	0	2.0	1.3	1.6
	Day 270	0	1.4	1.8	1.5
$T_{1/2}$, hr,	Day 1	0	-	0.5	1.9
	Day 135	0	2.6	0.6	1.3
	Day 270	0	1.0	1.8	0.9
DHTU[d]					
$AUC_{0\text{-}8hr}$, ng·hr/mL,	Day 1	0	24	181	128
	Day 135	0	110	281	120
	Day 270	0	146	255	142
C_{max}, ng/mL,	Day 1	0	14.8	88.6	70.5
	Day 135	0	36.5	114	53.5
	Day 270	0	34.4	89.8	68.7
T_{max}, hr,	Day 1	0	2.0	1.9	2.8
	Day 135	0	3.0	2.0	2.3
	Day 270	0	2.6	2.3	2.0
$T_{1/2}$, hr,	Day 1	0	-	2.8	-
	Day 135	0	-	1.0	-
	Day 270	0	6.1	5.0	-
T					
$AUC_{0\text{-}8hr}$, ng·hr/mL,	Day 1	14.1	39.0	85.9	163.9
	Day 135	17.7	39.2	80.3	166.9
	Day 270	14.4	42.5	70.2	190.4
C_{max}, ng/mL,	Day 1	3.1	15.3	37.5	73.9
	Day 135	4.2	14.2	34.9	80.4
	Day 270	4.2	17.5	30.0	90.3
T_{max}, hr,	Day 1	4.6	1.6	1.9	2.3
	Day 135	3.6	2.4	1.6	1.9
	Day 270	5.8	1.8	1.9	2.0
$T_{1/2}$, hr,	Day 1	-	4.2	2.5	1.3
	Day 135	19.3[c]	1.2	1.1	1.2
	Day 270	-	1.2	1.9	1.2
DHT					
$AUC_{0\text{-}8hr}$, ng·hr/mL,	Day 1	1.5	4.5	8.6	19.8
	Day 135	2.1	5.8	10.1	17.5
	Day 270	1.5	6.9	10.9	22.1
C_{max}, ng/mL,	Day 1	0.4	2.0	3.5	7.2
	Day 135	0.5	1.9	3.1	6.6
	Day 270	0.5	2.5	3.4	7.8
T_{max}, hr,	Day 1	4.1	2.0	2.0	2.3
	Day 135	4.6	3.4	2.0	2.3
	Day 270	2.2	1.9	2.0	2.0
$T_{1/2}$, hr,	Day 1	1.3	2.5	3.3	1.6
	Day 135	42.2	2.1	2.4	1.5
	Day 270	21.0	3.1	2.7	1.5

[a]Values in parentheses represent recovery animals.
[b]Upper case numbers represent severity grade: 1-minimal; 2-mild; 3-moderate; 4-marked; 5-severe
[b]One of eight animals in the control group (Animal #6) had a Day 1 pre-study plasma TU concentration of 2.02 ng/mL
[c]Two of eight animals from 60 mg/kg/day group (Animals #31 and #32) also had detectable levels of TU (3.14 and 1380 ng/mL, respectively) in the pre-study plasma samples collected on Day 1
*Statistically significant from controls at p=0.05
LLOQ=2 ng/mL for TU, T, and DHT; LLOQ=5 ng/mL for DHTU; ULOQ=2000 ng/dL (20 ng/mL) for T
-: not available

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Assay

Study no.:	AE50JJ.502ICH.BTL
Study report location:	Module 4.2.3.3.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 29, 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TU, L06837, 100.1%

Key Study Findings

- No increase in the number of revertant colonies of the test strains either in the presence or absence of S9 mix under the condition of the study (adequate tester strains, dose selection, background mutants/plate, and cell numbers)

Methods

Strains:	TA98, TA100, TA1535, TA97, TA1537, WP2 *uvr*A
Concentrations in definitive study:	50.0, 150, 500, 1500 and 5000 µg per plate
Basis of concentration selection:	Solubility (precipitate at ≥667 µg per plate based on a preliminary test)
Negative control:	Ethanol
Positive control:	-S9: sodium azide for TA100 and TA1535; 9-aminoacridine for TA1537; 2-nitrofluorene for TA98; methyl methanesulfonate for WP2 *uvr*A +S9; 2-aminoanthracene for TA98, TA100, TA1535, TA1537, and WP2 uvrA
Formulation/Vehicle:	Solution/Ethanol
Incubation & sampling time:	Tester strain and test article or vehicle with or without S9 (triplicate) were added to molten top agar at 45±2°C and vortexed (plate incorporation method). The mixture was overlaid onto the surface of minimal bottom agar. After the overlay had solidified, the plates were inverted and incubated for 48 to 72 hours at 37±2°C. Revertant colonies were counted by automated colony counter or by hand.

Study Validity: Valid

- All *Salmonella* tester strain cultures must demonstrate the presence of the deep rough mutation(*rfa*) and the deletion in the *uvr*B gene. Cultures of tester strains TA98 and TA100 must demonstrate the presence of the pKM101 plasmid R-factor. All WP2 *uvr*A cultures must demonstrate the deletion in the *uvr*A gene.
- All cultures must demonstrate the characteristic mean number of spontaneous revertants in the vehicle controls as follows (inclusive): TA98, 10-50; TA100, 80-240; TA1535, 5-45; TA1537, 3-21; WP2 *uvr*A, 10-60.
- Tester strain culture titers must be greater than or equal to $0.3x10^9$ cells/mL.
- The mean of each positive control must exhibit at least a 3-fold increase in the number of revertants over the mean value of the respective vehicle control.
- A minimum of 3 non-toxic dose levels is required to evaluate assay data. A dose level is considered toxic if one or both of the following criteria are met: (1) A >50% reduction in the mean number of revertants per plate as compared to the mean vehicle control value. This reduction must be accompanied by an abrupt dose-dependent drop in the revertant count. (2) At least a moderate reduction in the background lawn (background code 3, 4 or 5).
- Criteria for positive response: Dose-related increase in mean revertants per plate of any tester strains over a minimum of 2 increasing concentrations with ≥2-fold (TA98, TA100 and WP2 *uvr*A) or ≥3-fold (TA1535 and TA1537) increase in the mean revertants at the peak of the dose response

Results: Negative

Preliminary assay:

- No significant toxicity in all strains with and without S9
- Precipitate at ≥667 µg/plate

Mutagenicity assay:

- No increase in revertants with any of the tester strains in either presence or absence of S9
- No significant toxicity in all strains with and without S9
- Precipitate at ≥1500 µg/plate

7.2 *In Vitro* Assays in Mammalian Cells

Study title: In Vitro Mammalian Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) Cells

Study no.:	AE50JJ.331ICH.BTL
Study report location:	Module 4.2.3.3.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 28, 2016

GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TU, L06837, 100.1%

Key Study Findings

- No induction of structural and numerical chromosome aberrations in the presence and absence of S9 in CHO cells under the condition of the study

Methods

Cell line:	CHO-K1 cells
Concentrations in definitive study:	-S9: 2.5, 5, 10, 20, 40, 60, 80, 100, 125, and 150 µg/mL for 4 or 20 hours +S9: 2.5, 5, 10, 20, 30, 35, 40, 45, 50, 60, and 70 µg/mL for 4 hours
Basis of concentration selection:	Solubility, pH, osmolality, stability, and reduction in cell growth index relative to the vehicle control based on a preliminary test
Negative control:	Ethanol
Positive control:	Mitomycin C for -S9; Cyclophosphamide for +S9
Formulation/Vehicle:	Solution/Ethanol
Incubation & sampling time:	Cells were exposed to the test substance or controls for 4 or 20 hours with or without S9, were washed, and cultured for a further 20 hours for 4-hour group or 18 hours for 20-hour group. Colcemid solution was added to the culture, and cells were treated for 2 hours toward the end of incubation. The cells were collected by centrifugation, treated with 0.075M KCl, washed with fixative (methanol: glacial acetic acid, 3:1 v/v), capped and stored overnight or longer at 2 to 8°C. Glass microscope slides were prepared to stain with Giemsa and were permanently mounted for scoring. The mitotic index was recorded as the percentage of cells in mitosis per 500 cells counted. A minimum of 300 metaphase spreads containing 20±2 centromeres from each dose (150 per duplicate treatment) were examined and scored for chromatid-type and chromosome-type aberrations. The percentage of cells with numerical aberrations (polyploid and endoreduplicated cells) was evaluated for 150 cells per culture (a total of 300 per dose level). Cell growth was determined by Relative Increase in Cell Counts (RICC) as a measure of cytotoxicity.

Study Validity: Valid

- The frequency of cells with structural chromosomal aberrations must be significantly greater than the concurrent vehicle control (p≤0.05). In addition, the cytotoxicity response must not exceed the upper limit for the assay (55%).
- At least 300 metaphases must be analyzed from at least three appropriate test article concentrations. The number of metaphases scored may be reduced when high numbers of cells with chromosomal aberrations (≥10% metaphases) are observed as with a positive test article or the positive control article.
- The test article was considered to have induced a positive response if 1) at least one of the test concentrations exhibits a statistically significant increase when compared with the concurrent negative control (p≤0.05), 2) the increase is concentration-related (p≤0.05), and 3) results are outside the 95% control limit of the historical negative control data.

Results: Negative

Preliminary assay:

- Cytotoxicity (≥45% reduction in cell growth index relative to the vehicle control) at ≥137.1 µg/mL in the non-activated 4-hour exposure group; at 457 µg/mL in the S9-activated 4-hour exposure group; and at ≥45.7 µg/mL in the non-activated 20-hour exposure group
- Visible precipitate at ≥137.1 µg/mL in all three exposure groups at the conclusion of the treatment period

Initial assay:

- No significant or dose-dependent increases in structural or numerical (polyploid or endoreduplicated cells) aberrations in the 20-hour treatment group without S9 at 2.5 to 150 µg/mL
- Cytotoxicity (50 ± 5% reduction in cell growth index relative to the vehicle control) at ≥40 µg/mL in the non-activated 20-hour exposure group; 36% at 60 µg/mL in the non-activated 4-hour exposure group; 22% at 70 µg/mL in the S9-activated 4-hour exposure group
- Visible precipitate at ≥80 µg/mL in the non-activated 4 and 20-hour exposure groups at the conclusion of the treatment period; no precipitate in the S9-activated 4-hour exposure group

Repeat assay:

- No significant or dose-dependent increases in structural or numerical (polyploid or endoreduplicated cells) aberrations in the 4-hour treatment groups with or without S9 at 2.5 to 150 µg/mL
- Cytotoxicity (50 ± 5% reduction in cell growth index relative to the vehicle control) at ≥80 µg/mL in the non-activated 4-hour exposure group

- No significant cytotoxicity at any dose in the S9-activated 4-hour exposure group (up to 33%)
- Visible precipitate at ≥80 µg/mL in the non-activated and S9-activated 4-hour exposure groups at the conclusion of the treatment period

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Bone Marrow Micronucleus Evaluation

Study no:	AE50JJ.129GLP.BTL
Study report location:	Module 4.2.3.3.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 16, 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TU, L06837, purity not provided

Key Study Findings

- Negative in the rat micronucleus assay incorporated into a male fertility study at doses up to 80 mg/kg/day for 42 days (i.e., 4 weeks prior to mating and 2 weeks during the mating period) under the conditions of this study
- No criteria provided to determine the appropriateness of the top dose selected

Methods

Doses in definitive study:	0, 20, 40, 80 mg/kg/day
Frequency of dosing:	Test article, vehicle or positive control was administered for 42 days (4 weeks prior to mating and 2 weeks during the mating period). At least 4000 PCEs/animal were scored for the presence of micronuclei (MnPCEs) whenever possible (except for one LD animal with 1978 PCEs). In addition, at least 500 total erythrocytes (PCEs + NCEs) were scored per animal to determine the proportion of PCEs as an index of bone marrow cytotoxicity.
Route of administration:	Oral gavage
Dose volume:	3 mL/kg/day
Formulation/Vehicle:	Solution/Corn oil
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	5 males/group
Satellite groups:	None
Basis of dose selection:	Not provided
Negative control:	Corn oil
Positive control:	Cyclophosphamide (40 mg/kg)

Study Validity: Equivocal

- The vehicle control group should be consistent with the historical vehicle control range, and must be ≤0.4% MnPCEs.
- The positive control must induce a significant increase in MnPCE frequency ($p \leq 0.05$) as compared to the concurrent vehicle control.
- The test article was considered to be positive if it induced a significant increase in MnPCE frequency ($p \leq 0.05$) at any dose level or sampling time compared to the concurrent vehicle control.
- The test article was considered to be negative if no significant increase in MnPCE frequency was observed ($p > 0.05$) compared to the concurrent vehicle control.

Results

- No frank toxicity or cytotoxicity observed up to the HD tested
- No statistically significant increases in the incidence of MnPCEs in the low, mid and high dose test article treated groups relative to the vehicle control group

7.4 Other Genetic Toxicity Studies

None

8 Carcinogenicity

Study title: 26-Week Oral Carcinogenicity Study of Testosterone Undecanoate in Male CByB6F1-Tg(HRAS)2Jic (tg/wt) Mice

Study no.:	16-877
Study report location:	Module 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/20/2016 (1st dosing)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TU, # PD-16-013, PD16-078 and PD-16-130, purity not provided
CAC concurrence:	No

Key Study Findings

- Negative up to 80 mg/kg/day

Adequacy of Carcinogenicity Study: Inadequate

Dose selection and study protocol: not reviewed by the Exec CAC

- Inadequate to assess the risk of carcinogenicity, given that the study did not reach an MTD; no basis of dose selection was provided; and was insufficiently powered for one sex
- Doses selected based on a 28-day dose range-finding study in male CByB6F1 mice: no significant effects on clinical signs, body weights, food consumption, hematology, clinical chemistry, or organ weights except the histopathological finding of minimal multifocal atrophy/degeneration in the testes in 9 out of 10 mice at HD compared to 1 out of 10 in vehicle-treated mice administered 0, 20, 40, and 80 mg/kg/day using corn oil as a vehicle in lieu of peppermint oil
- Corn oil is not a recommended vehicle in carcinogenicity studies

Appropriateness of Test Models: See above

Evaluation of Tumor Findings: See above

Methods

Doses:	0, 20, 40, 80 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	10 mL/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	Solution/Corn oil
Basis of dose selection:	Not provided
Species/Strain:	Mouse/Tg·rasH2 [CByB6F1-Tg(HRAS)2Jic]
Number/Sex/Group:	25 males/group for TU, 15 males for positive control (75 mg/kg intraperitoneal, methylnitrosourea)
Age:	18-25 g (upon receipt)
Animal housing:	Individually
Paradigm for dietary restriction:	*Ad libitum*
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	No
Deviation from study protocol:	Dose formulations for the placebo or test material contained corn oil (Croda Super Refined) instead of peppermint oil used in the clinical formulation, due to deaths in male CByB6F1-Tg (HRAS)2Jic (Wild Type) mice (2 vehicle control and 1 LD TK animals) shortly after treatment initiation (Days 2 and 7) in a 28-day dose range-finding study. As the deaths occurred early during treatment, the sponsor elected to use replacement animals in this study.

Observations and Results

Mortality: once daily

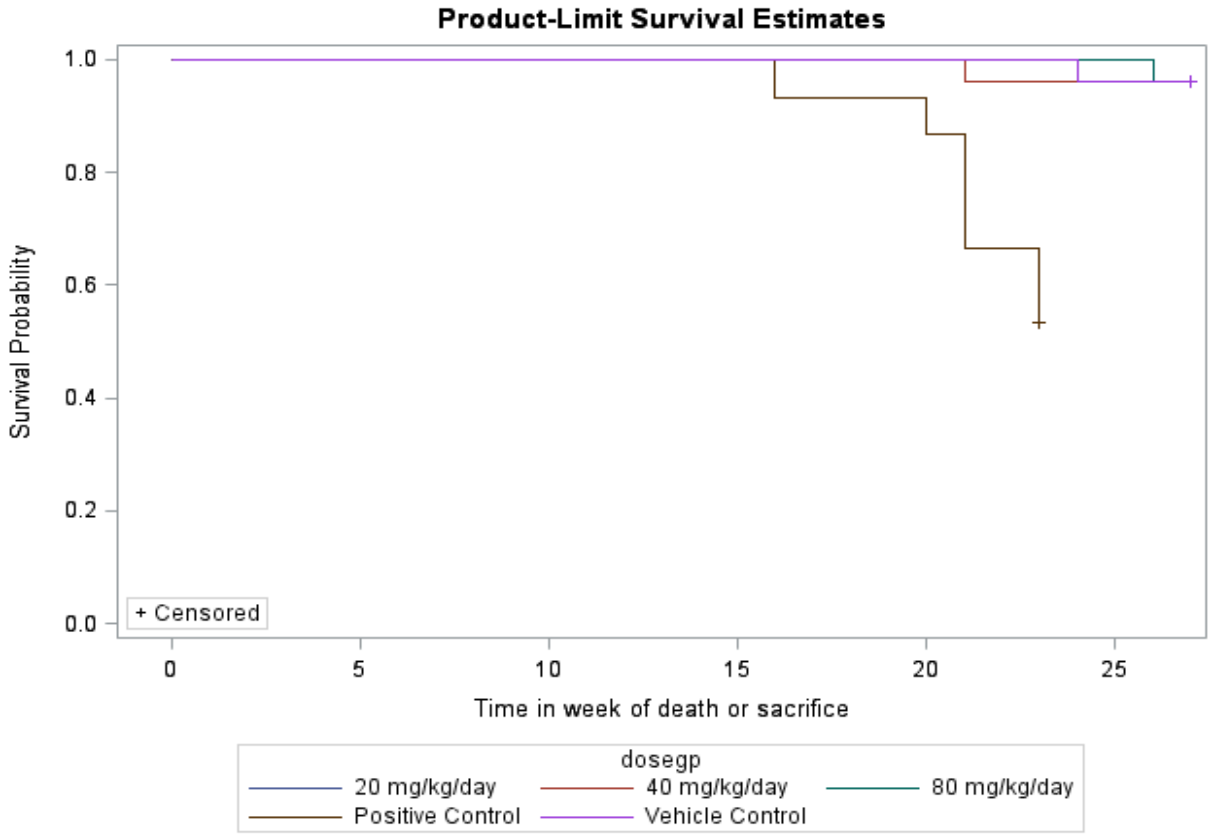
- TU: no statistically significant increase or decrease in mortality between the TU-treated groups and the vehicle control group: deaths in 1 vehicle-treated animal

Reference ID: 4227239

on Day 165 and in 1 MD animal on Day 144; sacrificed in a moribund condition in 1 animal each at LD and high dose (HD) on Days 166 and 180, respectively

- Positive control: spontaneous deaths on Days 106-158 in 7 mice resulting in early termination of this group on Day 159 (see Figure below)

Figure 1. Survival Curves for Male Tg·rasH2 Mice by Kaplan-Meier Plots



Clinical Signs: pre-study, Days 1, 4, and weekly thereafter for detailed observations, 1-2-hour post-dose during the 1st week for cage-side observations

- Unremarkable

Body Weights: pre-study, Days 1, 4, and weekly thereafter

- Unremarkable

Feed Consumption: pre-study, Days 1, 4, and weekly thereafter

- Unremarkable

Gross Pathology: Day 183

- Unremarkable

Histopathology: Day 183

- Unremarkable

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Peer Review

- No

Neoplastic Findings:

TU:

- No statistically significant tumor incidences in TU-treated groups at up to 80 mg/kg/day
- Numerical increase in incidence of tumor findings in TU-treated animals including lymphoma in the spleen in 1 MD animal, lung adenoma in 1 HD mouse, and carcinoma in the stomach in 1 HD animal, which were the type of neoplasms commonly found in mice of this strain and age

Methylnitrosourea:

- Expected range of changes consisting of papilloma/carcinoma of the stomach/intestines, and lymphoma of the spleen and in the other organs (adrenal cortex, heart, salivary gland, liver, mesenteric/mandibular lymph nodes, kidney, lungs, thymus, and thyroid gland), resulting in a total of 12 positive control mice with tumor incidence

Non Neoplastic Findings

- Unremarkable

Toxicokinetics: 2 hours post-dosing in Week 26

- T: less than dose-proportional increase in AUC and C_{max} values with increasing TU doses
- DHT: greater than dose-proportional increase in AUC and C_{max} values at 80 mg/kg/day
- DHT/T ratios: decrease from pre-dose values for all treated groups at 2-4 hour post-dose, followed by a steady increase through the 6 hour time-point on Day 27, with an increase in DHT/T ratio, suggesting a rapid rise in plasma T occurring shortly after TU administration, which was then followed by the metabolism of a portion of T to form DHT
- AUC ratios for T:
    - Day 1: 56, 94, and 137-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls
    - Day 27: 22, 34, and 42-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls
- AUC ratios for DHT:
    - Day 1: ~11, ~15, and ~59-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls

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- Day 27: ~43, ~72, and ~225-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls

- C_{max} ratios for T:
  - Day 1: ~26, ~29, and >40-fold (>upper limit of quantitation for this assay) over 20, 40, and 80 mg/kg/day, respectively, on Day 1 compared to controls
  - Day 27: ~8, >11 (>upper limit of quantitation for this assay), and >11-fold (>upper limit of quantitation for this assay) over 20, 40, and 80 mg/kg/day, respectively, compared to controls
- C_{max} ratios for DHT:
  - Day 1: ~4, ~6, and ~27-fold over 20, 40, and 80 mg/kg/day, respectively, on Day 1 compared to controls
  - Day 27: ~22, ~27, and ~115-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls

Table 1. Summary of TK Parameters for Male CByB6F1 Mice in 28-Day Dose Range-Finding Study

Dose, mg/kg / **TK Parameters**[a]		**0** 6♂	**20** 12♂	**40** 12♂	**80** 12♂
T					
$AUC_{0\text{-}6hr}$, ng·hr/dL,	Day 1	527	29492	49370	72269
	Day 27	1924	42039	65188	81276
C_{max}, ng/dL,	Day 1	504	13210	14680	>20000
	Day 27	1891	16050	>20000	>20000
T_{max}, hr,	Day 1	0	2	2	2
	Day 27	2	2	2	2
$T_{1/2}$, hr	Day 1	nc	nc	nc	nc
	Day 27	nc	nc	nc	nc
DHT					
$AUC_{0\text{-}6hr}$, ng·hr/dL,	Day 1	54	610	827	3194
	Day 27	26	1106	1874	5856
C_{max}, ng/dL,	Day 1	50	221	304	1351
	Day 27	18	402	487	2071
T_{max}, hr,	Day 1	0	2	2	2
	Day 27	2	2	2	2
$T_{1/2}$, hr	Day 1	nc	nc	nc	nc
	Day 27	nc	nc	nc	nc

[a]Samples were collected using EDTA-NaF tubes to prevent conversion of TU to T.
3/group/timepoint
nc: not calculated due to insufficient data in the terminal elimination phase
LLOQ=2 ng/dL, ULOQ=20000 ng/dL (200 ng/mL)
-: not available

Dosing Solution Analysis: 2 sets of duplicate samples (1 mL each) from the 1st and last study preparations on May and October 2016 for concentration, homogeneity, and stability analyses

- Within the target range (±15%) for prepared formulations

The following table summarizes the non-neoplastic findings observed in the 6-month male Tg·rasH2 mouse study.

Dose, mg/kg **Observations**	**0** 25♂	**MNU** 25♂	**20** 25♂	**40** 25♂	**80** 25♂
Mortality rate, %					
Agency analysis, Weeks 0-26	4	53.3[a]	4	4	4
Sponsor analysis, weeks 0-26	4	68	4	4	4
Body weight, g, Day 183	27.4	-	27.8	28.2	28.2
Body weight gain, g, Days 1-183	0.3	-	0.7	0.9	0.7
Food intake, g, Days 183	21.7	-	21.8	22.5	23.2*
Toxicokinetics, Week 26, 3/group					
T, C_{2hr}, ng/dL	13.13	-	12837	19400	>20000
DHT, C_{2hr}, ng/dL	10.11	-	308	1086	2140

MNU: methylnitrosourea
[a]Statistically significant from controls at p=0.001 using the Likelihood Ratio test for dose-response and the Log-Rank test for homogeneity
LLOQ and ULOQ not provided
Statistically significant from controls at p=0.05*
-: Not available

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Oral Reproductive Toxicity Study (Segment I) of Testosterone Undecanoate in Rats

Study no.:	16-881
Study report location:	Module 4.2.3.5.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 10, 2016 (protocol review)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TU, L06837, purity not provided

Key Study Findings

- Dose-related reduced (up to 28%) testis weights at ≥20 mg/kg/day associated with small testes and epididymides at ≥40 mg/kg/day
- NOAEL=80 mg/kg/day for reproductive performance

Methods

Doses:	0, 20, 40, 80 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	3 mL/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	Solution/Corn oil
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	23/sex/group
Satellite groups:	None

Study design:	Males were dosed for 4 weeks prior to and during a 2-week mating period and were mated with naive females. Dams scheduled for necropsy underwent a cesarean section on gestation day (GD) 13. Endpoints evaluated included unscheduled deaths, clinical signs, body weights, food consumption, vaginal smears, mating performance, male reproductive function (sperm count, morphology, motility), reproductive organ weights (epididymides, testes, ovaries/oviducts, uterus), micronucleus, fertility, embryonic/fetal survival, and gross examinations.
Deviation from study protocol:	Not significant

Observations and Results

Mortality: Twice daily

- None

Clinical Signs: Pre-study &weekly thereafter for males; GDs 0, 3, 6, 9, &12 for females

- Unremarkable

Body Weight: Pre-study & weekly thereafter for males; GDs 0, 3, 6, 9, &12 for females

- Reduced (~22%) body weight gains in males on Day 35 at 80 mg/kg compared to controls

Feed Consumption: Pre-study &weekly thereafter for males; GDs 0, 3, 6, 9, &12 for females

- Unremarkable

Toxicokinetics

- Not performed

Dosing Solution Analysis: Two sets of duplicate samples (2 mL each) from the middle of the dose formulation preparation vessel (including vehicle control)

- Homogeneous and stable and concentrations within the target range (±10%)

Necropsy: GD 13 for females and end of the mating period for males for epididymis, testis, ovary/oviduct, & uterus weights

- Dose-related reduced (up to 28%) testis weights at ≥20 mg/kg/day compared to controls
- Small testes and epididymides at ≥40 mg/kg/day

<u>Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)</u>

- Unremarkable

The following table summarizes the noteworthy observations made in the fertility and early embryonic development study in rats.

Dose, mg/kg / **Observations**	**0**		**20**		**40**		**80**	
	23♂	23♀	23♂	23♀	23♂	23♀	23♂	23♀
Body weight gain, Day 35, g	23	-	20	-	22	-	**18***	-
Organ weight, absolute, g								
Testis	3.52	-	**3.44**	-	**3.25***	-	**2.51***	-
Gross necropsy,								
Testes, small	-	-	-	-	1	-	10	-
Epididymis, small		-		-	1	-	2	-
Reproductive parameters,								
Pregnant	-	22	-	21	-	23	-	22
Resorptions	-	0.55	-	1.33	-	0.78	-	1.14
Sperm analysis,	n=11		n=11		n=11		n=11	
Detached head, %	9	-	-	-	9	-	14	-

-: not available
*Significantly different from controls at p=0.05

9.2 Embryonic Fetal Development

Not provided

9.3 Prenatal and Postnatal Development

Not provided

10 Special Toxicology Studies

Not provided

11 Integrated Summary and Safety Evaluation

Clarus Therapeutics has conducted pivotal nonclinical studies with oral TU to re-classify their NDA from a 505(b)(2) to a 505(b)(1) application. These included a 9-month oral toxicology study in male dogs, a battery of genotoxicity tests, a 6-month carcinogenicity study in Tg·rasH2 male mice (with a 28-day dose range finding study in male CByB6F1-Tg (HRAS) 2Jic mice), and a male-only treated fertility study in rats. The in vivo micronucleus test was integrated into the fertility study.

The pharmacology, pharmacokinetics, and toxicology profiles of endogenous and therapeutically administered T are well established in animals and humans. The sponsor's proposal to conduct a chronic toxicology study in dogs with TU was agreed by the Division, considering that orally administered TU is absorbed via the intestinal system and metabolized in dogs in a manner similar to humans. The sponsor's proposal to perform only one 6-month Tg·rasH2 male mice study was accepted by the Exec CAC based on the known clinical risks in men using T hormone therapies. However, the carcinogenicity study protocol and dose selection was not reviewed by the Exec CAC.

The following summary is based on the previous NDA review by Dr. Eric Andreasen, literature references, and results from the submitted studies.

Pharmacology:
TU acts as a pro-drug which is hydrolyzed by esterases in vivo to yield T and undecanoic acid. Based on its relative binding affinity for the androgen receptor displaying ~1000 times less binding affinity for TU (Ki=1.20 μM, IC_{50}=2.04 μM) compared to T (Ki= 1.12 nM, IC_{50}=1.91 nM) in human LNCaP clone FGC cells, it appears that TU itself has little potential for pharmacological activity. At 10 μM TU and DHTU inhibited by ~76% and 29%, respectively, androgen (testosterone) binding to the androgen receptor, in human LNCaP clone FGC cells.

T is a biologically active androgen in humans that acts through the androgen receptor. Androgens (e.g., T, DHT, androstanediol, androstenedione, dehydroepiandrosterone, androsterone) are essential for the biosynthesis of estrogens via aromatase (CYP19A1). T undergoes extensive phase I metabolism through two different pathways. T is converted to 17-β estradiol via aromatase, which has its highest activity in adipose tissue (particularly visceral fat) and, to a lesser extent, in the testis, prostate, and bone. T is also converted to DHT by 5α-reductase in target tissues including the prostate gland, seminal vesicles, epididymides, skin, hair follicles, liver and brain. In humans, type I 5α-reductase, present in sebaceous glands of skin, in liver, muscles, brain, and prostate, is responsible for approximately ⅓ of circulating DHT. Type II 5α-reductase is found in prostate, seminal vesicles, epididymis, hair follicles, and liver. Type III isoform was recently found in hormone-refractory prostate cancer cells. T is bound to sex hormone-binding globulin (SHBG) and albumin and only 1-2% of T is free in the circulation.

T and DHT are the major androgens responsible for the growth and development of the male sex organs as well as for the development and maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution.

Absorption, Distribution, Metabolism, and Elimination:
The sponsor previously submitted a review of some literature describing the ADME of TU and its metabolites in lieu of conducting ADME studies for their TU product. Published studies suggest that lymphatic absorption is promoted when T is esterified at the C17β-hydroxyl group with long chain fatty acids. TU is highly lipophilic compared to T. Lipophilic vehicles aid intestinal lymphatic absorption of TU into the intestinal lymphatics. However, both T and TU are still poorly absorbed orally with bioavailability being well below 10% in rats, dogs, and humans. In women after a single oral administration of TU or T delivered in miglyol 810, absolute bioavailability for TU (~7%) is approximately 2-fold higher than that for free T (~4%) (Eur J Drug Metab Pharmacokinet 11:145, 1986). After absorption, TU is metabolized in the intestinal wall to DHTU. TU and DHTU are distributed systemically where they are further metabolized to undecanoic acid, T, DHT, estradiol, numerous steroid metabolites, and glucuronide and sulfate conjugates. T is metabolized extensively by the liver via reduction and oxidation reactions, followed by glucuronidation. The half-lives of T and TU are roughly

10 to 100 minutes after they are in the systemic circulation. In humans, TU and T are eliminated primarily as androgen glucuronide conjugates in the urine within several hours of dosing. The primary route of elimination is the urine: a small amount (~6%) is excreted in the feces. T is a substrate and inducer of CYP3A4 (see original NDA review by Dr. Eric Andreasen for details).

Undecanoic acid (1-decanecarboxylic acid, hendecanoic acid, undecylic acid; N-undecanoic acid; N-undecoic acid) is an 11-carbon saturated fatty acid that is incorporated into glycerides and phospholipids, and metabolized by β-oxidation and the tricarboxylic acid pathways. Undecanoic acid is a medium chain length monocarboxylic acid that appears to be involved in the control of triacylglycerol synthesis in normal and cancer cells in humans in vitro (Biochem Pharmacol 43:175, 1992). It is found in breast milk produced by women in the United States, in infant formulas, in seminal plasma, and other fluids. It is an approved food additive in the Everything Added to Food in the United States (EAFUS) database. Based on the Joint FAO/WHO Expert Committee on Food Additives (JECFA), no safety concern was indicated at the average daily level of intake of 8.7 µg used as a flavoring agent. However, the extent of exposure to undecanoic acid following administration of TU in men is unknown.

General Toxicology:
Neither new nor significant findings have been identified in the completed nonclinical studies that were not previously observed with T. The major findings in the 13-week study in male dogs at 38 mg/kg BID (76 mg/day) and 126 mg/kg BID (252 mg/day) were moderate to marked adrenal cortex atrophy, minimal to marked atrophy of the testes, moderate to severely reduced sperm production in the epididymides, and marked hypertrophy of the prostate correlated with altered organ weights in all treated groups. Serum cholesterol was suppressed in all treated groups (up to ~48%) compared to controls, but resolved after drug withdrawal. A two-fold increase (~93%) in ALT (not statistically significant) without a histopathology correlate was noted at 126 mg/kg BID, which resolved after drug withdrawal. The histopathological findings in the adrenal cortex, epididymides, and testes were not completely reversed at the end of the 4-week recovery period. The severity was reduced (adrenal), remained (epididymides), or increased (testes) after the 4-week recovery period (see original NDA review by Dr. Eric Andreasen).

In the 9-month study in dogs dosed at 0, 7.5, 15, and 30 mg/kg BID, the expected findings related to androgenic effects were seen in the prostate and testis/epididymis. Dose-related increased (up to ~77%) reticulocytes and decreased (up to ~38%) cholesterol were observed in all treated groups compared to controls. There were no effects on cortisol levels. No atrophy was seen in adrenal cortex, but moderate vacuolation was noted in one dog at 60 mg/kg/day associated with small adrenals (bilateral) and dose-related decreased (up to ~42%) absolute adrenal weights at ≥7.5 mg/kg BID. There was increased incidence of minimal renal papillary mineralization associated with increased creatinine (~26%) and increased (~25%) kidney weights at high dose. In the prostate, dose-related increased absolute prostate weights were associated with enlarged prostate in all treated groups. Severe diffuse testicular

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atrophy/degeneration and correlative changes of severe hypospermia in the epididymis were associated with small testes (bilateral) and decreased (up to ~78%) absolute testis weights in all treated animals which persisted after an 8-week treatment-free period, possibly due to the negative feedback between circulating T and pituitary release of luteinizing hormone (LH).

The sponsor attributed the adrenal findings to the anticipated pharmacological effect of supraphysiological levels of T on the adrenal gland. However, in the absence of additional information, it would be difficult to determine whether the adrenal findings are caused by a direct effect or by other factors. The reduced cortisol level associated with increased CRH-stimulated ACTH in leuprolide-induced hypogonadal men administered T enanthate suggests that TU and/or its metabolite(s) may suppress cortisol secretion through CRH-stimulated hypothalamic-pituitary-adrenal (HPA) axis activity (Neuropsychopharmacology 30:1906, 2005). Measurement of other hormones and proteins such as cortisol, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone (DHEA), aldosterone, sex hormone binding globulin (SHBG), and corticosteroid binding globulin (CBG) may help interpret the data and determine the clinical relevance. Decrease in plasma levels of SHBG, GBG, and thyroxine binding globulin (TBG) were observed in hypogonadal men after T enanthate for 3-4 weeks, suggesting that plasma hormone concentration of the T ester may not reflect clinical interpretation of the hormone therapy (Horm Metab Res 5:271, 1973). In addition, many compounds that are toxic for adrenal cortex are lipophilic and one cannot exclude the possibility that the highly lipophilic TU would result in accumulation or retention in lipid-rich and/or well-perfused tissues and organs following chronic treatment. In order to evaluate the potential for TU and/or T to cause adrenal insufficiency in humans, a cosyntropin test was conducted. The result from the test in humans is considered incomplete and an additional clinical study is being requested (see Clinical review for details).

Oral TU administration resulted in increased plasma concentrations of both TU and T at all dose levels as early as 30 minutes post-dose, with maximum concentrations occurring typically 1-2 hours post-dose, and returning to pre-dose levels in most cases by 8 hours, prior to the second daily dose. Circulating levels of TU increased in a greater than dose-proportional manner between the low dose and mid dose, and was generally comparable between the mid dose and high dose, suggesting that saturation of absorption or de-esterification occurred at mid dose. The decrease followed by an increase in DHT/T ratios indicates a rapid rise in plasma T occurring shortly after administration, which was then followed by the metabolism of T to form DHT. In addition, plasma T generally increased in a dose-proportional manner after each daily dose over the duration of the study. Thus, it is unlikely that saturation of TU absorption limited systemic exposure to T and DHT at mid dose and high dose in male dogs.

The AUC exposure to TU ($AUC_{0\text{-}8h}$~4000 ng·hr/mL), DHTU ($AUC_{0\text{-}8h}$~130 ng·hr/mL), T ($AUC_{0\text{-}8h}$~170 ng·hr/mL), or DHT ($AUC_{0\text{-}8h}$~20 ng·hr/mL) at the high-dose (30 mg/kg BID) corresponded to approximately 2-, <1-, 1-, and 1-fold, respectively, the anticipated maximum human exposure at the MRHD of 396 mg BID ($AUC_{0\text{-}24h}$~1900 ng·hr/mL for

TU, $AUC_{0\text{-}24h}$~600 ng·hr/mL for DHTU, $AUC_{0\text{-}24h}$~150 ng·hr/mL for T, $AUC_{0\text{-}24h}$~20 ng·hr/mL for DHT). The C_{max} exposure to TU (C_{max}~2000 ng/mL), DHTU (C_{max}~60 ng/mL), T (C_{max}~80 ng/mL), and DHT (C_{max}~7 ng/mL) at the HD was roughly 4, <1, 3, and 4 times, respectively, the maximum anticipated human exposure (C_{max}~500 ng/mL for TU, C_{max}~110 ng/mL for DHTU, C_{max}~25 ng/mL for T, and C_{max}~2 ng/mL for DHT) at the maximum anticipated human exposure (see Table below). The doses of 15, 30 and 60 mg/kg/day in the dog represent multiples of roughly 0.7, 1.4, and 2.8-fold the maximum intended human dose of 792 mg/day (~11 mg/kg/day for 70 kg men), when normalized for body surface area.

Table 2: Summary of Exposure Multiples at High Dose (60 mg/kg/day) in Dogs Compared to the Maximum Anticipated Exposure in Humans

Compound	Exposure Multiple	
	$AUC_{0\text{-}t}$[a]	C_{max}
TU	~2	~4
DHTU	<1	<1
T	~1	~3
DHT	~1	~4

[a]Based on 0 to 8 hours following the 1st dose in dogs and morning or evening dose for humans

Genetic Toxicology:
TU did not induce bacterial reverse mutations and chromosomal aberrations in CHO cells. TU was negative in a bone marrow micronucleus test at doses up to 80 mg/kg/day for 42 days (i.e., 4 weeks prior to mating and 2 weeks during the mating period) integrated into the male fertility study. However, it is not clear if an adequate high dose was achieved for the in vivo test. There are no criteria provided for the selection of the top dose.

Carcinogenicity:
The dose selection for the 26-week Tg·rasH2 mouse study was based on a 1-month dose range-finding study utilizing wild type male CByB6F1 mice administered 0, 20, 40, and 80 mg/kg/day by oral gavage. The dose selection and study protocol was not reviewed by the Exec CAC prior to the conduct of the study. The dose formulation contained corn oil as vehicle in lieu of peppermint oil used in the clinical formulation, due to mortality of animals shortly after treatment initiation. Corn oil is not a recommended vehicle in carcinogenicity studies, because of its potential to confound the study. The only treatment-related finding in the 1-month study was minimal multifocal atrophy/degeneration in the testes, which is an expected pharmacodynamic response to T exposure, in 9 out of 10 mice at high dose compared to 1 out of 10 in vehicle-treated mice.

There were no statistically significant tumor incidences in TU-treated groups in Tg·rasH2 mice. The Exec CAC noted that the study was not acceptable, noting that the study did not reach an MTD; no basis of dose selection was provided; and the study was insufficiently powered for one sex.

There is a vast body of published literature suggesting the carcinogenicity potential of T products. Studies have also demonstrated that when co-administered with a carcinogen, T can promote tumor growth in various tissues (e.g., vagina, bladder, salivary gland, prostate) of rodent animal models. T has been extensively evaluated, employing various animal species and strains, as a hormonally active compound is expected to increase tumor incidence in hormone-responsive organs and tissues such as the endometrium (Acta Unio Int Contra Cancrum 18:197, 1962; Nature 192:1303, 1961), ovary (Cancer Res 48:2788, 1988; Br J Cancer 12:414, 1958), mammary gland (Carcinogenesis 20:1597, 1999), prostate (Endocrinology 155:4629, 2014; Prostate 20:339, 1992; Cancer Res 50:142, 1990; Cancer Lett 32:223, 1986; J Natl Cancer Inst 77:583, 1986; Prostate 6:389, 1985; Prostate 3:563, 1982; Cancer Res 40:3547, 1980; Oncology 34:138, 1977; Cancer Res 37:1929, 1977), and liver (Ann NY Acad Sci 1089:228, 2006 for details; Proc Natl Acad Sci 86:7505, 1989). In in vitro, T increased transformation frequency when SHE cells were incubated at 1, 5, 10, 20, and 100 µg/mL with a non-genotoxic carcinogen, TPA (Carcinogenesis 11:541, 1990). In another study, both T and T propionate caused some degree of SHE cell morphological transformation at 1, 3, 10 and 30 µg/mL (Carcinogenesis 16:1329, 1995), consistent with an epigenetic mechanism and with tumor promoting properties.

Numerous studies have also investigated the effects of perinatally or neonatally administered T on the development of tumors in adult animals (J Environ Pathol Toxicol 3:191, 1979; J Natl Cancer Inst 57:1057, 1976; J Steroid Biochem 6:673, 1975). Subcutaneous injections to neonatal mice caused increases in epidermoid carcinomas of the genital tract and mammary tumors (J Nat Cancer Inst 39:75, 1967). Administration of T to neonatal rats pre-initiated with 7,12 dimethylbenzanthracene, decreased mammary tumors (Am J Pathol 99:463, 1980; Gan 69:627, 1978), but enhanced auditory sebaceous gland tumors (Gan 68:851, 1977). 5β-Dihydrotestosterone, which is considered hormonally inactive in adults, also increased the incidence of mammary tumors in mice when given neonatally by subcutaneous injections (Cancer Res 37:4456, 1977).

A synthetic T derivative, oxymetholone (17α-methylated DHT) was tested in Tg·AC and p53 mice, and F344/N rats. Oxymetholone at 1.2, 6, or 12 mg/animal treated for 20 weeks produced dose-related increases in number of papilloma-bearing mice and number of papillomas per animal in the Tg·AC mice (Toxicol Pathol 27:507, 1999), but was negative in the p53 model administered 125, 625, and 1250 mg/kg/day for 6 months (Toxicol Pathol 27:513, 1999), suggesting that the synthetic T may be a non-genotoxic carcinogen. In the 2-year study in F344/N rats by oral gavage at 0, 3, 30, and 150 mg/kg/day in males and 0, 3, 30, and 100 mg/kg/day in females, NTP concluded that there was equivocal evidence of carcinogenic activity of oxymetholone in males based on increased incidences of subcutaneous tissue fibromas and fibromas or fibrosarcomas (combined) of the skin, variably increased incidences of benign and benign or malignant pheochromocytomas (combined) of the adrenal gland, and increased incidences of renal tubule adenomas. However, there was clear evidence of carcinogenic activity of oxymetholone in females based on increased incidences of hepatocellular neoplasms. Increased incidences of alveolar/bronchiolar neoplasms and

skin neoplasms in female rats were also related to oxymetholone administration (Natl Toxicol Program Tech Rep Ser 485:1, 1999).
International Agency for Research on Cancer (IARC, Supplement 7, 1987) noted that the evidence of carcinogenicity for T or androgenic (anabolic) steroids in humans is inconclusive, but is sufficient in animals. They further noted that prolonged androgen therapy may be associated with an increased risk of hepatocellular tumors, but the evidence is not conclusive. Androgenic (anabolic) steroids are probably carcinogenic to humans through epigenetic mechanisms that may result in proliferative responses in organs expressing T receptors (e.g., mammary tissue, uterus, ovary, liver).

The current T label contains the following information in Section 13.1: “Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.” In addition, potential risk of prostate cancer with androgens is included in Warnings and Precautions Section.

The following language is excerpted from the intramuscular TU (AVEED®) labeling: “Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.”

A package insert for an oral TU (Andriol® Testocaps®, Taro-Testosterone) available in Canada and other countries includes the following statements: “Carcinogenicity testing of testosterone propionate in mice and rats by subcutaneous implantation has produced cervical-uterine tumors in female mice and prostatic adenocarcinomas in male rats. Hyperplastic epithelial lesions of the genital tract and an increased incidence of mammary tumors have resulted from neonatal treatment of female mice by subcutaneous injection of testosterone. 5-beta-dihydrotestosterone also increased the incidence of mammary tumors in mice when given neonatally by subcutaneous injection. There are rare reports of hepatocellular carcinoma in patients receiving long term therapy with androgens, particularly the 17-alpha-alkyl-androgens, in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases. Whether there is a causal relationship or a connection between testosterone administration and formation of tumors occurring by chance remains unclarified.”

In response to the Division request to address the nonclinical requirement of a 505(b)(1) NDA based on the inadequate assessment of carcinogenicity of TU, the sponsor provided a response to revoke the decision of the Exec CAC and the Division on November 30, 2017. The sponsor believes that any meaningful new data will not be generated by the conduct of an additional oral TU carcinogenicity study, considering

that the T exposure in the mid- and high-dose groups was pharmacologically similar, this additional histopathology evaluation of the combined mid- and high-dose groups doubles the number of mice (to 50) exposed to exceptionally high supraphysiological concentrations of T and thus substantially increases the power of the study.

The following sponsor's justification in *italicized* text is followed by the Division's comments in regular font:

Adequacy of Clarus Tg·rasH2 Mouse Carcinogenicity Study:
The rationale for selection of the high dose in the mouse rasH2 carcinogenicity study was based on histologic minimal spermatid degenerative lesions noted at the same high dose (80 mg/kg/day) in a previous 4-week dose range finding study – a strategy supported by ICH S1(R2) guidance for both maximum tolerated dose and pharmacodynamically-active dose levels [see ***Appendix/Attachments*** *for justification of dose selection provided by toxicology laboratory (i.e., (b) (4) that conducted study in question]. The N of 25 mice (males) per group was consistent with the scientific rationale for gender-specific targets. And while the overall statistical power would have been greater with a higher N, there appears to be no scientific basis to support that this would have changed the outcome for this study. This conclusion is supported by the concordant results obtained (i.e., no evidence of a neoplastic signal in target or any other tissues) when tissues from both the mid- and high-dose groups were evaluated histologically and the data combined (see below for rationale based on data that indicates both maximal and equivalent TU exposure occurred in both the mid- and high-dose mice) thus yielding an N of 50 for each tissue. Furthermore, the International Agency for Research on Cancer has determined that there is already sufficient data to show that testosterone is tumorigenic in gender-specific targets in male rats and female mice, yet insufficient data that there is any translation of these findings to humans (Carcinogenesis 12:1751, 1001). On the basis of the rationale provided by (b) (4) (as well as additional arguments made below), we maintain that the study design of the 26-week transgenic mouse (rasH2) carcinogenicity study of oral TU was adequate and appropriate to assess the carcinogenicity of oral TU in a well-validated male mouse transgenic model.*

However, the sponsor's rationale for dose selection is not valid. High dose selection for 6-month carcinogenicity studies in transgenic animals is usually based on the MTD derived from a 1-month dose range-finding study. The high dose could be a maximum feasible dose (MFD), a dose at which saturation of exposure occurs or a limit dose. Typical transgenic carcinogenicity studies include 5 dose groups: a vehicle control group, 3 dose groups and a positive control group. An untreated control group is employed to evaluate toxicity of vehicles that may confound interpretation of carcinogenicity studies. Use of 20-25 animals per group per sex is recommended for which the number of animals per groups is to have a level of power between 80 and 90% in detecting a 15% difference. The 3 dose levels paradigm is useful when a high-dose group is found to exceed the MTD.

Based on the ICH S1C(R2) guidance, the top dose or MTD is defined as a dose which is predicted to produce a minimum toxic effect over the course of the carcinogenicity

study. The guidance indicates that both the toxicity profile and any dose-limiting toxicity should be characterized when undertaking dose range-finding study in order to select the high dose for the carcinogenicity study. However, there is no basis to establish the toxicity endpoint in the dose range-finding study submitted by the sponsor. The only finding was minimal testicular atrophy/degeneration in 9 out of 10 mice at high dose (80 mg/kg/day) compared to 1 out of 10 in vehicle-treated mice. The histopathological finding is an expected pharmacodynamic response to TU exposure, but not necessarily a MTD. Notably, there were no testicular findings in any TU-treated groups up to the same doses tested in male Tg·RasH2 mice following 6-month treatment. No changes were noted in body weight gains, target organ toxicity, or alterations in clinical pathology parameters, suggesting low exposure to TU and/or lack of a MTD.

In addition, dose formulations for the placebo or test material contained corn oil in lieu of peppermint oil used in the clinical formulation. The sponsor stated that deaths occurred in male mice (2 vehicle control and 1 low dose TK animals) shortly after treatment initiation (Days 2 and 7) in the 28-day dose range-finding study. The cause of death was determined to be associated with the peppermint oil in the vehicle. However, corn oil is not a recommended vehicle in carcinogenicity studies, because of its potential to confound the study.

T Exposure in Tg·rasH2 Mouse Carcinogenicity Study was at High Multiples of Expected Human Exposure Based on Phase 3 Trial Used to Support Efficacy:
In addition to the selection of dose levels for the mouse carcinogenicity study based on an MTD derived from a 28-day dose range-finding study, it is instructive to place the doses examined in the context of T exposure (both AUC and peak) when compared to expected human exposure based on the most recent Phase 3 study of oral TU, CLAR-15012. This is particularly true in light of the fact that the biologically active molecule of study is an endogenous hormone, namely, T. Pharmacokinetic sampling of T was performed in the 28-day dose-range-finding study of oral TU conducted to guide dose selection for the carcinogenicity study (b) (4) *Study Report No. 16-856). Table 1 summarizes T AUC and peak T data in mice and compares these to similar data generated by Clarus in clinical study CLAR-15012 (Phase 3 study conducted to support efficacy and safety for resubmitted NDA 206089) since this human clinical trial provides the best estimate of human exposure to T under proposed conditions of clinical use.*

Table 1: Comparison of T Exposure in 28-Day Mouse Dose-Range-Finding Study to Anticipated T Exposure from Oral TU under Expected Conditions of Clinical Use

28-Day Mouse Study Dose Group (TU mg/kg/day)	Mouse Mean Peak Plasma T (ng/dL)	Ratio of Mouse Peak T: Human Peak T (CLAR-15012)*	Mouse AUC (ng·hr/dL)	Ratio of Mouse T AUC: Human T AUC (CLAR-15012)**
20	16050	15.92	42039	4.35
40	20000	19.84	65188	6.75
80	20000	19.84	81276	8.41

**Mean T peak (i.e., C_{max}) observed on final PK day (Visit 7) in CLAR-15012 was 1008±581 ng/dL*
***Mean T AUC observed on final PK day (Visit 7; efficacy time point) in CLAR-15012 was 9659±3065 ng·hr/dL*

Based on the reasonable assumption that T exposure of mice in the Tg-rasH2 mouse carcinogenicity study mirrored that observed in the 28-day dose range-finding study, mice in the carcinogenicity study at the mid- and high-dose were exposed to approximately 20-times the peak T concentrations expected in man and approximately 7 to 8-times the AUC. We submit that exposure to these levels of a highly active sex steroid was: a) sufficient to exceed the androgen receptor binding capacity in any target tissue (e.g., prostate, testes, and muscle) that mediates T action; and b) provide sufficient exposure on which carcinogenicity can be assessed in the Tg-rasH2 mouse carcinogenicity model. Moreover, such high T concentrations assured that the all other organs [most notably liver, the target organ for oral toxicity (including neoplasias) of alkylated T derivatives such as methyl-T] were exposed to exceptionally high concentrations of T and its active endogenous metabolites (i.e., DHT and E2).

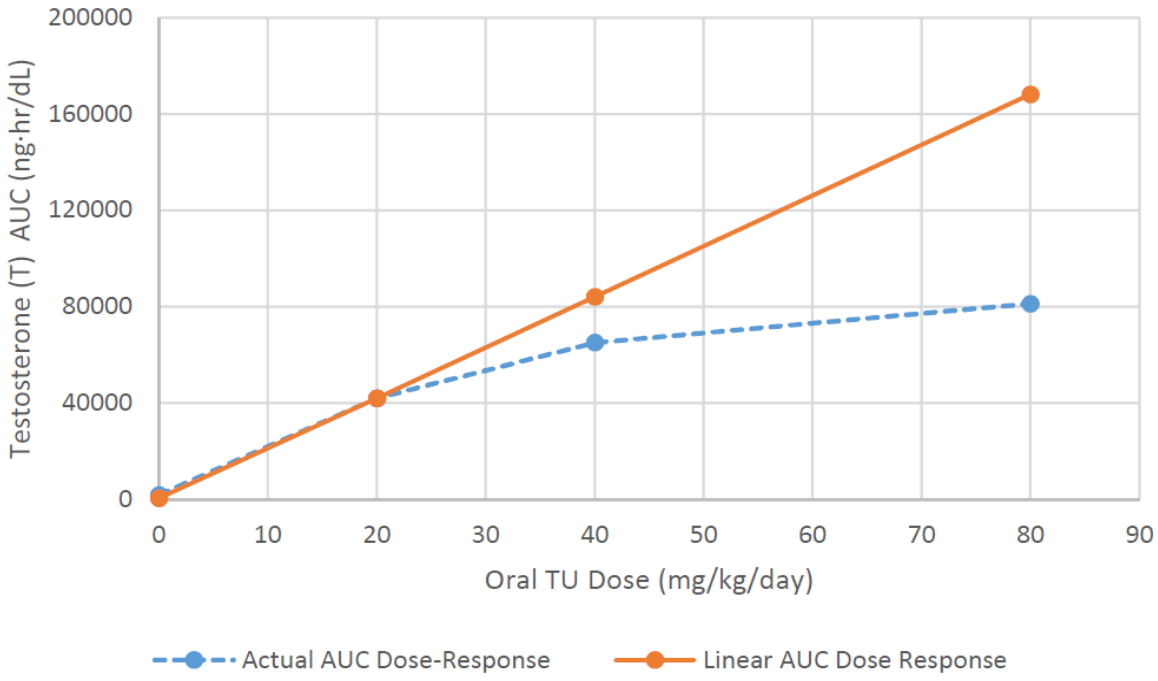
However, the sponsor's argument is inappropriate. As stated previously, high dose selection for 6-month carcinogenicity studies in transgenic animals is based on the MTD, MFD, saturation of exposure, or the limit dose. The transgenic mouse model is used for its ability to detect human carcinogens for the purposes of hazard identification. Thus, exposure margins are not considered with either dose selection or when interpreting drug-related results when using transgenic mouse models.

Nonetheless, the AUC exposure to T ($AUC_{0\text{-}6hr}$~80000 ng·hr/dL) at high dose would be approximately 5-fold the maximum anticipated exposure ($AUC_{0\text{-}24hr}$~15000 ng·hr/dL) in men. Based on C_{max}, the exposure to T (>20000 ng·hr/dL, upper limit of quantitation) at high dose would be approximately >8-fold the maximum anticipated C_{max} (~2500 ng·hr/dL) in men. The high dose used in the mouse transgenic carcinogenicity study (80 mg/kg/day, 240 mg/m^2) is less than the anticipated maximum dose (396 mg/day BID, ~490 mg/m^2) based on the body surface area.

<u>Highest TU Dosages Tested in Tg·rasH2 Mouse Carcinogenicity Study were at or Near Capacity of Animals to Absorb TU and Convert it to T</u>:
Notably, in the mouse 28-day dose range-finding study, the T response was not dose proportional as depicted in Figure 1 below. There is a clear reduction is circulating T

AUC with dose -- probably indicative of two concurrent processes. First, the capacity of the intestinal lymphatic pathway to absorb TU is limited; and second, once absorbed, the activity of non-specific esterases to cleave the ester bond between the fatty acid and T is overwhelmed. Compared to drug absorption into the portal circulation, lymphatic drug absorption is a low volume, high specificity pathway that requires the packaging of drug (TU in this case) into chylomicrons for eventual transport (i.e., secretion) into the intestinal lymph and then into the general circulation. The 'flow' of this pathway in rodents has been estimated to be 500 times less than portal drug absorption (Int J Pharmaceutics 34:175, 1986). Animal [rat (Acta Endocrinol 79:789, 1975); dog (J Pharmacol Exper Therap 306: 925, 2003) and human (Klin Wschr 54:875, 1976) studies have demonstrated that the exclusive pathway for TU to reach blood after oral administration is via the intestinal lymphatic system. So it stands to reason that at some TU dose (probably not much greater than the high TU dose evaluated in the Tg-rasH2 mouse carcinogenicity study), there will be little additional increase in circulating T. And, as depicted in Figure 1, this is precisely what happened.

Figure 1: Linear v. Actual AUC Response in Mice Exposed to Oral TU Dose Progression in 28-Day Dose Range Finding Study (Experimur Study No. 16-856)



However, the sponsor's assessment is not considered adequate. The sponsor believes that the Tg·rasH2 mice were exposed to maximal concentrations of T at the mid and high doses based on the similar AUC ratio of mouse to human at mid (7-fold) and high (8-fold) doses. On Day 1, AUC ratios for T were 56, 94, and 137-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls. AUC ratios for DHT were 11, 15, and 59-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls. On Day 27, AUC ratios for T were 22, 34, and 42-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls. AUC ratios for DHT were 43, 72, and 225-fold over 20, 40, and 80 mg/kg/day, respectively, compared to controls. Based on the AUC ratios for T and

DHT, the increased ratio for DHT relative to the decreased ratio for T suggests that conversion of T to DHT may have occurred. The decreased DHT/T ratios from pre-dose values for all treated groups at 2-4 hour post-dose followed by a steady increase through the 6 hour time-point on Day 27, with an increase in DHT/T ratio support the contention that a rapid rise in plasma T occurred shortly after TU administration, which was then followed by metabolism of a portion of T to form DHT. Therefore, it is unlikely that saturation of TU absorption limited systemic exposure to T and DHT at mid and high-dose groups. It should also be noted that the low upper limit of quantitation for T and DHT (20000 ng/dL=200 ng/mL) in this assay may have affected C_{max} ratios at mid and high-dose groups.

Maximal Androgen Receptor Binding of T was Achieved in Response to Highest TU Evaluated in Tg·rasH2 Mouse Carcinogenicity Study

Further evidence that the Tg-rasH2 mice were exposed to maximal concentrations of T in both the mid- and high-dose arms of the carcinogenicity study can be appreciated on the basis of androgen receptor kinetics. Saturation of androgen receptor binding in target tissues (e.g. prostate) by T occurs at a concentration of about 3 nM in rodents (J Androl 6:279, 1985). In other tissues, androgen receptor saturation occurs at even lower concentrations (Endocrinology 126:1165, 1990). Based on the T pharmacokinetic data observed in the 28-day dose range-finding study (b) (4) *Study No. 16-856 T-PK), mice exposed to 40 and 80 mg/kg/day TU achieved mean circulating T concentrations of 2717 and 3387 ng/dL, respectively. These values, in turn, equate to T concentrations of 94 and 117 nM. Thus, mice in the mid- and high-dose group in the carcinogenicity study were exposed to respective circulating T levels approximately 30- to 39-fold greater than the androgen receptor saturation point in androgen-sensitive tissues. If one considers the additional impact of DHT which is 12 times more potent than T based on receptor binding kinetics [i.e., 4xgreater binding to AR and 3x slower dissociation rate (Endocr Rev 38:220, 2017), then the androgen excess could have been appreciably larger. For instance, at the high oral TU dose in the 28-day mouse dose range-finding study, a mean DHT concentration of 246 ng/dL or 8.5 nM was observed* (b) (4) *Study No. 16-856 DHT-PK). This is about 3-fold higher than the androgen receptor saturation point on a numeric basis but is roughly 36-fold higher than the androgen receptor saturation point when one considers the difference in binding affinity and dissociation from androgen receptor between DHT and T. Hence, there is ample evidence to demonstrate that the mid- and high-dose T and DHT levels in the Tg-rasH2 mouse carcinogenicity study saturated androgen receptor binding and provided maximal pharmacological/physiological exposure to assess carcinogenicity in this model. Moreover, the pharmacologic exposure between the mid- and high-dose groups were sufficiently similar to justify the grouping of these animals for histopathological assessment as a means to increase the power of the study as discussed in sub-section above.*

However, the sponsor's information is not convincing. Intracellular concentration of androgens (particularly in androgen-sensitive tissues) are essentially independent of circulating hormones. Although androgens exert their action directly via the androgen receptor, tissue androgen receptor levels would not contribute much to the retention of

androgen in target organs (e.g., prostate). There is no direct correlation between androgen receptor levels and androgen contents in the target organs based on the findings that even though androgen receptor levels in the ventral prostate in rats were 2-3 times those of the dorsolateral lobe or anterior prostate, they accounted for less than 1/30th-1/60th of the total amount of androgen present in the lobe (J Androl 6:279, 1985). In addition, the vast majority of the steroid is bound to SHBG (40-70%) and to albumin (30-60%) and only a small fraction (1-2%) of the unbound T present in the blood is biologically active. T is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. However, albumin-bound T has to dissociate from albumin before they diffuse into target tissues for action. Based on the sponsor's estimated circulating T concentration of ~3390 ng/dL (~117 nM) in Tg·rasH2 mice at the high dose, the tissue level of T would be ~1-2 nM, which is less than the concentration for saturation of androgen receptor in the prostate (~3 nM) in rats. Therefore, this reviewer does not agree with the sponsor that the high dose in the 6-month study reached maximal pharmacological/physiological levels of T and DHT, particularly in the absence of any pharmacological/biological effects observed at any dose tested up to 80 mg/kg/day in Tg·rasH2 mice.

Reproductive and Developmental Toxicology:
Oral TU dosed at 0, 20, 40, and 80 mg/kg/day for 4 weeks in male rats prior to and during a 2-week mating period caused dose-related a reduction in the size of testes. Slight increase in abnormal sperm morphology (detached head) was observed at 80 mg/kg/day (14% vs 9% in control group). The sponsor did not provide historical control data from the conducting laboratory. However, the toxicological significance of the findings is minimal, given that these values were within the historical control ranges (2.6-14.2%) from (b) (4) The lack of the effect on spermatogenesis and/or fertility in this study may be due to insufficient exposure to T. No toxicokinetic data are available to evaluate drug exposure.

Administration of exogenous T (T or T ester) has been reported to suppress testicular weights, spermatogenesis, and fertility in the rat, dog, and non-human primates (Spermatogenesis 4:1, 2014; PLoS ONE 8: e71705, 2013; J Androl 23:149, 2002; Recent Prog Horm Res 57:149, 2002; Arch Toxicol 67:131, 1993; Biol Reprod 35:1321, 1986; Biol Reprod 31:221, 1984), which were reversible on cessation of the treatment. T administered to the dam produced negative effects to dams, including delayed parturition, reduced litter size and low pup viability, resorptions or still births, masculinization, and reduced milk production, (Toxicol Sci 96:335, 2007; Toxicol Sci 65:71, 2002; Horm Behav 12:1, 1979; Arch Anat Micro Morphol Exp 66:207, 1977; Am J Obstet Gynecol 111:964, 1971; Acta Endocrinologica 50:379, 1965).

T is a known teratogenic substance that is contraindicated during pregnancy or in women who may become pregnant. Exposure of a fetus to androgens, such as T, may result in varying degree of virilization. T (in the form of T enanthate or T propionate) is also teratogenic and embryotoxic in animals, and adversely affects the sexual and behavioral development of offspring from treated dams (J Physiol Sci 62:123, 2012; Toxicol Sci 96:335, 2007; Horm Behav 10:40, 1978). Even a single-dose prenatal

exposure to T induced postnatal reproductive toxicity in animals (Fertil Steril 84:1277, 2005; Dev Neurosci 19:430, 1997). The marked increase in maternal and fetal T levels in rats after subcutaneous injections of T propionate (Toxicol Sci 65:71, 2002), suggests that the fetus can be directly exposed to androgens in utero. Across multiple species, anatomic masculinization of the fetus and increases in aggressive behavior are the end results of exposure to T during neonatal development. The exposure of young female animals to T resulted in life-long changes characterized by androgenization.

Numerous studies were published to determine fetal effects of T (T propionate, T enanthate) following various route of administration (oral, subcutaneous) in multiple animal species. After administration of different doses (5 µg-1.2 g) of T propionate in animals at various times during pregnancy, the observed changes in male fetuses and offspring included reduced anogenital distance, delayed onset of puberty, increased aggressive behavior, and altered pattern of sexual preference. Reduced T plasma levels were observed for adult male rats exposed prenatally to T propionate (J Physiol Sci 62:123, 2012; Behav Biol 13:401, 1975). Prenatal treatment with T propionate significantly increased T levels and mean arterial pressure in adult male and female rats, and delayed onset of puberty and increased aggression in males. Exposure of newborn male rat pups to T propionate (0.05 -1.75 mg via single subcutaneous injection) resulted in significant decreases in testis, seminal vesicle and ventral prostate weights in comparison to controls, a dose-related decrease in fertility, and notably diminished spermatogenesis. T propionate also acted as an endocrine disruptor adversely affecting steroidogenesis (Biol Repro 137:1, 2012; Biol Repro 35:1321, 1986).

Post-natal effects in females included nipple and mammary anlagen inhibition, vaginal atresia, retention of serous fluid in the uterine horns, increased anogenital distance, abridgment of the urovaginal septum, male type differentiation (e.g., urogenital sinus, phallus rudiment, urethral bulb), down growth of vagina, clitoris enlargement, absence of vaginal opening and oviducts, rudimentary uterus, presence of prostate and seminal vesicles, rudimentary vas deferens, hypospadiac clitoris, varying degrees of inhibition of Mullerian duct, stimulation of Wolffian duct derivatives, and developmental behavioral changes in mice (Teratog Carcinog Mutag 7:17, 1987), rats (Toxicol Sci 65:71, 2002; Life Sci 50:621, 1992; Acta Endoc 103:420, 1983; Experientia 39:108, 1983; Physio Behav 26:773, 1981; Arch Anat Micro Morph Exper 66:207, 1977; Behav Biol 13:401, 1975; Am J Obst Gynecol 111:964, 1971; Acta Endocrinol 47:37, 1964; Am J Anat 79:293, 1946; Science 86:200, 1937), hamsters (Am J Anat 79:293, 1946), guinea pigs (Fertil Steril 19:606, 1968; Anat Record 157:352, 1967; J Comp Physiol Psycho Behav 57:166, 1964), ewes (Acta Endocrinol 113:153, 1986; J Embryol Exp Morphol 36:87, 1976), and monkeys (Fertil Steril 77:167, 2002). There were irreversible ovary-independent vaginal cornification and uterine stratification with or without squamous metaplasia and fighting behavior later in life in mice following subcutaneous or intraperitoneal administration of T propionate (Physiol Behavior 23:23, 1979; Endocrinol 76:789, 1965).

Summary and Conclusion:
The findings observed in the 9-month toxicology study in male eugonadal dogs are expected androgenic effects that would not occur in hypogonadal men exposed to T in the eugonadal range, given the T levels of ~2-9 times and ~4-20 times the baseline AUC and C_{max} levels, respectively. However, the high dose of TU in the dog was ~1-2 times the maximum human dose based on AUC exposures to TU or T. The negative results from the carcinogenicity and male fertility studies may reflect insufficient exposure to T and/or TU. In the reviewer's view, the submitted studies are not optimal to characterize the potential effect of the T ester following chronic treatment. Additional information and data are needed to support the nonclinical requirements of a 505(b)(1) NDA unless there are sufficient clinical experiences for the oral TU product that supersede any nonclinical findings.

12 Appendix/Attachments

12.1 References

The following references were provided within the submission.

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/s/

YANGMEE SHIN
02/27/2018

MUKESH SUMMAN
02/27/2018
I concur

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206-089
Supporting document/s:	SN000
	SN003
Applicant's letter date:	January 3, 2014
	February 24, 2014
CDER stamp date:	January 3, 2014
	February 24, 2014
Product:	REXTORO™ (testosterone undecanoate)
Indication:	Testosterone replacement in hypogonadal men
Applicant:	Clarus Therapeutics Inc.
Review Division:	DBRUP
Reviewer:	Eric Andreasen, Ph.D.
Supervisor/Team Leader:	Lynnda Reid, Ph.D.
Division Director:	Hylton Joffe, MD
Project Manager:	Jeannie Roule

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Any information or data necessary for approval of NDA 206-089 that Clarus Therapeutics does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206-089.

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Reference ID: 3604305

Reference ID: 3604305

1 Executive Summary

1.1 Introduction

REXTORO[M] is a novel immediate release oral dose product with two strengths containing either 158 or (b) (4) mg of testosterone undecanoate (TU). REXTORO is indicated for testosterone replacement therapy in hypogonadal men. The Applicant proposes that REXTORO be taken with meals in the morning and evening with a maximum single dose of 475 mg TU BID. Testosterone undecanoate is a pro-drug that is metabolized to testosterone (T) and undecanoic acid, an unbranched 11 carbon fatty acid. Although an oral TU formulation is not available in the USA, oral TU products (Andriol®/Andriol® Testocaps) have been marketed outside of the USA for decades and an intramuscular TU product, AVEED[TM], recently gained marketing approval in the USA to treat male hypogonadism.

Although several products have been marketed to elevate serum testosterone (T) in men with hypogonadism by exposing them to testosterone or testosterone esters via intramuscular, dermal, or buccal exposure, an oral dose formulation containing T has not been developed because T is metabolized in the liver before it is distributed systemically. The Applicant developed a new oral dose formulation that was designed to promote absorption of TU into the intestinal lymphatics and subsequent metabolism to T and undecanoic acid thereby avoiding first pass metabolism of testosterone in the liver.

1.2 Brief Discussion of Nonclinical Findings

Because there are extensive clinical and nonclinical data regarding testosterone in published literature, the nonclinical evaluation of REXTORO was limited to assessing binding affinity of TU for the androgen receptor and assessing the toxicity of TU in the Applicant's oral formulation after 13 weeks of repeated dosing in male dogs. The Applicant relied upon published literature to assess the absorption, distribution, metabolism, and elimination of TU. Published literature was also supplied to assess the potential for reproductive toxicity and carcinogenicity. REXTORO also contains a novel excipient, borage seed oil. The safety of borage seed oil was qualified with published literature and was also supported by the lack of adverse findings in the 13-week toxicology study in dogs.

A. Primary Pharmacological Activity

Testosterone undecanoate (TU) is a fatty acid ester of testosterone. TU is an inactive pro-drug which is hydrolyzed by esterases in vivo to yield testosterone and undecanoic acid. TU itself has little potential for androgenic activity without being metabolized since its relative binding affinity for the androgen receptor was only 1% that of testosterone.

B. Absorption, Distribution, Metabolism, and Elimination

In lieu of conducting nonclinical absorption, distribution, metabolism, and elimination (ADME) studies with REXTORO, the Applicant submitted a review of some pertinent literature describing the ADME of testosterone and testosterone undecanoate.

In general the publications suggest that lymphatic absorption is promoted when testosterone is esterified at the C17β-hydroxyl group with long chain fatty acids such as undecanoic acid. Lipophilic vehicles aid intestinal lymphatic absorption and administration with food greatly aid oral absorption of TU into the intestinal lymphatics. However, TU is very poorly absorbed orally with bioavailability being well below 10% in rats, dogs, and humans. After absorption, a fraction of TU is metabolized in the intestinal wall to DHTU. TU and DHTU are distributed systemically where they are further metabolized to undecanoic acid, T, DHT, estradiol (E2), numerous steroid metabolites, and glucuronide and sulfate conjugates. The half-lives of T and TU are roughly 10 to 100 minutes after they are in systemic circulation. In humans, TU and T are metabolized and eliminated primarily as androgen glucuronide conjugates in the urine within several hours of dosing. Undecanoic acid exposure is not a safety concern because it is an 11 carbon fatty acid that is metabolized by beta-oxidation and the tricarboxylic acid pathways and it is an approved food additive in the FDA's Everything Added to Food in the United States Database (1).

C. Nonclinical Toxicology Findings

Repeat-Dose Toxicity in Male Dogs

A toxicology study was conducted in male dogs that were dosed orally with TU in the clinical formulation at 0, 38 (LD), or 126 (HD) mg/kg/BID for 13 weeks. Recovery was assessed four weeks after the last dose in the control and HD groups. Findings were limited to androgen responsive tissues and are consistent with excessive exposure to an androgen.

The multiple of the clinical exposure discussed below are derived from the exposure in dogs relative to the exposure in men who received a single 475 mg TU dose after a high fat meal. This exposure comparison is a worst case scenario because fat content of the diet had a significant effect on Cmax and AUC in men. Compared to fasted men, the high fat diet increased the exposure (AUC) to TU, T, and DHT by 5-, 2-, and 3-fold respectively (Clinical Study CLAR-09008).

In dogs, the testosterone exposures based on AUC were elevated 8 and 21 times the baseline level in the LD and HD groups, respectively. Although exposure to testosterone was greatly elevated above baseline, dogs in the LD and HD groups were only exposed to 2 and 8 times the AUC exposure in men on a high fat diet who received the maximum anticipated dose. Based on AUC, the exposure to DHT was elevated in dogs roughly 9 and 20 times the baseline level in the LD and HD groups, respectively. DHT exposure (AUC) was similar to that in men in the LD group and only twice the clinical exposure in the HD group. The exposure to TU based on AUC in the LD and HD groups was roughly 2 and 5-6 times the exposure in in men, respectively. TU was

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inefficiently metabolized to testosterone. Based on the molar ratios of AUC values, the exposure to TU ranged between 7 to 10 times the exposure to testosterone for all dose groups. However, this does not appear to be a safety issue since there were no toxicities reported that are not androgen related. The high TU to T ratio appears to be because of saturation of esterases activity in humans and dogs because the molar AUC ratio of TU to T was ≥ 7 for both dogs and humans. A high molar ratio of TU to T 6-7 to 1 has been reported in the literature with the oral TU product Androl Testocaps when it was taken with a normal to high fat diet (2).

All of the findings discussed below occurred in LD and HD groups and were all androgen dependent effects that would be expected following testosterone exposures that were 8 and 21 times the baseline level. Cholesterol was reduced by ≥ 45%. Moderate to marked atrophy of the adrenal cortex was sufficient to cause reduced adrenal weight and dogs did not fully recover after drug withdrawal. This may be due to feedback suppression of androgen synthesis in the adrenals. Marked testicular atrophy/degeneration caused reduced testes weight and severe reduction in epididymal sperm. The testes and epididymal effects were still observed after a one month recovery period because the recovery period was too short for a two month spermatogenic cycle to rebound. Marked prostate hypertrophy was associated with increase prostate weight but the dogs fully recovered from this.

Although adverse androgenic findings were observed in dogs in both TU dose groups, there were no clear non-androgen dependent adverse findings. Even though the exposure multiples in dogs for T and TU are not large relative to humans, the findings in dogs occurred at T levels well in excess of the baseline levels and the findings are well known androgenic effects that are not anticipated to occur in men exposed to testosterone in the eugonadal range.

D. Carcinogenicity and Reproductive Toxicity

The risk for reproductive toxicities and cancer is considered to be similar to other approved testosterone products based upon the established effects of testosterone.

Overall Conclusion

The safety profile of testosterone is well known. The preponderance of clinical data with testosterone and TU supersedes nonclinical findings. Other than expected androgen related findings in dogs, no significant safety concerns associated with TU were identified in the nonclinical program. Referenced literature and nonclinical data suggest that there should be no non-androgen related findings at the maximal clinical dose proposed for marketing. Overall the nonclinical program supports approval of this product for the proposed population and indication and a maximum single dose of 475 mg of TU to be administered twice daily.

1.3 Recommendations

1.3.1 Approvability

The Applicant's nonclinical program, supplied references, available literature, and general nonclinical and clinical knowledge of testosterone and testosterone undecanoate provide reasonable assurance of the safety of this oral dose testosterone undecanoate product in hypogonadal men. From a nonclinical perspective this NDA is approvable.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Recommended nonclinical revisions to the Applicant's proposed label are provided below. Annotations to Applicant's label can be found in Section 12.4 followed by a full unmarked version.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4)

(b) (4) (testosterone undecanoate), for oral use CIII
Initial U.S. Approval: 1953

----------**INDICATIONS AND USAGE**----------
(b) (4) is an androgen indicated for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

----------**CONTRAINDICATIONS**----------
Men (b) (4) or known or suspected prostate cancer. (4, (b) (4) (b) (4) Testosterone may cause fetal harm. (4, (b) (4), 8.3)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

(b) (4) for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

4 CONTRAINDICATIONS

(b) (4)

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

(b) (4)

Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays.

Impairment of Fertility

The administration of exogenous testosterone (b) (4) suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

2 Drug Information

2.1 Drug

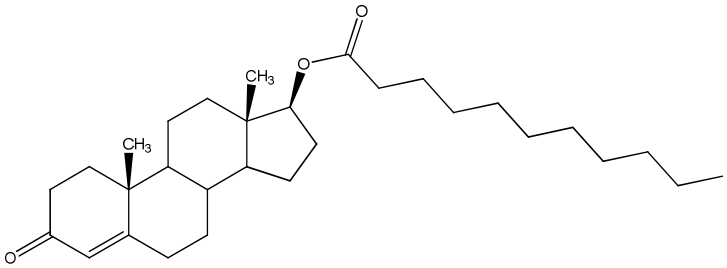
Generic Name: Testosterone Undecanoate (TU)

Chemical Name: 17β-hydroxyandrost-4-en-3-one undecanoate

CAS Registry Number: 5949-44-0

Molecular Formula/Molecular Weight: $C_{30}H_{48}O_3$ / 456.7

Structure:



Pharmacologic Class: Androgen

2.2 Relevant INDs, NDAs, and DMFs

The Applicant developed this product under IND 78,104. Letters of authorization were provided to the DMFs for the drug substance (DMF [redacted]) and drug product (DMF [redacted]).

2.3 Drug Formulation

Two strengths of immediate release soft gelatin capsules are proposed for marketing. The capsules contain 158 or [redacted] mg of testosterone undecanoate which is equivalent to 100 mg and 150 mg of testosterone. The product is manufactured by [redacted] under DMF [redacted]. The Applicant provided a letter of authorization from [redacted] to the NDA. The drug substance is sourced from [redacted] (DMF [redacted]) and [redacted] (DMF [redacted]). The Applicant provided letters of reference from the product manufacturer and the drug substance suppliers.

There are no safety issues with the amount of each excipient. The product contains one novel excipient, borage seed oil, and [redacted] three excipients (oleic acid, butylated hydroxyl toluene, and polyoxyl 40 hydrogenated castor oil) [redacted] The safety of the formulation was assessed in a 13-week toxicology study in dogs (Section 6.1). No adverse effects

other than androgen related findings were reported which supports the conclusion that the excipient formulation is reasonably safe. Although borage seed oil is a novel excipient, the Applicant submitted a comprehensive review that support its safe use in the product (See novel excipient section 2.4). The maximal daily dose of REXTORO is 475 mg TU BID (300 mg testosterone equivalents twice daily). The maximal total daily dose to oleic acid (b) (4) mg) exceeds the maximal amount in a marketed oral dose product (599 mg) but this is not a safety concern because oleic acid was qualified in the oral dose toxicology study in dogs with the Applicant's product, oleic acid is a long chain fatty acid, and it is considered generally regarded as safe (GRAS) in food products. Although the maximum potential dose of butylated hydroxytoluene ((b) (4) mg/day) exceeds the maximal amount in marketed oral pharmaceuticals in the USA (0.4 mg), this is not a safety concern. Butylated hydroxytoluene is roughly (b) (4)% of the REXTORO product and butylated hydroxytoluene is considered GRAS in food if it does not exceed (b) (4)% of the fat or oil content of food. Also the WHO set an acceptable daily intake of butylated hydroxyl toluene at up to 0.125 mg/kg/day (7.5 mg/day) which greatly exceeds the maximum daily exposure with REXTORO (3). The use of peppermint oil is not a concern since it is listed as a GRAS chemical it has been used in marketed pharmaceuticals for multiple 30 mg daily doses and is commonly used at up to 1.2 g per day for treatment of irritable bowel syndrome (1). The maximum daily dose of polyoxyl 40 hydrogenated castor oil ((b) (4) mg/day) exceeds the maximum dose in marketed oral dose pharmaceuticals (405 mg) but the marketed product with the maximum daily dose is indicated for BID dosing so this is not a safety issue. The amount of each component comprising the soft gel capsule shell was not supplied by the Applicant. However, the Applicant provided a letter of reference for the soft gel capsule DMF (b) (4) that is owned by (b) (4) After review of the DMF there are no toxicological concerns with the contents of the soft gelatin capsule shell.

Formulation (Applicant Described Capsule Strength in Testosterone Equivalents)					
Ingredient	**Function**	**Amount (mg) 100 mg Capsule**	**Amount (mg) 150 mg Capsule**	**Max Clinical Dose mg (300 mg BID)**	**Max (mg) in Approved Oral Pharmaceutical**
Testosterone Undecanoate	Active Ingredient	158.30[1]	237.46[2]	NA	-
Oleic Acid NF, EP	(b) (4)				
Borage Seed Oil[3]					
Butylated Hydroxytoluene, NF, EP					
Peppermint Oil, NF, FCC					
Polyoxyl 40 Hydrogenated Castor Oil, NF (Cremophor RH40)					
Total Fill Weight					
† Soft Gelatin Capsule Shell Composition					
Gelatin, NF, (b) (4)	(b) (4)				
Sorbitol – (b) (4)					
Iron Oxide Red, NF					
FD&C Yellow No. 6					
Titanium Dioxide, USP, EP					
Purified Water, USP, EP					

[1] Equivalent to 100 mg of testosterone. [2] Equivalent to 150 mg of testosterone.
[3] Borage seed oil is a novel excipient in the USA. It is supplied by (b) (4)

† The amount of ingredients in the soft gelatin capsule shell can be found in DMF (b) (4)

NA – not applicable

2.4 Comments on Novel Excipient (Borage Seed Oil)

Borage seed oil is a novel excipient. The Applicant submitted a safety assessment of borage seed oil that supports the safe use of this excipient in this product. A summary of the key safety data used to support the safety of borage oil is provided below. The Applicant's references to support the safety of borage seed oil can be found in section 12.2. A toxicological assessment of borage oil and the other excipients were reviewed under IND 78,104 and no safety issues were revealed (Review in DARRTS under IND 78,104 on July 30, 2007 and May 16, 2008).

2.4.1 Background on Borage Oil

Borage oil is a purified extract of the seeds from *Borago officinalis* L primarily consisting of fatty acids that are intended to help absorption of TU into the intestinal lymphatics

thereby avoiding first pass metabolism. In the USA borage seed oil is available as a dietary supplement but has not been used in marketed pharmaceuticals. Borage seed oil has been used as a source of gamma linoleic acid (~24%) in clinical settings to treat arthritis, inflammation, and atopic dermatitis in Europe. Borage oil was well tolerated in adult humans for up to a year at 5,000 mg/day (see table below). The dose of borage oil at the maximum proposed dose of REXTORO is (b) (4) mg per day.

Adverse findings of concern were not reported in the literature supplied by the Applicant which assessed the acute and chronic toxicity and reproductive and developmental toxicity (section 2.4.4).

The primary theoretical safety concern with borage oil is that pyrrolizidine alkaloids (PAs) are found in crude extracts of borage seeds. Some pyrrolizidine alkaloids are pulmonary and hepatotoxic in addition to being mutagenic and carcinogenic (4). The Applicant verified that PAs are below the level of detection ≤ (b) (4) µg/kg (ppb) in their supplier's borage oil. The specification for pyrrolizidine alkaloids in the purified borage oil was set at < (b) (4) µg/kg. Restricting PAs to levels below the limit of detection appear reasonable since it limits daily exposure to only (b) (4) ng assuming a maximal daily dose of (b) (4) mg of borage oil.

Clinical Oral Dose Borage Oil Studies where No Adverse Effects were Reported				
Population	**N**	**Indication**	**Oral Dose**	**Duration**
Elderly (5)	29	Dry Skin	1,000-3,000 mg/day	2 months
Adults and Children (6)	140	Atopic Dermatitis	Adult 4,000 mg/day Children 2,000 mg/day	12 weeks
Adults (7)	45	Weight Control	5,000 mg/day	1 year

2.4.2 Composition of Purified Borage Seed Oil

The Applicant's purified borage seed oil consists primarily of fatty acids (b) (4) and small fraction (b) (4) of non-fatty acids (b) (4)

The Applicant noted that the composition of fatty acids in purified borage oil is similar to other oils (sunflower, soybean, corn, and canola) with the exception that borage oil contains γ-linolenic acid while these other oils do not. They noted that evening primrose oil also contains a large fraction of γ-linolenic acid. Because of this, the Applicant addressed the toxicity of γ-linolenic acid with an extensive toxicological review of available literature including studies with borage oil and evening primrose oil (Section 2.4.4).

Composition of Supplier's Purified Borage Oil				
Fatty Acid Composition	(% of Total FAs)	(b) (4)	Composition *	mg/kg Oil
(b) (4)				

2.4.3 (b) (4) in Borage Oil

(b) (4)

2.4.4 Summary of Nonclinical Studies Referenced by the Applicant to Support Clinical Use of Borage Oil

Literature was supplied to address toxicity of borage seed oil (BO) after repeated doses and the effects on reproductive and development. Carcinogenicity and genotoxicity literature for evening primrose oil (EPO) was supplied because carcinogenicity and genotoxicity of borage oil has not been published. Studies with evening primrose oil (EPO) were provided by the Applicant to support the safety of borage oil since borage oil and EPO both have a large γ-linolenic acid (GLA) concentrations and other common oils (sunflower, soybean, corn and canola) do not. For this reason the GLA composition is listed in the table below that summarizes the referenced literature if the study investigated EPO instead of borage oil.

Multiple Dose Studies

Borage oil toxicities were not clearly evident in rats dosed for up to 20 weeks at oral doses up to 3.6 grams per day or in guinea pigs dosed for up to 8 weeks with diet containing up to 4% borage oil (8-13). The 3.6 gram dose in rats without reported adverse effects is equivalent to a human dose of 232 g/day based upon body surface

area which is (b) (4) times the maximal proposed dose in humans. Although these studies were not comprehensive toxicological investigations, consistent dose responsive toxicities were not revealed and acute toxicities were not mentioned. In addition to the literature, the Applicant conducted a 13-week toxicology study in dogs dosed orally with their product BID (See section 6.2). There were no adverse effects other than expected androgen responses which supports the safety of borage oil.

Reproductive and Developmental Toxicity

Mice were fed a diet containing 10% borage oil beginning two weeks prior to mating until postnatal day 32 (14). Pups were also fed borage oil after weaning. No adverse effects were observed on maternal toxicity, reproduction, development, or sensorimotor tests in offspring. Studies regarding reproductive affects in other species were not located by the Applicant.

Genetic Toxicity

Borage oil has not been assessed for genetic toxicity. A mouse micronucleus assay was conducted with GLA dosed IP at approximately 139 μg/kg (15). GLA did not cause an increase in polychromatic erythrocytes.

Carcinogenicity

The carcinogenicity of borage oil has not been assessed. However, evening primrose oil was studied in rats for 104 weeks (225 mg GLA/day), mice for 78 weeks (225 mg GLA/day) and dogs for 42 weeks (450 mg GLA/kg/day) without significant toxicity or increase in tumor insistence (16 and 17). These journal articles did not include individual animal data but they summarized the significant findings and indicated there were no adverse effects on clinical chemistry, hematology, organ weights, and histopathology. The maximum GLA dose in these chronic mouse, rat, and dog studies is (b) (4) times the maximum amount that patients will be exposed to with REXTORO based on body surface area conversion. There is little concern for carcinogenicity of borage oil since the Applicant indicated that their borage oil contains less than (b) (4) ug/kg of pyrrolizidine alkaloids, GLA was not clastogenic in mice, and GLA does not induce tumors in mice, rats, or dogs after chronic administration.

Human

No adverse effects were reported in hyperlipedimic patients dosed daily with 3 grams of EPO for four months but platelet aggregation was inhibited, bleeding time increased, triglycerides and LDL-cholesterol were lowed, and HDL-cholesterol increased compared to placebo treated patients (18).

Principal Nonclinical Publications Reference by Applicant			
Species	**Duration (citation)**	**Borage Oil, Evening Primrose Oil or γ-Linolenic Acid Concentration**	**Findings**
Rat	3 Weeks (13)	Oral BO (est. 5,000 mg/kg/day)	† Slight ↑ spleen wt at 5,000 Slight ↓ epididymal adipose at 5,000
	6 Weeks (19)	Oral BO (est. 3% to 7% of diet)	† No effect on organ wt or bw
	7 Weeks (8-10)	Oral BO (11% diet)	† ↓Slight blood pressure, ↑ Cholesterol
	12 Weeks (20)	Oral BO (15% diet est. 135 mg/day)	† Liver - slight focal fat infiltration
	15 Weeks (11)	Oral BO (10% diet) + 0.5% cholesterol	† ↓ Cholesterol in liver
	20 Weeks (12)	Oral BO (3.6 g/day) vs. normal diet Rats with partial renal ablation	↓ Effects of renal ablation
	53 Weeks (16)	Oral EPO (0-225 mg GLA/kg/day) vs. normal diet	Slight ↑ K females only, modest ↓liver wt males only. Histology, urinalysis, and hematology normal
	104 Weeks (17)	Oral EPO (0-225 mg/kg/day GLA) vs. normal diet	No adverse effect reported. No difference in tumor incidence.
Mouse	78 Weeks (17)	Oral EPO (0-225 mg/kg/day GLA) vs. normal diet	No adverse effect reported. No difference in tumor incidence.
	Pre-conception to PND 32 (14)	Oral BO (9.8% diet). Fed prior to mating to weaning and also to pups after weaning till PND 32	No adverse effects on maternal toxicity, reproduction, development or sensorimotor tests in offspring
Guinea Pig	8 Weeks (21)	Oral BO (4% diet)	† No adverse effects
Dog	52 Weeks (16)	Oral EPO (0-450 mg/kg/day GLA)	No adverse effects on clinical chemistry, hematology, urinalysis, or histopathology
Genotoxicity	Mouse Micronucleus (15)	Intraperitoneal GLA (139 µg/kg)	No effect on bone marrow derived polychromatic erythrocytes
Est- estimated intake from dietary exposure. Borage Oil (BO). γ-Linolenic Acid (GLA). Evening Primrose Oil (EPO). PND- postnatal day. † Findings in the study were in comparison to other oils or fatty acid treatments.			

Overall Conclusions Regarding Borage Oil

The literature supplied by the Applicant support the conclusion that there should be little concern for borage oil to cause toxicities after repeated dosing, adversely affect reproduction and development, or cause cancer.

Purified borage oil consists primarily of fatty acids which do not pose a safety concern. Borage oil related toxicities of significant clinical concerns were not observed in rats orally dosed for up to 20 weeks with up to (b) (4) times the maximal proposed dose in humans. Mice exposed to borage oil (9.8% of diet) from two weeks prior to fertilization, through in utero development, and growth after weaning resulted in no adverse effects on maternal toxicity, reproduction, development, or sensorimotor tests in offspring. There is little concern for borage oil to cause cancer since the specification for pyrrolizidine alkaloids will limit daily exposure to below the limit of detection (2 ng/day),

GLA was not clastogenic in mice, and evening primrose oil, an oil with similar fatty acid composition to borage oil, does not induce tumors in mice, rats, or dogs after chronic administration.

2.5 Comments on Impurities/Degradants of Concern

There are no toxicological concerns with the specifications levels of impurities or degradants in the drug substance.

The impurity specifications in the drug substance supplied by (b) (4) comply with ICH Q3A(R2) and ICH Q3C. The impurity specifications for the drug substance supplied by (b) (4). comply with ICH Q3A(R2) and ICH Q3C with the exception for the specifications of (b) (4) are slightly above the standard identification threshold of (b) (4) or qualification threshold of (b) (4). However, there are no toxicological concerns with the specification levels proposed by (b) (4)

Specifications for degradants in the drug product are acceptable from a toxicological perspective. Specifications for (b) (4) based on the 95% upper confidence limit and are not to be more than (b) (4) respectively. They also propose that individual unknowns may not exceed (b) (4) and total degradants must not exceed (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The Applicant proposes that REXTORO be indicated for testosterone replacement therapy in men with conditions associated with primary or secondary hypogonadism.

The Applicant described dosing based on testosterone equivalents not the dose of TU. In testosterone equivalents, the Applicant proposes a minimum dose of 100 mg BID (158 mg TU) and a maximum dose of 300 mg BID (475 mg TU). The starting dose is proposed to be 317 mg TU BID (2x 158 mg TU capsules BID). The Applicant proposes dose titration after seven days (b) (4)

2.7 Regulatory Background

Clarus Therapeutics submitted NDA 206-089 on January 3, 2014. NDA 206-089 contains data intended to support the use of REXTORO™ for testosterone replacement therapy in hypogonadal men. Nonclinical data used to support the NDA was submitted and reviewed under IND 78,104 which was opened on July 3, 2007. A pre-NDA meeting was held October 8, 2013 to discuss the data, format, organization, statistical methods, and unresolved issues needed to submit an NDA under 505(b)(1).

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

- Effect of Different Testosterone Esters on Androgen Receptor (AR) Binding Using Invitrogen's PolarScreen™ AR Fluroescence Polarization (FP) Assay (Study Number 013325-02)

Pharmacokinetics

- Absorption, Distribution, and Elimination (ADE) of Testosterone Undecanoate, a Prodrug of Testosterone (Applicant's Position Paper)

Toxicology

- 13-Week Oral (Capsule) Toxicity Study of Testosterone Undecanoate (TU) in Male Beagle Dogs (Study Number CLAR-PC-11001)
- Safety Assessment of Borage Oil as an Excipient in Oral Testosterone Formulations Under Development by Clarus Therapeutics (Applicant's Position Paper)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

Androgen Receptor Binding

The pharmacological activity of testosterone undecanoate (TU) is dependent upon metabolism of TU to testosterone and undecanoic acid by esterases and subsequent binding of testosterone (T) to the androgen receptor. The potential for pharmacological activity of TU was assessed by comparing the affinity of TU for the androgen receptor relative to T (Study 013325-02).

Methods: An in vitro assay was conducted using a commercial kit to evaluate the ability of test compounds to displace a fluorescent androgen receptor ligand from a fragment of the rat androgen receptor containing the ligand binding domain (PolarScreen™ Androgen Receptor Competitor Assay, Invitrogen Corp.). Each compound has a different maximal capacity (efficacy) to displace the fluorescent androgen receptor ligand (lowest point on the curve in the figure below). The potency of each test compound (EC_{50}) was described as the concentration of each test compound that was required to displace half of the maximal reduction of fluorescent AR ligand binding for each test compound. To estimate the relative binding affinity (RBA), the EC_{50} for each

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test compound was divided by the EC_{50} for testosterone and multiplied by 100. Testosterone (T) and dihydrotestosterone (DHT) were evaluated as positive controls. Progesterone (P) was also evaluated as a very week ligand. Testosterone undecanoate (TU) and one of its metabolites, dihydrotestosterone undecanoate (DHTU), were evaluated along with testosterone enanthate (TE) to determine the effect of the fatty acid ester on binding. Dehydroepiandrosterone (DHEA) was used as a negative control.

Significant binding of TU to the androgen receptor is not anticipated because esterification of the C17β-hydroxyl group eliminates the positive charge of the C17 hydroxyl group which is necessary for high affinity binding in the in the ligand binding pocket (22). In addition, substitutions at the C17β-hydroxyl group, especially long chain fatty acids, are known to reduce binding affinity.

This assay did not assess the competitive binding affinity to the human androgen receptor but this does not appear to be a significant deficiency because the difference between the human and rat ligand binding domain that was assessed was only seven amino acids in the hinge region and the positive and negative controls responded as expected. It is anticipated that this assay may be predictive of the relative binding affinity of ligands assessed for the human androgen receptor.

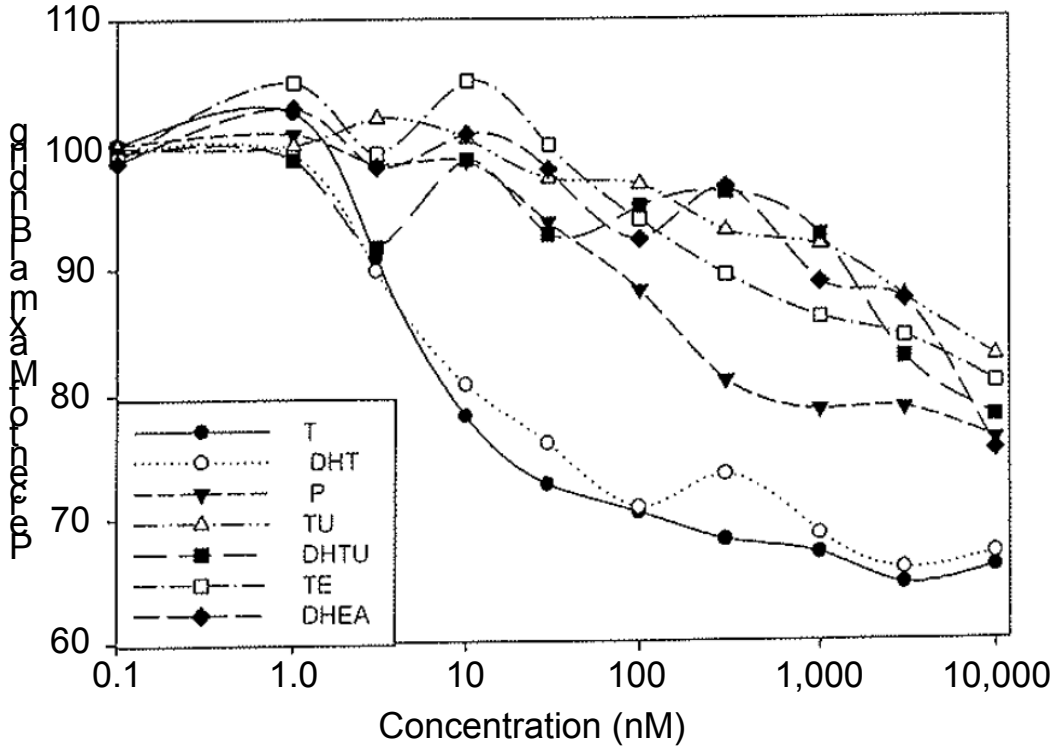
Results: Testosterone and DHT had fairly similar potency (EC_{50} 7 to 8.5 nM) and efficacy (maximal suppression of fluorescent ligand binding roughly 35%). The potency (EC_{50}) and efficacy of the remaining test compounds were much lower than T and DHT. This suggests that they are less potent ligands and their ability to maximally bind AR is suppressed compared to T and DHT. The maximal displacement of the fluorescent ligand was reduced to 17% to 25% for P, TU, TE, and DHTU compared to 35% for T and DHT. Progesterone demonstrated low potency as expected with a relative binding affinity of 9%. The relative binding affinities of T and DHT were reduced roughly 99% by the addition of the undecanoate ester side chain to testosterone (RBA of TU and DHTU ≅ 1%). Similarly the addition of an enanthate ester side chain to testosterone reduced the relative binding affinity of T by 95% (RBA of TE ≅ 5%). The negative control DHEA had similar RBA and maximal displacement of the florescent ligand as TU and DHTU confirming the low potential of these compounds to act as AR ligands.

Comment: It is unclear if the very low binding affinity of TU in this assay is due to TU or degradation products including T. The source and purity of the TU used in this assay were not provided. Since the relative binding affinity of TU was only 1% of T, TU is not anticipated to be a potent androgen receptor ligand, there is a possibility that binding observed with TU in this study could be due to impurities including T and/or due to degradation of TU to T and not due to binding of TU. Degradation of TU to T is expected since stability data found T in the TU product at (b) (4) and the specification for T in the drug product is (b) (4)

Conclusion: This assay only considers relative binding potency of compounds and does not assess the relative ability of the compounds to distribute to the target cell, induce

translocation of the AR to the nucleus, and enhance androgen receptor signaling. In general it suggests that TU and DHTU have low potential to act as AR ligands.

Displacement of Fluorescent Androgen Ligand by Test Compound



Binding Assay with the Rat Androgen Receptor Ligand Binding Domain			
Compound	**EC_{50} (nmol/L)**	**RBA**	**Maximal Displacement of Fluorescent Ligand**
Testosterone	7.0	100	35%
DHT	8.5	83	34%
P	82	8.6	24%
TE	143	5.0	19%
TU	573	1.2	17%
DHT-TU	1,005	0.7	22%
DHEA	916	0.8	25%

EC_{50} = concentration of each test compound that was required to displace half of the maximal reduction of fluorescent AR ligand binding for each test compound (difference between the highest and lowest point on the binding curve).
RBA - relative binding affinity = the EC_{50} of Testosterone divided by EC_{50} of the test compound x 100. Figure and table adapted from the Applicant.

5 Pharmacokinetics/ADME

5.1 PK/ADME

Overview

The REXTORO formulation was developed to promote absorption of TU into the intestinal lymphatics because oral exposure to testosterone results in very low systemic exposure since testosterone is metabolized in the liver before it can be distributed systemically. To bypass the portal circulation and first pass hepatic metabolism, the formulation was designed to support absorption into the intestinal lymphatics by incorporating TU into chylomicrons composed of oleic acid and borage seed oil. Once absorbed, the pro-drug, TU, is metabolized by nonspecific esterases to undecanoic acid and testosterone. The capacity of the esterases appears to be saturated in humans and dogs because the AUC ratio of TU to T based on moles was ≥ 7 for both dogs and humans (see toxicokinetics in Section 6.1).

In lieu of conducting nonclinical absorption, distribution, metabolism, and elimination (ADME) studies with REXTORO, the Applicant submitted a review of some pertinent literature describing the ADME of testosterone and testosterone undecanoate. Review of the pertinent literature provided by the Applicant is provided after this summary. A full list of the Applicant's ADME citations is provided in Section 12.3.

Briefly absorption, distribution, metabolism, and elimination were not assessed with the Applicants product other than describing the pharmacokinetics of TU, T, DHTU, and DHT in dogs and men (see Toxicokinetics in Section 6.1). In general the publications suggest that lymphatic absorption is promoted when testosterone is esterified at the C17β-hydroxyl group with long chain fatty acids. Lipophilic vehicles aid intestinal lymphatic absorption and administration with food greatly aid oral absorption of TU into the intestinal lymphatics. However, TU is very poorly absorbed orally with bioavailability being well below 10% in rats, dogs, and humans. After absorption, a fraction of TU is metabolized in the intestinal wall to DHTU. TU and DHTU are distributed systemically where they are further metabolized to undecanoic acid, T, DHT, estradiol (E2), numerous androgenic metabolites, and glucuronide and sulfate conjugates. The half-lives of T and TU are roughly 10 to 100 minutes after they are in systemic circulation. In humans, TU and T are metabolized and eliminated primarily as androgen glucuronide conjugates in the urine within several hours of dosing. Undecanoic acid is an 11 carbon fatty acid that is metabolized by beta-oxidation and the tricarboxylic acid pathways (1).

Absorption

Rats

Noguchi et al. 1985 -

Lymphatic absorption of TU was investigated in fasted rats after oral dosing (23). Mesenteric lymph duct-cannulated male rats were given a single 15 mg oral testosterone equivalent dose of TU (~23.75 mg TU) (~64 to 88 mg/kg) and lymphatic fluid was collected over 24 hours. Several fatty acid vehicles were investigated and lymphatic absorption of T + TU was greatest with an oleic acid formulation. However,

very little TU was absorbed into the lymphatics. The combined concentration of T + TU in the lymph fluid was only 0.5% of the administered dose when TU was administered orally in oleic acid. In lymph fluid, the levels of TU far exceeded the levels of T in rats dosed with the oleic acid vehicle (numerical values not provided). Plasma exposure to TU after a 23.75 mg TU oral dose in comparison to exposure after a 388 μg IV TU dose revealed that the bioavailability of TU was only 0.4%. Because the oral bioavailability of TU was similar to the total TU + T exposure in the lymphatic fluid, it is likely that most of the TU is absorbed through the lymphatics. The potential for exposure by intraduodenal absorption into the portal circulation was assessed to ensure that this route was a minor route of exposure. TU was not detected in the portal vein plasma after intraduodenal TU dosing which supports the theory that TU is absorbed through the intestinal lymphatics. Likewise the levels of T in the portal vein plasma after intraduodenal T dosing were 24 times the levels of T following intraduodenal TU dosing also supporting the theory that TU is primarily absorbed through the lymphatics.

Coert et al. 1975—
Another study evaluated the androgenic activity of oral TU in rats, the potential for liver toxicity in rabbits, and the route of oral absorption for TU (24). In rabbits dosed orally with TU for 10 days at 10 mg/kg there was no effect on AST, ALT, or bromsulphalein clearance. However, the known liver toxin 17 α-methyltestosterone increased all of these liver toxicity biomarkers by 2- to 3-fold. Castrated rats were dosed orally with 0, 10, or 40 mg of TU in arachis oil or 0.5% gelatin microcrystalline suspension or 0 or 10 mg of T in arachis oil for seven days BID. TU in arachis oil increased the weight of the seminal vesicle, ventral prostate, and levator ani muscle by 2.5 to 5.6 fold compared to vehicle control. Organ weight gains were less with the testosterone formulation and the TU gelatin formulation compared to the TU arachis oil formulation. After 21 hours of in vitro incubation, ^{3}H-TU was stable in gastric juices but 30% hydrolyzed in intestinal juices (metabolites were not mentioned). Only 13% of the dose remained in the stomach and intestines of rats five hours after receiving a single 4 mg oral dose of TU in arachis oil. Intact and thoracic lymph duct cannulated rats were administered a single 4 mg oral dose of ^{3}H-TU in arachis oil and aortic plasma, hepatic portal plasma, and lymph fluid were assessed for radioactivity and thin layer chromatography was used to detect metabolites. Only 2% of the ^{3}H-TU dose was detected in the lymph fluid unmetabolized over a five hour cumulative sampling period. In lymph duct cannulated rats, TU and DHTU were detected in lymph fluid within 1.5 hours of dosing but they were not detected in the portal vein or aorta plasma, suggesting that TU is absorbed through the lymphatics and is metabolized to DHTU in the intestines. In intact rats, radiolabeled ^{3}H-TU and ^{3}H-DHTU were detected in the portal vein plasma and aorta plasma within 90 minutes of a single 4 mg oral dose of ^{3}H-TU. ^{3}H-TU and ^{3}H-DHTU were predominantly associated with chylomicrons in the plasma from the portal vein of intact rats within 90 minutes of a 4 mg dose of ^{3}H-TU. TU and DHTU were also weakly associated with plasma lipoproteins. Overall this study suggests that TU is inefficiently absorbed through the lymphatics, partially metabolized to DHTU in the intestines, and is pharmacologically active after metabolism to T without causing liver toxicity.

Dogs

Shackleford et al. 2003 -

Thoracic lymph duct-cannulated female dogs were used to investigate the lymphatic absorption of TU after oral dosing with two oral TU formulations that are marketed outside of the USA (25). Hepatic portal vein was also cannulated to assess serum levels. Dogs received an 80 mg dose of TU in the form of Andriol and Andriol Testocaps within 45 minutes of consuming a standard 5% fat meal. Lymph fluid and serum from the portal vein were assessed for TU, T, DHT, and DHTU over a 12 hour period. Dogs were also dosed IV with (^{2}H)-TU in Intralipid (an emulsion of egg phospholipids, glycerin, and soy bean oil) to determine the systemic pharmacokinetics of TU, T, and DHT (DHTU was not detected).

TU was not extensively metabolized following IV dosing (see Table below). The ratio of AUC exposure was 1:9:62 for DHT, T, and TU, respectively. TU, T, and DHT were rapidly eliminated after IV dosing with half-lives of 15, 32, and 39 minutes, respectively.

Pharmacokinetics in Female Dogs after IV (^{2}H)-TU Exposure

Mean (± S.E.) systemic serum pharmacokinetic parameters for [^{2}H]-TU, [^{2}H]-T, and [^{2}H]-DHT determined after a 10-min i.v. infusion (3.91 mg) of [^{2}H]-TU to dogs that simultaneously received an oral dose of 80 mg of TU administered as either Andriol (n = 4) or Andriol Testocaps (n = 4)

Compound	i.v. Parameter	Oral Andriol Group (n = 4)	Oral Andriol Testocaps Group (n = 4)	p Value[a]	Combined i.v. Data[b] (n = 8)
[^{2}H]-TU	C_{max} (nM)	1,250 ± 116	1,217 ± 77	0.81	1,234 ± 65
	$AUC^{0-\infty}$ (nM · min)	36,137 ± 3,835	36,720 ± 2,089	0.90	36,429 ± 2,024
	$t_{1/2}$ (min)	15.2 ± 0.7	16.4 ± 0.7	0.25	15.8 ± 0.5
	CL (l/min)	0.228 ± 0.022	0.218 ± 0.012	0.70	0.222 ± 0.012
	V_D (l)	4.98 ± 0.50	5.17 ± 0.44	0.78	5.08 ± 0.31
[^{2}H]-T	C_{max} (nM)	74.3 ± 6.5	81.1 ± 5.3	0.44	77.7 ± 4.1
	t_{max} (min)	25 ± 5	26 ± 4	0.90	26 ± 3
	$AUC^{0-\infty}$ (nM · min)	5,187 ± 452	5,746 ± 261	0.33	5,466 ± 264
	$t_{1/2}$ (min)	32.3 ± 4.5	31.8 ± 3.5	0.93	32.1 ± 2.7
[^{2}H]-DHT	C_{max} (nM)	6.3 ± 1.3	9.3 ± 1.4	0.16	7.8 ± 1.1
	t_{max} (min)	42 ± 11	37 ± 6	0.68	49 ± 6
	$AUC^{0-\infty}$ (nM · min)	418 ± 73	760 ± 145	0.08	589 ± 99
	$t_{1/2}$ (min)	38.7 ± 11.7	36.3 ± 4.7	0.86	37.5 ± 5.8

[a] p values are the result of the two-tailed Student's t test of the mean parameter estimates between the two formulations.
[b] The mean ± S.E. values for all study dogs (n = 8) was calculated because there was no statistically significant difference ($p > 0.05$) between Andriol and Andriol Testocaps for any of the measured parameters.

Andriol soft gelatin capsules contain 40 mg of TU, oleic acid, gelatin, glycerol, Karion 83, sodium ethyl hydroxybenzoate, sodium propyl hydroxybenzoate, titanium dioxide (E171),and iron oxide red (E172).
Andriol Testocaps soft gelatin capsules contain 40 mg of TU, lauroglycol FCC, castor oil, gelatin, glycerol, and sunset yellow (E110).
Table copied from Shackleford et al. 2003.

After oral dosing the systemic, lymphatic, and portal pharmacokinetics were fairly similar for Andriol and Andriol Testocaps.

Although the intestinal lymphatic absorption of TU was very low, first pass metabolism was essentially averted. After oral dosing only 3% of the TU dose was absorbed into the lymphatics and < 0.06% was absorbed into the hepatic portal serum (See table below). Specifically only 3% and 0.12% of the administered oral dose of TU were recovered in the lymph fluid as TU and DHTU, respectively. The Tmax for TU in lymph fluid was one hour and TU was essentially undetected in lymph within four hours of dosing. Approximately 80% of the triglyceride vehicle was recovered in the lymph fluid confirming the integrity of the lymphatic sampling. T and DHT were not detected in

lymph fluid. TU was the only analyte detected in the portal serum and it only accounted for < 0.06% of the oral dose. Overall roughly 98% of the systemic TU exposure was from lymphatic absorption.

Oral Bioavailability of TU in Lymph and Portal Plasma

The systemic availability of TU expressed as a percentage of the administered dose (mean ± S.E., $n = 4$) arising from lymphatic transport (F_{lymph}) and portal blood transport ($F_{portal\ blood}$), and as the total transport (F_{total}) in thoracic duct cannulated dogs after postprandial administration of 80 mg of TU as either Andriol ($n = 4$) or Andriol Testocaps ($n = 4$)

Availability of TU[a]	Andriol	Andriol Testocaps
F_{lymph} (% dose)	3.20 ± 0.46	2.85 ± 0.89
$F_{portal\ blood}$ (% dose)	0.054 ± 0.029	0.036 ± 0.015
F_{total} (% dose)	3.25 ± 0.48	2.88 ± 0.88

[a] No significant difference ($p > 0.05$) between any parameter.

Table copied from Shackleford et al. 2003

Pharmacokinetic modeling suggests lymphatic absorption of TU and consequent metabolism to T accounted for roughly 84% of the circulating T (see Table below).

Contribution Lymphatic Absorbed TU to Total Systemic Exposure of T

80 mg of TU as either Andriol or Andriol Testocaps

Formulation	Dog Number	Testosterone Undecanoate	Testosterone			Percentage of Contribution of Lymphatically Transported TU to the AUC^{total} for T
		$AUC^{lymph\ derived}$	$AUC^{lymph\ derived}$	$AUC^{measured}$	AUC^{total}	
		nM · min	*nM · min*	*nM · min*	*nM · min*	
Andriol	2	22,217	2,016	493	2,509	80.3
	4	22,067	4,035	792	4,827	83.6
	5	36,330	4,516	968	5,474	82.4
	7	19,338	4,054	550	4,604	88.1
	Mean ± S.E.	24,988 ± 3,838	3,655 ± 558	701 ± 110	4,354 ± 642	83.6 ± 1.6[b]
Andriol Testocaps	1	14,650	2,544	239	2,787	91.4
	3	26,025	4,652	246	4,898	95.0
	6	7,696	1,073	723	1,796	59.7
	8	46,321	6,453	677	7,130	90.5
	Mean ± S.E.	23,673 ± 8,442	3,681 ± 1,180	471 ± 132	4,153 ± 1,185	84.1 ± 8.2[b]

[a] The $AUC^{lymph\ derived}$ value for TU was used to determine the $AUC^{lymph\ derived}$ value for T according to eq. 4.
[b] No significant difference ($p > 0.05$) in any parameter between Andriol and Andriol Testocaps.

Table copied from Shackleford et al. 2003.

Humans

Horst et al. 1976 -

Four oral cancer patients with cannulated thoracic ducts were administered oral TU (100 mg ± ^{3}H-TU) in arachis oil and cream; blood, lymph, and urine were assessed for TU and metabolites (26). Tmax of radioactivity was 2.5 to 5 hours in the plasma and lymph. Roughly 9% of the radioactive dose was recovered in lymph fluid within 10 hours of dosing. TU and DHTU were detected in lymph suggesting that TU is metabolized in the intestinal wall to DHTU. Elimination of radioactivity in urine had a Tmax of 10 hours. Within 24 hours of dosing 40% of the radioactivity was recovered in

urine and this increased to 45-48% seven days after dosing. The primary metabolites in urine were glucuronide conjugates of T and androsterone.

Tauber et al 1986 -
The mean half-life of T in six women after a 1.5 mg/kg IV dose of T was 10 minutes (27). The mean oral bioavailability of T and TU were 3.56% and 6.83%, respectively, in 12 women who received a 25 mg oral dose of T delivered in miglyol 810 or a 40 mg oral TU dose in miglyol 810 (27).

Bagchus et al. 2003 and Schnabel et al. 2007 -
Food increases the oral absorption of TU and increased fat content of the meal also enhances absorption. In women, the AUC for TU, T, and DHT increased 279-, 11-, and 13-times, respectively, when 80 mg of TU (Andriol Testocaps) was taken with a standard meal versus administration in fasted women (28). Another study was conducted in 24 postmenopausal women who were administered a similar 80 mg dose of TU (Andriol Testocaps) within five minutes of consuming a fat-free, low-fat, standard-fat, or fatty meal (2). In terms of AUC, the low, medium, and high fat meal increase exposure to TU by 2-, 20-, and 25-fold (Table below). The AUC for DHTU increased 3-, 18-, and 25-fold in the low to high fat diet groups, respectively. The AUC for T increased 1.4-, 5-, and 5-fold in the low to high fat diet groups, respectively. The AUC for DHT increased 1.4-, 7- and 9-fold in the low to high fat diet groups, respectively. The effect of food in the women correlates with the findings in men treated with REXTORO (see human PK in Section 6.1). The ratio of TU to T based on moles of each analyte increase with the fat content with ratios of 1, 2, 6, and 7 in the fat-free to fatty diet groups, respectively.

Reference ID: 3604305

Food Effect on PK after a Single 80 mg Dose of TU in in Women

Parameter (units)	Meal A	Meal B	Meal C	Meal D
TU				
C_{max} (nmol/l)	20·2 (181)	47·8 (124)	372 (84·5)	382 (87·7)
t_{max} (h)	5·0 (2·0–11·0)	5·0 (2·0–7·0)	5·0 (2·0–7·0)	5·0 (2·0–12·0)
$AUC_{0-tlast}$ (nmol h/l)	41·7 (176)	103 (149)	848 (53·3)	1050 (46·7)
DHTU				
C_{max} (nmol/l)	10·4 (160)	22·2 (91·0)	150 (53·7)	174 (56·2)
t_{max} (h)	5·0 (3·0–12·0)	5·0 (4·0–8·0)	5·0 (2·0–8·0)	6·0 (2·0–12·0)
$AUC_{0-tlast}$ (nmol h/l)	27·1 (192)	66·8 (116)	479 (39·9)	677 (34·7)
Testosterone				
C_{max} (nmol/l)	4·65 (80·8)	7·10 (70·0)	27·3 (44·7)	27·0 (51·6)
t_{max} (h)	3·0 (1·0–11·0)	5·0 (1·0–8·0)	5·0 (2·0–7·0)	6·0 (2·0–12·0)
$AUC_{0-tlast}$ (nmol h/l)	30·7 (59·9)	43·5 (48·2)	146 (30·6)	154 (32·2)
DHT				
C_{max} (nmol/l)	1·50 (65·8)	1·89 (53·7)	6·67 (45·7)	6·74 (49·3)
t_{max} (h)	3·0 (1·0–12·0)	6·0 (1·0–10·0)	7·0 (3·0–9·0)	7·0 (4·0–14·0)
$AUC_{0-tlast}$ (nmol h/l)	7·62 (78·9)	11·0 (73·8)	49·5 (42·0)	57·9 (38·7)

Presented are geometric means (geometric CV%), except for t_{max}: median (min – max).
$n = 24$ except for treatment type A, where $n = 22$ for TU and DHT and $n = 23$ for DHTU.
Meal A – "fat-free", Meal B – low-fat, Meal C – normal meal, Meal D – fatty meal.
Table copied from Schnabel et al. 2007.

Metabolism and Excretion

Rats

Farthing et al. 1982 -

The intestinal metabolism of T was assessed in male rats and in gastrointestinal tissue cultures (29). Male rats were dosed with 50 nM ^{3}H-testosterone into a closed loop of proximal jejunum and hepatic portal serum levels of metabolites were assessed within 10 minutes of dosing (Tmax = 5 min). Testosterone was metabolized to androstenedione, DHT, and an unknown metabolite in tissue cultures from the jejunum and everted sacs of the jejunum. Rapid and efficient metabolism of testosterone was observed in vivo. In the portal blood, testosterone only accounted for 3-6% of the radioactivity while androstenedione accounted for 43-64% of the radioactivity, the remaining metabolites were not identified (Table below). Similar findings were found in the jejunum tissue and luminal fluid. The activity of the enzyme responsible for metabolism of T to androstenedione (17β-hydroxysteroid dehydrogenase) was high in the mucosa of the stomach and duodenum and much lower in the jejunum, ilium, and colon. This suggests that the intestines readily metabolize testosterone primarily to androstenedione, a less potent androgen than T. This study suggests that absorption of

T or metabolism of TU to T in the gut is not anticipated be to a large source of T in systemic circulation.

Table 1 *[³H]-Testosterone metabolites in portal blood, gut lumen and gut tissue after introduction of [³H]-testosterone into a closed loop of proximal rat jejunum*

Sampling period (min)	Portal blood			Jejunum					
	% Total metabolites			Luminal fluid % Total metabolites			Tissue % Total metabolites		
	% T	% A	% Others	% T	% A	% Others	% T	% A	% Others
0-2	4·4	63·5	32·1	—	—	—	—	—	—
2-4	4·1	46·2	49·7	—	—	—	—	—	—
4-6	3·3	42·7	54·0	—	—	—	—	—	—
6-8	3·5	48·3	48·2	—	—	—	—	—	—
8-10	5·5	47·7	48·4	17·5	43·4	39·1	14·7	57·1	28·2

T, testosterone; A, androstenedione.

Table copied from Farthing et al. 1982.

Geelen et al. 1977 -
Metabolism of T and TU was assessed in the gastrointestinal tract of rats in vivo and in primary tissue cultures (30). Rats were given a single 4 mg oral dose of ^{3}H-TU or ^{3}H-T in a 0.5% gelatin solution and portal plasma was assessed for metabolites 90 minutes after dosing. Tissue preps from the small intestine, cecum, and colon/rectum of rats were incubated with 1 μg or 5 μg of ^{3}H-TU or ^{3}H-T for 3 hours. The metabolites of T and TU were similar in vivo and in vitro. Eleven of the thirteen TU metabolites identified in gastrointestinal tissue cultures were also detected in hepatic portal serum of rats. Metabolism of TU in the tissue cultures was most pronounced in the small intestine in comparison to the stomach, cecum, and colon/rectum. TU was metabolized to T throughout the length of the GI tract (stomach, small intestine, cecum, and colon/rectum cultures). A time course study with rat intestine culture found that T was the first metabolite of TU generated and it appeared within 2.5 minutes of incubation.

Metabolites Identified in Rat Plasma or Tissue Culture

1	5α-dihydrotestosterone undecanoate
2	testosterone undecanoate
3	5α-androstanedione
4	androstenedione
5	androsterone
6	epi-androsterone
7	5α-dihydrotestosterone
8	testosterone
9	5β-androstane-3β,17β-diol
10	5α-androstane-3α,17β-diol
11	5α-androstane-3β,17β-diol
12	5β-androstane-3α,17β-diol
13	not identified
14	not identified

Table copied from Geelen et al. 1977.

Reference ID: 3604305

Humans –

Sandberg and Slaunwhite 1956 -

Metabolites of testosterone were assessed in the plasma, bile, and urine of 20 male or female patients (8 healthy, 7 with prostate or breast cancer, and 5 with cholecystectomy due to bile fistula) (31). Patients received a single IV dose of 4-C^{14}-testosterone and blood was sampled for 4 hours, bile (5 cholecystectomy patients) and urine were collected for 48 hours, and feces were collected for 5 days. There was a large variance in all measures between individuals which may have been due to complications with their disease. Radioactivity was rapidly cleared from the plasma. There was a biphasic clearance of radioactivity associated with the unconjugated steroids from the plasma with the first half-life of 11 minutes and the second half-life of 100 minutes. Within 15 minutes of dosing, the glucuronide conjugates exceeded the unconjugated steroids by approximately threefold in the plasma. In plasma the sulfate conjugates were only 5% of the glucuronide conjugates. Approximately 50% of the radioactive dose was excreted in urine within 4 hours. Excluding the bile fistula patient, the average amount of radioactivity excreted in urine after 48 hours was 89% of the radioactive dose. Radioactivity excreted in urine was primarily glucuronide conjugates. Within 24 hours radioactivity excreted in bile only accounted for 11% to 14% of the dose and it consisted primarily of glucuronide and sulfate conjugates (n=4). Elimination of radioactivity in feces in the non-fistula patients only accounted for 6% (2-15% range) of the dose over five days of sampling.

Hellman et al. 1956 -

A very limited clinical study was conducted in men and women dosed orally or intravenously with 4-C^{14}-T to investigate absorption and elimination (32). Some patients were healthy others had significant disease and it is unclear if the disease state effected the findings. Dosing was not clear but appeared to be 2.5 to 4.2 mg IV or 1.5 to 4.2 mg orally. Radioactivity was eliminated in urine (50-61%) in two men and a woman dosed IV and in a male and female dosed orally (61-76%) within 24 hours of dosing. No radioactivity was detected in the lymph of one thoracic duct cannulated female after a single 4.2 mg oral dose of T but she excreted 60% of the dose in urine suggesting that lymphatic absorption is not a significant route of absorption. Excretion of radioactivity in bile was limited to 3-10% of the dose in a single male and female after IV dosing. Overall this study suggests after oral dosing T is not well absorbed into the intestinal lymphatics but is well absorbed into the hepatic portal system and T and its metabolites are eliminated primarily in urine.

Ishimaru et al. 1978 -

The metabolism of T to DHT-glucuronide in the liver was investigated in five young and five elderly men (33). Men received constant infusion of ^{3}H-T and 4-^{14}C-DHT and blood was sampled from the ascending aorta and hepatic vein 105 and 120 minutes after infusion began to determine unconjugated (free DHT) and conjugated DHT levels. There was no effect of age on the findings. The authors explained that if the unconjugated DHT was formed from ^{3}T in the liver, then the ^{3}H:^{14}C ratio of free DHT in the hepatic vein (leaving the liver) should be greater than that in the arterial blood

Reference ID: 3604305

sample (entering the liver). Alternatively, if unconjugated DHT is not formed in the liver, then the ^{3}H:^{14}C ratio should be the same in the hepatic vein and arterial blood. The ratios of ^{3}H:^{14}C in unconjugated DHT were similar in the arterial and venous blood suggesting that T is not converted to unconjugated DHT in the liver. However, the ratio of ^{3}H:^{14}C in conjugated DHT was high in the hepatic vein suggesting that the liver is a site of DHT glucuronidation. Together the authors suggest that T is rapidly converted to DHT and then glucuronidated all in the liver.

Shinohara et al. 1980 -
Absorption, metabolism, and elimination of T was assessed in two men after a single 20 mg oral dose of ^{3}H-T (34). Urine samples were collected over 24 hours. Thirty percent of the dose was excreted as glucuronide metabolites of T (androsterone glucuronide and etiocholanolone glucuronide) within 24 hours but most of the dose was excreted within 4 hours of dosing. The authors suggest that extensive metabolism of T may be the reason why circulating levels of T are not meaningfully enhanced by oral T dosing.

Peng et al. 2002 -
Urine and plasma metabolites of TU were assessed in six men after a single 120 mg oral dose (35). Plasma and urine samples were collected over 24 hours. This paper only assessed TU, T, and specific metabolites of T (see table below). TU was generally detected in the plasma from 0.5-6 hours after dosing (numerical values not provided). Strangely, despite large exposure to TU, the plasma levels of T did not appear to increase from baseline levels. Overall 44% of the administered dose was recovered in urine as glucuronide conjugates within 24 hours and the primary metabolites were androsterone glucuronide and epitestosterone glucuronide which is consistent with oral T dosing.

TU Recovery in Urine (% of Dose) 0-24 hr

	% (Mean ± SE, n = 5) Subjects # 1, 2, 4, 5, 6
TG	1.46 ± 0.32
EG	0.03 ± 0.00
AG	23.78 ± 1.57
EtG	16.26 ± 2.56
DHTG	0.10 ± 0.02
5β,3αDiolG	2.00 ± 0.51
5α,3αDiolG	0.35 ± 0.08
Total recovery	43.98 ± 3.34%

Table copied from Peng et al. 2002.
TG- testosterone glucuronide, EG- epitestosterone glucuronide, AG – androsterone glucuronide, etiocholanolone glucuronide, DHTG – DHT gulucronide, 5β-androstane-3α,17β-diol glucuronide, 5α-androstane-3α,17β-diol glucuronide

Reference ID: 3604305

Baume et al. 2006 -
Urinary excretion of testosterone, androsterone, and etiocholanolone were assessed in seven men who were given 80 mg TU three times per week for four weeks (36). Urine was assessed for steroid levels over 24 hours on day 1 and 24 and ten days after the last dose (day 39). The Applicant noted this study because no accumulation of metabolites was observed in urine, but the dosing was every other day so the relevance to REXTORO is unclear because REXTORO is to be administered more than once daily.

Distribution - male reproductive tissues and saliva

Rats
Horst et al. 1980 -
The absorption, metabolism, and distribution of ^{3}H-TU was assessed in castrated rats which were orally dosed with ^{3}H-TU in arachis oil (37). Distribution assessment was limited to the prostate, seminal vesicle, bulbocavernosus muscle, and skeletal muscle. Recovery of radioactivity in the form of undecanoate-bound androgens or free androgens was 54% in the plasma and up to 91% in the tissues. The radiolabel Tmax in plasma was 2.5 hours. Two equivalent radiolabel Tmax values were observed in the prostate (2.5 and 5 hrs) and the prostate Cmax exposures were 50% of the plasma Cmax. Several metabolites of TU were identified in plasma and tissues including testosterone, DHT, DHT-TU, 3β-diol, 3α-diol, epiandrosterone, androsterone, 4-androstenedione, and 5α-androstenedione (Table below). TU and DHTU were found in plasma at equal levels. Plasma levels of undecanoate-bound androgens (TU and DHTU) dominated over undecanoate-free metabolites by a factor of two while in plasma metabolites free of the undecanoate side chain (testosterone, DHT, and others) dominated over undecanoate bound androgens by a factor of 3 to 5 in tissues (prostate, seminal vesicle, bulbocavernosus muscle, and skeletal muscle) (see Table).

Distribution of TU & Metabolites in Castrated Rats 2.5 hrs after ^{3}H-TU Oral Dose (Percent of Total Radioactivity Detected in Each Organ)

	Plasma	Prostate	Seminal Ves.	Bulbocav.	Skeletal Mus.
TU	30	12	8	10	13
5α-DHT-TU	36	9	10	11	13
Total Undecaonoates	66	21	18	21	26
T	14	9	11	28	25
5α-DHT	4	47	34	9	-
3α-diol	5	4	8	17	22
3β-diol	3	-	4	4	4
Epiandrosterone	2	-	4	5	-
Androsterone	-	4	12	-	-
4-androstenedione	2	5	-	4	4
5α-androstenedione	-	5	-	-	-
Total Metabolites free of Undecanoate	34	79	82	79	74

Table adapted from Horst et al. (37).
Tissues- plasma, prostate, seminal vesicle, bulbocavernosus muscle, skeletal muscle.

Testosterone was the most abundant non-esterified androgen in the plasma, bulbocavernosus muscle, and skeletal muscle accounting for 14-28% of the radioactivity. However, DHT was the most abundant non-esterified androgen in the prostate and seminal vesicle accounting for 34-47% of the radioactivity which is likely due to local metabolism of T to DHT by 5α-reductase. *In vitro* experiments with plasma, prostate, and muscle homogenates suggested that TU is not appreciably metabolized in the plasma (94% remained as TU) or muscle (80% remained as TU, 11% metabolized to T). However, the prostate homogenates had considerable capacity to metabolize TU to testosterone since only 58% remained as TU while 27% was metabolized to T. This implies that hydrolysis of TU may occur in some target tissues. A molecular target for TU was not identified in in vitro studies attempting to find a high affinity cytosolic binding protein for TU. This suggests that metabolism of TU may be required to have pharmacological activity unless its activity is mediated through membrane associated or nuclear targets.

Clinical-

Marks et al. 2006 -

In a randomized trial, hypogonadal men with baseline T levels and a prostate biopsy received an intramuscular injection of 150 mg testosterone enanthate every 2 weeks for 6 months (n=21) or placebo (n=19) (38). Six months of TE therapy resulted in elevation of serum T to the eugonadal range, and elevation in serum DHT, E2, hemoglobin, hematocrit, PSA and decreased LH. Despite the elevation in serum T and DHT, intraprostatic levels of T and DHT were not affected and prostate volume, voiding symptoms and urinary flow rates were not affected by TE therapy.

Page et al. 2011 -

Daily transdermal exposure to DHT in 12 healthy men for one month resulted in a seven fold increase in serum DHT, decrease in serum testosterone (-50%), decrease in E2 (no numbers provided) and LH (-25%)(39). Dosing did not increase intraprostatic levels of T or DHT and did not affect PSA levels, prostate volume, or androgen regulated gene expression in the prostate epithelium.

Schurmeyer et al. 1983 -

Plasma and serum levels of T were investigated in 12 eugonadal and 8 hypogonadal men who received a single 120 mg oral dose of TU in arachis oil after a standard breakfast (40). The concentration vs. time profile for T in serum and saliva were parallel and levels of T in saliva were roughly 67% of the serum levels. Concentrations were highly variable between men in both fluids and T returned to baseline levels 2 and 4 hours after Tmax in hypogonadal and eugonadal men, respectively. Saliva levels of T were assessed as a surrogate for levels of fee testosterone absorbed in tissues. The authors speculate that because the ratio of salivary T to serum T remains constant over time, the T levels in tissues is due to absorption of T from serum and not from absorption and metabolism of TU in the target tissue. This is speculative.

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5.2 Toxicokinetics

Exposure to testosterone is usually based on plasma levels which incorporate free and protein bound testosterone and excludes the fraction that is bound to blood cells. The cell bound testosterone fraction is roughly 15-30% of testosterone is bound by human red blood cells (41 and 42). In plasma, testosterone and it's metabolites were highly protein bound within 15 minutes (71-99%) and 60 minutes (96-99%) of a single IV $4C^{14}$-T dose in 10 patients (41). In plasma of men, roughly only 2% of testosterone is unbound to proteins (free) while 44% is bound to sex hormone binding globulin (SHBG) and 50% is bound primarily to albumin (43). The binding affinity of SHBG for testosterone and dihydrotestosterone is so great that this store of androgen is considered biologically unavailable (44). However, free testosterone and albumin bound testosterone are considered bioavailable because testosterone is weakly bound to albumin.

Toxicokinetics in dogs dosed orally with TU and men dosed with REXTORO is described at the end of the 13-week dog toxicology study in section 6.1.

6 General Toxicology

6.1 Repeat-Dose Toxicity

Study Title: 13-Week Oral (Capsule) Toxicity Study of Testosterone Undecanoate (TU) in Male Beagle Dogs

Study no.:	CLAR-PC-1101
Study report location:	Original Submission Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	First dose August 31, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Testosterone undecanoate Lot LBN3040-112 (96.6% prior to first dose and 93.6% after study termination). Lot LBN3040-129 (98.4% prior to first dose and to 96.6% after study termination). Testosterone was not detected in the dosing solution prior to the first dose but analysis after completion of the study found testosterone at 1.34% (LBN3040-112) and 0.28% (LBN-3040-129). TU and testosterone were not detected in the placebo formulation.

Key Study Findings

Male dogs were dosed orally with TU at 0, 38 (LD), or 126 (HD) mg/kg/BID for 13 weeks. Recovery was assessed four weeks after the last dose in the control and HD groups.

Findings were restricted to androgen responsive tissues and are consistent with excessive exposure to an androgen

- Serum cholesterol declined in the LD (-45%) and HD (-48%) groups but it resolved after drug withdrawal.
- Adrenal cortex atrophy of moderate to marked severity was observed in all TU dosed animals and this correlated with a ≥ 30% decrease in adrenal weights. Even though the organ weights recovered four weeks after dosing ceased, the adrenal cortex atrophy was still observe but the severity was reduced from marked to minimal/mild severity.
- Testes atrophy/degeneration was observed in all dogs in the LD group (marked) and HD group (min-moderate). Dogs did not recover. The severity in the HD group increased to severe in all dogs after the four week recovery period. The severity of the pathology correlated with the severity of testicular weight loss at week 13 and after recovery.
- Epididimes – hypospermia was severe in all dogs in the LD group and moderate/marked in 2/4 dogs in the HD group. Hypospermia remained severe in all dogs in the HD group at the end of the recovery period.
- Marked prostate hypertrophy was observed in all dogs in the LD and HD group at week 13 of dosing this finding completely resolved after recovery. Increased prostate weight correlated with the extent of prostate hypertrophy and the reversibility of the finding.
- Testosterone exposure based on AUC in the LD and HD groups were elevated 8 and 21 times the baseline level, respectively. Based on AUC, dogs in the LD and HD groups were exposed to 2 and 8 times the testosterone exposure in men who were on a high fat diet and received the maxim anticipated dose.
- The Cmax for testosterone in both dose groups of dogs was greater than 48 times the baseline level. Based on Cmax the exposure to testosterone in the LD and HD groups were 6 and 12-16 times the exposure in men on a high fat diet at the maximum anticipated dose, respectively.
- The TU AUC in the LD and HD groups was roughly two and 5-6 times the exposure in men on a high fat diet at the maximum anticipated dose, respectively.
- TU was inefficiently metabolized to testosterone. Based on AUC the exposure to TU ranged between 7 to 10 times the exposure to testosterone for all dose groups. However, this does not appear to be a safety issue since there were no toxicities reported that are not androgen related.

Methods

Doses:	0, 38, or 126 mg/kg BID
Frequency of dosing:	BID approximately 30 minutes after feeding Approximately 12 hours between doses

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Methods

	Dosing occurred daily for 91 days
Route of administration:	Oral gelatin capsule
Dose volume:	0, 0.2, or 0.67 mL/kg/dose
Formulation/Vehicle:	Not reported in the study report but the Applicant's nonclinical summary indicated that they used their final commercial proprietary SEDDS formulation. Formulation of the placebo control was not mentioned but it is assumed to be the testosterone free clinical formulation.
Species/Strain:	Beagle Dogs
Number/Sex/Group:	4/males/group
Age:	Approximately 12 months old
Weight:	8.50 to 10.17 kg prior to first dose
Satellite groups:	3/male dogs/ placebo and 126 mg/kg group for recovery assessment
Unique study design:	Recovery period was four weeks after last dose
Deviation from study protocol:	Pharmacokinetic assessment was conducted under "general principles of GLP". (b) (4) conducted the pharmacokinetic analysis at their (b) (4) they are a CLIA-certified laboratory with a quality assurance program. This does not appear to have affected the study findings. Analysis of degradants in the drug product was not conducted under GLP/GMP but analysis of TU in the drug product was conducted under GLP/GMP so this does not appear to be a major deviation.

Observations and Results

Dose Selection
The doses were chosen because they were estimated to be three and ten times the maximum anticipated clinical dose (475 mg TU BID). The dose multiples calculated prior to initiating the study assumed an average human body weight of 70 kg.

Mortality
No mortality

Clinical Signs
Clinical signs were observed each day between 1 to 2 hours after the first daily dose.

No remarkable findings were reported.

Body Weights
Body weight was assessed prior to the first dose, and weekly throughout the study. Animals were fasted prior to the scheduled necropsy and the fasted body weight was used to calculate organ-to-body weight ratios.

No treatment related effects were observe on body weight or body weight gain during the study or during the four week recovery period.

Mean Body Weight			
	0	38 mg TU /kg BID	126 mg TU /kg BID
Week 0 (kg)	9.30	9.22	9.27
Week13 (kg)	10.27	9.82	10.23
Recovery Week 0	9.75	-	9.42
Recovery Week 3	9.83	-	9.50

Feed Consumption
Food consumption was not measured. Dogs were feed 200 g of Teklad certified canine diet (#2025) every 12 hours.

Ophthalmoscopy
Indirect funduscopic examinations were conducted prior to the first dose and prior to scheduled necropsy.

No treatment related effects were reported.

ECG
Six lead ECG was performed prior to study initiation on all animals. During the last week of dosing a single lead II ECG was conducted on all animals. The ECG exam in the last week of the study was conducted at "the end of the dosing period" which is interpreted to mean at C_{min}. The timing of the ECG assessment relative to Tmax was not described.

No adverse waveforms were reported. QTc was slightly lower in the LD group compared to control but this is unlikely to be due to treatment because it was not different from the value prior study initiation and no effect was observed in the HD group.

Hematology
Hematology was assessed prior to the first dose, at the end of the treatment period, and at the end of the recovery period. No clear treatment related findings were reported.

Compared to time matched controls, there was a slight increase in eosinophils and monocytes in both TU groups. Also WBCs and neutrophils were elevated in the high dose group only. However, these findings are not clearly treatment related. The values for these finding in the control group decreased from the pre-dose period to week 13. Although the percent change relative to time matched control increased for these values in the TU groups at week 13, it is because the control values declined for these

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parameters at week 13 not because of effects in the TU group. The dogs recovered from the effect after the recovery period.

Hematology (% Change Relative to Time Matched Control)				
	Time	0 mg/kg	38 mg/kg	126 mg/kg
WBCs (10^3 / μL)	Pre-dose	12.55 ± 4.29	10.49 ± 2.55	11.35 ± 1.95
	Week 13	8.93 ± 1.45	8.76 ± 1.67	12.70 ± 2.47 (+42%*)
	Recovery	8.01 ± 1.72	ND	6.54 ± 1.0 (-18%)
Neutrophils (10^3 / μL)	Pre-dose	8.40 ± 3.79	6.79 ± 2.62	7.28 ± 1.82
	Week 13	5.52 ± 1.41	5.29 ± 1.74	8.56 ± 2.14 (+55%*)
	Recovery	5.15 ± 2.04	ND	4.22 ± 0.77 (-18%)
Monocytes (10^3 / μL)	Pre-dose	0.81 ± 0.5	0.63 ± 0.2	0.69 ± 0.2
	Week 13	0.48 ± 0.16	0.64 ± 0.08 (+33%)	0.75 ± 0.18 (+58%*)
	Recovery	0.33 ± 0.15	ND	0.27 ± 0.08 (-18%)
Eosinophils (10^3 / μL)	Pre-dose	0.31 ± 0.18	0.37 ± 0.05	0.32 ± 0.10
	Week 13	0.28 ± 0.12	0.42 ± 0.15 (+50%)	0.44 ± 0.10 (+57%*)
	Recovery	0.31 ± 0.15	ND	0.34 ± 0.14 (+9%)
Statistically different from time matched control group, * P < 0.05. ND – not determined. N = 7, 4, and 7 in the control, LD, and HD groups, respectively, during the pre-dose and week 13 periods and N = 3 in the control and HD recovery groups.				

Clinical Chemistry

Clinical chemistry was assessed prior to the first dose, at the end of the treatment period, and at the end of the recovery period.

The only clear treatment related finding was a decrease in cholesterol in the LD (45%) and HD (48%) groups that resolved after dosing ceased.

Triglycerides were lower in the LD and HD groups compared to the time matched control at week 13. However, triglyceride values were either not different from their pre-dose levels within each group or the TU group values were not different from the control group prior to the first dose so this finding is inconclusive.

ALT values were not elevated to a statistically significant extent at the group mean level but it was elevated 2- to 3-fold above the pre-dose levels in two dogs in the HD group. Although this was correlated with a 70-78% increase in AST in these same two dogs, no

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effect was observed on LDH in these same dogs and there was no effects on AST or LDH at the group mean level of so the findings are inconclusive.

Creatinine was elevated 33% in the LD and HD groups compared to the time matched control but this does not appear to be a treatment related effect because the creatinine levels in the control group dropped 14% from baseline while the levels in the TU groups increased 14% from baseline. Additionally the levels of creatinine in the control and HD TU group at recovery were the same as in the TU groups at the end of the dosing period.

Clinical Chemistry (% Change Relative to Time Matched Control)				
	Time	0 mg/kg	38 mg/kg	126 mg/kg
Cholesterol (mg/dL)	Pre-dose	140 ± 23	142 ± 6	143 ± 15
	Week 13	157 ± 19	86 ± 14* (-45%)	81 ± 7* (-48%)
	Recovery	147 ± 31	ND	136 ± 8
Triglycerides (mg/dL)	Pre-dose	37 ± 6	45 ± 11	38 ± 9
	Week 13	49 ± 10	36 ± 5* (-27%)	35 ± 3* (-29%)
	Recovery	47 ± 23	ND	29 ± 2
ALT (U/L)	Pre-dose	28 ± 5	31 ± 14	37 ± 8
	Week 13	29 ± 8	33 ± 5	56 ± 38 (+93%)
	Recovery	25 ± 4	ND	36 ± 14
Creatinine (mg/dL)	Pre-dose	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1
	Week 13	0.6 ± 0.1	0.8 ± 0.0* (+33%)	0.8 ± 0.1* (+33%)
	Recovery	0.8 ± 0.0	ND	0.8 ± 0.1
Statistically different from time matched control group, * P < 0.05. ND – not determined. N = 7, 4, and 7 in the control, LD, and HD groups, respectively, during the pre-dose and week 13 periods and N = 3 in the control and HD recovery groups.				

Urinalysis
Urine was collected at necropsy for urinalysis. No treatment related effects were reported.

Gross Pathology
Treatment related effects include decreased testes and adrenal size and increased prostate size. Both testes were described as small in 4/4 LD dogs and 3/4 HD dogs and the testes remained small in 3/3 HD dogs after the recovery period. The adrenals were small in 4/4 LD dogs and 1/4 HD dogs. Adrenal pathology was not observed in dogs after the recovery period. The prostate was enlarged in all TU treated dogs but the dogs recovered from this.

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Gross Pathology - Incidence					
Finding	Week 13 (n=4/group)			Recovery (n=3/group)	
	0 mg/kg	38 mg/kg	126 mg/kg	0 mg/kg	126 mg/kg
No gross lesions	4	0	0	0	0
Adrenals – small - bilateral	0	4	1	0	0
Testes – small - bilateral	0	4	3	0	3
Epididymides - firm	0	1	0	0	0
Prostate - enlarged	0	4	4	0	0
Urinary Bladder – wall thickened – fluid yellow/cloudy	0	1	0	0	0

Organ Weights

Adrenal and testes weights were reduced in both TU groups while prostate weight was elevated in both TU groups. Adjusting organ weights to compensate for differences in body or brain weight had no significant effect on the findings. Therefore, organ weights discussed below are described as body weight adjusted unless otherwise noted.

Adrenal weights were depressed in the LD (-35%) and HD (-30%) groups but they were not affected after four weeks of drug withdrawal. Testes weights were severely depressed in the LD (-72%) and HD (-41%) groups and they remained depressed in the HD (-49%) group four weeks after dosing ceased. The prostate weight increased in the LD (+279%) and HD (+244%) groups but this did not persist after the four week drug withdrawal period. The thyroid weights were reduced 54% in the LD group and 27% in the HD group but it was only statistically significant in the low dose group and there was no histological correlate. Thyroid weights were not affected in the HD group after the four week recovery period.

Slight changes in heart and liver weight were observed in the HD recovery group but not in dogs assessed directly after the cessation of dosing so these findings are inconclusive.

Organ Weight						
		Week 13 (n=4/group)			Recovery (n=3/group)	
		0 mg/kg	38 mg/kg	126 mg/kg	0 mg/kg	126 mg/kg
Body Weight	Absolute (kg)	10.1	9.7	10.5	9.9	9.1
Brain Weight	Absolute (g)	73.5	69.8	72.7	70.4	76.6*
Adrenal	Absolute (g)	1.358	0.883*	0.949*	1.173	1.016
	Body Wt. Norm	0.014	0.009*	0.009*	0.012	0.011
	Brain Wt. Norm	1.86	1.27*	1.31	1.66	1.33
Testes	Absolute (g)	13.20	3.55*	8.18*	11.72	5.60
	Body Wt. Norm	0.132	0.036*	0.078*	0.119	0.061
	Brain Wt. Norm	17.9	5.1*	11.2*	16.6	7.3
Prostate	Absolute (g)	7.10	25.61*	25.12*	6.40	5.46
	Body Wt. Norm	0.070	0.265*	0.241*	0.065	0.060
	Brain Wt. Norm	9.7	37.1*	34.9*	9.1	7.2
Thyroid	Absolute (g)	1.368	0.602*	1.003	0.708	0.655
	Body Wt. Norm	0.013	0.006*	0.010	0.007	0.007
	Brain Wt. Norm	1.88	0.86*	1.37	1.01	0.86
Heart	Absolute (g)	81.0	82.7	84.9	85.1	72.6*
	Body Wt. Norm	0.803	0.848	0.810	0.861	0.804
	Brain Wt. Norm	111	118	117	121	95*
Liver	Absolute (g)	315.0	264.3	335.8	264.3	242.9
	Body Wt. Norm	3.11	2.71	3.21	2.67	2.67
	Brain Wt. Norm	430	378	463	375	318*
Statistically different from control group, $p \leq 0.05$. Adrenals, brain, heart, kidneys, liver, prostate, spleen, testes, and thyroids were the only organs weighed. Paired organs were weighed together.						

Histopathology
Adequate Battery: yes

Peer Review: No, only one board certified pathologist was listed in the report.

Histological Findings
All adverse histology findings are consistent with excessive androgen exposure. Atrophy of the adrenal cortex, atrophy of the testes, epididymal hypospermia, and prostate hypertrophy were observed in the low and high dose groups.

Adrenal cortex atrophy of moderate to marked severity was observed in all dogs in the LD and HD groups at week 13 but the severity declined to minimal to mild in all of the dogs in the HD group after the four week recovery period. This finding is consistent with the 30%-35% reduction in adrenal weight that was observed in both TU groups after 13 weeks of dosing and consequent weight recovery after drug withdrawal.

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Testes atrophy/degeneration, described as loss of the spermatogenic epithelium, was observed in all dogs dosed with TU and it did not resolve in intensity or incidence after the recovery period. Testes atrophy was marked in the LD group and minimal to mild in the HD group at week 13 but was marked in the HD animals after the four week recovery period. It is unclear why the severity in the HD animals in the main group had lower severity than the LD group animals and HD group recovery group. The extent of testicular atrophy in each group correlated with the suppression in testes weights. The lack of recovery of the testes weight also correlated with the histological findings.

Severe hypospermia was observed in the epididymides all of the dogs in the LD group but it was moderate to market severity in 2/4 dogs in the HD groups. However, it was observed at a severe intensity in all dogs in the HD group at the end of the recovery period. The incidence and severity correlated with the testicular atrophy findings. Epididymal organ weights were not assessed.

Marked prostate hypertrophy was observed in all LD and HD group dogs at week 13 of dosing but they fully recovered from this finding. Increased prostate weight correlated with the extent of prostate hypertrophy and the reversibility of the finding. Prostate atrophy was observed in all three dogs in the HD group four weeks after the last dose. Prostate atrophy in the recovery period is likely a compensatory response to the testosterone dependent hypertrophy observed during the dosing period.

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Histopathology - Incidence							
Organ	Finding	Severity	Week 13 (n=4/group)			Recovery (n=3/group)	
			0 mg/kg	38 mg/kg	126 mg/kg	0 mg/kg	126 mg/kg
Adrenal	atrophy	min					1
		mild					1
		mod		2	1		1
		marked		2	2		
		severe			1		
		total	0	4	4	0	3
	mineralization	mod		1			
	vacuolation	min		1	2		
Epididymides	hypospermia	mod			1		
		marked			1		
		severe		4			3
		total	0	4	2	0	3
Prostate	atrophy	mod					1
		marked					2
		total					3
	hypertrophy	mild				1	
		marked		4	4		
		total	0	4	4	1	0
Testes	atrophy / degeneration	min			3	1	
		mild			1		
		marked		4			3
		total	0	4	4	1	3

Toxicokinetics

Serum samples were collected for toxicokinetics of testosterone (T), testosterone undecanoate (TU), dihydrotestosterone (DHT), and dihydrotestosterone undecanoate (DHTU) pre-dose, 0.5, 1, 2, 4, 6, 8, and 12 hours after the first daily dose on day 1, 45, and 90. Serum samples were assessed for toxicokinetics of cortisol in the placebo and high dose groups only. Blood samples were treated with sodium fluoride to inhibit esterase activity and potassium oxalate as an anticoagulant. The exposure to all analytes was highly variable between animals. In general the rank order of exposure was TU >> T > DHTU >> DHT.

Exposure multiples discussed below are derived from the exposure in dogs relative to the exposure in men who received a single 475 mg TU dose after a high fat diet. This exposure comparison is a worst case scenario because fat content of the diet had a significant effect on Cmax and AUC in men (see clinical pharmacokinetics below the

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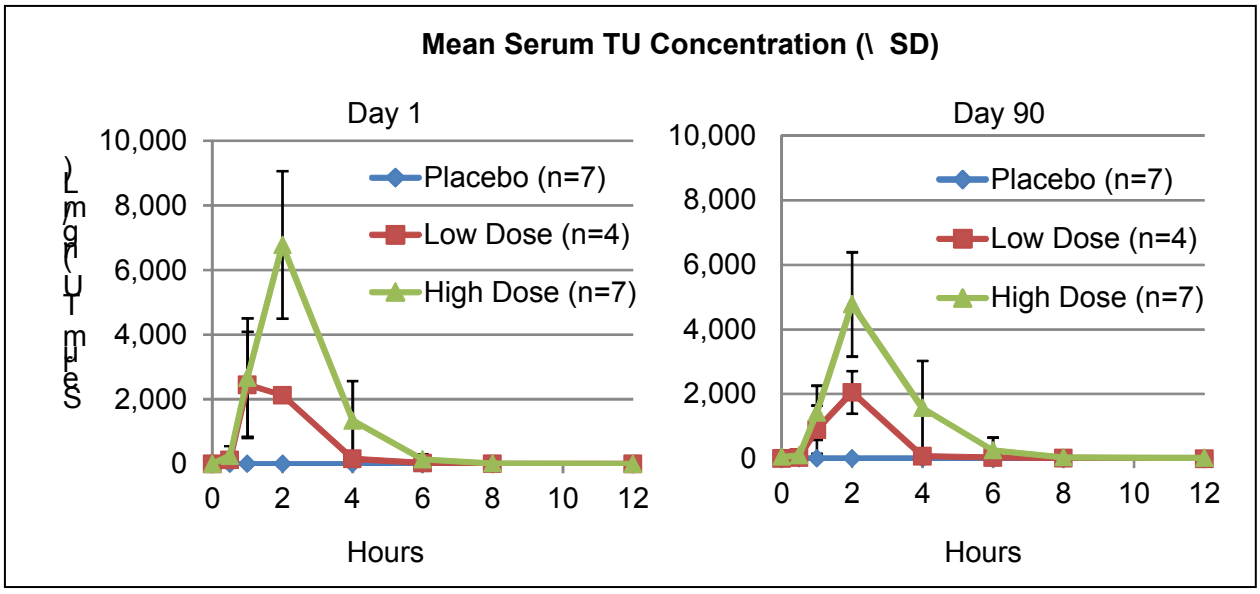
nonclinical data). The mean Cmax for TU in the food study in men ranged four-fold from 184 in the fasted group to 759 ng/mL in the high fat group. Similarly the mean AUC for TU ranged five-fold in men, from 466 ng-hr/mL in fasted men to 2,404 ng-hr/mL in men fed a 50% fat meal. Pharmacokinetics in men is described after the findings in dogs.

TU

Exposure to TU was dose proportional and did not accumulate with repeated dosing. The half-life and Tmax were roughly 1 to 2 hours suggestive of rapid absorption and elimination (see figure below).

The TU/T ratio was very large for both Cmax and AUC. The AUC and Cmax values used for the TU/T ratio are based on moles of each analyte because the molecular weights varied significantly between TU and T. On days 1, 45, and 90 the molar TU/T ratio for AUC were 10, 7, and 8 for the low dose group and 9, 8, and 9 in the high dose group, respectively. Similarly, the molar TU/T ratio for Cmax on days 1, 45, and 90 were 16, 10, and 10 for the low dose group and 12, 9, and 12 for the high dose group, respectively.

The TU exposure multiple in dogs based on AUC was roughly twice the exposure in in men in the LD group and 5 to 6 times the human exposure in the HD group at all times points (number in parentheses in the table below). Based on Cmax, the TU exposure multiple in the LD group was roughly 3 times the human exposure and 6 to 9 times the human exposure in the HD group at all of the time points.



Cmax in Dogs (Multiple of Exposure in Men on High Fat Diet after 475 mg TU Dose)									
Analyte	Control	Low Dose				High Dose			
	Baseline	Baseline	Day 1	Day 45	Day 90	Baseline	Day 1	Day 45	Day 90
TU (ng/mL)	0	0	2,900 (3.8x)	2,032 (2.7x)	2,135 (2.8x)	0	6,776 (8.9x)	4,142 (5.5x)	5,031 (6.6x)
T (ng/mL)	3.27	1.59	118 (5.5x)	129 (6.0x)	137 (6.4x)	5.46	348 (16.3x)	303 (14.2x)	263 (12.2x)
DHTU (ng/mL)	0	0	62† (0.4x)	38† (0.3x)	36† (0.2x)	0	111† (0.8x)	105† (0.7x)	166† (1.1x)
DHT (ng/mL)	0.24	0.13	6.53 (2.8x)	5.79 (2.5x)	6.39 (2.8x)	0.29	14.35 (6.2x)	11.96 (5.2x)	10.84 (4.7x)

Exposure in men after a 475 mg TU dose (Cmax ng/mL for TU = 759, T = 21.4, DHT = 2.3 ng/mL)
† Exposure in men after 90 days of 317 mg TU BID maintenance dosing (Cmax for DHTU = 147.4 ng/mL ng/mL)
LLOQ: TU (1.0 ng/mL), DHTU (1.0 ng/mL), T (0.02 ng/mL), DHT (0.02 ng/mL), Cortisol (1.0 μg/dL = 10 ng/mL).

$AUC_{0\text{-last}}$ in Dogs (Multiple of Exposure in Men on High Fat Diet after 475 mg TU Dose)						
Analyte	Low Dose			High Dose		
	Day 1	Day 45	Day 90	Day 1	Day 45	Day 90
TU (ng-hr/mL)	5,471 (2.3X)	3,510 (1.5x)	4,054 (1.7x)	15,285 (6.4x)	11,705 (4.9x)	12,067 (5.0x)
T (ng-hr/mL)	342 (2.1x)	332 (2.0x)	315 (1.9x)	1,036 (6.3x)	952 (5.8x)	843 (5.1x)
DHTU (ng-hr/mL)	175† (0.2x)	147† (0.2x)	112† (0.2x)	368† (0.5x)	437† (0.6x)	645† (0.9x)
DHT (ng-hr/mL)	26 (1.0x)	24 (0.9x)	25 (0.9x)	59 (2.2x)	59 (2.2x)	61 (2.2x)

Exposure in Men after a 475 mg TU dose (AUC ng-hr/mL for TU = 2,404, T = 165, DHT = 27.4)
† Exposure in men after 90 days of 317 mg TU BID maintenance dosing(AUC ng-hr/mL for DHTU = 737 ng-hr/mL)

Half-Life (hours)						
Analyte	Low Dose			High Dose		
	Day 1	Day 45	Day 90	Day 1	Day 45	Day 90
TU	1.9	1.6	2.2	0.8	1.9	1.0
T	1.8	2.5	3.2	1.8	1.9	1.8
DHTU	2.5	2.5	1.6	1.2	1.4	2.9
DHT	2.4	4.8	3.7	2.3	3.4	4.0

Tmax (hours)						
Analyte	Low Dose			High Dose		
	Day 1	Day 45	Day 90	Day 1	Day 45	Day 90
TU	1.3	1.0	1.8	2.0	2.3	2.3
T	1.8	1.5	2.0	2.0	2.3	2.3
DHTU	2.0	2.0	2.0	2.3	3.8	3.1
DHT	2.0	2.0	2.0	2.3	2.3	2.9

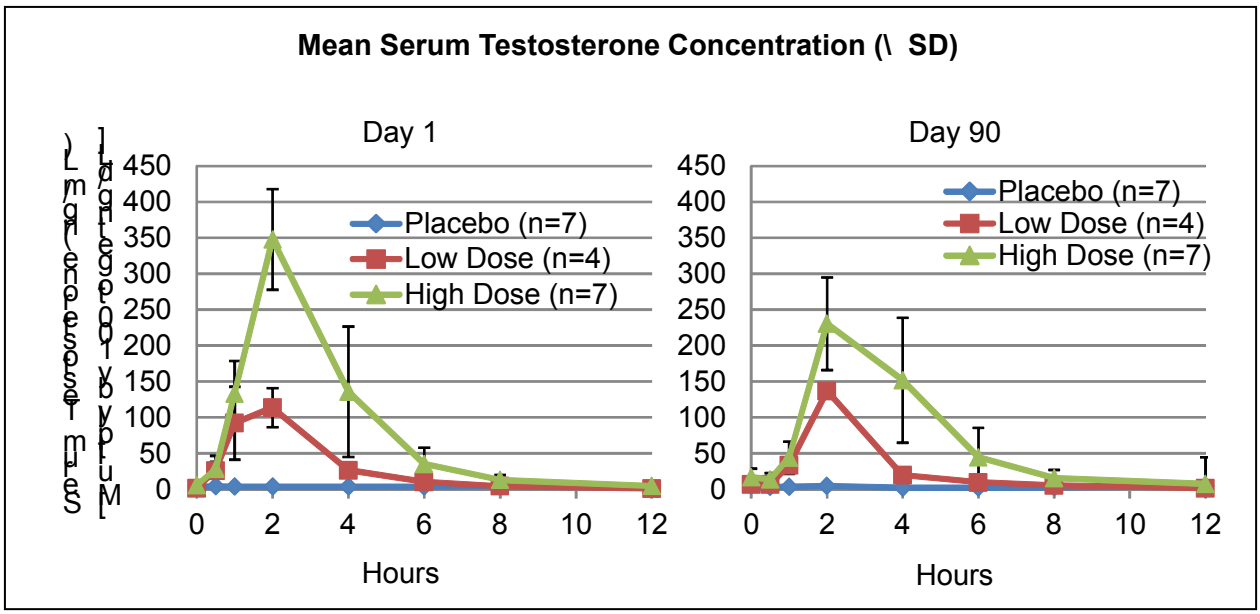
Testosterone

The half-life and Tmax for testosterone was similar to or slightly delayed in comparison to TU demonstrating a fairly rapid conversion of TU to T with a rapid elimination. Exposure to testosterone was roughly dose proportional and did not accumulate with repeated dosing.

In the control group, the baseline levels of testosterone in dogs (330 ng/dL = 3.3 ng/mL) were highly variable but similar to low normal range in men (eugonadal range Cave 300-1,000 ng/dL = 3-10 ng/mL). Baseline testosterone levels in the LD (1.6 ng/mL) and HD (4.5 ng/mL) groups were slightly lower and greater than the control group, respectively. It is unclear if the baseline levels in the TU treatment groups are due to differences in maturity of the dogs.

The Cmax concentrations were elevated 74- to 86-fold and 48- to 64-fold above the baseline in the low and high dose groups, respectively. The Cmax in dogs compared to men on a high fat diet at the highest recommended clinical dose were elevated 6-fold in the LD group and 12- to 16-fold in the HD group at all of the time points.

AUC for testosterone was not calculated for the control group in the study report but it is estimated to be roughly 40 ng-hr/mL assuming an average T level of 3.3 ng/mL over a 12-hour sampling period. Assuming a similar baseline for AUC among all groups, treatment elevated testosterone above baseline by roughly 8-fold in the LD group and 21- to 26-fold in the HD group based on AUC. Compared to men on a high fat diet, dogs were exposed to 2 and 6 times the clinical AUC in the LD and HD groups, respectively.



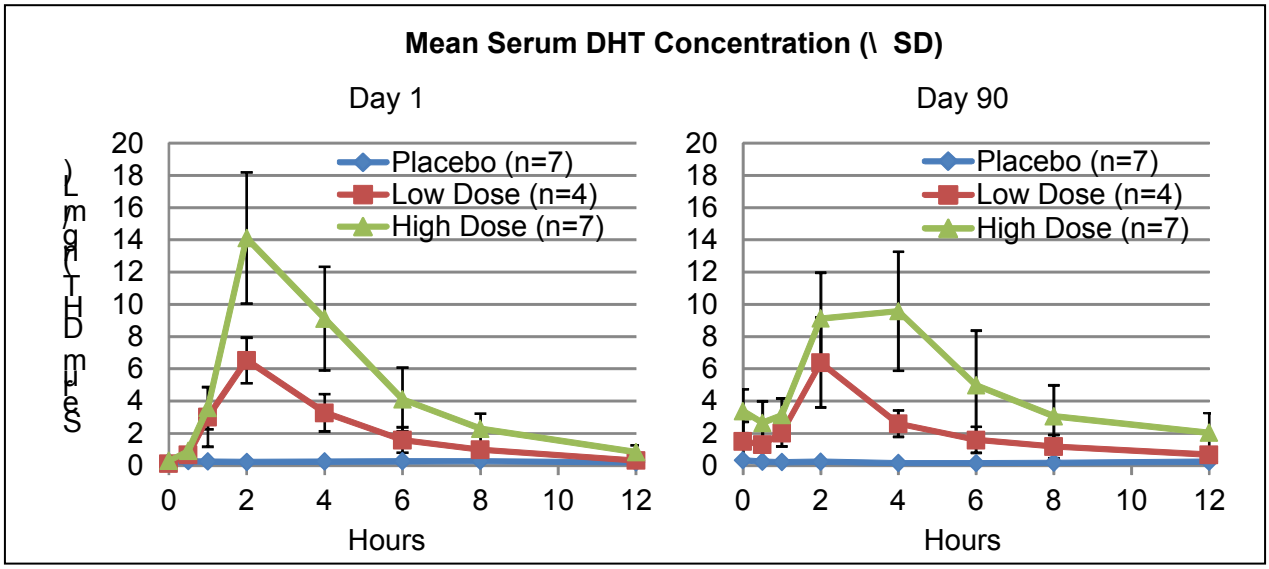
DHT

Exposure to DHT was the lowest among the metabolites assessed. The Tmax for DHT was in general slightly delayed in comparison to TU in both dose groups which is likely due to the time needed to metabolize TU to DHT. The half-life of DHT was also slightly longer than TU or T. DHT did not accumulate with repeated dosing even though DHT levels were still elevated in prior dosing (C_{min}) samples on days 45 and 90 in both dose groups. The exposure was slightly less than dose proportional.

The mean baseline DHT level on day 1 in the control group was 0.24 ng/mL with a range from 0.19 to 0.29 ng/mL over the 12-hour sampling period. Baseline levels of DHT were 0.13 and 0.29 ng/mL in the low and high dose groups, respectively. It is unclear if the difference in baseline levels relative to the control groups is due to differences in maturity of the animals but a similar trend was observed with testosterone levels. The baseline levels of DHT in dogs were roughly twice the baseline level in men. Baseline DHT levels in men were roughly 0.13 ng/mL (Study CLAR-09008). Assuming a constant baseline exposure over 12 hours, the AUC in the control group is roughly estimated to be 2.9 ng-hr/mL. Based on AUC, the exposure to DHT was elevated roughly 9 and 20 times the baseline level in the LD and HD groups, respectively. DHT exposure (AUC) was similar to that in men in the LD group and only twice the clinical exposure in the HD group. However, based on Cmax, DHT levels were 3 and 6 times the maximal clinical exposure in the LD and HD groups, respectively.

The exposure ratio of T to DHT did not appear to change from baseline based on AUC. However, the T to DHT ratio based on Cmax was slightly elevated compared to baseline in both the LD and HD groups which is because of the greater than proportional increase in T relative to DHT.

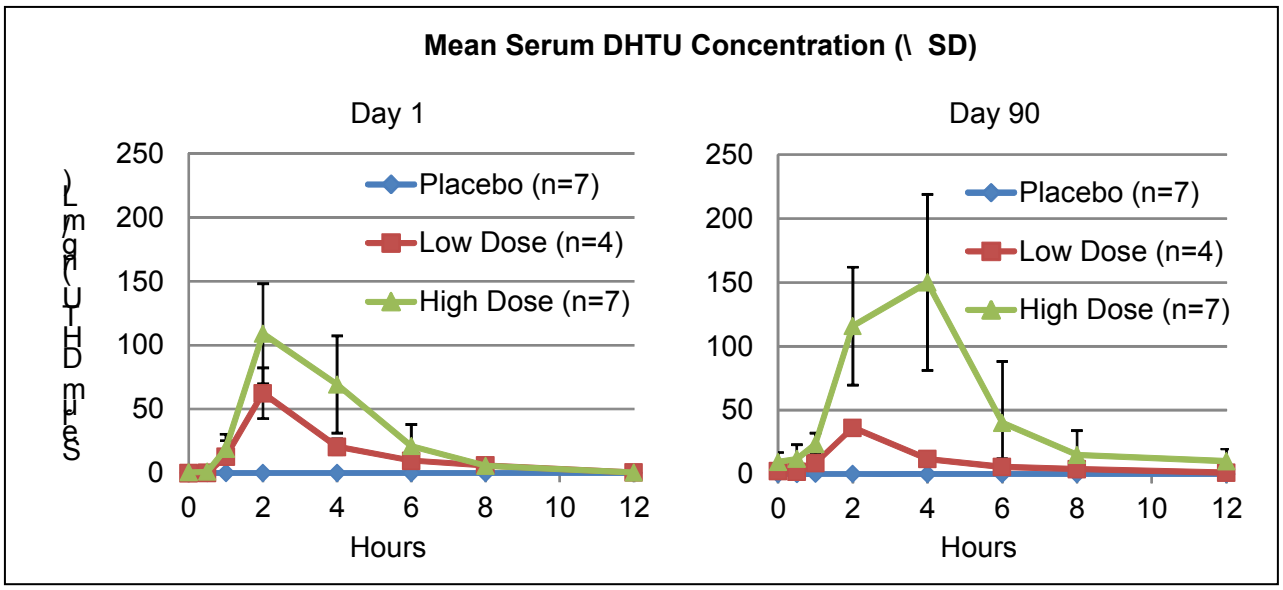
T:DHT Ratio					
	Baseline	Low Dose		High Dose	
	Day 1	Day 1	Day 90	Day 1	Day 90
Cmax	14	18	21	24	24
AUC_{0-12}	14	13	12	17	14
Baseline Cmax estimated to be 3.3 ng/mL for T and 0.24 ng/mL for DHT Baseline AUC0-12 was estimated to be 40 ng-hr/mL for T and 2.9 ng-hr/mL for DHT Ratio of T to DHT was not adjusted for differences in molecular weight between the analytes because the molecular weight of T and DHT very similar.					



DHTU

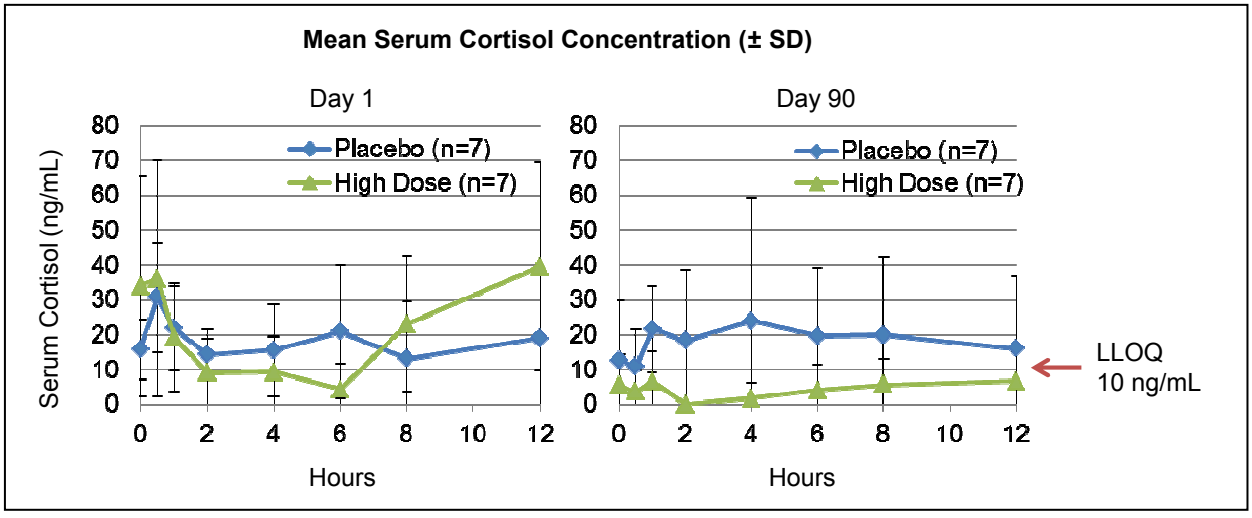
DHTU was the second most abundant metabolite evaluated generally being observed at levels slightly less than T. TU was rapidly but inefficiently converted to DHTU. TU exposures based on AUC were 19-42 times the DHTU levels in all groups suggesting that little TU was metabolized to DHTU. Suggestive of rapid elimination, the Tmax and half-life of DHTU was generally similar to or slightly delayed in comparison to TU which is expected of a metabolite.

Based on Cmax and AUC, the exposure to DHTU in the HD group was roughly similar to the exposure in men receiving a maintenance dose of 317 mg TU BID. DHTU levels were not determined in men at the maximal clinical dose (Study CLAR-09007).



Cortisol

The Applicant decided to assess cortisol in order to, "evaluate the potential effect of increased levels of circulating serum testosterone on the secretion of cortisol by the adrenal gland." Pharmacokinetics was not performed for cortisol. Definitive conclusions regarding the effects of TU dosing on cortisol levels can not be made because the levels of cortisol were highly variable and the lower limit of detection was near or above the levels that were reported (see figure below). Cortisol levels were near the lower limit of detection in the control group on day 1 and 90. Cortisol was below the limit of detection on day 90 in the high dose TU group which is consistent with the adrenal atrophy that was reported. The decreased adrenal weight and potential impaired function is an anticipated effect of superphysiological testosterone exposure. The Applicant noted two papers suggesting that the decreased adrenal weight observed in rats dosed with androgens is mediated by androgen receptor signaling (45 and 46).



Pharmacokinetics in Men

Pharmacokinetics of TU, T, and DHT were assessed in men after a single 475 mg TU dose (300 mg T equivalents) (CLAR-09008). Pharmacokinetics in this study were assessed in fasted men or men who were dosed within 30 minutes of consuming a very low, low, normal, or high fat meal (see table below). Effects of food on DHTU were not assessed but DHTU was evaluated in another clinical study without dietary restriction after 90 days of 317 mg BID TU maintenance dose (200 mg T equivalents) (CLAR-09007).

Compared to fasted men, the high fat diet increased the exposure (AUC) to TU, T, and DHT by 5-, 2-, and 3-fold respectively. Similarly to dogs the ratio of TU to T was very high in all groups. The TU to T ratio increased with the increased dietary fat content. The molar ratio of TU to T based on AUC was 4-fold for the fasted men and 5-, 7-, 8-, and 9-fold in the very low to high fat diet groups, respectively. Tmax in men was 4 to 8 hours for all analytes which is much longer than the 1-3 hours observed in dogs. The T to DHT ratio increased two fold from the fasted group (47-fold T:DHT) to the high fat group (88-fold T:DHT) due to a disproportional increase in testosterone.

Testosterone Pharmacokinetics in Men after Single 475 mg TU Dose (CLAR-09008)					
	Fasted	6-10% Fat	20% Fat	30% Fat	50% Fat
Cmax (ng/mL)	9.5 ± 8.0	13.7 ± 7.3	15.2 ± 7.1	17.6 ± 6.0	21.4 ± 9.0
AUCt (ng-hr/mL)	77.9 ± 36.7	108.4 ± 42.9	124.6 ± 50.3	136.3 ± 37.8	164.6 ± 55.8
Tmax (hours)	4.1	4.9	6.2	5.1	6.4
AUCt – AUC from time 0 to last concentration above the lower limit of detection. N = 12-16/group					

TU Pharmacokinetics in Men after Single 475 mg TU Dose (CLAR-09008)					
	Fasted	6-10% Fat	20% Fat	30% Fat	50% Fat
Cmax (ng/mL)	184 ± 231	414 ± 321	429 ± 292	573 ± 330	759 ± 417
AUCt (ng-hr/mL)	466 ± 624	967 ± 635	1,383 ± 821	1,614 ± 520	2,404 ± 982
Tmax (hours)	4.0	4.8	5.5	4.5	5.3
AUCt – AUC from time 0 to last concentration above the lower limit of detection. N = 12-16/group					

DHT Pharmacokinetics in Men after Single 475 mg TU Dose (CLAR-09008)					
	Fasted	6-10% Fat	20% Fat	30% Fat	50% Fat
Cmax (ng/mL)	1.0 ± 0.8	1.5 ± 1.0	1.7 ± 0.9	2.0 ± 1.0	2.3 ± 1.2
AUCt (ng-hr/mL)	9.9 ± 6.8	16.6 ± 11.3	20.2 ± 12.7	23.0 ± 14.1	27.4 ± 18.6
Tmax (hours)	4.1	5.8	7.1	5.8	8.2
AUCt – AUC from time 0 to last concentration above the lower limit of detection. N = 12-16/group					

Exposure to DHTU was assessed in men without dietary restriction after 90 days on a 317 mg/BID TU maintenance dose (200 mg BID T-equivalent dose) (CLAR-09007).

DHTU Pharmacokinetics in Men after 90 Days of 317 mg TU BID (CLAR-09007)	
Cmax (ng/mL)	147.4 ± 105.2
AUCt (ng-hr/mL)	736.9 ± 455.9
Tmax (hours)	3.7
AUCt – AUC from time 0 to last concentration above the lower limit of detection. N = 21.	

Dosing Solution Analysis
Testosterone undecanoate was 96.6% and 98.4% pure prior to first dose for the first and second batch, respectively. After study termination the purity decreased to 93.6% and 96.6% for the first and second batch, respectively.

7 Genetic Toxicology

The following standard androgen class labeling will be used to describe the genotoxicity of this product.

> *Testosterone was negative in the in vitro Ames and in the in vivo mouse micronucleus assays.*

8 Carcinogenicity

The citations listed below were provided by the Applicant to support the safety and labeling regarding carcinogenicity. The following standard androgen class labeling for carcinogenicity will be used for this product.

> *Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, implant induced cervical-uterine tumors metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.*

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Reference ID: 3604305

9 Reproductive and Developmental Toxicology

The citations listed below were provided by the Applicant to support the safety and labeling regarding fertility and pregnancy. The following standard androgen class labeling for fertility, pregnancy, and lactation will be used for this product.

Pregnancy

(b) (4) is contraindicated in pregnant women (b) (4) Testosterone is teratogenic and may cause fetal harm. (b) (4)

(b) (4)

Impairment of Fertility

The administration of exogenous testosterone (b) (4) suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

Applicant's Citations:

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10 Special Toxicology Studies

None

11 Integrated Summary and Safety Evaluation

Introduction

Several products have been marketed to elevate serum testosterone (T) in men with hypogonadism by exposing them to testosterone or testosterone esters via intramuscular, dermal, or buccal exposure. No oral dose formulations have been approved for marketing in the USA. Oral dose formulations containing testosterone are difficult to develop because T is metabolized in the liver before it can be distributed systemically. Manufactures of Andriol® found that esterification of the testosterone molecule with a long chain fatty acid ester (undecanoic acid) and incorporating this fatty acid ester of testosterone into a lipophilic formulation can promote oral absorption of testosterone undecanoate (TU) into the intestinal lymphatics and thereby avoid first pass metabolism of testosterone in the liver. TU is a pro-drug that is metabolized to T and undecanoic acid after absorption. Andriol®/Andriol® Testocaps are oral dose TU products that have been marketed outside of the USA for testosterone replacement therapy for over 20 years. The Applicant's oral dose capsule, REXTORO, is a novel TU formulation and it is indicated for testosterone replacement therapy in hypogonadal men. Although an oral TU formulation is not available in the USA, an intramuscular TU product, AVEED™, recently gained marketing approval in the USA to treat male hypogonadism.

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. These effects include the growth and maturation of the prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient production of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism may include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis. Male hypogonadism can present as primary hypogonadism caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia while secondary hypogonadism is the failure of the hypothalamus or pituitary to produce sufficient gonadotropins (FSH, LH).

Potential adverse effects of testosterone replacement therapy include worsening of benign prostatic hyperplasia and potential risk for cancer, polycythemia, decreased spermatogenesis, edema due to retention of sodium, gynecomastia, sleep apnea, changes in serum lipids, hypercalcemia, and decreased thyroxine-binding globulin.

Because of the extensive clinical and nonclinical data are available in published literature on testosterone, the nonclinical evaluation of TU was limited to assessing binding affinity of TU for the androgen receptor and assessing the toxicity of TU in the

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Applicant's oral formulation after 13 weeks of repeated dosing in male dogs. The Applicant relied upon published literature to assess the absorption, distribution, metabolism, and elimination of TU. Published literature was also supplied to assess the potential for reproductive toxicity and carcinogenicity. REXTORO also contains a novel excipient, borage seed oil, which was qualified with published literature and lack of adverse findings in the 13-week dog toxicology study.

TU is expected to have little to no pharmacodynamic effect without being metabolized to testosterone since it does not appreciably bind to the androgen receptor. Toxicities in male dogs after 13 weeks of BID dosing were limited to expected androgen dependent findings at exposures in excess of the eugonadal range in men.

A. Primary Pharmacological Activity

Testosterone undecanoate (TU) is a fatty acid ester of testosterone. TU is an inactive pro-drug which is hydrolyzed by esterases in vivo to yield testosterone and undecanoic acid. TU itself has little potential for pharmacological activity since its relative binding affinity for the androgen receptor was only 1% that of testosterone.

B. Absorption, Distribution, Metabolism, and Elimination

In lieu of conducting nonclinical absorption, distribution, metabolism, and elimination (ADME) studies with REXTORO, the Applicant submitted a review of some pertinent literature describing the ADME of testosterone and testosterone undecanoate.

In general the publications suggest that lymphatic absorption is promoted when testosterone is esterified at the C17β-hydroxyl group with long chain fatty acids. Lipophilic vehicles aid intestinal lymphatic absorption and administration with food greatly aid oral absorption of TU into the intestinal lymphatics. However, TU is very poorly absorbed orally with bioavailability being well below 10% in rats, dogs, and humans. After absorption, a fraction of TU is metabolized in the intestinal wall to DHTU. TU and DHTU are distributed systemically where they are further metabolized to undecanoic acid, T, DHT, estradiol (E2), numerous steroid metabolites, and glucuronide and sulfate conjugates. The half-lives of T and TU are roughly 10 to 100 minutes after they are in systemic circulation. In humans, TU and T are metabolized and eliminated primarily as androgen glucuronide conjugates in the urine within several hours of dosing. Undecanoic acid exposure is not a safety concern because it is an 11 carbon fatty acid that is metabolized by beta-oxidation and the tricarboxylic acid pathways and it is an approved food additive in the Everything Added to Food in the United States Database (1).

C. Nonclinical Toxicology Findings

<u>Repeat-Dose Toxicity in Male Dogs</u>
A toxicology study was conducted in male dogs that were dosed orally with TU in the clinical formulation at 0, 38 (LD), or 126 (HD) mg/kg/BID for 13 weeks. Recovery was

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assessed four weeks after the last dose in the control and HD groups. Findings were limited to androgen responsive tissues and are consistent with excessive exposure to an androgen.

The multiple of the clinical exposure discussed below are derived from the exposure in dogs relative to the exposure in men who received a single 475 mg TU dose after a high fat meal. This exposure comparison is a worst case scenario it is the greatest clinical dose proposed for marketing and the high fat content of the diet significantly elevated on Cmax and AUC in men. Compared to fasted men, a high fat diet increased the exposure (AUC) to TU, T, and DHT by 5-, 2-, and 3-fold respectively (Clinical Study CLAR-09008).

In dogs, the testosterone exposures based on AUC were elevated 8 and 21 times the baseline level in the LD and HD groups, respectively. Although exposure to testosterone was greatly elevated above baseline, dogs in the LD and HD groups were only exposed to 2 and 8 times the T AUC exposure in men on a high fat diet who received the maximum anticipated dose. Based on AUC, the exposure to DHT was elevated in dogs roughly 9 and 20 times the baseline level in the LD and HD groups, respectively. DHT exposure (AUC) was similar to that in men in the LD group and only twice the clinical exposure in the HD group. The exposure to TU based on AUC in the LD and HD groups was roughly 2 and 5-6 times the exposure in in men, respectively. TU was inefficiently metabolized to testosterone. Based on molar AUC values, the exposure to TU ranged between 7 to 10 times the exposure to testosterone for all dose groups. However, this does not appear to be a safety issue since there were no toxicities reported that are not androgen related. The capacity of the esterases appears to have been saturated in humans and dogs because the AUC ratio of TU to T adjusted for differences in molarity was ≥ 7 for both dogs and humans. A high molar ratio of TU to T (6-7 to 1) has been reported in the literature with the oral TU product Androl Testocaps when it was taken with a normal or high fat diet (2).

As expected following exposures 8 and 21 times the baseline level of testosterone, adrenal cortex atrophy, reduced cholesterol, atrophy of the testes, reduced sperm production, and hypertrophy of the prostate were observed in both dose groups. Serum cholesterol was suppressed in dogs in the LD (-45%) and HD (-48%) groups but it resolved after drug withdrawal. Adrenal cortex atrophy of moderate to marked severity was observed in all TU dosed dogs and this correlated with a ≥ 30% decrease in adrenal weights. Even though the organ weights recovered four weeks after dosing ceased, the adrenal cortex atrophy was still observed but the severity was reduced from marked to minimal/mild severity. Testes atrophy/degeneration was observed in all dogs in the LD group (marked) and HD group (min-moderate). Dogs did not recover from this. The severity in the HD group increased to severe in all dogs after the four week recovery period. The severity of the pathology in the testes correlated with the severity of testicular weight loss after 13 week of dosing and after the 4 week recovery period. Hypospermia was severe in the epididimes of all dogs in the LD group and it was moderate/marked in 2/4 dogs in the HD group. The decreased sperm production remained severe in all dogs in the HD group at the end of the recovery period. Marked

prostate hypertrophy was observed in all dogs in the LD and HD group at week 13 of dosing but this finding completely resolved after recovery. Prostate weight correlated with the extent of prostate hypertrophy and the reversibility of the finding.

Although adverse androgenic findings were observed in dogs in both TU dose groups, there were no clear non-androgen dependent adverse findings. Even though the exposure multiples in dogs for T and TU are not large relative to humans, the findings in dogs occurred at T levels well in excess of the baseline levels and the findings are well known androgenic effects that are not anticipated to occur in men exposed to testosterone in the eugonadal range.

D. Carcinogenicity and Reproductive Toxicity

The risk for reproductive toxicities and cancer is considered to be similar to other approved testosterone products based upon the established effects of testosterone.

Overall Conclusion

The safety profile of testosterone is well known. The preponderance of clinical data with testosterone supersedes nonclinical findings. No significant safety concerns associated with TU were identified in the nonclinical program other than expected androgen related findings in dogs at exposures well above the eugonadal range in men. Referenced literature and nonclinical data suggest that there should be no non-androgen related findings at exposures relative to the maximal clinical dose proposed for marketing. Overall the nonclinical program supports approval of this product in proposed population and indication and a maximum daily dose of 475 mg of TU BID.

12 Appendix/Attachments

12.1 References

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12.4 Annotated Nonclinical Labeling Revisions

Recommended text that was added to the Applicant's draft labeling is written in red text and underlined. Deletions are indicated by text that is struck through (i.e. ~~struck through~~).

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use (b) (4) safely and effectively. See full prescribing information for (b) (4)

(b) (4) (testosterone undecanoate), for oral use CIII
Initial U.S. Approval: 1953 (b) (4)

----------**INDICATIONS AND USAGE**----------

(b) (4) is an androgen indicated for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

----------**CONTRAINDICATIONS**----------

- Men (b) (4) or known or suspected prostate cancer. (4, (b) (4)
- (b) (4) (b) (4) Testosterone may cause fetal harm. (4, (b) (4) 8.1,

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

(b) (4) for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

4 CONTRAINDICATIONS

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)
Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

(b) (4)
Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays.

Impairment of Fertility
The administration of exogenous testosterone (b) (4) suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

(b) (4)

(b) (4)

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

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

/s/

LYNNDA L REID
08/04/2014