CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213953Orig1s000

MULTI-DISCIPLINE REVIEW

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

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 213953
Supporting document/s:	SDN 0038 (Original-1)
Applicant's letter date:	January 27, 2022
CDER stamp date:	January 27, 2022
Product:	Testosterone undecanoate (KYZATREX)
Indication:	Treatment of primary or hypogonadotropic hypogonadism
Applicant:	Marius Pharmaceuticals, LLC
Clinical Review Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Reviewer:	Yangmee Shin, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Clinical Division Director:	Audrey Gassman, MD (acting)
Project Manager:	Jeannie Roule

Disclaimer

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1 Executive Summary

1.1 Introduction

This Class 2 NDA resubmission constitutes a Complete Response (CR) to Clinical and Clinical Pharmacology deficiencies outlined in the CR letter issued on October 22, 2021. In the CR letter, the Division expressed concern that supportive evidence of effectiveness for the product cannot be established due to integrity and reliability issues of the PK data from a phase 3 study conducted with KYZATREX. In addition, the applicant failed to provide sufficient documentation and evidence assuring that sample handling and processing were conducted properly. To resolve the deficiency, a new phase 3, efficacy and safety trial with adequate number of hypogonadal subjects treated with the product was requested. The sponsor resubmitted the NDA on January 27, 2022 following a post-action meeting on January 21, 2022.

KYZATREX is an oral testosterone undecanoate product indicated for the treatment of primary or hypogonadotropic hypogonadism at a starting dose of 200 mg twice daily (400 mg total). The minimum recommended dose is 100 mg once daily in the morning. The maximum recommended dose is 400 mg twice daily. KYZATREX is formulated uniquely in a (b) (4), designed to promote TU absorption, and also contains phytosterol esters as excipients, which may exhibit affinity for the same targets and/or affect the pharmacokinetics/toxicity profile due to similarities in structure to sex steroids

The current resubmission contained no nonclinical studies. Pharmacology/Toxicology recommended approval of the initial NDA submission. There were no outstanding nonclinical deficiencies or comments in the CR letter. This review contains labeling recommendations to the applicant.

1.2 Brief Discussion of Nonclinical Findings

Reference is made to the full Pharmacology and Toxicology review and unireview, filed in DARRTS on October 21, 2021 and October 22, 2021, respectively.

In receptor binding studies to both estrogen and androgen receptor, testosterone undecanoate (TU), 5α-dihydrotestosterone undecanoate (DHTU), and the major phytosterol ((b) (4)) had no significant binding for estrogen receptor at up to the concentrations tested. Androgen receptor binding was up to ~56.3% for TU, up to ~19.3% for DHTU, and up to ~5.7% for (b) (4) . The low androgen binding for TU and DHTU suggests that the T esters may not possess the androgenic activity and may act instead via active metabolites including T. The highest concentrations tested for TU (10 µM, ~456700 ng/dL), DHTU (5 µM, ~229350 ng/dL), and (b) (4) ng/dL) were approximately 12-fold, 17-fold, and (b) (4) fold greater than the mean plasma C_{max} levels of the same entities in humans taking the maximum dose of 400 mg TU, BID. These results suggest that systemic exposure to TU, DHTU, or (b) (4)

from the oral TU product at the maximum human dose is within the range of concentrations that were shown not to significantly displace agonist binding to estrogen or androgen receptor.

Following a single oral administration to male CD rats at (b) (4) mg/kg (~40 mg/kg [^{14}C]-TU) using the proposed formulation with or without phytosterol esters, the distribution of radioactivity into tissues exhibited a maximum concentration between 2 to 6 hours post-dose. The highest concentration was observed in the GI tract (small intestine, stomach), reproductive organs (epididymis, prostate, epididymal white fat, seminal vesicle, testes), liver, and kidneys, with the muscle and skin accounting for the lowest concentration independent of formulations used. Radioactivity was below the limit of quantification at ~168 hours post-dose in most tissues except the epididymis for the formulation with phytosterols ((b) (4) mg) and the liver for the formulation without phytosterols. Drug-related radioactivity was primarily excreted into feces. The prolonged radioactivity in the epididymis at the final sampling time of 168 hours for the formulation containing phytosterol esters (half-life unknown) suggests potential tissue retention and/or accumulation of the excipient and/or the drug-related materials.

In the 13-week toxicology study in male dogs, treatment-related effects were noted in the adrenal glands (slight vacuolation of the zona fasciculata) and reproductive organs including the testis (small size associated with marked germ cell depletion and Leydig cell atrophy), epididymis (marked aspermia), and prostate gland (increased size associated with moderate glandular hypertrophy/hyperplasia) in TU groups with or without phytosterol esters. While the systemic exposures to TU and its metabolites were less than dose-proportional, the exposures to phytosterol esters were similar between the low-dose (1X) and high-dose (2X) groups, suggesting saturation of absorption of the phytosterol esters. No significant differences were observed in plasma levels of TU and its metabolites or estradiol levels with or without phytosterol esters under the conditions of the study. Following a 4-week drug-free period, the findings in the testes (germ cell depletion), epididymides (aspermia), and adrenal glands (vacuolation of the zona fasciculata) were not fully reversed in TU groups with phytosterol esters, but the reversibility is unknown in TU groups without phytosterol esters in the absence of data (this recovery dose arm was not included in the study). Of note, recovery groups were only included for vehicle (water), 2X excipients (containing phytosterol esters) without TU, and 2X excipients (containing phytosterol esters) with TU. Therefore, a precise conclusion on whether the phytosterol esters play a role in the non-reversibility of these findings cannot be drawn.

Reviewer Note: *The reviewer previously stated the following on page 28 in the unireview filed on October 22, 2021, and pages 6 and 56 in the full NDA review filed on October 21, 2021:*

> *Following a 4-week drug-free period, the findings in the testes (germ cell depletion), epididymides (aspermia), and adrenal glands (vacuolation of the zona fasciculata) were fully reversed in treated groups without phytosterol esters, but not in the high-dose group with phytosterol esters. The nonreversible nature of*

target organ findings at the high dose of TU in the presence of phytosterol esters in the dog plasma (no half-life provided) suggests the potential role of phytosterol esters on the persistent target organ toxicity.

The above statements are being corrected in this review (underlined) upon further review of the data. The submitted data suggest that TU rather than phytosterol esters may lead to persistent target organ toxicity following the 4-week recovery period. However, in the absence of recovery groups assessed for TU without phytosterol esters, it would be difficult to draw final conclusions on the role of phytosterol esters on reversibility.

These findings occurred at exposures of T less than or comparable to the maximum proposed human dose (400 mg BID) based on the maximum $AUC_{0\text{-}24h}$ and the maximum C_{max} measured in male subjects (Study #MRS-TU-2019EXT). The mean plasma exposures to TU, DHTU, T, and dihydrotestosterone (DHT) were approximately 3-, <1-, 2-, and 2-fold the $AUC_{0\text{-}24h}$ and approximately 6-, <1-, 4-, and 3-fold the C_{max}, respectively, of the mean human exposure to TU at 400 mg TU, BID. The plasma phytosterols measured in this study were approximately (b) (4)-fold the mean $AUC_{0\text{-}24h}$ and C_{max} for (b) (4), respectively, at 400 mg TU, BID (Study #SOV-TU-PK2013).

In the male fertility study where males were dosed for 71 to 73 days (prior to the initiation of the cohabitation period, 1 to 4 days during the cohabitation period, and for a minimum of 6 days and a maximum of 11 days following cohabitation), treatment-related findings included decreased body weight gains and reproductive organ weights for males, reduced fertility, pre-implantation loss associated with reduced mean number of implantation sites, reduced litter size and lower mean number of viable fetuses per litter in untreated gravid females, compared to the control group at the oral dose of (b) (4) mg/kg BID ((b) (4) mg/day/day). The systemic exposure corresponded to approximately 2 times the mean $AUC_{0\text{-}24h}$ for T and DHT and approximately 2-4 times the mean C_{max}, respectively, at 400 mg BID oral TU.

Overall, the nonclinical information and data provided to support safety of the new oral TU product are acceptable. The observations in the toxicology study in male eugonadal dogs and the fertility study in male eugonadal rats are expected androgenic effects of T. The findings in the adrenal gland (vacuolation of the zona fasciculata) are of unknown clinical significance. However, these were observed at T levels above the baseline AUC and at C_{max} exposures that would likely not occur in hypogonadal men exposed to T in the eugonadal range. The results from the submitted studies suggest that phytosterol esters in this formulation are unlikely to affect the pharmacology, toxicity, or pharmacokinetic profile at the anticipated mean plasma concentrations of TU and its metabolites up to the levels within the exposure achieved in clinical trials.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, the NDA contains adequate information to support approval of NDA 213953 via a 505(b)(2) pathway. Pharmacology/Toxicology recommends approval of the sponsor's labeling revisions submitted on June 28, 2022 with edits below.

1.3.2 Additional Non Clinical Recommendations

None at this time.

1.3.3 Labeling

The sponsor submitted updated labeling on June 28, 2022.

Provided below are the Division's final recommendations to the sponsor's proposed labeling edits. Additions are shown in red font.

FULL PRESCRIBING INFORMATION

(b) (4)

3 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YANGMEE SHIN
07/19/2022 04:10:03 PM

KIMBERLY P HATFIELD
07/19/2022 05:01:00 PM
I agree with the review and conclusions of Dr. Shin.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	213953
Priority or Standard	Standard
Submit Date(s)	January 27, 2022
Received Date(s)	January 27, 2022
PDUFA Goal Date	July 27, 2022
Division/Office	Division of Urology, Obstetrics, and Gynecology Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Reviewer Name(s)	Martin Kaufman, DPM, MBA
Review Completion Date	June 22, 2022
Established/Proper Name	Testosterone undecanoate
(Proposed) Trade Name	Kyzatrex
Applicant	Marius Pharmaceuticals, LLC
Dosage Form(s)	Oral Capsules
Applicant Proposed Dosing Regimen(s)	Starting dose is 200 mg orally twice daily, once in the morning and once in the evening with food, with an established minimum dose of 100 mg once in the morning and a maximum dose of 400 mg twice daily
Applicant Proposed Indication(s)/Population(s)	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	

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APPEARS THIS WAY ON ORIGINAL

Glossary

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

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

1. Executive Summary

1.1. Product Introduction

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

Kyzatrex is a soft gelatin capsule containing (b) (4) testosterone undecanoate (TU), a prodrug of testosterone, (b) (4). TU is converted to T by nonspecific esterases present in the body.

In the United States, products containing TU, currently approved for testosterone replacement therapy (TRT), include injection for intramuscular administration (Aveed) and capsule for oral administration (Jatenzo and Tlando).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness could not be established for Kyzatrex because of unresolved uncertainties about the reliability of the efficacy data in the single phase 3 study (MRS-TU-2019EXT) supporting approval.

Intended as TRT, the therapeutic goal for Kyzatrex is to restore T concentrations to the normal range (C_{avg}) while avoiding excessive T concentrations (C_{max}). For approval, a TRT product, including Kyzatrex, should meet both prespecified C_{avg} and C_{max} targets.

Study MRS-TU-2019EXT, an open-label, single arm efficacy and safety study that included 24-hour ambulatory blood pressure monitoring (ABPM) evaluated the to-be marketed dose and dosing regimen and provided the primary support for safety and efficacy of Kyzatrex. Because TU is a prodrug metabolized by nonspecific esterases in blood to T, an overestimation of T concentrations can occur if blood is collected in a plain tube (serum) without an esterase inhibitor such as NaF. To minimize the impact of this ex vivo TU to T conversion, the Applicant relied on plasma T C_{avg} and C_{max} (blood sample collected in NaF/EDTA tubes) as the primary and key secondary endpoints, respectively. In clinical practice, however, it is common for T concentrations to be measured in serum (plain tubes). Therefore, study MRS-TU-2019EXT

included a serum substudy where both serum (plain tubes) and plasma (NaF/EDTA tubes) samples are collected from the same subjects to determine the correlation between plasma and serum T concentrations and to support the use of serum sample in clinical practice. When a blood sample is handled and processed according to the steps specified in the central lab manual, serum T concentration is expected to be higher than plasma T concentration because of several factors, including the potential ex vivo TU to T conversion, and matrix effect. The Applicant notified the Agency in the July 2020 pre-NDA meeting of multiple subjects at clinical Site 104 of MRS-TU-2019EXT participating in the serum substudy who had NaF/EDTA plasma T concentrations that were paradoxically higher than serum T concentrations obtained at the same timepoint. According to the Applicant, post-study interview with the site coordinator indicated pharmacokinetic (PK) sample mishandling and processing; the Applicant proposed to exclude all data from Site 104. When the data were analyzed using the prespecified efficacy population that included subjects from all study sites, including Site 104 – the extension treated set, or EXTS - only the primary efficacy endpoint C_{avg} was met but not any of the key secondary endpoints for C_{max} outliers. When the Applicant modified the EXTS population to exclude subjects from Site 104 (modified extension treated set (mEXTS)), the study successfully met the criteria for both C_{avg} and C_{max} efficacy endpoints.

During the first cycle NDA review, the Division requested the Office of Scientific Integrity and Surveillance (OSIS) to inspect Site 104 to confirm whether there was mishandling/misprocessing of PK samples to justify excluding Site 104; based on the findings at Site 104, OSIS decided to inspect a second clinical site, Site 107, a high enrollment clinical site. At both sites, OSIS found no documented record of PK sample handling and processing at several clinic visits, including visit 12E (Day 90 of MRS-TU-2019EXT study), the time point of the primary efficacy evaluation for C_{avg} and C_{max}. OSIS concluded these objectionable conditions at Sites 104 and 107 were likely to be present at the other 17 clinical sites not inspected; thus, the reliability of the clinical data from the entire phase 3 study may be impacted. At OSIS's recommendation, the Agency requested the Applicant provide evidence of documentation of PK sample handling/processing for the other 17 clinical sites of study MRS-TU-2019EXT but the Applicant did not do so.

The lack of documentation of the PK sample handling/processing from any clinical sites in study MRS-TU-2019EXT poses significant uncertainties about the reliability of the PK data (serum and plasma T concentrations) forming the basis of Kyzatrex's approval. Blood samples collected from subjects receiving TU typically have variable T concentrations due to several factors, including potential post collection TU to T ex vivo conversion from the presence of endogenous nonspecific esterases in the blood. The use of NaF (esterase inhibitor)-containing tubes to inhibit esterase activity in plasma reduces the extent of possible TU to T ex vivo conversion. However, even with the use of NaF/EDTA tubes, ex vivo conversion of TU to T can still occur and the extent of that conversion depends on PK sample handling and processing conditions, such as temperature, time, and the concentration of TU. Therefore, the handling/processing of all PK samples need to follow the procedures prespecified in the central laboratory manual, such as

temperature and duration of each step of blood sample collection, processing, and storage, as well as the transfer of processed/frozen samples to the bioanalytical study site(s). Strict adherence to these procedures ensures that the T values obtained accurately reflect the actual serum or plasma T concentrations of study subjects. Documentation of the handling and processing of PK samples is needed to assure that these steps and procedures were appropriately followed to generate accurate and, hence, reliable PK results. The existence of the Central Laboratory Manual, training of staff on the Manual, and the Applicant's declaration that the Manual was consistently followed do not provide adequate assurance of the data reliability.

The Applicant did not submit any new clinical data in the resubmission. The resubmission consisted of multiple site level and subject level analyses of the data from MRS-TU-2019EXT. These analyses did not address the data reliability issue identified during the first review cycle. In addition, the Applicant's analysis of subject level data was not sufficient to rule out a T Cmax drug effect greater than 2000 ng/dL (2.5 X ULN) for two subjects in the trial.

Therefore, this reviewer concludes that due to the uncertainty still surrounding the PK data from MRS-TU-2019EXT, the Applicant has not provided substantial evidence that Kyzatrex is safe and effective for TRT in hypogonadal men.

1.3. Benefit-Risk Assessment

There are many approved testosterone products available with different routes of administration. These products include two for TU capsules, which are approved for the oral route of administration, similar to Kyzatrex.

The reliability of the PK data for MRS-TU-2019EXT cannot be assured. The primary and key secondary efficacy endpoints of the study are based on Cavg and Cmax, respectively, which are derived from the PK data. The efficacy of Kyzatrex could not be established with a sufficient degree of certainty because of uncertainties about the reliability of the PK data. Therefore, MRS-TU-2019EXT did not provide substantial evidence of efficacy.

In addition, analyses conducted during the second review cycle raised safety concerns regarding the risk that Kyzatrex could cause excessive T concentration peaks.

The benefit of Kyzatrex does not outweigh its risks because substantial evidence of effectiveness for Kyzatrex has not been established and the risk of excessive T concentration peaks has not been ruled out.

2. Therapeutic Context

2.1. Analysis of Condition

Male hypogonadism is a clinical syndrome resulting from insufficient/absent secretion of testosterone by the testis. Primary hypogonadism is caused by primary defects of the testes such as Klinefelter syndrome or Leydig cell aplasia. Secondary hypogonadism (also known as hypogonadotropic hypogonadism) is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (follicle-stimulating hormone (FSH), luteinizing hormone (LH)) to support adequate testicular function.

Hypogonadism is a serious medical condition. Testosterone replacement therapy is recommended for the treatment of men with testosterone deficiency from well-known structural or genetic/congenital etiologies. Although TRT use is more common in older men with testosterone concentrations lower than normal of younger men for no cause other than aging ("age-related" hypogonadism), the safety and efficacy of testosterone therapy in this patient population has not been demonstrated.

2.2. Analysis of Current Treatment Options

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
Injection	Depo-testosterone/ testosterone cypionate	50–400 mg every 2 – 4 weeks		085635
	testosterone cypionate	50–400 mg every 2–4 weeks		040530 040615 086030 090387 091244 201720 206368 207742 210362
	testosterone enanthate	50–400 mg every 2–4 weeks		040575 085598 091120
Intramuscular	Aveed/testosterone undecanoate	750 mg: second dose after 4 weeks, subsequent doses every 10 weeks	022219	
	Testosterone cypionate	50-400 mg every 2-4 weeks	216318	
Subcutaneous	Xyosted/testosterone enanthate	50-100 mg every 7 days	209863	

Oral	Testred/methyltestosterone	10-50 mg daily		083976
	Android/methyltestosterone	10-50 mg daily		087147
	methyltestosterone	10-50 mg daily		080767 204851
	Jatenzo/testosterone undecanoate	158-396 mg twice daily	206089	
	Tlando/ testosterone undecanoate	225 mg twice daily	208088	
Implant	Testopel/testosterone	150-450 mg every 3 to 6 months		080911
Transdermal	Androderm/testosterone	2-6 mg daily	020489	
	AndroGel/testosterone 1.62%	20.25-81 mg daily	022309	
	testosterone 1.62%	20.25-81 mg daily		204570 207373 208620 208560 204268 205781 209390
	AndroGel/testosterone 1%	50-100 mg daily	021015	
	testosterone gel 1%	50-100 mg daily		076737 076744 091073
	Testim/testosterone 1%	50-100 mg daily	021454	
	Fortesta/testosterone	10-70 mg daily	021463	
	testosterone gel	10-70 mg daily		204571
	Vogelxo/testosterone gel	50-100 mg daily	204399	
	testosterone topical solution	30-120 mg daily		205328 209533 208061 204255 209836 212882 212301
Nasal Gel	Natesto/testosterone	11 mg thrice daily	205488	

Source: Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), electronic version accessed June 22, 2022. Product labeling accessed at the DailyMed website and the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) June 22, 2022.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Marius Pharmaceuticals, LLC submitted the original NDA for Kyzatrex on December 31, 2020. On October 22, 2021, DUOG issued a Complete Response (CR) letter for the NDA. The CR letter provided the following reasons for the CR action:

> Approvability of your NDA depends on reliable evidence that the proposed dose and dosage regimen for your product restore testosterone (T) concentrations to the normal range (Cavg) and avoid unacceptably high T peak concentrations (Cmax). Therefore, reliable measurement of T concentrations in pharmacokinetic (PK) samples collected in your single efficacy and safety trial (MRS-TU-2019EXT) is critical to the acceptability of the PK data forming the basis of the efficacy and safety of your product.
>
> Multiple subjects at Site 104 (Manhattan Medical Research Practice, LLC, Jamaica, NY) had NaF/EDTA plasma T concentrations paradoxically higher than serum T concentrations obtained at the same timepoint. You stated a post-study interview with the site coordinator indicated PK sample handling/processing deviations from instructions in the central laboratory manual as the cause of these aberrant findings. As such, you requested to exclude Site 104 from the efficacy analysis of Cavg and Cmax. Although the Cavg efficacy endpoint was achieved with or without Site 104, the key secondary Cmax endpoints were achieved only after excluding Site 104.
>
> During the Agency's inspection of Site 104 to determine whether excluding this site was justified, the site personnel were unable to provide documentation on PK blood sample processing and handling. Based on the findings at Site 104, the Agency conducted an inspection of Site 107 (South Florida Medical Research, Maitland, FL). Similar to Site 104, multiple subjects at Site 107 had NaF/EDTA plasma T concentrations paradoxically higher than serum T concentrations obtained at the same timepoint and there was no documentation to support that the PK blood sample handling and processing were carried out properly. In addition, review of your responses to the Agency's information requests revealed lack of documentation for PK sample handling and processing in the other clinical study sites of MRS-TU-2019EXT.
>
> Without documentation of PK sample handling and processing at Sites 104 and 107, we do not know the cause of the aberrant results at that site and, therefore, cannot agree to exclude data from Site 104. Your product does not achieve any of the key secondary Cmax endpoint targets with the inclusion of data from Site 104. More importantly, absent contemporaneous documentation for PK sample handling and processing at all clinical sites of MRS-TU-2019EXT calls into question how the PK samples were processed and handled and poses significant uncertainties about the reliability of the PK data of the entire study.
>
> As the integrity and reliability of the PK data from MRS-TU-2019EXT cannot be assured, we cannot conclude that MRS-TU-2019EXT provides substantial evidence of effectiveness for your product.

The CR letter also provided the information needed to resolve the deficiency that resulted in the CR:

> Conduct a new phase 3, efficacy and safety trial with adequate number of hypogonadal subjects treated with your product. This trial needs to have reliable data to demonstrate

that your drug is safe and effective with your proposed dose, dosing regimen, and dose titration scheme. You need to have adequate documentation of PK sample collection, handling, processing, and storage to verify these steps are carried out according to the prespecified procedures, ensuring the reliability of the PK results. If you choose to rely on plasma T concentrations (e.g., NaF/EDTA tubes) for dose titration and safety and efficacy assessments in this new trial, but intend to label for serum T concentrations (i.e., plain tubes) in clinical practice, we strongly recommend you measure T concentrations in both plasma and serum from all PK blood samples in your trial to inform serum-based dose titration thresholds for labeling purposes.

3.2. Summary of Presubmission/Submission Regulatory Activity

On November 12, 2021, the Applicant requested a Type A post-action meeting to discuss their planned resubmission of NDA 213953. The meeting was granted on November 24, 2021.

Preliminary Comments for the meeting were conveyed to the Applicant on January 19, 2022. The Preliminary Comments provided the following responses to the four questions posed in the Applicant's meeting package.

Question 1:
Does the FDA agree that based on its review of the information provided in the NDA, amendments to the NDA and this briefing package that it would be reasonable to exclude Site 104 data from the primary efficacy (percent in normal range) and Cmax secondary endpoint analysis supporting product approval in Marius' resubmission?

FDA Response to Question 1:
No. We do not agree to exclude data from Site 104. In your Bioanalytical Sample Stability Substudy, you conclude that processing conditions such as time and temperature are critical factors for accurate T concentration measurements. As such, the assurance of proper sample handling and processing of both serum and plasma samples are critical.

We inspected clinical Sites 104 and 107 to uncover the reasons for the aberrant PK results and to determine whether excluding these results were warranted. Without evidence of written documentation of the actual steps taken to handle and process the blood samples to help clarify the PK results, we do not have the necessary information to justify excluding the aberrant PK data. We acknowledge the central laboratory manual, staff training, and deductive reasoning of possible PK blood sample mishandling/processing steps that could result in abnormal PK results. However, these do not provide factual evidence of what actually occurred to render these results aberrant.

We also observed some noteworthy findings in the PK results from the serum substudy. You stated, in general, it is expected that higher serum T concentrations would be observed compared to NaF/EDTA plasma T concentrations. However, we note there are also subjects from clinical study sites other than 104 and 107 who showed an inverse relationship between NaF/EDTA plasma T concentrations and serum T concentrations across the 24-hour PK profiles (for example, Subjects (b) (6), and (b) (6)). Additionally, we note the serum T concentrations between 5- and 18- hours post-dose from Subject (b) (6) appear to be abnormally high and does not mimic the expected PK profile that the corresponding NaF/EDTA T concentrations show. The lack of documentation on sample handling/processing precludes our ability to uncover the reasons to explain these anomalous observations in sites other than sites 104 and 107.

In the context of abnormal PK findings without contemporaneous documentation, or other evidence, regarding the conditions under which the blood samples were handled, we are unable to conclude the reliability of the plasma and serum PK data.

Question 2:
If the FDA's answer to Question #1 is no, does the FDA believe that the aberrant data from Site 104 can be (b) (4)?

FDA Response to Question 2:
No. This is an approvability issue and cannot be (b) (4).

Question 3:
Given the information provided in NDA 213953 and in this briefing package, does FDA agree that the data from MRS-TU-2019EXT is reliable and acceptable to support approval of NDA 213953 without data from an additional Phase 3 study?

FDA Response to Question 3:
No. We do not agree the data from MRS-TU-2019EXT is reliable to support approval of NDA 213953 without additional data from a new phase 3 study. See our response to Question 1.

Question 4
If agreement can be reached regarding the questions posed above, does FDA agree that (b) (4)?

FDA Response to Question 4:
No. We do not agree (b) (4)

(b) (4)

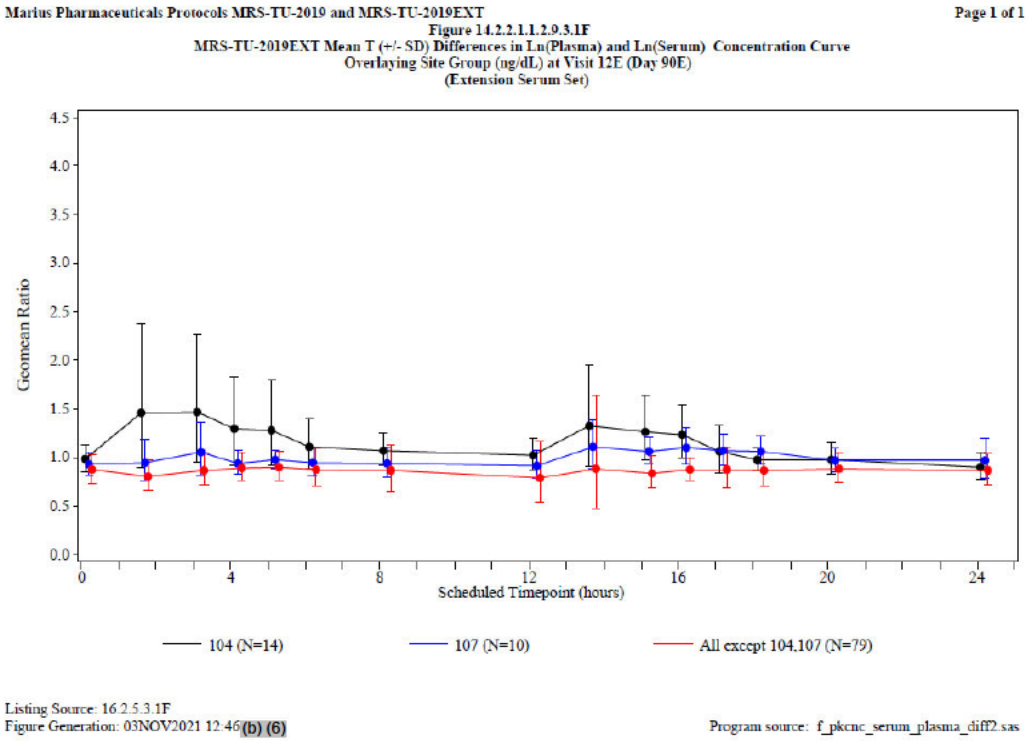
The Preliminary Comments also included the following Additional Comment:

> Due to the uncertainty regarding the reliability of the testosterone concentration data from MRS-TU-2019EXT, a new ABPM study may need to be conducted. We are consulting the Interdisciplinary Review Team for Cardiac Safety Studies regarding this issue and will provide additional guidance when it becomes available.

The post-action meeting was held via teleconference on January 21, 2022. The discussion during the meeting is summarized below:[1]

> The FDA prefaced its remarks by stating all sponsors are treated consistently and fairly by the FDA. Each NDA review involves a rigorous process to ensure all drugs are safe and effective before they are approved; FDA applied the same process to the Kyzatrex NDA. The FDA started the discussion by asking the Sponsor to discuss the Cmax excursions at Site 104 and explain whether those excursions could have been attributed to Kyzatrex and not solely to possible mishandling of the PK samples.
>
> The Sponsor reiterated their findings of aberrant PK profiles where plasma testosterone concentrations were higher than serum testosterone concentrations in certain samples obtained from subjects enrolled in the Serum Substudy at Site 104, and the 5 highest plasma Cmax outliers in the study were all from Site 104. The Sponsor stated they conducted telephone interviews with the site staff involved with handling and processing PK samples at Sites 104 and 107. The Sponsor stated these interviews indicated noncompliance of PK sample handling and processing (e.g., not using ice-water baths for post-collection storage) of NaF/EDTA plasma samples.
>
> The Sponsor believes the mishandling of PK samples at Sites 104 and 107 do not imply there was an issue with the reliability of the PK data from the other 17 clinical sites and referred to the figure below (included in their meeting package, page 27). They noted the PK profile from Sites 104 and 107 differed significantly from that of the other 17 sites. The FDA stated that the figure emphasized the mean values and stated that the Sponsor should not focus on the means only. The Sponsor noted the primary endpoint of Cavg is met in all scenarios (with or without Sites 104 and 107) and the data from all 19 clinical sites can be included in the safety profile of Kyzatrex.

[1] See NDA 213953, FDA Meeting Minutes, entered in DARRTS on February 16, 2022, by Jeannie M Roule.



While the FDA acknowledged the possibility of PK sample mismanagement contributing to the aberrant PK profiles of Site 104 and Site 107, FDA explained it is unknown whether Kyzatrex contributed to excessive Cmax excursions and that PK sample mishandling alone may not be the only cause of excessive Cmax outliers. Without any documentation, FDA reminded the Sponsor it is a matter of speculation regarding the exact nature of deviations in sample mishandling that could result in certain quantitative values in the PK samples. For example, it is unclear how long the sample was left out and at what temperature, that could entirely explain a certain observed Cmax outlier value.

The Sponsor stated it was the same person handling all the plasma and serum samples at Site 104, and they believe the samples were left at room temperature, instead of being in a chilled ice bath, for up to 2 hours. The FDA inquired if there was any available information documenting that the samples were left at room temperature. The Sponsor stated they can only speculate as to what happened because documentation of PK sample handling and processing does not exist. Sponsor acknowledged noncompliance to protocol, including instructions in the central laboratory manual, are to be documented as a protocol deviation, and conceded the deviations were not reported.

FDA commented, if in fact, the outlier data was due to ex vivo TU to T conversion caused by human error, how would the Sponsor explain the fact that four out of five Cmax outliers had TU Cmax concentrations 30-100% higher than the average Cmax of TU. Such observations indicate these subjects had higher than average drug exposure, as reflected in their plasma Cmax outlier values. Therefore, these Cmax outliers may have been attributed to the drug itself.

FDA stated the Sponsor's sample stability study showed ratios of approximately 1.4 in some of the longer held samples compared to nominal concentrations. Applying the worst-case scenario of 40% increase to the 5 subjects at Site 104 with excessive plasma Cmax, outliers, two subjects would still have plasma Cmax above 2000 ng/dL (the >2.5-fold outlier threshold).

Sponsor countered that these T Cmax excursions only last 1 or 2 hours in duration and are transitory in nature. The Sponsor also commented no unexpected AEs or SAEs were seen in subjects with the Cmax outliers. The FDA reminded the Sponsor the efficacy of testosterone replacement therapy, including Kyzatrex, is demonstrated by successfully achieving the criteria for both Cavg and Cmax outlier thresholds, and limits on Cmax outliers are to guardrail against excessively high Cmax testosterone exposure. The pivotal trial for Kyzatrex is insufficient in sample size and duration of treatment to evaluate the long-term clinical outcomes that could result from chronic exposure to excessively high Cmax testosterone concentrations.

The FDA indicated there are still gaps in the NDA submission regarding Cmax outliers, precluding FDA to conclude that drug attribution to the observed outliers would be highly unlikely. The Sponsor indicated they will submit new analyses to support that the Cmax outliers were highly unlikely to be due to its drug.

The Division conveyed the FDA Meeting Minutes to the Applicant on February 16, 2022,[2] however, the Applicant resubmitted NDA 213953 on January 27, 2022, prior to issuance of the Meeting Minutes.

3.3. Foreign Regulatory Actions and Marketing History

Kyzatrex is not currently approved in any country.

4. Sources of Clinical Data and Review Strategy

[2] See NDA 213953, FDA Meeting Minutes, entered in DARRTS on February 16, 2022, by Jeannie M Roule.

4.1. Table of Clinical Studies

No new studies were included in the resubmission. See Section 7.1. Table of Clinical Studies of the Unireview for the first review cycle entered in DARRTS October 22, 2021.

4.2. Review Strategy

No new studies were included in the resubmission. Therefore, the primary focus of the clinical review for the resubmission is based on the Applicant's reanalysis of data derived from MRS-TU-2019EXT.

5. Review of Relevant Individual Trials Used to Support Efficacy

5.1. MRS-TU-2019EXT

See Unireview for the first review cycle entered in DARRTS on October 22, 2021, for a discussion of the trial design, data quality/integrity, and efficacy results.

5.2. Analyses Included in the Resubmission

The resubmission included five analyses: four were based on site level data and one was based on subject level data. The Applicant believes the site level analyses show that the T Cmax values obtained from Site 104 comprise a different population than the rest of MRS-TU-2019EXT and the observed T Cmax values at Site 104 were the result of both the drug effect and another effect, which they identified as sample mishandling.

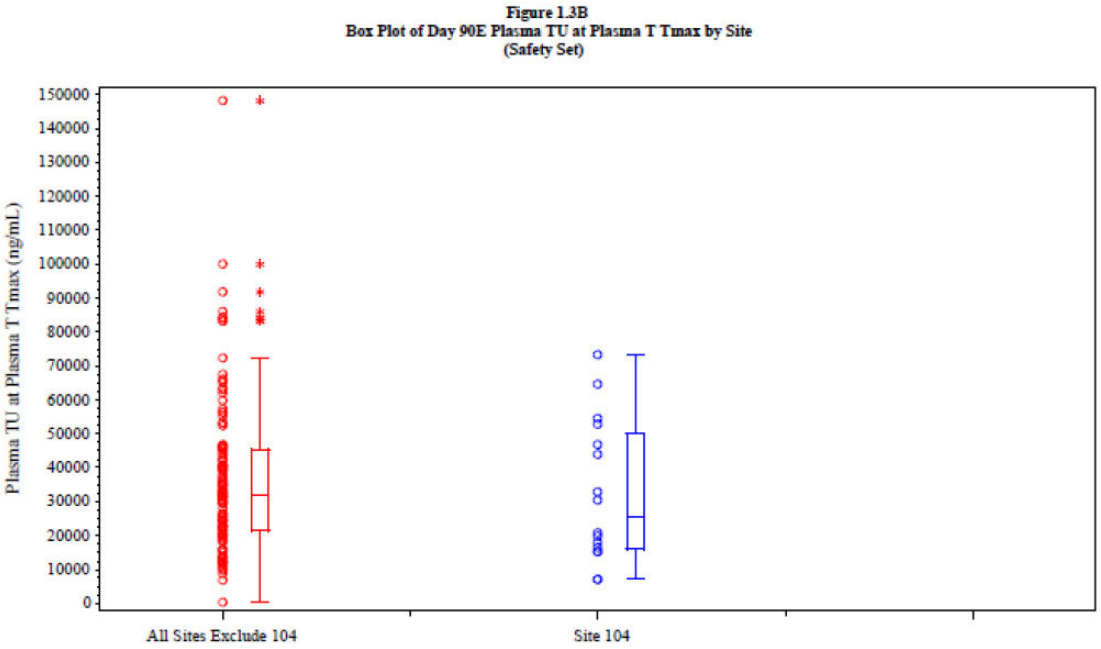
The subject level analysis consists of the Applicant's model, which they believe accurately predicts the contribution of the drug (i.e., the drug effect) to the observed plasma T Cmax values.

The Applicant's site and subject level analyses are presented below.

5.2.1. Site-level: TU and T Cmax populations

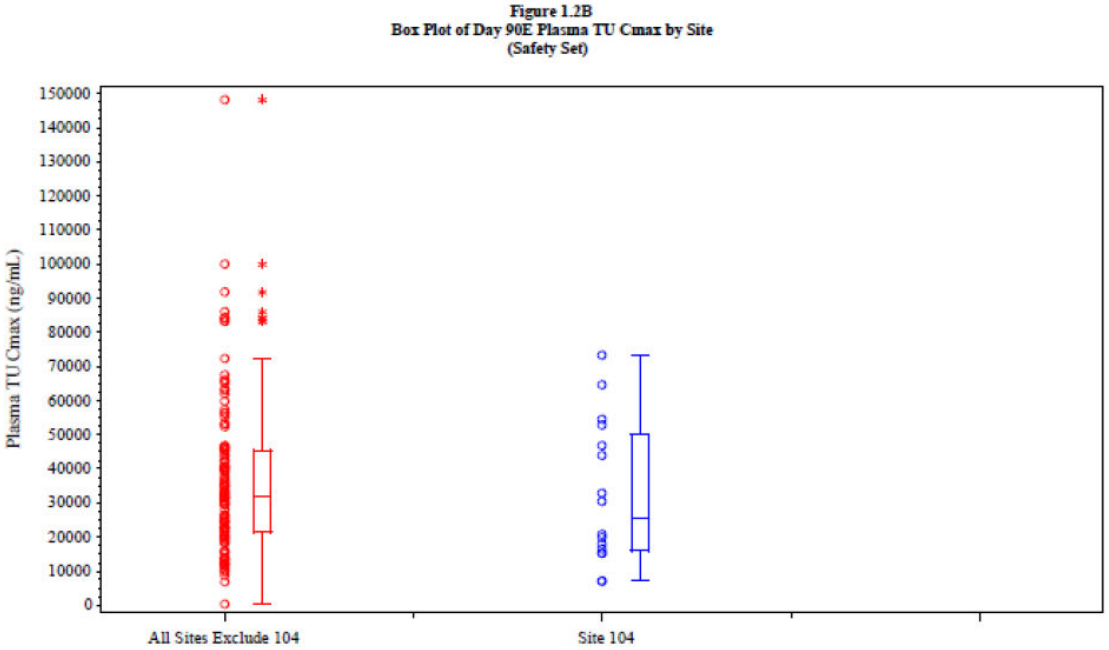
This analysis included two comparisons. One compared plasma TU concentrations at either T Tmax (Figure 1) or TU Tmax (Figure 2) for Site 104 to plasma TU concentrations for the other 18 sites in MRS-TU-2019EXT. The other compared plasma T Cmax concentrations for Site 104 to plasma T Cmax concentrations for the other 18 sites in the study.

Figure 1: Box Plot of Visit 12E/Day 90E Plasma TU at Plasma T Tmax by Site



Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Figure 1.

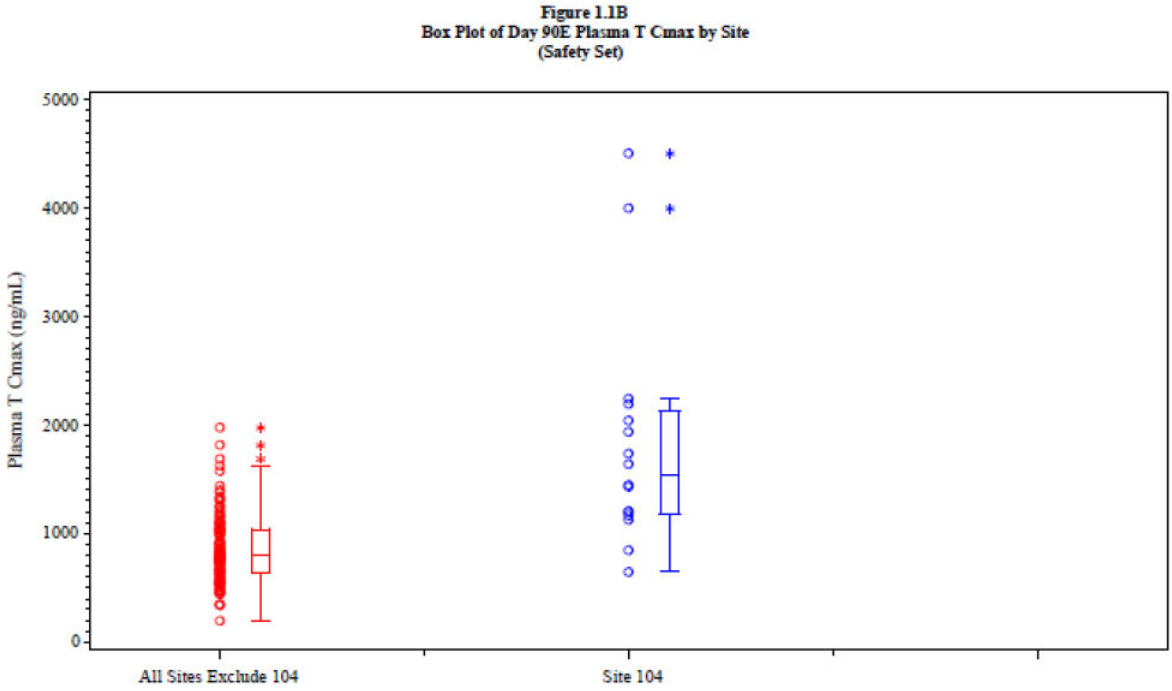
Figure 2: Box Plot of Visit 12E/Day 90E Plasma TU Cmax by Site



Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Figure 2.

Figure 3 presents the T Cmax data in the same box plot format. The Applicant notes that the Site 104 T Cmax population appears shifted to higher concentrations and they conducted a statistical test to determine whether the two samples of T Cmax values are different. In Table 1 a t-test is applied to the samples given in the three box plots. For both TU comparisons, the difference is not significant, as expected. For the comparison of T Cmax, the p-value is 0.002.

Figure 3: Box Plot of Visit 12E/Day 90E Plasma T Cmax by Site



Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Figure 3.

Table 2: T-test for difference in T and TU concentrations, Site 104 vs. all others

Comparison	Test	Reference	P value
TU at T Tmax	Site 104 (n=16)	All other subjects (n=129)	0.4232
TU Cmax	Site 104 (n=16)	All other subjects (n=129)	0.5061
T Cmax	Site 104 (n=16)	All other subjects (n=129)	0.002

Note: P-value from 2 sample t-test, Satterthwaite method

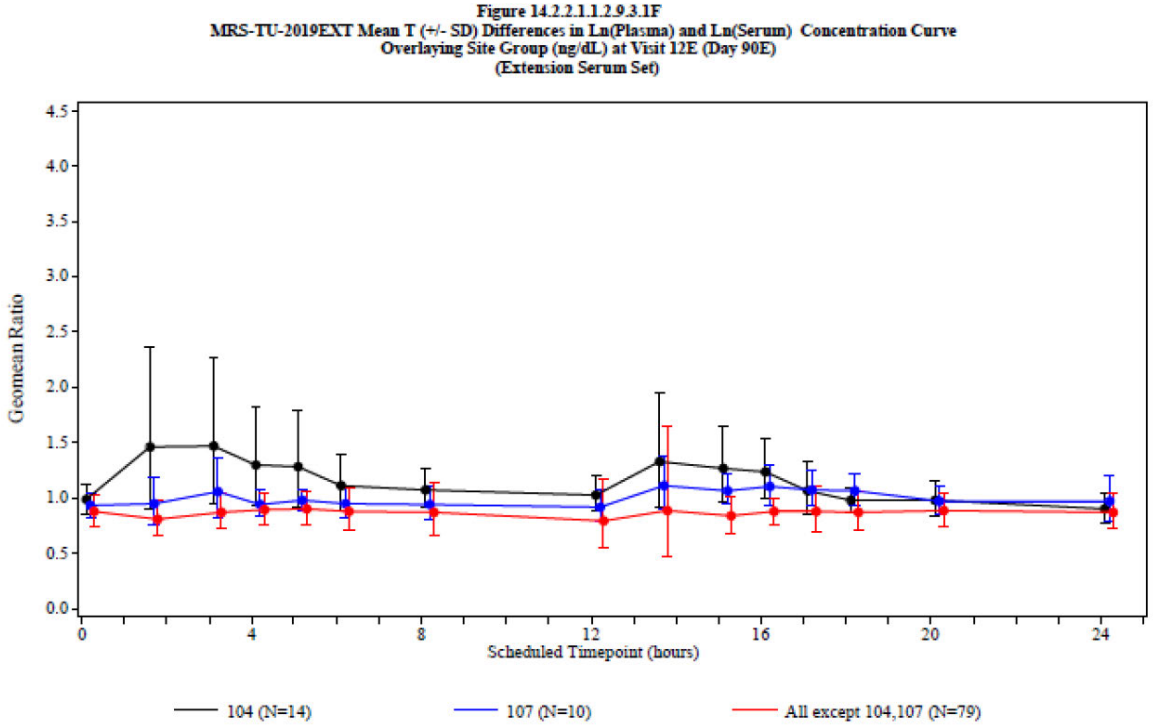
Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Table 1.

The Applicant concludes from this analysis that while the TU concentration values (either at TU Tmax or at T Tmax) from Site 104 and all other sites are not statistically different, the T Cmax values for Site 104 are statistically different from all other sites. The Applicant interprets this finding to indicate an additional factor (sample mishandling) makes a significant contribution to the T concentrations obtained at Site 104, beyond the expected drug effect of TU.

5.2.2. Site level: Significance of mean plasma over serum ratios

The Applicant references a plot of the mean plasma over serum ratios for Site 104, Site 107, and all other sites for the 24-hour Day 90E PK profile presented in the Briefing Package for the January 21, 2022, post-action meeting[3] and notes that the standard errors overlap, indicating that statistical significance did not exist at the individual timepoints. This plot is reproduced below as Figure 4.

Figure 4: Plasma over serum ratios MRS-TU-2019EXT, Visit 12E/Day 90E, Sites 104, 107, and all others



Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Figure 4.

In this analysis, to test for statistical significance, the Applicant tested the null hypothesis that the mean ratios for Site 104, Site 107, and all other sites are similar. In Table 3, an Area-Under-Curve (AUC) comparison for the ratio data of Figure 4 is presented where the Geometric Least Square Means of the populations are compared.

[3] NDA 215953 (SDN 035), Module 1.6.2, Briefing Package.

Table 3: Plasma T over Serum T Ratio AUC Comparison

PK Comparison	Test GLSM	Reference GLSM	Ratio of AUC	95% Confidence Intervals	p-value
Site 104 (Test) vs. Sites excluding 104 and 107 (Reference)	27.51	20.77	1.325	1.218, 1.441	< 0.0001
Site 104 (Test) vs. Sites excluding 104 (Reference)	27.51	21.10	1.304	1.199, 1.419	< 0.0001
Sites 104 + 107 (Test) vs. Sites excluding 104 and 107 (Reference)	25.94	20.77	1.249	1.168, 1.336	< 0.0001
Site 107 (Test) vs. Sites excluding 104 and 107 (Reference)	23.89	20.77	1.150	1.054, 1.255	0.0019

GLSM: Geometric Least Square Mean; AUC: Area-under-curve

Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Table 2.

The Applicant notes that the three tests where Site 104 is compared against the reference populations, the p-value indicates statistical significance at the 0.0001 level. For Site 107, the p-value indicates significance at the 0.0019 level and the null hypothesis of similarity is rejected.

The Applicant concludes that the plasma over serum ratios observed for the samples from Site 104 are not of the same population as all other sites (with or without Site 107). and that a factor other than drug effect contributes to the observed plasma T Cmax values from Site 104.

5.2.3. Site level: Serum to plasma correlation 3, 4 and 5 hours after dosing

This analysis compares the confidence intervals for the serum versus plasma correlation slopes 3, 4, and 5 hours after dosing for Site 104, 107, and all other sites during Visits 8E, 10E, and 12E. This analysis is summarized in Table 4.

Table 4: Confidence intervals for serum vs. plasma correlation slopes

Serum versus Plasma correlation (subjects)	Slope	Lower 95%CI	Upper 95% CI
Visit 8E and 10E Site 104 (n=16)	1.040	0.993	1.087
Visit 8E and 10E Site 107 (n=14)	0.988	0.899	1.077
Visit 8E and 10E All other sites excluding 104 (n=130)	1.048	1.020	1.075
Visit 8E and 10E All other sites excluding 104 and 107 (n=116)	1.055	1.025	1.084
Visit 12E Site 104 (n=14)	0.342	0.205	0.479
Visit 12E Site 107 (n=10)	0.839	0.701	0.977
Visit 12E All other sites excluding 104 (n=89)	1.004	0.950	1.059
Visit 12E All other sites excluding 104 and 107 (n=79)	1.071	1.012	1.129
Visit 12E All sites (n=103)	0.722	0.654	0.789

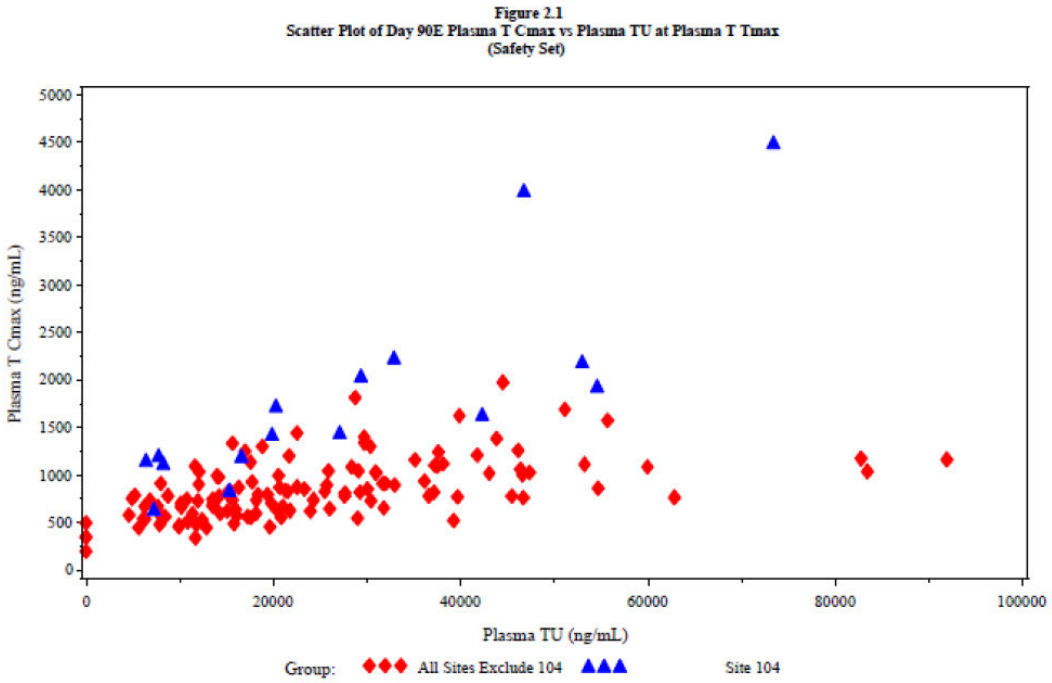
Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Table 3.

From this analysis, the Applicant concludes that the V12E/Day 90E data from Site 104 differs substantially from all other sites and from the Visit 8E and 10E data from the site (Site 104).

5.2.4. Site level: Plasma T Cmax Correlation from TU Concentrations

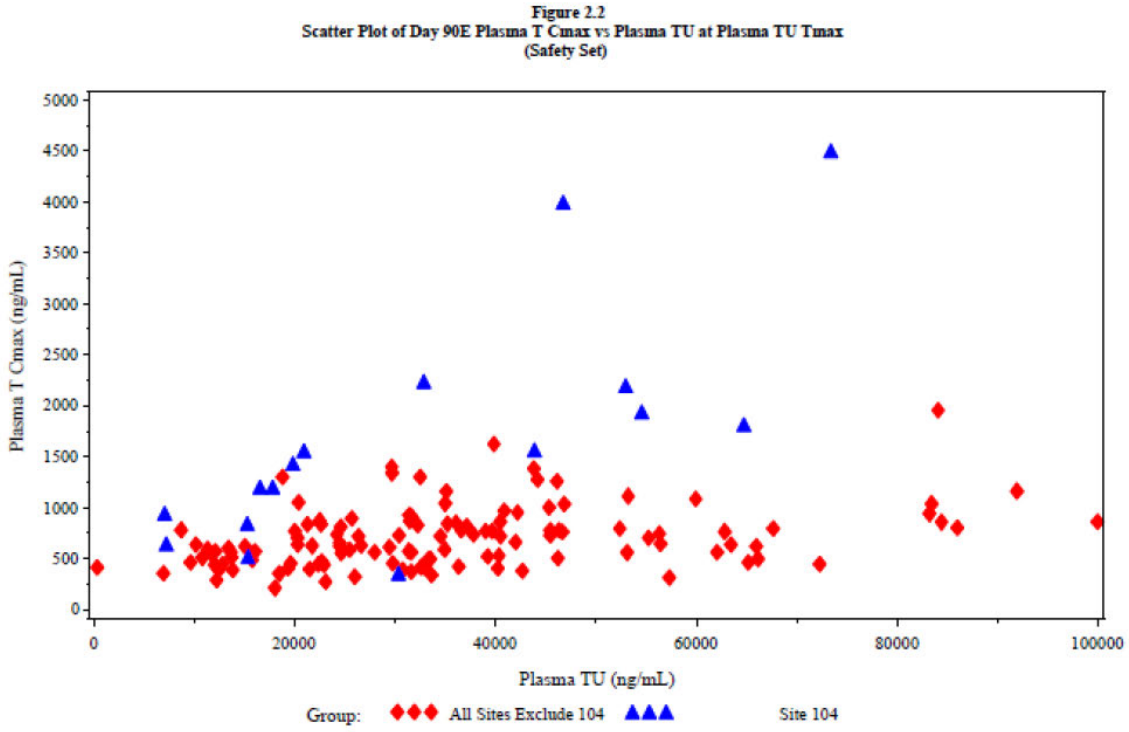
This analysis consists of two scatter plots that show the difference between the T Cmax levels resulting from the TU levels at either T Tmax or TU Tmax. Figure 5 shows the T Cmax values resulting from the corresponding TU value at T Tmax and Figure 6 the T Cmax values versus the TU at Tmax for TU. Plasma TU levels for all sites except Site 104 are represented by red diamonds and Site 104 data are represented by blue triangles.

Figure 5: Scatter Plot of NaF/EDTA Plasma T Cmax versus TU at T Tmax



Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Figure 5.

Figure 6: Scatter Plot of NaF/EDTA Plasma T Cmax versus TU at TU Tmax



Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Figure 6.

The Applicant believes these figures demonstrate that the T Cmax values for Site 104 show a different relationship with TU concentrations than for all other sites and concludes that this different relationship for Site 104 T Cmax values to the TU prodrug concentrations result from an extrinsic factor (non-drug effect) contributing to the observed T Cmax values for Site 104.

5.2.5. Subject level: Prediction of T C max concentrations from TU concentrations in MRS-TU-2019EXT

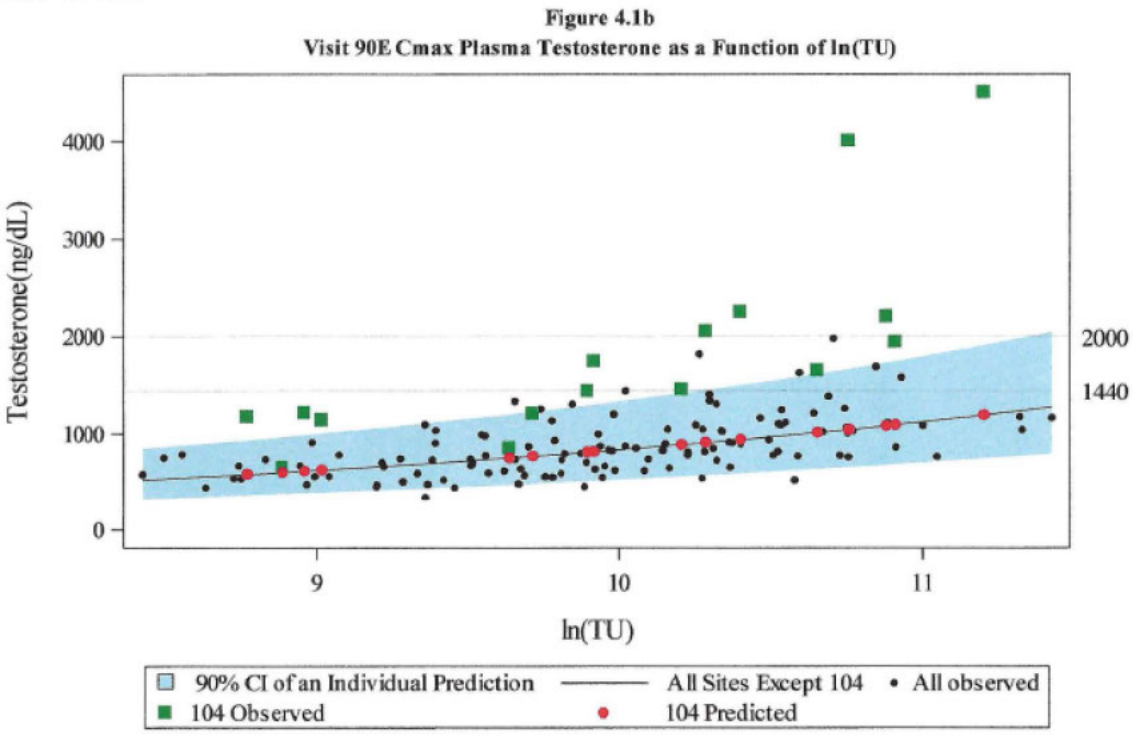
Based on the relationship between TU and T Cmax levels seen in Figure 5 and Figure 6, the Applicant tested whether T Cmax for subjects in MRS-TU-2019EXT could be predicted from the observed T Cmax and the associated TU concentrations for all other subjects.

The model was developed by using linear regression on all Visit 12E Cmax data except site 104, (ln(T) as a function of ln(TU)); a prediction line and associated confidence intervals were developed. This relationship was used to better qualify the plasma disparities at Site 104.

Figure 7 presents the MRS-TU-2019EXT T Cmax data (V12E/Day 90E) plotted as a function of the TU concentration at the T Tmax timepoint and includes the predicted (black) line. The T Cmax and TU values from all sites other than Site 104 were used to develop the model plotted as the

black line, and the observed values plotted as black circles. Green squares are the observed Site 104 T Cmax concentrations and red circles are the model-predicted values for Site 104. The blue-shaded area represents the 90% confidence interval of the model prediction of T Cmax based on all subjects (n=130), excluding Site 104 subjects (n=16). The 90%CI is used as it is the accepted practice for bioequivalence studies.

Figure 7: Plasma Testosterone Cmax vs. Ln(TU) at T Tmax, MRS-TU-2019EXT



Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Figure 7.

The Applicant had the following observations for the plot:

- All 5 T Cmax above 2000 ng/dL (2.5X ULN) fall outside the 90% CI
- All of the 9 Site 104 subjects above 1440 ng/dL and less than 2000 ng/dL (>1.8X-2.5X ULN) fall outside the upper 90% CI limit.
- For the 16 subjects from Site 104, 14 fall above the predicted line and above the upper 90% CI limit.
- The upper limit of the 90% CI at the maximum observed TU concentration (right most black circle) in the 2019EXT study is about 2000ng/dL, indicating the low probability of actually observing a T Cmax above 2000 ng/dL.
- The Site 104 data points appear to be a different population than that of all other sites.

5.2.6. Subject Level: Examination of Observed and Predicted T Cmax for All subjects from Site 104 and estimation of contribution of sample mishandling.

Using the model displayed in Figure 7, the observed and predicted T Cmax values are shown in Table 5 (all Site 104 subjects) and Table 6 (all other subjects with Cmax > 1.8X ULN) along with an estimate of the contribution from a factor other than the drug effect, i.e., sample mishandling. Two estimates of the sample mishandling effect are shown, to indicate a realistic range, rather than a single number. The higher percentage of possible mishandling effect comes from the difference between the observed and predicted, and the lower estimate comes from the difference between the observed and the upper limit of the 90% CI.

Table 5: Observed and Predicted Cmax Values for All Site 104 Subjects

Site	Subject	Observed Plasma T (ng/dL)	Plasma TU	Predicted Plasma T	Observed Minus Predicted	Observed Minus 90%UCIL	% Non-drug Effect Relative to Predicted	% Non-drug Effect Relative to 90% UCIL
104	(b) (6)	1163	6410	580	583	240	50	21
104		642	7212	601	41	-302	6	-47
104		1208	7770	614	593	231	49	19
104		1129	8236	625	504	138	45	12
104		844	15329	750	94	-348	11	-41
104		1199	16536	767	432	-15	36	-1
104		1430	19819	809	621	145	43	10
104		1735	20273	814	921	450	53	26
104		1449	27055	886	563	56	39	4
104		2045	29300	907	1137	603	56	29
104		2241	32879	939	1302	760	58	34
104		1640	42264	1011	629	36	38	2
104		3999	46714	1041	2958	2341	74	59
104		2197	52929	1080	1118	492	51	22
104		1936	54579	1090	847	211	44	11
104		4500	73333	1189	3312	2685	74	60

Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Table 4.

Table 6: Observed and Predicted Cmax Values for Subjects with Cmax>1.8X ULN, Except Site 104

Site	Subject	Observed Plasma T (ng/dL)	Plasma TU	Predicted Plasma T	Observed Minus Predicted	Observed Minus 90%UCLI	Non-drug Effect Relative to Predicted	Non-drug Effect Relative to 90% UCLI
107	(b) (6)	1815	28704	902	913	380	50	21
121		1624	39837	993	631	42	39	3
107		1976	44486	1026	950	340	48	17
107		1687	51101	1069	618	-18	37	-1
107		1576	55670	1096	480	-174	30	-11

Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Table 5.

The Applicant had the following observations and conclusions regarding Tables 5 and 6:

- For the two subjects (both from Site 104) with T Cmax values of 3999 and 4500 ng/dL, the size of non-drug effect from the 90% CI is about 60%. As can be seen from Figure 7 (and Figure 5 and Figure 6), these two Cmax values are far from the rest of the 144 subjects completing Day 90E. The non-drug effect alone is larger than the predicted T Cmax (the drug effect) based on the TU concentration. There is no safety risk from these

values because the observed values do not bear a meaningful relationship to the drug effect.

- For the 5 subjects with T Cmax >2000 ng/dL (2.5X ULN), who are all from Site 104, correction using the 90% CI upper limit of the predicted concentration brings the T Cmax below 2000 ng/dL. The sample mishandling contribution for these subjects ranges from 22% to 60% using the 90% CI upper limit, which is a conservative estimate. Again, with the substantial non-drug effect, there is not a safety risk from the observed values.
- Of the 4 Site 104 subjects with T Cmax > 1.8X to 2.5X the ULN, the sample mishandling contribution using the model-predicted 90% CI ranges from 2% to 26% of the observed T Cmax.
- For the 5 subjects not from Site 104 with T Cmax >1.8X ULN, the size of the nondrug effect appears to be similar for three subjects, with the non-drug contribution ranging from 3% to 21% using the 90% CI. Two other subjects fall within the 90% CI.

5.2.7. Applicant's overall conclusions from site-level and subject-level examination of T Cmax concentrations

The Applicant believes it has shown by each of the following that the T Cmax values obtained from Site 104 comprise a different population than the rest of MRS-TU-2019EXT.

- T Cmax values at Day 90E for Site 104 (n=16) differs significantly from all other subjects (18 sites, n=129), (p = 0.002), whereas the TU populations do not differ.
- AUC analysis of the plasma:serum ratio across the Day 90E PK profile (p< 0.0001)
- Correlation line slopes for Site 104 for plasma:serum ratio at 3, 4 and 5 hours have 95% CI's entirely separate from those for the rest of the study and separate from Visits 8E and 10E for Site 104 itself.
- Modeling and T Cmax vs. TU demonstrates the consistent non-drug effect seen for Site 104 subjects.

They also believe that the sum of these tests rules out the possibility of the observed T Cmax values at Site 104 arising only from drug effect and demonstrate a substantial contribution from another effect, identified as sample mishandling. The Applicant concludes that the T Cmax outliers > 2.5X ULN are highly unlikely (those observed were due to large non-drug effects) and that non-drug effects at Site 104 also inflate the percentage of outliers >1.8X-2.5X ULN.

5.2.8. Clinical reviewer comments regarding the resubmission

Site level analyses:
In the resubmission, the Applicant submitted additional site level analyses that suggest the T Cmax values obtained from Site 104 comprise a different population than the T Cmax values from the rest of MRS-TU-2019EXT and that the observed T Cmax values at Site 104 were the result of both the drug effect and another effect due to sample mishandling. However, these were not the issues that resulted in the CR for the first review cycle.

The disparity between the Site 104 data and data from the other sites was known during the first review cycle. The analyses submitted in the original submission highlighted these differences. More importantly, the post-study interview with the study coordinator who processed the Site 104 pharmacokinetic (PK) samples during Visit 12E indicated that the samples from this site were not handled and processed correctly (in accordance with the instructions in the lab manual).[4] The issue that resulted in the CR during the first review cycle was the "significant uncertainties about the reliability of the PK data of the entire study."[5] Showing that the Site 104 data were different from the other sites does not resolve the concerns regarding the reliability of the data from the entire study.

That the observed T Cmax values at Site 104 were the result of both the drug effect and another effect (ex vivo conversion of TU to T) was also not an issue during the first review cycle: based on the sample mishandling detailed by the Site 104 study coordinator and the known conversion of TU to T with sample mishandling, it is obvious that the observed T Cmax values at Site 104 included T from mishandling as well as the drug (drug effect). The issue during the first review cycle was the quantity of T resulting from the drug effect.

Subject level analyses:
For the subject level analyses, the Applicant developed a model using linear regression on all Visit 12E Cmax data except Site 104, (ln(T) as a function of ln(TU)) and developed a prediction line and associated confidence interval for this relationship.[6] The Applicant hypothesizes that their model can be used to predict the T concentration if the samples had been processed per the lab manual (i.e., at 4°C). No data were submitted to support the accuracy of this model in predicting these T concentration values.

To gain additional insight regarding the ability of the Applicant's model to accurately predict T concentration values, this reviewer analyzed these predicted T values in comparison to the clinical data derived from the Biological Sample Stability Substudy (BSSS). The BSSS is a clinical study that evaluated T concentrations for various sample holding temperatures (room temperature and 4°C) and times (15 – 120 minutes).[7]

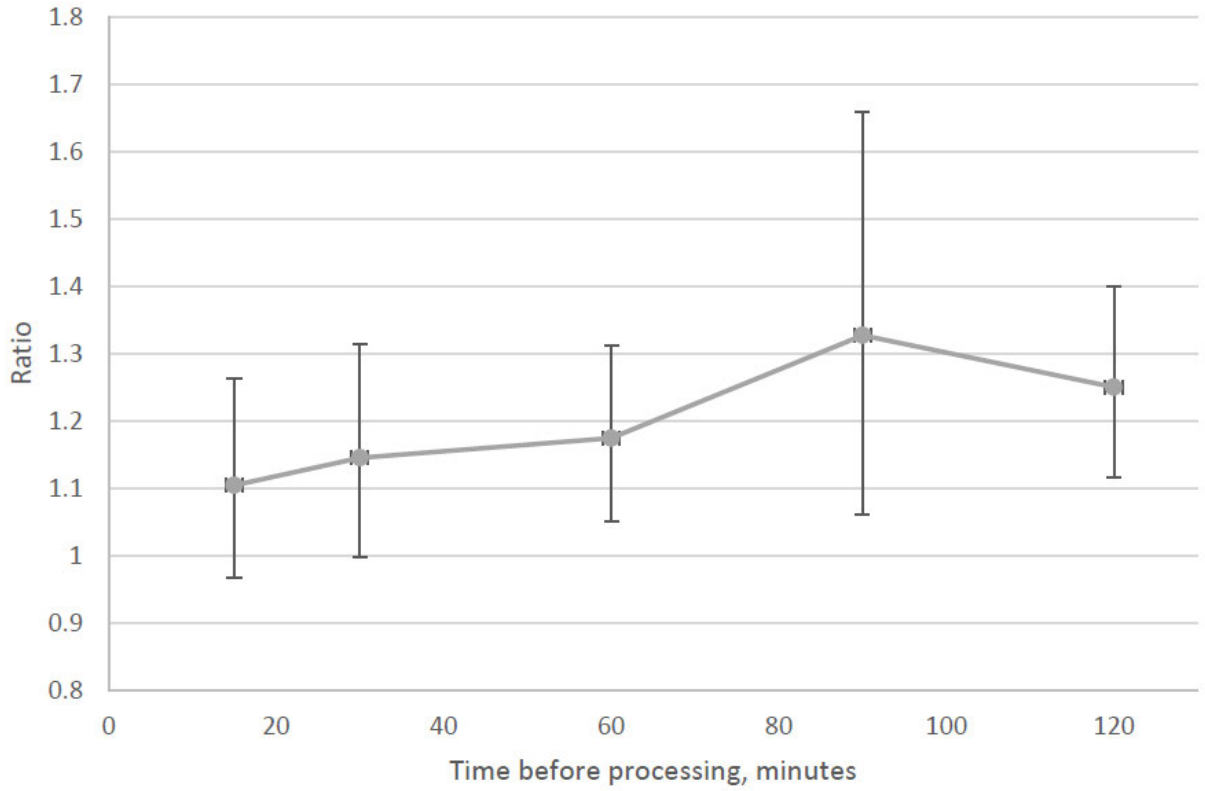
The purpose of the BSSS was to investigate the stability of blood samples used for titration and efficacy endpoint determination in the Phase 3 clinical studies. Since TU is an ester prodrug of T and is converted by non-specific esterases in the blood, there is post-collection conversion of TU to T that varies under various sample handling and processing conditions. The BSSS protocol

[4] NDA 215953 (SDN 017), Module 1.11.3, Clinical Information Amendment, Appendix 2, page 8.
[5] See NDA 215953, Complete Response Letter, entered in DARRTS on October 22, 2021, by Samantha Bell.
[6] The Applicant chose the 90% confidence interval. The Applicant's rationale for choosing this confidence interval is: "it is the accepted practice for bioequivalence studies."
[7] NDA 215953 (SDN 001), Module 5.3.5.1, Biological Sample Stability Substudy Report.

collected whole blood samples into various types of tubes, which were then processed under various sample holding temperatures (room temperature or 4°C) and times (15 – 120 minutes). Twelve (12) subjects at six clinical sites participated in this study.

Because the sample mishandling (as proposed by the Applicant) at Site 104 was the result of errors involving sample holding temperature, the BSSS data for NaF/EDTA plasma tubes held at room temperature compared to 4°C were relevant to this reviewer's analysis. The BSSS used an ANOVA model to analyze the ratio between samples held at room temperature and 4°C for plasma samples collected in NaF/EDTA tubes. The T concentration ratios for room temperature over 4°C for NaF/EDTA samples are plotted versus processing time in Figure 8.

Figure 8: T Concentration Ratio (90% CI) of Room Temperature over 4°C NaF/EDTA Plasma Samples vs. Processing Time (min)



Source: NDA 215953 (SDN 001), Module 5.3.5.1, Biological Sample Stability Substudy Report, Figure 5, p. 14.

The plasma T concentration values predicted by the Applicant's model should approximate the T concentration had the blood samples been processed at the temperature specified in the lab manual (i.e., at 4° C). The observed plasma T concentration values represent the T concentration that resulted with the holding temperature actual used at Site 104 (assumed to be room temperature). Therefore, if the model is accurate, the ratio of the observed T concentration value over the model predicted T concentration value should be reasonably

consistent with the T concentration ratio of samples held at room temperature over samples held at 4º C derived in the BSSS.

The analysis to assess the accuracy of the Applicant's model focused on Subjects (b) (6) and (b) (6). The Applicant used the T concentration values predicted by the model to quantify the non-drug and, by calculation, the drug effect of the observed T Cmax values for Site 104 subjects. Subjects (b) (6) and (b) (6) had the highest observed plasma T Cmax values in MRS-TU-2019EXT and quantifying the drug effect for these subjects is critical for determining both the efficacy and the safety of the drug. For subject (b) (6) the observed T concentration is 4500 ng/dL, and the predicted value is 1189 ng/dL. The ratio of the observed value over the model predicted value is 3.8. For subject (b) (6) the observed T concentration is 3999 ng/dL, and the predicted value is 1041 ng/dL. The ratio of the observed T concentration value over the model predicted value for this subject is also 3.8.

The ratio of the observed T concentration value over the model predicted T value for subjects (b) (6) and (b) (6) far exceeds the ratio of the T concentration for samples held at room temperature over the T concentration for samples held at 4º C derived in the BSSS. This is true for the upper bound of the 90% confidence interval for the BSSS derived ratios for all holding times including 120 minutes.

If, as proposed in the resubmission, the upper bound of the 90% confidence interval for the Applicant's model is used, the predicted T concentration value for subject (b) (6) is 1815 ng/dL and the predicted value for subject (b) (6) is 1658 ng/dL. The ratios of the observed T concentration value over the model predicted value for subjects (b) (6) and (b) (6) are 2.5 and 2.4, respectively. These ratios also exceed the upper bound of the 90% confidence interval for the BSSS ratios for the T concentration of samples held at room temperature over the T concentration of samples held at 4º C for all holding times including 120 minutes.

These findings imply that the T concentrations predicted by the model underestimate what would be expected if the holding time for the samples had been 4º C and raise serious concerns that the Applicant's model does not accurately predict T concentrations used to estimate the drug effect component of the observed T concentration in MRS-TU-2019EXT. The observed T concentration values are comprised of T that is the result of the drug (drug effect) and T that is the result of ex vivo conversion due to mishandling. Based on the reviewer's comparisons of the model predicted T concentration values to actual clinical data derived in the BSSS, it appears that the model underestimated the T concentration values for subjects (b) (6) and (b) (6) and consequently the drug effect component of the observed T concentration. Although the exact amount of the underestimation of the drug effect cannot be definitively determined, the uncertainty of the model predicted T concentration values precludes us from concluding that the drug effect of the observed T Cmax values for Subjects (b) (6) and (b) (6) was less than 2000 ng/dL (2.5 X ULN).

It should also be noted that the holding conditions used in the BSSS were room temperature for up to 120 minutes. It is likely that the actual holding conditions (temperature and time) at Site 104 were less than the holding conditions in the BSSS. The sample mishandling detailed by the Site 104 study coordinator during the post-study interview on January 9, 2020, described holding the plasma samples in a refrigerated centrifuge chilled to 4º C (not at room temperature) for 30 minutes (not 120 minutes).[8] The only time the samples were held at room temperature was during the blood draw and while the samples were moved from the exam room to the lab (this time interval was not specified). Therefore, it is possible that the Applicant's model underestimates T concentrations by more than the comparison with the BSSS has indicated.

6. Conclusions

During the first review cycle, NDA 213953 received a Complete Response action due to the review team's conclusion that the lack of contemporaneous documentation for PK sample handling and processing at all clinical sites of MRS-TU-2019EXT posed significant uncertainties about the reliability of the PK data for the entire study.

This conclusion was based on site inspections of Site 104 and Site 107 by the Office of Scientific Integrity and Surveillance (OSIS). During these inspections, neither site was able to provide documentation regarding PK blood sample processing and handling. OSIS concluded that "the reliability of the data from site 104 and site 107 may be impacted. Because the same study design and laboratory manual for sample processing was followed at all the clinical sites including the sites not inspected, we believe the objectionable conditions observed at the two inspected clinical sites were likely present at the other 17 clinical sites that were not inspected. Thus, the reliability of the clinical data from the entire study may be impacted. We recommend the review division to contact the Applicant to determine if similar objectionable conditions from sites 104 and 107 existed at the other 17 clinical sites that were not inspected."[9] The Division requested documentation regarding sample handling and processing at the other clinical sites from the Applicant. The Applicant's responses revealed a lack of documentation for PK sample handling and processing at the other clinical study sites of MRS-TU-2019EXT.

In the resubmission, the Applicant submitted site level and subject level analyses. Although the site level analyses may suggest that the Site 104 data are different from the other sites in the

[8] NDA 215953 (SDN 017), Module 1.11.3, Clinical Information Amendment, Appendix 2, page 8.
[9] NDA 213953, Bioequivalence Establishment Inspection Report Review, entered in DARRTS on September 28, 2021, by Yiyue Zhang.

study, they do not address the concerns regarding the reliability of the data from the entire study and are not sufficient to resolve the deficiency from the first review cycle.

The subject level analyses were based on the Applicant's unvalidated model, which attempted to predict the Site 104 T Cmax values from their TU concentrations. When model generated T concentration values were compared to actual clinical data from the Biological Sample Stability Substudy (BSSS), the model generated T concentration values were less than the values expected from the BSSS data. This reviewer concluded that the model did not rule out a drug effect greater than 2000 ng/dL (2.5 X ULN) for the two subjects with the highest T Cmax values in MRS-TU-2019EXT. This finding and the fact that Subject (b) (6) exceeded the T Cmax > 2.5 X ULN criterion for both plasma and serum samples raised concerns that Kyzatrex did not avoid excessive T concentration peaks. For a drug that is expected to be administer chronically over a long period of time, this is a safety concern.

This reviewer continues to believe that having reliable and accurate PK data are foundational to the clinical review of NDA 213953 and the uncertainty still surrounding these data precludes a conclusion that the Applicant has provided substantial evidence that the drug is safe and effective.

7. Recommendation

This reviewer recommends issuing a Complete Response for the resubmission of NDA 213953.

8. Labeling Recommendations

See Section 10 Labeling Recommendations of the Unireview for the first review cycle entered in DARRTS October 22, 2021.

9. Risk Evaluation and Mitigation Strategies (REMS)

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

10. Postmarketing Requirements and Commitments

None required.

APPEARS THIS WAY ON ORIGINAL

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

/s/

MARTIN E KAUFMAN
07/15/2022 10:46:51 AM

SURESH KAUL
07/15/2022 11:55:35 AM

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 213953
Link to EDR	\\CDSESUB1\evsprod\NDA213953\0037 [SDN 38 (1/27/2022) and SDN 42 (3/18/2022)]
Submission Date	1/27/2022
Submission Type	Complete Response - Resubmission
Brand Name	Kyzatrex®
Generic Name	Testosterone undecanoate (TU)
Dosage Form and Strength	Kyzatrex® soft gelatin capsules: 100 mg, 150 mg, and 200 mg
Route of Administration	Oral
Proposed Indication	Testosterone replacement therapy (TRT) in adult males for conditions associated with a deficiency or absence of endogenous testosterone (T)
Applicant	Marius Pharmaceuticals, LLC
Associated IND	IND 118675
OCP Review Team	Chongwoo Yu, PhD Yanhui Lu, PhD Shirley Seo, PhD
OCP Final Signatory	Shirley Seo, PhD Division Director Division of Cardiometabolic and Endocrine Pharmacology (DCEP), Office of Clinical Pharmacology (OCP)
OND Division	Division of Urology, Obstetrics and Gynecology (DUOG)

Table of Contents

1. EXECUTIVE SUMMARY

On January 27, 2022, the Applicant submitted a response to the Agency's October 22, 2021 complete response (CR) action on new drug application (NDA) 213953 for Kyzatrex® (testosterone undecanoate [TU]) oral soft gelatin capsules, to seek approval as testosterone replacement therapy (TRT) in adult males for conditions associated with a deficiency or absence of endogenous testosterone (T).

Kyzatrex® is available in the strengths of 100 mg, 150 mg, and 200 mg soft gelatin capsules and the recommended starting dose is 200 mg orally once in the morning and once in the evening with a meal. Prior to initiating Kyzatrex®, the diagnosis of hypogonadism should be confirmed by ensuring that serum T concentrations have been measured in the morning on at least two separate days and that these concentrations are below the normal T range. The dose of Kyzatrex® should be adjusted to a minimum of 100 mg once daily (QD) in the morning and a maximum of 400 mg twice daily (BID) based on serum T concentration from samples drawn 3 to 5 hours after the morning dose at least 7 days after starting treatment or following dose adjustment and periodically thereafter.

The Applicant submitted draft labeling, addendum to their analysis on subjects with T C_{max} > 1,200 ng/dL from Phase 3 trial, MRS-TU-2019EXT, safety conlcusions, and narratives to address the Agency's concern about the integretiy and reliability on data from study Site 104 and to support approval of Kyzatrex®. There were no new clinical trials conducted.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP)/Division of Cardiometabolic and Endocrine Pharmacology (DCEP) reviewed the Applicant's CR for NDA 213953 submitted on January 27, 2022 and March 18, 2022. The overall Clinical Pharmacology information submitted to support this NDA is **acceptable** and Kyzatrex® is **recommended for approval** as a TRT in adult males for conditions associated with a deficiency or absence of endogenous T from the Clinical Pharmacology standpoint.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Kyzatrex® contains TU, a fatty-acid ester of T, an androgen that is formed by cleavage of the ester side chain of TU. Endogenous androgens, including T, 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.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of T, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (e.g., follicle-stimulating hormone [FSH], luteinizing hormone [LH]).

Absorption, Distribution, Metabolism, and Excretion (ADME)
See Section 3.2 of this review for ADME information of Kyzatrex®.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended starting dose is 200 mg orally BID, once in the morning and once in the evening. Kyzatrex® should be taken with food. Kyzatrex® is not substitutable with other oral TU products.

2.2.2 Therapeutic individualization

The dosage of Kyzatrex® should be individualized based on the patient's serum T concentration response to Kyzatrex®. To ensure proper dose adjustment, serum T concentrations should be checked 7 days after starting treatment or after dosage adjustment, 3 to 5 hours after the morning dose. The Kyzatrex® dose should be adjusted as shown in Table 1, as necessary. Thereafter, periodically monitor serum T concentrations. The minimum recommended dose is 100 mg QD in the morning. The maximum recommended dose is 400 mg (two 200 mg capsules) BID. For total daily doses greater than 100 mg, the same dose should be administered in the morning and evening.

Table 1: Kyzatrex® Dosage Adjustment Scheme

Serum Testosterone Concentration	Current KYZATREX Dosage	New KYZATREX Dosage
Less than 460 ng/dL	100 mg with breakfast only	100 mg twice daily with meals
	100 mg twice daily with meals	200 mg twice daily with meals
	200 mg twice daily with meals	300 mg twice daily with meals
	300 mg twice daily with meals	400 mg twice daily with meals
460 to 971 ng/dL	No Dosage Change	
More than 971 ng/dL	400 mg twice daily with meals	300 mg twice daily with meals
	300 mg twice daily with meals	200 mg twice daily with meals
	200 mg twice daily with meals	100 mg twice daily with each meals
	100 mg twice daily with meals	100 mg with breakfast only
	100 mg with breakfast only	Discontinue treatment

Source: Table 15, Module 2.7.3, NDA 213953 (submitted December 31, 2020)

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Clinical Pharmacology review team's labeling recommendations include the following:

Section 2 Dosage & Administration

- Revised the entire section together with Division of Urology, Obstetrics and Gynecology (DUOG) multi-disciplinary revew team for clarity and conveyed the recommended edits and comments to the Applicant on September 30, 2021 (i.e., previous review cycle) and the Applicant has incorporated the Division's recommendations in the draft product label submitted on January 27, 2022.

Section 7 Drug Interactions

- The proposed content is acceptable.

Section 12.3 Pharmacokinetics (PK)

- [redacted] (b) (4) as the efficacy and safety of Kyzatrex® was established based on sodium fluoride (NaF)/ethylenediaminetetraacetic acid (EDTA) plasma T data.
- [redacted] (b) (4) as the Dosage & Administrion instructions (Section 2) state that Kyztrex® needs to be taken with food [redacted] (b) (4) .
- [redacted] (b) (4) as it is not relevant to the Dosage & Administration instructions (Section 2) of Kyzatrex®.

Section 14 Clinical Studies

- This section should be focused on the design and the efficacy outcomes (e.g., achievement of responder rates and T C_{max} endpoint) of the Phase 3 clinical trial. Information related to [redacted] (b) (4) Edits are proposed accordingly.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Product

Kyzatrex® is a soft gelatin capsule containing (b) (4) TU, a prodrug of T, (b) (4). TU is converted to T by nonspecific esterases present in the body. Kyzatrex® is available in the strengths of 100 mg, 150 mg, and 200 mg. The recommended starting dose is 200 mg orally once in the morning and once in the evening with a meal.

Endogenous androgens, including T, are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. The Applicant has developed Kyzatrex® as a TRT for the treatment of male hypogonadism, a clinical syndrome resulting from insufficient secretion of T.

Regulatory History

The Applicant opened investigational new drug (IND) application 118675 on March 17, 2016 for the clinical development of this oral TU product. The original NDA 213953 was submitted on December 31, 2020. Reference is made to DUOG's multi-disciplinary review and evaluation (i.e., unireview) dated October 22, 2021. Substantial evidence of effectiveness could not be established for Kyzatrex® because of unresolved uncertainties about the reliability of the efficacy data in the single Phase 3 trial (MRS-TU-2019EXT) supporting approval. The Applicant notified the Agency at the July 2020, pre-NDA meeting that multiple subjects at clinical study Site 104 of Study MRS-TU-2019EXT had NaF/EDTA plasma T concentrations that were paradoxically higher than serum T concentrations obtained at the same timepoint and proposed to exclude Site 104 for efficacy analysis.

Due to matrix effect, endogenous T concentrations are usually higher in serum compared to that in plasma (when blood samples are collected from same subject at the same timepoint and then split up for analysis) (Study MRS-TNR2019). In addition, TU to T *ex vivo* converstion may occur during sample handling. The following factors are known to contribute to the TU to T *ex vivo* conversion that affects the concentration measurements in both serum and plasma (LaChance, 2015):

- Post-collection incubation temperature: Lowering the temperature reduces conversion.
- Post-collection incubation time: TU to T *ex vivo* conversion occurs most rapidly during the first 30 minutes post-collection. Reducing the incubation time will help reduce the TU to T *ex vivo* conversion.
- TU concentration: The TU to T *ex vivo* conversion is TU concentration-dependent.
- Presence of esterase inhibitor (e.g., NaF) in test tubes: The presence of esterase inhibitor (e.g., NaF in NaF/EDTA tube) further reduces the TU to T *ex vivo* conversion

TU to T ex vivo conversion can be prevented more efficiently in NaF/EDTA plasma compared to serum as esterase inhibitor, sodium fluoride (NaF) is present the tubes and plasma sanples can be placed in a ice bath at a lower temperature compared to serum that needs to sit at room temperature for the first 30 minutes. As a result, lower T concentrations are expected in NaF/EDTA plasma compared to serum, in general.

Deviation from standard procedures of sampling handling and processing may lead to unexpectedly higher T concentration from plasma compared to serum prepared from blood collected at the same timepoint from the same subject. During the original NDA review cycle, the Division requested the Office of Scientific Integrity and Surveillance (OSIS) to inspect clinical study Site 104 to confirm whether there was mishandling of PK samples to justify excluding Site 104. The OSIS also decided to inspect a second clinical study site, Site 107, a high enrollment clinical study site. At both study sites, the OSIS found no

documented record of PK sample handling and processing. At the OSIS's recommendation, the Division requested the Applicant to provide evidence of documentation of PK sample handling/processing for the other 17 clinical sites of Study MRS-TU-2019EXT but the Applicant was not able to submit the requested information. The lack of documentation of the PK sample handling/processing from any clinical study sites in Study MRS-TU-2019EXT posed significant uncertainties about the reliability of the PK data (i.e., serum and plasma T concentrations) forming the basis of Kyzatrex®'s approval. As a result, the Agency took a CR action on October 22, 2021. In the CR letter dated October 22, 2021, the Agency conveyed to the Applicant that a new Phase 3, efficacy and safety trial with adequate number of hypogonadal subjects treated with their product needs to be conducted. This trial needs to have reliable data to demonstrate that their drug is safe and effective with the proposed dose, dosing regimen, and dose titration scheme.

Subsequently, a Type A, Post-action meeting was held between the Division and the Applicant on January 21, 2022 to discuss resubmission of NDA 213953. In particular, the Applicant requested this meeting to respond to the Agency's concerns and to demonstrate that the totality of the evidence provided in NDA 213953 was sufficient. At the end of the meeting, the Division indicated there were still gaps in the NDA submission regarding T C_{max} outliers, precluding the Agency's ability to conclude that drug attribution to the observed outliers would be highly unlikely. The Applicant indicated they would submit new analyses to support that the T C_{max} outliers were highly unlikely to be due to drug effect. Reference is made to the official minutes of the January 21, 2022, Type A, Post-action meeting dated February 16, 2022 in the Agency's Document Archiving, Reporting and Regulatory Tracking System (DARRTS) for details of the meeting outcome. On January 27, 2022, the Applicant submitted this response to CR (i.e., resubmission) to the Agency's CR action on NDA 213953.

Clinical Deveopment Porgram

The clinical development program of Kyzatrex® consists of 10 clinical studies. SOV2012-F1 was selected as the to be marketed (TBM) formulation and was used in 4 clinical trials (SOV-TU-PK2017 [dose timing study], MRS-TU-PK2018 [food and alcohol effect study], MRS-TU-2019EXT [Phase 3, efficacy and safety study], and SOV-TNR2019 [normal T concentration range determination study]) that generated the essential data supporting the approval of this NDA.

Detail information about the Applicant's clinical development program can be found in DUOG's multi-disciplinary review and evaluation (i.e., unireview) for NDA 213953 dated October 22, 2021 in DARRTS. There were no new clinical trials conducted for this resubmission.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Absorption

Table 2 summarizes the PK parameters for NaF/EDTA plasma total T and TU in patients completing at least 90 days of Kyzatrex® treatment.

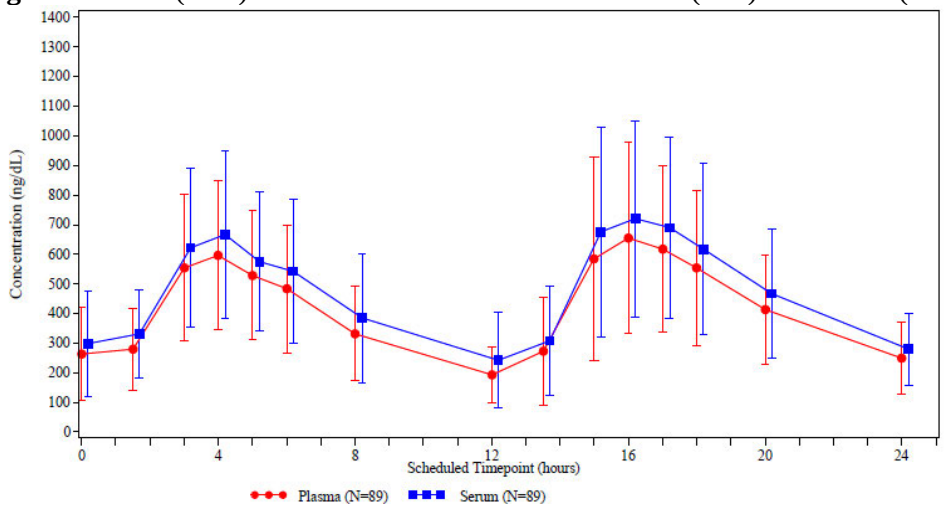
Table 2: NaF/EDTA Plasma T and TU C_{avg} and C_{max} on Day 90

PK Parameter		Plasma T (N=130)	Plasma TU (N=130)
C_{avg} (ng/dL)	n	127	119
	Mean	393.3	7806.4
	SD	113.6	4129.2
C_{max} (ng/dL)	n	130	126
	Mean	852.4	36258.9
	SD	311.3	22100.6

Source: Table 29, MRS-TU-2019 and MRS-TU-2019EXT CSR, NDA 213953 (submitted December 31, 2020)

Figure 1 summarizes the mean (±SD) plasma and serum total T PK profiles on Day 90.

Figure 1: Mean (±SD) T PK Profiles in NaF/EDTA Plasma (Red) and Serum (Blue)



Source: Figure 7, Study MRS-TU-2019EXT CSR, NDA 213953 (Submitted December 31, 2020)

Food Effect and Alcohol Interaction

When Kyzatrex® was given with 16%, 33%, and 45% fat breakfast, the exposure (i.e., area under the curce [AUC]) was increased by 37%, 87%, and 94%, respectively, compared to when given under fasted conditions. There was no effect on T PK when Kyzatrex® was administered with 20% alcohol along with a high-fat meal vs. a high-fat meal alone. See Section 6.3.2 of DUOG's multi-disciplinary review and evaluation (i.e., unireview) for NDA 213953 dated October 22, 2021 in DARRTS for detail information.

Metabolism

The androgenic activity of TU occurs after the ester bond linking the T to the undecanoic acid is cleaved by endogenous non-specific esterases. Undecanoic acid is metabolized like all fatty acids via the beta-oxidation pathway. T is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of T are DHT and estradiol (E2).

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The efficacy and safety of Kyzatrex® was evaluated in the Phase 3 trial, MRS-TU-2019EXT. The primary efficacy endpoint (i.e., T C_{avg} responder rate) and the key secondary endpoint (i.e., T C_{max} distribution) are PK-driven endpoints.

Multiple number of subjects from clinical study Site 104 had NaF/EDTA plasma T concentration results paradoxically higher than serum T concentrations obtained at the same time. As a result, the Applicant excluded all subjects from this site (N=16) for efficacy analysis. The primary efficacy endpoint was met regardless of the exclusion of Site 104 as shown in Table 3.

Table 3: Percentage of Kyzatrex®-Treated Subjects Achieving NaF/EDTA Plasma T C_{avg} within Normal Range after 90 days of Treatment with or without excluding Site 104)

Measure	Target	Without excluding Site 104 (N=155)	With excluding Site 104 (N=139)
T C_{avg} Within Normal Range after 90 Days, n (%)	≥ 75%	136 (87.7)	122 (87.8)
95% Confidence Intervals	≥ 65% (Lower Bound)	82.6, 92.9	82.3, 93.2

The normal range for plasma T is 222-800 ng/dL.
Source: Table 18, DUOG's multi-disciplinary review and evaluation (i.e., unireview) for NDA 213953 dated October 22, 2021 in DARRTS

The key secondary PK endpoint (i.e., T C_{max}) was not met when including all 155 subjects, However, the key secondary PK endpoint was met after excluding subjects from Site 104 as shown in Table 4.

Table 4: Percentage of Kyzatrex®-Treated Subjects Achieving Maximum Plasma T C_{max} within Pre-determined Limits after 90 days (without or with excluding Site 104)

Measure	Target	Without excluding Site 104 (N=155)	With excluding Site 104 (N=139)
Cmax <1200 ng/dL, n (%)	≥ 85%	119 (81.5)	114 (87.7)
1440 ≤ C_{max} ≤ 2000 ng/dL, n (%)	≤ 5%	9 (6.2)	5 (3.8)
C_{max} > 2000 ng/dL, n (%)	0%	5 (3.4)	0 (0)

Source: Table 20, DUOG's multi-disciplinary review and evaluation (i.e., unireview) for NDA 213953 dated October 22, 2021 in DARRTS

As described in Section 3.1 of this review, the Division concluded that there was no supportive evidence of effectiveness due to the data integrity and reliability concerns during the original NDA review cycle. Reference is made to Sections 6.2.1 and 6.3.2 of the DUOG's multi-disciplinary review and evaluation (i.e., unireview) for NDA 213953 dated October 22, 2021 in DARRTS for detailed information.

As shown in Table 4, there were 5 NaF/EDTA plasma T C_{max} outliers. This review will focus on the Applicant's explanation/justification of these 5 NaF/EDTA plasma T C_{max} outliers who had T C_{max} > 2.5x of upper limit normal (ULN) to determine whether they were due to a drug-related effect or not.

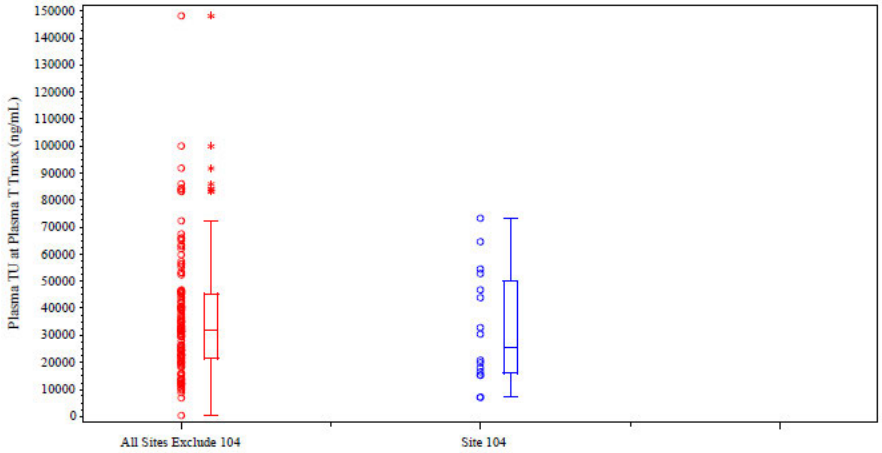
In this resubmission, the Applicant has submitted new analyses. The Applicant's assessment of the drug and sample mishandling effects focused on the following 3 points:

- The comparison of observed TU concentrations at T T_{max} and TU T_{max} from Site 104 to that from other sites in Study MRS-TU-2019EXT.

- The observed T C_{max} values from Site 104 were statistically different from that observed from other sites in Study MRS-TU-2019EXT.
- Contributions to T C_{max} from non-drug effect (e.g., sample mishandling) created a distinct T C_{max} population at Site 104. This was tested by examining on a subject level by predicting T C_{max} values based on TU concentration at T T_{max} and calculating the contributions from biological sample mishandling.

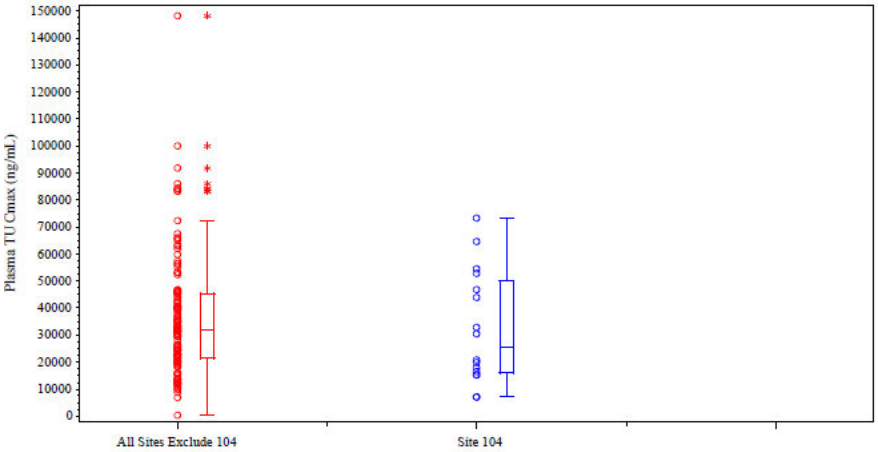
Comparison of NaF/EDTA Plasma T C_{max} and TU Concentrations, Site 104 vs. All Other Sites

Figure 2: Box Plot of Day 90E (Visit 12E) NaF/EDTA Plasma TU at T T_{max}



Source: Figure 1, SDN 038, NDA 213953 (Submitted January 27, 2022)

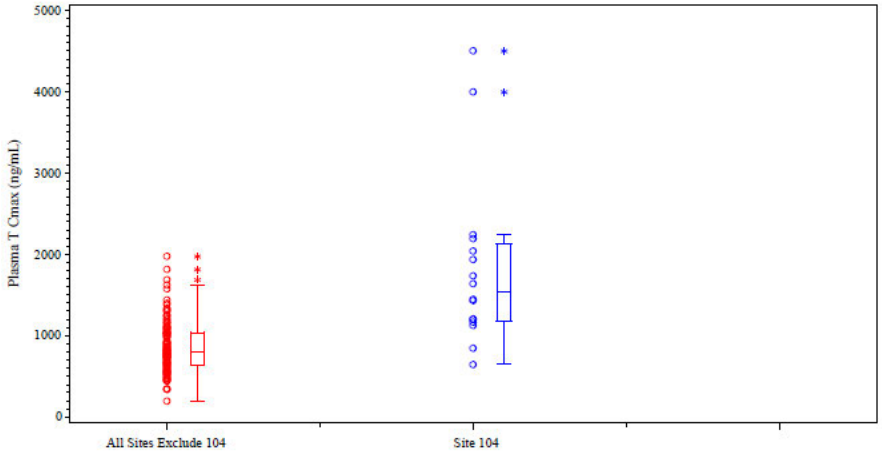
Figure 3: Box Plot of Day 90E (Visit 12E) NaF/EDTA Plasma TU C_{max}



Source: Figure 2, SDN 038, NDA 213953 (Submitted January 27, 2022)

Figures 2 and 3 show that the Site 104 TU concentrations, either at the T T_{max}, or at the TU T_{max}, appear to be a similar population of TU concentrations as the other 18 sites in Study MRS-TU-2019EXT. The median values from Site 104 and all other sites are within the inner quartiles for each other, and the lower and upper quartiles are similar in range. There were no TU C_{max} outliers identified at Site 104. In comparison, NaF/EDTA plasma T C_{max} concentrations from Site 104 were higher compared to other sites (Figure 4).

Figure 4: Box Plot of Visit 12E/Day 90E Plasma T C_{max}



Source: Figure 3, SDN 038, NDA 213953 (Submitted January 27, 2022)

Table 5 shows the Applicant's t-test applied to the samples plotted in Figures 2, 3, and 4. For both TU comparisons, Site 104 is not statistically different while for the comparison of NaF/EDTA plasma T C_{max}, the p-value is 0.002 indicating that plasma T C_{max} values of Site 104 are stastically different from other sites.

Table 5: T-test for Difference in T and TU Concentrations, Site 104 vs. All Other Sites

Comparison	Test	Reference	P value
TU at T Tmax	Site 104 (n=16)	All other subjects (n=129)	0.4232
TU Cmax	Site 104 (n=16)	All other subjects (n=129)	0.5061
T Cmax	Site 104 (n=16)	All other subjects (n=129)	0.002

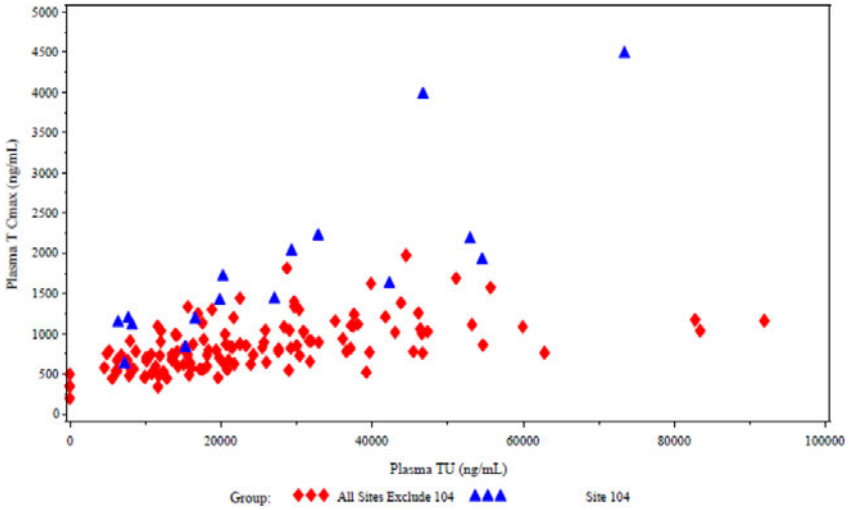
Note: P-value from 2 sample t-test, Satterthwaite method

Source: Table 1, SDN 038, NDA 213953 (Submitted January 27, 2022)

Reviewer's Comment: *While Figures 2 and 3 indicate that the TU concentrations observed from Site 104 were not outstanding compared to the TU concentrations observed from other study sites, Figure 4 shows that the T C_{max} values from Site 104 were higher compared with those from other sites.*

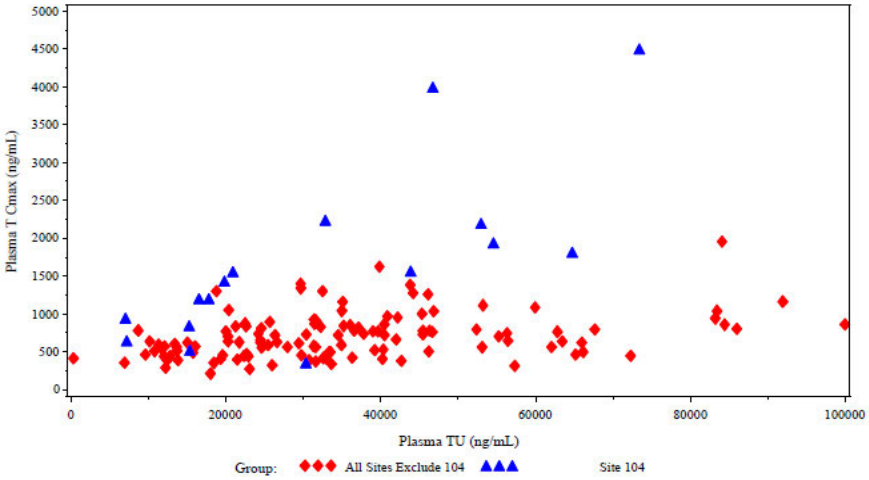
To visualize the difference in T and TU relationship between Site 104 and other sites, Figure 5 and Figure 6 presents the NaF/EDTA plasma T C_{max} and TU concentrations for all sites (except Site 104) in red diamonds and the Site 104 data in blue triangles. Figure 5 shows the T C_{max} values vs. the corresponding TU value at T_{max} for T, and Figure 6 shows the T C_{max} values vs. the TU concentrations at T_{max} for TU.

Figure 5: Scatter Plot of NaF/EDTA Plasma T C_{max} versus TU at T T_{max}



Source: Figure 5, SDN 038, NDA 213953 (Submitted January 27, 2022)

Figure 6: Scatter Plot of NaF/EDTA Plasma T C_{max} versus TU at TU T_{max}

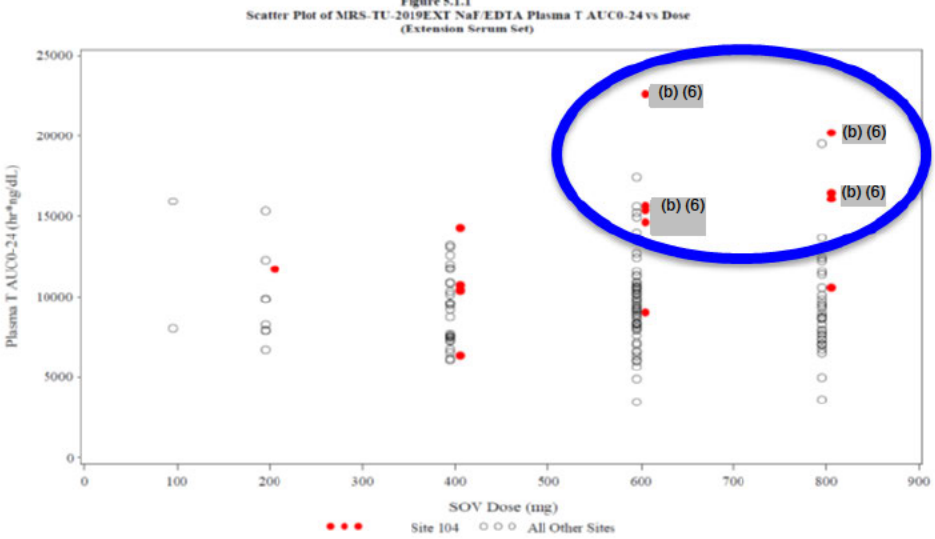


Source: Figure 6, SDN 038, NDA 213953 (Submitted January 27, 2022)

Reviewer's Comment: *Figures 5 and 6 indicate that the T C_{max} values for Site 104 subjects (i.e., not only the 5 T C_{max} outliers with > 2.5x ULN) exhibit a different relationship with TU concentrations than for all other sites.*

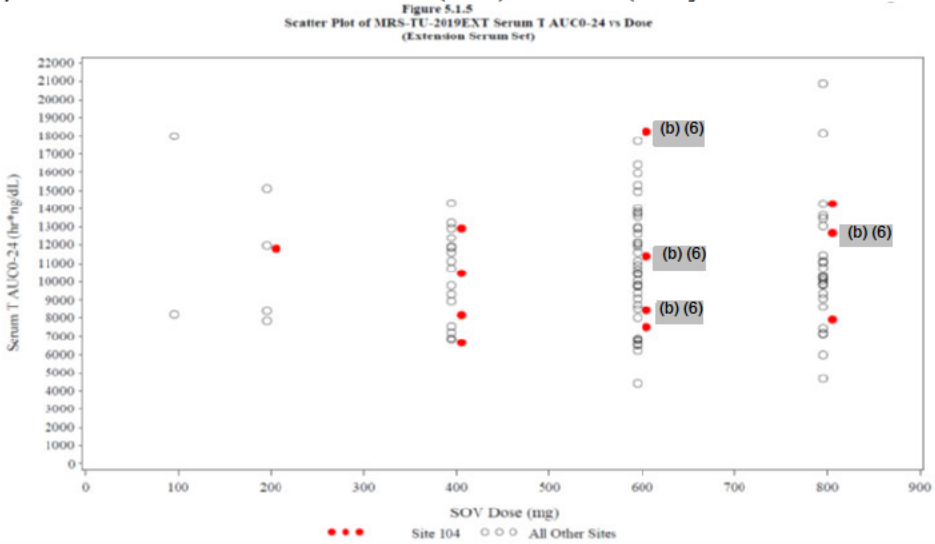
The Applicant examined how T exposure in subjects from Site 104 compares with subjects from other study sites based on their dose. Figures 7, 8, and 9 are scatter plots of NaF/EDTA plasma T, serum T, and NaF/EDTA plasma TU AUC(0-24) vs. dose, respectively.

Figure 7: Scatter Plot of NaF/EDTA Plasma T AUC(0-24) vs. Dose (Study MRS-TU-2019EXT)



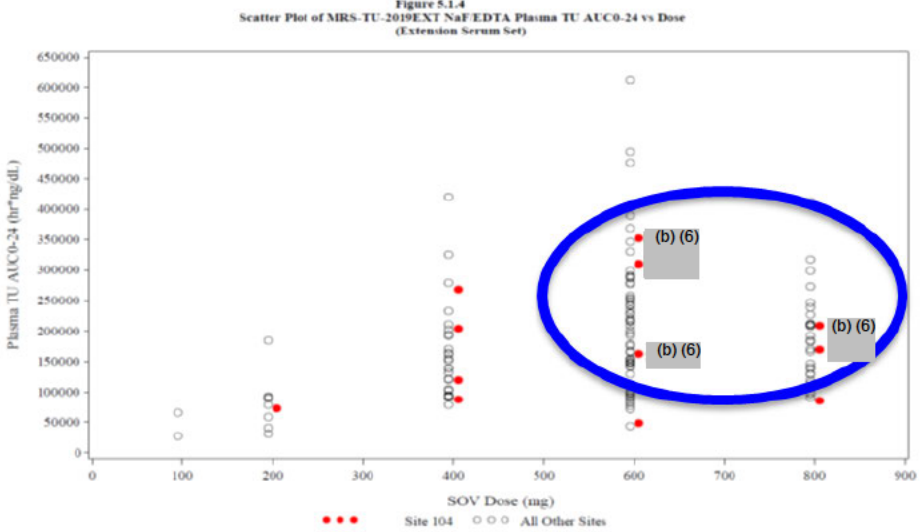
Source: Figure 5.1.1, SDN 042, NDA 213953 (submitted: March 18, 2022)

Figure 8: Scatter Plot of Serum T AUC(0-24) vs. Dose (Study MRS-TU-2019EXT)



Source: Figure 5.1.5, SDN 042, NDA 213953 (submitted: March 18, 2022)

Figure 9: Scatter Plot of NaF/EDTA Plasma TU AUC(0-24) vs. Dose (Study MRS-TU-2019EXT)



Source: Figure 5.1.4, SDN 042, NDA 213953 (submitted: March 18, 2022)

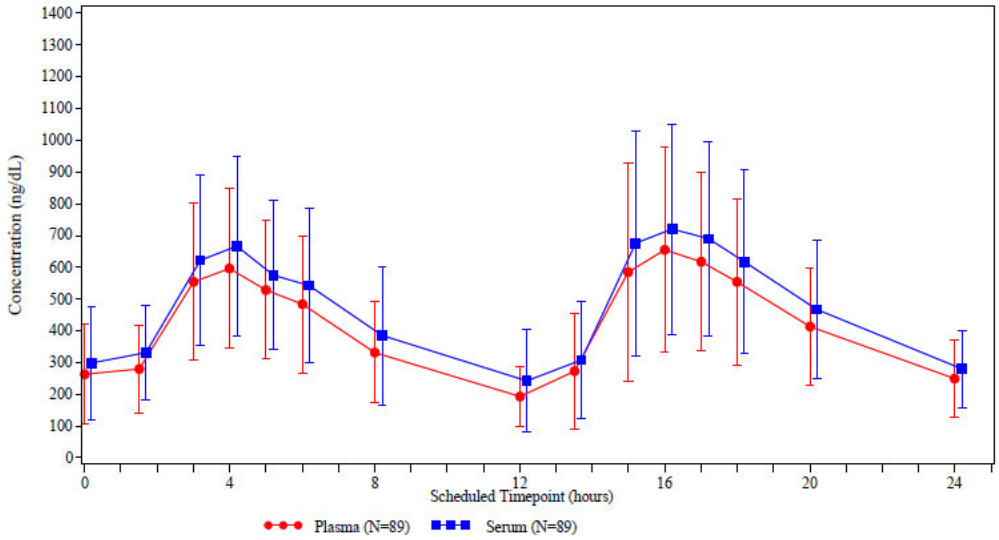
Reviewer's Comment: *As shown in Figures 7 and 8, almost all T exposures (i.e., AUC) observed in NaF/EDTA plasma and serum from Site 104 fell within the range of observed T AUC values from other study sites. The distribution pattern of AUC values for NaF/EDTA plasma T, serum T, and NaF/EDTA plasma TU in each dose group appears to be similar between Site 104 and other sites except for NaF/EDTA plasma T AUC values at 600 mg and 800 mg doses.*

As highlighted with the blue circle in Figure 7, the 5 T C_{max} outliers subjects from Site 104 generally had higher NaF/EDTA plasma T exposure compared to other subjects in the respective dose groups of 600 mg and 800 mg (i.e., red dots appeared to be on the top of the 600 mg and 800 mg dose groups). However, it should be noted that this was not the case for NaF/EDTA TU exposure as highlighted in the blue circle in Figure 9. In general, it is expected that higher TU concentrations (and AUCs) will result in higher T concentrations. This observation indicates that most of these 5 T C_{max} outliers were not expected to have so high NaF/EDTA plasma T exposure because their serum T exposures and NaF/EDTA plasma TU exposures were within the range of observed values from other sites.

Mean plasma over serum ratios

Figures 10 shows the mean (±SD) T PK profiles in NaF/EDTA plasma and serum.

Figure 10: Mean (±SD) T PK Profiles in NaF/EDTA Plasma (Red) and Serum (Blue)



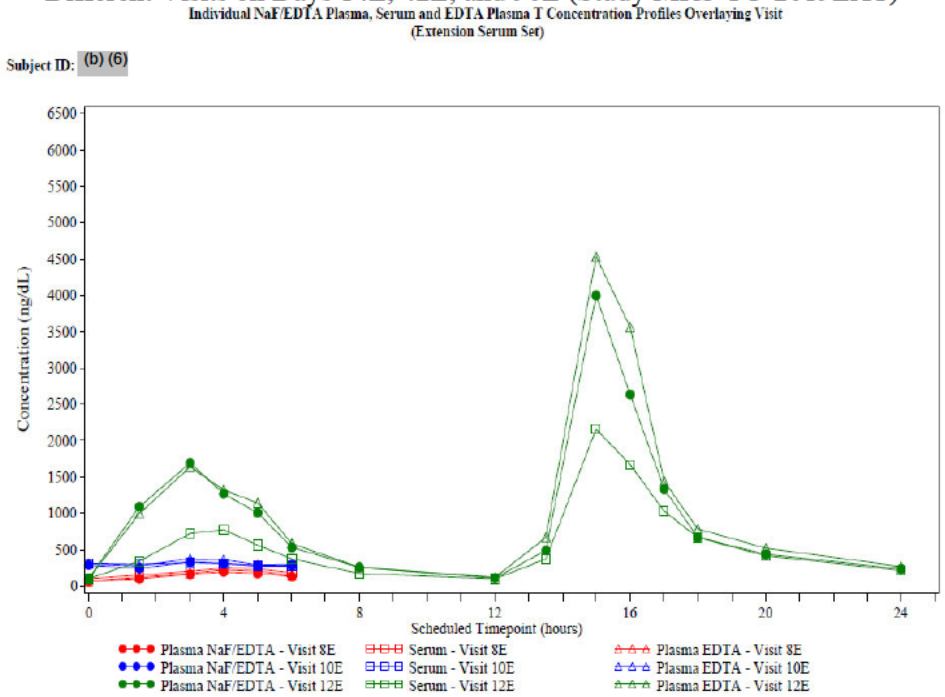
Source: Figure 7, Study MRS-TU-2019EXT CSR, NDA 213953 (Submitted December 31, 2020)

As shown in Fugures 10 above, mean concentrations of serum T were higher than that of NaF/EDTA plasm T at most of the time points. This was possibly due to factors including: (1) sample matrix (i.e., serum vs. plasma); (2) TU to T *ex vivo* conversion (i.e., because sample preparation conditions including temperature and time are different) and (3) sample tube types (i.e., serum prepared from blood collected in plain tubes vs. plasma prepared from blood collected in NaF/EDTA tubes). Therefore, it is expected that serum T concentrations are generally higher than NaF/EDTA plasma T concentrations. However, as mentioned earlier, multiple subjects from clinical study Site 104 had NaF/EDTA plasma T concentrations paradoxically higher than serum T concentrations obtained at the same time. Reference is made to Section 19.4.1 of the DUOG's multi-disciplinary review and evaluation (i.e., unireview) for NDA 213953 dated October 22, 2021 in DARRTS for detailed information.

Individual PK Profiles of the 5 T C_{max} Outliers

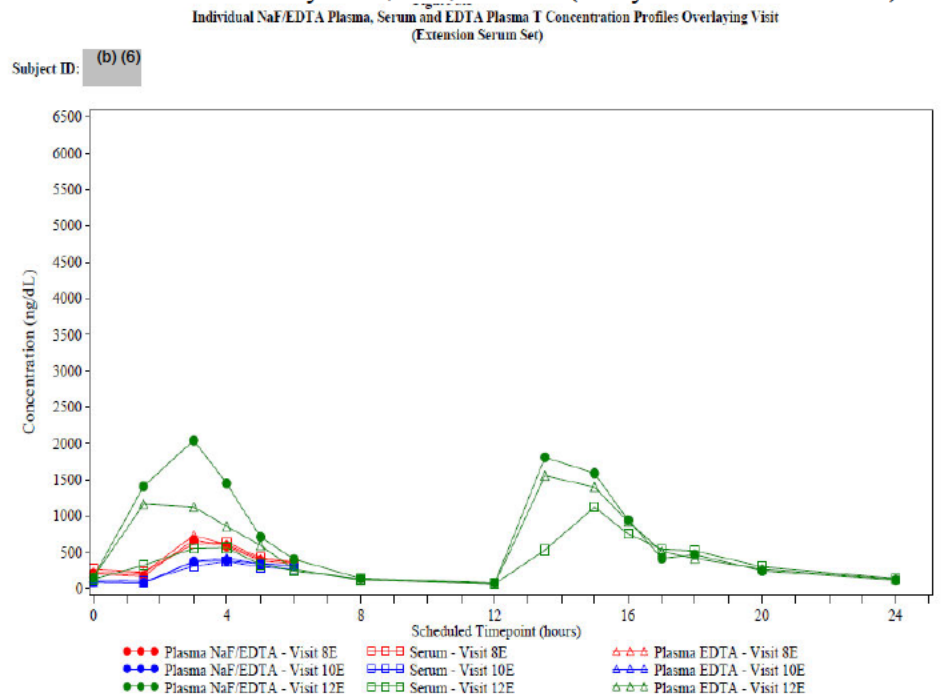
Figures 11, 12, 13, 14, and 15 are the overlaying NaF/EDTA plasma, EDTA plasma, and serum T PK profiles of the 5 T C_{max} outliers from 3 different visits (i.e., Days 14E, 42E, and 90E) in Study MRS-TU-2019EXT.

Figure 11: NaF/EDTA Plasma, EDTA Plasma, and Serum T PK Profiles of Subject (b) (6) From 3 Different Visits on Days 14E, 42E, and 90E (Study MRS-TU-2019EXT)



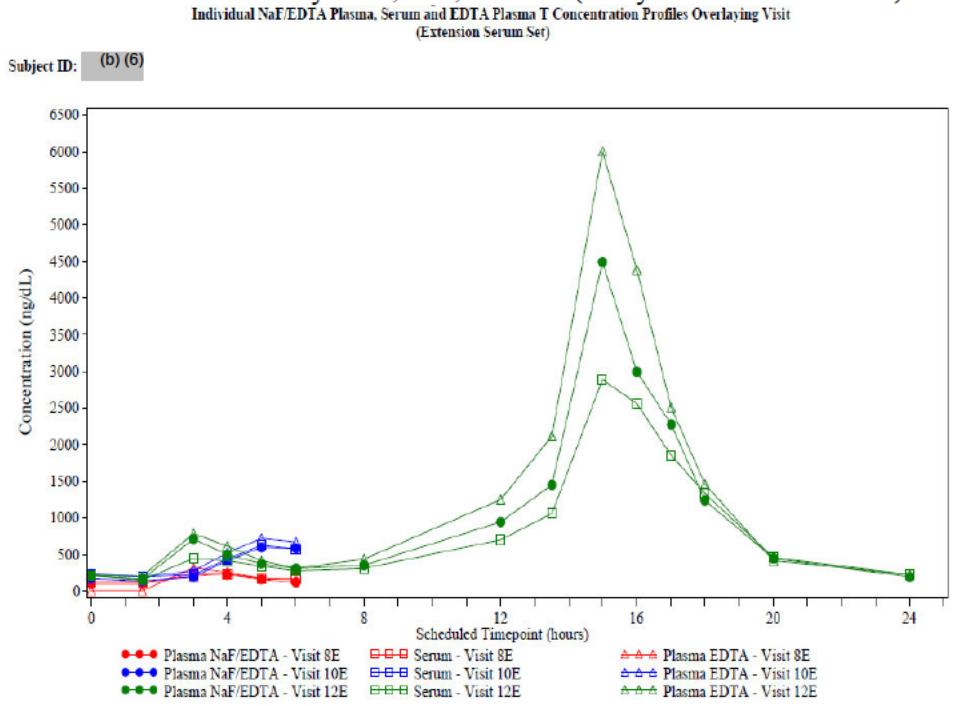
Source: Figure 3.1, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Figure 12: NaF/EDTA Plasma, EDTA Plasma, and Serum T PK Profiles of Subject (b) (6) From 3 Different Visits on Days 14E, 42E, and 90E (Study MRS-TU-2019EXT)



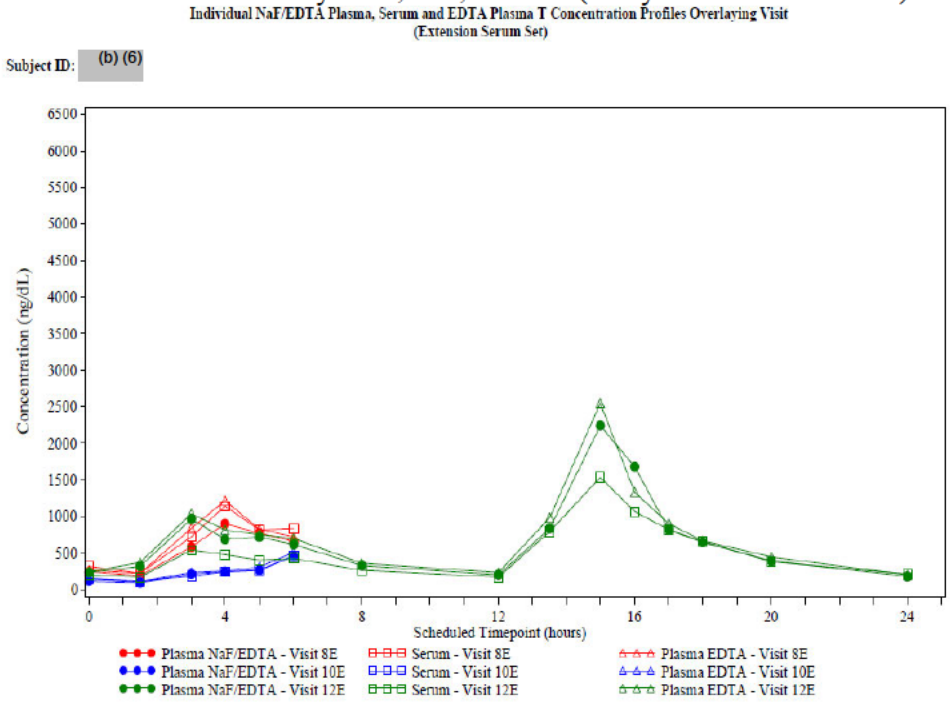
Source: Figure 3.1, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Figure 13: NaF/EDTA Plasma, EDTA Plasma, and Serum T PK Profiles of Subject (b) (6) From 3 Different Visits on Days 14E, 42E, and 90E (Study MRS-TU-2019EXT)



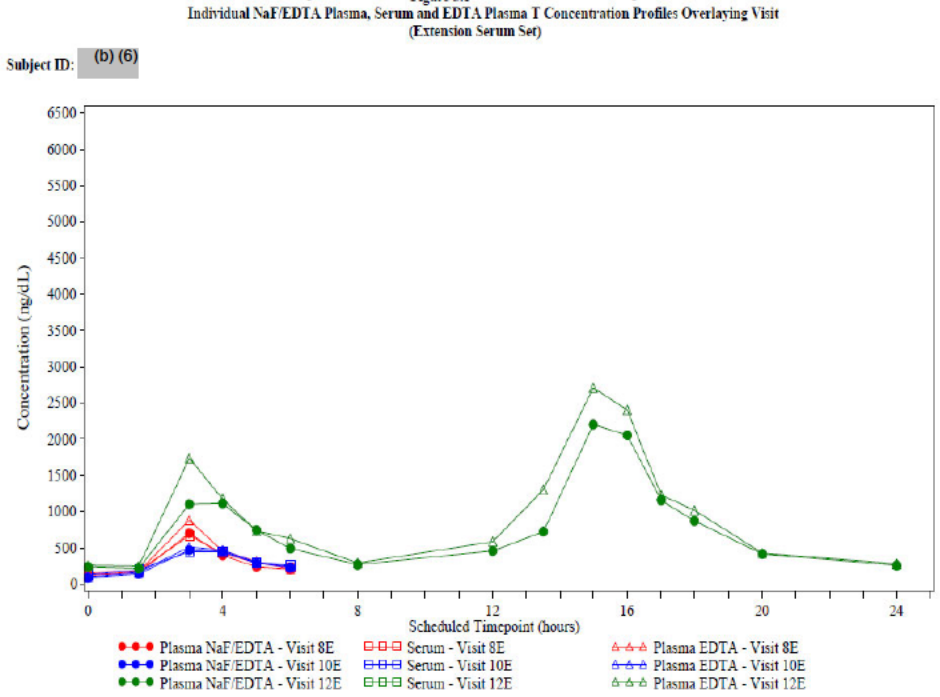
Source: Figure 3.1, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Figure 14: NaF/EDTA Plasma, EDTA Plasma, and Serum T PK Profiles of Subject (b) (6) From 3 Different Visits on Days 14E, 42E, and 90E (Study MRS-TU-2019EXT)



Source: Figure 3.1, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Figure 15: NaF/EDTA Plasma, EDTA Plasma, and Serum T PK Profiles of Subject (b) (6) From 3 Different Visits on Days 14E, 42E, and 90E (Study MRS-TU-2019EXT)



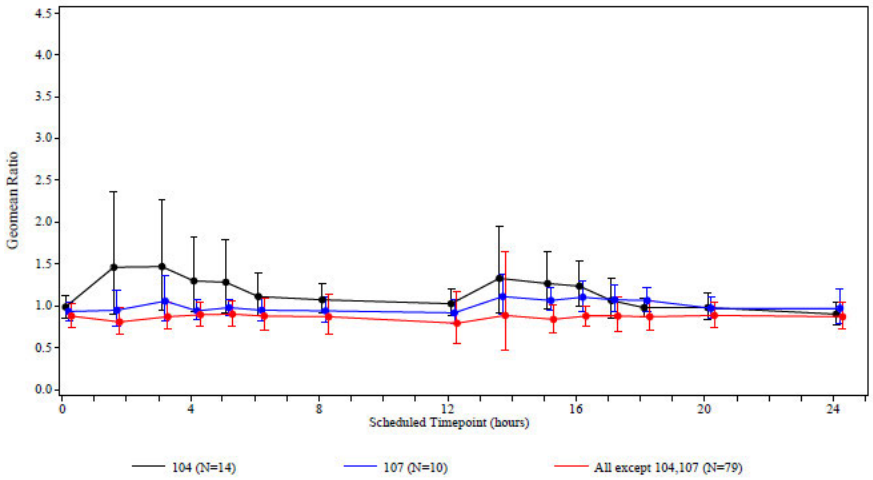
Source: Figure 3.1, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Reviewer's Comment: *Four (4) out of the 5 T C_{max} outliers participated in the serum substudy (except Subject* (b) (6) *) and had PK profiles obtained from NaF/EDTA plasma, EDTA plasma, and serum. All 4 of these subjects, paradoxically had higher T exposure from plasma than from serum. It should be noted that the difference between plasma and serum exposure was larger around T_{max} than at other time points. TU T_{max} was 15 hours post-morning dose (i.e., 3 hours post-evening dose) for Subjects* (b) (6) *, and* (b) (6) *while it was 3 hours post-morning dose for Subject* (b) (6) *.*

Plasma to Serum Ratios

Figure 16 is a plot of the geometric mean of plasma to serum ratios (with errors expressed as multiplied or divided by geometric SD factor) for Site 104, Site 107, and all other sites for the 24-hour Day 90E PK profile. The Applicant conducted a test comparing the geometric least square means (GLSM) of NaF/EDTA plasma to serum T AUC ratio of Site 104 subjects (Test) to other sites (Reference) excluding Site 104 subjects in one case and excluding both Sites 104 and 107 subjects in another case (data not shown). In both casaes, the p-value was < 0.0001 and the Applicant believes that this indicates that Site 104 NaF/EDTA plasma to serum concentration ratios are different from other study sites' ratios with a statistical significance.

Figure 16: Geometric Mean of Plasma Over Serum Ratios (with errors expressed as multiplied or divided by geometric SD factor) from Visit 12E/Day 90E at Sites 104, 107, and All Other 17 Study Sites (Study MRS-TU-2019EXT)



Source: Figure 4, SDN 038, NDA 213953 (Submitted January 27, 2022)

Reviewer's Comment: Mean *plasma to serum ratios > 1 were observed from Site 104 subjects while mean plasma to serum ratios of < 1 were observed from subjects from other sites as expected. While the standard error bars overlap, individual level PK profile observations vary across subjects and this does not explain what happened to the 5 NaF/EDTA plasma T C_{max} outliers who are of particular interest.*

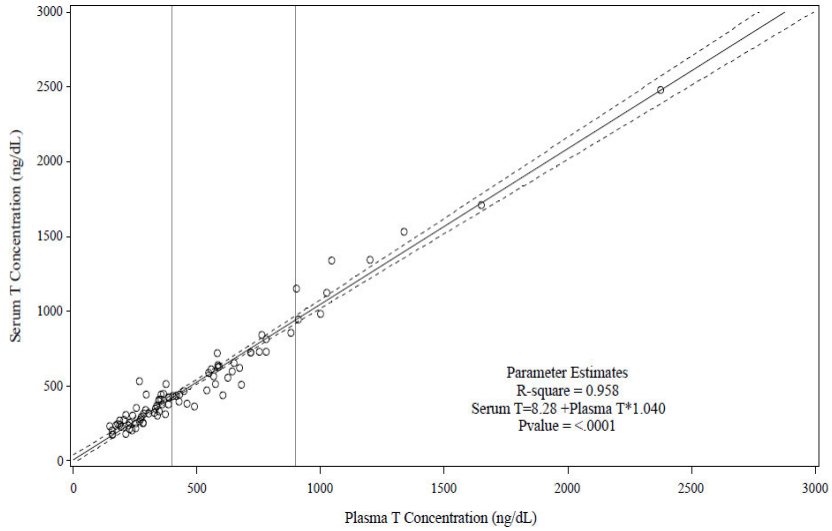
Serum to Plasma Correlation at 3, 4, and 5 hours Post-dose

In the Phase 3 trial, MRS-TU-2019EXT, dose titration of Kyzatrex® was conducted using NaF/EDTA plasma T concentrations from randomized (1:1:1) time points (i.e., 3-, 4-, or 5-hours post-morning dose) at two study visits (i.e., Days 14E and 42E). Independent randomizations were applied to the first (Day 14E) and second (Day 42E) titration visits. Titration decisions were based on pre-determined titration thresholds (400 and 900 ng/dL for NaF/EDTA plasma T).

The Applicant acquired both serum and plasma sample pairs at each titration timepoint for all subjects (n>130) and used the actual measured T concentrations to establish the correlation between plasma and serum. Per the laboratory manual, the NaF/EDTA blood samples were supposed to be immediately placed on ice and processed to plasma within 110 minutes and blood samples for serum held at room temperature for 30 minutes before processing to serum. The resulting correlation between serum and NaF/EDTA plasma T concentrations accounts for the contributions from type of blood collection tube, sample processing temperature and time, TU concentration and matrix factors at the proposed titration timepoints.

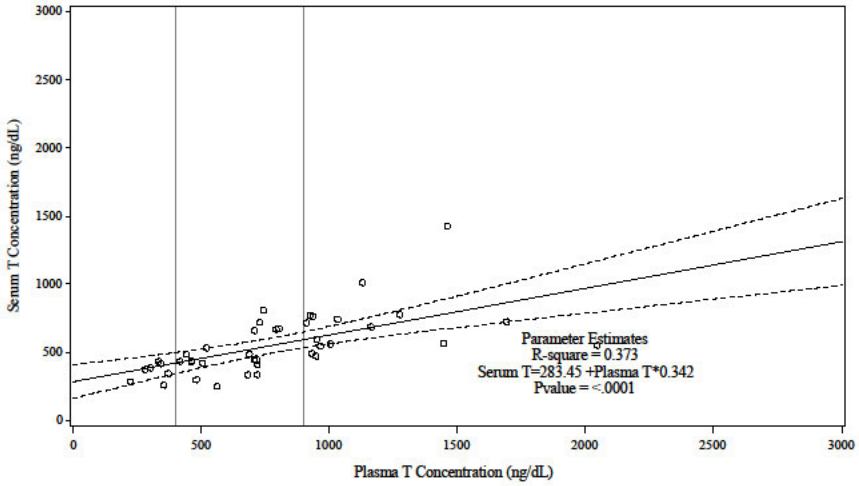
Figure 17 is the combined 3, 4, and 5 hour post-dose data collected on Day 14E (Visit 8E) and Day 42E (Visit 10E) from Site 104 subjects only. Figure 18 and 20 are the 3, 4, and 5 hour post-dose data collected on Day 90E (Visit 12E) from Site 104 subjects only and all sites except Site 104, respectively. Figure 19 is the combined 3, 4, and 5 hour post-dose data collected at Day 14E (Visit 8E) and Day 42E (Visit 10E) from all 19 clinical study site subjects that were utilized in establishing the dose titration scheme. The vertical bars in these 3 figures indicate the 400 and 900 ng/dL plasma-based titration thresholds used in Study MRS-TU-2019EXT.

Figure 17: Scatter Plots of Serum T Concentration vs. NaF/EDTA Plasma T Concentration at 3, 4, and 5-hours Post-dose on Day 14E (Visit 8E) and Day 42E (Visit 10E), Site 104 Subjects Only (Study MRS-TU-2019EXT)



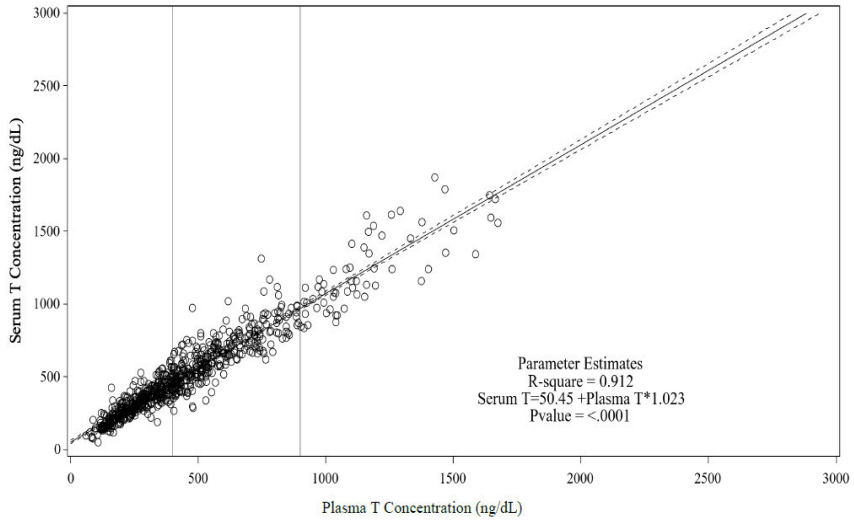
Source: Figure 14, SDN 035, NDA 213953 (Submitted November 12, 2021)

Figure 18: Scatter Plots of Serum T Concentration vs. NaF/EDTA Plasma T Concentration at 3, 4, and 5-hours Post-dose on Day 90E (Visit 12E), Site 104 Subjects Only (Study MRS-TU-2019EXT)



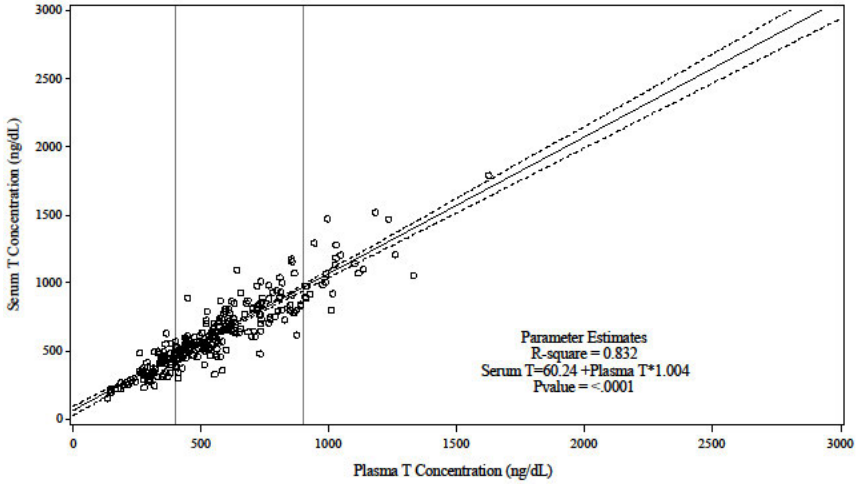
Source: Figure 9, SDN 035, NDA 213953 (Submitted November 12, 2021)

Figure 19: Scatter Plots of Serum T Concentration vs. NaF/EDTA Plasma T Concentration at 3, 4, and 5-hours Post-dose on Day 14E (Visit 8E) and Day 42E (Visit 10E), All Sites (Study MRS-TU-2019EXT)



Source: Figure 14.2.2.1.4.4, Study MRS-TU-2019EXT CSR, NDA 213953 (submitted December 31, 2020)

Figure 20: Scatter Plots of Serum T Concentration vs. NaF/EDTA Plasma T Concentration at 3, 4, and 5-hours Post-dose on Day 90E (Visit 12E), All Sites Except Site 104 (Study MRS-TU-2019EXT)



Source: Figure 7, SDN 035, NDA 213953 (Submitted November 12, 2021)

Table 6 summarizes the correlation parameters for serum vs. NaF/EDTA plasma T at 3, 4, and 5 hours post-dose on Days 14E and 42E combined or on Day 90E obtained from Figures 17, 18, 19, and 20.

Table 6: Summary of Serum vs. Plasma Correlation Parameters for Serum vs. NaF/EDTA Plasma at 3, 4, and 5 Hours Post-dose

Data Set	Slope	Intercept (ng/dL)	R^2	Figure Reference
Days 14E & 42E, Site 104 only	1.040	8.28	0.958	Figure 17
Day 90E, Site 104 only	0.342	283.45	0.373	Figure 18
Days 14E & 42E, All sites	1.023	50.45	0.912	Figure 19
Day 90E, All sites except Site 104	1.004	60.24	0.832	Figure 20

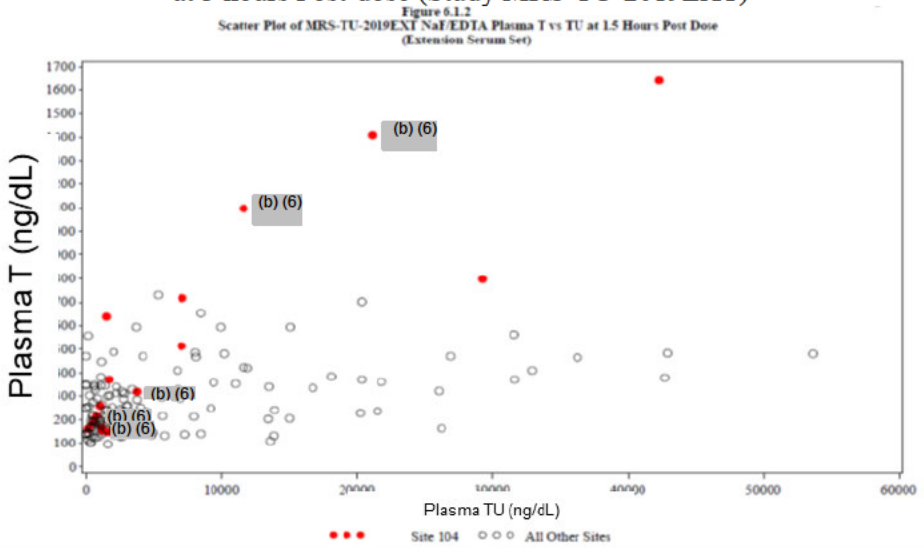
Reviewer's Comment: *When comparing the correlations established between NaF/EDTA plasma and serum T at Site 104 on Days 14E (Visit 8E) and 42E (Visit 10E) combined (Figure 17) vs. Day 90E (Visit 12E) (Figure 18), they were significantly different from each other.*

It should be noted that the correlation shown in Figure 17 appears to be much closer (compared to Figure 18) to those shown in Figures 19 and 20 which suggests that execution of study procedures (e.g., sample handling) on Day 90E (Visit 12E) at Site 104 may be markedly different from those on Days 14E and 42E at all sites including Site 104 (Figure 19) and on Day 90E at all sites except Site 104 (Figure 20).

NaF/EDTA Plasma TU and T Concentration Correlation as a function of Time

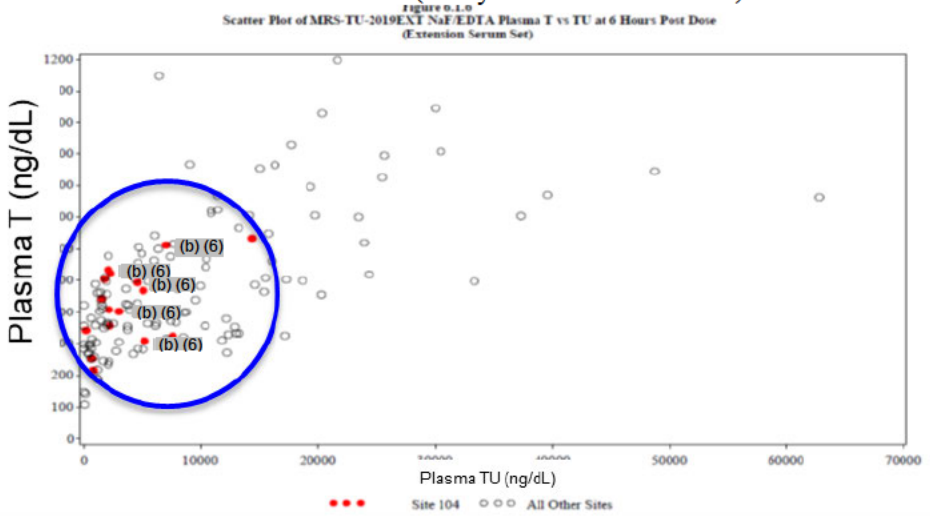
Figures 21, 22, and 23 are scatter plots of NaF/EDTA plasma T concentrations vs. NaF/EDTA plasma TU concentrations at 3 hours, 6 hours, and 15 hours post-dose. It should be noted that the Applicant incorrectly labeled the x- and y-axis as "plasma TU AUC(0-24)" and "plasma T AUC(0-24)", respectively. These should be read as "plasma TU concentrations (ng/dL)" and "plasma T concentrations (ng/dL)", respectively.

Figure 21: Scatter Plot of NaF/EDTA Plasma T vs. TU Concentrations (ng/dL) at 3 hours Post-dose (Study MRS-TU-2019EXT)



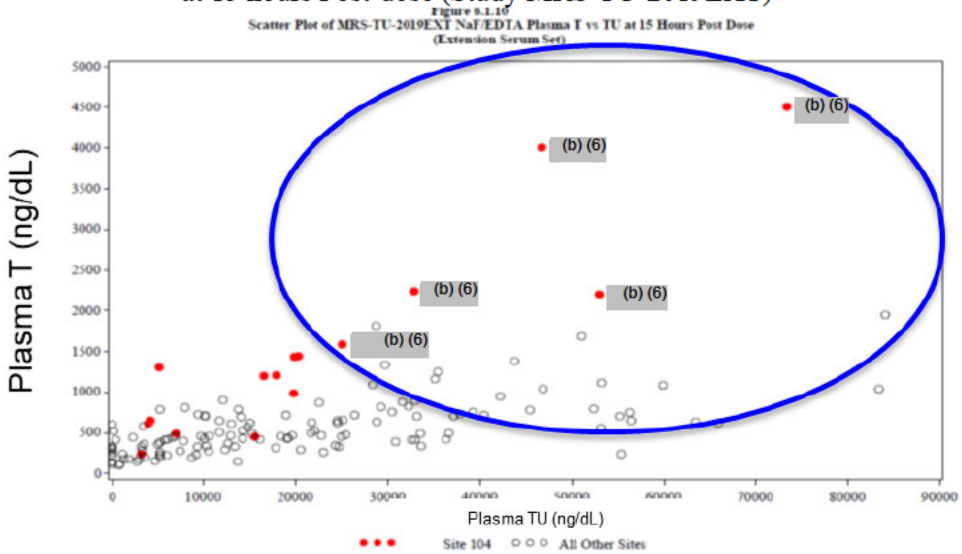
Source: Figure 6.1.3, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Figure 22: Scatter Plot of NaF/EDTA Plasma T vs. TU Concentrations (ng/dL) at 6 hours Post-dose (Study MRS-TU-2019EXT)



Source: Figure 6.1.6, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Figure 23: Scatter Plot of NaF/EDTA Plasma T vs. TU Concentrations (ng/dL) at 15 hours Post-dose (Study MRS-TU-2019EXT)



Source: Figure 6.1.10, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Reviewer's Comment: *The Applicant has submitted respective scatter plots for pre-dose and each post-dose time point (i.e., 1.5, 3, 4, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20, and 24 hours post-dose) but only the 3, 6, and 15 hour post-dose scatter plots are shown here for illustration purpose.*

While Site 104 subjects (i.e., red dots) were not separated from other site subjects on these scatter plots at pre-dose and after 6 hour post-morning dose (Figure 22; the Site 104 subjects in red dots mingled with subjects from other study sites in the blue circle) timepoints and after 20 hour post-dose (i.e., 8 hours post-evening dose; data not shown) timepoints, they appear to be clearly separated from subjects from other sites around T_{max} (i.e., 3 hours or 15 hours post-dose, which are both 3 hours post-dose of the morning/evening dose). This indicates that subjects from Site 104 are not different from other sites by nature but something may have happened to samples from some Site 104 subjects which resulted in notably

high T concentrations compared to other subjects while they had comparable TU concentrations. Especially, the 5 T C_{max} outliers stood out (see the subject in the blue circle) on the plot of Figure 23 (i.e., at 15 hours post-dose [3 hours post-evening dose], which were their TU T_{max} except for Subject (b) (6)).

Table 7 is this reviewer's summary of the T, DHT, and TU exposures of subjects from Site 104. The subjects highlighted in yellow are the 5 T C_{max} outliers (i.e., with > 2.5x ULN).

Table 7: Summary of T, DHT, and TU Exposures from Site 104 Subjects (Study MRS-TU-2019EXT)

Subject	Day 90 Dose (mg)	Plasma T Cmax (ng/dlL)	Plasma DHT at T Tmax (ng/dlL)	DHT/T Ratio	Plasma TU at T Tmax (ng/dL)	Plasma TU Cmax (ng/dL)	T/TU Cmax Ratio	Serum T Cmax (ng/dlL)	Plasma/Serum T Ratio
(b) (6)	600	1163	219.8	0.189	6410	7103	0.164	712	1.63
	400	642	186.0	0.290	7212	7212	0.089	780	0.82
	200	1208	198.5	0.164	7770	17843	0.068	1213	1.00
	400	1129	190.2	0.168	8236	15346	0.074	1790	0.63
	600	844	147.4	0.175	15329	15329	0.055	911	0.93
	400	1199	144.5	0.121	16536	16536	0.073	757	1.58
	800	1430	154.8	0.108	19819	19819	0.072	927	1.54
	800	1735	248.5	0.143	20273	20931	0.083	1298	1.34
	400	1449	166.9	0.115	27055	30377	0.048	NA	NA
	600	2045	314.0	0.154	29300	29300	0.070	1123	1.82
	600	2241	162.0	0.072	32879	32879	0.068	1535	1.46
	400	1640	138.8	0.085	42264	43842	0.037	1421	1.15
	800	3999	313.5	0.078	46714	46714	0.086	2157	1.85
	800	2197	309.7	0.141	52929	52929	0.042	NA	NA
	600	1936	173.6	0.090	54579	54579	0.035	1472	1.32
	600	4500	379.9	0.084	73333	73333	0.061	2890	1.56
Avg		1834.8	215.5	0.136	28790	30255	0.070	1356	1.33

In general, the 5 T C_{max} outliers were on high doses of Kyzatrex® (i.e., either 600 mg or 800 mg) and 3 of them (i.e., Subjects (b) (6)) had higher NaF/EDTA plasma TU concentrations at T T_{max} than most of other subjects. Relatively high TU exposure in these three subjects could possibly be a contributing factor for the NaF/EDTA plasma T C_{max} values being greater than 2.5x ULN of 2,000 ng/dL and DHT concentration at T T_{max} being greater than most of other subjects shown in Table 7.

However, in some cases despite plasma TU exposures being similar, NaF/EDTA plasma T exposures were significantly different (e.g., Subject (b) (6) vs. Subject (b) (6); Subject (b) (6) vs. (b) (6) – in both of these cases, one subject was one of the 5 T C_{max} outliers while the other subject was not and the cause of this is unknown).

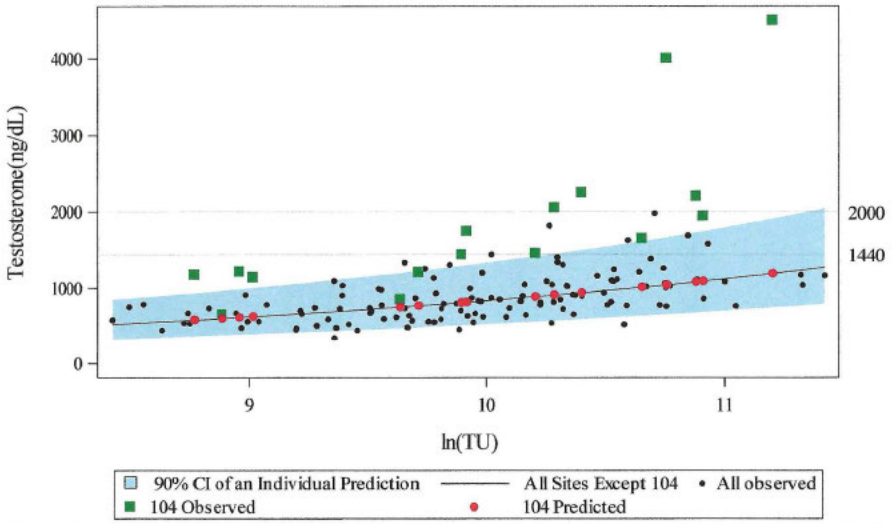
It should be noted that only one subject (i.e., Subject (b) (6)) among the NaF/EDTA plasma T C_{max} outliers (i.e., with T C_{max} value > 2.5x ULN of 2,000 ng/dL) also had the corresponding serum T C_{max} value > 2.5x ULN (i.e., > 2,500 ng/dL).

Model Predicted T C_{max} from TU Concentration

The Applicant investigated whether NaF/EDTA plasma T C_{max} for Site 104 subjects can be predicted using the observed NaF/EDTA plasma T C_{max} and the associated NaF/EDTA plasma TU concentrations for all subjects from all other study sites. The model was developed by using linear regression on all Day 90E log-transformed T C_{max} data except Site 104 (i.e., ln(T) as a function of ln(TU)). A prediction line and associated confidence intervals were derived.

Figure 24 presents the NaF/EDTA plasma T C_{max} data (i.e., Day 90E) from Study MRS-TU-2019EXT plotted as a function of the NaF/EDTA plasma TU concentration at the T T_{max} timepoint and includes the predicted (black) line. The NaF/EDTA plasma T C_{max} and TU values from all sites other than Site 104 were used to develop the model plotted as the black line, and the observed values plotted as black circles. Green squares are the observed Site 104 T C_{max} concentrations and red circles are the model-predicted values for Site 104. The blue-shaded area represents the 90% confidence interval (CI) of the model prediction of NaF/EDTA plasma T C_{max} based on all subjects (n=130), excluding Site 104 subjects (n=16). The Applicant used the 90% CI as it is the accepted limit for bioequivalence studies.

Figure 24: Plasma T C_{max} vs. Log(TU) at T T_{max} on Day 90 (Study MRS-TU-2019EXT)



Note: model: ln(t)=ln(tu)- developed using all sites except 104. Four subjects did not have quantifiable TU and were excluded from the model.

Source: Figure 7, Module 5, Section 12.3.4, NDA 213953 (Submitted on January 27, 2022)

The observed and predicted NaF/EDTA plasma T C_{max} values based on this regression are shown in Table 8 for all Site 104 subjects.

Table 8: Observed and Predicted C_{max} Values (Based on Regression) for All Site 104 Subjects

Site	Subject	Observed Plasma T (ng/dL)	Plasma TU	Predicted Plasma T	Observed Minus Predicted	Observed Minus 90%UCIL	% Non-drug Effect Relative to Predicted	% Non-drug Effect Relative to 90% UCIL
104	(b) (6)	1163	6410	580	583	240	50	21
104		642	7212	601	41	-302	6	-47
104		1208	7770	614	593	231	49	19
104		1129	8236	625	504	138	45	12
104		844	15329	750	94	-348	11	-41
104		1199	16536	767	432	-15	36	-1
104		1430	19819	809	621	145	43	10
104		1735	20273	814	921	450	53	26
104		1449	27055	886	563	56	39	4
104		2045	29300	907	1137	603	56	29
104		2241	32879	939	1302	760	58	34
104		1640	42264	1011	629	36	38	2
104		3999	46714	1041	2958	2341	74	59
104		2197	52929	1080	1118	492	51	22
104		1936	54579	1090	847	211	44	11
104		4500	73333	1189	3312	2685	74	60

Reviewer's Comment: *Fourteen (14) out of the 16 subjects from Site 104 fall above the predicted line and almost all of them fall above the upper 90% CI limit in Figure 24. The linear regression underpredicted the NaF/EDTA plasma T C_{max} for Site 104 subjects especially, for the 5 T C_{max} outliers (i.e., Subjects*

(b) (6), and (b) (6)). For the 4 T C_{max} outliers who had serum data available, the predicted NaF/EDTA plasma T C_{max} values were lower and underestimated when compared to observed serum T C_{max} shown in Table 7.

It appears that Site 104 data points are different from those from of all other sites. This analysis shows that the discordance of Site 104 subjects may have been due to a combination of drug related effect (i.e., T exposure resulting from the drug administered) and a potential non-drug related effect (e.g., sample mishandling).

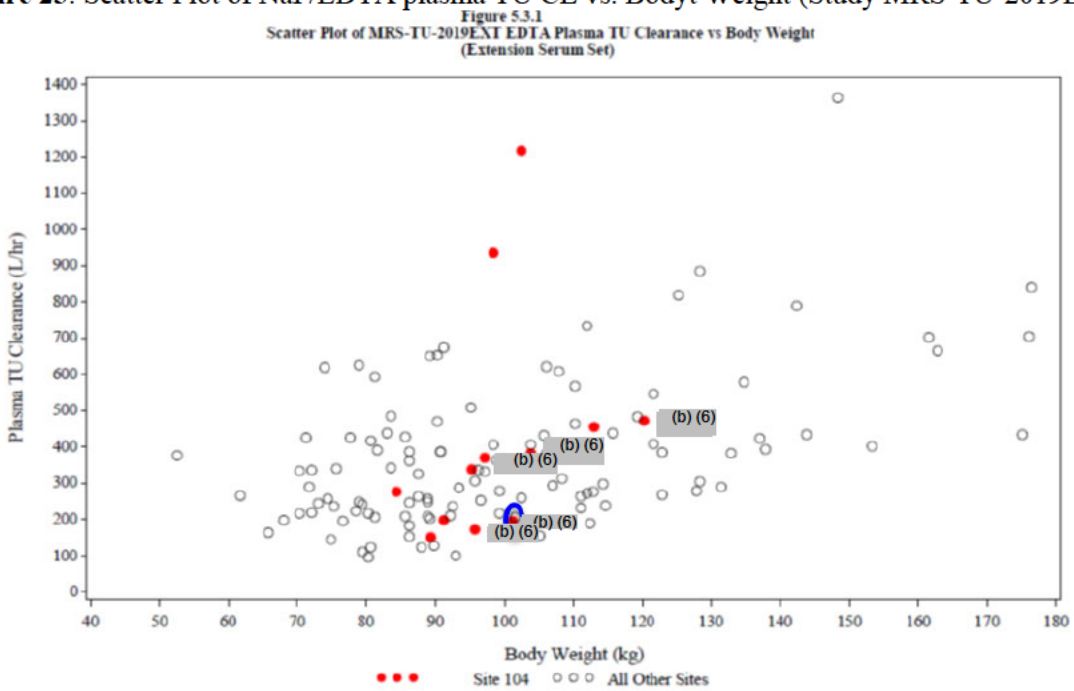
Body weight effect on T, DHT, and TU exposure

The Applicant explored whether there is a body weight effect on the exposure (i.e., AUC) of T, DHT, and TU in plasma and serum, respectively. No relationship between exposure of T, DHT, and TU and body weight were observed (data not shown).

TU CL for Subject (b) (6)

The Applicant also explored whether there is a correlation between TU clearance (CL) and body weight. Figure 25 is a scatter plot of NaF/EDTA plasma TU CL vs. body weight.

Figure 25: Scatter Plot of NaF/EDTA plasma TU CL vs. Bodyt Weight (Study MRS-TU-2019EXT)



Source: Figure 5.3.1, SDN 042 , NDA 213953 (Submitted on March 18, 2022)

Reviewer's Comment: *It appears that there is a positive correlation between body weight and TU CL and in general, individuals with lower body weight had lower TU CL. It appears that Subject (b) (6) (circled in blue) had a mid-weight but a relatively low TU CL and this may be a potential explanation for Subject (b) (6)'s high T exposure.*

Subjects with NaF/EDTA Plasma T C_{max} > 1.8x ULN (1,440 ng/dL)

Table 9 is this reviewer's summary of the T, DHT, and TU exposures of subjects with NaF/EDTA Plasma T C_{max} > 1.8x ULN (i.e., > 1,440 ng/dL). The subjects highlighted in yellow are the 5 T C_{max} outliers.

Table 9: Summary of T, DHT, and TU Exposures
from Subjects with NaF/EDTA Plasma T C_{max} > 1.8x ULN (> 1,440 ng/dL)

Subject	Day 90 Dose (mg)	Plasma T Cmax (ng/dlL)	Plasma DHT at T Tmax (ng/dlL)	DHT/T Ratio	Plasma TU at T Tmax (ng/dL)	Plasma TU Cmax (ng/dL)	T/TU Cmax Ratio	Serum T Cmax (ng/dlL)	Plasma/Serum T Cmax Ratio
(b) (6)	400	1449	167	0.115	27055	30377	0.048	NA	NA
	600	1576	131	0.083	55670	73729	0.021	NA	NA
	600	1624	134	0.083	39637	39637	0.041	1787	0.91
	400	1640	139	0.085	42264	43842	0.037	1421	1.15
	800	1687	201	0.119	51101	99889	0.017	1644	1.03
	800	1735	249	0.143	20273	20931	0.083	1298	1.34
	800	1815	142	0.078	28704	40869	0.044	1412	1.29
	600	1936	174	0.090	54579	54579	0.035	1472	1.32
	600	1976	251	0.127	44486	84032	0.024	1728	1.14
	600	2045	314	0.154	29300	29300	0.070	1123	1.82
	800	2197	310	0.141	52929	52929	0.042	NA	NA
	600	2241	162	0.072	32879	32879	0.068	1535	1.46
	800	3999	314	0.078	46714	46714	0.086	2157	1.85
	600	4500	380	0.084	73333	73333	0.061	2890	1.56
Avg		2173	219	0.104	42780	51646	0.048	1679	1.35

Reviewer's Comment: *While it is still unknown what happened at Site 104 on Day 90E, it should be noted that the 5 NaF/EDTA plasma T C_{max} outliers had higher T/TU C_{max} ratios compared to most of the other subjects.*

Among subjects with NaF/EDTA plasma T C_{max} > 1.8x ULN (> 1,440 ng/dL in plasma), only Subject (b) (6) *had both NaF/EDTA plasma T C_{max} and serum T C_{max} values > 2.5x ULN (i.e., > 2,000 ng/dL in NaF/EDTA plasma and > 2,500 ng/dL in serum) and Subject* (b) (6) *was the only subject who had a corresponding serum T C_{max} between 1.8x ULN and 2.5x ULN. Among 11 subjects who had available serum T C_{max} values, 9 subjects' serum T C_{max} (i.e., all except Subjects* (b) (6) *and* (b) (6)*) were < 1.8x ULN (< 1,800 ng/dL) and therefore, within the acceptable range of C_{max} thresholds.*

Conclusion

It is still unknown what definitively happened to the NaF/EDTA plasma T data obtained from Site 104 but it appears that these data, in particular on Day 90E, are different from those of the rest of the study participants at other study sites. When considering the available serum T data, Subject (b) (6) was the only subject with a high T C_{max} value (i.e., > 2.5x ULN) both in serum and NaF/EDTA plasma.

Based on the totality of information/data submitted by the Applicant, the Clinical Pharmacology review team finds the Applicant's proposal to exclude data from Site 104 to be reasonable and concludes that the available clinical pharmacology information provide sufficient evidence of effectiveness (i.e., the primary efficacy endpoint of responder rate has been achieved regardless of the inclusion of data from Site 104 subjects) for Kyzatrex®.

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

Yes. The proposed starting dose and titration scheme were selected based on results from Study MRS-TU-2019 and evaluated in Study MRS-TU-2019EXT. Based on the Clinical Pharmacology review team's assessment summarized in Section 3.3.1 of this review, it is concluded that the proposed dosage regimen of Kyzatrex® is appropriate for male with hypogonadism.

3.3.3 Is there a management strategy required for subpopulations based on intrinsic factors?

No. The Applicant has conducted subgroup analyses regarding age, body weight and body mass index (BMI), and race for efficacy as discussed in Section 6.3.2 of the DUOG's multi-disciplinary review and evaluation (i.e., unireview) for NDA 213953 dated October 22, 2021 in DARRTS. The Clinical Pharmacology review team concludes that there are no alternative dosing regimens or management strategies required for subpopulations based on intrinsic factors.

3.3.4 Are there clinically relevant food-drug interactions or drug-drug interactions (DDIs) and what is the appropriate management strategy?

Yes. The absorption of T (administered as TU) is increased in the presence of food and thus dosing instructions include taking with food. Although the Applicant did not conduct any DDI studies with Kyzatrex®, the labeling would include DDI information for the drug class. Reference is made to Section 6.3.2 of the DUOG's multi-disciplinary review and evaluation (i.e., unireview) for NDA 213953 dated October 22, 2021 in DARRTS for detail information.

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

/s/

CHONGWOO YU
06/03/2022 10:46:37 AM

YANHUI LU
06/03/2022 10:52:17 AM

SHIRLEY K SEO
06/06/2022 09:19:27 AM

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number(s)	NDA 213953
Priority or Standard	Standard
Submit Date(s)	December 31, 2020
Received Date(s)	December 31, 2020
PDUFA Goal Date	October 31, 2021
Division/Office	Division of Urology, Obstetrics, and Gynecology Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Review Completion Date	October 29, 2021
Established/Proper Name	testosterone undecanoate
(Proposed) Trade Name	Kyzatrex
Pharmacologic Class	Androgen
Code name	N/A
Applicant	Marius Pharmaceuticals, LLC
Dosage form	Oral
Applicant proposed Dosing Regimen	Starting dose is 200 mg orally twice daily, once in the morning and once in the evening with food, with an established minimum dose of 100 mg once in the morning and a maximum dose of 400 mg twice daily
Applicant Proposed Indication(s)/Population(s)	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommendation on Regulatory Action	Complete Response (CR) action
Recommended Indication(s)/Population(s) (if applicable)	Adult males for conditions associated with a deficiency or absence of endogenous testosterone

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Samantha Bell/Jeannie Roule
Nonclinical Reviewer	Yangmee Shin
Nonclinical Team Leader	Kimberly Hatfield
Office of Clinical Pharmacology Reviewer	Chongwoo Yu
Office of Clinical Pharmacology Team Leader	Yanhui Lu
Clinical Reviewer	Martin Kaufman/Jordan Dimitrakoff
Clinical Team Leader	Suresh Kaul
Statistical Reviewer	Jia Guo
Statistical Team Leader	Tsae Yun (Daphne) Lin
Cross-Disciplinary Team Leader	Suresh Kaul
Division Director (OCP)	Shirley Seo
Division Deputy Director (OB)	Tsae Yun (Daphne) Lin
Division Director (DUOG)	Christine Nguyen

Abbreviations: DUOG, Division of Urology, Obstetrics, and Gynecology; OB, Office of Biostatistics; OCP, Office of Combination Products

Additional Reviewers of Application

OPQ	Hong Cai, Venkateswara Pavuluri, Wendy Wilson-Lee, Jeffery Medwid, Donna Christner, Jia Yin, Vidula Kolhatkar, Amit Kokate, Vaikunth Prabhu, Sreenivasa Eturi, Zedong Dong, Marquita Burnett
OPDP	Elvy Varghese, Matthew Falter
OSI	N/A
OSIS	Arindam Dasgupta, Gopa Biswas, Mohsen Rajabi, Yiyue Zhang
OSE/DEPI	Adebola Ajao, Wei Liu
OSE/DMEPA	Denise Baugh, Stephanie DeGraw
OSE/DRISK	Courtney Cunningham, Laura Zendel
OSE/DPV	Karen Konkel, Lynda McCulley
DMPP	Lonice Carter, Marcia Williams
CSS	Joshua Hunt
Associate Director of Labeling	Aisha Johnson

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

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Yangmee Shin, PhD	ORPURM/DPT	Sections: 5	Select one: __X_ Authored ___ Approved
	Signature: Yangmee Shin -S Digitally signed by Yangmee Shin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yangmee Shin -S, 0.9.2342.19200300.100.1.1=1300163502 Date: 2021.10.20 15:12:58 -04'00'			
Nonclinical Team Leader	Kimberly Hatfield, PhD	ORPURM/DPT	Sections: 5	Select one: ___ Authored _X__ Approved
	Signature: Kimberly P. Hatfield -S Digitally signed by Kimberly P. Hatfield -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300387215, cn=Kimberly P. Hatfield -S Date: 2021.10.20 16:50:33 -04'00'			
Clinical Pharmacology Reviewer	Chongwoo Yu, PhD	OCP/DCEP	Sections: 6 and 18.4	Select one: _X__ Authored ___ Approved
	Signature: Chongwoo Yu -S Digitally signed by Chongwoo Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chongwoo Yu -S, 0.9.2342.19200300.100.1.1=1300417687 Date: 2021.10.19 11:27:10 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Yanhui Lu, PhD	OCP/DCEP	Sections: 6 and 18.4	**Select one:** ___ Authored _X__ Approved
	Signature: Yanhui Lu -S Digitally signed by Yanhui Lu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yanhui Lu -S, 0.9.2342.19200300.100.1.1=2001501324 Date: 2021.10.19 10:53:00 -04'00'			
Clinical Pharmacology Division Director	Shirley Seo, PhD	OCP/DCEP	Sections: 6 and 18.4	**Select one:** ___ Authored _X__ Approved
	Signature: Shirley K. Seo -S Digitally signed by Shirley K. Seo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shirley K. Seo -S, 0.9.2342.19200300.100.1.1=1300365375 Date: 2021.10.19 13:17:24 -04'00'			
Office of Pharmaceutical Quality, Application Technical Lead	Hong Cai	CDER/OPQ/ONDP/DNDPII/NDPB4	Section:4.2	**Select one:** _X__ Authored _X__ Approved
	Signature: Hong Cai -S Digitally signed by Hong Cai -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Cai -S, 0.9.2342.19200300.100.1.1=2001467971 Date: 2021.10.19 10:57:20 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Martin Kaufman, DPM, MBA	ORPURM/DUOG	Sections: 1, 2, 3, 7, 8.1	**Select one:** _X__ Authored ___ Approved
	Signature: Martin E. Kaufman -S Digitally signed by Martin E. Kaufman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222976, cn=Martin E. Kaufman -S Date: 2021.10.20 09:20:14 -04'00'			
Clinical Reviewer	Jordan Dimitrakoff, MD, PhD	ORPURM/DUOG	Sections: 8.2	**Select one:** _X__ Authored ___ Approved
	Signature: Jordan D. Dimitrakoff -S Digitally signed by Jordan D. Dimitrakoff -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001393996, cn=Jordan D. Dimitrakoff -S Date: 2021.10.20 13:58:14 -04'00'			
Statistical Reviewer	Jia Guo, PhD	OB/DB4	Sections: 8.1	**Select one:** _X__ Authored ___ Approved
	Signature: Jia Guo -S Digitally signed by Jia Guo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jia Guo -S, 0.9.2342.19200300.100.1.1=2000520093 Date: 2021.10.20 09:40:51 -04'00'			
Statistical Team Leader/Division Deputy Director (OB)	Tsae Yun (Daphne) Lin	OB/DB4	Sections: 8.1	**Select one:** ___ Authored _X__ Approved
	Signature: Tsaeyun D. Lin -S Digitally signed by Tsaeyun D. Lin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tsaeyun D. Lin -S, 0.9.2342.19200300.100.1.1=1300049055 Date: 2021.10.20 10:03:50 -04'00'			

Glossary

ABPM	ambulatory blood pressure monitoring
ACTH	adrenocorticotropic hormone
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice daily
BLA	biologics license application
BMI	body mass index
BP	blood pressure
BSSS	bioanalytical sample stability substudy
C_{avg}	average plasma drug concentration
CFR	Code of Federal Regulations
C_{max}	maximum plasma drug concentration
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
CR	complete response
CRO	contract research organization
CSR	clinical study report
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
DCEP	Division of Cardiometabolic and Endocrine Pharmacology
DDI	drug-drug interaction
DHOT	Division of Hematology Oncology Toxicology
DHT	dihydrotestosterone
DHTU	5α-dihydrotestosterone undecanoate
DMF	drug master file
DNA	deoxyribonucleic acid
DUOG	Division of Urology, Obstetrics, and Gynecology
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EOT	end of treatment
EXTS	extension treated set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GLP	good laboratory practice
HDL	high-density lipoprotein

HMG CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
17β-HSD	17β-hydroxy-steroid dehydrogenase
ICH	International Council for Harmonisation
IIEF	International Index of Erectile Function Questionnaire
IND	investigational new drug
IPSS	International Prostate Symptom Score
IR	information request
ISR	incurred sample reproducibility
LC-MS/MS	liquid chromatography tandem mass spectrometry
LDL	low-density lipoprotein
(b) (4)	(b) (4)
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
mEXTS	modified extension treated set
NaF	sodium fluoride
NDA	new drug application
NMT	not more than
OCP	Office of Clinical Pharmacology
ORA	Office of Regulatory Affairs
OSIS	Office of Scientific Integrity and Surveillance
PDQ	Psychosexual Daily Questionnaire
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	preferred term
RRR	remote record review
SAE	serious adverse event
SBP	systolic blood pressure
SHBG	sex hormone-binding globulin
SOC	system organ class
T	testosterone
TEAE	treatment-emergent adverse event
TU	testosterone undecanoate
ULN	upper limit of normal
WRO	written response only

1 Executive Summary

1.1. Product Introduction

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

Kyzatrex (proposed tradename) is a soft gelatin capsule containing (b) (4) testosterone undecanoate (TU), a prodrug of testosterone, (b) (4) . TU is converted to T by nonspecific esterases present in the body.

In the United States, products containing TU, currently approved for testosterone replacement therapy (TRT), include injection for intramuscular administration (Aveed) and capsule for oral administration (Jatenzo).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness could not be established for Kyzatrex because of unresolved uncertainties about the reliability of the efficacy data in the single phase 3 study (MRS-TU-2019EXT) supporting approval.

Intended as TRT, the therapeutic goal for Kyzatrex is to restore T concentrations to the normal range (C_{avg}) while avoiding excessive T concentrations (C_{max}). For approval, a TRT product, including Kyzatrex, should meet both prespecified C_{avg} and C_{max} targets.

Study MRS-TU-2019EXT, an open-label, single arm efficacy and safety study that included 24-hour ambulatory blood pressure monitoring (ABPM) evaluated the to-be marketed dose and dosing regimen and provided the primary support for safety and efficacy of Kyzatrex. Because TU is a prodrug metabolized by nonspecific esterases in blood to T, an overestimation of T concentrations can occur if blood is collected in a plain tube (serum) without an esterase inhibitor such as NaF. To minimize the impact of this ex vivo TU to T conversion, the Applicant relied on plasma T C_{avg} and C_{max} (blood sample collected in NaF/EDTA tubes) as the primary and key secondary endpoints, respectively. In clinical practice, however, it is common for T concentrations to be measured in serum (plain tubes). Therefore, study MRS-TU-2019EXT included a serum substudy where both serum (plain tubes) and plasma (NaF/EDTA tubes) samples are collected from the same subjects to determine the correlation between plasma and serum T concentrations and to support the use of serum sample in clinical practice. When a

blood sample is handled and processed according to the steps specified in the central lab manual, serum T concentration is expected to be higher than plasma T concentration because of several factors, including the potential ex vivo TU to T conversion, and matrix effect. The Applicant notified the Agency in the July 2020 pre-NDA meeting of multiple subjects at clinical Site 104 of MRS-TU-2019EXT participating in the serum substudy who had NaF/EDTA plasma T concentrations that were paradoxically higher than serum T concentrations obtained at the same timepoint. According to the Applicant, post-study interview with the site coordinator indicated pharmacokinetic (PK) sample mishandling and processing; the Applicant proposed to exclude all data from Site 104. When the data were analyzed using the prespecified efficacy population that included subjects from all study sites, including Site 104 – the extension treated set, or EXTS - only the primary efficacy endpoint C_{avg} was met but not any of the key secondary endpoints for C_{max} outliers. When the Appliciant modified the EXTS population to exclude subjects from Site 104 (modified extension treated set (mEXTS)), the study successfully met the criteria for both C_{avg} and C_{max} efficacy endpoints.

During the NDA review, the Division requested the Office of Scientific Integrity and Surveillance (OSIS) to inspect Site 104 to confirm whether there was mishandling/misprocessing of PK samples to justify excluding Site 104; based on the findings at Site 104, OSIS decided to inspect a second clinical site, Site 107, a high enrollment clinical site. At both sites, OSIS found no documented record of PK sample handling and processing at several clinic visits, including visit 12E (Day 90 of MRS-TU-2019EXT study), the time point of the primary efficacy evaluation for C_{avg} and C_{max}. OSIS concluded these objectionable conditions at Sites 104 and 107 were likely to be present at the other 17 clinical sites not inspected; thus, the reliability of the clinical data from the entire phase 3 study may be impacted. At OSIS's recommendation, the Agency requested the Applicant provide evidence of documentation of PK sample handling/processing for the other 17 clinical sites of study MRS-TU-2019EXT but the Applicant did not do so.

The lack of documentation of the PK sample handling/processing from any clinical sites in study MRS-TU-2019EXT poses significant uncertainties about the reliability of the PK data (serum and plasma T concentrations) forming the basis of Kyzatrex's approval. Blood samples collected from subjects receiving TU typically have variable T concentrations due to several factors, including potential post collection TU to T ex vivo conversion from the presence of endogenous nonspecific esterases in the blood. The use of NaF (esterase inhibitor)-containing tubes to inhibit esterase activity in plasma reduces the extent of possible TU to T ex vivo conversion. However, even with the use of NaF/EDTA tubes, ex vivo conversion of TU to T can still occur and the extent of that conversion depends on PK sample handling and processing conditions, such as temperature, time, and the concentration of TU. Therefore, the handling/processing of all PK samples need to follow the procedures prespecified in the central laboratory manual, such as temperature and duration of each step of blood sample collection, processing, and storage, as well as the transfer of processed/frozen samples to the bioanalytical study site(s). Strict adherence to these procedures ensures that the T values obtained accurately reflect the actual serum or plasma T concentrations of study subjects. Documentation of the handling and processing of PK samples is needed to assure that these steps and procedures were appropriately followed to generate accurate and, hence, reliable PK results. The existence of

the Central Laboratory Manual, training of staff on the Manual, and the Applicant's declaration that the Manual was consistently followed do not provide adequate assurance of the data reliability.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit of Kyzatrex does not outweigh its risks because substantial evidence of effectiveness for Kyzatrex has not been established (see Section 1.2 Conclusions on the Substantial Evidence of Effectiveness).

Kyzatrex, an oral capsule containing testosterone undecanoate (TU), is intended for testosterone replacement therapy (TRT) in males for conditions associated with a deficiency or absence of endogenous testosterone, including congenital or acquired primary or secondary hypogonadism. There are multiple TRT products of various formulations and modes of administration, including oral capsule, approved for the same indication.

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

- ≥85% of subjects with T C_{max} <1.5x upper limit of normal (ULN);
- ≤5% with T C_{max} between 1.8 and 2.5x ULN; and
- 0% with T C_{max} greater than 2.5x ULN.

The Applicant seeks the marketing approval for Kyzatrex, with a recommended starting dose of 200 mg twice-daily with possible titration to a minimum dose of 100 mg once daily in the morning up to a maximum dose of 400 mg twice daily, based on findings from the single phase 3 study (MRS-TU-2019EXT). Based on the prespecified EXT efficacy population that included subjects from all clinical sites, Kyzatrex met the Cavg criterion but failed on all three Cmax outlier targets. Only with the exclusion of Site 104 did Kyzatrex successfully meet the criteria for both C_{avg} and C_{max} targets. The Applicant justified excluding Site 104 based on the site coordinator indicating that the PK samples were not properly handled and processed, resulting in the paradoxical finding of plasma T concentration being higher than serum T concentrations. To confirm the Applicant's assertion to determine whether the exclusion of Site 104 was warranted, the Division requested an Office of Scientific Integrity and Surveillance (OSIS) inspection of Site 104; OSIS also inspected clinical Site 107. The OSIS's inspections of clinical Sites 104 and 107 cited objectionable conditions at both sites with lack of documentation for sample handling and processing to assure appropriate procedures were followed to generate accurate PK results. The lack of evidence of documentation of PK sample handling/processing from all sites of study MRS-TU-2019EXT presents significant uncertainties regarding the integrity and reliability of data from the single phase 3 PK-based study.

In the absence of documentation, the Clinical Pharmacology review team attempted to use the serum substudy (i.e., both NaF/EDTA plasma and serum T concentrations were measured from the serum substudy participants) of study MRS-TU-2019EXT to assess data reliability based on the principle that, in general, a higher serum T concentration is expected compared to the NaF/EDTA plasma T concentration when the same blood sample is split and processed into NaF/EDTA plasma and serum after collection. However, given the serum substudy included only 66% of study subjects (103 of 155) and determination of "abnormal" pattern of serum and plasma PK profile could be subjective, it was not possible to rely on serum substudy to conclude data reliability for the entire phase 3 study.

The safety database for Kyzatrex includes two phase 3 studies, MRS-TU-2019 and MRS-TU-2019EXT. The safety profile of Kyzatrex appears consistent with the known safety profile for other testosterone products. In particular, Kyzatrex causes small increases in blood pressure similar to the approved oral TU product. This safety finding can be adequately mitigated with labeling. There was a nonclinical safety signal of vacuolation of zona fasciculata in the adrenal gland. A cosyntropin stimulation substudy was conducted which did not show any significant differences in cortisol responses to synthetic adrenocorticotropic hormone (ACTH) administration between Kyzatrex and the active comparator.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Male hypogonadism is a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa as a result of disruption to one or more levels of the hypothalamic-pituitary-testicular axis (Bhasin et al. 2018). • Signs and symptoms of androgen deficiency are generally nonspecific and include reduced sexual desire (libido), decreased spontaneous erections, loss of body (axillary and pubic) hair, loss of height, low bone mineral density and osteoporotic fracture, decreased energy, poor concentration and memory, reduced muscle mass and strength, and increased body fat. • Men diagnosed with hypogonadism have "classical" hypogonadism, which refers to hypogonadism caused by specific, well-recognized medical conditions, such as Klinefelter's syndrome, pituitary injury, or toxic damage to the testicles. It is unclear whether older men who have symptoms similar to hypogonadal and with low T concentrations	Male hypogonadism from well-established etiologies ("classic" hypogonadism) has important adverse health consequences known to result directly from deficient/absent testosterone.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to young, healthy men ("age-related" hypogonadism) have the clinical syndrome requiring testosterone replacement.	
Current Treatment Options	• TRT is currently available in the United States as a buccal tablet, subcutaneous implant, transdermal patch, transdermal gel, transdermal solution, nasal gel, and parenteral injection. TU is approved as an intramuscular injection and an oral capsule. • These products are approved for testosterone replacement therapy in men with "classical" hypogonadism and have demonstrated effectiveness in maintaining testosterone concentrations within the eugonadal range while avoiding unacceptably high serum testosterone concentrations. • TRT is commonly used off-label in men who do not have classical hypogonadism, such as those with age-related hypogonadism, although the effectiveness and safety of testosterone has not been established for these uses.	• There are many approved testosterone products available with different routes of administration. In March 2019, a TU capsule was approved for the oral route of administration. In addition, a second oral TU capsule was tentatively approved in December 2020. Approval of Kyzatrex would provide another oral treatment option for male hypogonadism. • Testosterone replacement therapy is approved for men with hypogonadism from well-recognized structural or genetic/congenital etiologies. The safety and effectiveness of testosterone therapy for other conditions associated with lower levels of T concentrations, such as "age-related" hypogonadism have not been established.
Benefit	• The primary efficacy and safety study submitted in this NDA was MRS-TU-2019EXT. Based on inconsistencies in the PK data for the study, OSIS conducted site inspections of two clinical sites. During the inspections, neither clinical sites could provide documentation regarding sample processing and handling for the blood samples used for the PK assessment. We requested that Applicant provide documentation of PK	• The reliability of the PK data for the efficacy and safety study cannot be assured. • The primary and key secondary efficacy endpoints of Kyzetrex are based on C_{avg}

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	handling/processing from the remaining 17 clinical sites but the Applicant did not provide such documentation. • We cannot assure the reliability of data without proper documentation of PK sample handling/processing for this PK-based phase 3 study where the efficacy PK results are known to be impacted by sampling/processing procedures.	and C_{max}, respectively, which are derived from the PK data. • The efficacy of Kyzatrex could not be established with a sufficient degree of certainty because uncertainties about the reliability of the PK data. • MRS-TU-2019EXT did not provide substantial evidence of efficacy.
Risk and Risk Management	Study MRS-TU-2019EXT was a 180-day trial that included ambulatory blood pressure monitoring (ABPM) and enrolled hypogonadal men treated with the 200 mg twice daily dose with titration to a minimum dose of 100 mg daily to a maximum dose of 400 mg twice daily. ABPM assessments were conducted at baseline and at Day 120 and Day 180. The trial showed small increase in blood pressure consistent with what was seen with approved TU product. The increase in blood pressure (BP), with its attendant risk of major adverse cardiovascular events [MACE], can be mitigated with labeling (a Boxed Warning, Contraindications, Warnings/Precautions, and Medication Guide) consistent with the other approved oral TU product. There was a nonclinical safety signal of adverse changes seen in the adrenal gland.	• Safety results from Study MRS-TU-2019EXT demonstrated a comparable safety profile to other TRT products, including oral products. • The increase in BP with Kyzatrex can be adequately mitigated with labeling to monitor BP periodically as with similar text to that of the currently approved oral TU product (Jatenzo). • The Applicant conducted a cosyntropin stimulation substudy that did not show significant differences in cortisol responses to synthetic adrenocorticotropic hormone (ACTH) administration between Kyzatrex and the active comparator.

1.4. Patient Experience Data

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

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient-reported outcome (PRO)	Section 8.1.3
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Male hypogonadism is a clinical syndrome resulting from insufficient/absent secretion of testosterone by the testis. Primary hypogonadism is caused by primary defects of the testes such as Klinefelter syndrome or Leydig cell aplasia. Secondary hypogonadism (also known as hypogonadotropic hypogonadism) is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (follicle-stimulating hormone (FSH), luteinizing hormone (LH)) to support adequate testicular function.

Hypogonadism is a serious medical condition. Testosterone replacement therapy is recommended for the treatment of men with testosterone deficiency from well-known structural or genetic/congenital etiologies. Although TRT use is more common in older men with testosterone concentrations lower than normal of younger men for no cause other than aging ("age-related" hypogonadism), the safety and efficacy of testosterone therapy in this patient population has not been demonstrated.

2.2. Analysis of Current Treatment Options

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication

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

Route of Administration	Trade/Generic Name	Dose	NDA	ANDA
Implant	Testopel/Testosterone	150-450 mg every 3 to 6 months		080911
Transdermal	Androderm/Testosterone	2-6 mg daily	020489	
	AndroGel/Testosterone 1.62%	20.25-81 mg daily	022309	
	Testosterone 1.62%	20.25-81 mg daily		204570 207373 208620 208560 204268 205781 209390
	AndroGel/Testosterone 1%	50-100 mg daily	021015	
	testosterone gel 1%	50-100 mg daily		076737 076744 091073
	Testim/Testosterone 1%	50-100 mg daily	021454	
	Fortesta/Testosterone	10-70 mg daily	021463	
	Testosterone gel	10-70 mg daily		204571
	Vogelxo/Testosterone gel	50-100 mg daily	204399	
	Testosterone topical solution	30-120 mg daily		205328 209533 208061 204255 209836 212882 212301
Nasal	Natesto/Testosterone	11 mg thrice daily	205488	

Source: Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), electronic version accessed October 3, 2021. Product labeling accessed at the DailyMed website and the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) October 3, 2021.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This is the original submission of NDA 213953. Kyzatrex is not marketed in any countries.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant opened investigational new drug (IND) 118675 on March 17, 2016, to study oral testosterone undecanoate. During the drug development program, FDA and the Applicant held the following meetings:

- September 16, 2013: Type B; Pre-IND
- March 25, 2015: Type B; end of phase 2
- April 3, 2019: Type C; Guidance

- October 7, 2019 (WRO): Type C; Guidance
- January 27, 2020 (WRO): Type C; Guidance
- April 6, 2020: Type B; Pre-NDA (CMC)
- July 22, 2020: Type B; Pre-NDA
- October 20, 2020 (WRO): Type C; Guidance (Office of Pharmaceutical Quality)

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

4.1. Office of Scientific Integrity and Surveillance (OSIS)

At the request of the Division, OSIS conducted an inspection of Manhattan Medical Research Practice LLC, New York, NY (Site 104) in June 2021 and South Florida Medical Research, Aventura, FL (Site 107) in August 2021; and remote record review (RRR) of (b) (4) . Refer to OSIS Bioequivalence Establishment Inspection Report Review dated September 28, 2021, in the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) under NDA 213953.

OSIS concluded the following:

> **"Manhattan Medical Research Practice LLC, New York, NY (Site 104)**
>
> Objectionable conditions were observed during the inspection and Form FDA 483 was issued at the inspection close-out for a) not documenting the PK samples handling and processing and b) several subjects had visits outside of the protocol specified window. The final inspection classification is Voluntary Action Indicated. The objectionable conditions may impact the reliability of the study data.
>
> **South Florida Medical Research, Aventura, FL (Site 107)**
>
> Objectionable conditions were observed during the for-cause inspection and Form FDA 483 was issued at the inspection close-out for lacking detailed written documentation of blood sample processing. The final inspection classification is Voluntary Action Indicated. This observation may impact the reliability of study data.
>
> (b) (4)
>
> We observed objectionable conditions during the RRR. Specifically, (b) (4)

(b) (4)

. Based on our review of the RRR observation and the firm's response, we conclude the observation does not impact the reliability of data from the analytical portion of the reviewed studies."

Recommendation Made by OSIS

"Based on our review of the objectionable conditions observed during the inspections and the firms' response to the observations, we conclude the reliability of the data from Site 104 and Site 107 may be impacted. Because the same study design and laboratory manual for sample processing was followed at all the clinical sites including the sites not inspected, we believe the objectionable conditions observed at the two inspected clinical sites were likely present at the other 17 clinical sites that were not inspected. Thus, the reliability of the clinical data from the entire study may be impacted. We recommend the review division to contact the Applicant to determine if similar objectionable conditions from Sites 104 and 107 existed at the other 17 clinical sites that were not inspected.

Based on our review of the objectionable conditions observed during the RRR and the firm's response, we conclude the RRR observation does not impact the reliability of analytical data from the audited studies. However, we cannot exclude the possibility that the potential mismanagement of sample handling and processing after blood collection observed at the clinical sites may have contributed to the ex vivo conversion of testosterone undecanoate (TU) to testosterone (T) in blood samples. We recommend the review division to request more information on blood sample handling and processing from the Applicant and assess the impact of the findings on data reliability."

Clinical Reviewer Comment: *Without proper documentation, we cannot conclude that there was no mismanagement of PK sample handling and processing impacting the reliability of the PK data in the single phase 3 study. The accuracy of the efficacy analyses for Kyzatrex is predicated on reliable PK data points; when the reliability of those data points are uncertain, it follows that the findings from these analyses are also uncertain.*

For specific details regarding clinical reviewer's concerns arising from OSIS inspections, see detailed review under Section 8.1.2, Data Quality and Integrity.

4.2. Product Quality

Recommendation and Conclusion on Approvability

Labeling negotiations have not yet been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201. Therefore, this NDA is not ready for APPROVAL from the Office of Pharmaceutical Quality perspective.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging, and testing facilities have acceptable Current Good Manufacturing Practice status. An overall manufacturing inspection recommendation of APPROVE was issued on September 14, 2021.

A 24-month expiration dating period for the drug product when stored at 20°C to 25°C has been granted.

The request for a categorical exclusion from an environmental assessment, is accepted.

For additional details on the product quality review, the reader is referred to the Integrated Quality Assessment from the Office of Pharmaceutical Quality dated October 7, 2021, in DARRTS.

4.3. Clinical Microbiology

No clinical microbiology supporting information was submitted or requested.

4.4. Devices and Companion Diagnostic Issues

The product does not include a device or companion diagnostic.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

In order to satisfy nonclinical requirements and nonclinical sections of the labeling for the NDA, the Applicant is relying on its own data and on published scientific literature. The Applicant's own nonclinical studies include: in vitro binding studies of TU, 5α-dihydrotestosterone undecanoate (DHTU), and a major excipient component of phytosterol esters ((b) (4)); a distribution and excretion study in male rats; a 13-week repeated dose toxicology study in male dogs; and a fertility study in male rats. These studies were requested primarily to evaluate the safety of the phytosterol esters excipient, which may exhibit affinity for the same targets and/or affect the pharmacokinetics/toxicity profile of the TU product due to similarities in structure to sex steroids and for accumulation in target organ tissues (e.g., adrenal gland, gonads, liver). The Division was concerned that the proposed TU formulation (b) (4) – designed to promote TU absorption – is highly lipophilic and may accumulate in lipid-rich and/or well-perfused tissues and organs such as the adrenal gland, gonads, liver, kidney, fat, and heart following repeated administration.

In addition, the Applicant submitted published literature references to support the chronic toxicology, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology of testosterone (T), the active moiety of TU, for chronic use of the new oral formulation.

Additional information including acceptable daily intake levels and CFR references were provided by the Applicant to support the use of excipients that are either not present (phytosterol esters) or exceed levels ((b) (4), DL-α-tocopherol acetate) in currently approved oral products. In silico (computational) assessments, in vitro mutagenicity assays, and in vitro plasma stability studies were conducted to qualify the degradants exceeding acceptance criteria in long-term stability studies.

TU, DHTU, and the major phytosterol ((b) (4)) had no significant binding for estrogen receptor at up to the concentrations tested. Androgen receptor binding was up to 56.3% for TU, up to 19.3% for DHTU, and up to (b) (4)% for (b) (4). The highest concentrations tested for TU (10µM, ~456700 ng/dL), DHTU (5µM, ~229350 ng/dL), and (b) (4) ng/dL) were approximately 12-fold, 17-fold, and (b) (4) fold higher than the mean plasma C_{max} levels of the same entities in humans taking the maximum dose of 400 mg twice daily (BID) TU, suggesting that TU, DHTU, and (b) (4) may not significantly affect the ligand-specific agonist binding to estrogen or androgen receptor at clinically relevant C_{max} concentrations. The low androgen binding for TU and DHTU suggests that the T esters may possess low potential for androgenic activity and may act via active metabolites including T.

Following a single oral administration to male Sprague Dawley rats at (b) (4) mg/kg (~40 mg/kg [^{14}C]-TU) using formulations with or without phytosterol esters, the distribution of radioactivity into tissues exhibited a maximum concentration between 2 to 6 hour postdose. The highest concentration was observed in the gastrointestinal tract (small intestine, stomach), reproductive organs (epididymis, prostate, epididymal white fat, seminal vesicle, testes), liver, and kidneys, with the muscle and skin accounting for the lowest concentration independent of formulations used. Radioactivity was below the limit of quantification at 168 hour postdose in most tissues except the epididymis for the formulation containing phytosterols ((b) (4) mg), and the liver for the formulation without phytosterols. Drug-related radioactivity was primarily excreted into feces. The prolonged radioactivity in the epididymis at the final sampling time of 168 hours for the formulation with phytosterol esters (half-life unknown) suggests potential tissue retention and/or accumulation of the excipient and/or the drug-related materials.

In the 13-week oral toxicology study in male dogs, treatment-related effects were noted in the adrenal glands (vacuolation of the zona fasciculata) and the reproductive organs including the testis (small size associated with marked germ cell depletion and slight Leydig cell atrophy), epididymis (aspermia), and prostate glands (enlarged size associated with glandular hypertrophy/hyperplasia) in TU groups with or without phytosterol esters. While the systemic exposures to TU and its metabolites were less than dose-proportional, the exposures to phytosterol esters were similar between the low-dose and high-dose groups, suggesting saturation of absorption of the phytosterol esters. No significant differences were observed in plasma levels of TU and its metabolites or estradiol levels with or without phytosterol esters under the conditions of the study. Following a 4-week drug-free period, the findings in the testes (germ cell depletion), epididymides (aspermia), and adrenal glands (vacuolation of the zona fasciculata) were fully reversed in treated groups without phytosterol esters, but not in the high-dose group with phytosterol esters. The nonreversible nature of target organ findings

at the high dose of TU in the presence of phytosterol esters in the dog plasma (no half-life provided) suggests the potential role of phytosterol esters on the persistent target organ toxicity.

The mean plasma exposures to TU, DHTU, T, and DHT at the low dose were approximately 3-, <1-, 2-, and 2-fold the AUC_{0-24h} and approximately 6-, <1-, 4-, and 3-fold the C_{max}, respectively, of the mean human exposure to oral TU at 400 mg BID TU (Study #MRS-TU-2019EXT). The plasma phytosterols measured in this study were approximately (b) (4)-fold the mean AUC_{0-24h} and C_{max} for (b) (4), respectively, at 400 mg BID TU (Study #SOV-TU-PK2013).

Table 2. Summary of Exposure Multiples in Humans Taking 400 mg BID Oral TU Based on the Low Dose of SOV2012-F1 in Male Dogs

Species	Compound				
TK Parameters	TU	DHTU	T	DHT	(b) (4)
Human (Day 84/90)					(b) (4)
AUC_{0-24h}, ng·hr/mL	~1870	~920	~90	~18	
C_{max}, ng/mL	~380	~135	~9	~1.2	
Dog (Day 90)					
AUC_{0-24h}, ng·hr/mL	~6300	~260	~190	~40	
C_{max}, ng/mL	~2490	~39	~35	~4	
EM					
AUC_{0-24h}	3	<1	2	2	
C_{max}	6	<1	4	3	

Abbreviations: AUC_{0-24h}, area under the plasma concentration-time curve from hour 0 to hour 24; BID, twice daily; C_{max}, maximum plasma drug concentration DHT, dihydrotestosterone; DHTU, 5α-dihydrotestosterone undecanoate; EM, exposure multiples; T, testosterone; TK, toxicokinetic; TU, testosterone undecanoate

In the male fertility study where males were dosed for 71 to 73 days (prior to the initiation of the cohabitation period, 1 to 4 days during the cohabitation period, and for a minimum of 6 days and a maximum of 11 days following cohabitation), treatment-related findings included decreased body weight gains and reproductive organ weights for males, reduced fertility, pre-implantation loss associated with reduced mean number of implantation sites, reduced litter size and lower mean number of viable fetuses per litter in untreated gravid females, compared to the control group at the oral dose of (b) (4) mg/kg BID ((b) (4) mg/day/day), corresponding to approximately 2 times the mean AUC_{0-24h} for T and DHT and approximately 2-4 times the mean C_{max}, respectively, at 400 mg BID oral TU.

Overall, the nonclinical data and information provided to support the safety of the new oral TU product are acceptable. The observations from the toxicology and the reproductive studies in male eugonadal animals are expected androgenic effects of T although the findings in the adrenal gland (vacuolation of the zona fasciculata) are of unknown clinical significance. However, these were observed at T levels above the baseline AUC and at C_{max} exposures that would likely not occur in hypogonadal men exposed to T in the eugonadal range. The results from the submitted studies suggest that phytosterol esters are unlikely to affect the

pharmacology, toxicity, or pharmacokinetic profile at the anticipated plasma concentrations of TU and its metabolites up to the levels within the exposure achieved in clinical trials.

5.2. Referenced NDAs, BLAs, DMFs

IND 118675

Drug master file (DMF) [redacted]

5.3. Pharmacology

TU is the undecanoic acid (C-11 linear, alkyl) ester and the prodrug of T that is readily hydrolyzed via local and systemic nonspecific esterase to T and undecanoic acid. TU is absorbed through the lymphatic system, rather than through the portal vein circulatory system.

The Applicant has not conducted any nonclinical studies with the drug substance or drug product to assess primary pharmacodynamics, safety pharmacology, or pharmacodynamic interactions. The Applicant, however, completed in vitro displacement of specific radiolabeled ligand agonist binding to cell-derived human estrogen and androgen receptors with TU, DHTU, and [redacted] (excipient component) as requested by the Division to address the question of how phytosterol esters may exhibit affinity for the same targets of TU and its metabolites due to similarities in structure to sex steroids.

This in vitro binding study showed mean percent inhibition of androgen or estrogen ligand-specific binding of <50% by TU at 10µM (~456700 ng/dL), DHTU at 5µM (~229350 ng/dL), and [redacted] ng/dL), which are approximately 5-34 fold, 8-72 fold, and [redacted] fold greater than the minimum and maximum plasma C_{max} levels for TU, DHTU, and [redacted], respectively, at the maximum recommended human daily dose of 400 mg BID TU (Study #MRS-TU-2019EXT). These results indicate that TU, DHTU, and [redacted] may not significantly affect the ligand-specific agonist binding of T to estrogen or androgen receptor at clinically relevant concentrations.

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. It is identified as an approved food additive up to the maximum level of 2 ppm (2 mg/kg, 120 mg for a 60 kg person) in baked goods according to the Flavor and Extract Manufacturers Association of the United States Flavor Ingredient Library. [redacted].

5.4. ADME/PK

The Applicant conducted a distribution and excretion study and provided a summary of the metabolic pathway for T based on published literature.

In the tissue distribution and excretion study in male Sprague Dawley rats, there was extensive distribution to all investigated tissues at 1 hour with the maximum concentration between 2 to 6 hour postdose following a single (b) (4) mg/kg oral dose (~40 mg/kg TU) of the complete Formulation 1 with phytosterol esters ((b) (4) mg) and Formulation 2 without phytosterol esters. The radioactivity was below the limit of quantification at 168 hour postdose apart from the epididymis for Formulation 1 with phytosterol esters and apart from the liver for Formulation 2 without phytosterol esters. The highest radioactivity was detected in the gastrointestinal tract (small intestine, stomach) followed by prostate, perirenal white fat, seminal vesicle, epididymal white fat, liver, kidneys, adrenal gland, plasma, testes, heart, blood, lungs, levator ani, preputial gland, epididymis, skin, and muscle at 4 hours with the complete Formulation 1. The radioactivity was fully recovered within 168 hour postdose and was primarily recovered in feces (see the Applicant's table below).

Table 3. Mean Concentration of Radioactivity Following a Single (b) (4) mg/kg Oral Dose of TU Formulation 1 Containing Phytosterol Esters to Male Sprague-Dawley Rats

	Concentration (ng-eq/g)						
Sample	1 h	2 h	4 h	6 h	24 h	48 h	168 h
Skin	4252	4530	4062	3007	709	411	BLQ
Lungs	10457	9161	8094	7712	BLQ	BLQ	BLQ
Testes	14727	9739	11676	20036	1047	1001	BLQ
Preputial Gland	6994	10948	7492	8436	2872	1162	BLQ
Epididymal White Fat	5697	80860	121741	120771	20759	BLQ	BLQ
Small Intestine	1661763	1216201	2057627	737225	201504	27321	BLQ
Epididymis	10167	5266	6418	5028	2040	3212	2359
Levator ani	4808	28617	7756	17910	7153	346	BLQ
Stomach	1135027	1126236	922225	352247	18586	BLQ	BLQ
Kidneys	24307	33103	85816	31689	5541	1059	BLQ
Blood	10771	7356	9660	5162	BLQ	BLQ	BLQ
Seminal Vesicles	7081	46124	155594	80765	19757	BLQ	BLQ
Plasma	13761	9860	15632	4838	BLQ	BLQ	BLQ
Muscle	4459	5119	3393	2763	701	BLQ	BLQ
Perirenal White Fat	6609	31195	166465	56150	4207	BLQ	BLQ
Prostate	73627	30234	205216	127234	5400	BLQ	BLQ
Liver	129580	134868	106102	65356	14488	3210	BLQ
Adrenal Gland	12715	21961	19708	18389	2023	BLQ	BLQ
Heart	9798	8979	9774	7868	1254	BLQ	BLQ

The formulation consists of (b) (4) phytosterol esters and (b) (4) DL-α-tocopherol acetate
Abbreviations: BLQ, below the limit of quantification (ranging from 162-3868 ng-eq/g) depending on tissues; TU, testosterone undecanoate

Fatty acid esters of T including TU are partially cleaved by nonspecific esterases in vivo to release the parent compound, T (IARC 1979). In the human body, circulating T is mainly bound in serum to sex hormone-binding globulin (SHBG) and albumin (only ~2% unbound), while the fatty acid ester side chain is metabolized by the β-oxidation pathway (Wishart et al. 2018). T undergoes subsequent reduction by different pathways to yield a variety of 17-keto steroids.

The primary metabolites of T biotransformation are 5α/β-dihydrotestosterone (5α/β-DHT) and estradiol, which are metabolized by 5α/β-reductase and aromatase, respectively. Formation of 5α-DHT and 5β-DHT are then converted by 3α/β-hydroxy-steroid dehydrogenase to produce 3α/β-androstanediol and 3α/β-etiocholanediol, respectively. 17β-hydroxy-steroid dehydrogenase (17β-HSD) further converts 3α/β-androstanediol into androsterone and epiandrosterone, while 3α/β-etiocholanediol is converted into etiocholanolone and epietiocholanolone.

Production of aforementioned metabolites are then conjugated via sulfation (i.e., sulfotransferases) and glucuronidation (i.e., glucuronosyltransferases). T can also be metabolized by glucuronosyltransferases, sulfotransferases, and 17β-HSD to generate T glucuronide, T sulfate and androstenedione, respectively. In addition to production of active and inactive T metabolites, it was suggested that T is metabolized by the CYP2C and CYP3A enzymes to form hydroxylated metabolites at positions 2α-, 2β-, 6β-, 15α-, 11β-, 15β-, and 16β- as identified from reactions using recombinant CYP3A enzyme and/or human liver microsome assays (Kandel et al. 2017; Niwa et al. 2015).

5.5. Toxicology

5.5.1. General Toxicology

The Applicant conducted a 13-week toxicology study in male dogs to evaluate whether the phytosterol esters excipient present in the TU formulation influenced PK/toxicity profile of the TU product due to similarities in structure to sex steroids and potential for accumulation in target organ tissues. The Applicant also provided toxicology findings of T based on published literature.

The new formulation also contains excipients that are either not present ((b) (4) (phytosterol esters)) or exceed levels ((b) (4) , DL-α-tocopherol acetate) in currently approved oral products. The safety of these excipients was evaluated as part of the 13-week oral toxicity study below, and are also further addressed in Section 5.5.5 later in this review.

Study title/number: 13-Week Oral Gavage Toxicity Study of SOV Oral Testosterone Undecanoate Formulation (SOV2012-F1) in Beagle Dogs to Evaluate Any Effect of Excipients (#0470DS97.001)

- Decreased cholesterol (up to ~39%) and triglyceride (up to ~40%) in all TU groups with (Groups 5 and 6) and without (Groups 7 and 8) phytosterol esters compared to vehicle group
- Histopathological findings in the testis (decreased size associated with marked germ cell depletion and Leydig cell atrophy), epididymis (marked aspermia), adrenal glands (slight vacuolation of the zona fasciculata) and prostate gland (increased size associated with moderate glandular hypertrophy/hyperplasia) in TU groups with or without phytosterol esters (partially or nonreversible in the adrenal glands, epididymides, and testes in high-dose TU groups with phytosterol esters)
- No significant difference in toxicokinetic parameters in the presence of phytosterol esters at exposures (b) (4) fold ((b) (4)) or less ((b) (4)) than the mean exposure in male subjects given the maximum proposed human dose of Kyzatrex (400 mg BID TU)

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 4. Methods, Study #0470DS97.001

Methods	Details
Dose and frequency of dosing	See study design table below
Route of administration	Oral gavage
Formulation/Vehicle	Milky white emulsion/Water
Species/Strain	Dog/Beagle
Number/Sex/Group	4 males/group for main study groups
Age	9-10 months (7.2-9.8 kg)
Satellite groups/ unique design	2 males/groups 1, 4, and 6 for recovery groups
Deviation from study protocol affecting interpretation of results	Not significant

Table 5. Experimental Design of the 13-Week Toxicity Study in Male Dogs

Group	Treatment Regimen [Relative to MHRDD]	Dose (mg/kg/day)					
		Total	(b) (4)	(b) (4)	(b) (4)	Tocopherol acetate	TU
1	Vehicle Control (Water)	-	0	0	0	0	0
2	(b) (4) [3X]						0.0
3	(b) (4) [1X]						0.0
4	(b) (4) [2X]						0.0
5	SOV2012-F1 [1X]						24.0
6	SOV2012-F1 [2X]						48.1
7	TU [1X] + (b) (4) [1X]						(b) (4)
8	TU [3X] + (b) (4) [3X]						
MRHDD[1] (mg/kg/day)							-
Safety Margin[2]							-
MRHDD[3] (mg/kg/day) at equivalent Dog HED							-
Safety margin[4] at equivalent Dog HED							-

Source: Applicant's table

(b) (4) = phytosterol esters

[1] 1x, 2x, 3x =1, 2, or 3 times the MRHDD based on HED.
[2] Two dogs designated for a 4-week recovery (nondosing) period following the completion of dosing
The MRHDD of SOV2012-F1 is 13.3 mg/kg of TU administered in (b) (4) In the formulations used in Groups 1, 7 and 8, (b) (4) replaced (b) (4) thus the amounts present are greater than the amounts of (b) (4) present in the SOV2012-F1 formulation.
Abbreviations: -, not applicable; HED, human equivalent dose; MRHDD, maximum recommended human daily dose; (b) (4), complete excipient formulation without TU; bolded numbers represent the highest dose level of the excipient tested in the study and used in the calculation of safety margins; TU, testosterone undecanoate

Table 6. Observations and Results, Study #0470DS97.001

Parameters	Major Findings
Mortality	None
Clinical signs	Unremarkable
Body weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	Dose-related increase (up to ~30%) in platelets and reticulocytes (up to ~62%) in Groups 7 and 8 without phytosterol esters compared to vehicle (water) control group
Clinical chemistry	Decreased triglyceride (up to ~40%) and cholesterol (up to ~39%) in all TU Groups with or without phytosterol esters compared to control group
Urinalysis	Absent sperm in all TU groups with no recovery in Group 6 (complete TU 2x)
Gross pathology	• Decreased testis size in all TU groups with no recovery at the end of 4-week treatment-free period in Group 6 with phytosterol esters compared to control group • Increased prostate size in TU group 6 with phytosterol esters and TU group 8 without phytosterol esters compared to control group
Organ weights	• Increased absolute heart (up to ~22%) and spleen (up to ~64%) weights in all treated groups compared to control group • Increased absolute kidney weights (up to ~25%) and dose-dependent increases in prostate weights (up to ~3-fold) in all TU groups compared to control group • Dose-dependent decreased absolute testis weights (up to ~74%) in TU groups with or without phytosterol esters compared to control group (partially reversible in Group 6 with phytosterol esters)
Histopathology Adequate battery: Yes	Main Group (Day 92/93) • Adrenal glands: slight cytoplasmic vacuolation in the zona fasciculata in TU Groups 6, 7, and 8 • Epididymides: marked aspermia (devoid of spermatozoa within tubular lumens) in all animals of TU Groups 5, 6, 7, and 8 • Testes: diffuse, marked germ cell depletion characterized by marked reduction in cross-sectional diameter of seminiferous tubules that were lined predominantly by Sertoli cells with few residual germ cells, accompanied by diffuse, slight atrophy of interstitial (Leydig) cells that was often associated microscopically with increased cytoplasmic vacuolation in all animals of TU Groups 5, 6, 7, and 8 • Prostate gland: Moderate severity of hypertrophy/hyperplasia noted as an apparent increase in the size and number of glandular epithelial cells in TU Groups 6 and 8, characterized by notable convoluted infoldings of the glandular epithelium within lumens (suggesting increased numbers of glandular epithelial cells), increased variability in the size and shape of glandular epithelial cell nuclei, and increased amounts of apical cytoplasm Recovery Group (Day 120/121) • Adrenal glands: adrenocortical cytoplasmic vacuolation in the zona fasciculata in a single Group 4 (excipients only) male (bilateral, slight intensity) and a single Group 6 (TU with phytosterol esters) male (unilateral, minimal intensity)

Parameters	Major Findings
	• Epididymides: devoid of spermatozoa in TU Group 6 with phytosterol esters • Testes: germ cell depletion and seminiferous tubules with slightly larger cross-sectional diameter as compared to the earlier time point and lined with spermatogonia and a few spermatocytes in TU Group 6 with phytosterol esters • Prostate: moderate severity of glandular atrophy in one TU Group 6 (with phytosterol esters) male
Toxicokinetics (NaF/Na_2 EDTA plasma)	• Less than dose-proportional increase in AUC and C_{max} for TU, DHTU, T, and DHT with no apparent accumulation upon repeat-dosing • Increased plasma estradiol levels in TU group 6 with phytosterols compared to vehicle or excipients only group • Similar phytosterol exposure levels in the presence or absence of TU (Groups 4, 5, 6) with accumulation upon repeat-dosing

Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma drug concentration; DHT, dihydrotestosterone; DHTU, 5α-dihydrotestosterone undecanoate; ECG, electrocardiogram; T, testosterone; TU, testosterone undecanoate

The following table summarizes noteworthy observations made in the 3-month study in male beagle dogs.

Table 7. Summary of Noteworthy Observations Made in the 13-Week Study in Male Beagle Dogs

	Study Group[a]							
	0	(b) (4) 3X	E 1X	E 2X	TU+E 1X	TU+E 2X	TU+ (b) (4) 1X	TU+ (b) (4) 3X
Observations	6♂	4♂	4♂	6♂	4♂	6♂	4♂	4♂
Hematology, Day 92/93								
Platelet, 10^3/µL	221.2	251.8	258.8	224.2	225.8	242.8	**277.0**	**293.0***
Reticulocytes, x10^9/L	32.42	41.15	31.60	35.38	38.40	38.32	**42.65**	**52.68**
Clinical chemistry, Day 92/93								
Triglyceride, mg/dL	43.2	36.5	44.8	38.2	**25.8**	**30.5**	**33.5**	**26.8**
Cholesterol, mg/dL	125.2	130.3	135.8	135.0	**85.3****	**93.5***	88.8*	**76.8****
Organ weights, absolute, g	n=4(2)	n=4	n=4	n=4(2)	n=4	n=4(2)	n=4	n=4
Heart	65.13	**77.65**	**72.48**	**73.90**	**74.78**	**79.40**	**72.48**	78.65
Kidneys	42.78	42.08	46.08	47.40	**53.50**	**51.53**	**50.75**	**52.05**
Prostate gland	6.70	6.48	8.63	**4.78***	**11.85**	**18.35***	**9.40**	**18.10***
Spleen	54.93	**63.43**	**67.83**	**68.63**	**90.15**	**73.10**	**71.45**	**79.45**
Testes, Day 92/93	11.47	12.87	12.85	11.76	3.51*	3.18*	3.24*	3.04*
(Day 120/121)	(10.71)	-	-	(15.03)	-	(5.05)	-	-
Thymus	18.57	16.41	23.40	15.92	14.35	18.81	**8.44**	**12.72**
Gross pathology, Day 92/93 (Day 120/121)	n=4(2)	n=4	n=4	n=4(2)	n=4	n=4(2)	n=4	n=4
Prostate, enlarged, size						3		**3**
Testis, small, size					4	4(2)	4	4
Histopathology, Day 92/93 (Day 120/121)	n=4(2)	n=4	n=4	n=4(2)	n=4	n=4(2)	n=4	n=4
Adrenal glands, vacuolation, zf				(1^2)		1^2(1^1)	2^2	1^2
Epididymides, aspermia					4^4	4^4(2^4)	4^4	4^4
Pituitary gland, cyst	(1^1)			1^1	1^2	(1^1)	1^2	1^2
Prostate, hypertrophy/hyperplasia						3^3		4^3
Atrophy, glandular						(1^3)		
Testes, depletion, germ cells	1^1(1^2)			(1^1)	4^4	4^4(2^3)	4^4	4^4
Atrophy, Leydig cells					4^2	4^2	4^2	4^2
Hypospermatogenesis				(1^1)				

Source: Reviewer generated table

[a] (b) (4), E, all excipients; TU+E, complete formulation; TU+ (b) (4) testosterone undecanoate + (b) (4)

Numbers in superscripts represent severity grades: 1 = minimal, 2 = slight, 3 = moderate, 4 = marked

-; Not available

Statistically significant from controls at p=0.05* or p=0.01*

The following tables summarize toxicokinetic parameters for the 3-month study in male beagle dogs.

Table 8. Summary of Toxicokinetic Parameters in the 13-Week Study in Male Beagle Dogs

	Study Group[a]							
	0	(b) (4) 3X	E 1X	E 2X	TU+E 1X	TU+E 2X	TU+ (b) (4) 1X	TU+ (b) (4) 3X
Toxicokinetics[b]	6♂	4♂	4♂	6♂	4♂	6♂	4♂	4♂
TU								
$AUC_{0\text{-}24hr}$, ng·hr/mL								
Day 1	-	-	-	-	5780	12230	5885	10332
Day 90	-	-	-	-	6321	9604	8040	13085
C_{max}, ng/mL								
Day 1	-	-	-	-	2275	3527	2655	3073
Day 90	-	-	-	-	2487	3046	3466	3311
T_{max}, hr								
Day 1	-	-	-	-	1.0	7.5	1.0	1.0
Day 90	-	-	-	-	1.0	1.0	13.0	7.0
$T_{1/2}$, hr								
Day 1	-	-	-	-	0.77	1.23	0.62	0.80
Day 90	-	-	-	-	1.10	1.12	0.58	0.87
DHTU								
$AUC_{0\text{-}24hr}$, ng·hr/mL								
Day 1	-	-	-	-	290	457	261	359
Day 90	-	-	-	-	258	354	262	393
C_{max}, ng/mL								
Day 1	-	-	-	-	44	69	39	62
Day 90	-	-	-	-	39	55	41	67
T_{max}, hr								
Day 1	-	-	-	-	1.0	2.0	2.0	2.0
Day 90	-	-	-	-	8.0	2.0	7.5	8.0
$T_{1/2}$, hr								
Day 1	-	-	-	-	-	-	-	-
Day 90	-	-	-	-	-	-	-	-

	Study Group[a]							
Toxicokinetics[b]	**0 6♂**	**(b)(4) 3X 4♂**	**E 1X 4♂**	**E 2X 6♂**	**TU+E 1X 4♂**	**TU+E 2X 6♂**	**TU+(b)(4) 1X 4♂**	**TU+(b)(4) 3X 4♂**
T								
$AUC_{0\text{-}24hr}$, ng·hr/mL								
Day 1	41	-	-	46	208	393	219	419
Day 90	68	-	-	50	189	284	239	504
C_{max}, ng/mL								
Day 1	4	-	-	4.4	43.5	67.4	61.4	80.5
Day 90	5.8	-	-	4.4	35.4	48.4	53.2	99.7
T_{max}, hr								
Day 1	10.0	-	-	9.5	1.0	2.0	1.0	2.0
Day 90	4.0	-	-	18.0	13.5	13.5	13.0	14.0
$T_{1/2}$, hr								
Day 1	-	-	-	-	-	-	-	-
Day 90	-	-	-	-	-	-	-	-
DHT								
$AUC_{0\text{-}24hr}$, ng·hr/mL								
Day 1	NA	-	-	NA	35.8	46.3	30.4	45.7
Day 90	NA	-	-	NA	28.9	39.8	31.1	46.1
C_{max}, ng/mL								
Day 1	NA	-	-	NA	5.0	6.1	5.2	6.5
Day 90	NA	-	-	NA	3.9	4.3	5.0	6.6
T_{max}, hr								
Day 1	NA	-	-	NA	8.0	2.0	1.0	2.0
Day 90	NA	-	-	NA	8.0	14.0	14.0	8.0
$T_{1/2}$, hr								
Day 1	-	-	-	-	-	-	-	-
Day 90	-	-	-	-	-	-	-	-
DHT/T ratio for $AUC_{0\text{-}24hr}$								
Day 1	NA	-	-	NA	0.17	0.12	0.14	0.11
Day 90	NA	-	-	NA	0.15	0.14	0.13	0.09

	Study Group[a]							
Toxicokinetics[b]	**0 6♂**	**(b) (4) 3X 4♂**	**E 1X 4♂**	**E 2X 6♂**	**TU+E 1X 4♂**	**TU+E 2X 6♂**	**TU+ (b) (4) 1X 4♂**	**TU+ (b) (4) 3X 4♂**
Estradiol								
$AUC_{0\text{-}24hr}$, pg·hr/mL								
Day 1	36.2	-	-	33.9	-	116.4	-	-
Day 90	42.7	-	-	35.4	-	108.4	-	-
C_{max}, pg/mL								
Day 1	3.0	-	-	2.8	-	9.7	-	-
Day 90	3.4	-	-	3.0	-	9.8	-	-
T_{max}, hr								
Day 1	10.0	-	-	1.0	-	14.0	-	-
Day 90	9.0	-	-	0.0	-	14.0	-	-
$T_{1/2}$, hr								
Day 1	-	-	-	-	-	-	-	-
Day 90	-	-	-	-	-	-	-	-
(b) (4)								
$AUC_{0\text{-}24hr}$, ng·hr/mL								(b) (4)
Day 1								
Day 90								
C_{max}, ng/mL								
Day 1								
Day 90								
T_{max}, hr								
Day 1								
Day 90								
$T_{1/2}$, hr								
Day 1								
Day 90								

Toxicokinetics[b]	Study Group[a] 0 6♂	(b) (4) 3X 4♂	E 1X 4♂	E 2X 6♂	TU+E 1X 4♂	TU+E 2X 6♂	TU+ (b) (4) 1X 4♂	TU+ (b) (4) 3X 4♂
(b) (4)								
$AUC_{0\text{-}24hr}$, ng·hr/mL								
Day 1								
Day 90								
C_{max}, ng/mL								
Day 1								
Day 90								
T_{max}, hr								
Day 1								
Day 90								
$T_{1/2}$, hr								
Day 1								
Day 90								
(b) (4)								
$AUC_{0\text{-}24hr}$, ng·hr/mL								
Day 1								
Day 90								
C_{max}, ng/mL								
Day 1								
Day 90								
T_{max}, hr								
Day 1								
Day 90								
$T_{1/2}$, hr								
Day 1								
Day 90								

Source: Reviewer generated table

[a] (b) (4), E, all excipients, TU+E, complete formulation, TU+ (b) (4) testosterone undecanoate + (b) (4)

LLOQ =12 ng/mL for TU, 3 ng/mL for DHTU, 0.4 ng/mL for T and DHT, 1 pg/mL for estradiol, 100 ng/mL for (b) (4), 11.5 ng/mL for (b) (4) (4-6/sex/timepoint)

NA; not applicable due to <3 concentrations observed in all animal profiles

Abbreviations: -, not available; $AUC_{0\text{-}24hr}$, area under the plasma concentration-time curve from hour 0 to hour 24; C_{max}, masimum plasma drug concentration; DHT, dihydrotestosterone; DHTU, 5α-dihydrotestosterone undecanoate; LLOQ, lower limit of quantitation; T, testosterone; $T_{1/2}$, elimination half-life; T_{max}, time to reach maximum plasma concentration following drug administration; TU, testosterone undecanoate

The Applicant provided toxicology/safety of chronic exposure to T, documenting the findings based on published literature.

Target organs identified in animals receiving T or related esters in chronic or extended dosing schemes are mainly hormone-sensitive reproductive organs/tissues. The most prominent of these are the prostate (hypertrophy/hyperplasia) with up to 6 months exposure in rodents, dogs, and nonhuman primates (Karr et al. 1984; Li et al. 2018; Udayakumar et al. 1998), seminal vesicles (increased weight) and testes (atrophy) with up to 3-month exposure in rats (Bansal and Davies 1986; Chin and Pennefather 1990; Flickinger 1978; Mohd Mutalip et al. 2013), uterus (myometrium growth) with up to 25 months of exposure in rabbits (Meissner and Sommers 1966), and mammary glands (ductal proliferation and acinotubular differentiation) with up to 6 months of exposure in rats (Chambô-Filho et al. 2005), and are likely related to disturbances in the physiological pituitary/hypothalamus LH/FSH feedback system. Other organs/tissues that are also affected by chronic exposure to T include the adrenal gland (atrophy of the zona fasciculata) with chronic administration in rats (Mazzocchi et al. 1983), muscle (increased mass) with dosing for 8 weeks or more in rats (Gao et al. 2005), and altered liver function with dosing for up to 32 months in nonhuman primates (Nucci et al. 2017; Tyagi et al. 1999).

5.5.2. Genetic Toxicology

The Applicant did not conduct genetic toxicology tests for TU but provided a genotoxicity profile of T reported in the literature. T and related androgens were negative in vitro for mutagenic (e.g., bacterial reverse mutation assays) and clastogenic activity, for unscheduled DNA synthesis, and in in vivo mouse micronucleus assays (IARC 1987; Joosten et al. 2004; Morita et al. 1997).

The Applicant conducted two in vitro genetic toxicology tests for the degradant, (b) (4) that was considered potentially mutagenic and classified as Class 3, per International Council for Harmonisation (ICH) M7. The Applicant stated that it has not been possible to isolate it in more than 31% purity due to the instability of the (b) (4) functional group in (b) (4) during isolation and/or storage. Liquid chromatography tandem mass spectrometry (LC-MS/MS) of the isolated material showed that the remainder of the material (~70%) was very likely to be (b) (4) . This material was used regardless in the Ames and the micronucleus assays (see evaluation below).

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number: Mutagenicity Assessment of [redacted] (b) (4) as Determined by a Bacterial Reverse Mutation Assay (#52618.00201DS)

Key study findings:

- No increase in the number of revertant colonies for 31.2% [redacted] (b) (4) either in the presence or absence of S9 mix under the conditions of the study.

GLP compliance: Yes

Test system: Plate incorporation method

Study is valid: Yes (adequate tester strains, dose selection, background mutants/plate, but no cell numbers and media provided)

In Vitro Assays in Mammalian Cells

Study title/number: Genotoxicity Test of [redacted] (b) (4) in an In Vitro Micronucleus Assay in Human TK6 Cells (#52618.00202DS)

Key study findings:

- No dose-related increase in micronucleus frequency for 31.2% [redacted] (b) (4) at any of the tested concentrations following exposures to the test article for 4 hours with and without S9 or for 24 hours without S9 under the conditions of the study.

GLP compliance: Yes

Test system: Micronucleus assay in human TK6 cells

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Not conducted

Other Genetic Toxicity Studies

None

5.5.3. Carcinogenicity

The Applicant has not conducted any carcinogenicity bioassays but provided a summary of literature findings on the carcinogenicity potential of T in support of class labeling for Kyzatrex.

A substantial body of literature demonstrates that, as expected for a hormonally active compound, tumor incidence can be increased in hormonally responsive organs and tissues with expressed receptors for T including, for example, endometrium (Van Nie et al. 1961), ovary (Beamer et al. 1993), mammary glands (Xie et al. 1999), and liver (Giannitrapani et al. 2006; Reuber 1976). As such, IARC (1979) concluded that there is sufficient evidence (Group 2A) for the carcinogenicity of T (and related androgens) in experimental animals; however, evidence in humans was inconclusive (IARC 1987).

T is most probably associated with an increased risk for carcinogenicity through epigenetic mechanisms as genotoxicity data are overall negative. In vitro, T increased transformation frequency of Syrian Hamster Embryo cells when co-incubated with a promotor, 12-O-tetradecanoyl-phorbol-13-acetate (Lasne et al. 1990). Both T and T propionate were also noted to cause some degree of morphological transformation in Syrian hamster embryo cells (Tsutsui et al. 1995), consistent with an epigenetic mechanism and with tumor promoting properties.

T 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 (Glucksmann and Cherry 1968). There is suggestive evidence that injection of T into some strains of female mice increases their susceptibility to hepatoma (Agnew and Gardner 1952). T is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats (Firminger and Reuber 1961).

5.5.4. Reproductive and Developmental Toxicology

The Applicant conducted a fertility and early embryonic developmental toxicology study in male rats for the new TU formulation but provided a summary of published literature, documenting the reproductive and developmental effects of T.

Extensive data are available on the reproductive and developmental effects of T. T is a potent androgenic hormone and its effects on developing fetuses are pronounced.

Administration of T or T ester suppresses testicular weights, spermatogenesis, and fertility in several species (Feigelson 1986; Ježek et al. 1993; McLachlan et al. 2002; Robaire et al. 1984; Zhang et al. 2016), 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 (Fels and Bosch 1971; Hotchkiss et al. 2007; Swanson and Werff ten Bosch 1965; Wolf et al. 2002). Postnatal 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 various

species. Irreversible ovary-independent vaginal cornification and uterine stratification with or without squamous metaplasia and fighting behavior later in life have been noted in mice following subcutaneous or intraperitoneal administration of T (Gandelman et al. 1979). Across multiple species, masculinization of the fetus anatomically and increases in aggressive behavior, are the end results of exposure to T during neonatal development (Dela Cruz and Pereira 2012; Eisner et al. 2002; Wolf et al. 2002).

Fertility and Early Embryonic Development

Study title/number: A Fertility Study with Testosterone Undecanoate Formulation (SOV2012-F1) Administered Twice Daily by Oral Gavage in Male Rats, Including a Toxicokinetic Evaluation (#0325RS97.001)

Key study findings (no historical control data provided)

- Statistically significant decrease in mean body weight gains in treated males and in untreated females (possibly secondary to lower gravid uterine weights) mated with treated males at the high dose of (b) (4) mg/kg/day compared to control group
- Dose-related decrease in absolute epididymis (up to ~29%), testis (~45%), and prostate (up to ~23%) weights in all treated male groups compared to control group
- Reduced fertility index (71%) and increased mean percent pre-implantation loss (34%) associated with lower mean total litter size, mean total number of implantation sites, and mean number of viable fetuses per litter for untreated gravid females mated to high dose males compared to control group

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 9. Methods, Study #0325RS97.001

Methods	Details
Dose and frequency of dosing:	0, (b) (4) mg/kg BID ((b) (4) mg/kg/day), (b) (4) mg/kg BID ((b) (4) mg/kg/day), twice daily
Route of administration:	Oral gavage
Formulation/Vehicle:	**Formulation** TU: (b) (4) Phytosterol Esters:dl-Alpha Tocopherol Acetate at a ratio of (b) (4) **Vehicle control** Deionized water
Species/Strain:	Rat/ CD®IGS rat [Crl:CD®(SD)]
Number/Sex/Group:	24/sex/group
Satellite groups:	3 males/group/timepoint for toxicokinetics (NaF/Na_2 EDTA plasma)
Study design:	Males (8 weeks old) were dosed twice daily (12 hours apart ±2 hours), for 71 to 73 days prior to the initiation of the cohabitation period, 1 to 4 days during the cohabitation period, and for a minimum of 6 days to a maximum of 11 days following cohabitation until the day of scheduled euthanasia for a total of 82/83 consecutive days. Females were not dosed. Each untreated female (14 weeks old) was placed in cohabitation with one male. The pair remained in cohabitation until the female was determined to have been mated, based on the examination of vaginal smears or the presence of a copulatory plug in situ.
Deviation from study protocol affecting interpretation of results:	Not significant

Abbreviations: BID, twice a day; EDTA, ethylenediaminetetraacetic acid

Table 10. Observations and Results, Study #0325RS97.001

Parameters	Major Findings
Mortality	One male at (b) (4) mg/kg/day euthanized for humane reasons on Day 48 possibly due to a technical error
Clinical signs	Increased incidence and severity of hair loss on limbs, forepaws, dorsal/abdominal regions, and/or thorax in treated males and in females mated to males
Body weights	• Dose-related decrease in mean body weights (up to ~9%) in males starting from dosing Day 8, with statistical significance at (b) (4) mg/kg/day during the 6th week (Day 43) throughout dosing days up to the end of treatment (cohabitation Day 13) compared to control group • Reduced mean body weight gains (up to ~82%) in males starting from Day 8 with occasional statistical significance at (b) (4) mg/kg/day throughout dosing phase compared to control group • Reduced mean body weight gains (up to ~34%) in untreated females mated with treated males during GDs 14 - 18 and GD 18, with statistical significance at (b) (4) mg/kg/day compared to control group, possibly secondary to lower gravid uterine weights
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]*	• Dose-related decreases in absolute epididymis (up to ~29%) and testis (up to ~45%) weights (correlated with small testes at (b) (4) mg/kg/day) in all treated groups compared to control group • Dose-related increase in absolute prostate weights (up to ~23%) in all treated groups compared to control group • Hair loss on the abdomen or ventral thoracic region in males at (b) (4) mg/kg/day • Decreased absolute uterus weights (~30%), but not mean corrected body weights (gravid uterus weight subtracted from the GD 18 body weight) or mean corrected body weight changes (GD 0 body weight subtracted from the corrected body weight) in females mated with (b) (4) mg/kg/day males compared to those mated with control group males • Elevated (~29%) number of nongravid females for those cohabited with males treated with (b) (4) mg/kg/day compared to those cohabited with control group (~8%) • Lower mean litter size, lower mean total number of implantation sites, and lower mean number of fetuses per litter for gravid untreated females mated with treated males at (b) (4) mg/kg/day compared to gravid untreated females mated with control group males • Reduced fertility index (~71%) and higher mean percent pre-implantation loss (~34%) for untreated females mated to (b) (4) mg/kg/day males compared to untreated females mated to control group males

Abbreviations: GD, gestation day

The following table summarizes noteworthy observations in the male rat fertility study.

Table 11. Summary of Noteworthy Observations in the Male Rat Fertility Study

	Dose[a], mg/kg/day					
	0		(b) (4)		(b) (4)	
Observations	**24♂**	**24♀**	**24♂**	**24♀**	**24♂**	**24♀**
Mortality[b]					1	
Body weights, g						
Day 43, dosing phase	531.6	-	**520.5**	-	**502.9***	-
Day 60, dosing phase	578.3	-	**570.4**	-	**536.4****	-
Day 71, dosing phase	603.3	-	**593.0**	-	**552.8****	-
Day 3, cohabitation phase	593.3	-	**580.7**	-	**543.1****	-
Day 13, cohabitation phase	615.0	-	**604.0**	-	**560.9***	-
GD 0, gestation phase	-	306.2	-	305.6	-	304.7
GD 18, gestation phase	-	428.9	-	**423.9**	-	**412.1**
Body weight gains, g						
Day 25, dosing phase	19.5	-	**18.8**	-	**13.7****	-
Day 43, dosing phase	16.1	-	**15.6**	-	**11.2***	-
Day 60, dosing phase	6.5	-	8.0	-	**1.2***	-
Day 71, dosing phase	8.6	-	**7.9**	-	**5.4****	-
GD 18, gestation phase	-	15.4	-	15.5	-	**10.2***
GD 14-18, gestation phase	-	46.8	-	47.2	-	**34.7***
GD 0-18, gestation phase	-	122.6	-	**118.3**	-	**107.4**
Organ weights, absolute, g						
Brain	2.16	2.01	**2.07***	1.98	**2.05***	2.01
Epididymides (left + right)	1.52	-	**1.48**	-	**1.08****	-
Prostate gland	1.08	-	**1.15**	-	**1.33**	-
Testes (left + right)	3.79	-	**3.16****	-	**2.10****	-
Uterus	-	48.89	-	49.37	-	**34.39**
Corrected uterus weights[c]	-	379.97	-	374.5	-	377.66
Corrected body weight change[d]	-	73.74	-	68.91	-	72.96
Gross pathology						
Skin, hair loss, ventral abdomen/thoracic					2 (n=2)	
Testes, small, size	1				7	
Caesarean/Reproductive data, GD 18						
Nongravid	-	2	-	2	-	**7**
Gravid	-	22	-	22	-	**17**
Total litter	-	15	-	15	-	**10**
Viable fetuses	-	14	-	15	-	**10**
Corpora lutea/dam	-	17	-	18	-	**15**
Total implantation/dam	-	15	-	15	-	**10**
Pre-implantation loss, %	-	11.7	-	12.9	-	**33.9**
Days in cohabitation	-	66	-	58	-	**61**
Fertility index, %	-	92	-	92	-	**71**

[a] TU content was ~ (b) (4) % of the concentration.
[b] One male at TU (b) (4) mg/kg/day was euthanized on Day 48 probably due to a dosing error.
[c] Day 18 body weight - uterus weight
[d] Corrected Day 18 body weight - Day 0 body weight
Statistically significant from controls at p=0.05* or p=0.01**
-; not available
Abbreviations: GD, gestation day; TU, testosterone undecanoate

The following table summarizes toxicokinetic parameters in the male rat fertility study.

Table 12. Summary of Toxicokinetic Parameters in the Male Rat Fertility Study

	Dose[a], mg/kg/day					
	0		(b) (4)		(b) (4)	
Toxicokinetics[b]	**24♂**	**24♀**	**24♂**	**24♀**	**24♂**	**24♀**
T						
$AUC_{0\text{-}24hr}$, ng·hr/mL						
Day 1	-	-	118.6	-	150.8	-
Day 71	-	-	81.1	-	173.2	-
C_{max}, ng/mL						
Day 1	-	-	17.4	-	20.9	-
Day 71	-	-	18.0	-	33.7	-
T_{max}, hr						
Day 1	-	-	1.0	-	14.0	-
Day 71	-	-	13.0	-	14.0	-
$T_{1/2}$, hr						
Day 1	-	-	-	-	-	-
Day 71	-	-	1.9	-	3.5	-
DHT						
$AUC_{0\text{-}24hr}$, ng·hr/mL						
Day 1	-	-	13.2	-	27.4	-
Day 71	-	-	11.6	-	32.0	-
C_{max}, ng/mL						
Day 1	-	-	2.8	-	4.8	-
Day 71	-	-	2.7	-	5.6	-
T_{max}, hr						
Day 1	-	-	2.0	-	14.0	-
Day 71	-	-	13.0	-	14.0	-
$T_{1/2}$, hr						
Day 1	-	-	1.2	-	2.4	-
Day 71	-	-	1.0	-	3.3	-

[a] TU content was ~ (b) (4)% of the concentration.
[b] Mean T baseline concentration observed at predose on Day 1 was 1.69 and 5.41 ng/mL in Groups 4 and 5, respectively. The T baseline level (predose sample) on Day 1 was within 8% to 31% of the maximum T concentrations observed following twice daily administrations of TU doses. Predose DHT concentrations were only observed in animals from toxicokinetic Group 5 (TU (b) (4) mg/kg/day) on Day 71 (3/group/timepoint).
Due to increase of T levels in rats with age from birth to 80 days, no baseline correction was performed.
LLOQ =0.4 ng/mL for T and DHT
-; not available
Abbreviations: $AUC_{0\text{-}24hr}$, area under the plasma concentration-time curve from hour 0 to hour 24; C_{max}, maximum plasma drug concentration; DHT, dihydrotestosterone; LLOQ, lower limit of quantitation; T, testosterone; $T_{1/2}$, elimination half-life; T_{max}, time to reach maximum plasma concentration following durg administration

Embryo-Fetal Development

Not conducted.

Prenatal and Postnatal Development

Not conducted.

5.5.5. Other Toxicology Studies

The new formulation contains excipients that are either not present (phytosterol esters) or exceed levels ((b) (4), DL-α-tocopherol acetate) in currently approved oral products (see the Applicant's table below).

Table 13. List of (b) (4) Inactive Ingredients in SOV2012-F1 (Clinical, Nonclinical, and Commercial Formulations)

Inactive Ingredient in (b) (4)	CAS No.	Unit Dose (mg) [1]	MRHDD [2] (mg)	FDA IID MDE (mg)
Propylene glycol monolaurate ((b) (4))	(b) (4)			
Polyoxyl 40 hydrogenated castor oil (b) (4)				
dl-α-Tocopherol acetate				
Phytosterol esters (b) (4)				

[1] SOV2012-F1 200 mg TU unit dose capsule
[2] MRHDD =4 x 200 mg TU capsules (800 mg TU/day)

(b) (4)

Abbreviations: FDA IID, FDA Inactive Ingredient Database; MRHDD, maximum recommended human daily dose; MDE, maximum daily exposure; (b) (4); TU, testosterone undecanoate

To qualify the excipients in the final drug product, the Applicant provided additional information including acceptable daily intake levels and CFR references, and reliance on published literature or DMF with appropriate Letter of Authorization, along with conducting a 13-week toxicology study in male dogs. The proposed amounts of the excipients, propylene glycol monolaurate ((b) (4)), DL-α-tocopherol acetate, and phytosterol esters are considered generally regarded as safe that do not exceed the food content or maximum daily intake level, and showed no indication of toxicity in the 13-week study.

The drug product also contains 4 (b) (4) degradation products that exceed a qualification threshold per ICH Q3B(R2) guidance (0.2% or 3 mg/day), including (b) (4) identified during long-term stability testing.

Table 14. Proposed Specification Limits for Identified Degradants in SOV2012-F1

Identified Impurity	CAS No.	MRHDD (mg/day)	Qualification Threshold (ICH Q3B)	TDI (mg/day)[2]	Proposed Specification NMT(%)	Degradant Exposure (mg/day)
[redacted] (b) (4)						

To qualify the degradants that were above the level of qualification in long-term stability studies, the Applicant conducted in silico (computational) assessments, in vitro mutagenicity assays, and in vitro plasma stability studies.

Stability Evaluation of [redacted] (b) (4) in Human and Dog Plasma Using LC-MS/MS (Study #MAR02-001)

[redacted] (b) (4) was found to degrade rapidly by 1 hour in human and dog plasma to 20% and 29%, respectively, of the initial value. Increases in [redacted] (b) (4) were observed in human (0.5 h, 2 h, and 1 h, respectively) and dog (2 h, 4 h, and 2 h, respectively) [redacted] (b) (4). When human or dog plasma was spiked with [redacted] (b) (4), levels of [redacted] (b) (4) rapidly decreased by almost 80% or 71% after 1 hour (half-life ~10 minutes in in human plasma or <10 minutes in dog plasma), with an apparent increase in [redacted] (b) (4) (5 to 24 h). [redacted] (b) (4).

ICH M7 Evaluation of [redacted] (b) (4) (Study # [redacted] (b) (4) -2020)

The potential mutagenicity of a degradant [redacted] (b) (4) was assessed based on two complementary Quantitative Structure-Activity Relationship prediction methodologies to meet the requirements of ICH M7(R1) (step 4) guidelines: an expert rule-based (DEREK) and a statistically based Leadscope Model Applier.

[redacted] was predicted to be plausible for in vitro mutagenicity by DEREK analysis based on the presence of a structural alert, [redacted]. The Leadscope Model Applier predicted with a positive probability of [redacted], a value close to the indeterminate range based on the presence of a [redacted] feature. Therefore, [redacted] was considered potentially mutagenic and classified as Class 3, per ICH M7. The expert review concluded that it should be controlled to the appropriate Threshold of Toxicological Concern or tested for mutagenicity. Accordingly, the Applicant conducted two in vitro genetic toxicology tests for the degradant that were negative (see Section 5.5.2 for details).

The Mutagenic and Toxic Potential of 3 [redacted] Degradation Products: [redacted] and [redacted] (Study #MRS-NC-01)

The impurity [redacted] degradant was initially identified as [redacted] but was subsequently identified and confirmed as [redacted]. The degradant [redacted] also exists as [redacted], but only one [redacted] appears to be present at levels above the ICH Q3B qualification limit of 0.2%. For the three degradants [redacted].

Using two complementary Quantitative Structure-Activity Relationship prediction methodologies (statistical-based and expert-rule based) according to ICH M7 guideline, [redacted] and [redacted] were predicted to be Class 5 nonmutagenic compounds per ICH M7 guideline.

Based on these results, information on related structure was employed to construct a margin of safety for estimating a permissible daily exposure to these degradation products using surrogates [redacted], including the [redacted]. Using a permissible daily exposureof [redacted] mg/day as a conservative measure, the Applicant calculated margin of safety based on the equation (calculated permissible daily exposure level for impurity of interest divided by anticipated daily amount of patient exposure to impurity in drug of interest). When compared to proposed acceptance criteria levels for these impurities in TU in SOV2012-F1, margin of safety levels (which are values for the safety level of compounds or substances of interest) were well above 1 at the maximum recommended dose of 800 mg/day TU for all the degradants.

The Applicant's calculated safety margin was ~[redacted]-fold for [redacted] at the proposed specification of [redacted]%, ~[redacted]-fold for [redacted] at the proposed specification of NMT [redacted]%, and ~[redacted]-fold for the [redacted] degradant relative to TU at the proposed specification of NMT [redacted]% for the maximum recommended dose of 400 mg BID TU.

Taken together, the Applicant's justification for the identified degradants at the specified levels appears reasonable. The degradants [redacted], and [redacted] are considered qualified based on the absence of structural alerts for [redacted] (based on DMF [redacted]) and [redacted]

(b) (4)

the negative results from in vitro genotoxicity assays with (b) (4), the formation of the (b) (4) and (b) (4) degradants in dog and human plasma with incubation of the (b) (4) degradant, along with information from the published scientific literature.

5.5.6. Integrated Summary of Nonclinical Findings

As the pharmacology, PK, and toxicology profiles of endogenous and therapeutically administered T are well established in animals and humans, the Applicant's additional nonclinical studies were focused on the excipient phytosterol esters since they may exhibit affinity for the same targets, and/or affect the PK/toxicity profile of TU based on similarities in structure to sex steroids and potential for accumulation in target organ tissues such as adrenal gland, gonads, and liver. The Applicant also provided additional information and data to support the excipients and degradants that exceeded the qualification thresholds.

The Applicant's data and information provided to support the justification on the identified impurities including degradants and the excipients exceeding acceptance criteria appear reasonable.

Although the utility of animal models for evaluating potential hormonally-dependent adverse effects is limited due to different intraspecies and interspecies responses, the findings in the studies were consistent with those observed with other T products. The adverse effects observed in the androgen-responsive tissues and organs in the 13-week repeat-dose toxicology study and the effects on the fertility and early embryo-fetuses in the reproductive study in eugonadal animals are expected effects at T levels above the baseline exposure levels (AUC ~3 times and C_{max} ~6 times) that are not anticipated to occur in hypogonadal men exposed to T in the eugonadal range. The findings in the adrenal gland (vacuolation of the zona fasciculata) are of unknown clinical significance. To investigate the potential for adverse clinical effects on the adrenal gland, a cosyntropin stimulation substudy was conducted under a long-term clinical study (#MRS-TU-2019). There were no significant differences in cortisol responses to synthetic adrenocorticotropic hormone (ACTH) administration between the SOV2012-F1 (n=30) and AndroGel (testosterone gel 1.62%) (n=15) groups at 30 and 60 minutes both at baseline and after 365 days, while numerically greater post-ACTH cortisol levels were observed in both groups at the end of the study, suggesting that the administration of the exogenous TU may not be associated with adrenal insufficiency.

Phytosterols are plant-derived steroids that are known to act as endocrine-disrupting chemicals (Dean et al. 2017; Moghadasian 2000; Nieminen et al. 2002), and their endocrine-disrupting activity has been reported in animals and humans (Awad et al. 1998; Liu et al. 2012; Mushtaq et al. 2007; Qasimi et al. 2017; Singh and Gupta 2016; Solca et al. 2013). In humans with a rare phytosterolaemia (sitosterolaemia), there was accumulation of elevated plant sterol levels that could interfere with endocrine hormone synthesis, particularly for adrenal cholesterol metabolism, accounting for adrenal insufficiency (Mushtaq et al. 2007). Studies have also

reported that the intake of oxidized phytosterols are atherogenic although the risk remains to be established (Alemany et al. 2014; Assmann et al. 2006; Baumgartner et al. 2013; Scholz et al. 2015; Strandberg et al. 2006).

There are a considerable number of studies reported in evaluating the potential reproductive effects of phytosterols. Studies have shown that the phytosterols and their oxidation products can produce estrogenic, anti-estrogenic, antiprogestational, gonadotrophic, antigonadotrophic, and antiandrogenic effects (Cosmetic Ingredient Review Expert Panel 2004; Dean et al. 2017; Di Gioia and Petropoulos 2019; (b) (4) ; (b) (4); Rárová et al. 2012). Studies have also shown that phytosterols may accumulate in tissues such as the brain, liver, adrenal gland, ovary, and testis, indicating the high affinity for steroid-synthesizing tissues, possibly due to the long elimination half-life of phytosterols (e.g., (b) (4)) ((b) (4); Lindenthal et al. 2002; (b) (4); Sugano et al. 1978; Swell and Treadwell 1961; Vanmierlo et al. 2012). A recent study suggests that phytosterols may also play a role in regulation of the hypothalamic-pituitary-gonadal axis in the reproductive endocrine functions of male Japanese quails by inducing the expression of gonadotropin-inhibitory hormone in the brain and testes that results in reduction of gonadotropin-releasing hormone gene expression and luteinizing hormone secretion, and subsequent attenuation of T production by the testes. Moreover, phytosterols may induce gonadotropin-inhibitory hormone and its receptor locally in the Leydig cells of quail testes, and thereby perturb T production (Qasimi et al. 2018). These data suggest the potential role of phytosterol esters on the endocrine and reproductive systems, and clarify the need to investigate the actions of this excipient with additional nonclinical studies.

The results from the Applicant's own studies, however, showed that phytosterol esters in this formulation would not significantly alter the expected pharmacology, toxicity, or absorption of TU within the anticipated mean plasma concentrations of TU and its metabolites in humans given 400 mg BID TU. However, the persistent effect on the testis, epididymis, and adrenal gland at the end of the 4-week treatment-free period and the greater exposure (no half-life provided) to phytosterol esters in the dog following 90-day daily dosing of the TU formulation at the high dose suggest that the potential role of phytosterol esters on the steroid receptors and/or reproductive endocrine function cannot be completely ruled out upon prolonged administration of the TU formulation at high systemic exposures.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical development program of Kyzatrex consists of 10 clinical studies. SOV2012-F1 was selected as the to be marketed formulation and was used in 4 clinical trials (SOV-TU-PK2017 [dose timing study], MRS-TU-PK2018 [food and alcohol effect study], MRS-TU-2019EXT [phase

3, efficacy and safety study], and SOV-TNR2019 [normal T concentration range determination study]) that this review focuses on.

The Office of Clinical Pharmacology (OCP)/Division of Cardiometabolic and Endocrine Pharmacology (DCEP) finds the overall clinical pharmacology information submitted to support this NDA is **unacceptable** and Kyzatrex is **recommended for complete response (CR)** from a clinical pharmacology standpoint.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The key clinical pharmacology review issues were as follows:

Use of Plasma in NaF/EDTA Tubes for Efficacy and Safety Assessments in the Phase 3 Study

It is known that blood samples collected from subjects receiving TU typically have unstable T concentrations due to postcollection TU to T ex vivo conversion due to endogenous nonspecific esterases. It was demonstrated that the use of NaF (esterase inhibitor)-containing tubes to inhibit esterase activity in plasma provides the most stable sample for determination of the primary efficacy endpoint and key secondary endpoint (LaChance, 2015). Main factors affecting the TU to T ex vivo conversions are:

- Sample handling and processing conditions including temperature and time
- Sample collection tube types (e.g., plain tubes vs. NaF/EDTA tubes)
- TU concentration

The Applicant conducted a bioanalytical sample stability substudy (BSSS) during development to investigate this matter and confirmed this finding. Therefore, efficacy and safety analysis in the phase 3 study was done based on the T concentration measured from plasma in NaF/EDTA tubes. Detailed discussion about this approach can be found in Section 18.4.1 of this review. The Applicant's approach was found to be acceptable from a Clinical Pharmacology standpoint.

Reviewer Comment*: Regardless of the sample matrix (serum [plain tubes] vs. plasma [NaF/EDTA tubes]), the TU to T ex vivo conversion is impacted by sample preparation conditions, such as temperature, time, and the concentration of TU. To reliably measure T concentrations in both serum and plasma, it is critical that handling and processing of the PK samples from the phase 3, efficacy and safety study (MRS-TU-2019EXT) follow the procedures and steps prespecified in the Central Laboratory Manual (see more details in Section 6.3.2 of this review) and such adherence be appropriately documented.*

Because the efficacy and safety of Kyzatrex are expected to be demonstrated with PK endpoints, including the primary efficacy endpoint and key secondary endpoint, proper handling/processing procedure and documentation are critical to ensure that the results are an

accurate reflection of T concentrations. Therefore, PK sample handling and processing integrity becomes an approvability issue.

Determination of Normal T Concentration Range

The Applicant conducted Study MRS-TNR2019 in 105 healthy, eugonadal males to determine their normal T concentration range. No Kyzatrex treatments were administered in this study. Subjects were fasted for at least 8 hours before blood collection and provided 2 types of samples (NaF/EDTA plasma and serum) for analysis of T and DHT. Table 15 summarizes the normal T and DHT concentration ranges in NaF/EDTA plasma and serum derived from Study MRS-TNR2019.

Table 15. Reference Range Based on the Central 95% of Population for Plasma and Serum Concentration (ng/dL) of T and DHT (N=105)

Analyte	Matrix	Reference Range (2.5th to 97.5th percentile)
Testosterone	Plasma	222.29, 800.23
	Serum	286.05, 990.72
Dihydrotestosterone	Plasma	11.32, 72.65
	Serum	16.57, 81.51

Source: Table 2, Module 2.7.3
Abbreviations: DHT, dihydrotestosterone; T, testosterone

Considering the well accepted normal serum T concentration range of 300-1000 ng/dL, the Applicant's proposed normal plasma T concentration range obtained from this study is found to be acceptable from a Clinical Pharmacology standpoint.

Serum T Concentration-Based Dose Titration Scheme

While dose titration was based on plasma T concentrations from randomized (1:1:1) time points (3-, 4-, or 5-hours postmorning dose) in the phase 3, efficacy and safety study (MRS-TU-2019EXT), the Applicant is proposing the dose titration to be performed in the clinic based on serum T concentrations.

In the phase 3 study, MRS-TU-2019EXT, the Applicant collected and analyzed paired plasma and serum samples from study participants at their titration visits on Days 14 and 42. In addition, at their end of treatment visit on Day 90, paired plasma and serum samples from a subgroup of study participants (N=103) were collected and analyzed. The Applicant used the regression of the serum T concentration as a function of the NaF/EDTA plasma T concentration to derive the serum-based dose titration thresholds of 460 and 971 ng/dL from the NaF/EDTA plasma-based dose titration thresholds of 400 and 900 ng/dL. Details regarding the development of the dose titration scheme can be found in Section 6.3.2 of this review.

Establishment of Key Secondary Endpoint (C_{max}) Thresholds

During the development of Kyzatrex, the Applicant proposed [redacted] (b) (4) to determine the proportion of C_{max} outliers. However, in the January 27, 2020 Division's Written Responses to the Applicant's Type C Guidance meeting package questions, the Division recommended that the Applicant use 1.5-, 1.8-, and 2.5-fold of the upper limit of the normal T concentration range as the three C_{max} thresholds to determine proportion of C_{max} outliers. Further discussion about this topic can be found in Section 6.3.2 of this review. The Applicant followed the Division's advice and the C_{max} thresholds used in determining the proportion of the C_{max} outliers are acceptable from the Clinical Pharmacology standpoint.

The Office of Study Integrity and Surveillance Inspections

After the study completion and data review, a pattern in the relationship of NaF/EDTA plasma and serum T concentrations from Site 104 in Study MRS-TU-2019EXT was called into question by the Applicant. There were multiple subjects at Site 104 whose NaF/EDTA plasma T concentrations were paradoxically higher than serum T concentrations obtained at the same timepoint. This was extensively discussed with the Applicant at the Type B, pre-NDA meeting on July 22, 2020. Reference is made to the meeting minutes for outcome of the meeting.

After the NDA was submitted, inspections of Clinical Sites 104 (Manhattan Medical Research Practice, LLC, Jamaica, NY), 107 (South Florida Medical Research, Maitland, FL) and the Bioanalytical site ([redacted] (b) (4)) were conducted by the OSIS and the Office of Regulatory Affairs (ORA). The Applicant failed to provide sufficient documentation and evidence assuring that sample handling and processing were conducted properly. The finding of the lack of written documentation for PK sample handling at both Clinical Sites 104 and 107 calls into question how the PK samples were processed and handled at the other 17 clinical study sites and the reliability of the data in general. More details about the OSIS inspection findings can be found in Section 6.3.2 of this review. As the integrity and reliability of the data from the other 17 clinical study sites in addition to Sites 104 and 107 cannot be assured, the Clinical Pharmacology review team finds the data from the phase 3, efficacy and safety study, MRS-TU-2019EXT to be **unacceptable**.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended starting dose is 200 mg orally BID, once in the morning and once in the evening. Kyzatrex should be taken with food. Kyzatrex is not substitutable with other oral TU products.

Therapeutic Individualization

The dosage of Kyzatrex should be individualized based on the patient's serum T concentration response to Kyzatrex. To ensure proper dose adjustment, serum T concentrations should be checked 7 days after starting treatment or after dosage adjustment, 3-5 hours after the morning dose. The Kyzatrex dose should be adjusted as shown in Table 16, as necessary. Thereafter, periodically monitor serum T concentrations. The minimum recommended dose is 100 mg once daily in the morning. The maximum recommended dose is 400 mg (two 200 mg capsules) BID. For total daily doses greater than 100 mg, the same dose should be administered in the morning and evening.

Table 16. Kyzatrex Dosage Adjustment Scheme

Testosterone Concentration	Current Kyzatrex Dosage	New Kyzatrex Dosage
Less than 460 ng/dL	100 mg with breakfast only	100 mg twice daily with meals
	100 mg twice daily with meals	200 mg twice daily with meals
	200 mg twice daily with meals	300 mg twice daily with meals
	300 mg twice daily with meals	400 mg twice daily with meals
460 to 971 ng/dL	No dosage change	
More than 971 ng/dL	400 mg twice daily with meals	300 mg twice daily with meals
	300 mg twice daily with meals	200 mg twice daily with meals
	200 mg twice daily with meals	100 mg twice daily with each meals
	100 mg twice daily with meals	100 mg with breakfast only
	100 mg with breakfast only	Discontinue treatment

Source: Table 15, Module 2.7.3

Outstanding Issues

PK Sample Handling and Data Integrity of Study MRS-TU-2019EXT

See subsection entitled, "The Office of Study Integrity and Surveillance Inspections" in Section 6.2.1 of this review.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Absorption

Table 17 summarizes the PK parameters for plasma total T and TU in patients completing at least 90 days of Kyzatrex treatment.

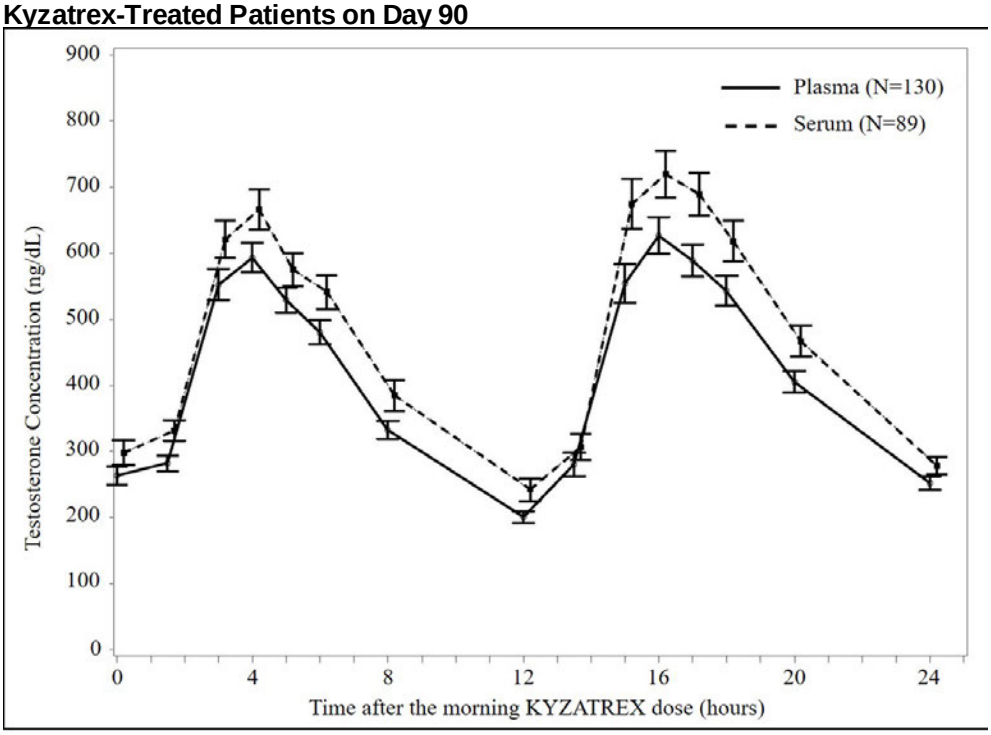
Table 17. NaF/EDTA Plasma T and TU C_{avg} and C_{max} on Day 90

PK Parameter		Plasma T (N=130)	Plasma TU (N=130)
C_{avg} (ng/dL)	n	127	119
	Mean	393.3	7806.4
	SD	113.6	4129.2
C_{max} (ng/dL)	n	130	126
	Mean	852.4	36258.9
	SD	311.3	22100.6

Source: Table 29, MRS-TU-2019 and MRS-TU-2019EXT CSR
Abbreviations: EDTA, ethylenediaminetetraacetic acid; PK, pharmacokinetic; SD, standard deviation; T, testosterone; TU, testosterone undecanoate

Figure 1 summarizes the mean plasma and serum total T PK profiles on Day 90.

Figure 1. Mean (±SEM) Concentration-Time Profiles for NaF/EDTA Plasma and Serum Total T in Kyzatrex-Treated Patients on Day 90



Source: Figure 1, Module 2.7.2
Abbreviations: EDTA, ethylenediaminetetraacetic acid; SEM, standard error of the mean; T, testosterone

Food Effect and Alcohol Interaction

When Kyzatrex was given with 16%, 33%, and 45% fat breakfast, the exposure (AUC) was increased by 37%, 87%, and 94%, respectively, compared to when given under fasted conditions. There was no effect on T PK when Kyzatrex was administered with 20% alcohol along with a high-fat meal versus a high-fat meal alone. See Section 6.3.2 of this review for detailed information.

Metabolism

The androgenic activity of TU occurs after the ester bond linking the T to the undecanoic acid is cleaved by endogenous nonspecific esterases. Undecanoic acid is metabolized like all fatty acids via the beta-oxidation pathway. T is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of T are DHT and estradiol (E2).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

No. The efficacy and safety of Kyzatrex was evaluated in the phase 3 study, MRS-TU-2019EXT. The primary efficacy endpoint (i.e., C_{avg} responder rate) and the key secondary endpoint (i.e., C_{max} distribution) are PK-driven endpoints. Due to the data integrity and reliability concerns discussed in Section 6.2.1 and under the next question in the current Section 6.3.2 of this review, the Clinical Pharmacology review team concludes that there is no supportive evidence of effectiveness.

Study Design of Efficacy and Safety Study, MRS-TU-2019EXT

Study MRS-TU-2019EXT enrolled male hypogonadal subjects 18-65 years of age. All subjects received Kyzatrex starting at a total daily dose of 400 mg (200 mg with the breakfast and 200 mg with the dinner) and dose was adjusted, if needed, using the plasma-based dose titration thresholds of 400 and 900 ng/dL for up- and down-titration, respectively. The duration of treatment in Study MRS-TU-2019EXT was approximately 6 months (180 days) with efficacy assessment conducted upon completion of 90 days treatment.

Primary Efficacy Endpoint

The primary efficacy endpoint for Study MRS-TU-2019EXT was the percentage of subjects with a NaF/EDTA plasma T C_{avg} within the normal T concentration range after 90 days of treatment. A total of 155 subjects were enrolled and received at least one dose of Kyzatrex (EXTS population).

As shown in Table 18 below, the percentage of subjects with T C_{avg} in the normal T concentration range was similar whether measured in NaF/EDTA plasma or serum.

Multiple number of subjects from Clinical Site 104 had NaF/EDTA plasma T concentration results paradoxically higher than serum T concentrations obtained at the same time. As a result, the Applicant excluded all subjects from this site (N=16) for efficacy analysis. The primary efficacy endpoint of C_{avg} was met regardless of the exclusion of Site 104 as shown in Table 18.

Table 18. Percentage of Kyzatrex-Treated Subjects Achieving NaF/EDTA Plasma T C_{avg} Within Normal Range after 90 Days of Treatment (mEXTS) With or Without Excluding Site 104)

Measure	Target	Without Excluding Site 104 (N=155)	With Excluding Site 104 (N=139)
T C_{avg} within normal range after 90 days, n (%)	≥75%	136 (87.7)	122 (87.8)
95% confidence intervals	≥65% (lower bound)	82.6, 92.9	82.3, 93.2

The normal range for plasma T is 222-800 ng/dL.
Abbreviations: EDTA, ethylenediaminetetraacetic acid; mEXTS, modified extension treated set; T, testosterone

Key Secondary (C_{max}) Endpoint

The key secondary endpoint were the percentage of Kyzatrex-treated subjects on Day 90 with plasma T C_{max} within the predetermined ranges summarized in Table 20.

Table 19. Key Secondary Endpoint Thresholds

Plasma C_{max} Threshold	Plasma Range (ng/dL)	Target Percentage of Population
≤ 1.5 x ULN	≤1200	≥85%
>1.8 x ULN to ≤2.5 x ULN	>1440 to ≤2000	≤5%
>2.5 x ULN	>2000	0%

ULN = upper limit of normal of testosterone in plasma (800 ng/dL) collected in NaF/EDTA tubes as determined in MRS-TNR2019. The approach to calculation of C_{max} thresholds was recommended in FDA Written Response to Marius dated 27 Jan 2020.
Source: Table 3, Module 2.7.3
Abbreviations: EDTA, ethylenediaminetetraacetic acid

Table 20. Percentage of Kyzatrex-Treated Subjects Achieving Maximum Plasma T C_{max} Within Predetermined Limits After 90 Days (Without or With Excluding Site 104)

Measure	Target	Without Excluding Site 104 (N=155)	With Excluding Site 104 (N=139)
C_{max} <1200 ng/dL, n (%)	≥85%	119 (81.5)	114 (87.7)
1440≤C_{max} ≤2000 ng/dL, n (%)	≤5%	9 (6.2)	5 (3.8)
C_{max} >2000 ng/dL, n (%)	0%	5 (3.4)	0 (0)

Abbreviations: T, testosterone

The key secondary endpoint (C_{max}) was not met when including all 155 subjects; the key secondary PK endpoint (C_{max}) was met only after excluding subjects from Site 104, as shown in Table 20.

OSIS Inspection Findings and Data Reliability

After the NDA was submitted, inspections of Clinical Sites 104 (Manhattan Medical Research Practice, LLC, Jamaica, NY), 107 (South Florida Medical Research, Maitland, FL) and the Bioanalytical site ([redacted] (b) (4)) were conducted by the OSIS and the ORA. The inspection findings are summarized below.

On June 25, 2021, a Form 483 was issued as a result of an ORA inspection of Site 104 with the following key findings:

- Record review revealed there was not accurate or adequate documentation prepared or maintained regarding the PK sample handling and sample processing for any of the PK samples taken during Visits 4, 6, and 8 for all subjects enrolled at the clinical trial site.
- Although Visit 12E (Day 90) was not indicated in the Form 483 observation, the OSIS inspection report states that the ORA investigator confirmed that there was no documentation of the PK samples processing and handling for Visit 12E as well.

In addition, similar findings were observed at Site 107 for having no written laboratory sample processing documentations. On August 26, 2021, a Form 483 was issued as a result of an ORA inspection. The key findings are summarized below:

- Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, according to the Central Laboratory Manual, Appendix VII and VIII, blood collection tubes with NaF/EDTA for T/DHT testing were to be collected, mixed by inversion 7-8 times, allowed to stand in an ice water bath immediately after sampling for no longer than 110 minutes, centrifuged at 2000 g for 10 minutes at 4°C, transferred to two plasma tubes, and then stored at -70°C until shipping. However, for five out of the five subjects reviewed, there is no laboratory sample processing documentation to indicate these laboratory manual specific procedures were followed.

The OSIS Bioequivalence Establishment Inspection Report Review (dated September 18, 2021) further states that this inspection also revealed that the Applicant and the contract research organization (CRO), (b) (4)

Therefore, without documentation ensuring proper sample handling and processing, the reliability of data from Site 107 is under question.

While there were some issues identified with (b) (4), the Clinical Pharmacology review team concurs with the OSIS assessment that it does not have impact on the reliability of the study data. Detailed discussion on this topic can be found in Section 18.4.1 of this review.

Reference is made to the OSIS Bioequivalence Establishment Inspection Report Review dated September 28, 2021, in DARRTS under NDA 213953. The OSIS inspection report concludes that lack of written documentation for PK sample handling and processing at both Clinical Sites 104

and 107 may impact the reliability of the study data from these 2 sites. In addition, the report states that the same objectionable conditions observed at these 2 inspected sites were likely present at the other 17 clinical sites that were not inspected.

The finding of a lack of written documentation for PK sample handling at both Clinical Sites 104 and 107 calls into question how the PK samples were processed and handled at other 17 clinical study sites and the reliability of data. As a result, the Division sent the following information request (IR) to the Applicant on September 16, 2021:

> *We have the following comments and information requests. We request a written response by September 22, 2021, in order to continue our evaluation of your NDA.*
>
> *Provide complete documentation describing the sample processing and handling for the following blood samples at Visit 12E of Study MRS-TU-2019EXT from all clinical sites other than sites 104 and 107:*
>
> - *Blood samples for NaF/EDTA plasma (T/DHT)*
> - *Blood samples for NaF/EDTA plasma (TU/DHTU)*
> - *Blood samples for EDTA plasma (T/DHT)*
> - *Blood samples for serum (T/DHT)*
>
> *The documentation should include records on temperature and duration of each step from blood sample collection, precentrifugation sample placement and storage, centrifugation, transferring of processed samples to vials, storage, and shipping. Also, provide applicable records and documentation on the identifications of the sample tubes that were used for blood sample collection and processing.*

In the Applicant's initial response submitted on September 21, 2021, the Applicant stated that "Marius was truly surprised at the information being requested in the IR as in our experience or that of our global contract research organization ((b) (4)), this information is not routinely collected from study sites in a clinical trial like MRS-TU-2019EXT. Accordingly, our study sites were not required to record this level of sample processing information." The Applicant failed to provide documentation showing that the predefined sample handling and processing procedures were followed adequately.

Subsequently, the Applicant submitted the following in their follow-up IR response on September 29, 2021:

- Sample condition and storage temperatures for the Visit 12E bioanalytical samples as received at the (b) (4) Central Laboratory from the clinical sites
- Evidence of training of the clinical sites on the laboratory procedures for bioanalytical samples.

***Reviewer Comment**: In the absence of documentation ensuring that sample handling and processing were performed properly, the Clinical Pharmacology review team attempted to use the serum substudy (i.e., both NaF/EDTA plasma and serum T concentrations were measured from serum substudy participants) data from the phase 3 study, MRS-TU-2019EXT, to determine data reliability based on the principle that, in general, a higher serum T concentration is expected compared to the NaF/EDTA plasma T concentration when the same blood sample is split and processed into NaF/EDTA plasma and serum after collection. However, given that there was serum substudy data available from only 103 of 155 subjects (66%) and 3 out of the 19 clinical study sites did not have a single subject that participated in the serum substudy, it was impossible to use the paired NaF/EDTA plasma and serum samples to determine data reliability for the entire phase 3 study. In addition, using this approach to select subjects/samples that had abnormal pattern of serum and plasma PK profiles could be subjective. Therefore, there were limitations in the applicability of this analysis across all study participants at all clinical study sites.*

Upon completion of review on the materials submitted by the Applicant, the Clinical Pharmacology review team concludes that these materials do not provide documentation and sufficient evidence assuring that sample handling and processing were conducted properly according to predefined process in the laboratory manual. Therefore, the Clinical Pharmacology review team finds the uncertainty of proper sample handling and processing to be a significant concern regarding the integrity and reliability of the data potentially across all study sites. As a result, the Clinical Pharmacology team finds the data from the phase 3, efficacy and safety study, MRS-TU-2019EXT **unacceptable**.

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

No. The proposed starting dose and titration scheme were selected based on results from Study MRS-TU-2019 and evaluated in Study MRS-TU-2019EXT. However, due to the data integrity and reliability issues discussed in Section 6.2.1 of this review, it is unknown if the proposed dosage regimen is appropriate for the general patient population.

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

No. The Applicant has conducted subgroup analyses for efficacy. In summary, the subgroup analyses findings are as follows:

- **Age**: Efficacy (i.e., percentage of subjects having T C_{avg} within the normal T concentration range) was slightly higher for men below the age of 50 years (91.7%; 66 out of 72 subjects) than for those above 50 years (83.6%; 56 out of 67 subjects). No apparent difference in the efficacy results based on age are observed.
- **Weight and body mass index (BMI)**: C_{avg} was lower in patients with higher weight and higher BMI but there doesn't appear to be a difference between the two groups of weight

or BMI regarding efficacy. For subjects with baseline weight ≤93 kg, the mean (SD) T C_{avg} after 90 days was 416.5 (123.7) ng/dL and 47 of 52 (90.4%) subjects had T C_{avg} within the normal range while for subjects with baseline weight >93 kg, the mean (SD) T C_{avg} after 90 days was 379.2 (105.3) ng/dL and 75 out of 87 (86.2%) subjects had T C_{avg} within the normal range. For subjects with baseline BMI <30 kg/m^2, 37 out of 41 (90.2%) subjects had T C_{avg} within the normal range while for subjects with baseline BMI ≥30 kg/m^2, 85 of 98 (86.7%) subjects had T C_{avg} within the normal range. The Applicant also examined subjects who had high T C_{max} values (≥1200 ng/dL) in the phase 3 study, MRS-TU-2019EXT, but there were no correlation between the T exposure and body weight found.

- **Race**: The T C_{avg} was similar between White subjects (mean (SD): 398.9 (111.0) ng/dL, N=110) and Black or African American subjects (mean (SD): 379.6 (141.7) ng/dL, N=17). For White subjects, 100 of 110 (90.9%) subjects had T C_{avg} within the normal range.

Based on these findings, the Clinical Pharmacology review team concludes that there are no alternative dosing regimens or management strategies required for subpopulations based on intrinsic patient factors.

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

Yes. The absorption of T (administered as TU) is increased in the presence of food and thus dosing instructions include taking with food. Although the Applicant did not conduct any drug-drug interaction (DDI) studies with Kyzatrex, the labeling would include DDI information for the drug class.

Food Effect and Alcohol Interaction

When Kyzatrex was given with 16%, 33%, and 45% fat breakfast, the exposure (AUC_{0-24h}) was increased by 37%, 87%, and 94%, respectively, compared to when given under fasted conditions. There was no effect on T PK when Kyzatrex was administered with 20% alcohol along with a high fat meal (i.e., point estimates for AUC_{0-24h}: 93.8%; C_{max}: 105%) vs. a high fat meal alone.

In the phase 3, efficacy and safety study, MRS-TU-2019EXT, subjects were instructed to take Kyzatrex 30 minutes after beginning a meal, and to consume their normal diet. Participants completed a survey to identify eating patterns relating to both meal size and fat content and made meal choices for breakfast and dinner meals for in-clinic PK days. The breakfast and dinner meals were designed to deliver varying percentages of calories from fat: low-fat meals (≤20% calories from fat), normal-fat meals (>20% to 35%), and high-fat meals (>35%). All lunches were normal fat meals as no drug was administered with lunch. It should be noted that these meal choices were complemented for 3 out of the 90 days (i.e., Days 14, 42, and 90) of active treatment and therefore, did not reflect what the meal choices of the participant were for the other 87 days as there were no restrictions in meal choices for the participants on those days.

DDI Potential

While the Applicant did not conduct any DDI studies with Kyzatrex, the Applicant proposes to include the following drug class labeling information on the product label of Kyzatrex:

- **Insulin**: Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and therefore necessitate a decrease in the dose of antidiabetic medication.
- **Oral Vitamin K Antagonist Anticoagulants**: Changes in anticoagulant activity may be seen with androgens; therefore, more frequent monitoring of international normalized ratio and prothrombin time are recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy.
- **Corticosteroids**: The concurrent use of testosterone with corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal, or hepatic disease.
- **Medications that May Also Increase Blood Pressure**: Some prescription medications and nonprescription analgesic and cold medications contain drugs known to increase blood pressure. Concomitant administration of these medications with Kyzatrex may lead to additional increases in blood pressure

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 21. Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
MRS-TU-2019	03198728	Randomized, open-label, active-controlled, efficacy and safety study	Starting dose 600 mg daily (400 mg with am meal, 200 mg with pm meal); with dose adjustment, if needed, at Visits 5 and/or 7 based on the titration algorithm. The study drug was administered through the oral route. AndroGel was applied transdermally at a starting dose of 40.5 mg QD in the am and titrated per prescribing information.	Primary: Percentage of Kyzatrex treated subjects with a 24-hour T C_{avg} in the normal range after 90 days of treatment. Secondary: Percentage of Kyzatrex treated subjects at Day 90 with T C_{max} values: • ≤1.5x ULN • >1.8 to ≤2.5x ULN • >2.5x ULN.	365 days/ 14 days	314	Adult hypo-gonadal men	39 – USA
Uncontrolled Studies to Support Efficacy and Safety								
MRS-TU-2019EXT	04467697	Open-label, single arm efficacy and safety study that included 24-hour ambulatory BP	Starting dose 400 mg daily (200 mg with am meal, 200 mg with pm meal); with dose adjustment, if needed, at Visits 9E and/or 11E based on the	***Efficacy*** – Primary: Percentage of Kyzatrex treated subjects with a 24-hour T C_{avg} in the normal range after 90 days of treatment.	180 days/ 7 days	155	Adult hypo-gonadal men	19 – USA

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
		monitoring (ABPM)	revised titration algorithm. The study drug was administered through the oral route.	Secondary: Percentage of Kyzatrex treated subjects at Day 90 with T C_{max} values: • ≤1.5x ULN • >1.8 to ≤2.5x ULN • >2.5x ULN. ***ABPM*** – Primary: change from Baseline in 24-hour average ambulatory SBP after ~120 (±3) days of treatment. Secondary: Change from baseline in: (1) 24-hr average ambulatory SBP after ~180 days of treatment; (2) 7 AM to 10:30 PM -hr average ambulatory SBP ~120 and 180 days of treatment; (3) 11 PM to 6:30 AM -hr average ambulatory SBP after ~120 and 180 days of treatment; (4) 24-hour mean DBP measured by ABPM after ~120 and 180 days of treatment; (5) 7 AM to 10:30 PM -hr average ambulatory DBP after ~120 and 180 days of treatment;				

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
				(6) 11 PM to 6:30 AM -hr average ambulatory DBP after ~120 and 180 days of treatment; (7) 24-hr average ambulatory HR and 7 AM to 10:30 PM -hr average ambulatory heart rate (daytime) after ~120 and 180 days of treatment; (8) 11 PM to 6:30 AM -hr average ambulatory heart rate after ~120 and 180 days of treatment; (9) Observed and change from baseline in hourly SBP, DBP, and heart rate after ~120 and 180 days of treatment.				

Abbreviations: ABPM, ambulatory BP monitoring; BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; QD, once daily; SBP, systolic blood pressure; ULN, upper limit of normal

7.2. Review Strategy

The primary focus of the clinical review is data derived from Study MRS-TU-2019EXT – the extension study of MRS-TU-2019. MRS-TU-2019 was a phase 3, randomized, multicenter, open-label, active-controlled, efficacy and safety trial that evaluated twice daily dosing of Kyzatrex in adult hypogonadal men. The extension study (MRS-TU-2019EXT) was an open-label, nonrandomized, single-arm trial that evaluated efficacy and safety with a lower starting dose of Kyzatrex than the original study and a revised titration algorithm. The extension study also examined the blood pressure (BP) effects of Kyzatrex using in-clinic BP monitoring and 24-hour ABPM.

Supportive safety data was derived from study MRS-TU-2019.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. MRS-TU-2019EXT

Trial Design

MRS-TU-2019EXT was an open-label, single arm efficacy and safety study that included 24-hour ABPM. The duration of the study was approximately 8.5 months (195 days), and included an 8-week washout period, a 180-day treatment period, and a 1-week safety evaluation period at the conclusion of treatment.

All subjects received Kyzatrex at a starting dose of 400 mg daily (200 mg with the breakfast meal and 200 mg with the dinner meal). Each subject's dose was adjusted, if needed, after 28 and/or 56 days of treatment, to a minimum daily dose of 100 mg and a maximum daily dose of 800 mg (400 mg twice a day). Efficacy was assessed on Day 90 of the study.

Study Endpoints

The primary efficacy endpoint of MRS-TU-2019EXT was the percentage of Kyzatrex treated subjects with a plasma T C_{avg} within the normal range after 90 days of treatment. The normal range for plasma T was 222 to 800 ng/dL, which was obtained using data from study MRS-TNR2019.

The key secondary efficacy endpoints were the percentages of Kyzatrex treated subjects with plasma T C_{max} values after 90 days of treatment that were:

- ≤1.5x upper limit of normal (ULN)
- >1.8x ULN to ≤2.5x ULN
- >2.5x ULN

where ULN (800 ng/dL, obtained from study MRS-TNR2019) is the upper limit of normal range for plasma T.

Statistical Analysis Plan

The analysis populations for this study were defined as follows:

1. EXTS, which included all dosed subjects (i.e., including site 104) in the study. This was the prespecified population prior to the Applicant's discovery of the abnormalities in serum vs. plasma T concentrations in subjects at clinical Site 104 after the completion of the phase 3 study and analysis of the study's data.
2. Modified EXTS (mEXTS), which included all dosed subjects in the study excluding site 104 (16 subjects from site 104). The Applicant proposed this as the primary efficacy population after its discovery described in #1.

The Applicant estimated the efficacy endpoints of C_{avg} and C_{max} using mEXTS. The 95%, 2-sided, confidence interval for the percentage was also calculated. Missing T C_{avg} values at Day 90 were imputed as failures in the analysis. For each secondary plasma T C_{max} endpoint specified above, the percentage was estimated using observed data without imputing the missing data. The C_{max} outliers endpoints are intended to limit the maximum plasma concentrations associated with a testosterone product for testosterone replacement therapy.

To demonstrate the efficacy for a TRT, at least 75% of the study population has plasma T C_{avg} in the normal range, with the lower bound of the 95% confidence interval (CI) at least 65%. In addition, (1) at least 85% of subjects have C_{max} ≤1.5x ULN (2) not more than 5% of subjects have C_{max} >1.8x ULN to ≤2.5x ULN; and (3) no subject has C_{max} >2.5x ULN.

The Applicant conducted sensitivity analysis on the EXTS population using the same analysis approach as the primary analysis.

Protocol Amendments

MRS-TU-2019EXT is an extension study of MRS-TU-2019. The protocol for the extension study was added to the protocol for the original study as Amendment 6 (Version 7.0) dated June 27, 2018. There were two amendments to the protocol after the addition of MRS-TU-2019EXT. The amendments affecting the extension study are summarized in Table 22.

Table 22. Summary of Protocol Amendments to MRS-TU-2019/MRS-TU-2019EXT Affecting the Extension Study

Version	Brief Description of Changes	Date
Amendment 6 Version 7.0	An extension study (MRS-TU-2019EXT) has been added as Appendix 16.12. Its purpose is to further examine the BP effects of Kyzatrex, using 24-hour ambulatory blood pressure monitoring (ABPM). A secondary objective will be to demonstrate the feasibility of using a lower starting dose of Kyzatrex (daily dose of 400 mg [200 mg with breakfast meal and 200 mg with dinner meal]) to minimize the number of subjects exposed to a higher starting dose than is needed. Another secondary objective is to collect a single set of samples to evaluate bioanalytical effects of serum versus plasma samples. Approximately 135 men who complete the 52-week study, MRS-TU- 2019, and are willing to consent to participate in the extension study will be eligible to participate. Study Procedures and Schedule of Assessments for D365 will be revised to include the assessments required for MRS-TU-2019EXT as well as information for D364 will be added for those subjects continuing in the extension study. Adding information for the 100 mg and 150 mg Kyzatrex strengths to Section 7.4.2 Identity of Investigational and Comparator Products. Adding analysis of HbA1c at D365 for MRS-TU- 2019 subjects (from an already planned and collected hematology sample at D365). Addition of sample collection for bioanalytical sample stability from 12 or more Kyzatrex subjects in MRS-TU-2019, at Visit 10 (Day 180) or Visit 12 (Day 270). Changing (b) (4) to (b) (4), due to a merger with (b) (4).	27 June 2018
Amendment 7 Version 8.0	For bioavailability sample stability substudy (BSSS), an unscheduled option was given for the sampling visit, within one week of either Visit 10 for Visit 12. This was done to accommodate some subjects who experienced dose level changes making them eligible, on the morning of the associated visit and could not extend the visit without notice. Eligibility criteria for BSSS sampling study was revised to Hgb >13 g/dL, from >14 g/dL. Per FDA feedback, the ABPM MRS-TU-2019EXT study has been extended to provide ABPM data collection after 4 months of treatment at a subject's final dose. Subjects are expected to reach their final dose by Day 28E or Day 56E and remain on that dose throughout the remainder of the treatment. The overall treatment period was extended to 6 months total to provide a minimum 4-month treatment	

Version	Brief Description of Changes	Date
	period at final dose for all subjects. The visit schedule and objectives have been revised to align with the extended 6-month treatment period. Per FDA feedback the enrollment target for the MRS-TU-2019EXT was increased from 135 enrolled to up to approximately 170 enrolled, with a target completion of 135 evaluable subjects at 4 months of treatment. Site participation numbers were also increased in an effort to enroll larger subject numbers. A pathway for enrollment into MRS-TU-2019EXT ABPM extension study was added for subjects having already completed MRS-TU-2019 by the start of MRS-TU-2019EXT, whereby subjects could enroll, bypassing the D364-365 requirements and beginning participation at the required 8-week washout visits. An option has also been added to enroll non-MRS-TU-2019 subjects, from a few select sites, to the ABPM extension study in order to increase the likelihood of reaching the desired total number of participating subjects in MRS-TU-2019EXT. There are revisions to which MRS-TU-2019EXT ABPM extension study visits require fasting to assure in-clinic BP is measure in a fasted state across all visits which include vital signs. An addition of a "no smoking within 30min of the start of the study visit" was added to avoid impact of smoking on in-clinic BP assessments. The prior requirement of a "passing" ABPM assessment at Day365/Visit 2E (EOT main MRS-TU-2019 study) was removed. The requirement for "passing" ABPM assessment was added to Visit 7E/ Day1E of treatment in the extension study, because this timepoint is considered necessary as the baseline from which to measure changes during the ABPM extension study. Per FDA request for MRS-TU-2019EXT, ABPM Extension Study only: added Eligibility Inclusion limitation for MRS-TU-2019EXT, for newly enrolled subjects of BP <140/90, and requirement for all subjects to have BP <140/90 in order to continue past Visit 6E to dosing. Clarified Exclusion Criteria for ABPM Extension Study Only, Newly Enrolled Subjects: main study exclusion criteria #2: patients must not have received prior testosterone replacement therapy within 8 weeks of the start of the study, with the exception of T implantable pellets which are excluded for 6 months. *For ABPM Extension Study Only: Newly Enrolled Subjects to MRS-TU-2019EXT ABPM Extension Study, patients must not have received prior testosterone replacement therapy within 8 weeks of the start of the	

Version	Brief Description of Changes	Date
	study, with the exception of T implantable pellets which are excluded for 6 months.	
Amendment 8 Version 9.0	Removed CBG analysis from the ACTH substudy timezero sample on Day 365. Replaced the FTZ method of Free T calculation with the FTV method. Clarified that added Eligibility Inclusion limitation for MRS-TU-2019EXT, for newly enrolled subjects of BP <140/90, and requirement for all subjects to have BP <140/90 at V6E in order to continue to V7E dosing, is based on in-clinic BP assessment (average of those assessments required for the visit). Clarified that if new enrollment subjects have a normal physical exam at Screening V2(EXT), they are not required to have a repeat physical exam at V7E. Added the clarifications stated in the 23 October 2019, Protocol V8.0 Clarification Letter: At selected new enrollment centers, subjects who completed the main MRS-TU-2019 study >8 weeks prior and had not yet entered into MRS-TU-2019EXT, may be enrolled as a new enrollment subject, providing they meet all eligibility criteria specified for new enrollment subjects. This removes the requirement of an additional 8-week washout period for prior subjects off of treatment for 8 or more weeks already. Clarified additional information being collected in the CRF at time of 24-hr ABPM readings, i.e., the eCRF will collect basic information about any unusual events that may impact BP, as follows: Did the subject experience any of the following during this 24-hour home BP monitoring period? • Unusual activity? • Unusual diet? • Unusual stressful event? Unusual events are described as those events that are unusual to the individual subject's activities or experiences of daily living. Added a 24-hr Serum T/DHT substudy for select centers in ABPM Extension Study MRS-TU-2019EXT (approximately 100 subjects), to include added Serum T collection at all 24-hr PK timepoints at V12E/D90E for up to approximately 100 subjects. Added definitions of analysis populations for MRS-TU-2019EXT.	18 Feb 2019

Version	Brief Description of Changes	Date
	Added efficacy (C_{avg} and C_{max}) analyses to primary and secondary objectives of MRS-TU-2019EXT. Removed LiHeparin tubes from sample collection for bioanalytical analysis. Added exploratory analysis of serum T and DHT values obtained at V12E/D90E in the serum substudy. Added exploratory analysis of titration decisions comparing all sample types.	

Abbreviations: ACTH, adrenocorticotropic hormone; BP, blood pressure; CBG, corticosteroid-binding globulin; CRF, case report form; DHT, dihydrotestosterone; EOT, end of treatment; T, testosterone

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant indicated that this trial was designed and monitored to comply with the ethical principles of GCP as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

The Applicant also indicated that written informed consent of the subject to participate in the study was obtained by the investigator at the Pretreatment Visit 1 prior to any assessments being conducted, in accordance with the Declaration of Helsinki and in accordance with the U.S. FDA regulations set forth in Part 50 of Title 21 of the US Code of Federal Regulations.

Financial Disclosure

The Applicant submitted FDA Form 3454 for studies MRS-TU-2019 and MRS-TU-2019EXT. The form was signed by Om Dhingra, Ph.D., the chief executive officer of Marius Pharmaceuticals, and included an attachment listing the studies covered by the form and the investigators participating in each of these studies.

The Applicant certified that (1) they had not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study; (2) each listed clinical investigator required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant did not disclose any such interests; and (3) no listed investigator was the recipient of significant payments of other sorts.

Patient Disposition

Of the 155 subjects who were dosed in MRS-TU-2019EXT, nine withdrew from the study before the efficacy assessment at Visit 12E (Day 90E). A total of 20 subjects withdrew before Visit 16E (Day 180E), the end of treatment visit. The reasons for discontinuation are summarized in Table 23.

Table 23. Reason for Discontinuation of Study Drug, MRS-TU-2019EXT[1]

Reason for Discontinuation of Study Drug	All Dosed N=155 n (%)
Adverse event	2 (1.3)
Lost to follow-up	6 (3.9)
Physician decision	0
Protocol violation	0
Withdrawal by subject	9 (5.8)
Death	0
Other	4 (2.6)

Source: NDA 215953 (SDN 001), Module 5.3.5.1, Table 14.1.1.3.
[1] Subject (b) (6) presented at Visit16E/Day 180E and indicated that he had stopped study drug on or around Day 155, between Visit 14E/Day 120E and Visit 16E/Day 180E. Thus, this subject was not included in the count of subjects (20) withdrawing prior to Visit 16E/Day 180E but was included in the count of subjects (21) who withdrew from study drug

Protocol Violations/Deviations

There were 160 major clinical protocol deviations during MRS-TU-2019EXT, with 52.9% of the 155 treated subjects experiencing at least one major protocol deviation. Major protocol deviations are summarized in Table 24.

Table 24. Major Protocol Deviations, MRS-TU-2019EXT (N=155)

Deviation Type	n (%)	Events
Any deviation	82 (52.9)	160
Drug noncompliance	24 (15.5)	36
Visit/Procedure required	23 (14.8)	26
Visit window	21 (13.5)	39
Visit procedure-meal	15 (9.7)	19
Unable to calc compliance	9 (5.8)	11
Dosing	8 (5.2)	8
Consent version	7 (4.5)	8
Enrollment criteria	5 (3.2)	6
Laboratory	3 (1.9)	3
Procedure schedule	2 (1.3)	2
Informed consent	1 (0.6)	2

Source: NDA 215953 (SDN 001), Module 5.3.5.1, Table 14.1.2.1.1.

Poststudy, during the PK analysis of MRS-TU-2019EXT data, the Applicant identified "aberrant" plasma PK values for Site 104. Per the Applicant, poststudy interview with the study coordinator at the site revealed significant deviations to the required lab processing procedures for NaF/EDTA plasma PK samples. The Applicant created the mEXTS population to exclude Site 104 PK data for the efficacy C_{avg} and C_{max} analyses. The mEXTS population included 139 subjects: the 155 subjects in the EXTS population less the 16 subjects enrolled at Site 104.

Table 25. Demographic Characteristics of the Primary Efficacy Analysis, MRS-TU-2019EXT (mEXTS)

Demographic Parameters	Control Group (N=) n (%)	Treatment Arm #1 (N=139) n (%)
Sex		
Male		139 (100)
Female		0
Age		
Mean years (SD)		50.6 (9.51)
Median (years)		50.0
Min, max (years)		22, 66
Age group		
≤50 years		72 (51.8)
>50 years		67 (48.2)
Race		
White		110 (79.1)
Black or African American		22 (15.8)
Asian		4 (2.9)
American Indian or Alaska Native		1 (0.7)
Native Hawaiian or Other Pacific Islander		
Other		2 (1.4)
Ethnicity		
Hispanic or Latino		50 (36.0)
Not Hispanic or Latino		87 (62.6)
Missing		2 (1.4)

Source: NDA 215953 (SDN 001), Module 5.3.5.1, Table 14.1.3.1.2.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Table 26. Other Baseline Characteristics, MRS-TU-2019EXT (mEXTS)

Characteristic Statistic	Kyzatrex N=139
Weight at baseline (kg)	
n	139
Mean (SD)	105.09 (24.994)
CV (%)	23.8
Median	98.88
Min, max	57.6, 181.4
Weight category, n (%)	
≤93	52 (37.4)
>93	87 (62.6)
Height (cm)	
n	139
Mean (SD)	175.42 (9.025)
CV (%)	5.1
Median	175.26
Min, max	137.2, 198.1
BMI (kg/m^2)	
n	139
Mean (SD)	34.28 (7.526)
CV (%)	22.0
Median	32.64
Min, max	19.6, 72.3
BMI (kg/m^2), n (%)	
<30	41 (29.5)
≥30	98 (70.5)
Hypogonadal status,[1] n (%)	
Primary	6 (4.3)
Secondary	133 (95.7)
Diabetic status, n (%)	
With diabetes mellitus	30 (21.6)
Without diabetes mellitus	109 (78.4)
Hypertensive status, n (%)	
Hypertensive	82 (59.0)
Not hypertensive	54 (38.8)
Missing	3 (2.2)

Source: NDA 215953 (SDN 001), Module 5.3.5.1, Table 14.1.3.1.2.
[1] Primary hypogonadism (LH and FSH above the upper limit of normal [ULN]).
Secondary hypogonadism where serum LH is within the normal range or below the lower limit of normal [LLN] and/or FSH is within the normal range or below the LLN).
Abbreviations: BMI, body mass index; CV, coefficient of variation; FSH, follicle-stimulating hormone; LH, luteinizing hormone; mEXTS, modified extension treated set; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Two calculations are used to determine the percent compliance. The first calculation is a worst-case calculation to evaluate compliance if a subject took all capsules dispensed minus capsules returned. The second calculation evaluates compliance if a subject followed their assigned dose, but failed to return excess capsules. The calculations are equivalent if the subject follows

instructions but differ when capsules are reported lost or missing by subjects, in which case the first calculation shows 'overcompliance'.

Assuming any missing capsules were taken, the mean (range) study drug compliance to Visit 12E/Day 90E (n=143) was 96.0% (63.7% to 130.3%). Two (1.4%) subjects had >120% study drug compliance to Visit 12E/Day 90E. If missing capsules were assumed not taken, the mean compliance was 93.6% and one subject (0.7%) had drug compliance >120%.

Concomitant Medications

In MRS-TU-2019EXT, concomitant medications were defined as medications that were started after the first dose of study drug in MRS-TU-2019EXT or started before the first dose of study drug in MRS-TU-2019EXT and continued on or after the first dose of study drug in MRS-TU-2019EXT. The most common concomitant medications (>10% of subjects) were 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA)-reductase inhibitors, plain angiotensin-converting enzyme inhibitors, plain angiotensin II antagonists, propionic acid derivatives, plain multivitamins, vitamin D and analogues, biguanides, anilides, SSRIs, propionic acid derivatives, platelet aggregation inhibitors excl. heparin, dihydropyridine derivatives, and other respiratory system products.

Rescue Medication Use

Rescue medication was not used during the study.

Data Quality and Integrity

In the NDA submission, the Applicant stated: "Post-study, during PK analysis of MRS-TU-2019EXT data, aberrant plasma PK values were identified for Site 104. Post-study interview of the study coordinator at the site, revealed significant deviations to the required lab processing procedures for NaF/EDTA plasma PK samples."[1] The aberrant plasma PK values that the Applicant referred to were from subjects who had enrolled in the Serum Substudy of MRS-TU-2019EXT and had NaF/EDTA plasma T-concentration results that were paradoxically higher than serum results obtained at the same time.

To address the aberrant findings from Site 104, the Applicant modified the primary efficacy EXTS population to exclude Site 104 for the efficacy analyses (modified EXTS, or mEXTS). The Applicant amended the statistical analysis plan (statistical analysis plan Final Version 5.0, dated August 28, 2020) so that the mEXTS analysis set (N=139), which excluded the 16 subjects from Site 104, would be used for the analyses of the primary (C_{avg}) and key secondary (C_{max})

[1] NDA 215953 (SDN 001), Module 5.3.5.1, Clinical Study Report: MRS-TU-2019 and MRS-TU-2019EXT, p. 119.

endpoints, rather than prespecified the EXTS analysis set (N=155). It should be noted that when the EXTS population was used, none of the key secondary endpoints of Cmax were met. When the mEXTS analysis set was used, all of the key secondary endpoints of C_{max} were met.

During the clinical review of the NDA, review team found that aberrant plasma PK values were not limited to the subjects enrolled at Site 104. This raised concerns deviations to the required lab processing procedures that the Applicant noted for Site 104, might not be limited to that site.

The review team requested OSIS inspect Site 104 to determine whether there were justifiable reasons to exclude Site 104, as the Applicant asserted. In addition to Site 104, OSIS also inspected clinical Site 107. OSIS observed objectionable conditions at both clinical sites. For Site 104, a Form 483 was issued for a) not documenting the PK sample handling and processing and b) several subjects that had visits outside of the protocol specified window. For Site 107, the Form 483 was issued for lacking detailed written documentation of blood sample processing. OSIS noted that the objectionable conditions at both clinical sites may impact the reliability of the study data.

Based on their review of the objectionable conditions observed during the inspections and the firms' response to the observations, OSIS concluded that the reliability of the data from Sites 104 and 107 may be impacted, and because the same study design and laboratory manual for sample processing was followed at all the clinical sites, including the sites not inspected, OSIS believes the objectionable conditions observed at the two inspected clinical sites were likely present at the other 17 clinical sites that were not inspected. Thus, the reliability of the clinical data from the entire study may be impacted.

OSIS recommended Division request additional information on blood sample handling and processing from the Applicant and assess the impact of the findings on data reliability. The Division sent an IR to the Applicant on September 16, 2021, for the following:

> "Provide complete documentation describing the sample processing and handling for the following blood samples at Visit 12E of Study MRS-TU-2019EXT from all clinical sites other than sites 104 and 107:
>
> - Blood samples for NaF/EDTA plasma (T/DHT)
> - Blood samples for NaF/EDTA plasma (TU/DHTU)
> - Blood samples for EDTA plasma (T/DHT)
> - Blood samples for serum (T/DHT)
>
> The documentation should include records on temperature and duration of each step from blood sample collection, precentrifugation sample placement and storage, centrifugation, transferring of processed samples to vials, storage, and shipping. Also, provide applicable records and documentation on the identification of the sample tubes that were used for blood sample collection and processing."

In its initial response to the Division's IR emailed by Ms. Samantha Bell, regulatory project manager supporting DUOG, on September 21, 2021, the Applicant provided the following:

1. A summary of bioanalytical sample control procedures for MRS-TU-2019EXT

The Summary of Bioanalytical Sample Control Procedures for MRS-TU-2019EXT provided information regarding (1) laboratory requisitions, kits, and sample chain of custody from site to (b) (4) Central Laboratory to PK Referral Lab ((b) (4)); and (2) steps in the drawing and processing of the PK samples by the site.

Reviewer Comment*: None of this information documented PK sample handling and processing procedures.*

2. A copy of the central laboratory manual for MRS-TU-2019EXT

The Central Laboratory Manual for MRS-TU-2019EXT specified the steps to be followed during the PK sample handling and processing procedures.

Reviewer Comment*: The Manual did not provide any evidence in the form of documentation that these steps were actually followed.*

3. A draft questionnaire to the clinical sites about whether specific PK sample handling and processing procedures were followed (yes/no)

Reviewer Comment*: The questionnaire did not request specific documentation to ascertain that the PK samples were actually handled and processed according to the specifications detailed in the Central Laboratory Manual. The questionnaire queried the site staff member to "confirm if the PK camples" were collected and processed at the site in accordance to the central lab manual.*

4. A summary of document explaining the handling of clinical samples, validation of the NaF/EDTA plasma samples for determining T concentrations in TU-dose subjects, and proposal to send the questionnaire (#3 above) to the MRS-TU-2019EXT clinical sites to confirm adherence to the laboratory manual procedures and to assess whether further documentation may be available.

In the Summary document #4, the Applicant stated:

> "Marius was truly surprised at the information being requested in the IR as in our experience or that of our global contract research organization ((b) (4)), this information is not routinely collected from study sites in a clinical trial like MRS-TU-2019EXT. Accordingly, our study sites were not required to record this level of sample processing information. Marius is confident that the sample procurement and processing framework described in the lab manual and reinforced by site-level training and monitoring provided a robust framework for the collection, processing, and analysis of study samples in compliance with established regulatory standards. Our

understanding is confirmed by the nature and consistency of the data generated in MRS-TU-2019EXT. In addition, Marius successfully developed an outlier analysis tool which helped identify potential site sample issues and subsequently did identify and share details of an outlier site who did not follow procedures correctly. Marius is confident that our data generated is reliable and can be used to support product approval."

Clinical Reviewer Comment*: Based on the Applicant's comment and submission content, we conclude documentation of PK sample handling/processing is not systemically available for MRS-TU-2019EXT. It is reasonable to expect such documentation for phase 3 trial with PK efficacy endpoints, especially when the necessity for proper handling and processing of blood samples for the measurement of testosterone concentrations in subjects dosed with TU is well known. Documentation assures us the T concentrations measures reflect accurate values, and that the C_{avg} and C_{max} analyses based on these T concentration values are reliable. The existence of the Central Laboratory Manual, evidence of staff training on the Manual, and the Applicant's declaration that proper steps were followed at the clinical sites do not provide assurance of data reliability. For instance, OSIS inspection revealed that the Applicant and the CRO* (b) (4) *Without documentation, it is not possible to know the facts of the events.*

On September 29, 2021, the Applicant responded to the Division's IR by submitting sample condition and storage temperatures for the Visit 12E bioanalytical samples as received at the (b) (4) Central Laboratory from the clinical sites and evidence of training of the clinical sites on the laboratory procedures for bioanalytical samples. The Applicant's response did not include any documentation of blood sampling times and process for any of the clinical sites including sites 104 and 107. The clinical pharmacology and clinical review teams concluded that the Applicant's response did not address the concerns regarding reliability of clinical data in study MRS-TU-2019EXT because it did not provide specific documentation that includes temperature and duration of each step from blood sample collection, precentrifugation sample placement and storage, centrifugation and transferring of processed samples to ensure proper steps were followed to produce accurate T concentration measurements.

In addition to the September 16, 2021 IR, the Clinical Pharmacology team sent an IR on September 22, 2021, requesting individual subject level analysis to identify all samples in the Serum Substudy from all sites in MRS-TU-2019EXT that had a higher NaF/EDTA plasma testosterone (T) concentration compared to that from serum. The Clinical Pharmacology team concluded that it was not possible to rely on the substudy to determine data reliability for the phase 3 study because the substudy included only 66% of the study population and the "abnormal" PK profile could be an subjective assessment.

Because both the primary and key secondary efficacy endpoints are based on PK parameters, the clinical review team concludes that the quality and integrity of the data submitted for MRS-TU-2019EXT is not sufficient to conclude that there is substantial evidence of efficacy to support approval of this NDA.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the percentage of mEXTS subjects with plasma T C_{avg} within the normal range (222 to 800 ng/dL) after 90 days of treatment. Missing values of plasma T C_{avg} were imputed as failures in the analysis. The results are summarized in Table 27. 87.8% subjects (122/139) had a T C_{avg} that was within the normal range after 90 days of treatment; the 95% CI was 82.3% to 93.2%.

Table 27. Percentage of Kyzatrex-Treated Subjects Achieving Plasma T C_{avg} Within Normal Range After 90 Days of Treatment (mEXTS)

Measure	Target	Kyzatrex N=139
T C_{avg} within normal range after 90 days, n (%)	≥75%	122 (87.8)
95% CI	≥65% (lower bound)	82.3, 93.2

Source: Table 22 in study report. FDA reviewer's analysis.
The normal range for plasma T C_{avg} is 222 to 800 ng/dL.
Abbreviations: CI, confidence interval; mEXTS, modified extension treated set; T, testosterone

Efficacy Results – Secondary and Other Relevant Endpoints

The results for Kyzatrex treated subjects who achieved plasma T C_{max} values within the predetermined limits are displayed in Table 28. 87.7% of subjects had plasma T C_{max} <1200 ng/dL (≥85%); 3.8% of subjects had plasma T C_{max} between 1400 to 2000 ng/dL (<5%) and no subject had plasma T C_{max} >2000 ng/dL (0).

Table 28. Percentage of Kyzatrex-Treated Subjects Achieving Maximum Plasma T C_{max} Within Predetermined Limits After 90 Days (mEXTS, No Imputation)

Measure	Target	Kyzatrex N=139 n (%)
C_{max} <1200 ng/dL	≥85%	114 (87.7)
1440≤ C_{max} ≤2000 ng/dL	≤5%	5 (3.8)
C_{max} >2000 ng/dL	0%	0 (0)

Source: Table 72 in study report, FDA reviewer's analysis.
Abbreviations: mEXTS, modified extension treated set; T, testosterone

***Reviewer Comment**: Although the Applicant identified mEXTS as the primary efficacy analysis population, we advised them during the July 2020 preNDA meeting that this would be a review issue. The Applicant justified excluding Site 104 because of mismanagement of PK sample handling/processing. However, without documentation of PK sample handling/processing at Site 104, we do not know the cause of the aberrant findings and do not have the necessary information to justify excluding Site 104.*

Dose/Dose Response

The dose response for Kyzatrex was adequately evaluated. The Applicant conducted SOV-TU-PK2011 and SOV-TU-PK2013 to evaluate the dose-response of escalating doses of TU capsules, and MRS-TU-2019EXT to evaluate a lower starting dose of the drug. In addition, the dose of the drug in both MRS-TU-2019 and MRS-TU-2019EXT was individually titrated for each subject.

Durability of Response

Efficacy was assessed at only one timepoint (Day 90) during MRS-TU-2019EXT, therefore, the durability of response could not be determined in this trial.

Persistence of Effect

Efficacy was assessed at only one timepoint (Day 90) during MRS-TU-2019EXT, therefore, the persistence of effect could not be determined in this trial.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

MRS-TU-2019EXT did not include any COA (PRO) endpoints.

Additional Analyses Conducted on the Individual Trial

Sensitivity Analysis for the Primary and Key Secondary Endpoints

The Applicant performed a sensitivity analysis to determine the effect of including Site 104 on the results of the primary and key secondary efficacy endpoints. These analyses were based on the EXTS dataset, which included subjects from all study sites, including the 16 subjects from Site 104. The EXTS population was the prespecified efficacy population prior to the Applicant's discovery of the aberrant serum/plasma PK results at Site 104.

For the primary efficacy endpoint, which imputed missing values as treatment failures, 136/155 (87.7%) subjects had a 24-hour plasma total T C_{avg} within the normal range after 90 days of treatment and the 95% CI was 82.6% to 92.9%. Thus, the Division's required target was met. The results for the primary efficacy endpoint are summarized in Table 29.

Table 29. Percentage of Kyzatrex-Treated Subjects Achieving Plasma T C_{avg} Within Normal Range After 90 Days of Treatment (EXTS)

Measure	FDA Target	Kyzatrex (N=155)
T C_{avg} within normal range after 90 days, n (%)	≥75%	136 (87.7)
95% CI	≥65% (lower bound)	82.6, 92.9

Source: NDA 215953 (SDN 001), Module 5.3.5.1, CSR Table 23.
Abbreviations: CI, confidence interval; EXTS, extension treated set; T, testosterone

For the key secondary endpoints, the percentage of Kyzatrex-treated subjects with C_{max} ≤1200 ng/dL, between 1440 to 2000 ng/dL, and >2000 ng/dL, after 90 days of treatment, was 81.5%, 6.2%, and 3.4%, respectively. The results for the key secondary efficacy endpoints are summarized in Table 30.

Table 30. Percentage of Kyzatrex-Treated Subjects Achieving Maximum Plasma T C_{max} Within Predetermined Limits After 90 Days (EXTS, No Imputation)

Measure	FDA Target	Kyzatrex (N=155)
C_{max} <1200 ng/dL, n (%)	≥85%	119 (81.5)
1440≤ C_{max} ≤2000 ng/dL, n (%)	≤5%	9 (6.2)
C_{max} >2000 ng/dL, n (%)	0%	5 (3.4)

Source: NDA 215953 (SDN 001), Module 5.3.5.1, CSR Table 72.
Abbreviations: EXTS, extension treated set; T, testosterone

Based on the sensitivity analyses, when the 16 subjects from Site 104 were included in the analysis (i.e., when the EXTS dataset was used rather than the mEXTS dataset), the study met the primary efficacy endpoint of Cavg, but did not meet any of the key secondary endpoints of Cmax.

Reviewer's Comment: *Without documentation at Site 104, we do not have information to justify excluding Site 104. Kyzatrex does not achieve any of the key secondary Cmax endpoints when data from all clinical sites, including Site 104, are included in the efficacy analyses.*

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

The Applicant submitted the results for Study MRS-TU-2019 as supportive data for the efficacy for Kyzatrex. This study used a different starting dose and titration algorithm than were used in MRS-TU-2019EXT. Because the efficacy (Cavg, Cmax) for a TRT product is dose/dose titration specific, we do not consider MRS-TU-2019 supportive of efficacy of Kyzatrex other than to indicate TU increases T concentrations in hypogonadal men. For the purpose of being complete, the results of this study are presented separately because of these design differences, and are not integrated with the efficacy results of MRS-TU-2019EXT.

MRS-TU-2019 was a randomized, multicenter, open-label, active-controlled, efficacy (based on T C_{avg} and T C_{max}), and safety study in adult hypogonadal men. Subjects were randomized 2:1 (214 subjects to Kyzatrex and 100 subjects to AndroGel). Kyzatrex was started at a total daily dose of 600 mg (400 mg with the morning meal and 200 mg with the evening meal). AndroGel was applied at a starting dose of 40.5 mg daily and titrated according to the product label. The study duration was 12 months (365 days), including a 90-day, open-label efficacy period and a 9-month (275-day) safety evaluation period.

For Kyzatrex, dose titration blood samples for plasma T were taken within a 3 to 5-hour window postmorning dose on Day 14 (Visit 4) and Day 42 (Visit 6). Subjects were randomized at each titration visit 1:1:1 to use the blood samples from either 3, 4, or 5 hours postdose. Dose titration occurred on Day 28 (Visit 5) and Day 56 (Visit 7) based on a titration threshold between 235 and 1120 ng/dL for up- and down-titration, respectively.

On Day 14 (Visit 4), Day 42 (Visit 6), and Day 90 (Visit 8), 24-hour serial PK samples were collected for all subjects at predose, and 1.5, 3, 45, 5, 6, 8, 12, 13.5, 15, 16, 17, 18, 20 and 24-hours after the morning dose. The total T C_{avg} values from the Day 90 PK visit were used to

assess the primary efficacy endpoint (T C_{avg} from Day 14 and Day 42 were used in imputation procedures) and T C_{max} values were used to assess the key secondary efficacy endpoint.

Primary Endpoints

The primary endpoint of MRS-TU-2019 was the percentage of Kyzatrex –treated subjects with a 24-hour T C_{avg} (based on NaF/EDTA tube plasma samples) within the normal range after 90 days of treatment. The normal range was defined using the NaF/EDTA plasma endogenous testosterone from study MRS-TNR-2019.

Missing T C_{avg} values at Day 90 (Visit 8) in the full analysis set were imputed using multiple imputation procedures. Multiple Imputation was only applied when there was at least one evaluable post baseline 24 hour T C_{avg}.

Using multiple imputation, after 90 days of treatment, 89.7% of Kyzatrex subjects in the full analysis set population (166 of 185 with T C_{avg} values) had a 24-hour T C_{avg} within the normal range, with a 95% CI of 85.4 to 94.1%.

The results for the primary efficacy endpoint for MRS-TU-2019 met the FDA criteria for the demonstration of efficacy.

Secondary and Other Endpoints

Key Secondary Endpoints

The key secondary endpoints of MRS-TU-2019 were the percentage of Kyzatrex -treated subjects at Day 90 (Visit 8) with plasma T C_{max} values that were:

- ≤1.5x ULN (≤1200 ng/dL)
- >1.8x ULN to ≤2.5x ULN (>1440 to ≤2000 ng/dL)
- >2.5x ULN (>2000)

where ULN is the upper limit of normal of T in plasma collected in NaF/EDTA tubes as determined in MRS-TNR2019.

Of the proportion of subjects receiving Kyzatrex, 76.9% had C_{max} ≤1200 ng/dL, 7.5% had C_{max} between 1440 to 2000 ng/dL, and 3.2% had C_{max} >2000 ng/dL after 90 days of treatment.

The results for each of the key secondary endpoints for MRS-TU-2019 did not meet the FDA's criteria for the demonstration of efficacy.

Exploratory Endpoints

The following patient-reported outcomes were assessed as secondary endpoints during the trial: The International Prostate Symptom Score (IPSS), Psychosexual Daily Questionnaire (PDQ), Short Form Survey (SF-36), and the International Index of Erectile Function Questionnaire (IIEF) were administered in MRS-TU-2019.

IPSS

The IPSS questionnaire was used to assess the severity and impact of urinary symptoms. It is based on the answers to 7 questions (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia). Answers were assigned points from 0 to 5; the total score could therefore range from 0 to 35 (asymptomatic to very symptomatic). Because of the potential that testosterone could worsen urinary symptoms, men with an IPSS score >19 at Screening were excluded from the study.

At the end of treatment, the mean change from Baseline in the IPSS questionnaire total score for Completers was 0.6 in the Kyzatrex group and 1.0 in the AndroGel group. For the 7 individual questions, Change from Baseline results at the end of treatment were small and consistent between the Kyzatrex and AndroGel groups.

Question 8 of the IPSS questionnaire refers to the perceived quality of life on a scale of 0 (delighted) to 6 (terrible). The mean change from Baseline in the IPSS quality of life question at the end of treatment was 0.1 in the Kyzatrex group and 0.3 in the AndroGel group.

PDQ

The PDQ is a self-reporting instrument with 6 questions used to assess the subject's daily sexual function and mood changes. The questionnaire covers three different domains: 1) sexual desire, enjoyment, and performance; 2) sexual activity score; and 3) mood. Domain 1 and Domain 3 were rated on a 7-point Likert-type scale with a higher score indicating improvement. Domain 2 was assessed using a checklist format.

At the End of Treatment, the mean change from Baseline in Question 1 (overall level of sexual desire) of the PDQ for Completers was 1.6 in the Kyzatrex group and 1.4 in the AndroGel group. Change from Baseline at the End of Treatment for the other questions were consistent between the Kyzatrex and AndroGel groups.

SF-36

The SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. This multi-item scale assesses 8 health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. Each domain is scored from 0-100 with a score of 0 representing maximum disability and a score of 100 representing no disability.

At the end of treatment, the mean change from baseline in the SF-36 total score for completers was 83.7 in the Kyzatrex group and 70.2 in the AndroGel group. In most cases, change from baseline to end of treatment results for the 7 additional questions were small and consistent

between the Kyzatrex and AndroGel groups.

IIEF

The IIEF is a widely used, multidimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials. A score of 0 - 5 (higher score indicating improvement) is awarded to each of the 15 questions that examine overall satisfaction (2 questions, total possible score =10), and the 4 main domains of male sexual function: erectile function (6 questions, total possible score =30), orgasmic function (2 questions, total possible score =10), sexual desire (2 questions, total possible score =10), and intercourse satisfaction (3 questions, total possible score =15).

At the end of treatment, the mean change from Baseline in the overall satisfaction score of the IIEF was 2.3 in the Kyzatrex group and 1.6 in the AndroGel group. Change from Baseline to end of treatment results for the 4 domains of male sexual function were small and consistent between the Kyzatrex and AndroGel groups.

***Reviewer's Comment**: We consider the exploratory endpoints to be exploratory* (b) (4) .

Subpopulations

Subgroup analyses were performed on plasma T C_{avg} within the normal range after 90 days by race and age using the mEXTS with missing C_{avg} values imputed as failures. The results are presented in Table 31. 90.9% of White subjects and 68.2% of Black subjects had plasma T C_{avg} within the normal range after 90 days of treatment. Because the number of Black subjects is small (n=22), the impact of subjects with missing data (n=5) on the percentage within the normal range is high in the analysis with the efficacy criteria not satisfied. Using the observed data only, 88.2% (15 out of 17) of Black subjects had T C_{avg} within the normal range after 90 days of treatment. The number of subjects in other race subgroups are too small to draw conclusions regarding the efficacy criteria.

For subjects with baseline age ≤50 years, 91.7% (66 out of 72) subjects had T C_{avg} within the normal range after 90 days of treatment with 95% CI of 85.3 to 98.1%. For subjects with baseline age >50 years, 83.6% (56 out of 67) subjects had T C_{avg} within the normal range after 90 days of treatment with 95% CI of 74.7 to 92.5%. No apparent difference in the efficacy results based on age are seen in this subgroup analysis.

Table 31. Subgroup Analysis of Primary Efficacy Endpoint by Race and by Age (mEXTS)

Category	Subgroup	Target	Kyzatrex N=139
Race	White	N	110
		n (%)	100 (90.9%)
		95% CI	(85.5%, 96.3%)
	Black	N	22
		n (%)	15 (68.2%)
		95% CI	(48.7%, 87.6%)

Category	Subgroup	Target	Kyzatrex N=139
	Other	N	7
		n (%)	7 (100%)
		95% CI	-
Age	≤50 yrs	N	72
		n (%)	66 (91.7%)
		95% CI	(85.3%, 98.1%)
	>50 yrs	N	67
		n (%)	56 (83.6%)
		95% CI	(74.7%, 92.5%)

Source: Table 14.2.1.1.7.2, Table 14.2.1.1.7.4 in study report, FDA reviewer's analysis.
Abbreviations: CI, confidence interval; mEXTS, modified extension treated set; yrs, years

Subgroup analyses were performed on plasma T C_{avg} within the normal range after 90 days of treatment by weight and BMI using the mEXTS. For subjects with baseline weight ≤93 kg, 90.4% (47/52) subjects had plasma T C_{avg} within the normal range after 90 days of treatment. For subjects with baseline weight >93 kg, 86.2% (75/87) subjects had plasma T C_{avg} within the normal range after 90 days of treatment. Only a slight difference in the efficacy results based on weight is seen in this subgroup analysis, although a trend to lower plasma T C_{avg} is seen with higher body mass. Very similar trend was observed for the subgroup analysis results by BMI.

Table 32. Subgroup Analysis of Primary Efficacy Endpoint by Weight and by BMI (mEXTS)

Category	Subgroup	Target	Kyzatrex N=139
Weight	≤93 kg	N	52
		n (%)	47 (90.4%)
		95% CI	(82.4%, 98.4%)
	>93 kg	N	87
		n (%)	75 (86.2%)
		95% CI	(79.0%, 93.5%)
BMI	<30 kg/m^2	N	40
		n (%)	36 (90%)
		95% CI	(80.7%, 99.3%)
	≥30 kg/m^2	N	99
		n (%)	86 (86.9%)
		95% CI	(80.2%, 93.5%)

Source: Table 14.2.1.1.7.1 and Table 14.2.1.1.7.3 in study report, FDA reviewer's analysis.
Abbreviations: BMI, body mass index; CI, confidence interval; mEXTS, modified extension treated set

8.1.4. Integrated Assessment of Effectiveness

The Applicant conducted two efficacy and safety phase 3 trials for Kyzatrex for TRT: MRS-TU-2019 and MRS-TU-2019EXT.

MRS-TU-2019 met the FDA criteria for the demonstration of efficacy for the primary efficacy endpoint of Cavg, but did not meet the FDA criteria for any of the C_{max} secondary endpoints. Therefore, this study did not support the efficacy of Kyzatrex for TRT in hypogonadal men.

The Applicant then conducted MRS-TU-2019EXT. This trial was an extension study of MRS-TU-2019, but tested a lower starting dose and a different titration algorithm than that used in the

original study. The findings of MRS-TU-2019EXT are described above. Lack of documentation of PK handling/processing raises significant uncertainties about data integrity and reliability precluding the conclusion that substantial evidence of effectiveness has been demonstrated.

In summary, the Applicant submitted the results of two phase 3 studies to support the efficacy of Kyzatrex. Neither of these studies provided substantial evidence of efficacy for Kyzatrex for TRT in hypogonadal men.

8.2. Review of Safety

[Insert text here ONLY if explaining that this section is not applicable to this review. Otherwise, begin text in the next section]

8.2.1. Safety Review Approach

The primary source of safety data for this NDA was derived from MRS-TU-2019 EXT with supportive longterm data from MRS-TU-2019.

8.2.2. Review of the Safety Database

Overall Exposure

The overall exposure included 296 subjects who received Kyzatrex for a mean (SD) of 311 (165) days. The Applicant calculated the total dose consumed in 2 ways: assuming missing capsules were taken and assuming missing capsules were not taken. Overall, the mean (SD) total dose of Kyzatrex in the OSS population was 168 g (95 g) assuming any missing capsules were taken. For those subjects who received Kyzatrex in both studies (N=72), the mean (SD) total dose was 273 g (64 g).

In MRS-TU-2019, 214 subjects received Kyzatrex for a mean (SD) of 309 (115) days. From the starting daily dose of 600 mg Kyzatrex, 61.0% remained at the starting dose, 6.8% and 1.1% were up titrated to 800 mg and 1000 mg, respectively, and 27.8% and 3.2% were down titrated to 400 mg and 200 mg, respectively. At the last visit at which doses were adjusted (Day 270; N=164), the 600-mg dose group had the largest number of subjects (57 [34.5%] subjects). Assuming that any missing capsules were taken, the mean (SD) total dose in the Kyzatrex group was 171.0 g (73.355 g).

In MRS-TU-2019EXT, 155 subjects received Kyzatrex for a mean (SD) of 168 (38) days. Twelve of 146 subjects (8.3%) had a dose reduction by Day 90E; the lower frequency of dose reduction in this study was hypothesized to originate from a lower starting dose of 400 mg compared to MRS-TU-2019. At Day 90E, the 600-mg dose group had the most subjects (64 [43.5%] subjects). Assuming that missing capsules of study drug were taken, the mean (SD) total dose of Kyzatrex was 85.11 g (29.801 g).

For the OSS, the overall Kyzatrex extent of exposure is summarized in Table 33 (see below). Overall, 296 subjects received Kyzatrex for a mean (SD) of 311 (165) days for a total of 252

subject years. For the 72 subjects who received Kyzatrex in both studies, the mean (SD) duration of exposure was 535 (40) days.

The 600-mg dose had the highest exposure in the OSS (271 subjects receiving 600 mg for a mean of 179 days, equivalent to 133 subject years). A total of 78 (26.4%) subjects received the 600-mg dose for >9 months in duration

Overall, the mean (SD) total dose of Kyzatrex for the OSS was 168 g (95) assuming any missing capsules were taken. For those subjects who received Kyzatrex in both studies, the mean (SD) total dose was 273 g (64) (Table 33).

Table 33. Study Drug Exposure by Dose (OSS)*

Dose Group	Parameter	Statistic	Kyzatrex
	Number of subjects who took any dose		296
100 mg	Total time on dose (days)	N	3
		Mean (SD)	111.3 (17.79)
		CV (%)	16.0
		Median	119.0
		Min, max	91, 124
	Total subjects days	N	334
	Total subjects years	N	0.91
200 mg	Total time on dose (days)	N	27
		Mean (SD)	151.6 (90.62)
		CV (%)	59.8
		Median	154.0
		Min, max	28, 397
	Total subjects days	N	4092
	Total subjects years	N	11.20

Dose Group	Parameter	Statistic	Kyzatrex
400 mg	Total time on dose (days)	N	199
		Mean (SD)	134.2 (124.43)
		CV (%)	92.7
		Median	91.0
		Min, max	10, 517
	Total subjects days	N	26702
	Total subjects years	N	73.11
600 mg	Total time on dose (days)	N	271
		Mean (SD)	179.3 (139.82)
		CV (%)	78.0
		Median	152.0
		Min, max	1, 525
	Total subjects days	N	48598
	Total subjects years	N	133.05
800 mg	Total time on dose (days)	N	85
		Mean (SD)	124.2 (70.43)
		CV (%)	56.7
		Median	120.0
		Min, max	1, 337
	Total subjects days	N	10557
	Total subjects years	N	28.90

Source: Reproduced from Applicant submission, Table 14.3.4.7.3.1
* Exposure by dose was calculated only for the OSS and not for the individual phase 3 studies. Note: Total Time on Dose is calculated per subject and then summarized across subjects
Note: Total Subject Exposure in Days is the sum of all subject exposure.
Note: Total subject exposure in years is the sum of all subject exposure in days divided by 365.25.
Abbreviations: CV, coefficient of variation; OSS, overall safety set; SD, standard deviation

Adequacy of the Safety Database

Exposure to Kyzatrex is adequate. The Applicant met the predefined goal of enrolling at least 100 subjects exposed to Kyzatrex for at least 52 weeks. The demographic baseline characteristics are representative of the target patient population which is likely to use Kyzatrex.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Refer to Section 4.1 and Section 8.1.2 (Data Quality and Integrity) concerning issues with reliability of PK data from lack of documentation of PK blood sample handling/processing for the phase 3 study, MRS-TU-2019EXT.

Categorization of Adverse Events

Treatment-emergent adverse events (TEAEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or later. TEAE definitions were as follows:

- An adverse event (AE) was considered treatment-emergent if it begins or worsens in severity after the first dose of any study drug.

- An AE was considered MRS-TU-2019 treatment-emergent if it began or worsened in severity after the first dose of randomized study drug and before the first dose of any study drug in MRS-TU-2019EXT.
- An AE was considered MRS-TU-2019EXT treatment-emergent if it began or worsened in severity after the first dose of study drug in MRS-TU-2019EXT.
- An AE was considered Kyzatrex treatment-emergent if it began or worsened in severity after the first dose of Kyzatrex.

Treatment-emergent AEs were summarized for both studies combined (Kyzatrex TEAEs only for all subjects in the OSS and for all subjects who took Kyzatrex in both studies). Treatment-emergent AEs were summarized by system organ class (SOC) and preferred term (PT). Subjects were counted once at the SOC level and once at each PT within the SOC level. Where applicable, summaries included the number and percentage of subjects who report at least one TEAE, the number and percentage of subjects reporting at least one TEAE in a SOC, the number and percentage of subjects reporting at least one TEAE in a PT, and the total number of events within a SOC and within a PT. Tables were sorted by decreasing frequency (overall) of SOC, and then, within a SOC, descending frequency (overall) of PT.

Routine Clinical Tests

The following laboratory safety tests were performed at various points throughout the studies and were unremarkable.

Hematology

Hematology included Hb, hematocrit, white blood cells, and platelets, and also HbA1c in MRS-TU-2019EXT only. After study initiation, examination of hematocrit results revealed a pattern of variability. The central laboratory reported that hematocrit results are only reliable within 24-hours of sample collection; for this reason safety analyses were not carried out on hematocrit, but used hemoglobin instead.

Biochemistry

Biochemistry included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase (ALP), creatinine, blood urea nitrogen, epidermal growth factor receptor, lactate dehydrogenase, glucose, total protein, albumin, sodium, potassium, calcium, and phosphorous.

Lipid Panel

The lipid panel included total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins, and triglycerides. At Visit 2, LDL was normally calculated from total cholesterol, high-density lipoprotein (HDL), and triglycerides. If triglyceride levels fell outside the range for valid use of the LDL calculation employed by the central lab, then LDL levels were obtained by a direct measurement on a second sample.

Endocrinology

Endocrinology assessments included LH, FSH, SHBG, and thyroid-stimulating hormone were done.

Urinalysis

Urinalysis assessed pH, glucose, ketones, blood, protein, microscopy, and specific gravity.

8.2.4. Safety Results

Deaths

In the pooled phase 3 studies, 1 (0.3%) subject (Subject (b) (6)) experienced a fatal serious TEAE (myocardial infarction) in Study MRS-TU-2019. The same subject also experienced SAEs of cellulitis and diabetic foot. The subject did not receive Kyzatrex for 30 days prior to the myocardial infarction resulting in death (reported in clinical study report (CSR) MRS-TU-2019.The event was considered by the investigator to be not related to Kyzatrex. This was the only death in the entire clinical development program as there were no deaths in the phase 1 or phase 2 studies.

Serious Adverse Events

In MRS-TU-2019, 9 (4.2%) subjects receiving Kyzatrex experienced one or more serious TEAE for a total of 14 serious TEAEs, with all serious TEAEs having one occurrence each. In MRS-TU-2019EXT, 2 (1.3%) subjects experienced serious TEAEs, each of which occurred only once and only in a single subject (total of two serious TEAE).

In the pooled phase 3 studies, 11 (3.7%) subjects reported 16 serious TEAEs, and Table 34. Atrial fibrillation was reported in 2 (0.7%) subjects. All other serious TEAEs were reported in a single subject.

For subjects who received Kyzatrex in both studies (n=72), 5 (6.9%) subjects reported five serious TEAEs. While the overall incidence of serious TEAEs was higher in subjects who received Kyzatrex in both studies, consistent with their greater duration of exposure (more than 12 months and up to 18 months), the types and incidence of individual serious TEAEs were similar between all subjects and those who received Kyzatrex in both studies.

Table 34. MRS-TU-2019 and MRS-TU-2019EXT Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Kyzatrex Group of MRS-TU-2019, EXTS, and OSS)

	MRS-TU-2019, Kyzatrex Group N=214		MRS-TU-2019EXT N=155		Subjects Who Took Kyzatrex in Both Studies N=72		All Subjects (OSS) Who Took Kyzatrex N=296	
System Organ Class Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Subjects with at least one serious TEAE	9 (4.2)	14	2 (1.3)	2	5 (6.9)	5	11 (3.7)	16
Cardiac disorders	3 (1.4)	4	1 (0.6)	1	1 (1.4)	1	4 (1.4)	5
Atrial fibrillation	1 (0.5)	1	1 (0.6)	1	1 (1.4)	1	2 (0.7)	2
Acute myocardial infarction	1 (0.5)	1	0		0		1 (0.3)	1
Cardiac failure congestive	1 (0.5)	1	0		0		1 (0.3)	1
Myocardial infarction	1 (0.5)	1	0		0		1 (0.3)	1
Gastrointestinal disorders	2 (0.9)	2	1 (0.6)	1	2 (2.8)	2	3 (1.0)	3
Colitis	1 (0.5)	1	0		1 (1.4)	1	1 (0.3)	1
Diverticular perforation	0		1 (0.6)	1	1 (1.4)	1	1 (0.3)	1
Hemorrhoids	1 (0.5)	1	0		0		1 (0.3)	1
Skin and subcutaneous tissue disorders	1 (0.5)	2	0		0		1 (0.3)	2
Diabetic foot	1 (0.5)	2	0		0		1 (0.3)	2
Infections and infestations	1 (0.5)	1	0		0		1 (0.3)	1
Cellulitis	1 (0.5)	1	0		0		1 (0.3)	1
General disorders and administration site conditions	1 (0.5)	1	0		1 (1.4)	1	1 (0.3)	1
Chest pain	1 (0.5)	1	0		1 (1.4)	1	1 (0.3)	1
Musculoskeletal and connective tissue disorders	1 (0.5)	1	0		1 (1.4)	1	1 (0.3)	**1**
Osteoarthritis	1 (0.5)	1	0		1 (1.4)	1	1 (0.3)	1
Renal and urinary disorders	1 (0.5)	1	0		0		1 (0.3)	**1**
Renal tubular acidosis	1 (0.5)	1	0		0		1 (0.3)	1
Respiratory, thoracic, and mediastinal disorders	1 (0.5)	1	0		0		1 (0.3)	**1**
Chronic obstructive pulmonary disease	1 (0.5)	1	0		0		1 (0.3)	1
Surgical and medical procedures	1 (0.5)	1	0		0		1 (0.3)	**1**
Finger amputation	1 (0.5)	1	0		0		1 (0.3)	1

Source: Table 14.3.1.2.4, Table 14.3.1.1.4, and Table 14.3.1.3.4
Note: AEs are coded using MedDRA version 20.0.
Note: Kyzatrex TEAEs are AEs that occurred, or worsened, after the first dose of Kyzatrex.
Note: Subjects who experienced the same coded event more than once were counted once in each SOC or PT.
Note: Percentages are based on the number of subjects in the group in the OSS.
Abbreviations: E, number of events; EXTS, extension treated set; n, number of subjects; OSS, overall safety set; TEAE, treatment-emergent adverse event

Three subjects were randomized into MRS-TU-2019 twice in error.

- Subject (b) (6) was active at 2 sites and received both Kyzatrex and AndroGel. This subject was counted in the Kyzatrex group based on their first randomization and was excluded from AndroGel summaries; all exposure data for this subject was included in listings and tables for each study drug separately.
- Subject (b) (6) was not dosed on the first randomization, but only on the second randomization at a second site. Thus, extent of exposure data for the second randomization was summarized as normal.
- Subject (b) (6) only attended one dosing visit at the first site before being lost to follow-up at that site, then was randomized sometime later at a second site and completed the study there. For this subject, data from the first randomization was excluded from calculations and summaries of extent of exposure and was flagged in the data listings.

Dropouts and/or Discontinuations Due to Adverse Effects

Ten (4.7%) subjects receiving Kyzatrex in MRS-TU-2019 reported 16 TEAEs that resulted in permanent discontinuation from the study drug. With the exception of prostate-specific antigen (PSA) increased (2 [0.9%] subjects), all TEAEs leading to discontinuation occurred in single subjects.

One (0.5%) subject in MRS-TU-2019EXT reported a TEAE of acne and was permanently discontinued from study drug due to this TEAE.

In the pooled phase 3 studies, 11 (3.7%) OSS subjects reported 17 TEAEs that led to withdrawal from the study, and for subjects who received Kyzatrex in both studies, none reported TEAEs that led to withdrawal (Table 35). Atrial fibrillation leading to withdrawal was reported in 2 (0.7%) subjects. All other TEAEs leading to withdrawal were reported in single subjects.

Table 35. MRS TU 2019 and MRS TU 2019EXT Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term (Kyzatrex Group of MRS-TU-2019, EXTS, and OSS)

System Organ Class Preferred Term	MRS-TU-2019, Kyzatrex Group N=214 n (%)	E	MRS-TU-2019EXT N=155 n (%)	E	Subjects Who Took Kyzatrex in Both Studies N=72 n (%)	E	All Subjects (OSS) N=296 n (%)	E
Subjects with at least one TEAE leading to permanent discontinuation of study drug	10 (4.7)	16	1 (0.6)	1	0		11 (3.7)	17
Investigations	4 (1.9)	4	0		0		4 (1.4)	4
Prostatic-specific antigen increased	2 (0.9)	2	0		0		2 (0.7)	2
Hemoglobin increased	1 (0.5)	1	0		0		1 (0.3)	1
Hepatic enzyme increased	1 (0.5)	1	0		0		1 (0.3)	1
Cardiac disorders	2 (0.9)	3	0		0		2 (0.7)	3
Acute myocardial infarction	1 (0.5)	1	0		0		1 (0.3)	1
Cardiac failure congestive	1 (0.5)	1	0		0		1 (0.3)	1
Palpitations	1 (0.5)	1	0		0		1 (0.3)	1
Psychiatric disorders	2 (0.9)	4	0		0		2 (0.7)	4
Aggression	1 (0.5)	1	0		0		1 (0.3)	1
Anxiety	1 (0.5)	1	0		0		1 (0.3)	1
Irritability	1 (0.5)	1	0		0		1 (0.3)	1
Libido decreased	1 (0.5)	1	0		0		1 (0.3)	1
Skin and subcutaneous tissue disorders	1 (0.5)	2	1 (0.6)	1	0		2 (0.7)	3
Acne	0		1 (0.6)	1	0		1 (0.3)	1
Diabetic foot	1 (0.5)	2	0		0		1 (0.3)	2
Reproductive system and breast disorders	1 (0.5)	1	0		0		1 (0.3)	1
Erectile dysfunction	1 (0.5)	1	0		0		1 (0.3)	1
Respiratory, thoracic, and mediastinal disorders	1 (0.5)	1	0		0		1 (0.3)	1
Chronic obstructive pulmonary disease	1 (0.5)	1	0		0		1 (0.3)	1
Vascular disorders	1 (0.5)	1	0		0		1 (0.3)	1

Source: Table 14.3.1.2.7, Table 14.3.1.1.7, and Table 14.3.1.3.7 (Reproduced from the Applicant submission)
Note: AEs are coded using MedDRA version 20.0.
Note: Kyzatrex TEAEs are AEs that occurred, or worsened, after the first dose of Kyzatrex.
Note: Subjects who experienced the same coded event more than once were counted once in each SOC or PT. Note: Percentages are based on the number of subjects in the group in the OSS.
Abbreviations: E, number of events; EXTS, extension treated set; n, number of subjects; OSS, overall safety set; TEAE, treatment-emergent adverse event

Significant Adverse Events

Ten (4.7%) subjects receiving Kyzatrex in MRS-TU-2019 reported 16 TEAEs that resulted in permanent discontinuation from the study drug. With the exception of PSA increased (2 [0.9%] subjects), all TEAEs leading to discontinuation occurred in single subjects.

One (0.5%) subject in MRS-TU-2019EXT reported a TEAE of acne and was permanently discontinued from study drug due to this TEAE. In the pooled phase 3 studies, 11 (3.7%) OSS subjects reported 17 TEAEs that led to withdrawal from the study, and for subjects who received Kyzatrex in both studies, none reported TEAEs that led to withdrawal (Table 35). Atrial fibrillation leading to withdrawal was reported in 2 (0.7%) subjects. All other TEAEs leading to withdrawal were reported in single subjects. Treatment-Emergent Adverse Events and Adverse Reactions

Laboratory Findings

Key observations for the pooled phase 3 studies:

- There were no clinically significant changes in mean values for liver function tests throughout the two studies. There were also no trends over time in percentage of subjects between 1 to 2x, 2 to 3x or >3x the ULN for ALT, AST, ALP, or bilirubin. Four subjects receiving Kyzatrex had liver-related AEs but were deemed by the Investigator as unrelated to the study drug.
- There was minimal change in serum glucose and HbA1C in either study, both in subjects with and without diabetes.
- There were no clinically significant changes in blood urea nitrogen, creatinine, sodium, potassium, or calcium.
- In MRS-TU-2019, mean hemoglobin in the Kyzatrex group displayed a mean increase of 0.99 g/dL from baseline to Day 365, with the increase plateauing by Day 90. Mean hemoglobin increased by 0.48 g/dL in MRS-TU-2019EXT and also plateaued within 90 days of treatment. In MRS-TU-2019, 15 (7.0%) Kyzatrex subjects had an increase in hemoglobin level to >18 g/dL. In MRS-TU-2019EXT, 7 (4.5%) subjects had an increase in hemoglobin level to >18 g/dL, 4 of whom also had a hemoglobin >18 g/dL in MRS-TU-2019.
- There was a modest decrease in the mean change from baseline at Visit 13/Day 365 (MRS-TU-2019) and at Visit 16E/Day 180E (MRS-TU-2019EXT) in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in subjects receiving Kyzatrex. In MRS-TU-2019, mean decreases in total cholesterol and HDL were larger for the Kyzatrex treatment group than the AndroGel group.
- Among subjects receiving Kyzatrex in either study, there were seven AEs of PSA increased, three AEs of prostatitis, two AEs of prostatomegaly, and one AE of prostate tenderness. Additionally, there was a small mean increase of 0.6 in the total International Prostate Symptom Score for the Kyzatrex group and an increase of 1.0 for the AndroGel group in

MRS-TU-2019. Mean change from baseline in serum PSA was also larger in the AndroGel group (0.4 ng/mL) than the Kyzatrex group (0.2 ng/mL).

- The PSA data illustrate the complexity of analyzing group PSA data in such studies. A minority of elevated PSAs were suspicious for prostate cancer, and many were isolated increases that could have been due to laboratory or sample handling errors.
- In MRS-TU-2019, LH and FSH decreased as expected due to negative feedback of androgen replacement on the pituitary and hypothalamus. SHBG also decreased in Kyzatrex treated subjects in MRS-TU-2019. Similar decreases in LH, FSH and SHBG occurred with Kyzatrex in MRS-TU-2019EXT. In MRS-TU-2019EXT, 95.2% of subjects had DHT C_{avg} below 2x the ULN. Thyrotropin remained essentially unchanged in the extension study.

Biochemistry Data

In MRS-TU-2019, ALT, calcium, creatinine, glucose, potassium, and phosphate were above the normal range for >10% of subjects at various timepoints including baseline in the Kyzatrex treatment group. None of these subjects needed any clinical intervention. At end of treatment (EOT), glucose levels in the Kyzatrex group were 4.6 mg/dL lower than at baseline. Insulin levels in Kyzatrex subjects were also slightly deceased at EOT relative to baseline (change of -5.2 µU/L). No trends in liver function tests were noted with regards to percentage of subjects above the normal reference range across timepoints. Two (0.9%) subjects in the Kyzatrex group had a TEAE of hepatic enzyme increased; one of these subjects was permanently discontinued from study drug.

In MRS-TU-2019EXT, the same parameters with the exception of potassium (ALT, calcium, creatinine, glucose, and phosphate) were above the normal range for >10% of subjects at various timepoints, including baseline. Liver function tests decreased slightly over time. One subject participated in both MRS-TU-2019 and MRS-TU-2019EXT and developed elevated liver function tests during the second study and evident at baseline; this subject was withdrawn due to persistent elevation of liver function tests (ALP > ALT and AST).

Hematology Data

Hematocrit values obtained by the central lab in MRS-TU-2019 were deemed unreliable, as hematocrit values increase with storage time and duration between sample collection and sample analysis at the central lab varied widely. As hemoglobin was more stable over time during storage, it was instead used to index red blood counts rather than hematocrit.

In MRS-TU-2019, mean hemoglobin in the Kyzatrex group was 14.42 g/dL at baseline and 15.42 g/dL at Visit 13/Day 365, with a mean increase of 0.99 g/dL. For the AndroGel group, mean hemoglobin at baseline was 14.23 g/dL and 15.10 g/dL at Day 365 (0.85 g/dL change from baseline). The increase in hemoglobin plateaued by Visit 8/Day 90 for the Kyzatrex group, but increased throughout the duration of treatment for AndroGel subjects. Four (1.9%) subjects in the Kyzatrex group and no subjects in the AndroGel group reported a TEAE of hemoglobin

increased; 1 (0.5%) Kyzatrex subject had a TEAE of hematocrit increased. Fifteen Kyzatrex subjects had an increase in hemoglobin level to >18 g/dL.

At EOT in MRS-TU-2019, the magnitude of change from baseline in mean HbA1c appeared to be similar for subjects with and without diabetes mellitus and increased slightly for both groups. In MRS-TU-2019EXT, mean hemoglobin was 14.7 g/dL at baseline and 15.2 g/dL at Visit 16E/Day 180E with a mean increase of 0.48 g/dL, again plateauing within 90 days of treatment. Seven (4.5%) subjects had an increase in hemoglobin level to >18 g/dL, 4 of whom also had hemoglobin >18 g/dL in MRS-TU-2019. Three (1.9%) subjects reported a TEAE of hemoglobin increased. At EOT in MRS-TU-2019EXT, mean HbA1c increased slightly from baseline for diabetic subjects but decreased slightly for nondiabetic subjects.

Lipid Panel

Modest decreases in mean change from baseline (% change from baseline) at Day 365 for several lipid panel parameters occurred in the Kyzatrex group of MRS-TU-2019:

- Total cholesterol: -14.0 mg/dL (6.7%)
- LDL cholesterol: -4.8 mg/dL (-2.0%)
- HDL cholesterol: -7.9 mg/dL (-14.3%)
- Triglycerides: -7.0 mg/dL (-2.0%); -5.0 mg/dL median change from Baseline at Visit 13/Day 365 (5.7%).

Larger drops in total cholesterol and HDL were observed for the Kyzatrex group (mean change from baseline at Day 365 of -14.0 and -7.9 mg/dL respectively) as compared to the AndroGel group (mean change from baseline at Day 365 of -5.5 and -2.8 mg/dL respectively) in MRS-TU-2019.

In MRS-TU-2019EXT, the following changes from baseline (mean % change from baseline) were observed for lipid panel parameters:

- Total cholesterol: -11.1 mg/dL (5.2%)
- LDL cholesterol: -4.0 mg/dL (-0.8%)
- HDL cholesterol: -6.9 mg/dL (-14.0%)
- Triglycerides: -18.6 mg/dL (-1.2%); -6.0 mg/dL median decrease from baseline (-6.1%). These lipid changes are consistent with what is already known about TRTs as a class.

Serum PSA

In MRS-TU-2019, the mean PSA at baseline was 0.87 ng/mL in the Kyzatrex group. At Day 365, the mean increase in PSA was 0.23 ng/mL. Five (2.3%) subjects in the Kyzatrex group had serum PSA ≥4 ng/mL at any time during the study; 15 (7.0%) subjects in the Kyzatrex Marius Pharmaceuticals group had a change from Baseline in serum PSA >1.4 ng/mL. Five (2.3%)

Kyzatrex subjects had a TEAE of PSA increased. Two (0.9%) subjects in the Kyzatrex group discontinued study drug due to this TEAE. There was a small mean increase of 0.6 in the total International Prostate Symptom Score for the Kyzatrex group.

For subjects receiving AndroGel in MRS-TU-2019, the mean change from baseline at Day 365 (0.4 mg/mL) was double that of the Kyzatrex group (0.2 ng/mL). Four (4.0%) AndroGel subjects had serum PSA ≥4 ng/mL at any time during the study, and 7 (7.0%) subjects had a change from baseline in serum PSA >1.4 ng/mL. Five (5.0%) AndroGel subjects reported a TEAE of PSA increased; 3 of these subjects discontinued study drug due to the TEAE. The total International Prostate Symptom Score increased more in the AndroGel group (increase of 1.0) as compared to the Kyzatrex group (increase of 0.6).

In MRS-TU-2019EXT, the mean PSA at baseline was 1.0 ng/mL. The mean change from baseline was 0.2 ng/mL at both Visit 12E/Day 90E and Visit 16E/180E. Two subjects had an increase in PSA >1.4 ng/mL and the same two subjects had a PSA ≥4.0 ng/mL. The smaller increase in PSA in MRS-TU-2019EXT, compared to MRS-TU-2019, may have been due to the lower starting dose of Kyzatrex in MRS-TU-2019EXT. One (0.6%) subject in the extension study had a TEAE of PSA increased and withdrew due to lack of relief from low T symptoms.

One subject had a prostate biopsy after withdrawing from MRS-TU-2019, which was positive for a Gleason 6 cancer in 1 of 12 cores, involving about 5% of the biopsy.

Across the 2 studies, 13 subjects had an isolated PSA rise followed by a return to Baseline, 6 subjects had variable PSAs throughout the studies, 4 subjects had a single elevated PSA at the end of the study, and three subjects had a continuous PSA rise throughout the studies. Bias and confounding present a challenge with the interpretation of PSA data. Therefore, a definitive conclusion regarding the observed changes in PSA in the context of TRT cannot be reached.

Endocrinology Parameters

In MRS-TU-2019, mean values of FSH, LH, and SHBG (Kyzatrex group only) decreased from baseline by Day 90 and EOT, as expected due to negative feedback of androgen replacement on the pituitary and hypothalamus.

In the MRS-TU-2019EXT, mean FSH, LH, and SHBG also decreased from baseline to Day 90E and EOT. While thyrotropin levels decreased slightly at Day 90E, they returned to levels similar to baseline by EOT. The percentage of subjects with DHT C_{avg} below the ULN was 41.3%. Six subjects (4.8%) had DHT C_{avg} above 2x the ULN; one of these had DHT C_{avg} above 3x (but less than 5x) the ULN.

Vital Signs

For in-clinic BP measurements in MRS-TU-2019, where there was a higher starting dose of Kyzatrex compared with the MRS-TU-2019EXT study, small increases from baseline in systolic blood pressure (SBP) (2.4 mm Hg for Kyzatrex subjects and 3.2 mm Hg for AndroGel subjects)

were observed. Overall, there were similar changes in SBP between the Kyzatrex group and the AndroGel group throughout the study, with an apparent plateauing of increase by Visit 8/Day 90 in both groups. At every timepoint, the relative increase in SBP was lower for the Kyzatrex group. Higher proportions of study participants assigned to AndroGel had increases in SBP of 5 to 10 and 10 to 15 mm Hg versus Kyzatrex. A total of 23 (10.7%) subjects in the Kyzatrex- group and 7 (7.0%) subjects in the AndroGel group began taking new antihypertensive medications after baseline. Four (1.9%) subjects in the Kyzatrex group had a dose increase in their antihypertensive medication by the end of treatment.

In MRS-TU-2019EXT, the mean in-clinic SBP change from baseline at Visit 15E/Day 179 was +2.4 mm Hg and was similar to that observed in MRS-TU-2019. The mean in-clinic diastolic BP change from baseline at Visit 15E/Day 179 was +1.7 mm Hg. Concordance analyses indicated that changes from baseline for in-clinic BP were comparable to changes from baseline in BP derived from ABPM. This suggests that in-clinic BP measurements may be used to detect changes in BP classification following initiation of Kyzatrex treatment.

ElectrocardiogramsThere were no clinically significant electrocardiogram (ECG) findings in either study.

QT Interval Prolongation

One of eight subjects had a borderline QTcB prolongation that was interpreted as clinically significant at 8 hours post drug administration on Day 1. His baseline ECG on that day also showed borderline QTcB prolongation which was interpreted as not clinically significant. Several ECGs on other days were interpreted as either normal (n=8) or not clinically significant borderline QTcB prolongation and/or incomplete right bundle branch block (n=9). There were no other associated significant cardiovascular findings in this subject.

Immunogenicity

No studies of immunogenicity were done to support this application.

8.2.5. Analysis of Submission-Specific Safety Issues

Blood Pressure

An increase in BP was observed in the ABPM study, as evidenced by a mean increase in 24-hour mean systolic BP of +1.9 mm Hg with an upper bound of 3.1 mm Hg. While a numerically lower increase in BP was observed in the ABPM study for this oral TU compared to other oral TU products, this ABPM study was not designed to compare the increase in BP between different products. Hence, it is unclear if the observed numerical differences are due to chance alone or reflect study design or analytical differences.

(b) (4)

The effect of Kyzatrex was evaluated in the dedicated ABPM study MRS-TU-2019EXT, a single-arm, open-label study in hypogonadal men receiving daily dosing titrated to a plasma testosterone of 400 to 900 ng/dL. The results for the average systolic and diastolic BP parameters are shown in Table 36.

Table 36. Point Estimates and the 95% CIs (FDA Analysis) for Day 180

ABPM Parameter	Treatment	Metric	Δ	95% CI
Systolic BP	Kyzatrex	24-h mean	1.9	(0.7, 3.1)
Systolic BP	Kyzatrex	Daytime	1.4	(0.1, 2.6)
Systolic BP	Kyzatrex	Nighttime	3.2	(1.6, 4.7)
Diastolic BP	Kyzatrex	24-h mean	0.7	(-0.2, 1.6)
Diastolic BP	Kyzatrex	Daytime	0.3	(-0.7, 1.2)
Diastolic BP	Kyzatrex	Nighttime	1.7	(0.5, 2.9)

Source: Interdisciplinary Review Team for Cardiac Safety Studies ABPM Study Review, dated 1/5/2021. DARRTs Reference ID: 4801902
Abbreviations: ABPM, ambulatory BP monitoring; BP, blood pressure; CI, confidence interval

Hemoglobin

In MRS-TU-2019, mean hemoglobin in the Kyzatrex group displayed a mean increase of 0.99 g/dL from baseline to Day 365, with the increase plateauing by Day 90. Mean hemoglobin increased by 0.48 g/dL in MRS-TU-2019EXT and also plateaued within 90 days of treatment. In MRS-TU-2019, 15 (7.0%) Kyzatrex subjects had an increase in hemoglobin level to >18 g/dL. In MRS-TU-2019EXT, 7 (4.5%) subjects had an increase in hemoglobin level to >18 g/dL, 4 of whom also had a hemoglobin >18 g/dL in MRS-TU-2019. None required any medical intervention.

Adrenal Response

Since TRT can impair the adrenal cortisol response to ACTH, ACTH stimulation tests were done at baseline and EOT in a subset of subjects in MRS-TU-2019. All subjects in the Kyzatrex and the AndroGel groups had normal cortisol response to synthetic ACTH, both at baseline and after 365 days of TRT. The mean post-ACTH cortisol levels were numerically greater in both groups at the end of the study . These results indicate that the effects of Kyzatrex and AndroGel on ACTH-stimulated serum cortisol levels were similar, and neither product had an adverse effect on adrenal cortisol production.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessments were performed.

8.2.7. Safety Analyses by Demographic Subgroups

Drug-Demographic Interactions

Age and Weight on Ambulatory SBP

The Applicant conducted a multivariate analysis of Kyzatrex dose and ambulatory SBP using age, body weight, diabetic status, and antihypertensive treatment status as covariates. Results demonstrated that both weight and age had limited contribution to the models.

Age on Adverse Events

Overall, the incidence of TEAEs was similar in subjects in the ≤50 year old subgroup compared to those in the >50 year old subgroup (Table 37).

Hypertension was the only reported TEAE with a difference of ≥5% in the ≤50 year old subgroup (6 [4.0%] subjects) compared to the >50 year old subgroup (15 [10.3%] subjects) (Table 37). The observed difference remained consistent when events of hypertension and increased blood pressure were combined (Table 37).

With the exception of age-related hypertension, there were no apparent age-specific TEAEs.

Table 37. MRS-TU-2019 and MRS-TU-2019EXT Kyzatrex Treatment-Emergent Adverse Events - Overall Summary by Baseline Age Category (OSS)

	Subjects Who Took Kyzatrex in Both Studies				All Subjects			
	≤50 Yrs N=35		50 Yrs N=37		≤50 Yrs N=150		50 Yrs N=146	
Parameter	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAEs	27 (77.1)	116	24 (64.9)	112	83 (55.3)	250	74 (50.7)	253
Any serious TEAEs	2 (5.7)	2	3 (8.1)	3	3 (2.0)	3	8 (5.5)	13
Any treatment-related TEAEs	11 (31.4)	24	12 (32.4)	18	29 (19.3)	51	37 (25.3)	63
Any treatment-related serious TEAEs	0		0		0		0	
Any severe TEAEs	2 (5.7)	2	4 (10.8)	6	5 (3.3)	5	7 (4.8)	9
Any treatment-related severe TEAEs	0		0		2 (1.3)	2	0	
Any TEAEs leading to discontinuation from study drug	0		0		3 (2.0)	3	8 (5.5)	14
Any TEAEs leading to death	0		0		0		1 (0.7)	1
Any MACE	0		0		0		2 (1.4)	3
Any TEAEs of hypertension or blood pressure Increased	4 (11.4)	4	7 (18.9)	8	12 (8.0)	13	19 (13.0)	23

Source: Reproduced from Table 14.3.1.3.1.1 from the Applicant submission
Note: Kyzatrex TEAEs are adverse events that occurred, or worsened, after the first dose of Kyzatrex.
Note: A subject may be counted in more than one category.
Note: Treatment-related TEAEs are those with a relationship to study drug of 'possible' or 'probable'.
Note: Percentages are based on the number of subjects in the group in the Overall Safety Set.
Abbreviations: E, number of events; MACE, major adverse cardiac events; n, number of subjects; OSS, overall safety set; TEAE, treatment-emergent adverse event

Weight

Overall, a higher incidence of TEAEs was reported in subjects in the >93 kg subgroup (123 [59.1%] subjects) compared to those in the ≤93 kg subgroup (34 [38.6%] subjects) (Table 38).

Upper respiratory tract infection was the only TEAE reported with a difference of ≥5% in the >93 kg subgroup (20 [9.6%] subjects compared to the ≤93 kg subgroup (2 [2.3%] subjects (Table 38). However, when events of hypertension and blood pressure increased were combined, there was a higher incidence of these events in the >93 kg subgroup (26 [12.5%] subjects) compared to the ≤93 kg subgroup (5 [5.7%] subjects) (Table 38).

With the exception of weight-related hypertension, there were no apparent weight-specific TEAEs.

Table 38. MRS-TU-2019 and MRS-TU-2019EXT Kyzatrex Treatment-Emergent Adverse Events - Overall Summary by Baseline Weight Category (OSS)

	Subjects Who Took Kyzatrex in Both Studies				All Subjects			
	≤93 kg N=27		>93 kg N=45		≤93 kg N=88		>93 kg N=208	
Parameter	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAEs	15 (55.6)	49	36 (80.0)	179	34 (38.6)	92	123 (59.1)	411
Any serious TEAEs	1 (3.7)	1	4 (8.9)	4	1 (1.1)	1	10 (4.8)	15
Any treatment-related TEAEs	6 (22.2)	9	17 (37.8)	33	12 (13.6)	22	54 (26.0)	92
Any treatment-related serious TEAEs	0		0		0		0	
Any severe TEAEs	1 (3.7)	1	5 (11.1)	7	1 (1.1)	1	11 (5.3)	13
Any treatment-related severe TEAEs	0		0		0		2 (1.0)	2
Any TEAEs leading to discontinuation from study drug	0		0		4 (4.5)	7	7 (3.4)	10
Any TEAEs leading to death	0		0		0		1 (0.5)	1
Any MACE	0		0		0		2 (1.0)	3
Any TEAEs of hypertension or blood pressure increased	2 (7.4)	2	9 (20.0)	10	5 (5.7)	5	26 (12.5)	31

Source: Table 14.3.1.3.1.2 (Reproduced from the Applicant submission)
Abbreviations: E, number of events; MACE, major adverse cardiac events; n, number of subjects; OSS, overall safety set; TEAE, treatment-emergent adverse event

Race and Ethnicity

There were too few subjects in the Asian or other subgroups to draw meaningful conclusions. Similarly, as the majority of subjects in the phase 3 studies were not Hispanic or Latino, ethnicity analyses could not be conducted.

Overall, subjects in the Black subgroup reported fewer TEAEs of any category compared to White subjects. No TEAEs were reported with a difference of ≥5% in the White compared to Black subgroups (Table 39).

There were no apparent race-specific TEAEs.

Testosterone *C_{max}*

In study MRS-TU-2019EXT (mEXTS), for the subgroup analyses by age, race, and ethnicity, greater than 85% of subjects had an NaF/EDTA plasma T C_{max} ≤1200 ng/mL after 90 days of treatment with Kyzatrex (CSR MRS-TU-2019 Section 12.3.3). For the subgroup of BMI <30 kg/m^2, a slightly lower (81.6%) proportion of subjects had a plasma T C_{max} ≤1200 ng/mL after 90 days of treatment with Kyzatrex:

- Baseline BMI <30 kg/m^2: 31 (81.6%) subjects
- Baseline BMI ≥30 kg/m2: 83 (90.2%) subjects
- Baseline age ≤50 years: 61 (87.1%) subjects
- Baseline age >50 years: 53 (88.3%) subjects
- Race = Asian: 4 (100%) subjects
- Race = Black or African American: 17 (94.4%) subjects
- Race = White: 90 (85.7%) subjects
- Race = Other: 3 (100%) subjects)
- Ethnicity = Hispanic or Latino: 43 (89.6%) subjects
- Ethnicity = Not Hispanic or Latino: 69 (86.3%).

Table 39. MRS-TU-2019 and MRS-TU-2019EXT Kyzatrex Treatment-Emergent Adverse Events - Overall Summary by Race (OSS)

	Subjects Who Took Kyzatrex in Both Studies								All Subjects (OSS)							
	Asian N=1		Black N=15		White N=53		Other N=3		Asian N=4		Black N=48		White N=236		Other N=8	
Parameter	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAEs	1 (100)	7	10 (66.7)	45	37 (69.8)	169	3 (100)	7	1 (25.0)	7	21 (43.8)	71	130 (55.1)	413	5 (62.5)	12
Any serious TEAEs	1 (100)	1	0		4 (7.5)	4	0		1 (25.0)	1	1 (2.1)	1	9 (3.8)	14	0	
Any treatment-related TEAEs	0		4 (26.7)	8	19 (35.8)	34	0		0		8 (16.7)	13	58 (24.6)	101	0	
Any treatment-related serious TEAEs	0		0		0		0		0		0		0		0	
Any severe TEAEs	1 (100)	1	0		5 (9.4)	7	0		1 (25.0)	1	0		11 (4.7	13	0	
Any treatment-related severe TEAEs	0		0		0		0		0		0		2 (0.8)	2	0	
Any TEAEs leading to discontinuation from study drug	0		0		0		0		0		1 (2.1)	1	10 (4.2)	16	0	
Any TEAEs leading to death	0		0		0		0		0		0		1 (0.4)	1	0	
Any MACE	0		0		0		0		0		0		2 (0.8)	3	0	
Any TEAEs of hypertension or blood pressure increased	0		0		11 (20.8)	12	0		0		2 (4.2)	2	29 (12.3)	34	0	

Source: Table 14.3.1.3.1.3 (Reproduced from the Applicant submission)
Abbreviations: E, number of events; MACE, major adverse cardiovascular event; OSS, overall safety set, TEAE, treatment-emergent adverse event

Drug-Disease Interactions

Weight, Diabetic Status, and Antihypertensive Therapy on Dose

A logistic regression approach was used to assess the impact of weight, diabetic status and antihypertensive therapy on the final dose given to subjects in a single model. Dose (the outcome variable) was broken into three distinct categories: 800 mg, 600 mg, and ≤400 mg. Weight was categorized into >93 kg vs ≤93 kg. The other categories were with and without diabetes at baseline, and with or without antihypertensive stats at Visit 7E. Odds ratios (OR) were estimated along with 95% Wald CIs.

Table 38 demonstrates that weight was strongly associated with the final dose (OR =3.928 and 95% CI = (1.896,8.136)). Diabetes was also strongly associated (OR=2.646 and 95% CI = (1.111, 6.300). Model results suggested that the inclusion of hypertensive therapy at baseline had no influence on the final dose when evaluated with diabetic status and weight category.

Table 40. Covariate Analysis of Dose as Outcome as a Function of Weight, Diabetic Status and History of Antihypertensive Treatment Status

	Odds Ratio	
Covariate	**Estimate**	**95% CI**
With antihypertensive therapy at Visit 7E (Day 1E) vs. without antihypertensive therapy at Visit 7E (Day 1E)	1.000	(0.485, 2.062)
With diabetes mellitus vs. without diabetes mellitus	2.646	(1.111, 6.300)
Weight: >93 kg vs. ≤93 kg	3.928	(1.896, 8.136)

Source: Table 14.2.2.1.3.6, reproduced from the Applicant submission
Abbreviations: CI, confidence interval

Testosterone C_{max}

In study MRS-TU-2019EXT (mEXTS), regardless of baseline weight subgroup, greater than 85% of subjects had an NaF/EDTA plasma T C_{max} ≤1200 ng/mL after 90 days of treatment with Kyzatrex (CSR MRS-TU-2019 Section 12.3.3):

- Baseline weight ≤93 kg: 43 (87.8%) subjects
- Baseline weight >93 kg: 71 (87.7%) subjects

Subgroup analyses for T C_{max} in terms of BMI, age, race, and ethnicity are described in Section 9.1.5 of the Applicant submission.

Diabetic Status

Overall TEAEs for all Kyzatrex subjects were reported at a similar incidence in subjects with diabetes compared to those without diabetes (Table 41). The number of Kyzatrex subjects with diabetes who participated in both studies may be too small (n=7) to make meaningful conclusions.

No TEAEs were present with a difference of ≥5% in subjects with diabetes compared to those without diabetes . There were no apparent diabetes-specific TEAEs .

Table 41. MRS-TU-2019 and MRS-TU-2019EXT Kyzatrex Treatment-Emergent Adverse Events - Overall Summary by Baseline Diabetic Status Category (OSS)

	Subjects Who Took Kyzatrex in Both Studies				All Subjects			
	With DM N=7		Without DM N=65		With DM N=48		Without DM N=248	
Parameter	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAEs	6 (85.7)	36	45 (69.2)	192	26 (54.2)	105	131 (52.8)	398
Any serious TEAEs	2 (28.6)	2	3 (4.6)	3	4 (8.3)	9	7 (2.8)	7
Any treatment-related TEAEs	5 (71.4)	13	18 (27.7)	29	11 (22.9)	26	55 (22.2)	88
Any treatment-related serious TEAEs	0		0		0		0	
Any severe TEAEs	2 (28.6)	3	4 (6.2)	5	3 (6.3)	4	9 (3.6)	10
Any treatment-related severe TEAEs	0		0		0		2 (0.8)	2
Any TEAEs leading to discontinuation from study drug	0		0		3 (6.3)	6	8 (3.2)	11
Any TEAEs leading to death	0		0		1 (2.1)	1	0	
Any MACE	0		0		2 (4.2)	3	0	
Any TEAEs of hypertension or blood pressure increased	1 (14.3)	1	10 (15.4)	11	4 (8.3)	5	27 (10.9)	31

Source: Table 14.3.1.3.1.4 from the Applicant submission
Abbreviations: DM, diabetes mellitus; E, number of events; MACE, major adverse cardiovascular event; OSS, overall safety set, TEAE, treatment-emergent adverse event

HbA1c Data

MRS-TU-2019

When analyzing HbA1c data by diabetic status for subjects in the Kyzatrex group, mean HbA1c at baseline was 7.2% for subjects with diabetes mellitus and 5.6% for subjects without diabetes mellitus; mean HbA1c at the End of Treatment was 7.3% for subjects with diabetes mellitus and 5.7% for subjects without diabetes mellitus.

MRS-TU-2019EXT

When analyzing HbA1c data by diabetic status, mean HbA1c at Baseline was 6.9% for subjects with diabetes mellitus and 5.7% for subjects without diabetes mellitus; mean HbA1c at the End of Treatment was 7.1% for subjects with diabetes mellitus and 5.6% for subjects without diabetes mellitus.

Hypertensive Treatment Status

Adverse Events

Overall, a somewhat higher incidence of TEAEs was reported in subjects who were taking antihypertension therapy (57 [60.0%] subjects) at baseline compared to those who were not (100 [49.8%] subjects) (Table 33)

Hypertension was the only TEAE reported with a difference of ≥5% in subjects taking antihypertensive treatment at baseline (10 [10.5%] compared to subjects who were not taking antihypertensive treatment at baseline (11 [5.5%] . However, when events of hypertension and

blood pressure increased were combined, there was no difference between subgroups (Table 33).

8.2.8. Specific Safety Studies/Clinical Trials

Blood Pressure

A dedicated single-arm, open-label trial, MRS-TU-2019 EXT, comprehensively evaluated blood pressure changes on the basis of ABPM. The patient population included hypogonadal men who received Kyzatrex daily following a dose titrating algorithm to a plasma testosterone level of 400 to 900 ng/dL.

ABPM Measurements

Twenty-four-hour ABPM measurements were performed at baseline (Visit 6E), and at the following two time-points: following 120 and 180 days of treatment with Kyzatrex.

The goal of the 6-month (120 days) timepoint was to determine whether the BP had plateaued following 4 months of treatment with Kyzatrex.

The primary safety endpoint in MRS-TU-2019EXT was the change from baseline in 24-hr average SBP following 120 days of treatment with Kyzatrex.

The average SBP and diastolic BP changes following 180 days with Kyzatrex are presented in Table 42. Based on the FDA analysis of Applicant submission, data is presented in the form of point estimates with the corresponding 95% CI (Table 42).The effect of Kyzatrex was evaluated in a dedicated ABPM study MRS-TU-2019EXT, a single-arm, open-label study in hypogonadal men receiving daily dosing titrated to a plasma testosterone of 400 to 900 ng/dL. A significant increase in change from baseline in 24-h systolic BP (Section 4.2). The results for the average parameters for systolic and diastolic BP are shown in Table 42.

Table 42. The Point Estimates and the 95% CIs (FDA Analysis) for Day 180 (ABPM)

ABPM Parameter	Treatment	Metric	Δ	95% CI
Systolic BP	Kyzatrex	24-h mean	1.9	(0.7, 3.1)
Systolic BP	Kyzatrex	Daytime	1.4	(0.1, 2.6)
Systolic BP	Kyzatrex	Nighttime	3.2	(1.6, 4.7)
Diastolic BP	Kyzatrex	24-h mean	0.7	(-0.2, 1.6)
Diastolic BP	Kyzatrex	Daytime	0.3	(-0.7, 1.2)
Diastolic BP	Kyzatrex	Nighttime	1.7	(0.5, 2.9)

Source: Interdisciplinary Review Team for Cardiac Safety Studies ABPM Study Review, dated 1/5/2021. DARRTs Reference ID: 4801902.
Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CI, confidence interval

Per the information presented in the Applicant submission, the 24-hour mean ambulatory SBP LSM difference (95% CI) from baseline (mmHg) in MRS-TU 2019EXT was 1.7 (0.3 to 3.1) at Day 120E and 1.8 (0.3 to 3.2) at Day 180 E (mixed model repeated measures analysis). The increase in 24-hr mean SBP (95% CI) was greater in subjects on antihypertensive drug therapy compared

to those not taking such medications: 3.4 (1.0 to 5.9) vs. 0.7 (-1.0 to 2.4) at Day 120E, and 3.1 (0.6 to 5.6) vs 1.0 (-0.7 to 2.8) at Day 180E .

The primary analysis was mixed model for repeated measures with prior randomized treatment status, baseline hypertensive treatment status and baseline diabetic status as covariates for change from baseline in 24-h average systolic BP.

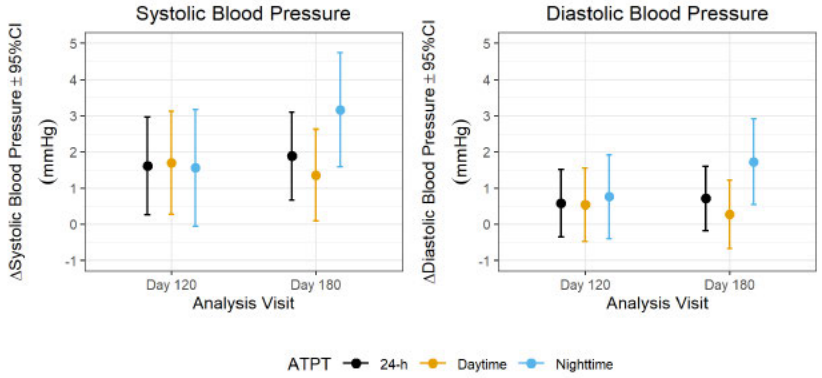
Per FDA analysis, the results of mixed model for repeated measures analysis did not exclude an increase in 24-h average systolic BP at either day 120 (1.7 [95% CI: 0.3 to 3.1] mmHg) or day 180 (1.8 [0.3 to 3.2] mmHg) (Table 42).

In the FDA analysis, greater increase in systolic BP was observed for patients with antihypertensive treatment status at baseline. Sensitivity analysis to censoring of subjects (n=5) who started new antihypertensive medication had minimal impact on results.

Primary Endpoint Analysis

Figure 2 demonstrates FDA reviewer analysis results for the primary endpoint, daytime (7a to 11p) and nighttime (11p to 7a) for systolic BP and diastolic BP using an ANCOVA model with baseline as a covariate. The results of this analysis show an increase in systolic BP at days 120 and 180. Consistent results were observed for patients with reported drug compliance >80%.

Figure 2. Change From Baseline and Placebo (Primary Endpoint)



Source: Interdisciplinary Review Team for Cardiac Safety Studies ABPM Study Review, dated 1/5/2021. DARRTs Reference ID: 4801902.

Secondary Endpoint Analysis

The mixed model for repeated measures used for the primary endpoint was used for 24-h diastolic BP and heart rate:

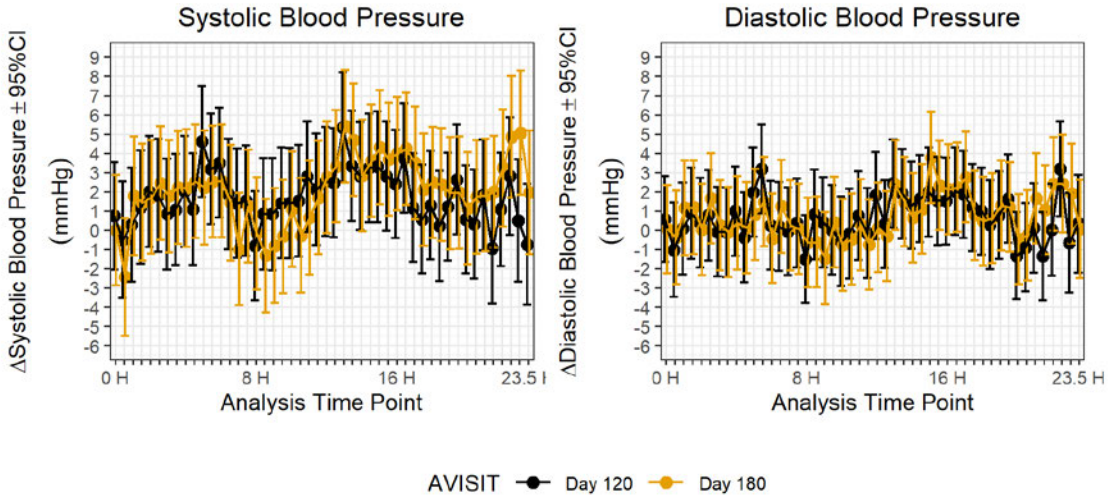
- Diastolic BP: 0.6 (-0.3 to 1.6) and 0.6 (-0.4 to 1.6) mmHg for days 120 and 180 respectively
- Heart rate: 0.7 (-0.5 to 1.9) and 1.9 (0.6 to 3.1) beats/min for days 120 and 180 respectively.

Hourly Averages

FDA analysis of hourly changes was conducted using a linear mixed-effects model with average baseline and time as fixed effects and a random intercept by subject. Time in this analysis is time after morning dose and the data was analyzed independently by day. The results of this analysis are shown in Figure 3 with systolic BP in the left panel and diastolic BP in the right panel. The confidence limits from this analysis should be interpreted with caution as the study was not powered for hourly averages.

The results of this analysis suggest a potential time-course to the changes in systolic BP, but not diastolic BP, and a similar time-course between the two days.

Figure 3. Placebo and Baseline-Adjusted Changes in Hourly Averages

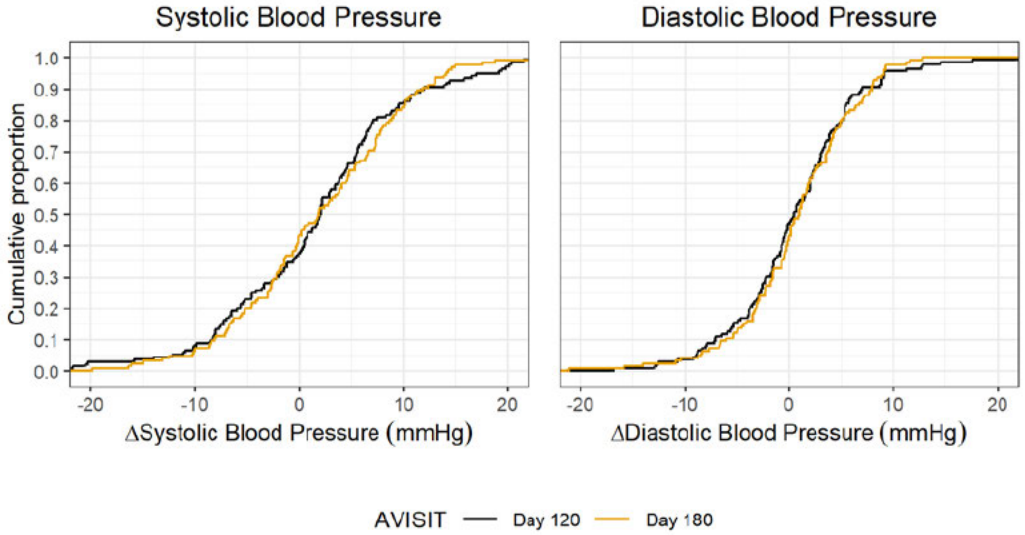


Source: Interdisciplinary Review Team for Cardiac Safety Studies ABPM Study Review, dated 1/5/2021. DARRTs Reference ID: 4801902.

Outlier Analysis

The cumulative distribution was used to visualize differences in the distribution of change from baseline in 24-h average for systolic BP and diastolic BP (Figure 4). Consistent with the primary endpoint, this analysis shows a slight increase for both days in systolic BP with a lesser increase in diastolic BP.

Figure 4. Cumulative Distribution for Change in 24-h Average



Source: Interdisciplinary Review Team for Cardiac Safety Studies ABPM Study Review, dated 1/5/2021. DARRTs Reference ID: 4801902.

In-Clinic BP Measurements

In MRS-TU-2019EXT, the mean change from baseline (95% CI) in clinic SBP was 2.1 (0.4 to 3.8) mmHg at Day 90E and was 2.4 (0.6 to 4.2) mm Hg at Day 179E . The increase in SBP plateaued between Day 90E and 119E . Although it is tempting to compare in-clinic BP changes with ABPM BP changes, there are two factors limiting this analysis. The in-clinic BP measurements are all done fasting in the morning as opposed to throughout 24 hours for the ABPMs.

The mean change from baseline (95% CI) in 24-hr average heart rate as assessed by ABPM was 0.7 (-0.5 to 1.9) bpm at Days 120E and 1.9 (0.6 to 3.1) bpm at Day 180E. Changes in heart rate were similar between subjects with or without hypertension and with or without diabetes. As with SBP, the changes in heart rate with treatment were most pronounced in the evening, 12-17 hours after the morning dose, and were minimal at other times of the day. An increase in BP was observed in this ABPM study as evidenced by a mean increase in 24-h mean systolic BP of 1.9 mm Hg with an upper bound of 3.1 mm Hg. While a numerically lower increase in BP was observed in the ABPM study for this oral TU compared to other oral TU products this study was not designed to compare the increase in BP between different products. (b) (4)

8.2.9. Additional Safety Explorations

Human Reproduction and Pregnancy

Risk Summary

Kyzatrex is contraindicated in pregnant women. Testosterone is teratogenic and may cause fetal harm based on data from animal studies and its mechanism of action. 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 do not meet current standards for nonclinical development toxicity studies.

Animal Data

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 restriction, 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.

Pediatrics and Assessment of Effects on Growth

N/A

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Withdrawal Effects

Testosterone abuse may result in dependence and withdrawal symptoms upon significant dose reduction or abrupt discontinuation of use.

Drug Abuse

Kyzatrex contains TU, which is a controlled substance under Schedule III of the Controlled Substances Act.

Abuse

Drug abuse is intentional nontherapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids, and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse by men taking higher doses of

legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility, and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following adverse reactions have been reported in male adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dependence

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

Overdose

There are no available information concerning overdose with Kyzatrex. Treatment of overdosage consists of discontinuation of Kyzatrex and appropriate symptomatic and supportive care. Assuming that missing capsules were taken, overall compliance rates were high (mean rates of 132.23% and 101.3% in MRS-TU-2019 and MRS-TU-2019EXT, respectively).

Sixteen (7.5%) subjects had >120% study drug compliance overall in MRS-TU-2019; 13 (8.4%) subjects had >120% study drug compliance overall in MRS-TU-2019EXT.

One case of potential overdose with testosterone was reported in clinical trials with Kyzatrex. The subject enrolled in both the AndroGel and Kyzatrex treatment arms of MRS-TU-2019 by changing his name initials and enrolling at a second clinical site. He was dispensed overlapping doses for a period of about 8 months. His final dose level (Day 90 to EOT) for Kyzatrex was 400 mg per day, and his final dose level for AndroGel from Day 56 to Day 270 was 60.75 mg and 40.5 mg from Day 270 to EOT. The only PK measurements that would have occurred during the overlapping drug dispensing would have been those associated with the AndroGel treatment, as the 90-day titration period of his Kyzatrex enrollment was complete before he enrolled in the study a second time. All of the subject's serum testosterone values collected for the AndroGel treatment arm (V4 predose, V6 predose, and V8 24-hr PK) were within the normal range for serum T (300 to 1000 ng/dL). He did not report any adverse reactions associated with the potential overdose.

The highest dose level tested in the Kyzatrex program was 1000 mg/day (12 subjects in MRS-TU-2019 for a mean duration of 154 days with a maximum duration of 304 days).

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Kyzatrex is not currently approved in any country. Therefore, there are no postmarketing data for Kyzatrex.

Expectations on Safety in the Postmarket Setting

Not applicable

8.2.11. Integrated Assessment of Safety

- The OSS included 296 subjects randomized (MRS-TU-2019) or assigned (MRS-TU-2019EXT) to receive Kyzatrex in the OSS. Overall, in the OSS, 210 (71%) subjects completed the studies, and 86 (29%) subjects discontinued. The primary reasons for study drug discontinuation in the OSS were lost to follow-up (33 [11.1%] subjects) and withdrawal by subject (27 [9.1%] subjects). For those who received Kyzatrex in both studies, 62 (86%) subjects completed the studies, and 10 (14%) subjects discontinued. The primary reasons

for study drug discontinuation were withdrawal by subject (4 [5.6%] subjects) and "other" (3 [4.2%]).

- Overall, 157 (53.0%) subjects reported a TEAE, and for subjects who received Kyzatrex in both studies, 51 (70.8%) subjects reported a TEAE. A total of 31(10.5%) subjects reported a TEAE of hypertension or BP increased, and for subjects who received Kyzatrex in both studies, 11 (15.3%) subjects reported a TEAE of hypertension or BP increased. Two (0.7%) subjects reported major adverse cardiovascular events.
- There was 1 (0.3%) subject death (myocardial infarction) in the pooled phase 3 studies. This event occurred in the MRS-TU-2019 study and was not considered by the Investigator to be related to Kyzatrex.
- Few subjects reported TEAEs of special interest (depression, aggression, anger, suicidality). Overall, 4 (1%) subjects reported TEAEs of special interest, and for those subjects who received Kyzatrex in both studies, 1 (1.4%) subject reported a TEAE of special interest. None of the subjects received any clinical intervention.
- Overall, 11 (3.7%) subjects reported 16 serious TEAEs, and for the subjects who received Kyzatrex in both studies, 5 (6.9%) subjects reported serious TEAEs. None of the serious TEAEs were considered by the Investigator to be related to study drug.
- 3.7% subjects were permanently discontinued from study drug due to a TEAE. None of these subjects received Kyzatrex in both studies.
- A total of 26 subjects across both studies had either a PSA value ≥4 ng/mL or an increase from baseline >1.4 ng/mL. Few elevated PSAs were suspicious for prostate cancer, and many were isolated increases that may have been due to laboratory or sample handling errors, demonstrating the complexity of analyzing group PSA data in such studies. Seven AEs of PSA increased, three AEs of prostatitis, two AEs of prostatomegaly, and one AE of prostate tenderness were noted for subjects receiving Kyzatrex. There was a small mean increase in the total International Prostate Symptom Score in MRS-TU-2019, though the increase in score was higher in the AndroGel group than the Kyzatrex group.
- Seven (2.4%) subjects reported a TEAE of hemoglobin increased, and one subject reported a TEAE of hematocrit increased. In 15 subjects, hemoglobin levels increased to >18 g/dL. As TRT is known to increase hemoglobin and hematocrit, these changes were expected. No clinical intervention was required.
- Across both studies, mean values of FSH, LH, and SHBG had a modest decrease at Day 90 relative to baseline. Decreases in LH and FSH were expected due to negative feedback of androgen replacement on the pituitary gland and hypothalamus. Sixty-four (41.3%) subjects had a DHT C_{avg} below the upper limit of normal, and 6 (4.8%) of subjects had a DHT C_{avg} 2x-3x above the upper limit of normal.
- There was a decrease in mean total cholesterol, HDL, LDL, and triglycerides levels from baseline to the end of treatment in both studies.

- Adverse reactions commonly reported with other approved oral TRTs were observed; however, incidences were consistent with others seen with other TRTs. Regarding changes to vital signs, modest increases in blood pressure and heart rate were observed. ABPM in MRS-TU-2019EXT revealed a 24-hour mean SBP LSM change from baseline of 1.7 mm Hg on Day 120E; increases in SBP were greater for subjects who were taking antihypertensive drugs or had diabetes.
- Overall, the safety profile of Kyzatrex is consistent with testosterone replacement therapies as a class.

8.3. Statistical Issues

None

8.4. Conclusions and Recommendations

Adult men with conditions (of structural or genetic etiologies) associated with a deficiency or absent endogenous testosterone require testosterone replacement. Currently, various testosterone-containing products, including those containing TU, in various formulations administered in multiple modes of administration are approved for this use. Kyzatrex was developed as another oral TRT option.

After completing the phase 3 study and analyzing its data, the Applicant identified aberrant plasma/serum PK results at clinical Site 104 they attributed to improper handling/processing of PK samples. As such, the Applicant proposed to exclude Site 104 from the efficacy analyses. Although the phase 3 study met the success criteria for the primary efficacy endpoint of C_{avg} with or without Site 104, the key secondary endpoints of C_{max} thresholds were achieved only with the exclusion of Site 104. Given the Agency's concerns of mismanagement of PK sample handling/processing and the need to determine whether excluding Site 104 was justified, OSIS inspected Site 104 and a second clinical site, Site 107. OSIS's inspection revealed objectionable conditions that included lack of record for blood sample collection, processing, and handling at both sites. OSIS concluded that the data reliability from these two sites, and also likely for the remainder 17 clinical sites not inspected, may be impacted. The Agency subsequently requested for evidence of documentation of PK sample handling/processing, but the Applicant did not provide documentation of site specific record on temperature, duration of each step from blood sample collection, precentrifugation sample placement and storage to centrifugation and transferring of processed samples. The accuracy of T concentration measurements, be it in serum or plasma, depends on the proper handling and processing of PK samples because T measurements may be impacted by several factors, including the known ex vivo TU to T conversion. Lack of documentation that the clinical sites in the phase 3 study followed the proper procedures specified in the central laboratory manual poses significant uncertainties about the reliability of the PK results. This poses an approvability deficiency for a drug development program that relies solely on PK endpoints (C_{avg} and C_{max}) for demonstration of efficacy. Because of uncertain reliability, substantial evidence of effectiveness for Kyzatrex is not established, and we recommend a CR.

To address the CR, we recommend the Applicant conduct a new efficacy and safety trial evaluating Kyzatrex in hypogonadal men with proper documentation of PK sample handling/processing at all clinical sites of the trial.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee was convened during the review cycle of NDA 213953. The current review cycle did not raise any issues requiring external expert input.

Pediatrics

Prior to 2018, the Agency had waived Pediatric Research Equity Act (PREA) requirements for testosterone replacement products because studies would be impossible or highly impractical (because primary/secondary hypogonadism rarely occur in pediatrics). Since 2018 and after discussion at the April 2019 Pediatric Advisory Committee meeting, the Agency determined that PREA requirements apply to these products because there are adolescent boys with primary/secondary hypogonadism requiring testosterone replacement. Because the dosing amount per 24-hour period and the dosing regimen for Kyzatrex is different from that of the approved oral testosterone product, PREA requirement will apply to Kyzatrex. If approved, it will be granted a full PREA waiver for all females, a partial waiver for males from 0 to less than 12 years, and a deferral for males from 12 to <17 years of age. This is the same approach as that for the approved oral TU product.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

If approved, the labeling for Kyzatrex would include the following class labeling:

- A Boxed Warning and Warnings/Precautions regarding blood pressure increases
- A Contraindication limiting the use of Kyzatrex to men with hypogonadal conditions associated with structural or genetic etiologies
- A Medication Guide informing patients of the serious side effects associated with Kyzatrex including increased blood pressure.

Hb/Hematocrit

Increases in hemoglobin were reported in Study MRS-TU-2019EXT. None of these increases led to premature discontinuation of Kyzatrex. Hematocrit was not assessed in this study.

Geriatric Use

Clinical studies of Kyzatrex did not include any patients 65 years of age and older. Therefore, it cannot be determined whether these patients respond differently from younger adult patients. Additionally, there are insufficient long-term safety data in geriatric patients to assess the potentially increased risk of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens including Kyzatrex may be at risk for worsening of signs and symptoms of benign prostatic hyperplasia.

11 Risk Evaluation and Mitigation Strategies (REMS)

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

12 Postmarketing Requirements and Commitment

None required.

13 Division Director (DHOT) Comments

14 Division Director (OCP) Comments

15 Division Director (OB) Comments

16 Division Director (Clinical) Comments

I concur with the CDTL's and the clinical and clinical pharmacology teams' recommendation to issue a Complete Response for this NDA.

For a phase 3 study of a TU product where the efficacy endpoints are solely PK-based, it is critical to strictly adhere to PK sample handling/processing procedures outlined in the central lab manual to ensure the T values obtained accurately reflect the actual serum or plasma T concentrations of study subjects. Without evidence of documentation from any clinical sites, and especially in the presence of aberrant PK results, we cannot be assured the proper procedures were appropriately followed to generate accurate and, hence, reliable PK results for the entire phase 3 study. Even assuming the best case, however unlikely, scenario where PK handling/processing issues were confined to Site 104, without documentation of how the PK samples were handled/processed at that site, there is no information to justify excluding Site 104. When the PK efficacy analyses were based on data from all study sites, including Site 104, Kyzatrex did not achieve any of the key secondary Cmax endpoints, precluding its approval.

Possible options for handling the efficacy data for Kyzatrex is either to analyze the data from all clinical sites (not exclude Site 104) or not to accept the data because of uncertainties about the reliability of the PK data, with the latter being the primary deficiency. With either approaches, substantial evidence of effectiveness for Kyzatrex has not been established.

17 Office Director (or designated signatory authority) Comments

See Clinical Director's Comments.

APPEARS THIS WAY ON ORIGINAL

18 Appendices

18.1. References

The following include references provided within the submission and based on reviewers' search of public databases.

Agematu, H, N Matsumoto, Y Fujii, H Kabumoto, S Doi, K Machida, J Ishikawa, and A Arisawa, 2006, Hydroxylation of Testosterone by Bacterial Cytochromes P450 Using the *Escherichia coli* Expression System, Biosci Biotechnol Biochem, 70(1):307-311.

Agnew, LR and WU Gardner, 1952, The Incidence of Spontaneous Hepatomas in C3H, C3H (Low Milk Factor), and CBA Mice and the Effect of Estrogen and Androgen on the Occurrence of These Tumors in C3H Mice, Cancer Res, 12(10):757-761.

Alemany, L, R Barbera, A Alegria, and JM Laparra, 2014, Plant Sterols From Foods in Inflammation and Risk of Cardiovascular Disease: A Real Threat?, Food Chem Toxicol, 69:140-149.

Amory, JK, TF Kalhorn, and ST Page, 2008, Pharmacokinetics and Pharmacodynamics of Oral Testosterone Enanthate Plus Dutasteride for 4 Weeks in Normal Men: Implications for Male Hormonal Contraception, J Androl, 29(3):260-271.

Assmann, G, P Cullen, J Erbey, DR Ramey, F Kannenberg, and H Schulte, 2006, Plasma Sitosterol Elevations are Associated With an Increased Incidence of Coronary Events in Men: Results of a Nested Case-Control Analysis of the Prospective Cardiovascular Munster (PROCAM) Study, Nutr Metab Cardiovasc Dis, 16(1):13-21.

Awad, AB, MS Hartati, and CS Fink, 1998, Phytosterol Feeding Induces Alteration in Testosterone Metabolism in Rat Tissues, The Journal of Nutritional Biochemistry, 9(12):712-717.

Bansal, MR and AG Davies, 1986, Effect of Testosterone Oenanthate on Spermatogenesis and Serum Testosterone Concentrations in Adult Mice, J Reprod Fertil, 78(1):219-224.

Barbonetti, A, S D'Andrea, and S Francavilla, 2020, Testosterone Replacement Therapy, Andrology, 8(6):1551-1566.

Baumgartner, S, RP Mensink, C Husche, D Lutjohann, and J Plat, 2013, Effects of Plant Sterol- or Stanol-Enriched Margarine on Fasting Plasma Oxyphytosterol Concentrations in Healthy Subjects, Atherosclerosis, 227(2):414-419.

Beamer, WG, KL Shultz, BJ Tennent, and LD Shultz, 1993, Granulosa Cell Tumorigenesis in Genetically Hypogonadal-Immunodeficient Mice Grafted With Ovaries From Tumor-Susceptible Donors, Cancer Res, 53(16):3741-3746.

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

Chambô-Filho, A, AF Camargos, and FE Pereira, 2005, Morphological Changes Induced by Testosterone in the Mammary Glands of Female Wistar Rats, Braz J Med Biol Res, 38(4):553-558.

Chao, J, KB Rubinow, M Kratz, JK Amory, AM Matsumoto, and ST Page, 2016, Short-Term Estrogen Withdrawal Increases Adiposity in Healthy Men, J Clin Endocrinol Metab, 101(10):3724-3731.

ChemIDPlus, 2020, ChemIDPlus, https://chem.nlm.nih.gov/chemidplus/.

Chin, JP and JN Pennefather, 1990, Effect of Long-Term Administration of Testosterone Oenanthate on Sympathetic Neurotransmission to Rat Isolated Seminal Vesicles, Clin Exp Pharmacol Physiol, 17(10):713-724.

Cosmetic Ingredient Review Expert Panel, 2004, Final Report of the Amended Safety Assessment of PEG-5, -10, -16, -25, -30, and -40 Soy Sterol, Int J Toxicol, 23 Suppl 2:23-47.

Dean, M, BT Murphy, and JE Burdette, 2017, Phytosteroids Beyond Estrogens: Regulators of Reproductive and Endocrine Function in Natural Products, Mol Cell Endocrinol, 442:98-105.

Dela Cruz, C and OC Pereira, 2012, Prenatal Testosterone Supplementation Alters Puberty Onset, Aggressive Behavior, and Partner Preference in Adult Male Rats, J Physiol Sci, 62(2):123-131.

(b) (4)

y/Ion Trap-Mass Spectrometry, J Chromatogr B Analyt Technol Biomed Life Sci, 828(1-2):21-26.

Di Gioia, F and SA Petropoulos, 2019, Phytoestrogens, Phytosteroids and Saponins in Vegetables: Biosynthesis, Functions, Health Effects and Practical Applications, Adv Food Nutr Res, 90:351-421.

Dobs, AS, AW Meikle, S Arver, SW Sanders, KE Caramelli, and NA Mazer, 1999, Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men, J Clin Endocrinol Metab, 84(10):3469-3478.

(b) (4)

Eisner, JR, MA Barnett, DA Dumesic, and DH Abbott, 2002, Ovarian Hyperandrogenism in Adult Female Rhesus Monkeys Exposed to Prenatal Androgen Excess, Fertil Steril, 77(1):167-172.

(b) (4)

(b) (4)

Feigelson, M, 1986, Suppression of Testicular Maturation and Fertility Following Androgen Administration to Neonatal Male Rats, Biol Reprod, 35(5):1321-1332.

Fels, E and LR Bosch, 1971, Effect of Prenatal Administration of Testosterone on Ovarian Function in Rats, Am J Obstet Gynecol, 111(7):964-969.

Feser, W, RS Kerdar, A Baumann, J Korber, H Blode, and W Kuhnz, 1998, DNA adduct formation of selected sex steroids in human liver slices in vitro, Toxicol In Vitro, 12(4):353-364.

Fessner, ND, M Srdič, H Weber, C Schmid, D Schönauer, U Schwaneberg, and A Glieder, 2020, Preparative-Scale Production of Testosterone Metabolites by Human Liver Cytochrome P450 Enzyme 3A4, Advanced Synthesis & Catalysis, 362(13):2725-2738.

Firminger, HI and MD Reuber, 1961, Influence of Adrenocortical, Androgenic, and Anabolic Hormones on the Development of Carcinoma and Cirrhosis of the Liver in A x C Rats Fed N-2-Fluorenyldicetamide, J Natl Cancer Inst, 27:559-595.

Flickinger, C, 1978, Effects of Testosterone Enanthate on the Structure of the Male Reproductive Tract of the Rat, Anat Rec, 192(4):555-584.

Foti, RS and DK Dalvie, 2016, Cytochrome P450 and Non-Cytochrome P450 Oxidative Metabolism: Contributions to the Pharmacokinetics, Safety, and Efficacy of Xenobiotics, Drug Metab Dispos, 44(8):1229-1245.

Gandelman, R, NG Simon, and NJ McDermott, 1979, Prenatal Exposure to Testosterone and Its Precursors Influences Morphology and Later Behavioral Responsiveness to Testosterone of Female Mice, Physiol Behav, 23(1):23-26.

Gao, W, CE Bohl, and JT Dalton, 2005a, Chemistry and structural biology of androgen receptor, Chem Rev, 105(9):3352-3370.

Gao, W, PJ Reiser, CC Coss, MA Phelps, JD Kearbey, DD Miller, and JT Dalton, 2005b, Selective Androgen Receptor Modulator Treatment Improves Muscle Strength and Body Composition and Prevents Bone Loss in Orchidectomized Rats, Endocrinology, 146(11):4887-4897.

Giannitrapani, L, M Soresi, E La Spada, M Cervello, N D'Alessandro, and G Montalto, 2006, Sex Hormones and Risk of Liver Tumor, Ann N Y Acad Sci, 1089:228-236.

Glucksmann, A and CP Cherry, 1968, The Effect of Oestrogens, Testosterone and Progesterone on the Induction of Cervico-Vaginal Tumours in Intact and Castrate Rats, Br J Cancer, 22(3):545-562.

Hana, HY, WK Khalil, AI Elmakawy, and GA Elmegeed, 2008, Androgenic profile and genotoxicity evaluation of testosterone propionate and novel synthesized heterocyclic steroids, J Steroid Biochem Mol Biol, 110(3-5):284-294.

Hotchkiss, AK, CS Lambright, JS Ostby, L Parks-Saldutti, JG Vandenbergh, and LE Gray, Jr., 2007, Prenatal Testosterone Exposure Permanently Masculinizes Anogenital Distance, Nipple Development, and Reproductive Tract Morphology in Female Sprague-Dawley Rats, Toxicol Sci, 96(2):335-345.

IARC, 1987, Androgenic (Anabolic) Steroids in Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs* Volumes 1 to 42, IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans:96-99.

IARC, 1979, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Sex Hormones (II), IARC Monogr Eval Carcinog Risk Chem Hum, 21:519-547.

JECFA, 1962, Estradiol-17beta-, progesterone, and testosterone, https://inchem.org/documents/jecfa/jecmono/v43jec05.htm.

JECFA, 1987, Joint FAO/WHO Expert Committee on Food Additives (JEFCA): Alpha-Tocopherol, http://www.inchem.org/documents/jecfa/jecmono/v21je05.htm.

JECFA, 2009, Phytosterols, phytostanols and their esters, https://inchem.org/documents/jecfa/jecmono/v43jec05.htm.

JECFA, 2008, WHO Joint FAO/WHO Expert Committee on Food Additives: Phytosterols, Phytostanols and Their Esters.

Ježek, D, L Šimunić-Banek, and R Pezerović-Panijan, 1993, Effects of High Doses of Testosterone Propionate and Testosterone Enanthate on Rat Seminiferous Tubules — A Stereological and Cytological Study, Archives of Toxicology, 67(2):131-140.

Joosten, HF, FA van Acker, DJ van den Dobbelsteen, GJ Horbach, and EI Krajnc, 2004, Genotoxicity of Hormonal Steroids, Toxicol Lett, 151(1):113-134.

Kaminetsky, J, JS Jaffe, and RS Swerdloff, 2015, Pharmacokinetic Profile of Subcutaneous Testosterone Enanthate Delivered via a Novel, Prefilled Single-Use Autoinjector: A Phase II Study, Sex Med, 3(4):269-279.

Kandel, SE, LW Han, Q Mao, and JN Lampe, 2017, Digging Deeper Into CYP3A Testosterone Metabolism: Kinetic, Regioselectivity, and Stereoselectivity Differences Between CYP3A4/5 and CYP3A7, Drug Metab Dispos, 45(12):1266-1275.

Karr, JP, U Kim, JA Resko, S Schneider, LS Chai, GP Murphy, and AA Sandberg, 1984, Induction of Benign Prostatic Hypertrophy in Baboons, Urology, 23(3):276-289.

Kawano, S, T Kamataki, T Yasumori, Y Yamazoe, and R Kato, 1987, Purification of human liver cytochrome P-450 catalyzing testosterone 6 beta-hydroxylation, J Biochem, 102(3):493-501.

(b) (4)

Lachance, S, O Dhingra, J Bernstein, S Gagnon, C Savard, N Pelletier, N Boudreau, and A Levesque, 2015, Importance of measuring testosterone in enzyme-inhibited plasma for oral testosterone undecanoate androgen replacement therapy clinical trials, Future Sci OA, 1(4):FSO55.

Lasne, C, YP Lu, L Orfila, L Ventura, and I Chouroulinkov, 1990, Study of Various Transforming Effects of the Anabolic Agents Trenbolone and Testosterone on Syrian Hamster Embryo Cells, Carcinogenesis, 11(4):541-547.

Leder, BZ, DH Catlin, C Longcope, B Ahrens, DA Schoenfeld, and JS Finkelstein, 2001, Metabolism of orally administered androstenedione in young men, J Clin Endocrinol Metab, 86(8):3654-3658.

(b) (4)

Lhasa, 2020, DEREK 6.0.0. Nexus 2.2.0, Leeds, United Kingdom: Lhasa Ltd.

Li, J, Y Tian, S Guo, H Gu, Q Yuan, and X Xie, 2018, Testosterone-Induced Benign Prostatic Hyperplasia Rat and Dog as Facile Models to Assess Drugs Targeting Lower Urinary Tract Symptoms, PLoS One, 13(1):e0191469.

Lindenthal, B, T Sudhop, P Schiedermaier, M Agnan, T Sauerbruch, and K von Bergmann, 2002, Serum Plant Sterols and Biliary Cholesterol Secretion in Humans: Studies With Ursodeoxycholic Acid, J Lipid Res, 43(7):1072-1077.

Liu, F, J Chen, F Shi, T Wang, G Watanabe, and K Taya, 2012, Phytosterol Additive Boosts Adrenal Response to ACTH in Male Japanese Quail (*Coturnix coturnix japonica*), Endocrine, 41(2):338-341.

Mazzocchi, G, LK Malendowicz, C Robba, P Rebuffat, G Gottardo, V Meneghelli, and GG Nussdorfer, 1983, Effects of Testosterone on the Zona Fasciculata of the Male Rat Adrenal Cortex. A Correlated Stereological and Biochemical Study, J Submicrosc Cytol, 15(4):991-1005.

McLachlan, RI, L O'Donnell, SJ Meachem, PG Stanton, DM de Kretser, K Pratis, and DM Robertson, 2002, Identification of Specific Sites of Hormonal Regulation in Spermatogenesis in Rats, Monkeys, and Man, Recent Prog Horm Res, 57:149-179.

Meissner, WA and SC Sommers, 1966, Endometrial Changes After Prolonged Progesterone and Testosterone Administration to Rabbits, Cancer Res, 26(3):474-478.

Moghadasian, MH, 2000, Pharmacological Properties of Plant Sterols In Vivo and In Vitro Observations, Life Sci, 67(6):605-615.

Mohd Mutalip, SS, GK Surindar Singh, A Mohd Shah, M Mohamad, V Mani, and SN Hussin, 2013, Histological Changes in Testes of Rats Treated With Testosterone, Nandrolone, and Stanozolol, Iran J Reprod Med, 11(8):653-658.

Morita, T, N Asano, T Awogi, YF Sasaki, S Sato, H Shimada, S Sutou, T Suzuki, A Wakata, T Sofuni, and M Hayashi, 1997, Evaluation of the Rodent Micronucleus Assay in the Screening of IARC Carcinogens (Groups 1, 2A and 2B) the Summary Report of the 6th Collaborative Study by CSGMT/JEMS MMS. Collaborative Study of the Micronucleus Group Test. Mammalian Mutagenicity Study Group, Mutat Res, 389(1):3-122.

Mushtaq, T, JK Wales, and NP Wright, 2007, Adrenal Insufficiency in Phytosterolaemia, Eur J Endocrinol, 157 Suppl 1:S61-65.

National Center for Biotechnology Information, 2021a, PubChem Compound Summary for CID 6013, Testosterone.

National Center for Biotechnology Information, 2021b, PubChem Compound Summary for CID 65157, Testosterone undecanoate.

Nieminen, P, AM Mustonen, P Lindstrom-Seppa, J Asikainen, H Mussalo-Rauhamaa, and JV Kukkonen, 2002, Phytosterols Act as Endocrine and Metabolic Disruptors in the European Polecat (*Mustela putorius*), Toxicol Appl Pharmacol, 178(1):22-28.

Niwa, T, N Murayama, Y Imagawa, and H Yamazaki, 2015, Regioselective Hydroxylation of Steroid Hormones by Human Cytochromes P450, Drug Metab Rev, 47(2):89-110.

Noguchi, T, WNA Charman, and VJ Stella, 1985, The effect of drug lipophilicity and lipid vehicles on the lymphatic absorption of various testosterone esters, International Journal of Pharmaceutics, 24(2):173-184.

Nucci, RAB, ACS Teodoro, W Krause Neto, WA Silva, RR de Souza, CA Anaruma, and EF Gama, 2017, Effects of Testosterone Administration on Liver Structure and Function in Aging Rats, Aging Male, 20(2):134-137.

Office of the Federal Register, 2021, 21 CFR 101.83 - Health claims: plant sterol/stanol esters and risk of coronary heart disease (CHD), https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-101/subpart-E/section-101.83.

Office of the Federal Register, 2012, 21 CFR 184.1890 - α-Tocopherols, https://www.govinfo.gov/app/details/CFR-2012-title21-vol3/CFR-2012-title21-vol3-sec184-1890.

Ostlund, RE, Jr., 2002, Phytosterols in human nutrition, Annu Rev Nutr, 22:533-549.

Pollard, M and PH Luckert, 1986, Promotional effects of testosterone and high fat diet on the development of autochthonous prostate cancer in rats, Cancer Lett, 32(2):223-227.

Qasimi, MI, K Nagaoka, and G Watanabe, 2017, The Effects of Phytosterols on the Sexual Behavior and Reproductive Function in the Japanese Quail (*Coturnix coturnix japonica*), Poult Sci, 96(9):3436-3444.

Qasimi, MI, K Nagaoka, and G Watanabe, 2018, Feeding of Phytosterols Reduced Testosterone Production by Modulating GnRH and GnIH Expression in the Brain and Testes of Male Japanese Quail (*Coturnix coturnix japonica*), Poultry Science, 97(3):1066-1072.

Rárová, L, S Zahler, J Liebl, V Kryštof, D Sedlák, P Bartůněk, L Kohout, and M Strnad, 2012, Brassinosteroids Inhibit In Vitro Angiogenesis in Human Endothelial Cells, Steroids, 77(13):1502-1509.

(b) (4)

Reuber, MD, 1976, 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(2):137-141.

Robaire, B, S Smith, and BF Hales, 1984, Suppression of Spermatogenesis by Testosterone in Adult Male Rats: Effect on Fertility, Pregnancy Outcome and Progeny, Biology of Reproduction, 31(2):221-230.

(b) (4)

Scholz, B, S Guth, KH Engel, and P Steinberg, 2015, Phytosterol Oxidation Products in Enriched Foods: Occurrence, Exposure, and Biological Effects, Mol Nutr Food Res, 59(7):1339-1352.

Singh, K and RS Gupta, 2016, Antifertility Activity of Î²-Sitosterol Isolated From *Barleria priontis* (L.) Roots in Male Albino Rats International Journal of Pharmacy and Pharmaceutical Sciences, 8(5):88-96.

(b) (4)

Snyder, PJ, 2015, Androgens. In: Brunton, LL, BA Chabner and BC Knollmann, editors, Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e, New York, NY: McGraw-Hill Education, accessmedicine.mhmedical.com/content.aspx?aid=1127869506.

Solca, C, GS Tint, and SB Patel, 2013, Dietary Xenosterols Lead to Infertility and Loss of Abdominal Adipose Tissue in Sterolin-Deficient Mice, J Lipid Res, 54(2):397-409.

Strandberg, TE, RS Tilvis, KH Pitkala, and TA Miettinen, 2006, Cholesterol and Glucose Metabolism and Recurrent Cardiovascular Events Among the Elderly: A Prospective Study, J Am Coll Cardiol, 48(4):708-714.

(b) (4)

Sudhop, T, D Lutjohann, and K von Bergmann, 2005, Sterol transporters: targets of natural sterols and new lipid lowering drugs, Pharmacol Ther, 105(3):333-341.

Sugano, M, H Morioka, Y Kida, and I Ikeda, 1978, The Distribution of Dietary Plant Sterols in Serum Lipoproteins and Liver Subcellular Fractions of Rats, Lipids, 13(6):427-432.

Swanson, HE and JJ Werff ten Bosch, 1965, The "Early-Androgen" Syndrome; Effects of Pre-Natal Testosterone Propionate, Acta Endocrinol (Copenh), 50(3):379-390.

Swell, L and CR Treadwell, 1961, Metabolic Fate of Injected C^{14}-Phytosterols, Proceedings of the Society for Experimental Biology and Medicine, 108(3):810-813.

Swerdloff, RS, C Wang, WB White, J Kaminetsky, MC Gittelman, JA Longstreth, RE Dudley, and TM Danoff, 2020, A New Oral Testosterone Undecanoate Formulation Restores Testosterone to Normal Concentrations in Hypogonadal Men, The Journal of Clinical Endocrinology & Metabolism, 105(8):2515-2531.

(b) (4)

(b) (4)

Tsutsui, T, A Komine, J Huff, and JC Barrett, 1995, Effects of Testosterone, Testosterone Propionate, 17 Beta-Trenbolone and Progesterone on Cell Transformation and Mutagenesis in Syrian Hamster Embryo Cells, Carcinogenesis, 16(6):1329-1333.

(b) (4)

Tyagi, A, M Rajalakshmi, DA Jeyaraj, RS Sharma, and JS Bajaj, 1999, Effects of Long-Term Use of Testosterone Enanthate. II. Effects on Lipids, High and Low Density Lipoprotein Cholesterol and Liver Function Parameters, Int J Androl, 22(6):347-355.

Udayakumar, TS, A Tyagi, M Rajalakshmi, SN Das, S Hashim, and JS Bajaj, 1998, Changes in Structure and Functions of Prostate by Long-Term Administration of an Androgen, Testosterone Enanthate, in Rhesus Monkey (*Macaca mulatta*), Anat Rec, 252(4):637-645.

Van Nie, R, EL Benedetti, and O MÜHlbock, 1961, A Carcinogenic Action of Testosterone, Provoking Uterine Tumours in Mice, Nature, 192(4809):1303-1303.

Van Thuyne, W, P Van Eenoo, P Mikulcikova, K Deventer, and FT Delbeke, 2005, Detection of androst-4-ene-3,6,17-trione (6-OXO) and its metabolites in urine by gas chromatography-mass spectrometry in relation to doping analysis, Biomed Chromatogr, 19(9):689-695.

Vanmierlo, T, O Weingartner, S van der Pol, C Husche, A Kerksiek, S Friedrichs, E Sijbrands, H Steinbusch, M Grimm, T Hartmann, U Laufs, M Bohm, HE de Vries, M Mulder, and D Lutjohann, 2012, Dietary Intake of Plant Sterols Stably Increases Plant Sterol Levels in the Murine Brain, J Lipid Res, 53(4):726-735.

von Bergmann, K, T Sudhop, and D Lutjohann, 2005, Cholesterol and plant sterol absorption: recent insights, Am J Cardiol, 96(1A):10D-14D.

Wishart, DS, YD Feunang, AC Guo, EJ Lo, A Marcu, JR Grant, T Sajed, D Johnson, C Li, Z Sayeeda, N Assempour, I Iynkkaran, Y Liu, A Maciejewski, N Gale, A Wilson, L Chin, R Cummings, D Le, A Pon, C Knox, and M Wilson, 2018, DrugBank 5.0: A Major Update to the DrugBank Database for 2018, Nucleic Acids Res, 46(D1):D1074-D1082.

Wolf, CJ, A Hotchkiss, JS Ostby, GA LeBlanc, and LE Gray, Jr., 2002, Effects of Prenatal Testosterone Propionate on the Sexual Development of Male and Female Rats: A Dose-Response Study, Toxicol Sci, 65(1):71-86.

Xie, B, SW Tsao, and YC Wong, 1999, Sex Hormone-Induced Mammary Carcinogenesis in Female Noble Rats: The Role of Androgens, Carcinogenesis, 20(8):1597-1606.

(b) (4)

Yucel, S, AG Cavalcanti, A Desouza, Z Wang, and LS Baskin, 2003, The effect of oestrogen and testosterone on the urethral seam of the developing male mouse genital tubercle, BJU Int, 92(9):1016-1021.

Zhang, XW, C Zhang, W Zhang, D Yang, S Meng, P Wang, J Guo, and DH Liu, 2016, Suppression of Spermatogenesis by Testosterone Undecanoate-Loaded Injectable In Situ-Forming Implants in Adult Male Rats, Asian J Androl, 18(5):791-797.

18.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): MRS-TU-2019 and MRS-TU-2019EXT

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 40		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

18.3. Nonclinical Pharmacology/Toxicology

No carcinogenicity studies were conducted by the Applicant. The Applicant relied on scientific literature to support the carcinogenicity of T, the active moiety of TU, which is well-documented.

18.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

18.4.1. Bioanalytical Methods

Liquid chromatography tandem mass spectrometry (LC-MS/MS) methods using liquid-liquid extractions for the measurement of total T and dihydrotestosterone (DHT) in plasma (using

NaF/EDTA tubes) and serum were developed, validated, and utilized in clinical studies supporting this NDA.

Blood samples collected from subjects receiving TU typically have unstable T concentrations due to postcollection TU to T ex vivo conversion due to endogenous nonspecific esterases. It was demonstrated that the use of NaF (esterase inhibitor)-containing tubes to inhibit esterase activity in plasma provides the most stable sample for determination of the primary efficacy endpoint and secondary PK endpoint (LaChance, 2015). Main factors affecting the TU to T ex vivo conversions are:

- Sample handling and processing conditions including temperature and time
- Sample collection tube types (e.g., plain tubes vs. NaF/EDTA tubes)
- TU concentration

During the development of Kyzatrex, the Applicant has conducted a BSSS. This study used whole blood samples collected from 12 subjects (from 6 investigator sites) in Study MRS-TU-2019 on Kyzatrex treatment, 3-5 hours postmorning dose of 400 mg Kyzatrex. Samples were then collected and processed in various types of tubes (i.e., NaF/EDTA tubes, K_2EDTA tubes, LiH tubes for plasma, and plain tubes for serum), at different temperatures and for different processing time. Serum and plasma samples analyzed by using a LC-MS/MS method. Reference is made to Dr. Chongwoo Yu's Clinical Pharmacology review dated April 11, 2019 under investigational new drug (IND) 118675 in the FDA Document Archiving, Reporting and Regulatory Tracking System (DARRTS) for details of the BSSS. Reference is also made to the minutes of the April 3, 2019 Type C Guidance meeting (dated May 1, 2019, under IND 118675 in DARRTS) held between the Division and the Applicant for discussion about the BSSS study results and the Applicant's proposal to use plasma in NaF/EDTA in tubes for efficacy and safety analyses in the phase 3 study.

Subsequently, plasma collected in NaF/EDTA tubes were used in all studies with PK endpoints based on the findings from the BSSS. Briefly, blood collection tubes with NaF/EDTA for T and DHT testing were collected, mixed by inversion 7-8 times, allowed to stand in an ice water bath immediately after sampling for no longer than 110 minutes, centrifuged at 2000 g for 10 minutes at 4°C, transferred to two plasma tubes, and then stored at -70°C until shipping. For total T and DHT measurements in NaF/EDTA plasma, the analytes (T and DHT), and internal standards (IS), T-d_5 and DHT-d_3, were extracted from 300 µL of human plasma by a liquid-liquid extractions procedure. The compounds were detected and quantified by LC-MS/MS in positive ion mode on an MDS Sciex API 5000 equipped with a Turbo Ionspray® interface. Calibration curves were obtained by performing a linear regression (weighted $1/x^2$) on the calibration standards with a dynamic range of 100-30000 pg/mL.

Table 43 summarizes the validation results for the T and DHT bioanalytical methods in NaF/EDTA plasma and Table 44 summarizes the validation results for the T and DHT bioanalytical methods in serum. Table 45 summarizes the validation results of TU and dihydrotestosterone undecanoate (DHTU) bioanalytical methods in NaF/EDTA plasma.

Table 43. Summary of Bioanalytical Method Validation Results for T and DHT in NaF/EDTA Plasma

Validation Report	Clinical Studies Supported	Analyte (Matrix)	Method Description and Performance	
The LC/MS/MS Quantification of Testosterone between 100 and 30000 pg/mL and Dihydrotestosterone between 100 and 5000 pg/mL in Human NaF/Na2EDTA Plasma Analytical method reference: (b) (4) (b) (4) Method validation reference: (b) (4) Report No. (b) (4)	SOV-TU-PK2011 SOV-TU-BA2012 SOV-TU-PK2013 SOV-TU-PK2017 MRS-TU-PK2018 MRS-TU-2019 MRS-TU-2019EXT	T and DHT (NaF/EDTA plasma)	The analytes, testosterone and dihydrotestosterone, and internal standards (IS), testosterone-d5 and dihydrotestosterone-d3, were extracted from 300 µL of human plasma by a liquid-liquid extraction procedure. The compounds were detected and quantified by tandem mass spectrometry in positive ion mode on an MDS Sciex API 5000 equipped with a Turbo Ionspray® interface.	
			Validated range	T: 100 to 30,000 pg/mL DHT: 100 to 5000 pg/mL
			Intra-batch Precision (%RSD)	T: 12.3% DHT: 8.66%
			Intra-batch Accuracy (%bias)	T: -1.40% DHT: 2.00%
			Selectivity: Mean matrix factor (Mid QC) Mean matrix factor (High QC) Precision (Mid QC) Precision (High QC)	 T: 0.943 DHT: 1.05 T: 0.982 DHT: 1.04 T: 9.99% DHT: 8.88% T: 13.8% DHT: 12.6%
			Precision and accuracy QCs: Within-run precision (LLOQ): Within-run accuracy (LLOQ): Within-run precision (Low, Mid, High): Within-run accuracy (Low, Mid, High): Between-run precision (LLOQ): Between-run accuracy (LLOQ): Between-run precision (Low, Mid, High): Between-run accuracy (Low, Mid, High):	 T: ≤11.5% DHT: ≤7.34% T: -10.8 to 11.0% DHT: -6.80 to 11.00% T: ≤6.41% DHT: ≤7.59% T: -4.30 to 5.44% DHT: -13.8 to 9.43% T: 12.3% DHT: 8.66% T: -1.40% DHT: 2.00% T: ≤6.82% DHT: ≤10.8% T: 0.00% DHT: 0.00%

Validation Report	Clinical Studies Supported	Analyte (Matrix)	Method Description and Performance	
			Stability (T & DHT) Post preparative (ambient): Reinjection (ambient): Short-term (ambient): Freeze/thaw (-80°C): Long-term (-80°C):	 72 hours 72 hours 29 hours 5 cycles 949 days
			Overall recovery	T: 68.7% DHT: 75.8%
			Matrix effects: Precision Accuracy	 T: 4.14% DHT: 10.8% T: 2.33% DHT: 5.51%
			Carryover	T: Acceptable DHT: Acceptable

Source: Table 7, Module 2.7.1
Abbreviations: DHT, dihydrotestosterone; EDTA, ethylenediaminetetraacetic acid; LLOQ, lower limit of quantitation; QC, quality control; RSD, relative standard deviation; T, testosterone

Table 44. Summary of Bioanalytical Method Validation Results for T and DHT in Serum

Validation Report	Clinical Studies Supported	Analyte (Matrix)	Method Description and Performance	
The LC/MS/MS Quantification of Testosterone Between 100 and 30000 pg/mL and Dihydrotestosterone Between 100 And 5000 pg/ml In Human Serum Analytical method reference: (b) (4) (b) (4) Method validation reference: (b) (4) Report No. (b) (4)	SOV-TU-PK2013 MRS-TU-2019 MRS-TU-2019EXT	T and DHT (serum)	The analytes, testosterone and dihydrotestosterone, and internal standards (IS), testosterone-d5 and dihydrotestosterone-d3, were extracted from 300 µL of human serum by a liquid-liquid extraction procedure. The compounds were detected and quantified by tandem mass spectrometry in positive ion mode on an MDS Sciex API 5000 equipped with a Turbo Ionspray® interface.	
			Validated range	T: 100 to 30,000 pg/mL DHT: 100 to 5000 pg/mL
			Intra-batch Precision (%RSD)	T: ≤6.15% DHT: ≤9.03%%
			Intra-batch Accuracy (%bias)	T: -3.60 to 5.0% DHT: -10.1 to 4.00%
			Selectivity: Mean matrix factor (Mid QC) Mean matrix factor (High QC) Precision (Mid QC) Precision (High QC)	 T: NR DHT: 1.06 T: 1.01 DHT: 1.09 T: NR DHT: 7.31% T: 7.95 DHT: 5.66%
			Precision and accuracy QCs: Within-run precision (LLOQ): Within-run accuracy (LLOQ): Within-run precision (Low, Mid, High): Within-run accuracy (Low, Mid, High): Between-run precision (LLOQ) [a]: Between-run accuracy (LLOQ) [a]: Between-run precision (Low, Mid, High): Between-run accuracy (Low, Mid, High):	 T: ≤ 6.15% [a] DHT: ≤ 9.03% T: -3.60 to 5.00% [a] DHT: -10.1 to 4.00% T: ≤ 10.6% DHT: ≤ 12.1% T: -7.80 to 7.11% DHT: -4.17 to 5.23% T: 6.12% DHT: 8.65% T: 2.00% DHT: -2.90% T: ≤ 9.94% DHT: ≤ 8.96% T: 0.00% DHT: 0.00%
			Stability	

Validation Report	Clinical Studies Supported	Analyte (Matrix)	Method Description and Performance	
			Post preparative (ambient): Reinjection (ambient): Short-term (ambient): Freeze/thaw (-80°C): Long-term (-80°C):	T: 62 hours DHT: NR T: 62 hours DHT: 62 hours T: 29 hours DHT: 29 hours T: 5 cycles DHT: 5 cycles T: 249 days DHT: 249 days
			Overall recovery	T: 95.8% DHT: 92.3%
			Matrix effects: Precision Accuracy	 T: 11.0% DHT: 12.6% T: -1.78% DHT: 0.655%

NR = Not Reported
a Statistics shown exclude statistical outlier based on Grubbs' test (95% confidence rate)

Source: Table 10, Module 2.7.1
Abbreviations: DHT, dihydrotestosterone; LLOQ, lower limit of quantitation; QC, quality control; RSD, relative standard deviation; T, testosterone

Table 45. Summary of Bioanalytical Method Validation Results for TU and DHTU in NaF/EDTA Plasma

Validation Report	Clinical Studies Supported	Analyte (Matrix)	Method Description and Performance	
The LC/MS/MS Quantification of Testosterone Undecanoate between 1.00 and 1000 ng/mL and Dihydrotestosterone Undecanoate between 0.500 and 500 ng/mL in Human Plasma Analytical method reference: (b) (4) (b) (4) Method validation reference: (b) (4) Report No. (b) (4)	SOV-TU-PK2013 MRS-TU-2019 MRS-TU-2019EXT	TU and DHTU (NaF/EDTA Plasma)	The analytes, testosterone undecanoate and dihydrotestosterone undecanoate, and internal standards (IS), testosterone undecanoate-2,2,4,6,6-d5 and dihydrotestosterone undecanoate-d21, were extracted from 150 µL of human plasma by a liquid-liquid extraction procedure. The compounds were detected and quantified by tandem mass spectrometry in positive ion mode on an MDS Sciex API 5000 equipped with a Turbo Ionspray® interface.	
			Validated range	TU: 1 to 1,000 ng/mL DHTU: 0.5 to 500 ng/mL
			Intra-batch Precision (%RSD)	TU: ≤ 5.48% DHTU: ≤ 7.60%
			Intra-batch Accuracy (%bias)	TU: -6.00 to 3.00% DHT: -1.60 to 2.40%
			Selectivity: Mean matrix factor Precision (Low) Precision (High)	 TU: 0.905 DHTU: 0.933 TU: 3.79% DHTU: 6.39% TU: 5.80% DHTU: 6.47%
			Precision and Accuracy QCs Within-run precision (Low, Mid, High): Within-run accuracy (Low, Mid, High): Between-run precision (LLOQ): Between-run accuracy (LLOQ): Between-run precision (Low, Mid, High):	 TU: ≤ 5.49% DHTU: ≤ 6.23% TU: -2.27 to 7.33% DHTU: -1.33 to 8.27% TU: 5.48% DHTU: 12.7% TU: -4.70% DHTU: -10.6% TU: ≤ 3.91% DHTU: ≤ 6.05%

Validation Report	Clinical Studies Supported	Analyte (Matrix)	Method Description and Performance	
			Between-run accuracy (Low, Mid, High):	TU: 1.67 to 6.27% DHTU: 2.67 to 5.07%
			Stability (TU & DHTU) Post preparative (Ambient): Reinjection (Ambient): Short-term (Ambient): Freeze/thaw (-80°C): Sample handling (ice water bath, ambient centrifuge): Sample handling (ice water bath, 4°C centrifuge): Long-term sample stability(-80°C):	 155 hours 56 hours 49 hours 5 cycles 1 hour 1 hour 398 days
			Overall recovery	TU: 79.6% DHTU: 83.3%
			Matrix effects: Precision Accuracy	 TU: 3.33% DHTU: NV* TU: -3.10% DHTU: NV
			Carryover	TU: Acceptable DHTU: Acceptable

* No valid result determined

Source: Table 10, Module 2.7.1

Abbreviations: DHTU, 5α-dihydrotestosterone undecanoate; EDTA, ethylenediaminetetraacetic acid; LLOQ, lower limit of quantitation; QC, quality control; RSD, relative standard deviation; TU, testosterone undecanoate

It should be noted that the established long-term stability (-80°C) of 249 days for T in serum shown in Table 46 was further extended to 1279 days in Bioanalytical Study Report (b) (4) (issued on November 12, 2020).

For the phase 3 study, MRS-TU-2019EXT, incurred samples and quality control (QC) samples were kept at approximately -80°C until analysis. For NaF/EDTA plasma, the longest interval that occurred from the first sample draw date to last analysis date for T and DHT was 904 days. Long-term stability for T and DHT has been established for 949 days at -80°C. The longest interval that occurred from the first sample draw date for TU and DHTU to last analysis date was 473 days. It should be noted that all except 2 samples (i.e., Subject (b) (6) Visit 8, 6 hr [472 days] and Subject (b) (6) Visit 8, 20 hr [473 days]) were within the established long-term stability of 398 days at -80°C. These 2 samples which surpassed the established long-term stability period did not impact the overall outcome of the study as these samples were not taken at the Day 90, End of Treatment visit. For serum, the longest interval that occurred from the first sample draw date to last analysis date for T and DHT was 401 days which is within the established long term stability of 1279 days at -80°C.

In both NaF/EDTA plasma and serum, back-calculated concentrations were within ±15.0% of nominal concentration and ±20.0% of the nominal concentration at the lower limit of quantitation for calibration standards and at least 75% of the calibration standards met minimum required accuracy. For low, mid, and high QC samples, more than 67% of QC samples were within 15% of the nominal concentrations, and at least 50% of QC samples per level were within 15% of their nominal concentrations.

(b) (4)

- The OSIS states that the observation has no impact on study data reliability. The Agency's *Bioanalytical Method Validation Guidance* states that (b) (4) The OSIS concludes that the (b) (4) results demonstrated that there were no issues in bioanalytical method performance.

***Reviewer Comment**: While there were some issues identified with (b) (4), the Clinical Pharmacology review team concurs with the OSIS assessment that it does not have impact on the reliability of the study data. Otherwise, the acceptance criteria and performance of the total T and DHT bioanalytical methods in NaF/EDTA plasma and serum were in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods used for this application are acceptable. It should be noted that the validation and performance of the bioanalytical methods for E2 were not reviewed in detail.*

18.4.2. Individual Study Reviews

Normal T Concentration Range Determination Study (MRS-TNR2019)

This study was conducted in 105 healthy, eugonadal male subjects (≥18 and <40 years of age, with a body mass index (BMI) ≤30 kg/m^2) to define the normal T concentration range. No Kyzatrex treatments were administered in this study. Subjects were fasted for at least 8 hours before blood collection that occurred between 6 am and 10 am, and provided 2 types of samples (NaF/EDTA plasma and serum) for analysis of T and DHT.

There was good correlation between plasma and serum concentrations for both T and DHT, with high coefficient of determination (R^2) values of 0.991 and 0.992, respectively. Table 46 summarizes the normal T and DHT concentration ranges in NaF/EDTA plasma and serum derived from Study MRS-TNR2019.

Table 46. Reference Range Based on Central 95% of Population for Plasma and Serum Concentration (ng/dL) of T and DHT (N=105)

Analyte	Matrix	Reference Range (2.5th to 97.5th percentile)
Testosterone	Plasma	222.29, 800.23
	Serum	286.05, 990.72
Dihydrotestosterone	Plasma	11.32, 72.65
	Serum	16.57, 81.51

Source: Table 2, Module 2.7.3
Abbreviations: DHT, dihydrotestosterone; T, testosterone

Based on the central 95% of population (2.5% to 97.5 percentile), the normal plasma T concentration range was determined to be 222-800 ng/dL and the normal serum T concentration range was determined to be 286-991 ng/dL.

Considering the well accepted normal serum T concentration range of 300-1000 ng/dL, the Applicant's proposed normal plasma T concentration range obtained from this study is found to be acceptable from the Clinical Pharmacology standpoint.

Phase 3, Efficacy and Safety Studies (MRS-TU-2019 and MRS-TU-2019EXT)

Initially, the starting dose for the phase 3 study, MRS-TU-2019 was 600 mg TU daily, administered as 400 mg TU with the morning meal and 200 mg TU with the evening meal. MRS-TU-2019EXT was planned to be a 6-month, safety extension study of MRS-TU-2019 and to generate ambulatory blood pressure monitoring (ABPM) data. However, while the Applicant was conducting the 12-month, phase 3 study, MRS-TU-2019, they approached the Division with a proposal to restart the study and have all subjects will begin at a lower dose of 200 mg oral TU twice daily (400 mg total daily dose) with morning and evening meals and a revised titration scheme. The lower starting dose was predicted to meet the requirements of achieving normal T concentrations while reducing the potential for subjects to receive initial doses which result in higher than necessary average or maximum T concentrations.

Data from Study MRS-TU-2019 were analyzed to establish an appropriate starting dose for Study MRS-TU-2019EXT, confirm the acceptable time frame for collection of titration samples, and revise the T concentration thresholds for up- or down-titration. These topics were discussed at the April 3, 2019, Type C, Guidance meeting. Reference is made to the official meeting minutes under IND 118675 in DARRTS for the meeting outcome.

As a result, Study MRS-TU-2019EXT became the pivotal phase 3, efficacy and safety study and this review will focus on Study MRS-TU-2019EXT.

Study Design

Study MRS-TU-2019EXT enrolled male hypogonadal subjects 18-65 years of age. Hypogonadism was defined as having 2 consecutive serum T concentrations ≤281 ng/dL (i.e., lower limit of normal range for the immunoassay used for screening) based on blood samples collected between 7 am and 10 am, at least 3 days apart. The overall mean age was 50.5 years; the majority of subjects were White (76.8%; 119 of 155 subjects) followed by Black/African Americans (18.7%; 29 out of 155 subjects) and Asians (2.6%; 4 out of 155 subjects). A total of 105 (67.7%) of 155 subjects had a BMI ≥30 kg/m^2 at baseline.

All subjects received Kyzatrex starting at a total daily dose of 400 mg (200 mg with the breakfast and 200 mg with the dinner) and dose was adjusted, if needed, using the plasma-based dose titration thresholds of 400 and 900 ng/dL for up- and down-titration, respectively. The duration of treatment in MRS-TU-2019EXT study was approximately 6 months (180 days) with efficacy assessment conducted upon completion of 90 days treatment.

In this study, subjects were instructed to take Kyzatrex 30 minutes after beginning a meal, and to consume their normal diet. Participants completed a survey to identify eating patterns relating to both meal size and fat content and made meal choices for breakfast and dinner meals for in-clinic PK days. The breakfast and dinner meals were designed to deliver varying percentages of calories from fat: low-fat meals (≤20% calories from fat), normal-fat meals (>20% to 35%), and high-fat meals (>35%). All lunches were normal fat meals as no drug was administered with lunch. It should be noted that these meal choices were complemented for 3

out of the 90 days (i.e., Days 14, 42, and 90) of active treatment and therefore, did not reflect what the meal choices of the participant were for the other 87 days as there were no restrictions in meal choices for the participants on those days.

Subjects were not allowed to use any forms of T except for study drug throughout the entire study. In addition, the use of any drug that could have interfered with measurement or assessment of androgen concentrations was prohibited. These drugs must have been stopped for at least 1 month prior to study entry (6 months in the case of dutasteride). The use of over-the-counter products including natural health products (e.g., food supplements and herbal supplements) that may have affected total T concentrations within 7 days prior to the first dosing and during the course of the study was prohibited.

Blood samples for determination of plasma T concentrations were collected on Day 14 (Visit 8E) and Day 42 (Visit 10E) at predose, 1.5, 3, 4, 5, and 6 hours postdose to inform titration decisions (dose adjustments occurred on Day 28 [Visit 9E] and Day 56 [Visit 11E]). Serum samples at these same timepoints were also collected for all subjects. At each titration visit, subjects were randomized 1:1:1 to be titrated based on the plasma T concentration at 3, 4, or 5 hours (±10 min) following the morning dose. On Day 90 (Visit 12E), 24-hour serial PK samples were collected for the primary efficacy assessment, T C_{avg} after 90 days of treatment. In addition, the Applicant collected and analyzed paired plasma and serum samples from a subgroup of study participants (N=103) at their end of treatment visit on Day 90.

Development of Dose Titration Scheme

The Applicant has carried out PK modeling and concordance simulations based on the 90-day efficacy results from Study MRS-TU-2019 (total 196 observed subjects data) for determining the optimum sampling window for titration decision. While Study MRS-TU-2019 study used a window from 3-5 hours postmorning dose, the simulations also tested the effect of sampling 6 hours postdose. The total concordance (C_x vs. C_{avg}) at Visit 4 (Day 14) were approximately 82%, 92%, and 90% for C_3, C_4, and C_5 respectively, while 73% for C_6. At Visit 6 (Day 42), total concordance (C_x vs. C_{avg}) was only about 51% for C_6 while those for C_3, C_4, C_5, were at 71%, 83%, and 75%, respectively. These results confirm that the 3-5 hour postdose window is optimum.

To determine the impact of titration timepoint (3, 4, or 5 hours postmorning dose) on efficacy results, analysis of plasma T C_{avg} within the normal T concentration range after 90 days of treatment was assessed by Day 42E titration timepoint in Study MRS-TU-2019EXT (Table 47).

Table 47. Analysis of Plasma T C_{avg} Within the Normal Range After 90 Days of Treatment (Day 90E) by Day 42E Titration Timepoint, Study MRS-TU-2019EXT

		SOV2012-F1 Visit 10E/Day 42E Titration Postdose Timepoint		
Measurement at Visit 12E (Day 90E)	**Statistic**	**3 Hours (N=45)**	**4 Hours (N=42)**	**5 Hours (N=43)**
	n	44	42	41
Plasma T Cavg Within Normal Range After 90 Days	n (%)	44 (100)	38 (90.5)	40 (97.6)
Plasma T Cavg Outside Normal Range After 90 Days	n (%)	0	4 (9.5)	1 (2.4)

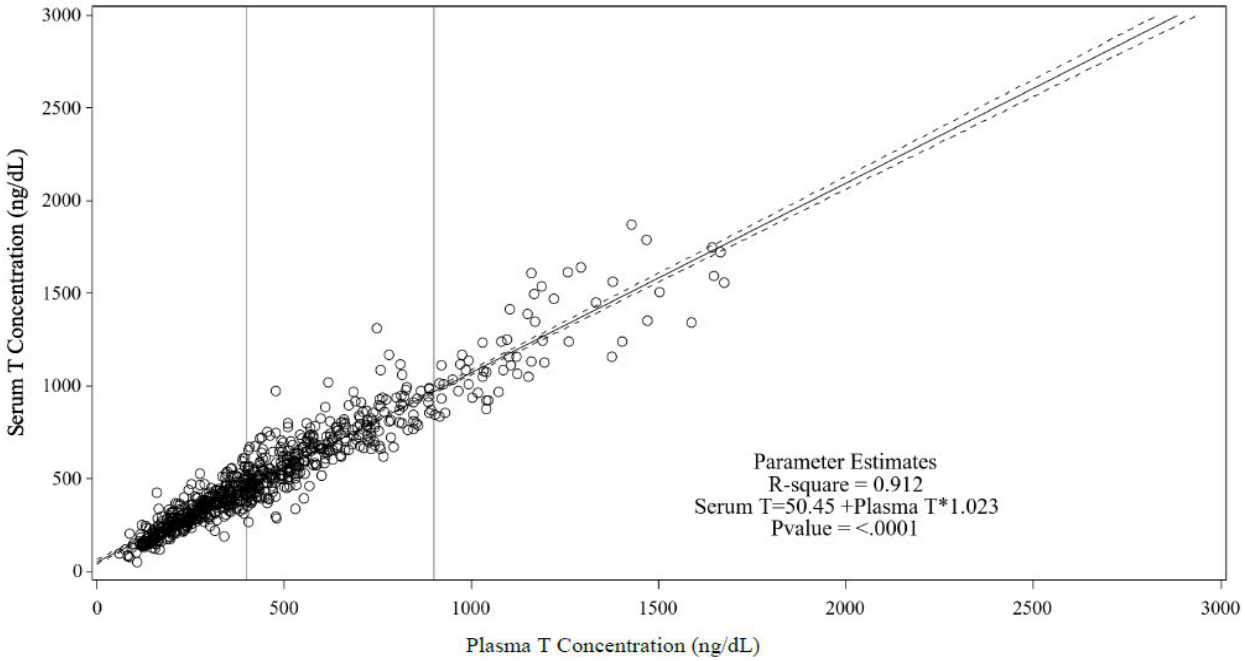
Source: Table 14.2.2.1.3.1, MRS-TU-2019EXT CSR
Abbreviations: T, testosterone

As shown above in Table 47, for more than 90% of subjects at each of the 3 titration timepoints (3, 4, or 5 hours postmorning dose), the plasma T C_{avg} was within the normal T concentration range after 90 days. Overall, no significant differences in serum or plasma C_{avg} were observed between the 3, 4, or 5-hour postdose sample collection times.

Determination of Serum-based Dose Titration Thresholds

To determine serum-based dose titration thresholds, the Applicant examined the relationship between NaF/EDTA plasma and serum T concentrations over 3-5 hours postdose window as this time window was used for dose titration Study MRS-TU-2019EXT. Figure 5 shows the regression of the serum T concentration as a function of the NaF/EDTA plasma T concentrations from Day 14 (Visit 8E) and Day 42 (Visit 10E) for 3-5 hours postdose. The vertical bars indicate the 400 and 900 ng/dL plasma titration thresholds used in Study MRS-TU-2019EXT.

Figure 5. Scatter Plots of Serum T Concentration Vs. NaF/EDTA Plasma T Concentration at 3, 4, and 5-Hours Postdose, Study MRS-TU-2019EXT



Source: Figure 14.2.2.1.4.4, Study MRS-TU-2019EXT CSR
Abbreviations: EDTA, ethylenediaminetetraacetic acid; T, testosterone; TU, testosterone undecanoate

Using the regression from Figure 5, the equation for the calculation of serum thresholds derived from the 3, 4, and 5-hour postdose regression on Days 14 and 42 is:

Serum T concentration =50.45 + (Plasma T concentration x 1.023)

The resulting serum-based dose titration thresholds for 3-5 hours postdose compared to plasma-based dose titration thresholds are shown in Table 48 below.

Table 48. Calculation of Serum-based Titration Thresholds for 3-5 Hours Postdose

Threshold	NaF/EDTA plasma (ng/dL)	Serum (ng/dL)
Up-titration	400	460
Down-titration	900	971

Source: Table 19, Module 5.3.5.3
Abbreviations: EDTA, ethylenediaminetetraacetic acid

Absorption

Table 49 summarizes the PK parameters for plasma total T and TU in patients completing at least 90 days of Kyzatrex treatment.

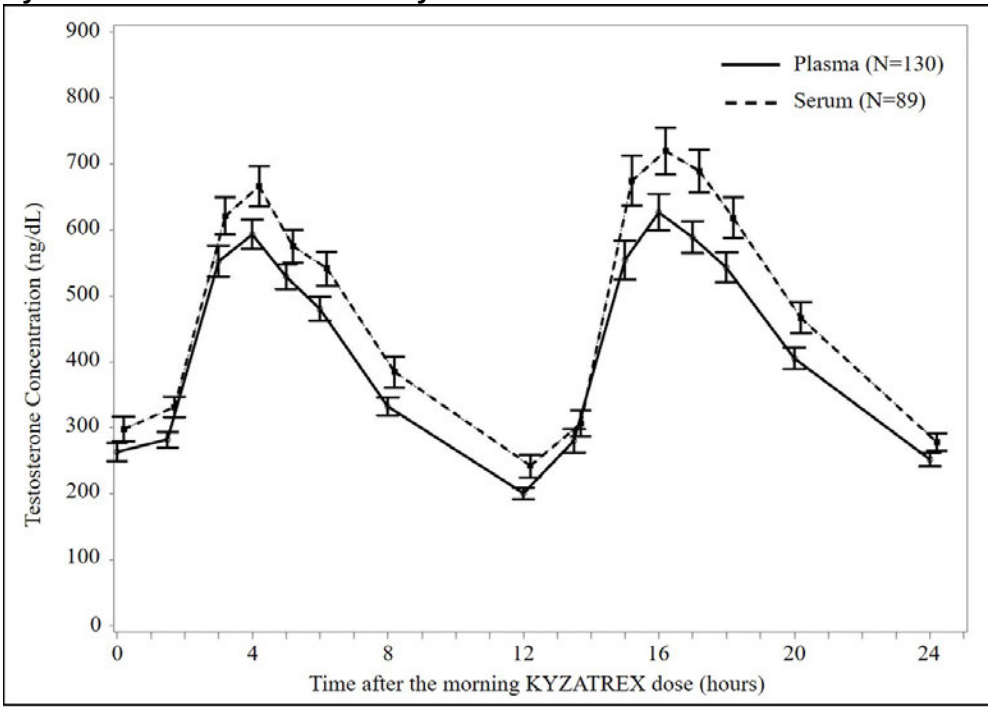
Table 49. NaF/EDTA Plasma T and TU C_{avg} and C_{max} on Day 90

PK Parameter		Plasma T (N=130)	Plasma TU (N=130)
C_{avg} (ng/dL)	n	127	119
	Mean	393.3	7806.4
	SD	113.6	4129.2
C_{max} (ng/dL)	n	130	126
	Mean	852.4	36258.9
	SD	311.3	22100.6

Source: Table 29, MRS-TU-2019 and MRS-TU-2019EXT CSR
Abbreviations: EDTA, ethylenediaminetetraacetic acid; PK, pharmacokinetic; SD, standard deviation; T, testosterone; TU, testosterone undecanoate

Figure 6 summarizes the mean plasma and serum total T PK profiles on Day 90.

Figure 6. Mean (±SEM) Concentration-Time Profiles for NaF/EDTA Plasma and Serum Total T in Kyzatrex-Treated Patients on Day 90



Source: Figure 1, Module 2.7.2
Abbreviations: EDTA, ethylenediaminetetraacetic acid; SEM, standard error of the mean; T, testosterone

DHT/T Ratio

The measured DHT concentrations increased as total T concentrations increased showing the PK profile of DHT mirrored that of total T. The plasma DHT/T ratio after 90 days of treatment for Kyzatrex was 0.2104. These values are comparable with the normal DHT/T reference range of 0.05-0.33 observed in other T replacement therapies (Wang *et al.*, 2000; Diver *et al.*, 2003).

Primary Efficacy Endpoint

The primary efficacy endpoint for Study MRS-TU-2019EXT was the percentage of subjects with a NaF/EDTA plasma T C_{avg} within the normal T concentration range after 90 days of treatment. A total of 155 subjects were enrolled and received at least one dose of Kyzatrex (extension treated set (EXTS) population).

A serum substudy was conducted to provide T concentrations in serum samples obtained simultaneously at Visit 12E (Day 90) with the NaF/EDTA plasma samples used for the primary efficacy analysis. The serum substudy included 103 subjects. As shown in Table 500 below, the percentage of subjects with T C_{avg} in the normal T concentration range was similar whether measured in NaF/EDTA plasma or serum.

In Study MRS-TU-2019EXT, multiple number of subjects from Clinical Site 104 had NaF/EDTA plasma T concentration results paradoxically higher than serum T concentrations obtained at the same time. As a result, the Applicant excluded all subjects from this site (N=16) for efficacy

analysis. The modified EXTS (mEXTS) population that was used for the primary efficacy and secondary PK endpoint analysis excluded the 16 subjects from Site 104, comprised of 139 subjects. The primary efficacy endpoint was met regardless of the exclusion of Site 104 as shown in Table 50.

Table 50. Summary of Primary Efficacy Analysis in NaF/EDTA Plasma or Serum, With or Without Site 104 Data

Measurement	Statistic	NaF/EDTA Plasma Without Site 104	NaF/EDTA Plasma With Site 104	Serum Without Site 104	Serum With Site 104
# Subjects Randomized	N	139	155	89	103
Average Total Testosterone (T Cavg) After 90 Days Observed (ng/dL)	n	127	143	88	102
	Mean (SD)	393.3 (113.60)	411.5 (132.59)	451.9 (131.40)	452.5 (130.88)
	CV (%)	28.9	32.2	29.1	28.9
	Median	382.3	392.9	439.8	439.8
	Min, Max	145, 813	145, 943	183, 869	183, 869
	Geo. Mean	377.7	392.1	432.9	433.7
	Geo. CV (%)	29.4	31.8	30.8	30.4
T Cavg Within Normal Range After 90 Days Observed	n (%)	122 (96.1)	136 (95.1)	77 (87.5)	90 (88.2)
	95% CI	(92.7% to 99.4%)	(91.6% to 98.6%)	(80.6% to 94.4%)	(82.0% to 95.4%)
T Cavg Missing at Visit 12 E (Day 90E)	n (%)	12 (8.6)	12 (7.7)	1 (1.1)	1 (1.0)
T Cavg Within Normal Range After 90 Days Using WCS* Imputation	n (%)	122 (87.8)	136 (87.7)	7 (86.5)	90 (87.4)
	95% CI	(82.3% to 93.2%)	(82.6% to 92.9%)	(79.4% to 93.6%)	(81.0% to 93.8%)

* WCS: Worst Case Scenario
Source: Table 22, 23, 25, and 26, MRS-TU-2019EXT CSR
Abbreviations: CI, confidence interval; CV, coefficient of variation; EDTA, ethylenediaminetetraacetic acid; SD, standard deviation; T, testosterone

Key Secondary (C_{max}) Endpoint

The key secondary endpoint were the percentage of Kyzatrex-treated subjects on Day 90 with plasma T C_{max} within the predetermined ranges summarized in Table 51.

Table 51. Key Secondary Endpoint Thresholds

Plasma C_{max} Threshold	Plasma Range (ng/dL)	Target Percentage of Population
≤ 1.5 x ULN	≤1200	≥85%
>1.8 x ULN to ≤2.5 x ULN	>1440 to ≤2000	≤5%
>2.5 x ULN	>2000	0%

ULN = upper limit of normal of testosterone in plasma (800 ng/dL) collected in NaF/EDTA tubes as determined in MRS-TNR2019. The approach to calculation of C_{max} thresholds was recommended in FDA Written Response to Marius dated 27 Jan 2020.
Source: Table 3, Module 2.7.3
Abbreviation: EDTA, ethylenediaminetetraacetic acid

Table 52. Summary of Secondary PK Endpoint Analysis in NaF/EDTA Plasma, With or without Site 104 Data

Measurement	Statistic	SOV2012-F1 N=139 Without Site 104 NaF/EDTA Plasma	SOV2012-F1 N=155 With Site 104 NaF/EDTA Plasma
Maximum Total Testosterone (T Cmax; ng/dL)	n	130	146
	Mean (SD)	852.37 (311.329)	960.04 (543.983)
	CV (%)	36.5	56.7
	Q1, Q3	635.52, 1031.63	655.60, 1112.50
	Median	796.14	829.37
	Min, Max	197.4, 1975.6	197.4, 4500.3
	Geo. Mean	798.11	862.17
	Geo. CV (%)	38.4	46.8
Plasma: T Cmax <=1200 ng/dL T Cmax 1440 to 2000 ng/dL T Cmax >2000 ng/dL	n (%)	 114 (87.7) 5 (3.8) 0	 119 (81.5) 9 (6.2) 5 (3.4)

Source: Table 72, MRS-TU-2019EXT CSR
Abbreviations: CV, coefficient of variation; EDTA, ethylenediaminetetraacetic acid; PK, pharmacokinetic; SD, standard deviation; T, testosterone

While the key secondary endpoint (C_{max}) was not met when including all 155 subjects, the key secondary PK endpoint (C_{max}) was met after excluding subjects from Site 104 as shown in Table 52.

Dose Timing Relative to Meal Study (SOV-TU-PK2017)

In order to assess the food-drug interaction potential, first, the Applicant conducted a study (SOV-TU-PK2017) to assess the effect on T exposure when a single oral dose of Kyzatrex 400 mg (2 x 200 mg capsules) was administered with 240 mL of water at defined times relative to the start of a standardized high-fat, high caloric breakfast in hypogonadal males. The defined times were immediately before starting the breakfast, 30, or 60 minutes after the start of breakfast. Breakfast was completed in 30 minutes. Each study treatment administration shown below occurred after a supervised fast of at least 8 hours. PK samples were collected in NaF/EDTA tubes each period for up to 12 hours postdose.

- Treatment A: Kyzatrex administered within 2 minutes prior to the start of the meal
- Treatment B: Kyzatrex administered 30±1 minute after the start of the meal
- Treatment C: Kyzatrex administered 60±1 minute after the start of the meal

Table 53. Geometric Mean Ratios (B/A, C/A, and B/C) and 90% CIs for AUC_{0-12}, AUC_{0-inf}, and C_{max} for Baseline Uncorrected T

PK Parameters	Comparison (1 vs. 2)	Geometric LSM 1	Geometric LSM 2	Point Estimate (1/2 Ratio)	90% CI
AUC_{0-12} (h·ng/dL)	Treatment	78250.68	46313.24	168.96	143.75, 198.59
AUC_{0-inf} (h·ng/dL)	B vs. A	92403.98	67840.50	136.21	118.85, 156.10
C_{max} (ng/dL)		12339.87	6269.27	196.83	163.87, 236.43
AUC_{0-12} (h·ng/dL)	Treatment	85717.22	46015.01	186.28	160.06, 216.80
AUC_{0-inf} (h·ng/dL)	C vs. A	100530.9	66298.01	151.63	131.65, 174.65
C_{max} (ng/dL)		15009.61	6219.93	241.31	205.21, 283.78
AUC_{0-12} (h·ng/dL)	Treatment	85565.69	78516.58	108.98	102.30, 116.09
AUC_{0-inf} (h·ng/dL)	C vs. B	100248.2	92806.89	108.02	100.77, 115.78
C_{max} (ng/dL)		14996.47	12384.81	121.09	110.53, 132.65

Source: Tables 1, 2, and 3, Clinical Information Amendment (MRS-TU-PK2017), Submitted on June 16, 2021.
For geometric LSM, Column 1 is for the Test treatment and Column 2 is for the Reference treatment. For example, for the comparison between Treatment B (Test) vs. A (Reference), Column 1 is for Treatment B and Column 2 is for Treatment A.
Abbreviations: AUC_{0-12}, area under the plasma concentration-time curve from hour 0 to hour 12; AUC_{0-inf}, area under the plasma concentration-time cruve from time zero to infinity; CI, confidence interval; C_{max}, maximum plasma drug concentration; LSM, least squares mean; PK, pharmacokinetic; T, testosterone

Baseline-uncorrected plasma T AUC_{0-12} values following TU administration 30 or 60 minutes after a meal were 1.7-fold and 1.9-fold, respectively, higher compared to that of TU administration immediately prior to a meal. When Kyzatrex was administered 60 minutes after a meal, baseline-uncorrected AUC values were similar while C_{max} slightly increased (1.21-fold) compared to dosing 30 minutes after a meal.

Food Effect and Alcohol Interaction Study (MRS-TU-PK2018)

This was a single center, open-label, randomized, single-dose study with a 5-period, 5-sequence design. A single oral dose of Kyzatrex (4 x 100 mg capsules) was administered with meals of various fat content (fixed caloric content) and with 240 mL water or alcohol, at 30 (±5) minutes after starting the meal. Meals were completed within 30 minutes. Subjects were randomized to receive each of Treatments A, B, C, D, and E in Periods 1 to 5 of the study:

- Treatment A: Kyzatrex administered under fasting conditions
- Treatment B: Kyzatrex administered with a low fat (16%) breakfast
- Treatment C: Kyzatrex administered with a moderate fat (33%) breakfast
- Treatment D: Kyzatrex administered with a high fat (45%), high caloric breakfast
- Treatment E: Kyzatrex administered with a high fat (45%), high caloric breakfast and 240 mL of 20% alcohol (in water). Subjects were required to consume all alcohol within 30 minutes.

For all study treatments, no food was allowed for at least 4 hours after the meal and dosing. Except for water given with study medication (Treatments A to D), or alcohol 20% (Treatment E only), no fluids were allowed from 1 hour predose until 1 hour postdose. Water was provided *ad libitum* at all other times. Plasma PK samples were collected in NaF/EDTA tubes each period for up to 24 hours postdose.

Table 54. Geometric Mean Ratios (B/A, C/A, D/A, and E/A) and 90% CIs for AUC_{0-24} and C_{max} for Baseline Uncorrected T to Assess Food Effect

PK Parameters	Comparison (1 vs. 2)	Geometric LSM 1	Geometric LSM 2	Point Estimate (1/2 Ratio)	90% CI
AUC_{0-24} (h·ng/dL)	Treatment	7292.95	5325.43	136.95	123.15, 152.28
C_{max} (ng/dL)	B vs. A	646.64	340.50	189.91	160.79, 224.31
AUC_{0-24} (h·ng/dL)	Treatment	10135.42	5434.37	186.51	165.40, 210.30
C_{max} (ng/dL)	C vs. A	1106.26	340.50	324.89	266.62, 395.90
AUC_{0-24} (h·ng/dL)	Treatment	10424.43	5374.65	193.96	174.81, 215.19
C_{max} (ng/dL)	D vs. A	1150.45	340.50	337.87	286.97, 397.81
AUC_{0-24} (h·ng/dL)	Treatment	9778.77	5408.34	180.81	161.66, 202.23
C_{max} (ng/dL)	E vs. A	1212.33	340.49	356.05	311.41, 407.09
AUC_{0-24} (h·ng/dL)	Treatment	9778.77	10424.43	93.81	87.02, 101.13
C_{max} (ng/dL)	E vs. D	1212.33	1150.45	105.38	92.39, 120.20

Source: Tables 4-7, Appendix 2, SDN 020, Submitted on June 16, 2021
Revised Table 39, Module 5.3.5.3, Submitted on September 24, 2021
For geometric LSM, Column 1 is for the Test treatment and Column 2 is for the Reference treatment. For example, for the comparison between Treatment B (Test) vs. A (Reference), Column 1 is for Treatment B and Column 2 is for Treatment A.
Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from hour 0 to hour 24; CI, confidence interval; C_{max}, maximum plasma drug concentration; LSM, least squares mean; PK, pharmacokinetic; T, testosterone

When Kyzatrex was given with 16%, 33%, and 45% fat breakfast, the exposure (AUC_{0-24h}) was increased by 37%, 87%, and 94%, respectively, compared to when given under fasted conditions. There was no effect on T PK when Kyzatrex was administered with 20% alcohol along with a high fat meal (i.e., point estimates for AUC_{0-24h}: 93.8%; C_{max}: 105%) versus a high fat meal alone.

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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 213953
Supporting document/s:	SDN 0001; SDN 0007; SDN 0009; SDN 0012 (Original-1)
Applicant's letter date:	12/31/2020; 2/24/2021; 2/26/2021; March 23, 2021
CDER stamp date:	12/31/2020; 2/24/2021; 2/26/2021; March 23, 2021
Product:	Testosterone undecanoate (KYZATREX)
Indication:	Treatment of primary or hypogonadotropic hypogonadism
Applicant:	Marius Pharmaceuticals, LLC
Review Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Reviewer:	Yangmee Shin, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	Christine Nguyen, MD
Project Manager:	Samantha Bell

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1 Executive Summary

1.1 Introduction

Marius Pharmaceuticals submitted an NDA for oral testosterone undecanoate (TU) capsules (SOV2012-F1) for the treatment of primary and hypogonadotropic hypogonadism under a 505(b)(2) regulatory pathway, relying on its own data and on published scientific literature.

The proposed starting dose is 200 mg TU twice daily (400 mg TU daily total), once in the morning and once in the evening. Dose adjustments can be made starting with a minimum dose of 100 mg once daily in the morning and a maximum dose of 400 mg TU twice daily (once in the morning and once in the evening; 800 mg daily total) based on T threshold plasma levels of < 460 and > 971 ng/dL for up- and down-titration, respectively.

The new oral TU product is formulated in a (b) (4) designed to promote TU absorption into the intestinal lymphatics. The new formulation also contains excipients that are either not present (phytosterol esters) or exceed levels ((b) (4), DL-α-tocopherol acetate) in currently approved oral products.

The sponsor's nonclinical studies conducted to support the NDA include: in vitro binding studies of TU, 5α-dihydrotestosterone undecanoate (DHTU), and a major excipient component of phytosterol esters ((b) (4)); a distribution and excretion study in male rats; a 13-week repeated dose toxicology study in male dogs; and a fertility study in male rats. These studies were requested primarily to evaluate the safety of the phytosterol esters excipient that may exhibit affinity for the same targets and/or affect the PK/toxicity profile of the TU product due to similarities in structure to sex steroids and for accumulation in target organ tissues (e.g., adrenal gland, gonads, liver). The Division was concerned that the proposed TU formulation in (b) (4) is highly lipophilic and may accumulate in lipid-rich and/or well-perfused tissues and organs such as the adrenal gland, gonads, liver, kidney, fat, and heart following repeated administration. In addition, the sponsor submitted published literature references to support the chronic toxicology, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology of testosterone (T), the active moiety of TU, for chronic use of the new oral formulation.

Additional information including acceptable daily intake levels and CFR references were provided by the sponsor to support use of the excipients that need to be qualified. In silico (computational) assessments, in vitro mutagenicity assays, and in vitro plasma stability studies were conducted to qualify the degradants exceeding acceptance criteria in long-term stability studies.

1.2 Brief Discussion of Nonclinical Findings

In receptor binding studies to both estrogen and androgen receptor, TU, DHTU, and the major phytosterol ([(b) (4)]) had no significant binding for estrogen receptor at up to the concentrations tested. Androgen receptor binding was up to 56.3% for TU, up to 19.3% for DHTU, and up to [(b) (4)]% for [(b) (4)]. The highest concentrations tested for TU (10 µM, ~456700 ng/dL), DHTU (5 µM, ~229350 ng/dL), and [(b) (4)] ng/dL) were approximately 12-fold, 17-fold, and [(b) (4)] fold higher than the mean plasma C_{max} levels of the same entities in humans taking the maximum dose of 400 mg TU, BID, suggesting that TU, DHTU, and [(b) (4)] may not significantly affect the ligand-specific agonist binding to estrogen or androgen receptor at clinically relevant C_{max} concentrations. The low androgen binding for TU and DHTU suggests that the T esters may not possess the androgenic activity and may act instead via active metabolites including T.

Following a single oral administration to male CD rats at [(b) (4)] mg/kg (~40 mg/kg [^{14}C]-TU) using the proposed formulation with or without phytosterol esters, the distribution of radioactivity into tissues exhibited a maximum concentration between 2 to 6 hours post-dose. The highest concentration was observed in the GI tract (small intestine, stomach), reproductive organs (epididymis, prostate, epididymal white fat, seminal vesicle, testes), liver, and kidneys, with the muscle and skin accounting for the lowest concentration independent of formulations used. Radioactivity was below the limit of quantification at 168 hour post-dose in most tissues except the epididymis for the formulation with phytosterols ([(b) (4)] mg) and the liver for the formulation without phytosterols. Drug-related radioactivity was primarily excreted into feces. The prolonged radioactivity in the epididymis at the final sampling time of 168 hours for the formulation containing phytosterol esters (half-life unknown) suggests potential tissue retention and/or accumulation of the excipient and/or the drug-related materials.

In the 13-week toxicology study in male dogs, treatment-related effects were noted in the adrenal glands (slight vacuolation of the zona fasciculata) and reproductive organs including the testis (small size associated with marked germ cell depletion and Leydig cell atrophy), epididymis (marked aspermia), and prostate gland (increased size associated with moderate glandular hypertrophy/hyperplasia) in TU groups with or without phytosterol esters. While the systemic exposures to TU and its metabolites were less than dose-proportional, the exposures to phytosterol esters were similar between the low-dose (1X) and high-dose (2X) groups, suggesting saturation of absorption of the phytosterol esters. No significant differences were observed in plasma levels of TU and its metabolites or estradiol levels with or without phytosterol esters under the conditions of the study. Following a 4-week drug-free period, the findings in the testes (germ cell depletion), epididymides (aspermia), and adrenal glands (vacuolation of the zona fasciculata) were fully reversed in treated groups without phytosterol esters, but not in the high-dose group with phytosterol esters. The non-reversible nature of target organ findings at the high dose of TU in the presence of phytosterol esters in the dog plasma (no half-life provided) suggests the potential role of phytosterol esters on the persistent target organ toxicity.

These findings occurred at exposures of T less than or comparable to the maximum proposed human dose (400 mg BID) based on the maximum $AUC_{0\text{-}24h}$ (~38000 ng·hr/dL) and the maximum C_{max} (~1800 ng/dL) measured in male subjects (Study #MRS-TU-2019EXT). The mean plasma exposures to TU, DHTU, T, and dihydrotestosterone (DHT) were approximately 3-, <1-, 2-, and 2-fold the $AUC_{0\text{-}24h}$ and approximately 6-, <1-, 4-, and 3-fold the C_{max}, respectively, of the mean human exposure to TU at 400 mg TU, BID. The plasma phytosterols measured in this study were approximately (b) (4)-fold the mean $AUC_{0\text{-}24h}$ and C_{max} for (b) (4), respectively, at 400 mg TU, BID (Study #SOV-TU-PK2013).

In the male fertility study where males were dosed for 71 to 73 days (prior to the initiation of the cohabitation period, 1 to 4 days during the cohabitation period, and for a minimum of 6 days and a maximum of 11 days following cohabitation), treatment-related findings included decreased body weight gains and reproductive organ weights for males, reduced fertility, pre-implantation loss associated with reduced mean number of implantation sites, reduced litter size and lower mean number of viable fetuses per litter in untreated gravid females, compared to the control group at the oral dose of (b) (4) mg/kg BID ((b) (4) mg/day/day), corresponding to ~2 times the mean $AUC_{0\text{-}24h}$ for T and DHT and 2-4 times the mean C_{max}, respectively, at 400 mg BID oral TU.

Overall, the information and data provided to support safety of the new oral TU product are acceptable. The observations in the toxicology study in male eugonadal dogs and the fertility study in male eugonadal rats are expected androgenic effects of T. The findings in the adrenal gland (vacuolation of the zona fasciculata) are of unknown clinical significance. However, these were observed at T levels above the baseline AUC and at C_{max} exposures that would likely not occur in hypogonadal men exposed to T in the eugonadal range. The results from the submitted studies suggest that phytosterol esters in this formulation are unlikely to affect the pharmacology, toxicity, or pharmacokinetic profile at the anticipated mean plasma concentrations of TU and its metabolites up to the levels within the exposure achieved in clinical trials.

1.3 Recommendations

1.3.1 Approvability

The current submission contains adequate information to support approval of NDA 213953 via a 505(b)(2) pathway from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

Additional nonclinical studies are not requested at this time.

1.3.3 Labeling

The sponsor submitted updated labeling on February 26, 2021 including literature references to support the proposed language for nonclinical labeling sections.

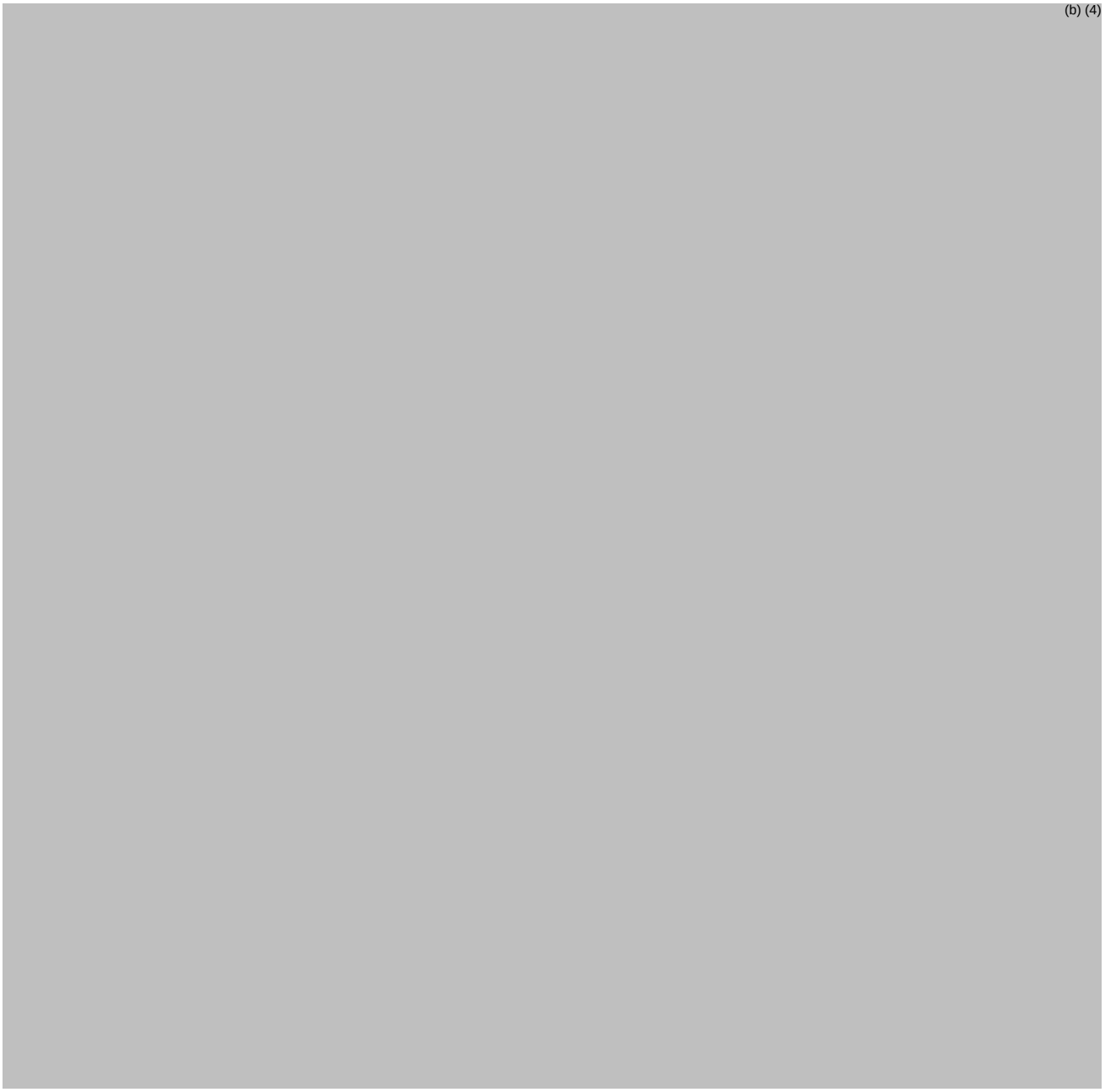
A final labeling review will be conducted under separate review. The Division plans to issue a Complete Response due to outstanding clinical and clinical pharmacology deficiencies.

The following annotated labeling represents edits made to the prescription label as of September 30, 2021. The final label will reflect any additional edits that have been agreed by the nonclinical team.

The recommended PLLR label in Section 8 is adopted from the previously approved and labeled T products, JATENZO®, XYOSTED®, AndroGel® 1.62%, and AndroGel 1%. The revisions are limited to sections where the text has been altered (in red) or deleted (strikethrough).

FULL PRESCRIBING INFORMATION

(b) (4)



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

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 5949-44-0

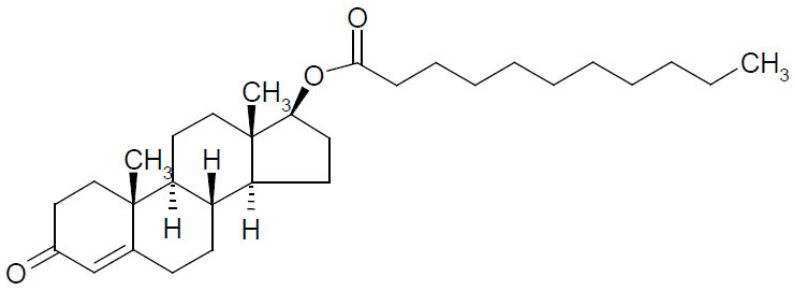
Generic Name: Testosterone undecanoate

Code Name: SOV2012-F1

Chemical Name: 3-Oxoandrost-4-en-17β-yl undecanoate; Androst-4-en-3-one, 17-[(1-oxoundecyl)oxy]-(17β)

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 118675
- NDA 209863 (Xyosted®, subcutaneous TE); NDA 206089 (Jatenzo®, oral TU); 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)

2.3 Drug Formulation

Opaque, white (b) (4), oval or oblong shape, soft gelatin capsules containing (b) (4) TU (b) (4).

The product is packaged in a high density polyethylene bottle with polypropylene screw top and sealed with a 1 mm induction-sealed liner. The drug product is manufactured, packaged and labeled at (b) (4).

Table 1: Composition of SOV2012-F1 Capsules, 200 mg, 150 mg and 100 mg

Component	Quality Standard	Function	(b) (4)	Unit Dose 200 mg	Unit Dose 150 mg	Unit Dose 100 mg
Testosterone Undecanoate	In-house, DMF# (b) (4)	Active ingredient		200.0	150.0	100.0
(b) (4) (propylene glycol monolaurate, (b) (4))	USP, DMF# (b) (4)					(b) (4)
Phytosterol Esters as (b) (4)	In-house, DMF# (b) (4)					
(b) (4) (Polyoxyl 40 Hydrogenated Castor Oil)	USP					
DL-alpha-tocopheryl acetate (Vitamin E)	USP					
Total fill (b) (4)	-	-	(b) (4)			(b) (4)
Approximate Total (b) (4) Shell Weight (mg)	In-house	Capsule	1 capsule shell			
Approximate Total Drug Product Weight (mg)	-	-	1 capsule			

Table 2: Composition of Capsule Shell for 100 mg, 150 mg, and 200 mg

Component	Function	Quality Standard	Unit Formulation (%)[1]	Unit Dose 200 mg[2]	Unit Dose 150 mg[2]	Unit Dose 100 mg[2]
Titanium dioxide						(b) (4)
Glycerin						
Sorbitol (b) (4)						
Purified Water						
Gelatin (b) (4)						
						(b) (4)
(b) (4) Red imprinting ink						(b) (4)
Approximate (b) (4) Shell Weight (mg)	-	-	-			(b) (4)
						(b) (4)

2.4 Comments on Novel Excipients

Following review of the submitted studies and information, all excipients are now considered to be qualified.

The proposed formulation contained excipients that are either not present (phytosterol esters) or exceed levels ((b) (4) , DL-α-tocopherol acetate) in currently approved orally administered products. The sponsor conducted a 13-week oral toxicology study in male dogs using the formulation containing these excipients. The sponsor also provided additional information including acceptable daily intake levels and CFR references, relying on published literature or DMF with appropriate Letter of Authorization to support use of the excipients.

The amount ((b) (4) mg in 800 mg/day) of sorbitol (b) (4) in the soft capsule shell is within the approved maximum daily exposure amount of (b) (4) mg in oral (b) (4) based on FDA Inactive Ingredient Database (IID).

2.5 Comments on Impurities/Degradants of Concern

There are no impurity issues. The justification of specifications provided to qualify the individual impurities for the drug substance and the drug product is acceptable.

The drug product contains 4 (b) (4) degradation products that exceeded qualification thresholds per ICH Q3B(R2) guidance (0.2% or 3 mg/day, whichever is lower), including (b) (4) , which were identified during long-term stability testing. The sponsor provided additional data and information including in silico and in vitro studies to justify the proposed impurity specifications.

The following table summarizes the proposed specification limits for the identified degradants in the oral TU formulation.

Table 3: Proposed Specification Limits for Identified Degradants in SOV2012-F1

(b) (4)

The [redacted] degradant impurity was initially identified as [redacted] but was subsequently identified and confirmed as [redacted]. The sponsor stated that [redacted]. A sample of the isolated material stirred with 0.1 N HCl generated a mixture of the [redacted] and [redacted]. Finally, treatment of TU with peracetic acid was shown to generate in small quantities the RRT [redacted] degradation product.

The degradant [redacted] also exists as [redacted], but only one [redacted] appears to be present at levels above the ICH Q3B qualification limit of 0.2%. For the 3 degradants with [redacted].

Qualification of [redacted], and [redacted] at the proposed specification limits was based on ICH Q3B(R2) and ICH M7(R1) guidelines, and information obtained from the published scientific literature. The sponsor also provided published studies suggesting the potential formation of [redacted] and its conversion to [redacted] and [redacted] as well as the interconversion of [redacted] and [redacted]. Additionally, in human and dog plasma [redacted], the formation of [redacted] and [redacted] were observed (see **Special Toxicology Studies** section for detailed review).

The sponsor did not perform additional tests for [redacted] and elemental impurities present in the oral capsule based on the risk assessments that the product complied with ICH [redacted] and USP<[redacted]> without testing. The sponsor also noted that the product including the [redacted] manufacturing equipment and excipients used in the soft gelatin capsule manufacture complied with ICH Q3D and USP<232> acceptance criteria for all of the Class 1, 2A, 2B, and 3 elements. The predicted maximum levels of the potential elemental impurities in the drug product indicate that the elemental impurities for all ICH Class 1, 2A, and any intentionally added elements are [redacted]% of the permissible daily exposure (PDE) limit (see CMC Review for details).

2.6 Proposed Clinical Population and Dosing Regimen

KYZATREX is indicated for the treatment of male primary and hypogonadotropic hypogonadism associated with a deficiency or absence of endogenous T in adult males (≥18 years old) at the recommended starting dose of 200 mg, taken orally twice daily-once in the morning and once in the evening [redacted]. The minimum recommended dose is 100 mg once daily in the morning and the maximum recommended dose is 400 mg TU (two capsules) twice daily. For total daily doses greater than 100 mg, administer the same dose in the morning and evening.

To ensure proper dose adjustment, the proposed label recommends measuring serum T concentrations 3-5 hours after the morning dose [redacted]. Adjust the dose based on this serum

T measurement as shown in table below and wait 7 days after starting treatment or adjusting the dose before checking the serum T concentration. Thereafter, periodically monitor serum T concentrations 3-5 hours after the morning dose.

The following sponsor's table summarizes the KYZATREX dosage adjustment proposal based on the revised labeling submitted on March 16, 2021.

Table 4: KYZATREX Dose Adjustment Scheme

(b) (4)

2.7 Regulatory Background

The enanthate, cypionate, and undecanoate esters of T are approved in the United States as intramuscular or subcutaneous injections for use in T replacement therapy in adults. Jatenzo®, oral TU was approved in 2019 for adult men for the same indication in the United States.

The original proprietor for the oral TU product examined in this review, SOV Therapeutics Inc., conducted the requested nonclinical studies. Marius Pharmaceuticals LLC has acquired all rights and responsibilities to the IND February 16, 2017. Marius submitted the NDA under a 505(b)(2) regulatory pathway, seeking approval of the oral formulation as a priority review designation. In a 74-day letter sent on March 8, 2021, the Division denied the sponsor's request for priority review designation. The Division does not believe that SOV2012-F1 provides a significant improvement in efficacy or

safety over the available products indicated to treat this condition although male hypogonadism is a serious condition.

There were multiple communications regarding the nonclinical information relied upon in the sponsor's 505(b)(2) application before a 74-day letter was issued on March 8, 2021. In the initial NDA submission, the sponsor provided conflicting statements about what information they plan to reference for their planned 505(b)(2) submission, with some sections noting (b) (4) to support the nonclinical information.

In response to the Division request for clarification of the reliance of information to support the nonclinical requirements for the NDA, the sponsor submitted additional information including literature references on February 15 and 26, and March 3, 2021, with the intent of relying on published literature in conjunction with their own conducted studies, not relying on the Agency's previous findings of safety or efficacy for any specific listed drug for gaining approval of the application. Additional published literature references were submitted to support the chronic use of the product on March 23, 2021 in response to the Division request in the 74-day letter. Information to support the nonclinical sections of the labeling is derived from nonclinical literature but will be modeled after the most recently approved oral TU products Xyosted® and Jatenzo® labels, which also used nonclinical literature to support labeling.

3 Studies Submitted

3.1 Studies Reviewed

- In Vitro Pharmacology Study of (b) (4) (Study 100014897)
- In Vitro Pharmacology Study of Dihydrotestosterone Undecanoate (Study 100015477-DHTU)
- In Vitro Pharmacology: Study of Testosterone Undecanoate (Study 100015477-TU)
- Validation of an Ultra Performance Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection for the Determination of Testosterone (0.4 to 400 mg/mL) and Dihydrotestosterone (0.4 to 200 ng/mL) in Dog NaF / Na_2EDTA Plasma (Study #135124AJCE)
- Validation of a High Performance Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Testosterone Undecanoate (12 to 12000 ng/mL) and Dihydrotestosterone Undecanoate (3 to 3000 ng/mL) in Dog NaF / Na_2EDTA Plasma (Study #135125AJCG)
- Validation of an Ultra Performance Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection for the Determination of Testosterone (0.4

to 400 ng/mL) and Dihydrotestosterone (0.4 to 40 ng/mL) in Rat NaF / Na_2EDTA Plasma (Study #135126AJCI)

- Thirteen-Week Oral Gavage Toxicity Study of SOV Oral Testosterone Undecanoate Formulation (SOV2012-F1) in Male Beagle Dogs to Evaluate Any Effect of Excipients (GLP)- Final Bioanalytical Report (Study #140056)
- Interference Evaluation of Testosterone, Dihydrotestosterone, Testosterone Undecanoate and Dihydrotestosterone Undecanoate in an Ultra Performance Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection for the Determination of Estradiol (1 to 200 pg/mL) in Dog NaF / Na_2EDTA Plasma (Study #145024AJQS)
- Validation of an Ultra Performance Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection for the Determination of Estradiol (1 to 200 pg/mL) in Dog NaF / Na_2EDTA Plasma (Study #145024AJQS)
- Distribution and Excretion of (b) (4) in Male Sprague-Dawley Rats (Study #R&D/14/0630)
- Thirteen-Week Oral Gavage Toxicity Study of SOV Oral Testosterone Undecanoate Formulation (SOV2012-F1) in Male Beagle Dogs to Evaluate Any Effect of Excipients (GLP) (Study #0470DS97.001)
- Mutagenicity Assessment of (b) (4) as Determined by a Bacterial Reverse Mutation Assay (Study #52618.00201DS)
- Genotoxicity Test of (b) (4) in an In Vitro Micronucleus Assay in Human TK6 Cells (Study #52618.00202DS)
- A Fertility Study with Testosterone Undecanoate Formulation (SOV2012-F1) Administered Twice Daily by Oral Gavage in Male Rats, Including a Toxicokinetic Evaluation (Study #0325RS97.001)
- Stability Evaluation of (b) (4) in Human and Dog Plasma Using LC-MS/MS (Study #MAR02-001)
- The Mutagenic and Toxic Potential of 3 Testosterone Undecanoate Degradation Products: (b) (4) and (b) (4) (Study #MRS-NC-01)
- ICH M7 Evaluation of (b) (4) (Study # (b) (4) -2020)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

IND 118675

4 Pharmacology

4.1 Primary Pharmacology

No studies were conducted. The pharmacology of T, the active moiety of TU is well-documented.

4.2 Secondary Pharmacology

- Androgen binding activity of TU with mean % inhibition of -10.1 to 41.3% at 0.1, 1, and 10 µM; DHTU of 4.1 to 15.4% at 0.5 and 5 µM; and (b) (4) µM using [^{3}H]methyltrienolone in cytosol LNCaP cells
- No significant estrogen binding activity of TU with mean % inhibition of -0.6 to 8.8% at 0.1, 1, 10 µM; DHTU of 4.9 to 8.1% at 0.5 and 5 µM; and (b) (4) µM on estrogen agonist using [^{3}H]estradiol in cytosol MCF-7 cells

Table 5: Summary of Mean Percent Inhibition of Control Specific Ligand Binding by TU, DHTU, and (b) (4) at the Maximum Concentration Tested

Receptor	Test Compound	Maximum Concentration (µM)	% Inhibition
			Mean
Estrogen	TU	10	8.8
	DHTU	5	4.9
	(b) (4)	(b) (4)	(b) (4)
Androgen	TU	10	41.3
	DHTU	5	15.4
	(b) (4)	(b) (4)	(b) (4)

4.3 Safety Pharmacology

No studies were conducted. The safety pharmacology of T, the active moiety of TU is well-documented.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Bioanalytical Method Validation:
Validated for determination of systemic exposures to TU, DHTU, T, DHT, estradiol, and phytosterols ([redacted] (b) (4)) in toxicology studies

- LC/MS/MS analytical methods initially developed for determination of T (LLOQ=100 pg/mL), DHT (LLOQ=100 pg/mL), TU (LLOQ=1 ng/mL) and DHTU (LLOQ=0.5 ng/mL) using NaF/Na_2EDTA, and estradiol (LLOQ=1 pg/mL) using K_3EDTA in human plasma and then cross-validated for rat NaF/Na_2EDTA plasma (LLOQ=0.4 ng/mL for T, LLOQ=0.4 ng/mL for DHT), and dog NaF/Na_2EDTA plasma for TU (LLOQ=12 ng/mL), DHTU (LLOQ=3 ng/mL), T (LLOQ=0.4 ng/mL), DHT (LLOQ=0.4 ng/mL), estradiol (LLOQ=1 pg/mL) and phytosterols [redacted] (b) (4)

Absorption
Not conducted

Distribution

- Extensive distribution in all investigated tissues at 1 hour with the maximum concentration achieved between 2 to 6 hour post-dose and below the limit of quantification at 168 hour post-dose in male CD rats following a single [redacted] (b) (4) mg/kg oral dose (~40 mg/kg TU) with no significant differences in tissue concentrations between the complete Formulation 1 with phytosterol esters and Formulation 2 without phytosterol esters except for the epididymis and the liver
- Below the limit of quantification at 168 hour post-dose apart from the epididymis for Formulation 1 and apart from the liver for Formulation 2
- Highest radioactivity in GI tract (small intestine > stomach) followed by prostate > perirenal white fat > seminal vesicle > epididymal white fat > liver > kidneys > adrenal gland > plasma > testes > heart > blood > lungs > levator ani > preputial gland > epididymis > skin > muscle at 4 hours post-dosing using the complete Formulation 1

Table 6: Mean Concentration of Radioactivity following a Single (b) (4) mg/kg Oral Dose of TU Formulation 1 or Formulation 2 to Male Sprague-Dawley Rats

Formulation 1

	Concentration (ng-eq/g)						
Sample	1 h	2 h	4 h	6 h	24 h	48 h	168 h
Skin	4252	4530	4062	3007	709	411	BLQ
Lungs	10457	9161	8094	7712	BLQ	BLQ	BLQ
Testes	14727	9739	11676	20036	1047	1001	BLQ
Preputial Gland	6994	10948	7492	8436	2872	1162	BLQ
Epididymal White Fat	5697	80860	121741	120771	20759	BLQ	BLQ
Small Intestine	1661763	1216201	2057627	737225	201504	27321	BLQ
Epididymis	10167	5266	6418	5028	2040	3212	2359
Levator ani	4808	28617	7756	17910	7153	346	BLQ
Stomach	1135027	1120236	922225	352247	18580	BLQ	BLQ
Kidneys	24307	33103	85816	31689	5541	1059	BLQ
Blood	10771	7356	9650	5162	BLQ	BLQ	BLQ
Seminal Vesicles	7081	46124	155594	80765	19757	BLQ	BLQ
Plasma	13761	9860	15632	4838	BLQ	BLQ	BLQ
Muscle	4459	5119	3393	2763	701	BLQ	BLQ
Perirenal White Fat	6609	31195	166465	56150	4207	BLQ	BLQ
Prostate	73627	30234	205216	127234	5400	BLQ	BLQ
Liver	129580	134868	106102	65356	14488	3210	BLQ
Adrenal Gland	12715	21961	19708	18389	2023	BLQ	BLQ
Heart	9798	8979	9774	7868	1254	BLQ	BLQ

Formulation 2

	Concentration (ng-eq/g)						
Sample	1 h	2 h	4 h	6 h	24 h	48 h	168 h
Skin	5204	3411	2663	6106	1198	267	BLQ
Lungs	13161	6417	8093	55621	BLQ	BLQ	BLQ
Testes	10454	12464	6314	9342	1301	600	BLQ
Preputial Gland	22035	12646	7632	13606	2749	701	BLQ
Epididymal White Fat	5207	55227	191142	125336	19624	BLQ	BLQ
Small Intestine	1312631	2947978	1015527	1392807	167680	20310	BLQ
Epididymis	8156	9767	7377	8179	3319	BLQ	BLQ
Levator ani	6394	8012	8675	304881	172796	213	BLQ
Stomach	2970807	1750945	1084684	2684706	23452	1394	BLQ
Kidneys	29313	31479	51760	52464	19826	1133	BLQ
Blood	9997	7011	3828	18500	BLQ	BLQ	BLQ
Seminal Vesicles	7705	128839	1099397	269432	86021	BLQ	BLQ
Plasma	14168	8696	5597	13687	BLQ	BLQ	BLQ
Muscle	5396	3678	2723	5636	756	BLQ	BLQ
Perirenal White Fat	14715	37516	129157	41414	14953	BLQ	BLQ
Prostate	33821	16901	114889	57385	17051	BLQ	BLQ
Liver	128774	82121	80063	110283	13703	2738	401
Adrenal Gland	12600	18822	14885	31754	5064	BLQ	BLQ
Heart	11512	7308	14202	14509	1147	BLQ	BLQ

Formulation 1 consisted of (b) (4) phytosterol esters and (b) (4) DL-α-tocopherol acetate.
Formulation 2 consisted of (b) (4), and (b) (4) DL-α-tocopherol acetate.
BLQ: Below the Limit of Quantification (ranging from 162-3868 ng-eq/g) depending on tissues

Metabolism

No studies were conducted. The sponsor relied on scientific literature to support the metabolism of TU, which is well-documented.

Excretion

- Primary excretion into feces in male CD rats following a single (b) (4) mg/kg (~40 mg/kg TU) oral dose

5.2 Toxicokinetics

Male eugonadal dogs (NaF/Na_2 EDTA plasma)

- Less than dose-proportional increase in plasma concentrations of TU and its metabolites with no apparent accumulation upon repeated 3-month daily doses of SOV2012-F1 containing TU at 24 and 48 mg/kg/day
- Increased plasma estradiol exposure following TU group 6 with phytosterols compared to vehicle or excipients only group
- Similar phytosterol exposure levels with or without TU (48 mg/kg) across dose groups tested, resulting in accumulation of phytosterols upon 3-month repeat-dosing in male eugonadal dogs

Male eugonadal rats (NaF/Na_2 EDTA plasma)

- Less than dose-proportional increase in T levels within dose ranges of (b) (4) mg/kg BID to (b) (4) mg/kg BID on Days 1 and 71

- Roughly dose-proportional increase in DHT levels over the ranges of (b) (4) mg/kg BID to (b) (4) mg/kg BID on Days 1 and 7

6 General Toxicology

6.1 Single-Dose Toxicity

No studies were conducted. The sponsor relied on scientific literature to support the acute toxicity of T esters.

6.2 Repeat-Dose Toxicity

Study title: 13-Week Oral Gavage Toxicity Study of SOV Oral Testosterone Undecanoate Formulation (SOV2012-F1) in Beagle Dogs to Evaluate Any Effect of Excipients

Study no.:	0470DS97.001
Study report location:	\\CDSESUB1\evsprod\nda213953\0000\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\0470ds97-001\0470ds97-001.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/4/2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TU, H76260, 98.51%

Key Study Findings

Clinical pathology:

- Decreased cholesterol (up to ~39%) and triglyceride (up to ~40%) in all TU-treated groups with (Groups 5 and 6) and without (Groups 7 and 8) phytosterol esters compared to vehicle group

Adrenal glands: slight cytoplasmic vacuolation in the zona fasciculata in TU Groups 6, 7, and 8 (non-reversible in group 6)

Epididymides: marked aspermia in all animals of TU-treated groups with (partially reversible in group 6) or without phytosterol esters

Testes: diffuse, marked germ cell depletion (partially reversible in group 6) and slight Leydig cell atrophy correlated with decreased size and weights, and absence of urinary sperm in all animals of TU-treated groups

Prostate gland: moderate hypertrophy/hyperplasia correlated with increased size and weights in high dose TU groups 6 and 8 with or without phytosterol esters

Phytosterols: no significant difference in toxicity or TK parameters in the presence of phytosterol esters at exposures (b) (4) fold ((b) (4)) or less ((b) (4)) than the mean exposure to phytosterols in male subjects given the maximum proposed human dose of SOV2012-F1 (400 mg TU BID)

TK:

- Less than dose-proportional increase in AUC and C_{max} for TU, DHTU, T, and DHT with no apparent accumulation upon repeat-dosing
- Similar phytosterol exposure levels with or without TU (48 mg/kg) across dose groups tested
- Accumulation of phytosterols after repeat-dosing

Methods

Doses:	TU doses investigated were 0, 24, 48 and 72 mg/kg/day (See Study Design tables below for details)
Frequency of dosing:	Twice daily
Route of administration:	Oral gavage
Dose volume:	(b) (4) mL/kg/dose
Formulation/Vehicle:	Milky white emulsion/Water
Species/Strain:	Dog/Beagle
Number/Sex/Group:	4 males/group for main study groups
Age:	9-10 month
Weight:	7.2-9.8 kg (Study Day 1)
Satellite groups:	2 males/groups 1, 4, and 6 for recovery groups
Unique study design:	Animals were dosed twice daily for 90 consecutive days.
Deviation from study protocol:	Not significant

Table 7: Experimental Design of the 13-Week Toxicity Study in Male Dogs

Group	Treatment Regimen [Relative to MHRDD]	Dose (mg/kg/day)					
		Total	(b) (4)	(b) (4)	(b) (4)	Tocopherol acetate	TU
1	Vehicle Control (Water)	-	0	0	0	0	0
2	(b) (4) [3X]						0.0
3	(b) (4) [1X]						0.0
4	(b) (4) [2X]						0.0
5	SOV2012-F1 [1X]						24.0
6	SOV2012-F1 [2X]						48.1
7	TU [1X] + (b) (4) [1X]						(b) (4)
8	TU [3X] + (b) (4) [3X]						
MRHDD[1] (mg/kg/day)							-
Safety Margin[2]							-
MRHDD[3] (mg/kg/day) at equivalent Dog HED							-
Safety margin[4] at equivalent Dog HED							-

HED: Human Equivalent Dose; MRHDD: Maximum Recommended Human Daily Dose; TU: Testosterone Undecanoate; -: Not applicable; (b) (4) = complete excipient formulation without TU; bolded numbers represent the highest dose level of the excipient tested in the study and used in the calculation of safety margins

[1]1x, 2x, 3x = 1, 2, or 3 times the MRHDD based on Human Equivalent Dose (HED). The MRHDD of SOV2012-F1 is 13.3 mg/kg of TU administered in (b) (4). In the formulations used in Groups 1, 7 and 8, (b) (4) replaced (b) (4), thus the amounts present are greater than the amounts of (b) (4) present in the SOV2012-F1 formulation.

[2]Two dogs designated for a 4-week recovery (non-dosing) period following the completion of dosing

Table 8: Formulation and Dilution Information for 13-Week Dog Study

Test Group	Treatment / Formulation	Description (1000 parts)	Formulation (grams) (b) (4) (b) (4)
1	Vehicle Control	Water	NA
2	(b) (4) 3x	(b) (4) (b) (4) : dl-alpha tocopherol acetate	(b) (4)
3	Excipients Only 1x	(b) (4) (b) (4) : Phytosterol esters : dl-alpha tocopherol acetate	
4	Excipients Only 3x	(b) (4) (b) (4) : Phytosterol esters : dl-alpha tocopherol acetate	
5	Complete Formulation 1x	TU : (b) (4) (b) (4) : Phytosterol esters : dl-alpha tocopherol acetate	
6	Complete Formulation 3x	TU : (b) (4) (b) (4) : Phytosterol esters : dl-alpha tocopherol acetate	
7	TU+ (b) (4) Formulation 1x	TU : (b) (4) (b) (4) : dl-alpha tocopherol acetate	
8	TU+ (b) (4) Formulation 3x	TU : (b) (4) (b) (4) : dl-alpha tocopherol acetate	

(b) (4)

Observations and Results

Mortality: twice daily and once prior to sacrifice

- Unremarkable

Clinical Signs: once pre- and post-dose during study, and once daily during recovery period

- Unremarkable

Body Weights: pre-dose on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, and following the final dose administration on Day 91/92, Days 99, 106, 113, and 119/120

- Unremarkable

Feed Consumption: once daily

- Unremarkable

Ophthalmoscopy: pre-treatment initiation and during the last week of dosing

- Unremarkable

ECG: prior to treatment initiation, during the final week of dosing at ~1 hour post-dose and during the last week of recovery

- Unremarkable

Hematology: prior to treatment initiation, prior to the first dose of the day on Day 34/36, on Day 92/93 and on Day 120/121

- Dose-related increase (up to ~30%) in platelets and reticulocytes (up to ~62%) in Groups 7 and 8 without phytosterol esters compared to vehicle group

Clinical Chemistry: Prior to treatment initiation, prior to the first dose of the day on Day 34/36, on Day 92/93 and on Day 120/121

- Decreased triglycerides (up to ~40%) and cholesterol (up to ~39%) in complete TU formulation (Groups 5 and 6) and TU without phytosterol esters compared to vehicle group

Urinalysis: Prior to treatment initiation, prior to the first dose of the day on Day 34/36, on Day 92/93 and on Day 120/121

- Absent sperm in all TU-treated groups with no recovery in Group 6 (complete TU 2X)

Gross Pathology: Day 92/93 or Day 120/121

- Decreased testis size in all TU-treated groups with no recovery at the end of 4-week treatment-free period in Group 6 with phytosterol esters
- Increased prostate size in TU-treated group 6 with phytosterol esters and TU-treated group 8 without phytosterol esters

Organ Weights: Adrenal glands, brain, heart, kidneys, liver, pituitary gland, prostate gland, spleen, testes, thymus and thyroid with parathyroid glands, and epididymides

- Increased absolute heart (up to ~22%) and spleen (up to ~64%) weights in all treated groups compared to vehicle group
- Increased absolute kidney weights (up to ~25%) and dose-related increases in prostate weights (up to ~3-fold) in all TU-treated groups compared to vehicle group
- Dose-dependent decreased absolute testis weights (up to ~74%, partially reversible in Group 6 with phytosterol esters) in all animals of TU-treated groups (with or without phytosterol esters) and thymus (up to ~55%) weights in TU-treated groups without phytosterol esters compared to vehicle group

Histopathology: Day 92/93 or Day 120/121
Adequate Battery: Yes
Peer Review: Yes

Histological Findings:

Main Group (Day 92/93)

- Adrenal glands: slight cytoplasmic vacuolation in the zona fasciculata in TU Groups 6, 7, and 8
- Epididymides: devoid of spermatozoa within tubular lumens (marked aspermia) in all animals of TU Groups 5, 6, 7, and 8
- Testes: diffuse, marked germ cell depletion characterized by marked reduction in cross-sectional diameter of seminiferous tubules that were lined predominantly by Sertoli cells with few residual germ cells, accompanied by diffuse, slight atrophy of interstitial (Leydig) cells that was often associated microscopically with increased cytoplasmic vacuolation in all animals of TU Groups 5, 6, 7, and 8
- Prostate gland:
    - Moderate severity of hypertrophy/hyperplasia noted as an apparent increase in the size and number of glandular epithelial cells in TU Groups 6 and 8, characterized by notable convoluted infoldings of the glandular epithelium within lumens (suggesting increased numbers of glandular epithelial cells), increased variability in the size and shape of glandular epithelial cell nuclei, and increased amounts of apical cytoplasm

Recovery Group (Day 120/121)

- Adrenal glands: adrenocortical cytoplasmic vacuolation in the zona fasciculata in a single Group 4 (excipients only) male (bilateral, of slight intensity) and a single Group 6 (high dose TU with phytosterol esters) male (unilateral, minimal intensity)
- Epididymides: devoid of spermatozoa in TU Group 6 (with phytosterol esters)
- Testes: germ cell depletion and seminiferous tubules with slightly larger cross-sectional diameter as compared to the earlier time point and lined with spermatogonia and a few spermatocytes in TU Group 6 (with phytosterol esters)
- Prostate: moderate severity of glandular atrophy in one TU Group 6 (with phytosterol esters) male

Special Evaluation: Not provided

Toxicokinetics: Pre-dose, 1, 2, 4, 6, 12 (prior to 2nd dose), 13, 14, 16, 18, and 24 hours post-dose on Days 1 and 90 in plasma containing NaF/Na_2 EDTA

- Less than dose-proportional increase in AUC and C_{max} for TU, DHTU, T, and DHT with no apparent accumulation upon repeat-dosing
- Increased plasma estradiol levels in TU Group 6 with phytosterols compared to excipients only group
- Similar phytosterol exposure levels in the presence or absence of TU (Groups 4, 5, 6) with accumulation of phytosterols upon repeat-dosing

Exposure Multiples:

- TU: ~6 fold the mean C_{max} and ~3 fold the mean AUC_{0-24h} at the low dose compared to the mean exposures in men taking 400 mg BID TU dose
- DHTU: < 1 fold the mean C_{max} and < 1 fold the mean AUC_{0-24h} at the low dose compared to the mean exposures in men taking 400 mg BID TU dose
- T: ~4 fold the mean C_{max} and ~2 fold the mean AUC_{0-24h} at the low dose compared to the mean exposures in men taking 400 mg BID TU dose
- DHT: ~3 fold the mean C_{max} and ~2 fold the mean AUC_{0-24h} at the low dose compared to the mean exposures in men taking 400 mg BID TU dose
- Phytosterol esters: (b) (4) fold the mean C_{max} and AUC_{0-24h} at the low dose of (b) (4), respectively, compared to the mean exposures in men taking 400 mg BID TU dose

Dosing Solution Analysis: Top, middle, and bottom of dosing solution on Days 1 and 92

- Concentration: (b) (4)
- Homogeneity: ≤10.0%

The following reviewer's table summarizes noteworthy observations made in the 13-week study in male beagle dogs.

Table 9: 13-Week Dog Study: Summary of Noteworthy Observations

Observations \ Study Group[a]	0 6♂	(b)(4) 3X 4♂	E 1X 4♂	E 2X 6♂	TU+E 1X 4♂	TU+E 2X 6♂	TU+(b)(4) 1X 4♂	TU+(b)(4) 3X 4♂
Hematology, Day 92/93								
Platelet, $10^3/\mu L$	221.2	251.8	258.8	224.2	225.8	242.8	**277.0**	**293.0***
Reticulocytes, x10^9/L	32.42	41.15	31.60	35.38	38.40	38.32	**42.65**	**52.68**
Clinical chemistry, Day 92/93								
Triglyceride, mg/dL	43.2	36.5	44.8	38.2	**25.8**	**30.5**	**33.5**	**26.8**
Cholesterol, mg/dL	125.2	130.3	135.8	135.0	**85.3****	**93.5***	**88.8***	**76.8****
Organ weights, absolute, g	n=4(2)	n=4	n=4	n=4(2)	n=4	n=4(2)	n=4	n=4
Heart	65.13	**77.65**	**72.48**	**73.90**	**74.78**	**79.40**	**72.48**	**78.65**
Kidneys	42.78	42.08	46.08	47.40	**53.50**	**51.53**	**50.75**	**52.05**
Prostate gland	6.70	6.48	8.63	**4.78***	**11.85**	**18.35***	**9.40**	**18.10***
Spleen	54.93	**63.43**	**67.83**	**68.63**	**90.15**	**73.10**	**71.45**	**79.45**
Testes, Day 92/93	11.47	12.87	12.85	11.76	**3.51***	**3.18***	**3.24***	**3.04***
(Day 120/121)	(10.71)	-	-	(15.03)	-	**(5.05)**	-	-
Thymus	18.57	16.41	23.40	15.92	**14.35**	18.81	**8.44**	**12.72**
Gross pathology, Day 92/93 (Day 120/121)	n=4(2)	n=4	n=4	n=4(2)	n=4	n=4(2)	n=4	n=4
Prostate, enlarged, size						3		3
Testis, small, size					4	4(2)	4	4
Histopathology, Day 92/93 (Day 120/121)	n=4(2)	n=4	n=4	n=4(2)	n=4	n=4(2)	n=4	n=4
Adrenal glands, vacuolation, zf				(1^2)		$1^2(1^1)$	2^2	1^2
Epididymides, aspermia					4^4	$4^4(2^4)$	4^4	4^4
Pituitary gland, cyst	(1^1)			1^1	1^2	(1^1)	1^2	1^2
Prostate, hypertrophy/hyperplasia						3^3		4^3
atrophy, glandular						(1^3)		
Testes, depletion, germ cells	$1^1(1^2)$			(1^1)	4^4	$4^4(2^3)$	4^4	4^4
atrophy, Leydig cells					4^2	4^2	4^2	4^2
hypospermatogenesis				(1^1)				

(b)(4), E=all excipients, TU+E=complete formulation, TU+(b)(4) testosterone undecanoate+ (b)(4)
zf = zona fasciculata
Numbers in superscripts represent severity grades: 1=minimal, 2=slight, 3=moderate, 4=marked
-; Not available
Statistically significant from controls at p=0.05* or p=0.01*
Reviewer generated table

The following table summarizes toxicokinetic parameters for the 13-week study in male beagle dogs.

Table 10: 13-Week Dog Study: Toxicokinetic Summary

Observations \ Study Group[a]	0 6♂	(b)(4) 3X 4♂	E 1X 4♂	E 2X 6♂	TU+E 1X 4♂	TU+E 2X 6♂	TU+(b)(4) 1X 4♂	TU+(b)(4) 3X 4♂
Toxicokinetics[b], 4-6/sex/timepoint								
TU								
$AUC_{0\text{-}24hr}$, ng·hr/mL, Day 1	-	-	-	-	5780	12230	5885	10332
Day 90	-	-	-	-	6321	9604	8040	13085
C_{max}, ng/mL, Day 1	-	-	-	-	2275	3527	2655	3073
Day 90	-	-	-	-	2487	3046	3466	3311
T_{max}, hr, Day 1	-	-	-	-	1.0	7.5	1.0	1.0
Day 90	-	-	-	-	1.0	1.0	13.0	7.0
$T_{1/2}$, hr Day 1	-	-	-	-	0.77	1.23	0.62	0.80
Day 90	-	-	-	-	1.10	1.12	0.58	0.87

DHTU									
$AUC_{0\text{-}24hr}$, ng·hr/mL,	Day 1	-	-	-	-	290	457	261	359
	Day 90	-	-	-	-	258	354	262	393
C_{max}, ng/mL,	Day 1	-	-	-	-	44	69	39	62
	Day 90	-	-	-	-	39	55	41	67
T_{max}, hr,	Day 1	-	-	-	-	1.0	2.0	2.0	2.0
	Day 90	-	-	-	-	8.0	2.0	7.5	8.0
$T_{1/2}$, hr	Day 1	-	-	-	-	-	-	-	-
	Day 90	-	-	-	-	-	-	-	-
T									
$AUC_{0\text{-}24hr}$, ng·hr/mL,	Day 1	41	-	-	46	208	393	219	419
	Day 90	68	-	-	50	189	284	239	504
C_{max}, ng/mL,	Day 1	4	-	-	4.4	43.5	67.4	61.4	80.5
	Day 90	5.8	-	-	4.4	35.4	48.4	53.2	99.7
T_{max}, hr,	Day 1	10.0	-	-	9.5	1.0	2.0	1.0	2.0
	Day 90	4.0	-	-	18.0	13.5	13.5	13.0	14.0
$T_{1/2}$, hr	Day 1	-	-	-	-	-	-	-	-
	Day 90	-	-	-	-	-	-	-	-
DHT									
$AUC_{0\text{-}24hr}$, ng·hr/mL,	Day 1	NA	-	-	NA	35.8	46.3	30.4	45.7
	Day 90	NA	-	-	NA	28.9	39.8	31.1	46.1
C_{max}, ng/mL,	Day 1	NA	-	-	NA	5.0	6.1	5.2	6.5
	Day 90	NA	-	-	NA	3.9	4.3	5.0	6.6
T_{max}, hr,	Day 1	NA	-	-	NA	8.0	2.0	1.0	2.0
	Day 90	NA	-	-	NA	8.0	14.0	14.0	8.0
$T_{1/2}$, hr	Day 1	-	-	-	-	-	-	-	-
	Day 90	-	-	-	-	-	-	-	-
DHT/T ratio for $AUC_{0\text{-}24hr}$,	Day 1	NA	-	-	NA	0.17	0.12	0.14	0.11
	Day 90	NA	-	-	NA	0.15	0.14	0.13	0.09
Estradiol									
$AUC_{0\text{-}24hr}$, pg·hr/mL,	Day 1	36.2	-	-	33.9	-	116.4	-	-
	Day 90	42.7	-	-	35.4	-	108.4	-	-
C_{max}, pg/mL,	Day 1	3.0	-	-	2.8	-	9.7	-	-
	Day 90	3.4	-	-	3.0	-	9.8	-	-
T_{max}, hr,	Day 1	10.0	-	-	1.0	-	14.0	-	-
	Day 90	9.0	-	-	0.0	-	14.0	-	-
$T_{1/2}$, hr	Day 1	-	-	-	-	-	-	-	-
	Day 90	-	-	-	-	-	-	-	-

(b) (4)

[redacted]

[redacted], E=all excipients, TU+E=complete formulation,
TU+[redacted] testosterone undecanoate+ [redacted]
NA; not applicable due to <3 concentrations observed in all animal profiles
[b]LLOQ=12 ng/mL for TU, 3 ng/mL for DHTU, 0.4 ng/mL for T and DHT, 1 pg/mL for estradiol, [redacted]

-; Not available
Reviewer generated table

7 Genetic Toxicology

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

Study title: Mutagenicity Assessment of [redacted] as Determined by a Bacterial Reverse Mutation Assay

Study no.:	52618.00201DS
Study report location:	\\CDSESUB1\evsprod\nda213953\0000\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\5261800201ds\5261800201ds.pdf
Conducting laboratory and location:	[redacted]
Date of study initiation:	November 25, 2020
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	[redacted], 2055-RKK-115, 31.2%

Key Study Findings

- No increase in the number of revertant colonies for 31.2% [redacted] either in the presence or absence of S9 mix under the conditions of the study (adequate tester strains, dose selection, background mutants/plate)

Methods

Strains:	TA98, TA100, TA1535, TA97a, WP2 *uvr*A pKM101
Concentrations in definitive study:	[redacted] µg per plate
Basis of concentration selection:	Precipitation and cytotoxicity (precipitate at [redacted] µg per plate based on a preliminary test)
Negative control:	Acetone
Positive control:	

Tester Strain	Without Metabolic Activation	With Metabolic Activation
TA97a	ICR191 acridine (0.25)	2-aminoanthracene (2.5)
TA98	2-nitrofluorene (3)	2-aminoanthracene (2)
TA100	sodium azide (1)	benzo[a]pyrene (2)
TA1535	sodium azide (1)	2-aminoanthracene (2.5)
E. coli WP2	4-nitroquinoline-N-oxide (0.25)	2-aminoanthracene (20)

Formulation/Vehicle:	Solution/Acetone
Incubation & sampling time:	Tester strain and test article or vehicle with or without S9 (triplicate) were added to top agar at ≥45°C (plate incorporation method). The mixture was overlaid onto the surface of minimal bottom agar and incubated for 48 ± 2 hours at 37 ± 1°C. Revertant colonies were counted by automated colony counter.

Study Validity: Valid

- A minimum of 3 non-toxic dose levels were tested with appropriate dose selection.
- Negative control values fell within an acceptable range based on values from historical laboratory controls.
- All strains passed tests for the presence of genetic markers.
- Each positive control exhibited at least a 2-fold increase in the number of revertants over the respective vehicle control.
- 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 (TA97a, TA100 and WP2 *uvr*A) or ≥3-fold (TA98 and TA1535) increase in the mean revertants at the peak of the dose response
- No description of test conditions (e.g., cell numbers, media)

Results: Negative

Preliminary assay:

- No cytotoxicity at any doses tested ((b) (4) µg/plate) in all strains with and without S9
- Precipitate at (b) (4) µg/plate

Mutagenicity assay:

- No increase in revertants with any of the tester strains in either presence or absence of S9
- No cytotoxicity in all strains with and without S9
- Precipitation
  - (b) (4) µg/plate for all strains
  - (b) (4) µg/plate with TA97a and TA1535 in the absence and TA98 in the presence and absence of metabolic activation

Reviewer Note: The sponsor stated that it has not been possible to isolate (b) (4) *in more than 31.2% purity due to the instability of the* (b) (4) *functional group during isolation and/or storage. LC-MS/MS of the isolated material showed that the remainder of the material (~70%) was very likely to be* (b) (4)

(b) (4)

7.2 In Vitro Assays in Mammalian Cells

Study title: Genotoxicity Test of (b) (4) in an In Vitro Micronucleus Assay in Human TK6 Cells

Study no.:	52618.00202DS
Study report location:	\\CDSESUB1\evsprod\nda213953\0000\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\5261800202ds\5261800202ds.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 25, 2020
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4), 2055-RKK-115, 31.2%

Key Study Findings

- No dose-related increase in micronucleus frequency for 31.2% (b) (4) at any of the tested concentrations following exposures to the test article for 4 hours with and without S9 or for 24 hours without S9 under the conditions of the study

Methods

Cell line:	Human TK6 lymphoblastoid cells
Concentrations in definitive study:	(b) (4) µg/mL
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:	Acetone
Positive control:	Vinblastine sulfate for -S9 (0.75 ng/mL for 24-hour exposures and 3.75 ng/mL for 4-hour exposures), Cyclophosphamide monohydrate +S9 for 4 hours (3 µg/mL)
Formulation/Vehicle:	Solution/Acetone
Incubation & sampling time:	Cells (2.0 ± 0.25 x 10^5 cells/mL, quadruplicate) were exposed to the test substance or controls for 4 ± 0.5 hours in the presence and absence of S9 and for 24 ± 1 hours without S9. At the end of the 4-hour exposures, media were removed, the cells were washed once with phosphate buffered saline and resuspended in complete TK6 medium for the remaining culture period; for 24-hour exposures -S9, cells remained in the same exposure media for the entire culture period. At the end of the culture periods, the cells were analyzed for cytotoxicity and micronucleus

induction by flow cytometry. Unless limited by cytotoxicity, 5000 (± 500) cells from each sample were analyzed for the frequency of micronuclei.

Micronuclei are identified using a combination of characteristics of size (as measured by light scatter) and fluorescence (based on differential staining steps) that differentiates debris and necrotic and apoptotic cells from "healthy" cells with true micronuclei. Cytotoxicity was measured as relative survival of cells from treated cultures compared to cells from vehicle control cultures using ratios of counted nuclei to counted beads (inert latex microspheres added to each sample). Higher nuclei to bead ratios correspond to increased cell survival. Viable cell counts were also determined from 1 replicate culture at each exposure level using trypan blue exclusion and the counts were used to calculate relative increase in cell count for each test article and positive control exposure.

Study Validity: Valid

- The dose selection was appropriate.
- The negative controls had <2% micronucleated cells and the test concentration of the positive controls used for each test condition induced a statistically significant increase in micronuclei.
- Criteria for a positive response:
    - For compounds that are cytotoxic, the top exposure level should be selected with the aim to induce 55 ± 5% cytotoxicity.
    - At least 1 test dose exhibits a statistically significant increase in a dose-related manner compared to the concurrent vehicle control and the results are outside the laboratory historical control range.

Results: Negative

Initial assay:

- No cytotoxicity up to (b) (4) µg/mL ((b) (4) µg/mL tested)
- Visible precipitate at ≥(b) (4) µg/mL ((b) (4) µg/mL tested)
- No changes in osmolality or pH compared to the corresponding vehicle control
- Osmolality of the media was within 100 mOsm and the pH was within 1 pH unit of the corresponding vehicle control at the highest tested concentration for all exposure conditions

Main assay:

- No dose-related, statistical difference from the concurrent vehicle control at any tested concentration
- Micronucleus frequencies within the laboratory historical vehicle control range of 0 - 0.96% for 4-hour without S9 exposures, 0 - 1.13% for 4-hour with S9 exposures, and 0 - 1.12% for 24-hour without S9 exposures at all test article exposure levels
- Cytotoxicity <60% (2.1 - 26.1%) at all analyzable exposure levels up to (b) (4) µg/mL under all exposure conditions

Reviewer Note: The sponsor stated that it has not been possible to isolate (b) (4) *in more than 31.2% purity due to the instability of the* (b) (4) *functional group during isolation and/or storage. LC-MS/MS of the isolated material showed that the remainder of the material (~70%) was very likely to be* (b) (4)

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

Not conducted

7.4 Other Genetic Toxicity Studies

None

8 Carcinogenicity

No studies were conducted. The sponsor relied on scientific literature to support the carcinogenicity of TU and T, which is well-documented.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: A Fertility Study with Testosterone Undecanoate Formulation (SOV2012-F1) Administered Twice Daily by Oral Gavage in Male Rats, Including a Toxicokinetic Evaluation

Study no.:	0325RS97.001 (SOV2013RS.001)
Study report location:	\\CDSESUB1\evsprod\nda213953\0000\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev\0325rs97001\0325rs97001.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/26/2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	TU, H76260, 98.51%

Key Study Findings

Body weights:

- Dose-related decrease in mean body weights (up to ~9%) and body weight gains (up to ~82% on Day 60) in treated males starting from dosing Day 8 and during the entire dosing period with statistical significance at the high dose of (b) (4) mg/kg/day compared to control group
- Reduced mean body weight gains (up to ~34%) in untreated females mated with treated males during GDs 14 - 18 and GD 18 at (b) (4) mg/kg/day compared to control group, possibly secondary to lower gravid uterine weights.

Reproductive organ weights:

- Dose-related decrease in absolute epididymis (up to ~29%), testis (~45%), and prostate (up to ~23%) weights in all treated male groups compared to control group
- Decreased absolute uterus weights (~30%) in untreated females mated with males dosed with (b) (4) mg/kg/day compared to control group

Caesarean/reproductive data:

- Reduced fertility index (~71%) and increased mean percent pre-implantation loss (~34%) associated with lower mean total litter size, lower mean total number of implantation sites, and lower mean number of viable fetuses per litter for untreated gravid females mated to (b) (4) mg/kg/day males compared to control group

NOAEL= (b) (4) mg/kg/day ((b) (4) mg/kg BID)

Methods

Doses: 0, (b) (4) mg/kg/day (~83 mg/kg TU), (b) (4) (~348 mg/kg TU) mg/kg/day

Group	Treatment [Relative to MHRDD]	Total Daily Dose of SOV2012-F1 (mg/kg/day)	Total Daily Dose of TU (mg/kg/day)	Dosing Volume (mL/kg/day)	No. Males/Group	
					Main	TK
1	Vehicle (water)	0	0	(b) (4)	24	21
2	SOV2012-F1 [1X]	(b) (4)	82.8		24	21
3	SOV2012-F1 [3X]		348.4		24	21

Frequency of dosing: Twice daily
Dose volume: (b) (4) mL/kg/dose
Route of administration: Oral gavage
Formulation/Vehicle: TU: (b) (4) :Phytosterol Esters:dl-α-Tocopherol Acetate at a ratio of (b) (4) /Deionized water
Species/Strain: Rat/ CD®IGS rat [Crl:CD®(SD)]
Number/Sex/Group: 24/sex/group
Satellite groups: 21 males/group for TK

Group No./ Treatment[2]	Dose Level[4] (mg/kg/day)	Dose Level (mg/kg/dose)	Concentration (mg/ml)	Dose Volume[3] (ml/kg/dose)	Number of Males
4. TU (1X human dose)[2]	[redacted]		(b) (4)	(b) (4)	21
5. TU (3X human dose)[2]					21

[2]TU = Testosterone Undecanoate Formulation (SOV2012-F1); females were not dosed
[3]Males were dosed twice daily, for a total daily volume of (b) (4) mL/kg
[4]Dose levels shown as mg/kg/day of SOV2012-F1 formulation; the TU content was (b) (4) % of the concentration listed in the table

Study design: Males (8 weeks old) were dosed twice daily (12 hours apart ± 2 hours) for 71 to 73 days prior to the initiation of the cohabitation period, 1 to 4 days during the cohabitation period and for a minimum of 6 days to a maximum of 11 days following cohabitation until the day of scheduled euthanasia for a total of 82/83 consecutive days. Each untreated female (14 weeks old) was placed in cohabitation with one male. Females were not dosed. The pair remained in cohabitation until the female was determined to have been mated, based on the examination of vaginal smears or the presence of a copulatory plug in situ.

Deviation from study protocol: Not significant

Table 11: Formulation and Dilution Information for Male Rat Fertility Study

Group No.	Treatment	Description and Ratio of Components (1000 parts)	Composition (mg of Component per Total Weight of Formulation)	Grams (b) (4) (b) (4) (b) (4) of Dose Formulation[1]
1	Vehicle Control	Water	-	-
2/4	Complete Formulation **1x** (b) (4)	TU: (b) (4) (b) (4) Phytosterol Esters: dl-Alpha Tocopherol Acetate (b) (4)	TU: (b) (4) (b) (4) (b) (4) Phytosterol Esters: (b) (4) mg dl-Alpha Tocopherol Acetate: (b) (4) mg **Total Weight of Formulation:** (b) (4) **mg**	(b) (4)
3/5	Complete Formulation **3x** (b) (4)	TU: (b) (4) (b) (4) Phytosterol Esters: dl-Alpha Tocopherol Acetate (b) (4)	TU: (b) (4) (b) (4) (b) (4) Phytosterol Esters: (b) (4) mg dl-Alpha Tocopherol Acetate: (b) (4) mg **Total Weight of Formulation:** (b) (4) **mg**	

(b) (4)
(b) (4) mL/kg is the daily dose volume, administered at (b) (4) mL/kg twice a day

Observations and Results

Mortality: twice daily

- One male at (b) (4) mg/kg/day euthanized for humane reasons on Day 48 possibly due to a technical error (struggled during the first dose on Day 47 while the gavage needle inside the animal's mouth; exhibited with decreased activity and red discharge through the nose on Day 48; perforated esophagus, enlarged heart, a discolored liver, and small testes)

Clinical Signs: twice daily (prior to each dose and within 3 hours following each dose) for males; once daily for females

- Increased incidence and severity of hair loss on limbs, forepaws, dorsal/abdominal regions, and/or thorax in treated males and in females mated to males

Body Weight: pre-study, twice weekly prior to initiation of cohabitation, during cohabitation and at terminal sacrifice for males; pre-study, twice weekly prior to initiation of cohabitation, during cohabitation and on GDs 0, 3, 7, 10, 14, 17, and 18 for females

- Dose-related decrease in mean body weights (up to ~9%) in males starting from dosing Day 8, with statistical significance at (b) (4) mg/kg/day during the 6th week (Day 43) throughout dosing days up to the end of treatment (cohabitation Day 13) compared to control group
- Reduced mean body weight gains (up to ~82%) in males starting from Day 8 with occasional statistical significance at (b) (4) mg/kg/day throughout dosing phase compared to control group
- Reduced mean body weight gains (up to ~34%) in untreated females mated with treated males during GDs 14 - 18 and GD 18 with statistical significance at (b) (4) mg/kg/day compared to control group, possibly secondary to lower gravid uterine weights

Feed Consumption: once weekly, beginning on the 1st day of dose administration, until the initiation of the cohabitation period for males; GD intervals 0-7, 7-14, and 14-17 for females

- Unremarkable

Toxicokinetics: Days 1, 71 (corresponding day prior to the initiation of the cohabitation period of males) and 83 (corresponding last day scheduled for dose administration of males) at 0 (immediate pre-dose 1), 0.5, 1, 2, 4, 6, 12 (immediate pre-dose 2), 12.5, 13, 14, 16, 18, and 24 hours

- Less than dose-proportional increase in AUC and C_{max} for T and DHT with no apparent accumulation following repeated BID dosing of TU

Dosing Solution Analysis: on the day prior to the 1st day of treatment, on the day of the initiation of cohabitation, and on the last day of treatment from top, middle and bottom of each formulation in duplicate

- Homogeneity: within acceptance criteria of (b) (4) %
- Concentration: within acceptance criteria of (b) (4) %

Necropsy: after completion of cohabitation period for males (epididymides with vas deferens, prostate, seminal vesicles with coagulating gland, testes, and brain for organ weights; gross lesions); GD 18 for females (uterus with horns and cervix, and brain gross lesions)

- Dose-related decreases in absolute epididymis (up to ~29%) and testis (up to ~45%) weights (correlated with small testes at (b) (4) mg/kg/day) in all treated groups compared to control group
- Dose-related increase in absolute prostate weights (up to ~23%) in all treated groups compared to control group
- Hair loss on the abdomen or ventral thoracic region in males at (b) (4) mg/kg/day
- Decreased absolute uterus weights (~30%), but not mean corrected body weights (gravid uterus weight subtracted from the GD 18 body weight) or mean corrected body weight changes (GD 0 body weight subtracted from the corrected body weight) in untreated females mated with (b) (4) mg/kg/day males compared to those mated with control group (~8%)

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.): GD18 (no historical control data provided)

- Elevated (29%) number of non-gravid females for those cohabited with males treated with (b) (4) mg/kg/day compared to control group (8%)
- Lower mean litter size, mean total number of implantation sites, and mean number of fetuses per litter for gravid untreated females mated with treated males at (b) (4) mg/kg/day compared to gravid untreated females mated with control group males
- Reduced fertility index (71%) and higher mean percent pre-implantation loss (34%) for untreated females mated to (b) (4) mg/kg/day males compared to untreated females mated to control group males

The following reviewer's table summarizes noteworthy observations in the male rat fertility study.

Table 12: Male Rat Fertility Study: Summary of Noteworthy Observations

Dose[a], mg/kg/day / Observations	0		(b) (4)		(b) (4)	
	24♂	24♀	24♂	24♀	24♂	24♀
Mortality[b]					1	
Body weights, g						
Day 43, dosing phase	531.6	-	**520.5**	-	**502.9***	-
Day 60, dosing phase	578.3	-	**570.4**	-	**536.4****	-
Day 71, dosing phase	603.3	-	**593.0**	-	**552.8****	-
Day 3, cohabitation phase	593.3	-	**580.7**	-	**543.1****	-
Day 13, cohabitation phase	615.0	-	**604.0**	-	**560.9***	-
GD 0, gestation phase	-	306.2	-	305.6	-	304.7
GD 18, gestation phase	-	428.9	-	**423.9**	-	**412.1**
Body weight gains, g						
Day 25, dosing phase	19.5	-	**18.8**	-	**13.7****	-
Day 43, dosing phase	16.1	-	**15.6**	-	**11.2***	-
Day 60, dosing phase	6.5	-	8.0	-	**1.2***	-
Day 71, dosing phase	8.6	-	**7.9**	-	**5.4****	-
GD 18, gestation phase	-	15.4	-	15.5	-	**10.2***
GD 14-18, gestation phase	-	46.8	-	47.2	-	**34.7***
GD 0-18, gestation phase	-	122.6	-	**118.3**	-	**107.4**
Organ weights, absolute, g						
Brain	2.16	2.01	**2.07***	1.98	**2.05***	2.01
Epididymides (left + right)	1.52	-	**1.48**	-	**1.08****	-
Prostate gland	1.08	-	**1.15**	-	**1.33**	-

Testes (left + right)	3.79		**3.16****	-	**2.10****	-
Uterus	-	48.89	-	49.37	-	**34.39**
Corrected uterus weights[c]	-	379.97	-	374.5	-	377.66
Corrected Body weight change[d]	-	73.74	-	68.91	-	72.96
Gross pathology, Skin, hair loss, ventral abdomen/thoracic					2 (n=2)	
Testes, small, size	1				7	
Caesarean/ Reproductive data, GD 18						
Non-gravid	-	2	-	2	-	**7**
Gravid	-	22	-	22	-	**17**
Total litter	-	15	-	15	-	**10**
Viable fetuses	-	14	-	15	-	**10**
Corpora lutea/dam	-	17	-	18	-	**15**
Total implantation/dam	-	15	-	15	-	**10**
Pre-implantation loss, %	-	11.7	-	12.9	-	**33.9**
Days in cohabitation	-	66	-	58	-	**61**
Fertility index, %	-	92	-	92	-	**71***

[a]TU content was (b) (4)% of the concentration.
[b]One male at TU (b) (4) mg/kg/day was euthanized on Day 48 probably due to a dosing error.
[c]Day 18 body weight - uterus weight
[d]Corrected Day 18 body weight - Day 0 body weight
Statistically significant from controls at p=0.05* or p=0.01**
-; Not available

The following table summarizes TK parameters in the male rat fertility study.

Table 13: Male Rat Fertility Study: Toxicokinetic Summary

Observations \ Dose[a], mg/kg/day	0		(b) (4)		(b) (4)	
	24♂	24♀	24♂	24♀	24♂	24♀
Toxicokinetics[b], 3/group/timepoint						
T						
AUC_{0-24hr}, ng·hr/mL, Day 1	-	-	118.6	-	150.8	-
Day 71	-	-	81.1	-	173.2	-
C_{max}, ng/mL, Day 1	-	-	17.4	-	20.9	-
Day 71	-	-	18.0	-	33.7	-
T_{max}, hr, Day 1	-	-	1.0	-	14.0	-
Day 71	-	-	13.0	-	14.0	-
$T_{1/2}$, hr Day 1	-	-	-	-	-	-
Day 71	-	-	1.9	-	3.5	-
DHT						
AUC_{0-24hr}, ng·hr/mL, Day 1	-	-	13.2	-	27.4	-
Day 71	-	-	11.6	-	32.0	-
C_{max}, ng/mL, Day 1	-	-	2.8	-	4.8	-
Day 71	-	-	2.7	-	5.6	-
T_{max}, hr, Day 1	-	-	2.0	-	14.0	-
Day 71	-	-	13.0	-	14.0	-
$T_{1/2}$, hr Day 1	-	-	1.2	-	2.4	-
Day 71	-	-	1.0	-	3.3	-

[a]TU content was ~(b) (4)% of the concentration.
[b]Mean T baseline concentration observed at pre-dose on Day 1 was 1.69 and 5.41 ng/mL in Groups 4 and 5, respectively. The T baseline level (pre-dose sample) on Day 1 was within 8% to 31% of the maximum T concentrations observed following twice daily administrations of TU doses. Pre-dose DHT concentrations were only observed in animals from TK Group 5 (TU (b) (4) mg/kg/day) on Day 71. Due to increase of T levels in rats with age from birth to 80 days, no baseline correction was performed.
LLOQ = 0.4 ng/mL for T and DHT
-; Not available

9.2 Embryonic Fetal Development

Not conducted

9.3 Prenatal and Postnatal Development

Not conducted

10 Special Toxicology Studies

The following safety assessments were provided for degradants, [redacted] (RRT [redacted]) identified after 6 months storage at 40°C/75%RH ([redacted]%), and [redacted] (RRT [redacted]) identified after 6 months at 40°C/75%RH ([redacted]%); 24 months at 25°C/60%RH [redacted]%); 36 months at 25°C/60%RH ([redacted]%) during the long-term stability testing of the drug product.

Stability Evaluation of [redacted] in Human and Dog Plasma Using LC-MS/MS (Study #MAR02-001)

[redacted] was found to degrade rapidly by 1 hour in human and dog plasma to 20% and 29%, respectively, of the initial value. Increases in [redacted] were observed in human (0.5 h, 2 h, and 1 h, respectively) and dog (2 h, 4 h, and 2 h, respectively) [redacted]. Levels of [redacted] rapidly decreased by almost 80% or 71% after 1 hour (half-life ~10 minutes in in human plasma or < 10 minutes in dog plasma), with an apparent increase in [redacted] (5 to 24 h). [redacted].

ICH M7 Evaluation of [redacted] (Study # [redacted]-2020)

The potential mutagenicity of degradant [redacted] was assessed based on 2 complementary (Q)SAR prediction methodologies to meet the requirements of ICH M7(R1) (step 4) guidelines: an expert rule-based (DEREK) and a statistically based Leadscope Model Applier (LSMA), given that there were no mutagenicity data in a literature search.

[redacted] was predicted to be plausible for in vitro mutagenicity by DEREK analysis based on the presence of a structural alert [redacted]. The LSMA predicted with a positive probability of [redacted], close to the indeterminate range based on the presence of a [redacted] feature. Therefore, [redacted] was considered potentially mutagenic and classified as Class 3, per ICH M7 and the expert review concluded that it should be controlled to the appropriate Threshold of Toxicological Concern (TTC) or tested for mutagenicity. Accordingly, the sponsor conducted two in vitro genetic toxicology tests for this degradant that were negative (see **Genetic Toxicology** section for details).

The Mutagenic and Toxic Potential of 3 (b) (4) Degradation Products: (b) (4) and (b) (4) (Study #MRS-NC-01)

In silico analyses on the potential toxicity and mutagenicity of the 3 degradants, (b) (4) and (b) (4) were conducted because no data are publicly available on the toxicological or mutagenic potential of these identified degradation products. In this report, the sponsor stated that resolution of the precise structure of the second degradation product is ongoing, but the assessment of both (b) (4) structures are addressed.

Two complementary (Q)SAR prediction methodologies (statistical-based and expert-rule based) were used to evaluate the potential of (b) (4) and (b) (4) according to ICH M7 guideline. Based on these results, information on related structure was employed to construct a margin of safety (MOS) for estimating PDE to these degradation products.

Table 14: Proposed Specification Limits for Identified Impurities

(b) (4)

Mutagenicity: According to DEREK (Version 6.0.0 Nexus 2.2.0) results, (b) (4) can exist as a (b) (4) did not match any structural alerts or examples of bacterial mutagenicity in DEREK. Because none of these impurities possessed any misclassified or unclassified features, the degradation products were predicted to be negative for mutagenicity using expert rule-based DEREK methodology. Misclassified features are defined as substructures that have been identified from non-alerting mutagens in the Lhasa Ames test reference set (i.e., false negative). Unclassified features are defined as not present in the Lhasa Ames test references set.

In the statistical-based LSMA models, predicted probability values were less than (b) (4), and (b) (4), respectively, supporting a negative contribution for mutagenicity. In addition, given that more than 90% of the nearest 50 reported analogs were accurately predicted for their respective potential mutagenic effect, this further supports the prediction call regarding negative mutagenic potential. As such, (b) (4)

(b) (4) and (b) (4) were predicted to be Class 5 non-mutagenic compounds per ICH M7 guideline.

Additional toxicity: The DEREK model alerted for α2μ-globulin nephropathy for (b) (4) and the (b) (4) at the doubted level. It has shown that the α2μ-globulin protein is found only in rats and has a binding site of finite size around 0.2 nm^3. Thus, chemicals with a molecular volume significantly > 0.2 nm^3 (equivalent to approximately 350 g/mol) will be unable to bind to the protein and thus cannot lead to α2μ-globulin nephropathy. Considering that the molecular weights of (b) (4), and (b) (4) ranged between approximately (b) (4) and (b) (4) g/mol and α2μ-globulin nephropathy is a species (rat) specific process, α2μ-globulin nephropathy is deemed not relevant for human risk assessment.

Reviewer Note: *This reviewer agrees with the sponsor that the α2μ-globulin nephropathy is gender- and species-specific, restricted to male rats, and does not generally occur in any other laboratory species or in humans. The amount of α2μ-globulin eliminated in the urine of female rats is up to 300 times lower than in male rats (Eur J Biochem 134:175, 1983).*

Carcinogenicity: (b) (4), and (b) (4) alerted for carcinogenicity at the EQUIVOCAL level in multiple species based on structure similarity (b) (4) as highlighted in Figure 1 below.

Figure 1: Substructure Responsible for the Equivocal Carcinogenic Alert in DEREK Model for (b) (4), and (b) (4)

Feature highlighted in gray signifies the substructures associated with the carcinogenic alert.

Based on available data and the structural similarities of identified impurities to the carcinogenic compounds, (b) (4), it is reasonable to predict that (b) (4), and (b) (4) may promote or induce carcinogenic activity. The predicted activity of these degradation products would be expected to be similar to (b) (4), which is present at a much higher concentration than the degradation products.

Teratogenicity: (b) (4), and (b) (4) alerted for teratogenicity at the plausible level in multiple species. Currently, the exact mechanism of teratogenic action is not completely understood, (b) (4)

Based on available data (b) (4), it is reasonable to predict that these impurities may induce teratogenic activity.

The following table summarizes results for the assessed degradation products using an expert-rule based methodology, DEREK (Nexus 6.0.0, version 2.2.0) and statistical-based methodology, Leadscope Model Applier (LSMA version 2.4.5-7).

Table 15: (Q)SAR Summaries for Requested Impurities

Structures	DEREK Results	LSMA Result**	ICH M7 Class	(Q)SAR Appendices
(b) (4)	**Mutagenicity *in vitro* (no misclassified or unclassified features) is INACTIVE in:** - Bacterium - *E. coli* - *S. typhimurium* **Carcinogenicity is EQUIVOCAL** (b) (4) **in:** - Multiple species* **Teratogenicity is PLAUSIBLE** (b) (4) **in:** - Multiple species*	**Overall Prediction: NEGATIVE** (Q)SAR Prediction: Negative Positive Prediction Probability: (b) (4)	Class 5	DEREK Appendix A1 LSMA Appendix A2

Structures	DEREK Results	LSMA Result**	ICH M7 Class	(Q)SAR Appendices
(b) (4)	**Mutagenicity *in vitro* (no misclassified or unclassified features) is INACTIVE in:** - Bacterium - *E. coli* - *S. typhimurium* **Carcinogenicity is EQUIVOCAL** (b) (4) **in:** - Multiple species* **Teratogenicity is PLAUSIBLE** (b) (4) **in:** - Multiple species*	**Overall Prediction: NEGATIVE** (Q)SAR Prediction: Negative Positive Prediction Probability: (b) (4)	Class 5	DEREK Appendix B1 LSMA Appendix B2
	Mutagenicity *in vitro* (no misclassified or unclassified features) is INACTIVE in: - Bacterium - *E. coli* - *S. typhimurium* **Carcinogenicity is EQUIVOCAL** (b) (4) **in:** - Multiple species* **Teratogenicity is PLAUSIBLE** (b) (4) **in:** - Multiple species*	**Overall Prediction: NEGATIVE** (Q)SAR Prediction: Negative Positive Prediction Probability: (b) (4)	Class 5	DEREK Appendix C1 LSMA Appendix C2
	Mutagenicity *in vitro* (no misclassified or unclassified features) is INACTIVE in: - Bacterium - *E. coli* - *S. typhimurium* **Carcinogenicity is EQUIVOCAL** (b) (4) **in:** - Multiple species* **Teratogenicity is PLAUSIBLE** (b) (4) **in:** - Multiple species*			

LSMA, Leadscope Model Applier
*Multiple species include dog, guinea pig, hamster, human, mammal, monkey, mouse, primate, rabbit, rat, rodent
**Leadscope Positive Mutagenicity Prediction Probability (b) (4)

Calculation of PDE Values: The MOS values for the impurities were determined as the calculated PDE (permissible daily exposure) limit divided by the worst-case scenario exposure level for these impurities as described in the equation below.

$$\text{MOS} = \frac{\text{Calculated PDE level for impurity of interest}}{\text{Anticipated daily amount of patient exposure to impurity in drug of interest}}$$

A MOS level at or above 1 is considered safe for exposure for each impurity of interest in the oral drug of interest.

Considering that toxicological data are not available for (b) (4) and (b) (4), PDE levels for these compounds were based on toxicological information available for surrogate compounds, (b) (4) and (b) (4) that share similar chemical and physical properties (see Table below).

Table 16: Structural Comparisons between (b) (4) and (b) (4) with the Surrogates, (b) (4) Impurities

Impurities of interest	Surrogate compounds
(b) (4)	

[redacted], the dosage level at [redacted] mg/day was selected because this was the most conservative level accepted [redacted], and a conservative safety precaution because of the unknown toxicological effects of the impurities, [redacted] and [redacted]. No further modifying factors were needed because the PDE limit of [redacted] mg/day has been accepted in humans and [redacted], and [redacted] are [redacted].

When compared to proposed acceptance criteria levels for these impurities in TU (drug substance) in SOV2012-F1 (drug product), MOS levels (which are values for the safety level of compounds or substances of interest) were well above 1 at the maximum recommended dose of 800 mg/day TU for all the degradants.

11 Integrated Summary and Safety Evaluation

Marius Pharmaceuticals, LLC has submitted an NDA for an oral administration of testosterone undecanoate (TU), an FDA approved drug substance for the treatment of primary and hypogonadotropic hypogonadism characterized by serum T levels <300 ng/dL in combination with at least one clinical sign or symptom consistent with diagnosis. The sponsor is seeking marketing approval for the new SOV2012-F1 formulation under the provisions of Section 505(b)(2). The sponsor's recommended starting dose is 200 mg taken orally BID, once in the morning and once in the evening [redacted]. Dosing can be adjusted with the minimum recommended dose of 100 mg once daily in the morning and the maximum recommended dose of 400 mg TU, BID depending on plasma T levels (< 460 ng/dL for up-titration and > 971 ng/dL for down-titration).

TU is the undecanoic acid (C-11 linear, alkyl) ester and the prodrug of T that is readily hydrolyzed via local and systemic non-specific esterases to T and undecanoic acid. The key physicochemical character of TU is its high lipophilicity compared to T, with estimated log P = 6.5. As such, TU is absorbed through the lymphatic system, rather than through the portal vein circulatory system.

Undecanoic acid (1-decanecarboxylic acid, hendecanoic acid, undecylic acid; N-undecanoic acid; N-undecoic acid) is an 11-carbon, medium chain length saturated fatty acid that is incorporated into glycerides and phospholipids and metabolized by β-oxidation to acetyl coenzyme A (CoA) and, in the final step, propionyl CoA. Undecanoic acid 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 identified as an approved food additive up to the maximum level of 2 ppm (2 mg/kg, 120 mg for a 60 kg person) in baked goods according to FEMA Flavor Ingredient Library. [redacted].

To date, the sponsor has conducted 10 clinical trials, including a comparative bioavailability study for different test formulations and two phase 3 studies with up to 12-month duration at doses titrated up to 1000 mg daily (#MRS-TU-2019). Initial clinical trials were focused on (b) (4) formulations, chemical and physical stability of the capsule fill (b) (4), and the relative biopharmaceutical performance of various formulations to create a stable (b) (4) formulation.

The original proprietor, SOV Therapeutics, completed several nonclinical studies including in vitro binding studies of TU, DHTU, and (b) (4) to assess potential interactions with estrogen and androgen receptors; a distribution and excretion study of SOV2012-F1 in rats; a 90-day oral repeated BID dose toxicology study in male dogs using formulations with and without phytosterol esters; and an oral BID fertility study in male rats using SOV2012-F1. Evaluation of phytosterols was based on a request from the Division to conduct nonclinical studies examining the affinity of these phytosterol esters excipients for the same targets of TU and/or their effects on the PK/toxicity profile of TU. This was due to similarities in phytosterol ester structure to sex steroids and the potential for accumulation in target organ tissues such as the liver, adrenal gland, and gonads.

The current sponsor conducted in silico (computational) assessments, in vitro mutagenicity assays, and in vitro plasma stability studies to qualify the degradants detected in the long-term stability studies, as requested at the pre-NDA meeting. To support chronic use of the excipients that are not present or exceed levels in currently approved orally administered products, the sponsor provided supporting data obtained from published literature including acceptable daily intake levels and DMF numbers.

The following summary is based on the results from the sponsor's own studies and the summary of literature references included in the submission.

Inactive Ingredients: SOV2012-F1 contains 100 mg, 150 mg, or 200 mg TU per soft gel capsule in a (b) (4), designed to promote absorption of TU (b) (4) by the lymphatic system.

The SOV2012-F1 formulation consists of (b) (4) (propylene glycol monolaurate), (b) (4) (polyoxyl-40 hydrogenated castor oil), (b) (4) *dl*-alpha-tocopherol acetate, and (b) (4) (phytosterol esters) as formulation excipients.

Phytosterol esters are not present as an excipient in currently approved orally administered products. (b) (4) and *dl*-alpha-tocopherol acetate are present in SOV2012-F1 at higher amounts than currently listed in the FDA Inactive Ingredient Database (IID).

Table 17: List of (b) (4) Inactive Ingredients in SOV2012-F1 (Clinical, Nonclinical, and Commercial Formulations)

Inactive Ingredient in (b) (4)	CAS No.	Unit Dose (mg) [1]	MRHDD [2] (mg)	FDA IID MDE (mg)
Propylene glycol monolaurate ((b) (4))	(b) (4)			
Polyoxyl 40 hydrogenated castor oil (b) (4)				
dl-α-Tocopherol acetate				
Phytosterol esters (b) (4)				

MRHDD = Maximum Recommended Human Daily Dose; FDA IID = FDA Inactive Ingredient Database; MDE = Maximum Daily Exposure;
[1]SOV2012-F1 200 mg TU unit dose capsule
[2]MRHDD = 4 x 200 mg TU capsules (800 mg TU/day)

(b) (4)

Propylene glycol esters of fatty acids are mixtures of propylene glycol mono- and diesters of saturated and unsaturated fatty acids derived from edible oils and fats. These are approved for use as food additives according to 21 CFR 172.856. The Scientific Committee on Food (SCF) in 1978 endorsed the acceptable daily intake (ADI) of 25 mg/kg/day, expressed as propane-1,2-diol of fatty acids, established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1974. (b) (4) is extensively hydrolyzed in the GI tract to (b) (4) and (b) (4). (b) (4) and other fatty acids are naturally occurring products of triglyceride digestion and have Generally Recognized as Safe (GRAS) status. Additional safety information for (b) (4) is found in DMF (b) (4) and a Letter of Authorization is included in the NDA submission. (b) (4) is present in (b) (4) therefore qualifying the proposed amount in SOV2012-F1.

DL-α-Tocopherol acetate (synthetic form of vitamin E) is a dietary supplement, listed as GRAS by FDA CFSAN (21 CFR 184.1890). JECFA has assigned an average daily intake of 0.15-2 mg/kg/day (9-120 mg/day for an individual with an average weight of 60 kg for α-tocopherol acetate (JECFA 30/55). This range covers the (b) (4) mg MRHDD in SOV2012-F1.

Although different average daily doses of various vitamin E and its derivatives are listed in FDA IID, USP considers all forms of vitamin E interchangeable. Biologically, the esterified forms of vitamin E are considered to deliver vitamin E following hydrolysis of the ester linkage. (b) (4) in terms of the active vitamin E, which is greater than the (b) (4) mg total daily exposure of all-*racemic*-α tocopherol acetate delivered at the maximum recommended human daily dose (MRHDD) of 800 mg of SOV2012-F1. On a mass basis, using the formula weights of vitamin E and vitamin E acetate, 246 mg of vitamin E is equivalent to 270 mg of vitamin E acetate.

[redacted] (phytosterol esters) consists of [redacted] of total sterols. Phytosterols are not listed in the FDA IID but are affirmed as GRAS use as a direct food additive in the United States and by JECFA in Europe and other countries (JECFA 2008). [redacted]. Plant sterol esters are also available as dietary supplements in the United States. Although varied diets typically contain similar amounts of phytosterols and cholesterol, serum phytosterol concentrations are usually several hundred times lower than serum cholesterol concentrations in humans (von Bergmann 2005). Less than 2% of dietary phytosterols are systemically absorbed, in contrast to about 50-60% of dietary cholesterol (Ostlund 2002). Low serum concentrations of phytosterols relative to cholesterol are a consequence of decreased intestinal absorption and increased excretion of phytosterols into bile (Sudhop 2005).

Commercially, phytosterols are isolated from vegetable oils, such as soybean oil, rapeseed (canola) oil, sunflower oil or corn oil, or from so-called "tall oil", a by-product of the manufacture of wood pulp (Cantrill 2008). By definition, plant sterol/stanol esters are a component of food and may also carry an FDA food health claim "… to be consumed as part of a diet low in saturated fat and cholesterol" (21 CFR 101.83). Dietary intake of phytosterols ranges from 150 to 400 mg/day in a typical western diet. The ADI level determined by JECFA is 40 mg/kg/day, based on an overall NOAEL of 4200 mg/kg/day in animal studies to which a safety factor of 100 was applied (JECFA 2009).

In addition, a 90-day repeated dose oral toxicity study in male dogs was conducted with SOV2012-F1, [redacted], and [redacted] DL-α-tocopherol acetate with and without TU at dose levels of ~2-fold higher TU than the MRHDD of 800 mg/day. Taken together, the excipients in [redacted] at the proposed levels used in the SOV21012-F1 formulation are considered qualified.

Degradation Products: In silico and in vitro studies on multiple degradants were conducted during the long-term stability studies with the drug product: [redacted] at RRT [redacted] and RRT [redacted] (up to [redacted]% after 6 months storage at 40°C/75%RH), [redacted] at RRT [redacted] ([redacted]% after 6 months storage at 40°C/75%RH), and [redacted] at RRT [redacted] ([redacted]% after 6 months at 40°C/75%RH; [redacted]% after 24-month at 25°C/60%RH; [redacted]% after 36 months at 25°C/60%RH) .

The sponsor's proposed specification limits are NMT [redacted]% for [redacted], NMT [redacted]% for [redacted], and NMT [redacted]% for [redacted]. The impurity [redacted] degradant was initially identified as a [redacted] but was subsequently identified and confirmed as [redacted] according to the sponsor. The degradant [redacted] also exists as [redacted] and RRT [redacted], but only one [redacted]) appears to be present at levels above the ICH Q3B qualification limit of 0.2%. For the three degradants [redacted]

(b) (4)

(b) (4): The drug substance manufacturer ((b) (4)) had performed a (Q)SAR mutagenicity assessment and reported this degradant to have no structural alerts in sections of DMF (b) (4) supplied to the sponsor. No mutagenicity or toxicity data were found in the published scientific literature for this degradant.

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

The sponsor's calculated safety margin was ~(b) (4)-fold (800 mg/day ÷ (b) (4) mg/day) for (b) (4) at the proposed specification of (b) (4)%, ~(b) (4)-fold (800 mg/day ÷ (b) (4)mg/day) for (b) (4) at the proposed specification of NMT (b) (4)%, and ~(b) (4)-fold (800 mg/day ÷ (b) (4) mg/day) for the (b) (4) at the proposed specification of NMT (b) (4)% for the maximum recommended dose of 800 mg/day TU.

Taken together, the sponsor's justification for the proposed specification limits for the identified degradants appears reasonable. The degradants (b) (4), and (b) (4) are considered qualified based on the absence of structural alerts for (b) (4) and (b) (4), the negative results from in vitro genotoxicity assays with (b) (4), the formation of the (b) (4) and (b) (4) degradants in dog and human plasma with incubation of the (b) (4) degradant, along with information from the published scientific literature. (b) (4) . Although all of these degradation products were predicted to possess potential carcinogenic and teratogenic effects based on their (b) (4) sub-structural features, respectively, impurity-associated fetal harm is unlikely given that (b) (4) and this drug product is not intended for pregnant women or women of child-bearing age.

Pharmacology: The sponsor has not conducted any nonclinical studies with the drug substance or drug product to assess primary pharmacodynamics, safety pharmacology, or pharmacodynamic interactions. These areas of nonclinical safety are already well-documented. The sponsor, however, completed in vitro displacement of specific radiolabeled ligand agonist binding to cell-derived human estrogen and androgen receptors with TU, DHTU, and (b) (4) (excipient component) as requested by the

Division to address the question of how phytosterol esters may exhibit affinity for the same targets of TU and its metabolites due to similarities in structure to sex steroids.

The in vitro binding study showed mean percent inhibition of androgen or estrogen ligand-specific binding of <50% by TU at 10 µM (~456700 ng/dL), DHTU at 5 µM (~229350 ng/dL), and [redacted] ng/dL), which are approximately 5-34 fold, 8-72 fold, and [redacted] fold greater than the minimum and maximum plasma C_{max} levels for TU, DHTU, and [redacted] respectively, at the maximum recommended human daily dose of TU 800 mg (Study #MRS-TU-2019EXT). These results indicate that TU, DHTU, and [redacted] may not significantly affect the ligand-specific agonist binding of SOV2021-F1 to estrogen or androgen receptor at clinically relevant C_{max} concentrations. The low androgen binding for TU and DHTU suggests that the T esters may not possess androgenic activity and likely act via active metabolites of this pro-drug, including T.

Absorption, Distribution, Metabolism, and Elimination: Measurement of plasma levels of TU and its metabolites in pivotal clinical and nonclinical studies were conducted with inclusion of NaF/EDTA in samples to inhibit esterase activity based on the potential for post-collection conversion of the T ester to T. Blood samples (plasma or serum) collected from subjects receiving T pro-drugs (T esters such as TU) typically undergo post-collection conversion of the T ester to T, and have unstable T concentrations due to endogenous non-specific esterases that induce conversion (LaChance, 2015). Although dose titration was based on NaF/EDTA plasma T levels in both Phase 3 studies, serum T concentrations are typically used in clinical practice. Therefore, to determine the correlation between plasma and serum-based titration thresholds, the sponsor examined T concentrations over 3- to 5-hour, 4- to 6- hour, and 3- to 6-hour windows in NaF/EDTA plasma and serum samples in Study #MRS-TU-2019EXT. The results indicate that no significant differences in serum or plasma C_{avg} were observed between the 3, 4, or 5-hour post-dose sample collection times (see Clinical Pharmacology Review for details).

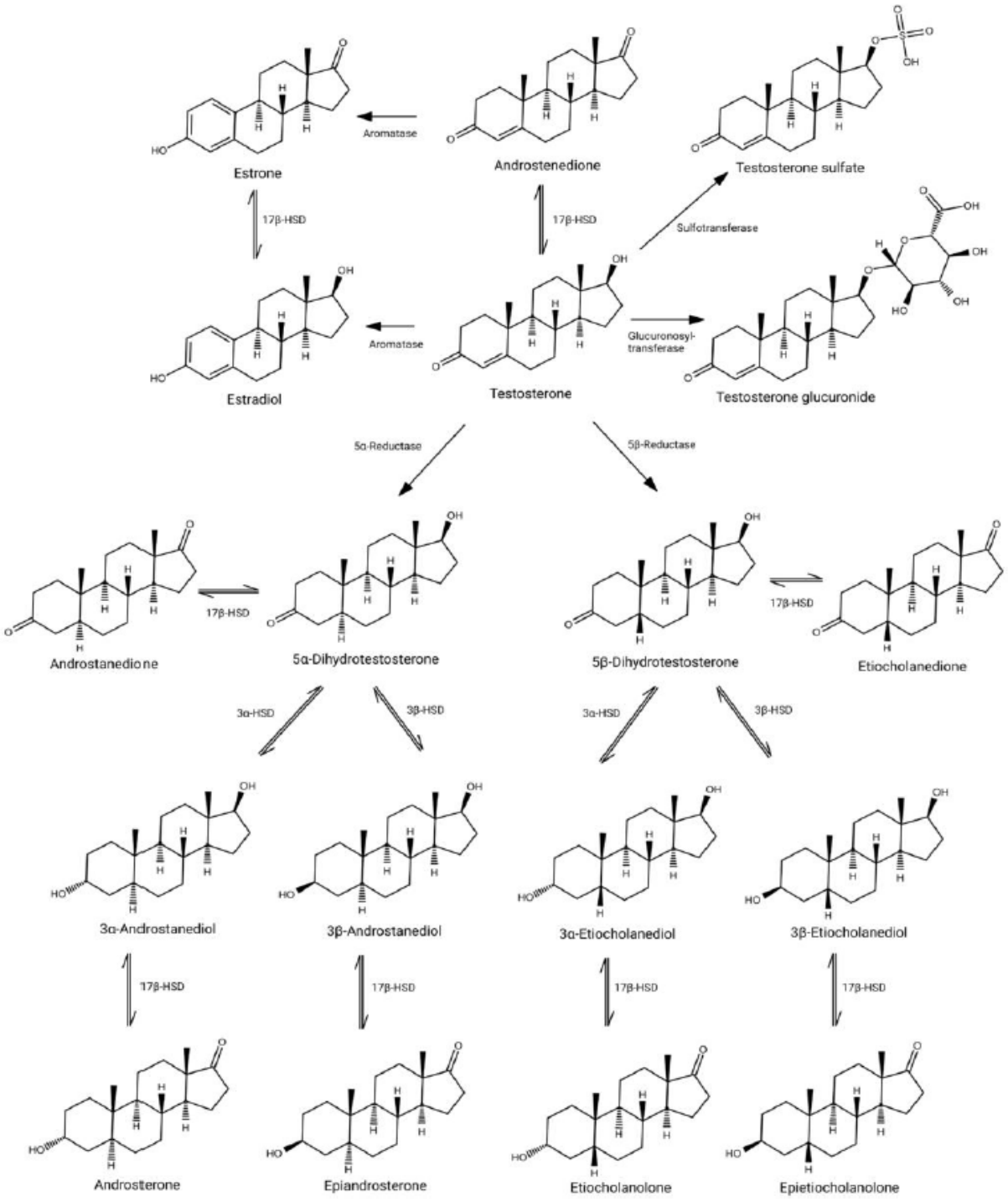
In the tissue distribution and excretion study in male Sprague Dawley rats conducted by the sponsor, there was extensive distribution to all investigated tissues at 1 hour with the maximum concentration between 2 to 6 hour post-dose following a single [redacted] mg/kg oral dose (~40 mg/kg TU) of the complete Formulation 1 with phytosterol esters ([redacted] mg) and Formulation 2 without phytosterol esters. The radioactivity was below the limit of quantification at 168 hour post-dose apart from the epididymis for Formulation 1 with phytosterol esters and apart from the liver for Formulation 2 without phytosterol esters.

The highest radioactivity was detected in the GI tract (small intestine, stomach) followed by prostate, perirenal white fat, seminal vesicle, epididymal white fat, liver, kidneys, adrenal gland, plasma, testes, heart, blood, lungs, levator ani, preputial gland, epididymis, skin, and muscle at 4 hours with the complete Formulation 1. The dosed radioactivity was fully recovered within 168 hour post-dose and was primarily recovered in feces. The prolonged radioactivity in the epididymis at the final sampling time of 168

hours for the formulation with phytosterol esters (half-life unknown) suggests potential tissue retention and/or accumulation of the excipient and/or the drug-related materials.

Fatty acid esters of T including T propionate, T enanthate, and TU are partially cleaved by non-specific esterases in vivo to release the parent compound, T (IARC Monograph, 1979). In the human body, circulating T is mainly bound in serum to sex hormone-binding globulin (SHBG) and albumin (only ~2% unbound), while the fatty acid ester side chain is metabolized by the β-oxidation pathway (DrugBank, 2020). T undergoes subsequent reduction by different pathways to yield a variety of 17-keto steroids. The primary metabolites of T biotransformation are 5α/β-dihydrotestosterone (5α/β-DHT) and estradiol, which are metabolized by 5α/β-reductase and aromatase, respectively. When T is metabolized by 5α/β-reductase, production of 5α-DHT is deemed as the active metabolite, while 5β-DHT is defined as the inactive metabolite. Formation of 5α-DHT and 5β-DHT are then converted by 3α/β-hydroxy-steroid dehydrogenase to produce 3α/β-androstanediol and 3α/β-etiocholanediol, respectively. 17β-Hydroxy-steroid dehydrogenase (17β-HSD) further converts 3α/β-androstanediol into androsterone and epiandrosterone, while 3α/β-etiocholanediol is converted into etiocholanolone and epietiocholanolone. Production of aforementioned metabolites are then conjugated via sulfation (i.e., sulfotransferases) and glucuronidation (i.e., glucuronosyltransferases). In addition to bioconversion of T to estradiol and 5α/β-DHT, T can be metabolized by glucuronosyltransferases, sulfotransferases and 17β-HSD to generate T glucuronide, T sulfate and androstenedione, respectively, as illustrated in the figure below. In addition to production of active and inactive T metabolites, it is suggested that T is metabolized by the CYP2C and CYP3A enzymes to form hydroxylated metabolites at positions 2α-, 2β-, 6β-, 15α-, 11β-, 15β-, and 16β- as identified from reactions using recombinant CYP3A enzyme and/or human liver microsome assays (Kandel et al., 2017; Niwa et al., 2015).

Figure 2: Metabolic Pathways Involved in Biotransformation of T in Humans



PK drug interaction studies were not identified in the public database. The sponsor stated that the mean T C_{max} for SOV2012-F1 was 892 ng/dL after 90 days (Study MRS-TU-2019EXT) which was lower than or comparable to C_{max} values for other approved TU products (e.g., T C_{max} of ~1000 ng/dL for an oral TU product, ~800 ng/dL for an intramuscular TU product (Barbonetti, 2020; Swerdloff, 2020). As such, there is no

potential for a greater risk of object or precipitant drug interactions for the TU product compared to other TU products currently approved for use in the United States (see Clinical Pharmacology Review for details).

General Toxicology: Some acute toxicity data are available for T enanthate and T propionate in the public domain. The oral LD_{50} values of the T esters are > 1000 mg/kg in mice and 1000 mg/kg in rats (ChemIDplus, 2020).

Table 18: Toxicological Effects of Testosterone Enanthate and Testosterone Propionate

Assay	Species	Route	Exposure	Effect	References
Testosterone enanthate					
Acute Dose Toxicity	Human (male)	Intramuscular	Single	TD_{Lo} = 7519 mg/kg	ChemIDplus, 2020
	Mouse	Intraperitoneal	Single	LD_{50} = 1770 mg/kg	
	Mouse	Oral	Single	LD_{50} > 3000 mg/kg	
	Mouse	Subcutaneous	Single	LD_{50} > 5000 mg/kg	
	Rat	Intraperitoneal	Single	LD_{50} = 755 mg/kg	
	Rat	Oral	Single	LD_{50} = 1000 mg/kg	
	Rat	Subcutaneous	Single	LD_{50} = 5000 mg/kg	
Testosterone propionate					
Acute Toxicity	Mouse	Intraperitoneal	Single	LD_{50} = 970 mg/kg	ChemIDplus, 2020
	Mouse	Oral	Single	LD_{50} = 1350 mg/kg	
	Mouse	Subcutaneous	Single	LD_{50} >5000 mg/kg	
	Rat	Intraperitoneal	Single	LD_{50} = 585 mg/kg	
	Rat	Oral	Single	LD_{50} = 1000 mg/kg	
	Rat	Subcutaneous	Single	LD_{50} >5000 mg/kg	

TD_{Lo}: the lowest toxic single dose

A 13-week toxicology study was conducted in male dogs to assess the effects of the phytosterol esters excipient that may exhibit affinity for the same targets and/or affect the PK/toxicity profile of the TU product due to similarities in structure to sex steroids and potential for accumulation in target organ tissues. The Division was concerned that the proposed TU formulation (b) (4) (designed to promote TU absorption) is highly lipophilic and may accumulate in lipid-rich and/or well-perfused tissues and organs such as the adrenal gland, gonads, liver, kidney, fat, and heart following repeated administration.

Neither new nor significant findings have been identified in the toxicology study that were not previously observed with T up to approximately 5 times (AUC) to 8 times (C_{max}) higher TU exposure than the mean human exposures given 400 mg TU, BID. Treatment-related effects were noted in the testis (decreased size associated with marked germ cell depletion and Leydig cell atrophy), epididymis (marked aspermia), adrenal glands (slight vacuolation of the zona fasciculata) and prostate gland (increased size associated with moderate glandular hypertrophy/hyperplasia) in TU groups with or without phytosterol esters. Following a 4-week drug-free period, the findings in the testes (germ cell depletion), epididymides (aspermia), and adrenal glands (vacuolation of the zona fasciculata) were fully reversed in treated groups without phytosterol esters, but not in the high-dose group with phytosterol esters.

These findings occurred at exposures of T less than or comparable to the maximum proposed human dose (400 mg TU BID) based on the maximum $AUC_{0\text{-}24h}$ (~38000 ng·hr/dL) and the maximum C_{max} (~1800 ng/dL) measured in male subjects (Study #MRS-TU-2019EXT). The mean plasma exposures to TU, DHTU, T, and DHT at the dose were approximately 3-, <1-, 2-, and 2-fold the $AUC_{0\text{-}24h}$ and approximately 6-, <1-, 4-, and 3-fold the C_{max}, respectively, of the mean human exposure at 400 mg BID. The plasma phytosterols measured in the study were approximately (b) (4)-fold the mean $AUC_{0\text{-}24h}$ and C_{max} for (b) (4) at 400 mg TU, BID (Table below). No significant differences were observed in plasma levels of TU and its metabolites or estradiol levels with or without phytosterol esters under the conditions of the study.

Table 19: Summary of Exposure Multiples in Humans Taking 400 mg BID Oral TU Based on the Low Dose of SOV2012-F1 in Male Dogs

Species	Compound / TK parameters	TU	DHTU	T	DHT	(b) (4)
Human (Day 84/90)	**$AUC_{0\text{-}24h}$**, ng·hr/mL	~1870	~920	~90	~18	(b) (4)
	C_{max}, ng/mL	~380	~135	~9	~1.2	
Dog (Day 90)	**$AUC_{0\text{-}24h}$**, ng·hr/mL	~6300	~260	~190	~30	
	C_{max}, ng/mL	~2490	~39	~35	~4	
EM	**$AUC_{0\text{-}24h}$**	3	<1	2	2	
	C_{max}	6	<1	4	3	

EM: exposure multiples

The findings in the adrenal gland could be secondary to androgen excess associated with TU treatment. TU may also disrupt normal steroidogenesis in the adrenal cortex and/or perturb the hypothalamic-pituitary-adrenal (HPA) axis, resulting in altered secretion and metabolism of adrenocorticotropic hormone (ACTH). The exogenous androgen and/or phytosterols may result in accumulation or retention in the adrenal glands and may cause an effect following chronic treatment. As such, a subset of patients was tested in a clinical trial, assessing an effect of the new formulation on HPA axis in hypogonadal men.

In the cosyntropin stimulation sub-study under MRS-TU-2019, there were no significant differences in cortisol responses to synthetic ACTH between the SOV2012-F1 (n=30) and AndroGel (n=15) groups at 30 and 60 minutes both at baseline and after 365 days with the numerically greater post-ACTH cortisol levels in both groups at the end of the study, suggesting that the administration of the exogenous TU may not be associated with adrenal insufficiency (see Clinical Review for details).

Systemic exposures to phytosterol esters were similar between the low-dose and high-dose groups, suggesting saturation of absorption of the phytosterol esters. The systemic exposures to TU and its metabolites tended to increase in a less than dose-proportional manner between the 12 mg/kg BID and the 24 mg/kg BID doses tested without accumulation upon repeat-dosing, indicating that phytosterols may not exhibit effect on the 5-alpha reductase enzyme which converts TU to DHTU and T to DHT. Similar phytosterol AUC and C_{max} values were observed when values from complete formulation with TU (SOV2012-F1) were compared to those from excipients only,

suggesting that the administration of TU may not affect the absorption of the phytosterols. Mean baseline plasma concentrations of T were similar between the control (1.1-4.6 ng/mL) and the 2X excipients only Group 4 (0.8-3.5 ng/mL) males on Day 1 and Day 90, indicating the excipients had no apparent effect on endogenous T levels. The similar T or estradiol levels between the control and the excipient groups indicate there was no significant effect of the excipients on endogenous T or estradiol levels. The higher AUC values for estradiol with 2X SOV2012-F1 Group 6 than with control group indicate some conversion of TU or T to estradiol. In addition, the absence of differences in total systemic exposures (dose normalized) to T or DHT in the presence (Groups 5 and 6) or absence (Group 8) of phytosterol esters indicates that the excipients may not exhibit activity against the 5α-reductase enzyme which converts T to DHT.

Phytosterols are plant-derived steroids that are known to act as endocrine-disrupting chemicals (Mol Cell Endocrinol 442:98, 2017; Toxicol Appl Pharmacol 178:22, 2002; Life Sci 67:605, 2000), and their endocrine-disrupting activity has been reported in animals and humans (Poult Sci 96:3436, 2017; Int J Pharm Pharma Sci 8:88, 2016; J Lipid Res 54:397, 2013; Endocrine 41:338, 2012; Eur J Clin Pharmacol 157:S61, 2007; J Nutr Biochem 9:712, 1998). In humans with rare phytosterolaemia (sitosterolaemia), there was accumulation of elevated plant sterol levels that may interfere with endocrine hormone synthesis, particularly for adrenal cholesterol metabolism, accounting for adrenal insufficiency (Eur J Endocrinol 157:S61, 2007). Studies have also reported that the intake of oxidized phytosterols are atherogenic (Mol Nutr Food Res 59:1339, 2015; Food Chem Toxicol 69:140, 2014; Atherosclerosis 227:414, 2013; Nutr Metab Cardiovasc Dis 16:13, 2006; J Am Coll Cardiol 48:708, 2006) although the risk remains to be established.

There are a considerable number of studies that have reported the potential endocrine and reproductive effects of phytosterols. Studies have shown that the phytosterols and their oxidation products can produce estrogenic, anti-estrogenic, antiprogestational, gonadotrophic, antigonadotrophic, and antiandrogenic effects (Adv Food Nutr Res 90:351, 2019; Mol Cell Endocrinol 442:98, 2017; Steroids 77:1502, 2012; Mol Nutr Food Res 51:888, 2006; Int J Toxicol 23:23, 2004; J Ethnopharmacol 35:149, 1993; Med Sci Res 19:821, 1991). Studies have also shown that phytosterols may accumulate in tissues such as the brain, liver, adrenal gland, ovary, and testis, indicating the high affinity for steroid-synthesizing tissues, possibly due to the long elimination half-life of phytosterol esters (e.g., (b) (4)) (Steroids 99:183, 2015; J Lipid Res 53:726, 2012; Drug Metab Dispos 40:2026, 2012; J Lipid Res 43:1072, 2002; Lipids 13:427, 1978; Biochim Biophys Acta 306:95, 1973; Proc Soc Exp Biol Med 108:810, 1961). A recent study suggests that phytosterols may also play a role in regulation of the hypothalamic-pituitary-gonadal (HPG) axis in the reproductive endocrine functions of male Japanese quails by inducing the expression of gonadotropin-inhibitory hormone in the brain and testes that results in reduction of gonadotropin-releasing hormone gene expression and luteinizing hormone secretion, and subsequent attenuation of T production by the testes. Moreover, phytosterols may

induce gonadotropin-inhibitory hormone and its receptor locally in the Leydig cells of quail testes, and thereby perturb T production (Poult Sci 97:1066, 2018).

In the sponsor's conducted study, there was no influence of the phytosterol esters on the incidence of androgen-related findings up to the levels within the exposure achieved in humans given 400 mg TU, BID from the 84-day repeat-dosing Phase 2b study (Study #SOV-TU-PK2013). Thus, it is unlikely that the phytosterols in this formulation would have an effect on the toxicity or PK profiles of TU at the anticipated plasma concentrations of TU and its metabolites. However, the persistent effect in the target organs at the end of the 4-week treatment-free period and the greater exposure (no half-life provided) to phytosterol esters in the dog following 90-day daily dosing of the complete formulation at the high dose suggest that the potential role of phytosterol esters on the steroid receptors and/or reproductive endocrine function cannot be completely ruled out upon prolonged administration of the TU formulation at high systemic exposures.

The sponsor also provided information on the toxicology and safety of chronic exposure to T documented through published literature. Target organs identified in animals receiving T or related esters in chronic or extended dosing schemes are mainly hormone-sensitive reproductive organs/tissues. The most prominent of these are the prostate (hypertrophy/hyperplasia) with up to 6 months exposure in rodents, dogs, and nonhuman primates (Li, 2018; Karr, 1984; Udayakumar, 1998), seminal vesicles (increased weight) and testes (atrophy) with up to 3-month exposure in rats (Trimel BioPharma SRL, 2014; Chin & Pennefather, 1990; Bansal, 1986; Flickinger ,1978; Mohd, 2013), uterus (myometrium growth) with up to 25 months of exposure in rabbits (Meissner, 1966), and mammary glands (ductal proliferation and acinotubular differentiation) with up to 6 months of exposure in rats (Chambô-Filho, 2005), and are likely related to disturbances in the physiological pituitary/hypothalamus LH/FSH feedback system. Other organs/tissues can also be affected by chronic exposure to T, including the adrenal gland (atrophy of the zona fasciculata) with chronic administration in rats (Mazzocchi, 1983), muscle (increased mass) with dosing for 8 weeks or more in rats (Gao, 2005), and altered liver function with dosing for up to 32 months in nonhuman primates (Tyagi, 1999; Nucci, 2017).

Genetic Toxicology: The sponsor did not conduct genotoxicity tests for the SOV2012-F1 oral TU but provided a genotoxicity profile of T reported in the literature. T and related androgens were negative in vitro for mutagenic (e.g., bacterial reverse mutation assays) and clastogenic activity, for unscheduled DNA synthesis, and in vivo mouse micronucleus assays (IARC, 1987; Morita, 1997; Joosten, 2004). An absence of DNA adducts was reported (Feser, 1998). In vivo tests with T in mice did not show evidence of chromosomal aberrations (sperm head morphology and chromosomal aberrations bone marrow) (Hana, 2008).

The potential mutagenic impurity, [redacted] (b) (4) at 31.2% was negative in the in vitro Ames test and micronucleus tests under the conditions of the studies.

Carcinogenicity: The sponsor has not conducted any carcinogenicity bioassays for the SOV2012-F1 oral TU but provided a summary of literature findings on the carcinogenicity potential of T in support of class labelling for SOV2012-F1.

A substantial body of literature demonstrates that, as expected for a hormonally active compound, tumor incidence can be increased in hormonally responsive organs and tissues with expressed receptors for T (and T esters) including, for example, endometrium (Van Nie, 1961), ovary (Beamer, 1988), uterus (Van Nie et al., 1961), mammary glands (Xie, 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 (Gianitrapani, 2006; Reuber, 1976). As such, the International Agency for Research on Cancer (IARC, 1979) concluded that there is sufficient evidence (Group 2A) for the carcinogenicity of T and related androgens in experimental animals; however, evidence in humans was inconclusive (IARC 1987). T is most probably associated with an increased risk for carcinogenicity through epigenetic mechanisms as genotoxicity data are overall negative. In vitro, T increased transformation frequency of Syrian Hamster Embryo (SHE) cells when co-incubated with a promotor, 12-O-tetradecanoyl-phorbol-13-acetate (Lasne, 1990). Both T and T propionate were also noted to cause some degree of morphological transformation in SHE cells (Tsutsui, 1997), consistent with an epigenetic mechanism and with tumor promoting properties.

T has been tested by subcutaneous injection and implantation in mice and rats. In mice, the T implant induced cervical-uterine tumors, which metastasized in some cases (Glucksmann and Cherry, 1968). There is suggestive evidence that injection of T into some strains of female mice increases their susceptibility to hepatoma (Agnew, 1952). T is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats (Firminger, 1961).

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).

Reproductive and Developmental Toxicology: The sponsor conducted a fertility and early embryonic developmental toxicology study in male rats for the new TU formulation (no historical control data provided) and also provided a summary of published literature, documenting the reproductive and developmental effects of T.

In the fertility study, healthy male rats administered (b) (4) mg/kg BID ((b) (4) mg/kg/day) of SOV2012-F1 showed expected responses from exposures to T. These included elevated number of non-gravid females, reduced fertility index (71%), and increased mean percent pre-implantation loss (34%) associated with lower mean total litter size, mean total number of implantation sites, and mean number of viable fetuses per litter in untreated gravid females mated with males compared to control group. Dose-related decrease in absolute male reproductive organ weights (epididymis up to ~29%, testis up to ~45%, prostate up to ~23%) in all treated groups and decrease in uterus weights (~30%) of untreated females mated with high dose males compared to those mated with control group were noted. In addition, there was dose-related decrease in mean body weights (up to ~9%) and body weight gains (up to ~82% on Day 60) starting from dosing Day 8 and during the entire dosing period in treated males, with statistical significance at (b) (4) mg/kg/day. Reduced mean body weight gains (up to ~34%) were observed in untreated females mated with treated males during GDs 14 - 18 and GD 18 at (b) (4) mg/kg/day compared to control group, possibly secondary to lower maternal uterine weights.

T plasma levels observed on Days 1 and 71 tended to increase in a less than dose-proportional manner over the dosing range when TU was given twice daily, while the formation of DHT was roughly dose-proportional to the TU dose administered. The mean T baseline concentration observed at pre-dose on Day 1 was 1.69 and 5.41 ng/mL in TK Groups 4 ((b) (4) mg/kg BID) and 5 ((b) (4) mg/kg BID), respectively. The mean baseline level was within 8% to 31% of the mean maximum T concentrations observed on Day 1. Pre-dose DHT concentrations were only observed in animals from Group 5 on Day 71. Exposures to T and DHT at the NOAEL ((b) (4) mg/kg BID) and high dose ((b) (4) mg/kg/BID) were approximately ≤1- and 2-fold for $AUC_{0\text{-}24h}$ and 2-and 4-fold for C_{max}, respectively, the mean human exposure at 400 mg TU, BID (Study #MRS-TU-2019EXT).

T is a potent androgenic hormone and its effects on developing fetuses are pronounced. Numerous studies have been published to determine fetal effects of T (T propionate, T enanthate) following various routes 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. Prenatal or neonatal T propionate also acted as an endocrine disruptor adversely affecting steroidogenesis (Biol Repro 137:1, 2012; Biol Repro 35:1321, 1986). Administration of T or T ester to adult or neonatal animals suppressed testicular weights, spermatogenesis, and fertility in several species (Zhang,

2016; McLachlan, 2002; Jezek, 1993; Feigelson, 1986; Robaire, 1984), which were reversible on cessation of the treatment.

Exposure of a fetus to T may result in varying degrees of virilization. The exposure of young female animals to T resulted in life-long changes characterized by androgenization. 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 various species. Irreversible ovary-independent vaginal cornification and uterine stratification with or without squamous metaplasia and fighting behavior later in life have been noted in mice following subcutaneous or intraperitoneal administration of T (Gandelman, 1979). Across multiple species, masculinization of the fetus anatomically and increases in aggressive behavior, are the end results of exposure to T during neonatal development (Wolf, 2002; Dela Cruz, 2012; Eisner, 2002).

T is contraindicated during pregnancy or in women who may become pregnant. T and T esters (T enanthate or T propionate) are teratogenic and embryotoxic in animals, and adversely affect 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 post-natal 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. T produced negative effects to dams, including delayed parturition, reduced litter size and low pup viability, resorptions or still births, masculinization, and reduced milk production (Hotchkiss, 2007; Wolf, 2002; Fels, 1971; Swanson, 1965).

Summary and Conclusion: From the Pharmacology and Toxicology perspective, the submitted nonclinical studies and relevant published literature are considered adequate to characterize the potential effects of the new oral TU formulation following chronic administration.

The pharmacology, PK, and toxicology profiles of endogenous and therapeutically administered T are well established in animals and humans. Although the utility of animal models for evaluating potential hormonally-dependent adverse effects is limited due to different intraspecies and interspecies responses, the findings in the studies were consistent with those observed with other T products. The adverse effects observed in eugonadal animals are expected androgenic effects at T levels above the baseline exposure levels (AUC ~3 times and C_{max} ~6 times) that are not anticipated to occur in hypogonadal men exposed to T in the eugonadal range. The findings in the adrenal glands (slight vacuolation of the zona fasciculata) are of unknown clinical

significance. It is unlikely that the phytosterols would have an effect on the expected pharmacology, toxicity, or absorption of TU in this formulation within the anticipated systemic exposure levels in men.

The potential risk of exposure of the TU formulation to women including pregnant women, fetuses, or women of reproductive potential will be communicated in the warning and contraindications sections under the labeled conditions of use. (b) (4) .

Pharmacology/toxicology recommends approval of KYZATREX (oral TU) for treatment of primary or hypogonadotropic hypogonadism.

12 Appendix/Attachments

12.1 References

The following references were provided within the submission. These do not include reviewer's references included in this review.

Agematu H, Matsumoto N, Fujii Y, et al. Hydroxylation of testosterone by bacterial cytochromes P450 using the Escherichia coli expression system. Biosci Biotechnol Biochem. 2006;70(1):307-311.

Agnew LR, Gardner WU. The incidence of spontaneous hepatomas in C3H, C3H (low milk factor), and CBA mice and the effect of estrogen and androgen on the occurrence of these tumors in C3H mice. Cancer Res. 1952 Oct;12(10):757-61.

Amory, J. K., Kalhorn, T. F., & Page, S. T. (2008). Pharmacokinetics and pharmacodynamics of oral testosterone enanthate plus dutasteride for 4 weeks in normal men: implications for male hormonal contraception. *Journal of andrology*, *29*(3), 260-271.

Bansal MR, Davies AG. Effect of testosterone oenanthate on spermatogenesis and serum testosterone concentrations in adult mice. J Reprod Fertil. 1986;78:219-224.

Barbonetti A, D'Andrea S, Francavilla S. Testosterone replacement therapy. Andrology. 2020 Nov;8(6):1551-1566. doi: 10.1111/andr.12774. Epub 2020 Mar 9.

Beamer WG, Shultz KL, Tennent BJ, Shultz LD. Granulosa cell tumorigenesis in genetically hypogonadal-immunodeficient mice grafted with ovaries from tumor-susceptible donors. Cancer Res. 1993 Aug 15;53(16):3741-6.

Bhasin S, et al. Testosterone therapy in men with hypogonadism: An Endocrine Society clinical practice guideline. J. Endocrinol Metab. 2018 May; 103(5): 1715-1744.

Cantrill, R. Phytosterols, Phytostanols and their Esters: Chemical and Technical Assessment. 2008: http://www.fao.org/fileadmin/templates/agns/pdf/jecfa/cta/69/Phytosterols.pdf

Chambô-Filho A, Camargos AF, Pereira FE. Morphological changes induced by testosterone in the mammary glands of female Wistar rats. Braz J Med Biol Res. 38: 553-558 (2005).

Chao, J., Rubinow, K. B., Kratz, M., Amory, J. K., Matsumoto, A. M., & Page, S. T. (2016). Short-Term Estrogen Withdrawal Increases Adiposity in Healthy Men. *The Journal of clinical endocrinology and metabolism*, *101*(10), 3724-3731.

ChemIDPlus. (2020). Available at: https://chem.nlm.nih.gov/chemidplus/

Chin, J. P., & Pennefather, J. N. (1990). Effect of long-term administration of testosterone oenanthate on sympathetic neurotransmission to rat isolated seminal vesicles. *Clinical and experimental pharmacology & physiology*, *17*(10), 713-724.

Dela Cruz C, Pereira OC. Prenatal testosterone supplementation alters puberty onset, aggressive behavior, and partner preference in adult male rats. J Physiol Sci. 2012 Mar;62(2):123-31.

(b) (4)

Dobs, A. S., Meikle, A. W., Arver, S., Sanders, S. W., Caramelli, K. E., & Mazer, N. A. (1999). Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism*, *84*(10), 3469-3478.

Drugbank. (2020). DrugBank Version 5.1.5. Accessed 12 January 2020.

Eisner JR, Barnett MA, Dumesic DA, Abbott DH. Ovarian hyperandrogenism in adult female rhesus monkeys exposed to prenatal androgen excess. Fertil Steril. 2002 Jan;77(1):167-72.

(b) (4)

(b) (4)

FDA GRAS Notifications (GR) 387, 61, 250, 176, and 177. https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?order=DESC&set=GRASNotices&search=Ajinomoto&cat=&sort=Substance&startrow=201&type=advanced

Feigelson M. Suppression of testicular maturation and fertility following androgen administration to neonatal male rats. Biol Reprod. 1986 Dec;35(5):1321-32.

Fels E, Bosch LR. Effect of prenatal administration of testosterone on ovarian function in rats. Am J Obstet Gynecol. 1971 Dec 1;111(7):964-9.

Feser W, Kerdar RS, Baumann A, Körber J, Blode H, Kuhnz W. DNA adduct formation of selected sex steroids in human liver slices in vitro. Toxicol In Vitro. 1998 Aug;12(4):353-64.

Fessner, Nico & Srdic, Matic & Weber, Hansjörg & Schmid, Christian & Schoenauer, David & Schwaneberg, Ulrich & Glieder, Anton. (2020). Preparative-Scale Production of Testosterone Metabolites by Human Liver Cytochrome P450 3A4. Advanced Synthesis & Catalysis. 362.10.1002/adsc.202000251

Firminger HI, Reuber MD. Influence of adrenocortical, androgenic, and anabolic hormones on the development of carcinoma and cirrhosis of the liver in A x C rats fed N-2-fluorenyldicetamide. J Natl Cancer Inst. 1961 Sep;27:559-95.

Flickinger C. Effects of testosterone enanthate on the structure of the male reproductive tract of the rat. Anat Rec. 192: 555-584 (1978).

Foti RS and Dalvie DK. Cytochrome P450 and Non-Cytochrome P450 oxidative metabolism: Contributions to the pharmacokinetics, safety, and efficacy of xenobiotics. Drug Metab Dispos 44: 1229-1245, 2016.

Gandelman R, Simon NG, McDermott NJ. Prenatal exposure to testosterone and its precursors influences morphology and later behavioral responsiveness to testosterone of female mice. Physiol Behav. 1979 Jul;23(1):23-6.

Gao, W., Bohl, C. E., & Dalton, J. T. (2005). Chemistry and structural biology of androgen receptor. *Chemical reviews*, *105*(9), 3352-3370.

Gao W, Reiser PJ, Coss CC, Phelps MA, Kearbey JD, Miller DD, Dalton JT. Selective androgen receptor modulator treatment improves muscle strength and body composition and prevents bone loss in orchidectomized rats. Endocrinology 146: 4887-4897 (2005).

(b) (4)

Giannitrapani L, Soresi M, La Spada E, Cervello M, D'Alessandro N, Montalto G. Sex hormones and risk of liver tumor. Ann N Y Acad Sci. 2006 Nov;1089:228-36.

Glucksmann A, Cherry CP. The effect of oestrogens, testosterone and progesterone on the induction of cervico-vaginal tumours in intact and castrate rats. Br J Cancer. 1968 Sep;22(3):545-62.

Hana HY, Khalil WK, Elmakawy AI, Elmegeed GA. Androgenic profile and genotoxicity evaluation of testosterone propionate and novel synthesized heterocyclic steroids. J Steroid Biochem Mol Biol. 2008 Jun;110(3-5):284-94.

Hotchkiss AK, Lambright CS, Ostby JS, Parks-Saldutti L, Vandenbergh JG, Gray LE Jr. Prenatal testosterone exposure permanently masculinizes anogenital distance, nipple development, and reproductive tract morphology in female Sprague-Dawley rats. Toxicol Sci. 2007 Apr;96(2):335-45.

IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Sex Hormone (II). Testosterone, Testosterone Oenanthate and Testosterone Propionate. 1979 Dec; 21: 519-547.

IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Androgenic (anabolic) Steroids. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs, vols. 1 to 42, 1987, Suppl. 7, 96-99.

IARC Monograph. (1979). International Agency for Research on Cancer. on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 21. Sex hormones (II). *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 21. Sex hormones (II).*

JECFA 30/55 (1987): Joint FAO/WHO Expert Committee on Food Additives (JEFCA): alpha-Tocopherol : http://www.inchem.org/documents/jecfa/jecmono/v21je05.htm

JECFA (2008): WHO Joint FAO/WHO Expert Committee on Food Additives. Phytosterols, Phytostanols and Their Esters.

JEFCA (2009): Safety Evaluation of Certain Food Additives. WHO Food Additives Series 60. Phytosterols, phytostanols and their esters, pages 117-163.
Jezek D, Simunić-Banek L, Pezerović-Panijan R. Effects of high doses of testosterone propionate and testosterone enanthate on rat seminiferous tubules-a stereological and cytological study. Arch Toxicol. 1993;67(2):131-40.

Joosten HF, van Acker FA, van den Dobbelsteen DJ, Horbach GJ, Krajnc EI. Genotoxicity of hormonal steroids. Toxicol Lett. 2004 Jun 15;151(1):113-34.

Kaminetsky, J., Jaffe, J. S., & Swerdloff, R. S. (2015). Pharmacokinetic profile of subcutaneous testosterone enanthate delivered via a novel, prefilled single-use autoinjector: a phase ii study. *Sexual medicine*, *3*(4), 269-279.

Kandel, S. E., Han, L. W., Mao, Q., & Lampe, J. N. (2017). Digging deeper into CYP3A testosterone metabolism: kinetic, regioselectivity, and stereoselectivity differences between CYP3A4/5 and CYP3A7. *Drug Metabolism and Disposition*, *45*(12), 1266-1275.

Karr JP, Kim U, Resko JA, Schneider S, Chai LS, Murphy GP, Sandburg AA. Induction of benign prostatic hypertrophy in baboons. Urology 3: 276-289 (1984).

(b) (4)

Kawano S, Kamataki T, Yasumori T, Yamazoe Y, Kato R. Purification of human liver cytochrome P-450 catalyzing testosterone 6 beta-hydroxylation. J Biochem. 1987;102(3):493-501.

(b) (4)

Lasne C, Lu YP, Orfila L, Ventura L, Chouroulinkov I. Study of various transforming effects of the anabolic agents trenbolone and testosterone on Syrian hamster embryo cells. Carcinogenesis. 1990 Apr;11(4):541-7.

Leder BZ, Catlin DH, Longcope C, Ahrens B, Schoenfeld DA, Finkelstein JS. Metabolism of orally administered androstenedione in young men. J Clin Endocrin Metab 86: 3654-3658, 2001.

Leder BZ, Catlin DH, Longcope C, Ahrens B, Schoenfeld DA, Finkelstein JS. Metabolism of orally administered androstenedione in young men. J Clin Endocrin Metab 86: 3654-3658, 2001.

(b) (4)

Lhasa. (2020). DEREK 6.0.0. Nexus 2.2.0 Accessed 10 January 2020. Lhasa Ltd., Leeds, United Kingdom

Li J, Tian Y, Guo S, Gu H, Yuan Q, Xie X. Testosterone-induced benign prostatic hyperplasia rat and dog as facile models to assess drugs targeting lower urinary tract symptoms. PLoS ONE 13(1): e0191469.

Mazzocchi G, Malendowicz LK, Robba C, Rebuffat P, Gottardo G, Meneghelli V, Nussdorfer GG. Effects of testosterone on the zona fasciculata of the male rat adrenal cortex. A correlated stereological and biochemical study. J Submicrosc Cytol. 15: 991-1005 (1983).

McLachlan RI, O'Donnell L, Meachem SJ, Stanton PG, de Kretser DM, Pratis K, Robertson DM. Identification of specific sites of hormonal regulation in spermatogenesis in rats, monkeys, and man. Recent Prog Horm Res. 2002;57:149-79.

Meissner, W.A. & Sommers, S.C. Endometrial changes after prolonged progesterone and testosterone administration to rabbits. Cancer Res. 26: 474-478 (1996).

Mohd Mutalip SS, Surindar Singh GK, Mohd Shah A, Mohamad M, Mani V, Hussin SN. Histological changes in testes of rats treated with testosterone, nandrolone, and stanozolol. Iran J Reprod Med. 11: 653-658.

Morita T, Asano N, Awogi T, Sasaki YF, Sato S, Shimada H, Sutou S, Suzuki T, Wakata A, Sofuni T, Hayashi M. Evaluation of the rodent micronucleus assay in the screening of IARC carcinogens (groups 1, 2A and 2B) the summary report of the 6th collaborative study by CSGMT/JEMS MMS. Collaborative Study of the Micronucleus Group Test. Mammalian Mutagenicity Study Group. Mutat Res. 1997 Feb 28;389(1):3-122.

Niwa, T., Murayama, N., Imagawa, Y., & Yamazaki, H. (2015). Regioselective hydroxylation of steroid hormones by human cytochromes P450. *Drug metabolism reviews*, *47*(2), 89-110.

Noguchi T, Charman WNA, Stella VJ (1985): The effect of drug lipophilicity and lipid vehicles on the lymphatic absorption of various testosterone esters. International Journal of Pharmaceutics 24: 173-184.

Nucci RAB, Teodoro ACS, Krause Neto W, Silva WA, de Souza RR, Anaruma CA, Gama EF. Effects of testosterone administration on liver structure and function in aging rats. Aging Male 20:134-137 (2017).

Ostlund RE Jr. Phytosterols in human nutrition. Annu Rev Nutr. 2002;22:533-49.

Pollard, M., & Luckert, P. H. (1986). Promotional effects of testosterone and high fat diet on the development of autochthonous prostate cancer in rats. *Cancer letters*, *32*(2), 223-227.

PubChem-A: CID 6013 Testosterone:
https://pubchem.ncbi.nlm.nih.gov/compound/Testosterone

PubChem-B: CID 65157 Testosterone undecanoate:
https://pubchem.ncbi.nlm.nih.gov/compound/Testosterone-undecanoate

(b) (4)

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.

Robaire B, Smith S, Hales BF. Suppression of spermatogenesis by testosterone in adult male rats: effect on fertility, pregnancy outcome and progeny. Biol Reprod. 1984 Sep;31(2):221-30.

(b) (4)

Snyder PJ. Androgens. Chapter 41 in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition, pages 1195-1208 (2011).

Sudhop T, Lütjohann D, von Bergmann K. Sterol transporters: targets of natural sterols and new lipid lowering drugs. Pharmacol Ther. 2005 Mar;105(3):333-41.

Swanson HE, Werff ten Bosch JJ. The "early-androgen" syndrome; effects of pre-natal testosterone propionate. Acta Endocrinol (Copenh). 1965 Nov;50(3):379-90.

Swerdloff RS, Wang C, White WB, Kaminetsky J, Gittelman MC, Longstreth JA, Dudley RE, Danoff TM. A New Oral Testosterone Undecanoate Formulation Restores Testosterone to Normal Concentrations in Hypogonadal Men. J Clin Endocrinol Metab. 2020 Aug 1;105(8):2515-31. Erratum in: J Clin Endocrinol Metab. 2020 Dec 1;105(12).

(b) (4)

(b) (4)

Tsutsui T, Komine A, Huff J, Barrett JC. Effects of testosterone, testosterone propionate, 17 beta-trenbolone and progesterone on cell transformation and mutagenesis in Syrian hamster embryo cells. Carcinogenesis. 1995 Jun;16(6):1329-33.

(b) (4)

Tyagi A, Rajalakshmi M, Jeyaraj DA, Sharma RS, Bajaj JS. Effects of long -term treatment with testosterone enanthate. II. Effects on lipids-, high- and low-density lipoprotein cholesterol and liver function parameters. International Journal of Andrology 22: 347-355 (1999).

Udayakumar TS, Tyagi A, Rajalakshmi M, Das SN, Hashim S, Bajaj JS. Changes in structure and functions of prostate by long-term administration of androgen, testosterone enanthate, in rhesus monkey (Macaca mulatta). The Anatomical Record 252: 637-645 (1998).

US Code of Federal Regulation 21CFR 184.1890:

US Code of Federal Regulation 21CFR 101.83: Health claims: plant sterol/stanol esters and risk of coronary heart disease (CHD)

(b) (4)

Van Nie R, Benedetti E, Muhlbock OA. Carcinogenic Action of Testosterone, Provoking Uterine Tumours in Mice. Nature 192, 1303 (1961).

von Bergmann K, Sudhop T, Lütjohann D. Cholesterol and plant sterol absorption: recent insights. Am J Cardiol. 2005 Jul 4;96(1A):10D-14D.

WHO 1962. Estradiol-17beta-, progesterone, and testosterone (WHO Food Additives Series 43)

Wikipedia contributors. (2020, February 24). Testosterone. In Wikipedia, The Free Encyclopedia. Retrieved 15:54, February 27, 2020.

Wolf CJ, Hotchkiss A, Ostby JS, LeBlanc GA, Gray LE Jr. Effects of prenatal testosterone propionate on the sexual development of male and female rats: a dose-response study. Toxicology Sciences 2002 Jan;65(1):71-86.

Xie B, Tsao SW, Wong YC. Sex hormone-induced mammary carcinogenesis in female Noble rats: the role of androgens. Carcinogenesis. 20 (8) 1597-1606, 1999.

(b) (4)

Yucel, S., Cavalcanti, A. G., Desouza, A., Wang, Z., & Baskin, L. S. (2003). The effect of oestrogen and testosterone on the urethral seam of the developing male mouse genital tubercle. *BJU international*, *92*(9), 1016-1021.

Zhang XW, Zhang C, Zhang W, Yang D, Meng S, Wang P, Guo J, Liu DH. Suppression of spermatogenesis by testosterone undecanoate-loaded injectable in situ-forming implants in adult male rats. Asian J Androl. 2016 Sep-Oct;18(5):791-7.

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/s/

YANGMEE SHIN
10/21/2021 05:07:07 PM

KIMBERLY P HATFIELD
10/21/2021 05:13:50 PM
I concur with the review and recommendations of Dr. Shin.