CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213953Orig1s000

OTHER REVIEW(S)

Clinical Safety Review
Jordan Dimitrakoff, MD, PhD
NDA 213953
Kyzatrex (testosterone undecanoate)

SAFETY 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)	Jordan Dimitrakoff, MD, PhD
Review Completion Date	June 29, 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	Approval
Recommended Indication(s)/Population(s) (if applicable)	

1. Review of Safety

1.1. Safety Review Approach

No new studies were included in the resubmission. See the Unireview for the first review cycle entered in DARRTS on October 22, 2021, for a discussion of the safety database, clinical safety assessments, safety results, submission-specific safety issues, safety analyses by demographic subgroups, and specific safety studies.

1.2. Safety Update

The Sponsor provided a PubMed literature search analysis performed to review the recent efficacy and safety literature for oral testosterone undecanoate (TU). The search term was comprised of "testosterone undecanoate oral" from 01 January 2020 to 17 March 2022. The Sponsor noted that NDA 213953 was submitted on December 31st, 2020, and included a literature review for the 5-year period 2015 through 2019. Therefore, the current literature survey covers the time from the previous literature review to the DSUR cut-off date of March 17th, 2022, for IND 118675.

The Sponsor identified a total of 27 relevant references. PubMed was also searched using the Chemical Abstracts System identifier for TU; no additional relevant articles for oral TU were found. After review of the extracted references, the Sponsor included a total of 7 references in their analysis (6 clinical study reports and 1 systematic/meta-analysis review).

The reasons for excluding other references were as follows: one report was an editorial comment on pediatric use for micropenis, one study was for treatment of type 2 diabetes, two reports were editorial summaries related to another testosterone product, one article discussed oral dosing of testosterone in animals, two reports were corrections to reviewed articles on another testosterone product, one in-vitro study investigated strawberry effects on hydrolysis of TU, three studies were on use of oral TU in pediatric settings, one study was for oral TU in the treatment of "late-onset" hypogonadism in men – the paper is in Chinese and was not translated (the abstract noted that no significant adverse effects were observed), one study concerned hypothalamic- pituitary-gonadal axis and sexual functioning discontinuation effects related to oral TU in metformin-treated men, one study examined only formulation considerations, six reports were concerned with formulation or animal models for conditions or drug combinations unrelated to Kyzatrex, and one study was concerned with use of dried blood spots for anabolic steroid testing. Other references identified using the search term "testosterone undecanoate" did not address safety or were concerned with the efficacy of TU injections.

Individual Summaries

Six of the seven abstract summaries submitted by the Sponsor relate to other approved testosterone products and are excluded from the present memorandum. The only study related to Kyzatrex™ is presented in more detail below.

White and Bernstein *et al.* [PMID 34114726] analyzed the ambulatory blood pressure effects of Kyzatrex™ (an unapproved oral TU medication and subject of NDA 213953) in 155 hypogonadal men at 120 and 180 days. Mean age was 50.5 years, 76.8% white, 36.1% on antihypertensive therapy. The ABP, heart rate and clinical assessments were obtained at baseline and following 120 and 180 days of therapy. Mean changes from baseline in 24-h ambulatory systolic BP of 1.7 mmHg (95% CI, 0.3, 3.1) at day 120 and 1.8 mmHg (95% CI, 0.3, 3.2) at day 180 were observed post-treatment. For those men on antihypertensive drug therapy, increases in mean 24-h systolic BP were greater than those not taking antihypertensive drugs (3.4 vs 0.7 mmHg at day 120 and 3.1 vs 1.0 mmHg at day 180, respectively). Changes from baseline in 24-h diastolic BP and heart rate at day 120 were smaller (<1 mmHg and <1 beat/min, respectively). There were no relationships observed between testosterone concentration or hemoglobin levels with ABP. Multivariable analyses showed that baseline ambulatory BP and antihypertensive therapy were significantly correlated with BP changes. These data demonstrate small increases in ambulatory BP following 120 days on this oral testosterone undecanoate with no further changes at 180 days. Changes in ambulatory BP were minimal in patients not taking antihypertensive therapy

Overall summary of blood pressure effects

As blood pressure effects are a significant safety focus for the testosterone replacement therapy, the Sponsor presented ambulatory BP data from White and Bernstein *et al.* [PMID 34114726, Table 1]. Study populations were broadly similar in age and other characteristics, although the study by White and Bernstein *et al.* has a slightly lower proportion of hypertensive subjects than the other studies (35% hypertensive versus 48% and 52%).

Table 1: Summary ambulatory blood pressure results for oral TU at baseline and change from baseline after 4 months (Modified from Sponsor submission, SDN 0043)

Reference/Subgroup	Systolic BP (mmHg)		Diastolic BP (mmHg)		Heart Rate (beats/minute)	
	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
White and Bernstein *et al.* 2021 (Kyzatrex) (95% CI)						
All subjects (n = 153)	128.9 (126.8,	1.7 (0.3, 3.1)	76.2	0.6	76.3	0.7

	131.0)		(74.6, 77.9)	(-0.3, 1.6)	(74.4, 78.3)	(-0.5, 1.9)
With antihypertensive therapy (n = 491)	131.3 (127.8, 134.8)	3.4 (1.0, 5.9)	75.9 (73.3, 78.6)	1.8 (0.2, 3.5)	75.8 (72.6, 79.3)	1.3 (−0.9, 3.5)
Without antihypertensive therapy (*n* = 90[1])	127.9 (124.9, 130.9)	0.7 (−1.0, 2.4)	78.2 (75.8, 80.5)	0.0 (−1.2, 1.2)	76.9 (73.9, 79.8)	0.4 (−1.1, 1.9)
With diabetes mellitus (*n* = 29[1])	130.8 (125.9, 135.6)	3.0 (−0.2, 6.2)	76.3 (73.1, 79.6)	1.7 (−0.3, 3.7)	77.7 (73.7, 81.7)	1.9 (−1.1, 4.9)
Without diabetes mellitus (*n* = 110[1])	127.9 (125.8, 130.1)	1.3 (−0.2, 2.9)	76.9 (75.2, 78.6)	0.4 (−0.8, 1.5)	74.5 (72.4, 76.6)	0.4 (−1.0, 1.7)

Abbreviations: NP - Not Published
[1]Population after 4 months

Based on the Sponsor submission, there have been no significant changes regarding the overall safety profile of oral testosterone undecanoate. The publications during this time period reported specifics of efficacy and safety for two approved oral TU products, including ambulatory blood pressure effects. For the unapproved product, Kyzatrex™, the publication focused on ambulatory blood pressure effects. There were no new non-clinical toxicology studies. In the non-clinical study reports examined, TU was used to assess pharmacological activity or as an example in formulation development studies.

2. Conclusions

No new studies were conducted and based on the PubMed review submitted by the Sponsor, there have been no significant changer of the overall safety profile of oral testosterone undecanoate.

3. Recommendation

From the safety perspective, an approval is recommended for the resubmission of NDA 213953.

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/s/

JORDAN D DIMITRAKOFF
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SURESH KAUL
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	June 28, 2022
To:	Jeannie Roule Regulatory Health Project Manager **Division of Urology, Obstetrics and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	KYZATREX (testosterone undecanoate)
Dosage Form and Route:	capsules, for oral use, CIII
Application Type/Number:	NDA 213953
Applicant:	Marius Pharmaceuticals

1 INTRODUCTION

On January 27, 2022, Marius Pharmaceuticals submitted for the Agency's review, a Resubmission to the original New Drug Application (NDA) 213953 for KYZATREX (testosterone undecanoate) capsules, for oral use, CIII. The original NDA for KYZATREX (testosterone undecanoate) capsules, for oral use, CIII was submitted on December 31, 2020, and received a Complete Response (CR) on October 21, 2021, due to Clinical/Clinical Pharmacology issues.

The proposed indication for KYZATREX (testosterone undecanoate) capsules, for oral use, CIII is for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Urology, Obstetrics and Gynecology (DUOG) on February 3, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KYZATREX (testosterone undecanoate) capsules, for oral use, CIII.

2 MATERIAL REVIEWED

- Draft KYZATREX (testosterone undecanoate) capsules, for oral use, CIII MG received on January 27, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on June 23, 2022.
- Draft KYZATREX (testosterone undecanoate) capsules, for oral use, CIII, MG received on January 27, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on June 23, 2022.
- Draft KYZATREX (testosterone undecanoate) capsules, for oral use, CIII Prescribing Information (PI) received on January 27, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on June 23, 2022.
- Draft KYZATREX (testosterone undecanoate) capsules, for oral use, CIII Prescribing Information (PI) received on January 27, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on June 23, 2022.
- Approved TLANDO (testosterone undecanoate) capsules, for oral use, CIII comparator labeling dated March 28, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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ELVY M VARGHESE
06/28/2022 01:27:20 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 28, 2022

To: Martin E. Kaufman, Clinical Reviewer
Division of Urology, Obstetrics, and Gynecology (DUOG)

Jordan D. Dimitrakoff, Clinical Reviewer, DUOG

Jeannie Roule, Regulatory Project Manager, DUOG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James S. Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for KYZATREX (testosterone undecanoate) capsules, for oral use CIII

NDA: 213953

In response to DUOG's consult request dated February 3, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG), and carton and container labeling for KYZATREX (testosterone undecanoate) capsules, for oral use, CIII (Kyzatrek).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DUOG (Jeannie Roule) on June 22, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on June 28, 2022.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 9, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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/s/

ELVY M VARGHESE
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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 24, 2022

To: Christine Nguyen, MD, Director
Division of Urology, Obstetrics, and Gynecology (DUOG)

Through: Dominic Chiapperino, PhD, Director
Joshua Lloyd, MD, Medical Officer
Team Leader Controlled Substance Staff

From: Shalini Bansil, MD,
Medical Officer
Controlled
Substance Staff

Subject: **NDA 213953** (product developed under IND 118675)
Product: Kyzatrex (testosterone undecanoate) Soft Gelatin Capsules
Dosage: 100 mg daily- 400 mg twice daily, orally
Indication: Treatment of male hypogonadism
Applicant: Marius Pharmaceuticals
PDUFA Goal Date: July 27, 2022

Materials Reviewed:

- SDN 38, January 27, 2022, NDA resubmission
- CSS review of Original NDA submission, Joshua Hunt; DARRTS September 30, 2021

1. Background

This memorandum responds to a consult request from the Division of Urology, Obstetrics, and Gynecology (DUOG) dated January 27, 2022, to the Controlled Substance Staff (CSS) for Kyzatrex (testosterone undecanoate) Soft Gelatin Capsules, NDA 213953, developed under IND 118675 by Marius Pharmaceuticals (referred to as "the Applicant"). DUOG requests that CSS provide input regarding abuse and dependence potential and review Section 9 (Drug Abuse and Dependence) of the submitted package insert (PI).

The original New Drug Application (NDA) was submitted December 31, 2020, and a Complete Response action was taken on October 22, 2021, because the integrity and reliability of the pharmacokinetic (PK) data could not be assured, and thus, it could not be concluded that there was substantial evidence of effectiveness for the product.

On January 27, 2022, the Applicant resubmitted their NDA for Kyzatrex (testosterone undecanoate) oral capsules with further analysis to substantiate that the PK (Cmax) outliers of concern were not a result of drug effect.

No new subjects have been dosed with Kyzatrex since the original NDA was submitted, and, therefore, there is no safety update. The Applicant seeks approval for Kyzatrex under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act using published literature only as references.

CSS previously reviewed this application (Joshua Hunt; DARRTS September 30, 2021) and stated: "The adverse event profile for the current product was similar to other marketed oral testosterone undecanoate products (i.e., TLANDO). Outside of a few cases of aggression, which is a known side effect of testosterone pharmacotherapy, the psychological adverse event (AE) profile did not differentiate from placebo."

2. Conclusions

- Kyzatrex contains testosterone undecanoate, which is a schedule III-controlled substance, as defined under the Anabolic Steroids Control Act (effective 1991).
- The Applicant's proposed Section 9 of Kyzatrex product labeling language is consistent with other testosterone products and is acceptable for approval.

3. Recommendations

- CSS has no recommendations for the Applicant at this time.

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DOMINIC CHIAPPERINO
06/24/2022 05:25:37 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 9, 2022
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213953
Product Name and Strength:	Kyzatrex (testosterone undecanoate) capsules 100 mg, 150 mg, and 200 mg
Applicant/Sponsor Name:	Marius Pharmaceuticals, LLC
OSE RCM #:	2020-2763-4
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on June 9, 2022 for Kyzatrex. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels for Kyzatrex (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to the email sent by the Agency on June 7, 2022.

2 REGULATORY HISTORY

NDA 213953 was originally submitted on December 31, 2020. We reviewed the proposed Kyzatrex PI, MG, and container labels and found the container labels acceptable.[a,b,c,d] However, the Office of Pharmaceutical Quality (OPQ) noted that the units on one of the temperature numerals on the container labels was incorrect (i.e., 59°C should be 59°F). Hence, the Agency

[a] Baugh D. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2020 JUN 09. RCM No.: 2020-2763.
[b] Baugh, D. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 AUG 26. RCM No.: 2020-2763-1.
[c] Baugh, D. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 SEP 27. RCM No.: 2020-2763-2.
[d] Kalonia, J. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAR 28. RCM No.: 2020-2763-3.

sent Marius an email on June 7, 2022 requesting they correct this typographical error on the container labels.

3 CONCLUSION

The Applicant implemented all of the Agency's recommendations and we have no additional recommendations at this time.

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/s/

JUSTINE H KALONIA
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STEPHANIE L DEGRAW
06/09/2022 08:51:16 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 28, 2022
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213953
Product Name and Strength:	Kyzatrex (testosterone undecanoate) capsules, 100 mg, 150 mg, and 200 mg
Applicant/Sponsor Name:	Marius Pharmaceuticals, LLC
OSE RCM #:	2020-2763-3
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

On January 27, 2022, Marius submitted their Class 2 Resubmission[a] to provide responses to the deficiencies included in the Agency's Complete Response Letter (CRL) dated October 22, 2021.[b] Thus, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed prescribing information (PI), medication guide (MG), and container labels for Kyzatrex (Appendix A) to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY AND DISCUSSION

NDA 213953 was originally submitted on December 31, 2020. Prior to the issuance of the October 22, 2021 CRL, we reviewed the proposed Kyzatrex PI, MG, and container labels and

[a] Resubmission: Response to CRL and Type A Meeting Comments for Kyzatrex (NDA 213953). Raleigh (NC): Marius Pharmaceuticals, LLC; 2022 JAN 27. Available from: \\CDSESUB1\evsprod\nda213953\0037\m1\us\12-cover-letters\cover-0037.pdf.

[b] Bell, S. Complete Response Letter for Kyzatrex. Silver Spring (MD): FDA, CDER, DUOG (US); 2021 OCT 22. NDA 213953. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8062046f&_afrRedirect=4559489582782125

found the container labels acceptable.[c,d,e] The Applicant's resubmission includes draft PI and MG, as well as the container labels. We confirmed that our previously implemented recommendations were retained on the container labels, however, we find one of our recommendations that we made during the previous review[c] was not implemented in the PI.

3 CONCLUSION

We find the container labels and MG are acceptable from a medication error perspective, however, we found that one recommendation we made in our previous review for the PI labeling was not implemented. Thus, we provide the Division with one recommendation for their consideration below.

4 RECOMMENDATION FOR THE DIVISION OF UROLOGY, OBSTETRICS, AND GYNECOLOGY (DUOG)

We recommend the following recommendation be considered prior to approval of this NDA:

Prescribing Information (PI)

A. In the DOSAGE AND ADMINISTRATION Sections (Highlights and Section 2.3), we note the use of an abbreviation for dose adjustments based on serum testosterone concentrations (i.e., '3-5 hours'). These abbreviations may be misinterpreted. Consider revising '3-5 hours' to read the '3 to 5 hours' to prevent misinterpretation and confusion.

[c] Baugh D. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2020 JUN 09. RCM No.: 2020-2763.

[d] Baugh, D. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 AUG 26. RCM No.: 2020-2763-1.

[e] Baugh, D. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 SEP 27. RCM No.: 2020-2763-2.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JANUARY 27, 2022

- Prescribing Information (image not shown), available from: \\CDSESUB1\evsprod\nda213953\0037\m1\us\114-labeling\draft\labeling\kyzatrex-pi-20220127.docx
- Medication Guide (image not shown), available from: \\CDSESUB1\evsprod\nda213953\0037\m1\us\114-labeling\draft\labeling\kyzatrex-med-guide-20220127.docx

Container labels

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 24, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies
Division of Cardiology and Nephrology / CDER

Through: Norman Stockbridge MD, PhD
Division Director
Division of Cardiology and Nephrology / CDER

To: Jeannie Roule, CPMS
DUOG

Subject: ABPM Study Results NDA 213953 (SDN 0034)

This memo responds to your consult to us dated 1/10/2022 regarding the Division's question of the ABPM study results. The IRT reviewed the following materials:

- Sponsor's briefing material (NDA 213953; SDN 0034); and
- Previous IRT review(s) for NDA 213953 dated *05/26/2021* in DARRTS.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 IRT Responses

Question: DUOG requests the ABPM Team's input on whether the Applicant will need to repeat the ABPM study due to the uncertainties about the blood levels of testosterone in the original study.

IRT Response*: In general, we do not think the sponsor should repeat the ABPM study. Study MRS-TU-2019EXT showed increases in blood pressure on days 120 and 180 which is consistent with other TU products and should be described in product labeling. It's not clear how a new ABPM study would impact the interpretation of the blood pressure findings.*

If, however, DUOG believes that testosterone levels from Kyzatrex in the new study would be significantly higher than other oral TU products, we would recommend a repeat ABPM study.

2 BACKGROUND

2.1 Product information

Marius Pharmaceuticals has developed Kyzatrex as a novel, oral formulation of Testosterone Undecanoate (TU), for the treatment of primary and secondary hypogonadism. Kyzatrex is a soft gelatin capsule containing (b) (4) . TU is an approved drug substance.

FDA issued a Complete Response Letter on October 22, 2021 due to PK issues.

2.2 ABPM Study Findings

The effect of KYZATREX was evaluated in a dedicated ABPM study MRS-TU-2019EXT in 155 subjects, a single-arm, open-label study in hypogonadal men receiving daily dosing titrated to a plasma testosterone of 400 to 900 ng/dL. There was a statistically significant change from baseline in mean 24-h systolic BP. The results for the average parameters for systolic and diastolic BP are shown in Table 1.

Table 1: The 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: IRT Review (dated 05/26/2021)

The missing data percentages across subject per time-point are generally low and without any apparent patterns in missing data indicating good data quality.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cder-ond-abpm@fda.hhs.gov

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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 30, 2021

To: Christine Nguyen, M.D., Director
Division of Urology, Obstetrics, and Gynecology (DUOG)

Through: Dominic Chiapperino, Ph.D., Director
Joshua Lloyd, M.D., Medical Officer Team leader
Controlled Substance Staff

From: Joshua Hunt, PharmD, MPH, Senior Regulatory Reviewer
Controlled Substance Staff (CSS)

Subject: KYZATREX (testosterone undecanoate), 100mg, 150mg, and 200mg capsules
NDA Number: 213953
IND Number: 118675
Indication(s): Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

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

Applicant: Marius Pharmaceuticals LLC
Labeling and PMR communication Goal Date to Applicant: Sep 30, 2021
PDUFA Goal Date: October 31, 2021

Materials Reviewed:

1. Applicant's Labeling/Package Insert Draft, dated March 16, 2021, eCTD sequence number 0010, supporting document number 11
2. NDA 213953 Clinical Filing Review (Efficacy and Safety), dated March 5, 2021, authored by Martin Kaufman, M.D. (Medical Officer - DUOG)

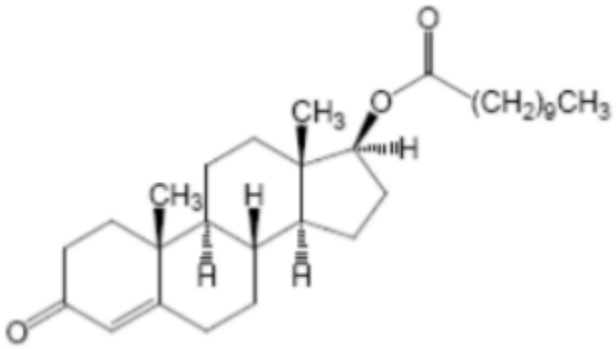
Background

This memorandum responds to a consult request by the Division of Urology, Obstetrics, and Gynecology (DUOG, or the division) on January 4, 2021, to evaluate the Package Insert (PI) labeling submitted by Marius Pharmaceuticals LLC in NDA 213953 (product developed under IND 118675) for KYZATREX (testosterone undecanoate). This product is an oral capsule formulation for testosterone replacement therapy. The drug product is indicated in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The recommended starting dose is 200mg orally (b) (4) with adjustment of the dose to a minimum of 100mg once in the morning and a maximum of 400mg twice daily based upon serum testosterone levels.

Currently, there is one commercially marketed oral testosterone undecanoate (TU) approved drug product. Clarus Therapeutics, Inc.'s JATENZO (testosterone undecanoate-NDA (b) (4)) oral capsules was approved on March 27, 2019, for testosterone replacement therapy (TRT) in adult males for conditions associated with a deficiency or absence of endogenous testosterone. TLANDO (testosterone undecanoate NDA 208088) oral capsules has a *tentative* approval application status as of December 8, 2020. Lipocine's Inc.'s TLANDO oral capsules, 112.5 mg, share the exclusivity-protected conditions of approval for Jatenzo oral capsules, 158 mg, 198 mg, and 237 mg. Therefore, the CDER Exclusivity Board concluded that the unexpired 3-year exclusivity for Jatenzo oral capsules, 158 mg, 198 mg, and 237 mg, would delay the approval of TLANDO oral capsules, 112.5 mg until March 27, 2022. TU is also available as an injectable product, brand name AVEED, in the US. AVEED was approved by the Agency on March 5, 2014. These TU drug products are schedule III under the Controlled Substances Act.

TU is a "pro-drug," in that de-esterification of the undecanoate at C17 yields systemic testosterone (T). The proposed drug product is formulated in (b) (4), which is aimed to enhance intestinal absorption of TU through the intestinal lymphatic pathway.

Fig. 1 Testosterone Undecanoate



The Applicant proposed Section 9 PI language that is consistent with the August 2016 Tracked Safety Issue (TSI) initiated Safety Labeling Change (SLC) update for Section 9 of all approved testosterone

products. In this NDA, the Applicant reflected the Section 9 labeling language already updated in the Section 9 labeling of currently marketed testosterone products.

The adverse event profile for the current product was similar to other marketed oral testosterone undecanoate products (i.e., TLANDO). Outside of a few cases of aggression, which is a known side effect of testosterone pharmacotherapy, the psychological adverse event (AE) profile did not differentiate from placebo.

2. Conclusions

- KYZATREX contains testosterone undecanoate, a prodrug of testosterone, which is a schedule III controlled substance, as defined under the Anabolic Steroids Control Act (effective 1991).
- The Applicant's proposed Section 9 of KYZATREX product labeling language is consistent with other testosterone products and is acceptable for approval.

3. Recommendations

- We have no additional recommendations for Marius Pharmaceuticals, at this time.

II. DISCUSSION

Recent Testosterone Labeling Changes to Section 9

Tracked Safety Issue (TSI) 1351: *Testosterone Misuse and Abuse* was opened on April 4th, 2014, under a standard 12-month review timeline, which included participants from DUOG (previously named 'Division of Bone Reproductive and Urologic Products - DBRUP), the Office of Surveillance and Epidemiology's (OSE) Division of Epidemiology (DEPI), Drug Utilization Analysis Staff, and Division of Pharmacovigilance (DPV), as well as CSS. The goal of the TSI was to evaluate the available evidence to accurately and appropriately inform Section 9 of labeling to assist healthcare providers in making prescribing decisions and in counseling patients. During the TSI review cycle, CSS provided DBRUP with a detailed memorandum outlining a justification for the necessity of updated Section 9 labeling language.

In response to this TSI, DUOG sent a "SAFETY LABELING CHANGE NOTIFICATION" letter to applicants of then approved testosterone drug products. This letter was based on Section 505(o)(4) of the FDCA authorizing the Agency to require holders of approved drug and biological product applications to make safety-related labeling changes based upon new safety information that becomes available after approval of the drug or biological product. These changes were agreed upon by all sponsors of approved testosterone products in August 2016,

Psychological AEs

A total of 82 subjects were administered at least one dose of KYZATREX in Phase ½ clinical development studies and there were no reported deaths or treatment-emergent adverse reactions (TEAEs) of special interest (e.g., depression, aggression, anger).

In the pooled Phase 3 studies, 296 subjects received KYZATREX. This total includes 155 subjects from the pivotal Phase 3 MRS-TU-2019EXT study and 214 subjects from the supportive Phase 3 MRS-TU-2019 study. Few subjects reported TEAEs of special interest with only 4 (1%) subjects reporting such psychological symptoms.

APPENDIX A – Draft Section 9 labeling from Applicant PI submission 03/16/2021

(b) (4)

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/s/

JOSHUA S HUNT
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PI labeling review

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M E M O R A N D U M

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

DATE: September 28, 2021

TO: Christine Nguyen, M.D.
Director
Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORDPUR)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Mohsen Rajabi Abhari, Ph.D.
DNDSI/OSIS

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI/OSIS

SUBJECT: Amendment: Inspections of Manhattan Medical Research Practice LLC, New York, NY (Site 104) and South Florida Medical Research, Aventura, FL (Site 107) and Establishment Evaluation Request (EER) Review (RRR) of [redacted] (b) (4)

1. Inspection and RRR Summary

This EIR review is being amended to include the evaluation of the written response to the Form FDA 483 observations issued at South Florida Medical Research, Aventura, FL (Site 107). Our recommendation and conclusion remain unchanged as communicated in the original review finalized on 9/8/2021.

Per the request of OND/ORDPUR/DUOG, OSIS arranged inspections of the clinical portion of **Studies MRS-TU-2019 and MRS-TU-2019EXT** (**NDA 213953,** Oral Testosterone Undecanoate) conducted at Manhattan Medical Research Practice LLC, New York, NY (Site 104). OSIS requested a for-cause inspection of South Florida Medical Research, Aventura, FL (Site 107) for clinical portion of study **MRS-TU-2019EXT**.

OSIS conducted a Remote Record Review (RRR) of the analytical portion of **Studies MRS-TU-2019** and **MRS-TU-2019EXT** conducted at (b) (4). An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

- **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 (VAI). 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 (VAI). This observation may impact the reliability of study data.

- (b) (4) We observed objectionable conditions during the RRR. Specifically, there was no (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.

1.1. Recommendation

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 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.

2. Reviewed Studies

NDA 213953

Study #1: MRS-TU-2019

Study Title: *"A 12-Month, Randomized, Active-Controlled, Open-Label Study of the Efficacy and Safety of Oral Testosterone Undecanoate in Hypogonadal Men"*

Dates of clinical conduct: July 2017 – March 2019

Study #2: MRS-TU-2019EXT

Study Title: *"Ambulatory Blood Pressure Monitoring Extension Study (Primary Efficacy Study)"*

Dates of clinical conduct: November 2018 – October 2019

- **Clinical Portion:**

Clinical Site #1: Manhattan Medical Research Practice LLC (Site 104)
215 Lexington Avenue, 21st Floor
New York, NY 10016
Study PI: Jed C. Kaminetsky, M.D.

Clinical Site #2: South Florida Medical Research (Site 107)

21150 Biscayne Blvd., Suite 300
Aventura, FL 33180

Study PI: Marc C. Gittelman, MD, FACS

- **Analytical Portion:**

(b) (4)

3. Inspectional Findings

Clinical Site #1: Manhattan Medical Research Practice, LLC (Site 104)

ORA investigator Benton Ketron inspected Manhattan Medical Research Practice LLC, New York, NY (Site 104) from June 21 - 25, 2021. This inspection was conducted as a Clinical Investigator (CI) inspection under the FEI# 3004028652. The previous OSIS inspection of Manhattan Medical Research Practice LLC was conducted from March 22 - 29, 2019. At the conclusion of the inspection, Form FDA 483 was issued for not conducting an investigation in accordance with the signed statement of investigator and investigational plan, and for failure to

maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. The final classification was VAI. The corrective actions were not verified during the current inspection.

The current inspection included auditing the following items:

- Case report forms (CRFs)
- Informed consent process
- Protocol and Protocol deviations
- Institutional review board approvals
- Test article accountability and storage
- Randomization
- Adverse events
- Collection, processing, and storage od study samples
- Individual responsibility and firm's training program
- Facility and records of instrument calibration and maintenance
- Electronic Data and audit trails

At the conclusion of the inspection, investigator Ketron observed objectionable conditions and Form FDA 483 was issued to the clinical site. The Form FDA 483 observations (**Attachment 1**), the firm's response dated 07/07/2021 (**Attachment 2**), and our evaluation are presented below.

FDA 483 Observations

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, the following observations were noted:

1). Record review revealed there was not accurate or adequate documentation prepared or maintained regarding the Pharmacokinetic (PK) sample handling and sample processing for any of the PK samples taken during visits 4, 6, and 8, for all subjects at the clinical trial site.

Firm's Response: The firm acknowledged the observation and stated that laboratory sample source documentation was reviewed at all monitoring visits by representatives of (b) (4) the study CRO responsible for regulatory and protocol compliance at all clinical sites. The firm stated that no concern was raised by the principal investigator or (b) (4) representatives about the source documentation to be inaccurate or inadequate with respect to PK sample handling or processing during the conduct of the study. As a corrective action, the

firm will maintain a log to document each step of sample processing and handling in PK studies and will update their SOP. The firm will also include a statement in source document stating that all samples were collected, processed and handled according to recent version of study specific lab manual.

OSIS Evaluation: Because no documentation is available for handling and processing of the PK samples, we cannot determine whether PK samples were processed according to the l atory manual that was provided by the central laboratory, (b) (4). During processing of subject samples, the whole blood for plasma extraction were required to be placed on ice water bath immediately after collection according to the lab manual to avoid the ex vivo conversion of unstable testosterone undecanoate (TU) to testosterone (T) during sample processing, which could have contributed to observed PK outliers.

Although visit 12E was not indicated in the observation, the ORA investigator confirmed that there was no documentation of the PK samples processing and handling for visit 12E as well. The firm's corrective actions are acceptable and should prevent recurrence of similar findings in future clinical studies if implemented correctly.

2). The clinical protocol states "Screening Visit 1 should occur between 7 a.m. and 10 a.m. and not more than 21 days before initial study medication use". Of the 16 subjects reviewed who were enrolled in the study, 10 were found to have screening periods between Visit 1 and Visit 3 that were greater than 21 days. During Visit 3, the subjects were prescribed the investigational or reference product.

Firm's Response: The firm acknowledged the observation and stated that the subjects who had screening windows exceeding 21 days required repeated laboratory tests during the screening period to confirm study eligibility. These repeated laboratory tests delayed subject enrollment beyond 21 days. The study medical monitor approved subject enrollment if repeated laboratory tests met eligibility criteria and each occurrence of subject enrollment exceeding 21 days was recorded in source documents by the PI and reported as "minor" deviations. As a corrective action, a change will be implemented in the enrollment process and the subjects exceeding the screening window will be considered screen failures at the discretion of

the PI. Such subjects may be rescreened if permitted by the study protocol or Sponsor/CRO.

OSIS Evaluation: This deviation has no impact on the study outcome. The subjects who exceeded 21 days screening period had repeated their required laboratory test and their eligibility were assessed before being enrolled in the study. In addition, the firm reported all the subjects who exceeded 21 days screening period before initial study medication use at visit 3. Since the subjects were reassessed for all the inclusion criteria to be enrolled in the study, subject's safety is not impacted and this deviation has no impact on the study outcome. The firm's corrective action to change enrollment process for the subjects exceeding the screening window to be considered screen failures will prevent occurrence of this observation in the future studies.

3). The clinical protocol designates that Visits 4 through 7 will have a study visit window period of +/-2 days, while Visit 8 through End of Treatment will have a window period of +/-3 days. Of the 16 subjects enrolled in the clinical trial, record review revealed that 10 subjects had at least one out of window study visits occur during the conduct of the trial. Study visits were conducted between 1 and 10 days outside of the allowable treatment window. These out of window visits included protocol required PK sampling visits where primary efficacy values were collected.

Firm's Response: The firm acknowledged the observation and stated that subject visits outside of the allowable study visit window were caused by unanticipated events such as family emergency, scheduling conflict, traveling, work schedule or religious holidays which were not attributable to the PI or site staff. The CRO (b) (4) recorded the reasons for all visits performed out of window and reported in the protocol deviation logs. As a corrective action, the PI or site staff will continue to educate subjects at all visits on the importance of attending scheduled visits. Subjects will also be scheduled at the earliest date of the visit window whenever possible to buffer unanticipated events. Subjects who show repeated non-compliance with the study visit windows will be discontinued from the study at the discretion of the PI.

OSIS Evaluation: This deviation has no impact on the study outcome. The firm reported all of the out of window study visits

for 10 out of 16 subjects in the study report. During each visit, subjects were assessed for any AEs that occurred since the previous visit and physical examination was performed on each subject to decide whether the subject can continue in the study. The investigator verified that there were no underreporting of adverse events and all adverse events were reported as required. The out of window visit did not impact the eligibility of subjects to continue in the study. The safety of the subjects was not impacted because of the out of window visits. The firm's corrective actions if implemented properly should prevent occurrence of the issue in the future studies.

Clinical Site #2: South Florida Medical Research (Site 107)

ORA investigator Craig Garmendia (OBIMO) inspected South Florida Medical Research, FL from August 17 - 26, 2021. This inspection was conducted as a CI inspection under the FEI# 1000526466.

The previous BIMO inspection of South Florida Medical Research was conducted from August 26 - 29, 2019. Form FDA 483 was not issued at the conclusion of the inspection and the final classification was NAI. However, two items were discussed with Dr. Gittelman regarding a lack of documentation of blood sample centrifugation and processing conditions and the unavailability of blood collection tubes for verification.

The current for-cause inspection focused on the records of blood sample collection, processing and handling of five subjects enrolled in Study MRS-TU-2019EXT. At the conclusion of the inspection, investigator Garmendia observed objectionable conditions and Form FDA 483 was issued. The study PI responded to the Form FDA 483 observation in an email dated 9/17/2021. The Form FDA 483 observation (**Attachment 3**), the firm's email response (**Attachment 4**), and our evaluation are presented below.

FDA 483 Observation

Observation 1: 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 2000g for 10 minutes at 4°C, transferred to two plasma tubes, and then stored at -70°C until shipping. However,

for 5 out of the 5 subjects reviewed there is no laboratory sample processing documentation to indicate these laboratory manual specific procedures were followed.

Firm's Response: The study PI acknowledged the observation. He stated that the sample processing steps were performed properly according to the laboratory manual, but the timing of each step was not recorded. The failure to record the sample processing steps and time was not recognized during the course of the study by himself or the clinical staff. It was first recognized at the close out of the study by the study monitor from (b) (4). At that point there was no opportunity to correct the source documents for future patients as the study was complete.

As corrective and preventive actions, the PI proposed to immediately implement the following for all protocols requiring special handling of the specimens:

1. when the source is created, the PI as well as the Senior Coordinator will independently review the source to be certain that all special processing is included in the source including time points for each of the special processing.
2. extra oversight will be employed during the course of the study to be absolutely certain that the special lab procedures and timepoints are documented properly in the source.

OSIS Evaluation: Due to the lack of written documentation for sample handling and processing at Site 107, we cannot determine whether PK samples were processed according to the laboratory manual that was provided by the central laboratory, (b) (4). The blood samples for plasma were required to be placed on ice water bath immediately after collection according to the lab manual to avoid the ex vivo conversion of unstable testosterone undecanoate (TU) to testosterone (T) during sample processing, which could have contributed to observed PK outliers.

This inspection also revealed that the sponsor and the CRO, (b) (4)

(b) (4)

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(b) (4). Therefore, this observation may impact reliability of the data from Site 107.

The proposed corrective and preventive actions are acceptable and should prevent recurrence of similar findings in future clinical studies.

4. RRR Findings

Analytical Site: (b) (4)

(b) (4)

The previous inspection of the site was conducted by OSIS from (b) (4) (b) (4). At the conclusion of the inspection, no Form F 3 was (b) (4)

(b) (4)

(b) (4)

At the conclusion of the RRR, we observed objectionable conditions and we discussed the following observation with the firm's management. Our n of the RRR observation and the firm's response dated (b) (4) (**Attachment 8**) are presented below.

(b) (4)

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(b) (4)

OSIS Evaluation: The observation has no impact on study data reliability. (b) (4)

The firm's investigation showed that the observations on (b) (4) were isolated events. Their proposed corrective actions appear to be adequate to prevent future occurrence of similar issues when implemented.

Additionally, we did not find any evidence to support that there was mismanagement of ling and processing at the analytical site. The (b) (4) results demonstrated that there

were no issues in analytical method performance during bioanalysis.

5. Specific concerns from OCP

The OCP reviewer expressed concerns regarding a pattern in the relationship of NaF/EDTA plasma and serum T concentrations in Study MRS-TU-2019EXT, especially from subjects enrolled at Site 104. Specifically,

- There were multiple subjects at Site 104 whose NaF/EDTA plasma T concentration results were paradoxically higher than serum results obtained at the same timepoint.
- The Applicant is proposing to exclude all 16 subjects from Site 104 for efficacy and safety (i.e., C_{max}) analysis, significantly impacting the outcome of their pivotal Phase 3 study.
- Potential ex vivo TU to T conversion during sample processing may have impacted the efficacy and safety outcome and the establishment of the dose titration scheme in the pivotal Phase 3 study (**Attachment 7**).

OSIS Evaluation: During the RRR of (b) (4), we focused on sample receipt, handling and storage, sample processing during bioanalysis for the suggested subjects of Study MRS-TU-2019EXT (**Attachment 7**). We did not find any evidence to support that there was mismanagement of sample handling and processing at the analytical site. The (b) (4) results from the affected subject samples demonstrated that there were no issues in analytical method performance during bioanalysis.

Additionally, based on the inspectional findings from clinical sites 104 and 107, there was no documentation of blood sample handling and processing for serum, EDTA plasma and NaF/EDTA plasma samples at all collection time points for all subjects. The clinical site staff verbally described whether or not they followed the instructions from the Lab Manual provided by the central lab (**Attachment 6)** without documenting each step. Therefore, we could not find documentation to support that sample handling and processing at the clinical sites were done according to the lab manual.

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 same objectionable

conditions likely occurred at the 17 clinical sites that were not inspected. Thus, the reliability of the clinical data from the entire study may be impacted. We recommend 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.

6. Conclusions

Based on our review of the objectionable conditions, we conclude the reliability of the data from sites 104 and 107 may be impacted. B on the study design and role of central laboratory (b) (4), the objectionable conditions likely occurred at the other clinical sites not inspected. Thus, the reliability of the data from the entire study may be impacted. We recommend the review division to request more information from the applicant regarding subject sample handling and processing by the clinical sites not inspected to assess the impact of the findings on data reliability for Studies MRS-TU-2019 and MRS-TU-2019EXT.

Based on our review of the objectionable conditions observed during the RRR of the analytical portion of the studies and the firm's response, we conclude the RRR observation does not impact the reliability of analytical data from the audited studies. We did not find any issues in analytical method performance during bioanalysis. However, if the plasma samples received from the clinical sites were not handled and processed according to the protocol leading to ex vivo conversion of TU to T, the reported results of T concentration in NaF/EDTA plasma samples may be unreliable.

Yiyue Zhang, Ph.D.
Senior Staff Fellow

Mohsen Rajabi Abhari, Ph.D.
Pharmacologist

Attachments:

Attachment 1. Form FDA 483 issued to Site 104 and Study PI Dr. Kaminetsky
Attachment 2. Site 104 and Study PI's written response to Form FDA 483

Attachment 3. Form FDA 483 issued to Site 107 and Study PI Dr. Gittelman
Attachment 4. Site 107 and Study PI's email response to Form FDA 483
Attachment 5. Investigation report of Site 107 conducted by the sponsor and CRO
Attachment 6. Central Lab Manual excerpt (Protocol 9.0, 18-FEB-2019)
Attachment 7. Email correspondence with the OCP reviewer
Attachment 8. (b) (4), s written response to RRR

Attachment 9. (b) (4)

Final Classification:

VAI - Manhattan Medical Research Practice LLC, New York, NY
(Site 104, Study PI: Jed C. Kaminetsky, M.D.)
FEI#: 3004028652 (CI)

VAI - South Florida Medical Research, Aventura, FL
(Site 107, Study PI: Marc C. Gittelman, MD, FACS)
FEI#: 1000526466 (CI)

cc:
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Draft: YZ 09/23/2021, 09/24/2021
Edit: GB 9/24/2021 AD 9/27/2021

ECMS:
Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Manhattan Medical Research Practice LLC, New York, NY, USA
Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/South Florida Medical Research, Aventura, FL, USA

OSIS File#: BE 9065
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09/28/2021 02:16:00 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 27, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213953
Product Name and Strength:	Kyzatrex (testosterone undecanoate) capsules, 100 mg, 150 mg, 200 mg
Applicant/Sponsor Name:	Marius Pharmaceuticals, LLC
OSE RCM #:	2020-2763-2
DMEPA 2 Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA 2 (Acting) Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on September 14, 2021 for Kyzatrex. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels for Kyzatrex (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Baugh, D. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 AUG 26. RCM No.: 2020-2763-1.

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/s/

DENISE V BAUGH
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M E M O R A N D U M

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

DATE: September 8, 2021

TO: Christine Nguyen, M.D.
Director
Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORDPUR)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Mohsen Rajabi Abhari, Ph.D.
DNDSI/OSIS

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI/OSIS

SUBJECT: Inspections of Manhattan Medical Research Practice LLC, New York, NY (Site 104) and South Florida Medical Research, Aventu ord Review (RRR) of (b) (4)

1. Inspection and RRR Summary

Per the request of OND/ORDPUR/DUOG, OSIS arranged inspections of the clinical portion of **Studies MRS-TU-2019 and MRS-TU-2019EXT** (**NDA 213953,** Oral Testosterone Undecanoate) conducted at Manhattan Medical Research Practice LLC, New York, NY (Site 104). OSIS requested a for-cause inspection of South Florida Medical Research, Aventura, FL (Site 107) for clinical portion of study **MRS-TU-2019EXT**.

OSIS conducted a Remote Record Review (RRR) of the analytical portion of **Studies MRS-TU-2019** and **MRS-TU-2019EXT** conducted at (b) (4). An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

- **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 (VAI). 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 (VAI). This observation may impact the reliability of study data.

- (b) (4)**:** We observed objectionable conditions during the RRR. Specifically, there was no (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.

1.1. Recommendation

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 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.

2. Reviewed Studies

NDA 213953

Study #1: MRS-TU-2019

Study Title: *"A 12-Month, Randomized, Active-Controlled, Open-Label Study of the Efficacy and Safety of Oral Testosterone Undecanoate in Hypogonadal Men"*

Dates of clinical conduct: July 2017 – March 2019

Study #2: MRS-TU-2019EXT

Study Title: *"Ambulatory Blood Pressure Monitoring Extension Study (Primary Efficacy Study)"*

Dates of clinical conduct: November 2018 – October 2019

- **Clinical Portion:**

Clinical Site #1: Manhattan Medical Research Practice LLC (Site 104)
215 Lexington Avenue, 21st Floor
New York, NY 10016
Study PI: Jed C. Kaminetsky, M.D.

Clinical Site #2: South Florida Medical Research (Site 107)
21150 Biscayne Blvd., Suite 300
Aventura, FL 33180
Study PI: Marc C. Gittelman, MD, FACS

- **Analytical Portion:**

(b) (4)

(b) (4)

3. Inspectional Findings

Clinical Site #1: Manhattan Medical Research Practice, LLC (Site 104)

ORA investigator Benton Ketron inspected Manhattan Medical Research Practice LLC, New York, NY (Site 104) from June 21 - 25, 2021. This inspection was conducted as a Clinical Investigator (CI) inspection under the FEI# 3004028652. The previous OSIS inspection of Manhattan Medical Research Practice LLC was conducted from March 22 - 29, 2019. At the conclusion of the inspection, Form FDA 483 was issued for not conducting an investigation in accordance with the signed statement of investigator and investigational plan, and for failure to maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. The final classification was VAI. The corrective actions were not verified during the current inspection.

The current inspection included auditing the following items:

- Case report forms (CRFs)
- Informed consent process
- Protocol and Protocol deviations
- Institutional review board approvals
- Test article accountability and storage
- Randomization
- Adverse events
- Collection, processing, and storage od study samples
- Individual responsibility and firm's training program
- Facility and records of instrument calibration and maintenance
- Electronic Data and audit trails

At the conclusion of the inspection, investigator Ketron observed objectionable conditions and Form FDA 483 was issued to the clinical site. The Form FDA 483 observations (**Attachment 1**), the firm's response dated 07/07/2021 (**Attachment 2**), and our evaluation are presented below.

FDA 483 Observations

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, the following observations were noted:

1). Record review revealed there was not accurate or adequate documentation prepared or maintained regarding the Pharmacokinetic (PK) sample handling and sample processing for any of the PK samples taken during visits 4, 6, and 8, for all subjects at the clinical trial site.

Firm's Response: The firm acknowledged the observation and stated that laboratory sample source documentation was reviewed at all monitoring visits by representatives of (b) (4), the study CRO responsible for regulatory and protocol compliance at all clinical sites. The firm stated that no concern was raised by the principal investigator or (b) (4) representatives about the source documentation to be inaccurate or inadequate with respect to PK sample handling or processing during the conduct of the study. As a corrective action, the firm will maintain a log to document each step of sample processing and handling in PK studies and will update their SOP. The firm will also include a statement in source document stating that all samples were collected, processed and handled according to recent version of study specific lab manual.

OSIS Evaluation: Because no documentation is available for handling and processing of the PK samples, we cannot determine whether PK samples were processed according to the laboratory manual that was provided by the central laboratory, (b) (4). During processing of subject samples, the whole blood for plasma extraction were required to be placed on ice water bath immediately after collection according to the lab manual to avoid the ex vivo conversion of unstable testosterone undecanoate (TU) to testosterone (T) during sample processing, which could have contributed to observed PK outliers.

Although visit 12E was not indicated in the observation, the ORA investigator confirmed that there was no documentation of the PK samples processing and handling for visit 12E as well. The firm's corrective actions are acceptable and should prevent recurrence of similar findings in future clinical studies if implemented correctly.

2). The clinical protocol states "Screening Visit 1 should occur between 7 a.m. and 10 a.m. and not more than 21 days before initial study medication use". Of the 16 subjects reviewed who were enrolled in the study, 10 were found to have screening periods between Visit 1 and Visit 3 that were greater than 21 days. During Visit 3, the subjects were prescribed the investigational or reference product.

Firm's Response: The firm acknowledged the observation and stated that the subjects who had screening windows exceeding 21 days required repeated laboratory tests during the screening period to confirm study eligibility. These repeated laboratory tests delayed subject enrollment beyond 21 days. The study medical monitor approved subject enrollment if repeated laboratory tests met eligibility criteria and each occurrence of subject enrollment exceeding 21 days was recorded in source documents by the PI and reported as "minor" deviations. As a corrective action, a change will be implemented in the enrollment process and the subjects exceeding the screening window will be considered screen failures at the discretion of the PI. Such subjects may be rescreened if permitted by the study protocol or Sponsor/CRO.

OSIS Evaluation: This deviation has no impact on the study outcome. The subjects who exceeded 21 days screening period had repeated their required laboratory test and their eligibility were assessed before being enrolled in the study. In addition,

the firm reported all the subjects who exceeded 21 days screening period before initial study medication use at visit 3. Since the subjects were reassessed for all the inclusion criteria to be enrolled in the study, subject's safety is not impacted and this deviation has no impact on the study outcome. The firm's corrective action to change enrollment process for the subjects exceeding the screening window to be considered screen failures will prevent occurrence of this observation in the future studies.

3). The clinical protocol designates that Visits 4 through 7 will have a study visit window period of +/-2 days, while Visit 8 through End of Treatment will have a window period of +/-3 days. Of the 16 subjects enrolled in the clinical trial, record review revealed that 10 subjects had at least one out of window study visits occur during the conduct of the trial. Study visits were conducted between 1 and 10 days outside of the allowable treatment window. These out of window visits included protocol required PK sampling visits where primary efficacy values were collected.

Firm's Response: The firm acknowledged the observation and stated that subject visits outside of the allowable study visit window were caused by unanticipated events such as family emergency, scheduling conflict, traveling, work schedule or religious holidays which were not attributable to the PI or site staff. The CRO (b) (4) recorded the reasons for all visits performed out of window and reported in the protocol deviation logs. As a corrective action, the PI or site staff will continue to educate subjects at all visits on the importance of attending scheduled visits. Subjects will also be scheduled at the earliest date of the visit window whenever possible to buffer unanticipated events. Subjects who show repeated non-compliance with the study visit windows will be discontinued from the study at the discretion of the PI.

OSIS Evaluation: This deviation has no impact on the study outcome. The firm reported all of the out of window study visits for 10 out of 16 subjects in the study report. During each visit, subjects were assessed for any AEs that occurred since the previous visit and physical examination was performed on each subject to decide whether the subject can continue in the study. The investigator verified that there were no underreporting of adverse events and all adverse events were reported as required. The out of window visit did not impact the

eligibility of subjects to continue in the study. The safety of the subjects was not impacted because of the out of window visits. The firm's corrective actions if implemented properly should prevent occurrence of the issue in the future studies.

Clinical Site #2: South Florida Medical Research (Site 107)

ORA investigator Craig Garmendia (OBIMO) inspected South Florida Medical Research, FL from August 17 - 26, 2021. This inspection was conducted as a CI inspection under the FEI# 1000526466.

The previous BIMO inspection of South Florida Medical Research was conducted from August 26 - 29, 2019. Form FDA 483 was not issued at the conclusion of the inspection and the final classification was NAI. However, two items were discussed with Dr. Gittelman regarding a lack of documentation of blood sample centrifugation and processing conditions and the unavailability of blood collection tubes for verification.

The current for-cause inspection focused on the records of blood sample collection, processing and handling of five subjects enrolled in Study MRS-TU-2019EXT. At the conclusion of the inspection, investigator Garmendia observed objectionable conditions and Form FDA 483 was issued. The firm's response to FDA Form 483 has not been received at the time of this review. We will amend the review accordingly when the firm's written response is received. The Form FDA 483 observation (**Attachment 3**) and our evaluation are presented below.

FDA 483 Observation

Observation 1: 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 2000g for 10 minutes at 4°C, transferred to two plasma tubes, and then stored at -70°C until shipping. However, for 5 out of the 5 subjects reviewed there is no laboratory sample processing documentation to indicate these laboratory manual specific procedures were followed.

Firm's Response: Response is not yet available.

OSIS Evaluation: Due to the lack of written documentation for sample handling and processing at Site 107, we cannot determine whether PK samples were processed according to the laboratory manual that was provided by the central laboratory, (b) (4) The blood samples for plasma were required to be placed on ice water bath immediately after collection according to the lab manual to avoid the ex vivo conversion of unstable testosterone undecanoate (TU) to testosterone (T) during sample processing, which could have contributed to observed PK outliers.

This inspection also revealed that the sponsor and the CRO, (b) (4)

(b) (4)

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emote Record Review (RRR) of [redacted]. Therefore, this observation may impact reliability of the data from Site 107.

4. RRR Findings

Analytical Site: [redacted]

The previous inspection of the site was conducted by OSIS from [redacted]. At the conclusion of the inspection, no Form F 3 was [redacted]

At the conclusion of the RRR, we observed objectionable conditions and we discussed the following observation with the firm's management. Our n of the RRR observation and the firm's response dated [redacted] (**Attachment 7**) are presented below.

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emote Record Review (RRR) of (b) (4)

(b) (4)

OSIS Evaluatio a

(b) (4)

(b) (4)

The firm's investigation showed that the observations on (b) (4) were isolated events. Their proposed corrective actions appear to be adequate to prevent future occurrence of similar issues when implemented.

Additionally, we did not find any evidence to support that there was mismanagement of sample handling and processing at the analytical site. The (b) (4) results demonstrated that there were no issues in analytical method performance during bioanalysis.

5. Specific concerns from OCP

The OCP reviewer expressed concerns regarding a pattern in the relationship of NaF/EDTA plasma and serum T concentrations in Study MRS-TU-2019EXT, especially from subjects enrolled at Site 104. Specifically,

- There were multiple subjects at Site 104 whose NaF/EDTA plasma T concentration results were paradoxically higher than serum results obtained at the same timepoint.
- The Applicant is proposing to exclude all 16 subjects from Site 104 for efficacy and safety (i.e., C_{max}) analysis, significantly impacting the outcome of their pivotal Phase 3 study.
- Potential ex vivo TU to T conversion during sample processing may have impacted the efficacy and safety outcome and the establishment of the dose titration scheme in the pivotal Phase 3 study (**Attachment 6**).

OSIS Evaluation: During the RRR of (b) (4), we focused on sample receipt, handling and storage, sample processing during bioanalysis for the suggested subjects of Study MRS-TU-2019EXT (**Attachment 6**). We did not find any evidence to support that there was mismanagement of sample handling and processing at the analytical site. The (b) (4) results from the affected subject samples demonstrated that there were no issues in analytical method performance during bioanalysis.

Additionally, based on the inspectional findings from clinical sites 104 and 107, there was no documentation of blood sample handling and processing for serum, EDTA plasma and NaF/EDTA plasma samples at all collection time points for all subjects. The clinical site staff verbally described whether or not they followed the instructions from the Lab Manual provided by the central lab (**Attachment 5)** without documenting each step. Therefore, we could not find documentation to support that sample handling and processing at the clinical sites were done according to the lab manual.

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 same objectionable conditions likely occurred at the 17 clinical sites that were not inspected. Thus, the reliability of the clinical data from the entire study may be impacted. We recommend 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.

6. Conclusions

Based on our review of the objectionable conditions, we conclude the reliability of the data from sites 104 and 107 may be impacted. B on the study design and role of central laboratory (b) (4), the objectionable conditions likely occurred at the other clinical sites not inspected. Thus, the reliability of the data from the entire study may be impacted. We recommend the review division to request more information from the applicant regarding subject sample handling and processing by the clinical sites not inspected to assess the impact of the findings on data reliability for Studies MRS-TU-2019 and MRS-TU-2019EXT.

Based on our review of the objectionable conditions observed during the RRR of the analytical portion of the studies and the firm’s response, we conclude the RRR observation does not impact the reliability of analytical data from the audited studies. We did not find any issues in analytical method performance during bioanalysis. However, if the plasma samples received from the clinical sites were not handled and processed according to the protocol leading to ex vivo conversion of TU to T, the reported results of T concentration in NaF/EDTA plasma samples may be unreliable.

Yiyue Zhang, Ph.D.
Senior Staff Fellow

Mohsen Rajabi Abhari, Ph.D.
Pharmacologist

Attachments:

Attachment 1. Form FDA 483 issued to Site 104 and Study PI Dr. Kaminetsky
Attachment 2. Site 104 and Study PI's written response to Form FDA 483
Attachment 3. Form FDA 483 issued to Site 107 and Study PI Dr. Gittelman
Attachment 4. Investigation report of Site 107 conducted by the sponsor and CRO
Attachment 5. Central Lab Manual excerpt (Protocol 9.0, 18-FEB-2019)
Attachment 6. Email correspondence with the OCP reviewer
Attachment 7. (b) (4)'s written response to RRR
Attachment 8. (b) (4)

Final Classification:

VAI - Manhattan Medical Research Practice LLC, New York, NY
(Site 104, Study PI: Jed C. Kaminetsky, M.D.)
FEI#: 3004028652 (CI)

VAI - South Florida Medical Research, Aventura, FL
(Site 107, Study PI: Marc C. Gittelman, MD, FACS)
FEI#: 1000526466 (CI)

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza/CDER-OSIS-BEQ@fda.hhs.gov
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Draft: YZ 8/25/2021, 08/30/2021, 09/01/2021, 09/07/2021, 09/08/2021; MR 08/27/2021, 09/03/2021
Edit: GB 08/31/2021, GB 09/03/2021, 09/07/2021; AD 09/07/2021; 09/08/2021; CB 9/8/2021

ECMS:
Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Manhattan Medical Research Practice LLC, New York, NY, USA
Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/South Florida Medical Research, Aventura, FL, USA
Cabinets/CDER OTS/Office of Study Integri (b) (4)

OSIS File#: BE 9065
FACTS: 121216 te 104)
eNSpect ID#: (b) (4); **OP ID#:** 204335 (Site 107)

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/s/

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ARINDAM DASGUPTA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 26, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213953
Product Name and Strength:	Kyzatrex (testosterone undecanoate) capsules, 100 mg, 150 mg, 200 mg
Applicant/Sponsor Name:	Marius Pharmaceuticals, LLC
OSE RCM #:	2020-2763-1
DMEPA 2 (Acting) Safety Evaluator:	Denise Baugh, PharmD
DMEPA 2 (Acting) Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on July 2, 2021 for Kyzatrex. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels for Kyzatrex (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

All of our recommendations were implemented. However, we have two additional recommendations. See Section 3 below.

3 RECOMMENDATIONS FOR MARIUS PHARMACEUTICALS, LLC

We recommend the following be implemented prior to approval of this NDA:

[a] Baugh D. Label and Labeling Review for Kyzatrex (NDA 213953). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2020 JUN 09. RCM No.: 2020-2763.

A. As currently presented, the 'Rx Only' Statement appears before the Medication Guide ('Med Guide') statement. We are concerned that the Med Guide statement may be overlooked given its low prominence. Therefore, we recommend you relocate the 'Med Guide' statement to appear above the 'Rx Only' statement to improve its prominence.

B. As currently presented, the proposed graphic and font color choices on the principal display panel distract from the readability of the proprietary name, 'Kyzatrex'. Specifically, we note the (b) (4), circular graphic could be misinterpreted as the letters "O" or "C", and the letters that (b) (4) (i.e., Y and X) are difficult to read. We recommend you consider revisions to the presentation of the proprietary name, as well as revisions to the placement, prominence, and/or opacity of the graphic in relation to the proprietary name.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

CONSULTATION

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 22, 2021

FROM: Shivangi Vachhani, MD, Reviewer, Division of General Endocrinology (DGE)

THROUGH: Marina Zemskova, MD – Team Leader, DGE
Naomi Lowy, MD – Deputy Director, DGE

TO: Jordan Dimitrakoff, MD – Clinical Reviewer, Division of Urology, Obstetrics and Gynecology (DUOG)

SUBJECT: A review of a sub-study of the phase 3 trial (MRS-TU-2019), assessing an effect of Kyzatrex (oral testosterone undecanoate) on hypothalamic-pituitary-adrenal axis function in hypogonadal men.

I. Basis for consult and background

On May 19, 2021, the Division of General Endocrinology (DGE) received a consultation request from the Division of Urology, Obstetrics and Gynecology (DUOG) requesting a review of the adrenocorticotropic hormone (ACTH) stimulation sub-study of the phase 3 trial of Kyzatrex (SOV2012-F1, oral testosterone undecanoate). Specifically, DGE was asked whether the study duration of 1 year is long enough to detect a potential effect of Kyzatrex on hypothalamic-pituitary-adrenal (HPA) axis function in hypogonadal men.

Background and regulatory history

The Applicant (Marius pharmaceuticals) has developed Kyzatrex, an oral testosterone undecanoate, for the treatment of male hypogonadism. NDA 213953 for Kyzatrex was submitted to DUOG on December 31, 2020.

During the nonclinical development of Kyzatrex, sporadic vacuolization of the adrenal cortex and a decrease in absolute and relative adrenal weights was observed in dogs. Hence, in order to determine the effect of Kyzatrex on adrenocortical function in subjects with hypogonadism, the Phase 3 trial of Kyzatrex (Study MRS-TU-2019) included a sub-study assessing the effect of Kyzatrex on the HPA axis function in hypogonadal men.

Review of HPA axis testing:

If HPA axis suppression is suspected, the patient should be evaluated with morning cortisol levels and/or cosyntropin (ACTH) stimulation test[1]. A morning cortisol of 15-18 mcg/dL predicts an intact HPA axis in most patients. Morning cortisol values below 3 mcg/dL are strongly suggestive of adrenal insufficiency. Cosyntropin stimulation test is considered the optimal test for diagnosing adrenal insufficiency.[2] An adequate response is defined by a peak

[1] Arlt Wiebke, et. al. Adrenal Insufficiency. *The Lancet.* 2003; 361:1881-1893

[2] Bornstein S, et al. Diagnosis and treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism*. 2016; 364-389.

cortisol level of at least 18 mcg/dL after 30 or 60 minutes of cosyntropin administration. It is not necessary to perform cosyntropin stimulation testing when morning cortisol levels are ≥ 18 mcg/dL; however, cosyntropin stimulation testing should be performed for morning cortisol levels lower than 18 mcg/dL when there is a clinical suspicion for adrenal insufficiency.

However, given that adrenal gland atrophy develops gradually after the onset of ACTH deficiency, the adrenals may still be responsive to cosyntropin in patients with a recent onset of secondary adrenal insufficiency. The time needed to develop adrenal atrophy is variable and dependent on the etiology of adrenal insufficiency. In general, cosyntropin stimulation test is more reliable when performed at least 4 months after surgery, or 9 months after radiation therapy.[3]

Review of human risk for adrenal insufficiency associated with testosterone therapy
Currently approved testosterone therapies include injectable, topical, and oral formulations. Labeled adverse reactions of testosterone therapy in patients with hypogonadism include worsening of benign prostatic hypertrophy, potential risk of prostate cancer, polycythemia, venous thromboembolism (including deep vein thrombosis and pulmonary embolism), increased risk of major adverse cardiovascular events, suppressed spermatogenesis, hepatic adverse events, edema, gynecomastia, sleep apnea, changes in serum lipids, hypercalcemia, decreased thyroxine-binding globulin, acne, alopecia, depression, and emotional lability.
Risk of HPA axis suppression in humans is not included in the majority of the labels.

Jatenzo label, Section 13.2 includes the nonclinical data on changes in adrenal gland morphology observed during the development program:

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

Jatenzo (testosterone undecanoate) is the only oral testosterone therapy approved for use as a replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (NDA 206089, approved in 2019).

During the Jatenzo development program, marked atrophy of the adrenal cortex and reduced adrenal weight were observed in both rats and dogs. Thus, the clinical development program of Jatenzo included a study evaluating the HPA axis in a small group of patients with hypogonadism. Abnormal cosyntropin stimulation test results were seen in 5/24 subjects exposed to Jatenzo and none of the subjects exposed to the comparator, topical Axiron. However, there were several confounding factors (e.g. one subject had prior exposure to high dose glucocorticoid and remaining 4 subjects had post-stimulation cortisol levels that were only mildly decreased) that may have contributed to these results. Additionally, no adverse events associated with HPA axis suppression were detected in the phase 3 trials. Hence, the

[3] Nieman L, et. al. (2019). Diagnosis of adrenal insufficiency in adults. In K. A. Martin (Ed.), *UpToDate.* Retrieved May 25, 2021, from https://www.uptodate.com/contents/diagnosis-of-adrenal-insufficiency-in-adults?search=diagnosis%20of%20secondary%20adrenal%20insufficiency&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H6

NDA approval letter for Jatenzo included a Post-Marketing Requirement (PMR) for an appropriately designed one-year trial to evaluate HPA axis function with chronic Jatenzo therapy (PMR 3582-2). Under this PMR, the sponsor was asked to assess adrenal function with cosyntropin stimulation testing prior to starting Jatenzo, and again six months and one year after the initiation of Jatenzo treatment (or sooner in subject's with signs or symptoms of adrenal insufficiency). The study is ongoing, and no data is available yet.

Summary of Cosyntropin Stimulation sub-study of the phase 3 trial MRS-TU-2019:
During the phase 3 trial MRS-TU-2019, cosyntropin stimulation testing was performed at baseline (Visit 3, Day 1) and at end of study (Visit 13, Day 365) in a subset of subjects with hypogonadism (n = 42; 29 subjects on Kyzatrex and 13 subjects on Androgel).

Cosyntropin 250 mcg was administered intravenously over 2 minutes, and serum cortisol was measured before, at 30 minutes, and at 60 minutes after cosyntropin administration.

All 42 subjects had normal response to cosyntropin stimulation test at baseline and after 365 days of testosterone replacement therapy. At baseline, the mean ± standard deviation (SD) maximum stimulated serum cortisol was 23.8 ± 3.6 nmol/L in the Kyzatrex group and 25.7 ± 2.4 nmol/L in the Androgel group. At Day 365, the mean ± SD maximum stimulated serum cortisol was 25.2 ± 4.6 in the Kyzatrex group and 27 ± 3.3 in the Androgel group.

II. Materials reviewed for consult

a. DUOG Consult request
b. Literature review
c. Synopsis of the ACTH Stimulation sub-study of MRS-TU-2019
d. Clinical Study Report for MRS-TU-2019 and MRS-TU-2019EXT

III. DGE Consult Response

To our knowledge, to date there are no definite data that testosterone suppresses HPA axis and that administration of exogenous testosterone formulations is associated with adrenal insufficiency. However, there was a nonclinical signal of sporadic vacuolization of the adrenal cortex and a decrease in absolute and relative adrenal weights in dogs upon treatment with Kyzatrex. Hence, in order to determine the effect of Kyzatrex on adrenocortical function in subjects with hypogonadism, the clinical development program of Kyzatrex included an adrenocorticotropic hormone (ACTH) stimulation sub-study during the phase 3 trial MRS-TU-2019.

The results of this sub-study demonstrated that there was no HPA axis suppression at the end of 12-month treatment with Kyzatrex. As discussed above, the time needed to develop HPA axis suppression is variable and in general it can take up to 6 months for adrenal atrophy and abnormal ACTH test results. Hence, if a drug were to result in adrenal insufficiency, an abnormal cosyntropin stimulation test would be expected after exposure to the drug for ≥6 months. Thus, we agree that the study duration of 1 year was sufficient to detect HPA axis suppression.

In addition, the overall risk of HPA axis suppression associated with testosterone use in humans is low. There is no definite data from published literature evaluating testosterone in various diseases that testosterone suppresses HPA axis and that administration of exogenous formulations is associated with adrenal insufficiency. There are multiple formulations of testosterone approved in the US for the treatment of hypogonadism in males. The risk of HPA

axis suppression/adrenal insufficiency is not listed in Sections 5 and 6 of labelling for any of the testosterone formulations. Lastly, monitoring for adrenal insufficiency during testosterone therapy is also not included in the Endocrine Society's Clinical Guidelines for Testosterone therapy in men with hypogonadism. Thus, given the reassuring clinical data on HPA axis at the end of 1-year treatment, the observed adrenal findings in animals treated with Kyzatrex is of unknown clinical significance at this point.

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LABEL, LABELING, AND PACKAGING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 9, 2021
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 213953
Product Name and Strength:	Kyzatrex (testosterone undecanoate) capsules, 100 mg, 150 mg, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Marius Pharmaceuticals, LLC
FDA Received Date:	December 31, 2020 and March 16, 2021
OSE RCM #:	2020-2763
DMEPA Safety Evaluator:	Denise Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 REASON FOR REVIEW

As part of the approval process for Kyzatrex (testosterone undecanoate) capsules, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed Kyzatrex container labels, prescribing information (PI), and medication guide for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Kyzatrex container label, prescribing information (PI), and Medication guide (MG), our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In section 2.2 ((b) (4) , we note the use of an abbreviation for dose adjustments based on	These abbreviations may be misinterpreted.	Consider revising '3-5 hours' to read '3 to 5 hours' to prevent misinterpretation and confusion.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	serum testosterone concentrations.		
Full Prescribing Information – Section 3 Dosage Forms and Strengths and Section 16 How Supplied			
1.	The dosage form used in the net quantity statement on the container label, [redacted], is inconsistent with the dosage form used in sections 3 and 16 of the Prescribing Information and in other parts of the container label.	We are concerned the term, [redacted], is the incorrect description of the capsule dosage form.	We defer to the Office of Pharmaceutical Quality (OPQ) to address the dosage form as it appears in the PI and the labels.

Table 3. Identified Issues and Recommendations for Marius Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	The format for the expiration date is not defined.	Clearly define the expiration date to minimize confusion and risk for 'deteriorated drug' medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the

Table 3. Identified Issues and Recommendations for Marius Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. In addition, ensure that there are no other numbers located in close proximity to the expiration date where it can be mistaken as the expiration date.
2.	The established name lacks prominence commensurate with the proprietary name and is not at least half the size of the proprietary name.	Important drug information may be overlooked and not in accordance with 21 CFR 201.10(g)(2).	Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3.	The manufacturer name appears more prominent than the established name on the principal display panel.	The manufacturer name should not compete in size and prominence with critical information on the principal display panel[a].	Consider minimizing the prominence of the manufacturer name on the principal display panel or relocate it to the side or back panel.

[a] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 3. Identified Issues and Recommendations for Marius Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The "Rx Only" statement appears more prominent than the established name on the principal display panel.	The Rx-only statement should not compete in size and prominence with critical information on the principal display panel[b].	Decrease the prominence of the statement "Rx Only".
5.	As currently presented, there appears to be incomplete product identifier information presented on the container label.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA)*. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. * The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf	We recommend you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. If you determine that the product identifier requirements apply to your product's labeling, add a placeholder for the human- and machine-readable product identifiers to your product's labeling. The DSCSA guidance on product identifiers recommends the format of the human-readable portion be located near the 2D data matrix barcode and recommends the following format: NDC: [insert NDC] Serial: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]

[b] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 3. Identified Issues and Recommendations for Marius Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
6.	As currently presented, there is no placeholder for the lot number on the container label.	The lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Ensure there are no other numbers located in close proximity to the lot number where it can be mistaken as the lot number[c] and ensure the lot number is clearly differentiated from the expiration date[d].
7.	The layout of the proprietary name, active ingredient, dosage form, and strength can be improved. In addition, the established name is not in parentheses.	The layout of the proprietary name, active ingredient, dosage form, and strength is not consistent with the presentation of the proprietary name, active ingredient, dosage form, and strength for drug products.[e]	Reformat the layout to list the active ingredient in parentheses below the proprietary name followed by the dosage form and strength as follows: 'TRADENAME (testosterone undecanoate) capsules, XXX mg' OR 'TRADENAME (testosterone undecanoate capsules), XXX mg'
8.	The colors used to differentiate the 100 mg and 150 mg strengths overlap with the colors used in the proprietary name.	The use of the same color font for the proprietary name and the strengths minimizes differences between the strengths which may lead to wrong strength selection errors.	Revise the color scheme of the 100 mg and 150 mg strengths such that each strength appears in its own unique color and the colors do not overlap with the colors used for the proprietary name.

[c] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

[d] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[e] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 3. Identified Issues and Recommendations for Marius Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
9.	The net quantity '90 (b) (4) capsules' is located just below the strength statement.	The risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	Relocate the net quantity statement away from the product strength, such as to the lower right corner of the principal display panel.
10.	The statement "Dispense the enclosed Medication Guide to each patient" is absent on the principal display.	A Medication Guide (MG) statement should be included on the principal display panel in accordance with 21 CFR 208.24 (d).	Revise the principal display panel to include a statement similar to, "Dispense enclosed Medication Guide to each patient", or "Dispense accompanying Medication Guide to each patient" in accordance with 21 CFR 208.24(d).
11.	The controlled substance symbol (CIII) is positioned between the proprietary name, Kyzatrex and the established name, testosterone undecanoate. The position of the controlled substance symbol, CIII contributes to intervening matter.	There should be no intervening printed, written, or graphic matter between the proprietary name, established name, and product strength per 21 CFR 201.10(a).	We recommend you re-locate the controlled substance symbol (CIII) to appear to the right of the drug identifying information on the principal display panel. Ensure the controlled substance symbol is clear and large enough to afford easy identification of the schedule upon inspection without removal from the dispenser's shelf in accordance with 21 CFR 1302.04.
12.	The statement, (b) (4) can be improved.	Labels for prescription drugs are required to bear a statement of the recommended or usual dosage per 21 CFR 201.100(b)(2). Furthermore, to ensure consistency with the Physician Labeling Rule	Revise the statement: "(b) (4) to read "Recommended Dosage: See prescribing information."

Table 3. Identified Issues and Recommendations for Marius Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(PLR) formatted prescribing information, we recommend the phrase "Recommended Dosage: See prescribing information."	

4 CONCLUSION

Our evaluation of the proposed Kyzatrex Prescribing Information and container labels identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Marius Pharmaceuticals, LLC so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Kyzatrex that Marius Pharmaceuticals, LLC submitted on December 31, 2020 and March 16, 2021.

Table 4. Relevant Product Information for Kyzatrex	
Initial Approval Date	Not applicable
Active Ingredient	Testosterone undecanoate
Indication	Testosterone replacement therapy in primary and secondary hypogonadal males
Route of Administration	oral
Dosage Form	capsule
Strength	100 mg, 150 mg, 200 mg
Dose and Frequency	Starting dose is 200 mg twice daily
How Supplied	Wide mouth, round, white, HDPE bottles with child resistant caps, 90 count
Storage	20˚C to 25˚C (68˚F to 77˚F), excursions permitted (b) (4) 15˚C to 30˚C (59˚F to 86˚F). Avoid exposing capsules to moisture (store in dry place).
Container Closure System	100 mg: 150 cc high density polyethylene (HDPE) with child resistant polypropylene (PP) screw tops with induction-sealed liner; 150 mg: 225 cc high density polyethylene (HDPE) with child resistant polypropylene (PP) screw tops with induction-sealed liner; 200 mg; 250 cc high density polyethylene (HDPE) with child resistant polypropylene (PP) screw tops with induction-sealed liner;

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 22, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Kyzatrex' and 'testosterone undecanoate'. Our search identified no relevant reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Kyzatrex labels and labeling submitted by Marius Pharmaceuticals, LLC.

- Container label(s) received on December 31, 2020
- Medication Guide (Image not shown) received on December 31, 2020: \\CDSESUB1\evsprod\nda213953\0000\m1\us\114-labeling\draft\labeling\kyzatrex-med-guide-20201231.pdf
- Prescribing Information (Image not shown) received on December 31, 2020 \\CDSESUB1\evsprod\nda213953\0000\m1\us\114-labeling\draft\labeling\kyzatrex-pi-20201231.docx; and March 16, 2021: \\CDSESUB1\evsprod\nda213953\0010\m1\us\114-labeling\draft\labeling\kyzatrex-pi-20210313.docx

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[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Interdisciplinary Review Team for Cardiac Safety Studies

ABPM Study Review

Submission	NDA 213953
Submission Number	001 (new NDA)
Submission Date	12/31/2020
Date Consult Received	1/5/2021
Drug Name	Testosterone undecanoate
Indication	Treatment of primary and secondary hypogonadism in adult males
Therapeutic dose	Starting dose of 200 mg BID. Titrated (100 mg qd to 400 mg BID) to target serum testosterone 460 to 971 ng/dL.
Clinical Division	DUOG

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's ABPM evaluation. The CSS-IRT reviewed the following materials:

- Previous CSS-IRT review under IND 118675 dated 08/08/2018 and 07/13/2020 in DARRTS;
- Advice letter for MRS-TU-2019EXT (DARRTS 08/20/2018; 07/08/2019);
- Clinical review for MRS-TU-2019EXT (DARRTS 08/13/2018); and
- Study report for MRS-TU-2019EXT (NDA 213953 / eCTD 0000; link).

1 SUMMARY

An increase in blood pressure (BP) was observed in this ABPM study as evidenced by a mean increase in 24-h mean systolic BP of 1.9 mmHg with an upper bound of 3.1 mmHg. 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 and it is unknown if the numerical differences are by chance due to study design or analysis differences. (b) (4)

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 1.

Table 1: The 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)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

The sponsor included the proposed label in SDN 0000 (link). We recommend similar labeling language to other oral TU products such as JATENZO.

3 SPONSOR'S SUBMISSION

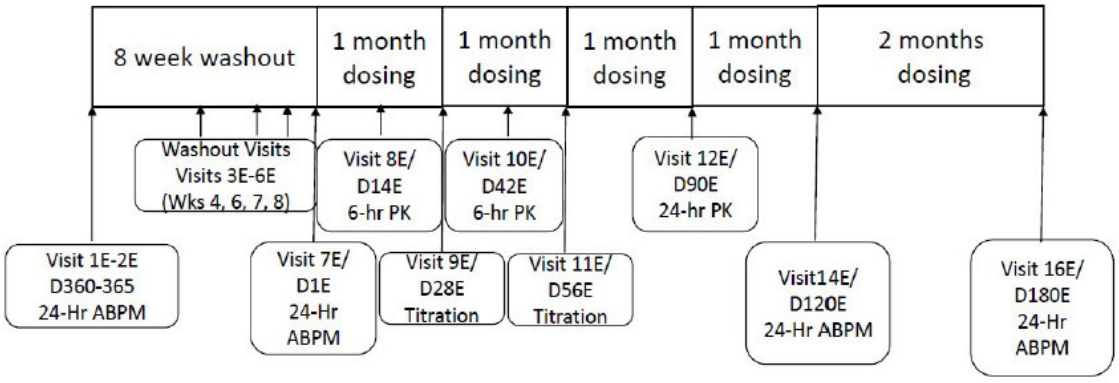
3.1 OVERVIEW

The study protocol for MRS-TU-2019EXT was reviewed under IND 118675 (DARRTS 08/08/2018) and found to be acceptable by DCN with a recommendation of substantial enrollment of both patients with and without hypertension at baseline. This recommendation was included in the advice letter along with increased enrollment to ensure 135 completers with ABPM data and for the study to include a four-month treatment duration. In a subsequent advice letter, the sponsor was recommended to exclude patients working nightshifts, required to perform strenuous manual labor during ABPM sessions or on anti-hypertensive medication who had not been on a stable dose for at least 4 weeks (DARRTS 07/08/2019). Of note, the last subject completed the extension study on October 17th, 2019.

The final study protocol addressed the recommendations of the first advice letter and the study design is shown in Figure 1. The study was a 180-day extension study starting with an 8-week washout (found acceptable by the division; DARRTS 08/13/2018) and a dose titration at days 28 and 56. Twenty-four-hour ABPMs were recorded prior to washout (in

a subset); baseline (after washout) and at days 120 and 180. The study included I/E criteria related to activities that could impact ABPM collection or expected changes to antihypertensive medication.

Figure 1: MRS-TU-2019EXT study design



Source: CSR, Figure 1, Page 54

The ABPM recorders were setup to collect measurements every 30 min during daytime (7a to 11p) and at nighttime (11p to 7a) with the following validity criteria:

- More than 10 measurements were missing/unreadable (>20%);
- > 2 consecutive hours of missing data (5 or more consecutive missing 30 min data points); or
- less than 22 hours of recording time.

ABPM recordings failing to meet the validity criteria were repeated. At the discretion of the investigator it could be permitted to repeat post-ABPM recordings a second time.

3.2 SPONSOR'S RESULTS

The ABPM analysis population was the EXTS population (all subjects who received at least one dose during the extension phase).

3.2.1 Primary endpoint

The primary analysis was MMRM 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. The results of this 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 47). 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 anti-hypertensive medication had minimal impact on results.

Reviewer's comment: A similar increase in 24-h average systolic BP was observed in the reviewer's analysis (see section 4.2).

3.2.2 Secondary endpoint

The MMRM used for the primary endpoint was used for 24-h diastolic BP (Table 58) and heart rate (Table 64):

- 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.

Reviewer's comment: A similar increase in 24-h average diastolic BP was observed in the reviewer's analysis (see section 4.2).

3.2.3 Cardiovascular risk in targeted patient population

The sponsor concluded that the combined measure of SBP and HR at 120 days indicate a low cardiovascular burden. No formal analysis done.

Reviewer's comment: No formal CV risk assessment was performed.

3.2.4 Missing data

No formal analysis of missing data.

Reviewer's comment: The reviewer's analysis did not show significant missing data (see section 4.5).

4 REVIEWERS' ASSESSMENT

The analysis population used in the reviewer's analysis was the EXTS population same population used by the sponsor.

4.1 DEMOGRAPHICS

The population demographics is presented in Table 2 by treatment arm. Smoking status was not collected in this study. The 10-year risk for atherosclerotic cardiovascular disease (ASCVD) events at baseline was predicted using the Pooled Cohort Equations and the results were categorized as low/borderline risk (<7.5%), intermediate risk (≥7.5% and <20%) and high risk (≥ 20%). The Pooled Cohort Equations include smoking status, which was not collected in this study and smoking status was therefore imputed using multiple imputation with NHANES (2003 – 2018) matching for age group and sex. This analysis showed that ~60%, ~32% and ~8% of the patients had a low/borderline, intermediate or high risk at baseline respectively.

Table 2: Demographics

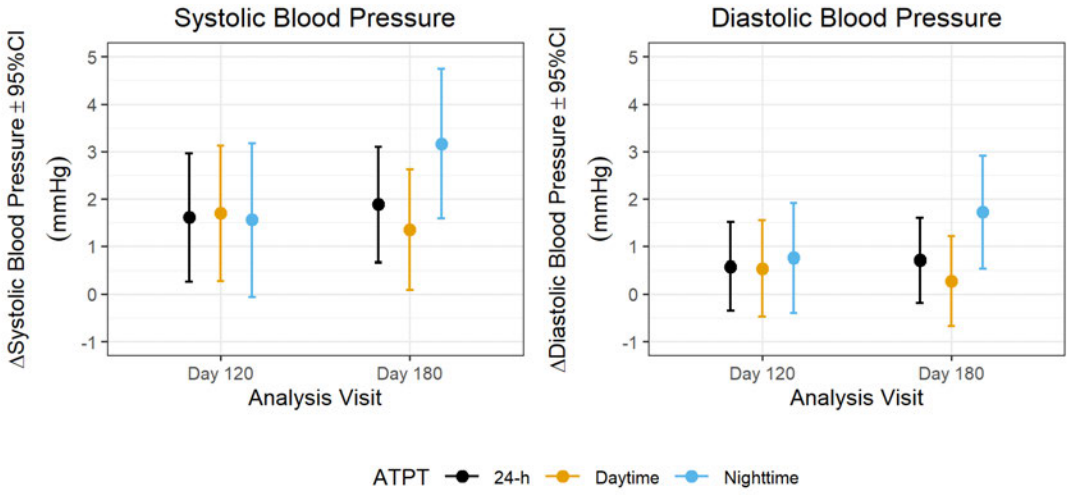
	KYZATREX (n=155)
Age (years), mean (sd)	50.5 (9.4)
Race	
Asian	4 (2.6%)
Black or African American	29 (18.7%)
Other	3 (1.9%)

	KYZATREX (n=155)
White	119 (76.8%)
Diabetes	34 (21.9%)
Pre-existing hypertension	
Yes	96 (61.9%)
missing (%)	3 (1.9%)
Treatment for HBP	56 (36.1%)
Systolic BP (mmHg)	
mean (sd)	126.1 (9.8)
missing (%)	3 (1.9%)
Diastolic BP (mmHg)	
mean (sd)	78.7 (6.7)
missing (%)	3 (1.9%)
HDL Cholesterol (mg/dL), mean (sd)	45.3 (11.9)
Total Cholesterol (mg/dL), mean (sd)	186.4 (38.4)

4.2 PRIMARY ENDPOINT

The primary endpoint for this study was change from baseline in 24-h average systolic BP at day 120 and 180. The figure below shows the results of the reviewer's analysis 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)



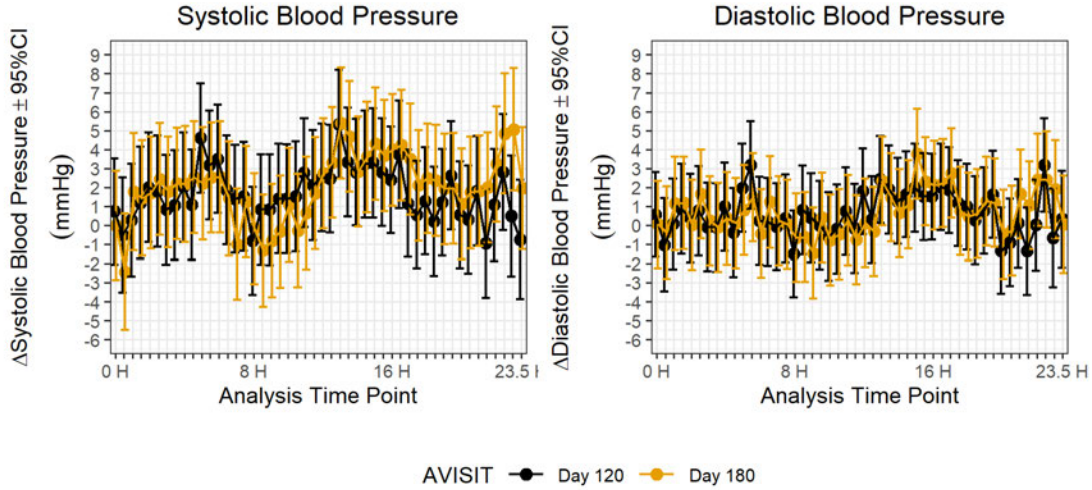
4.3 SECONDARY ENDPOINT

4.3.1 Hourly averages

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.

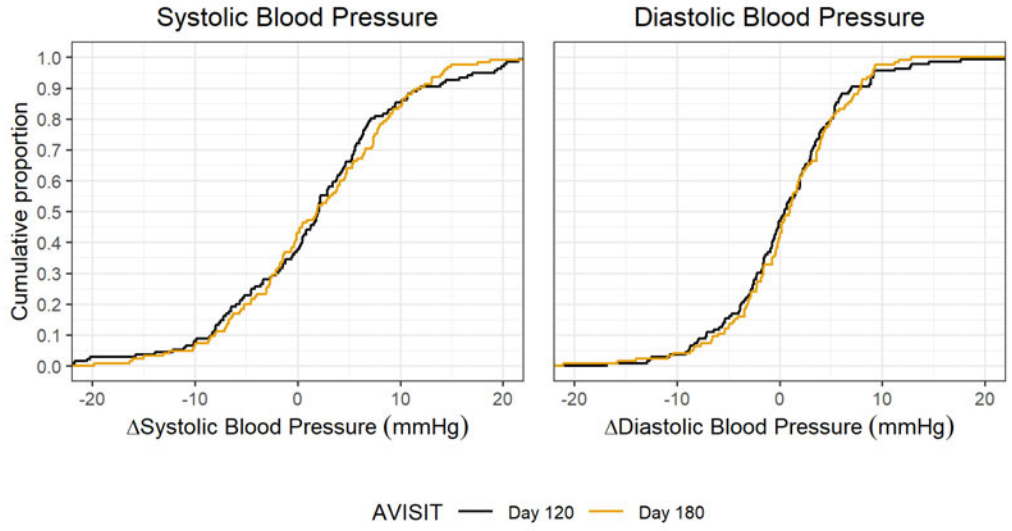
Figure 3: Placebo and baseline-adjusted changes in hourly averages



4.3.2 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



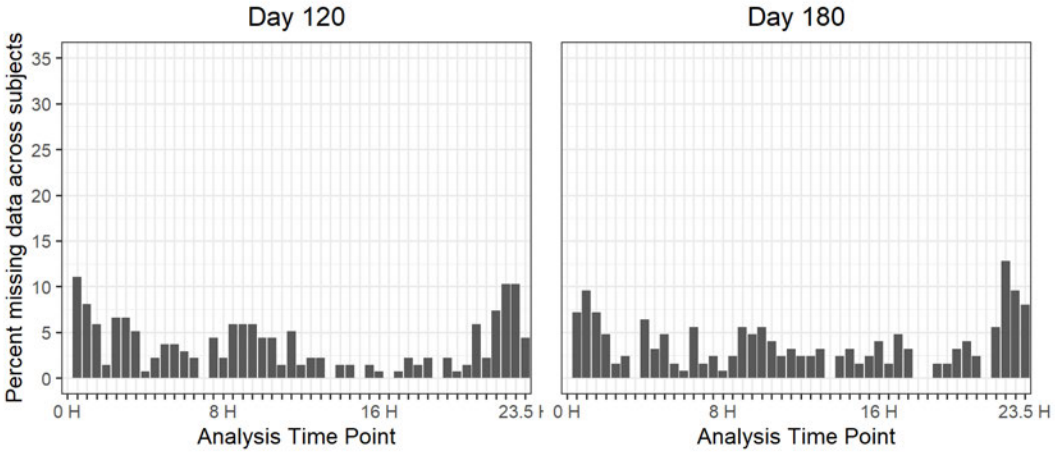
4.4 CARDIOVASCULAR RISK ASSESSMENT

No formal CV risk assessment performed.

4.5 MISSING DATA

The missing data percentage across subject per time-point is shown in Figure 5 showing a generally low missing data percentage without any apparent patterns in missing data indicating good data quality.

Figure 5: Missing data analysis



5 APPENDIX

5.1 PROTOCOL REVIEW

CSS-IRT has previously reviewed study protocol for this ABPM study (IND 118675, DARRTS 08/08/2018).

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