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APPLICATION NUMBER:

213953Orig1s000

SUMMARY REVIEW

CDTL Summary 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
CDTL Name	Suresh Kaul, MD, MPH
Review Completion Date	July 20, 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

CDTL Resubmission Summary Memo

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

Hypogonadism is a serious medical condition. Testosterone replacement therapy is recommended for the treatment of men with testosterone deficiency from well-known structural or genetic/congenital etiologies.

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

Kyzatrex is intended for testosterone replacement therapy (TRT) in males for conditions associated with a deficiency or absence of endogenous testosterone, including congenital or acquired primary or secondary hypogonadism.

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

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

- ≥85% of subjects with T C_{max} < 1500ng/dL;
- ≤5% with T C_{max} between 1800 – 2500ng/dL and
- 0% with T C_{max} greater than2500ng/dL.

The Applicant seeks the marketing approval for Kyzatrex, with a recommended starting dose of 200 mg twice-daily with possible titration to a minimum dose of 100 mg once daily in the morning up to a maximum dose of 400 mg twice daily, based on findings from the single phase 3 study (MRS-TU-2019EXT).

Drug Development History:
During the development of Kyzatrex, the Division recommended that the Applicant use 1.5-, 1.8-, and 2.5-fold of the upper limit of the normal T concentration range as the three C_{max} thresholds to determine the proportion of C_{max} outliers.

Study MRS-TU-2019EXT was a 180-day trial that included ambulatory blood pressure monitoring (ABPM) and enrolled hypogonadal men treated with the 200 mg twice daily dose with titration to a minimum dose of 100 mg daily to a maximum dose of 400 mg twice daily. ABPM assessments were conducted at baseline and at Day 120 and Day 180. The trial showed small increase in both systolic and diastolic blood pressure consistent with what was seen previously with two other approved TU products.

After the study completion and data review, a pattern in the relationship of NaF/EDTA plasma and serum T concentrations from Site 104 in Study MRS-TU-2019EXT was called into question by the Applicant. There were subjects at Site 104 whose NaF/EDTA plasma T concentrations were paradoxically higher than serum T concentrations obtained at the same timepoint. This was brought to the Agency's attention by the Applicant at the pre-NDA meeting on July 22, 2020. The Division acknowledged the Applicant's concern and their willingness to alert the Agency of such a finding at Clinical Site 104. "*The Division commented that this would be a review issue when the NDA is reviewed".*

After the NDA was submitted on December 31, 2021, inspections of Clinical Sites 104 (Manhattan Medical Research Practice, LLC, Jamaica, NY), 107 (South Florida Medical Research, Maitland, FL) and the Bioanalytical site ((b) (4)) were conducted by the Office of Scientific Integrity and Surveillance (OSIS) and the Office of Regulatory Affairs (ORA). OSIS was unable to secure any supporting documentation to certify that all processes and handling of PK blood samples at clinical Sites 104 and 107 were properly followed. Additionally, the Applicant failed to provide any documentation/evidence assuring that the sample handling and processing were conducted in accordance with the Central Laboratory Manual. This information was requested by the Division on the recommendation of OSIS. The finding of the lack of written documentation for PK sample handling at both Clinical Sites 104 and 107 called into question how the PK samples were processed and handled at the other 17 clinical study sites and the reliability of the data in general.

Kyzatrex met its primary efficacy endpoint but did not achieve any of the key secondary C_{max} endpoints (required for the approval action), when including data from Site 104. There was no information (for example, why there were multiple subjects with Cmax excursions) available to justify excluding Site 104 during the first cycle of review. Therefore, substantial evidence of effectiveness for Kyzatrex was not established. The application received a Complete response (CR) action on October 22, 2021. The CRL noted that Marius had failed to submit adequate evidence that the proposed dose and dosage regimen could restore testosterone levels to the normal range. Specifically, the integrity and reliability of the PK data from the clinical trial could not be assured and therefore this study did not support the safety and efficacy of Kyzatrex. The letter suggested that Marius should conduct a new Phase 3 clinical trial with an adequate number of hypogonadal subjects to demonstrate safety and efficacy of the drug product and that they should provide adequate documentation of laboratory processes.

This was followed by a Type A Post Action Meeting (T.CON) with the Marius Pharmaceuticals representatives on January 21, 2022.

Prior to this Post Action meeting the Applicant communicated with the Division where upon they defended their position for not having to conduct a new Phase 3 study as it would be unethical to subject more hypogonadal patients to unnecessary burden of a clinical trial for no apparent reason. The Applicant asserted that documentation for process handling from clinical sites is not required to be submitted as per FDA regulation.

During the Post Action Meeting, the Applicant was asked to explain the irregularities in process and handling of PK blood samples at Site 104. The Applicant once again acknowledged and explained that there were obvious irregularities in the process and handling of blood samples especially by one technician at their clinical Site 104. When asked by the Agency, Applicant stated there were at least 2 hours of lag time during which the blood samples remained at room temperature before the samples were centrifuged, resulting in noncompliance of PK sample handling and processing (e.g., not using ice-water baths for post-collection storage) of NaF/EDTA plasma samples.

The Applicant was asked to explain whether there could be a possible drug effect that could have contributed to C_{max} excursions in addition to process mishandling of PK samples. The Division queried, if in fact, the outlier data was due to ex-vivo TU to T conversion caused by human error, how would the Applicant explain the fact that five C_{max} outliers had TU C_{max} concentrations higher than the average C_{max} of TU. Such observations indicate these subjects had higher than average drug exposure (doses of 600 mg and 800 mg) as reflected in their plasma C_{max} outlier values (in at least one subject).

The Applicant assured the Agency that they do not believe that there was any drug effect contributing to high C_{max} values, but it was the mishandling in the processing of PK samples at Site 104 that resulted in these excursions. They reiterated that process issues at Site 104 do not imply that there was an issue with the reliability of the PK data from other clinical sites. They noted that the PK profile from Site 104 differed significantly from that of the other 18 clinical sites. That by itself, authenticates that there were process irregularities only at Site 104 as was notified to the Agency all along.

At the conclusion of the meeting, the Division indicated that there were still gaps in the NDA submission regarding T C_{max} outliers, precluding the Agency's ability to conclude that drug attribution to the observed outliers would be highly unlikely. The Applicant indicated they would submit new analyses to support that the T C_{max} outliers were highly unlikely to be due to drug effect.

This information was submitted as resubmission to NDA on January 27, 2022. The submitted data was reviewed by the clinical team including Dr. Martin Kaufman, clinical reviewer, and

Drs. Chongwoo Yu and Yanhui Lu, of the clinical pharmacology review team, during the current review cycle. Dr. Jordan Dimitrakoff, clinical reviewer DUOG, reviewed the safety section of this resubmission.

Clinical efficacy review by Martin Kaufman, clinical reviewer, DUOG

Recommendation Made by Clinical Reviewer, Martin Kaufman who reviewed the clinical efficacy during the second review cycle:
"From the clinical perspective, I recommend issuing a Complete Response for the resubmission of NDA 213953".

CDTL Comment

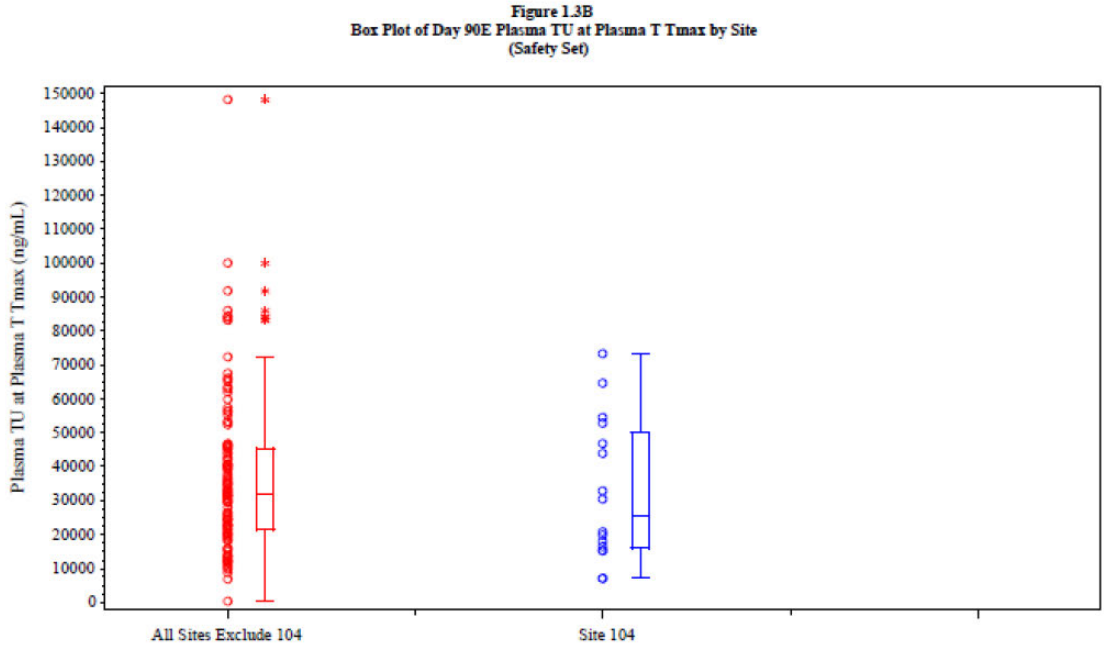
Dr. Kaufman cites a continued concern of overall data reliability. The Site in question is clinical Site 104, which showed significant process and sample handling irregularities. In my opinion, the Applicant has demonstrated in the resubmission that there is a significant non-drug effect for the C_{max} outliers, and the reason for the outliers is not indicative of a safety concern for the other 18 out of 19 clinical sites in theMRS-TU-2019EXT trial. Therefore, I recommend an Approval Action for Kyzatrex NDA 213953.

Dr. Kaufman in his review cites lack of documentation for Sites 104, 107 and other clinical sites as the predominant reason for unreliability of data. It should be noted that FDA regulation does not clearly indicate that an Applicant is required to submit documentation in support of the sample process handling at its clinical sites. However, the clinical sites in general, usually maintain documentation of processes that take place in their everyday sample handling. That documentation of sample processing becomes an important part of a clinical trial.

Additionally, the Cmax outliers were only seen at clinical Site 104, not at other clinical sites. Process irregularities contributing to these high Cmax values are highly likely a result of ex-vivo TU to T conversion. A possible contribution of drug effect in addition to ex-vivo TU to T conversion in couple of subjects in Dr. Kaufman's review who were otherwise on higher doses (600mg and 800mg) of Kyzatrex is unlikely.

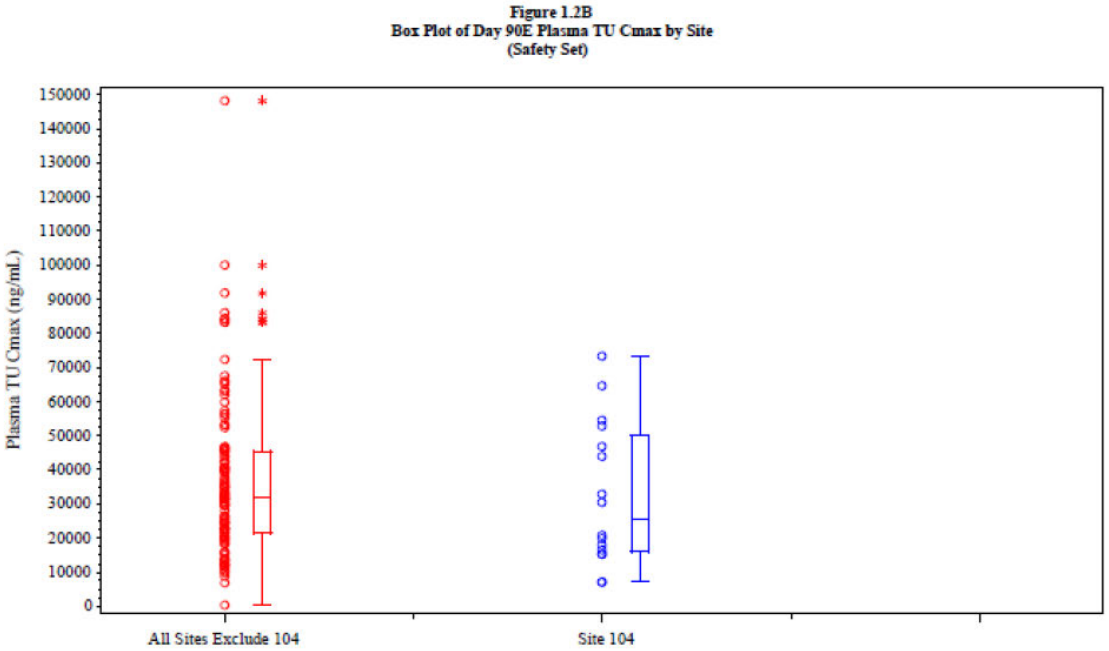
Dr. Kaufman in his review included two comparisons. One compared plasma TU concentrations at either T T_{max} (Figure 1) or TU T_{max} (Figure 2) for Site 104 to plasma TU concentrations for the other 18 sites in MRS-TU-2019EXT. The other compared plasma T C_{max} concentrations for Site 104 to plasma T C_{max} concentrations for the other 18 sites in the study.

Figure 1: Box Plot of Visit 12E/Day 90E Plasma TU at Plasma T T_{max} by Site



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

Figure 2: Box Plot of Visit 12E/Day 90E Plasma TU C_{max} by Site



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

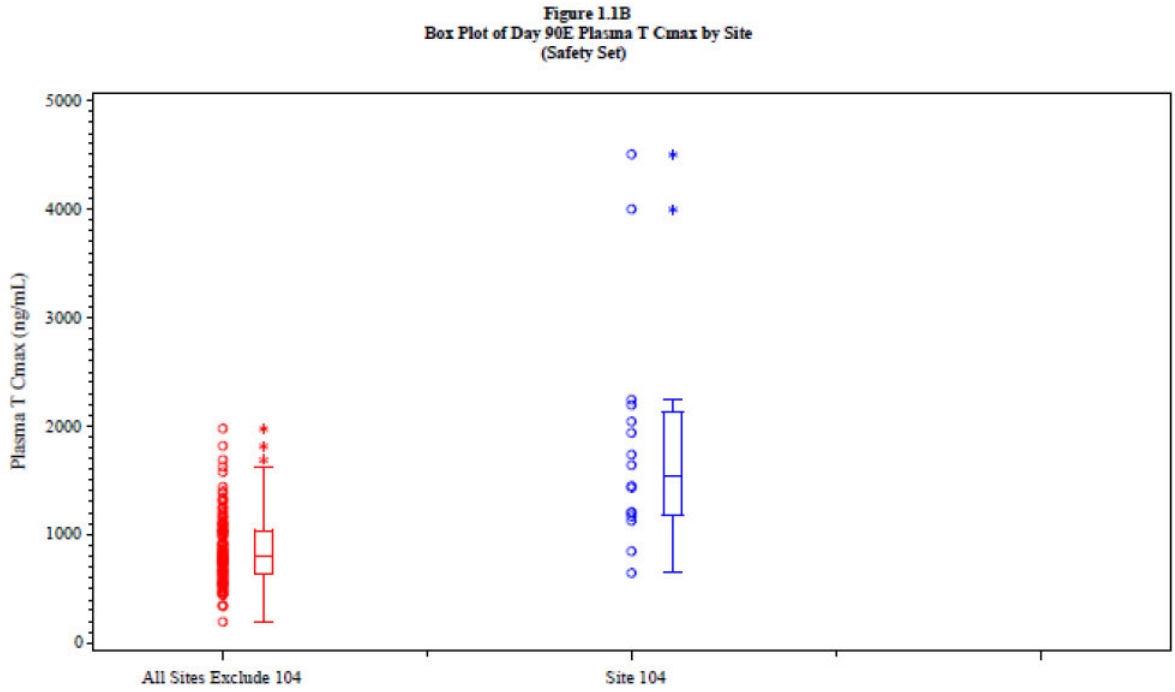
Figures 1 and 2 show that the Site 104 TU concentrations, either at T T_{max}, or at TU T_{max}, appear to be similar population of TU concentrations as other 18 sites in study MRS-TU-2019EXT. The median values from site 104 and all other sites are within the inner quartiles for each other,

and the lower and upper quartiles are similar in range. There were no TU C_{max} outliers identified at Site 104. In comparison, NaF/EDTA plasma T C_{max} concentrations from site 104 were higher compared to the other sites.

CDTL Comment

Figures 1 and 2 indicate that the TU concentrations observed from Site 104 did not outstand compared to the TU concentrations observed from other study sites.

Figure 3: Box Plot of Visit 12E/Day 90E Plasma T C_{max} by Site



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

Figure 3 below presents the T C_{max} data in the same box plot format. The Applicant notes that the Site 104 T C_{max} population appears shifted to higher concentrations and they conducted a statistical test to determine whether the two samples of T C_{max} values are different. For both TU comparisons, the difference is not significant, as expected. For the comparison of T C_{max}, the p-value is 0.002.

CDTL Comment

Figure 3 shows that T C_{max} values from Site 104 are higher compared to other sites.

Table 1: T-test for difference in T and TU concentrations, Site 104 vs. all others

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

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

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

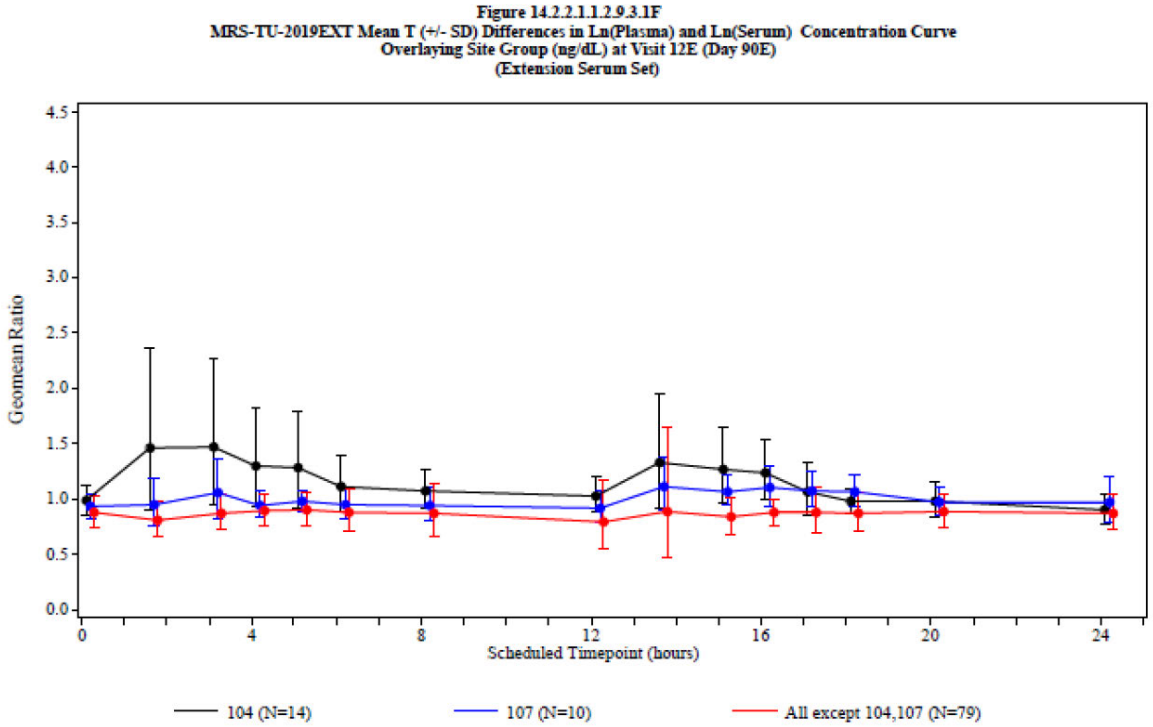
From the analysis as shown in the Table 1above, it can be concluded that while the TU concentration values (either at TU T_{max} or at T T_{max}) from Site 104 and all other sites are not statistically different, the T C_{max} values for Site 104 are statistically different from all other sites. This finding indicates an additional factor (such as PK sample mishandling) that makes a significant contribution to the T concentrations obtained at Site 104, beyond the expected drug effect of TU.

CDTL Comment

I agree with the analysis shown in the Table 1 above. There is a significant contribution to the T concentrations obtained at site 104 which is quite different than what is seen at the other 18 clinical sites. Such an effect could very well be a result of improper processing of PK blood samples that stayed out at room temperature for longer duration of time (at least for 90 to 120 minutes).

The Applicant further references a plot of the mean plasma over serum ratios for Site 104, Site 107, and all other sites for the 24-hour Day 90E PK profile and notes that the standard errors overlap, indicating that statistical significance did not exist at the individual timepoints.

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



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

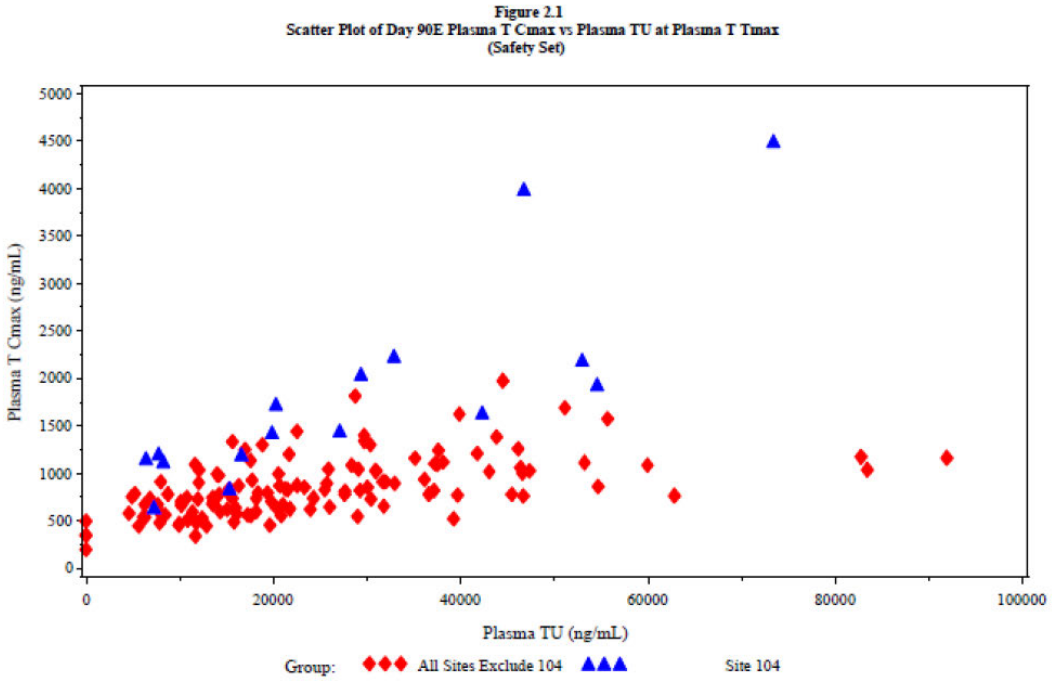
The Applicant concludes that the plasma over serum ratios observed for the samples from Site 104 are not of the same caliber as other clinical sites (with or without Site 107), and that a factor other than drug effect (such as blood sample process mishandling) contributed to the observed plasma T C_{max} values from Site 104.

CDTL Comment

I agree with the Applicant that the blood samples from Site 104 show a higher geometric mean ratio compared to samples obtained from all other clinical sites including Site 107 as seen in Figure 4. This indicates higher ex-vivo TU to T conversion as a result of sample handling irregularities which played a greater role at Site 104.

Dr. Kaufman in his resubmission review discusses Plasma T C_{max} correlation from TU concentrations. This analysis consists of two scatter plots that show the difference between the T C_{max} levels resulting from the TU levels at either T T_{max} or TU T_{max}. Figure 5 below shows the T C_{max} values resulting from the corresponding TU value at T T_{max} and Figure 6, the T C_{max} values versus the TU at T_{max} for TU.

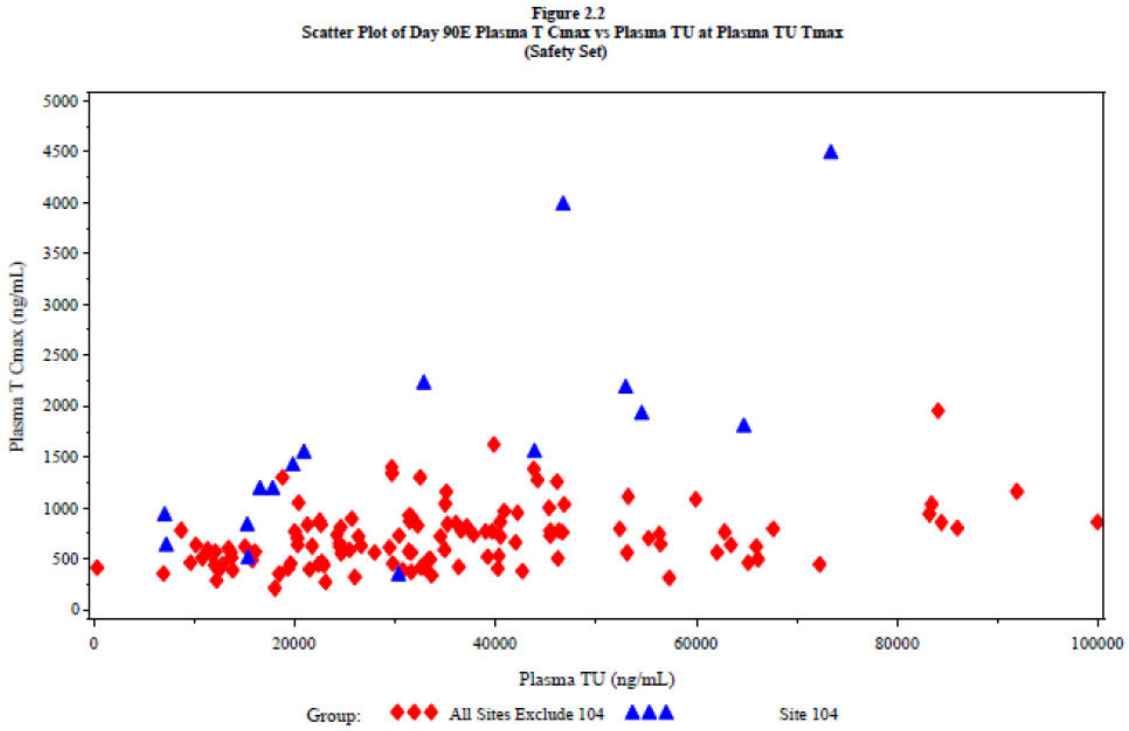
Figure 5: Scatter Plot of NaF/EDTA Plasma T C_{max} versus TU at T T_{max}



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

Plasma TU levels for all sites except Site 104 are represented by red diamonds and Site 104 data are represented by blue triangles. Figure 5.

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



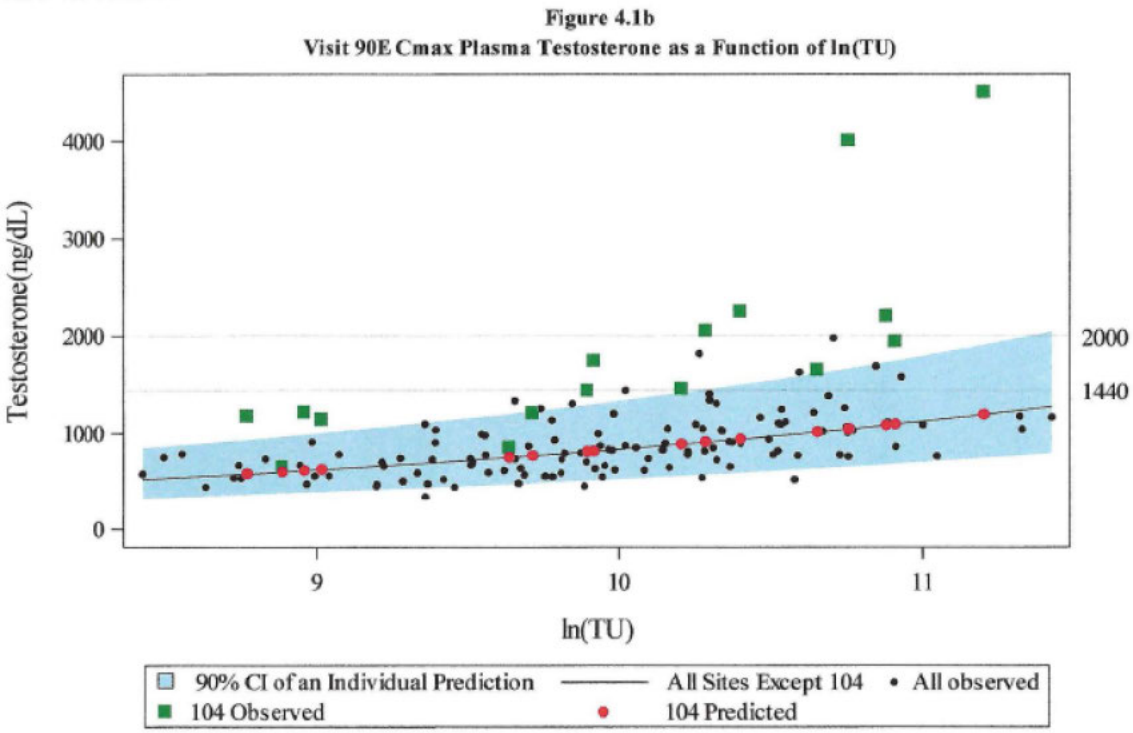
Source: NDA 215953 (SDN 038), Module 5.3.5.1, Clinical Study Report Addendum, Figure 6.

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

CDTL Comment

Figures 5 and 6 demonstrate that the T C_{max} values for Site 104 show a different relationship with TU concentrations than for all other sites and conclude that this different relationship for Site 104 T C_{max} values to the TU prodrug concentrations result from an extrinsic factor (non-drug effect) contributing to the observed T C_{max} values for Site 104. This observation is further reinforced by Figure 7 below.

Figure 7: Plasma Testosterone C_{max} vs. Ln (TU) at T T_{max}, MRS-TU-2019EXT



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

program: predictr.sas

Source: NDA 215953 (SDN 038), Module 5.3.5.1. Figure 7 as presented in Dr. Kaufman's Resubmission Review

Figure 7 presents the MRS-TU-2019EXT T C_{max} data (V12E/Day 90E) plotted as a function of the TU concentration at the T T_{max} timepoint and includes the predicted (black) line. The T C_{max} and TU values from all sites other than Site 104 were used to develop the model plotted as the black line, and the observed values plotted as black circles. Green squares are the observed Site 104 T C_{max} concentrations and red circles are the model-predicted values for Site 104. The blue-shaded area represents the 90% confidence interval of the model prediction of T C_{max} based on all subjects (n=130), excluding Site 104 subjects (n=16).

The following observations can be interpreted from Figure 7 above:

- *All 5 T C_{max} above 2000 ng/dL (2.5X ULN) fall outside the 90% CI*
- *All 9 Site 104 subjects above 1440 ng/dL and less than 2000 ng/dL (>1.8X-2.5X ULN) fall outside the upper 90% CI limit.*
- *For the 16 subjects from Site 104, 14 fall above the predicted line and above the upper 90% CI limit.*
- *The upper limit of the 90% CI at the maximum observed TU concentration (right most black circle) in the 2019EXT study is about 2000ng/dL, indicating the low probability of observing a T C_{max} above 2000 ng/dL.*

- ***The Site 104 data points appear to be a different population than that of all other sites.***

CDTL Comment

- **For the 5 subjects with T C_{max} >2000 ng/dL (2.5X ULN), who are all from Site 104, correction using the 90% CI upper limit of the predicted concentration brings the T C_{max} below 2000 ng/dL. Therefore, with a non-drug effect, there is not a safety risk from the observed values.**

Table 2: Observed and Predicted C_{max} Values for All Site 104 Subjects

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

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

The Applicant has the following observations from Table 2:

- ***For the two subjects (both from Site 104) with T C_{max} values of 3999 and 4500 ng/dL, the size of non-drug effect from the 90% CI is about 60%. As can be seen from Figure 5, 6 and 7, these two C_{max} values are far from the rest of the 144 subjects completing Day 90E. The non-drug effect alone is larger than the predicted T C_{max} (the drug effect) based on the TU concentration. Therefore, there is no safety risk from these values because the observed values do not bear a meaningful relationship to the drug effect.***
- ***For the 5 subjects with T C_{max} >2000 ng/dL (2.5X ULN), who are all from Site 104, correction using the 90% CI upper limit of the predicted concentration brings the T C_{max} below 2000 ng/dL. The sample mishandling contribution for these subjects ranges from 22% to 60% using the 90% CI upper limit, which is a conservative estimate. Again, with the substantial non-drug effect, there is not a safety risk from the observed values.***
- ***Of the 4 Site 104 subjects with T C_{max} > 1.8X to 2.5X the ULN, the sample mishandling contribution using the model-predicted 90% CI ranges from 2% to 26% of the observed T C_{max}.***

- *T C_{max} values at Day 90E for Site 104 (n=16) differ significantly from all other subjects (18 sites, n=129), (p = 0.002).*
- *AUC analysis of the plasma: serum ratio across the Day 90E PK profile (p< 0.0001)*
- *Correlation line slopes for Site 104 for plasma: serum ratio at 3, 4 and 5 hours have 95% CI's entirely separate from those for the rest of the study and separate from Visits 8E and 10E for Site 104 itself.*

CDTL Comment

- I firmly believe that the Applicant has clearly demonstrated that the T C_{max} values obtained from Site 104 comprise of a different population than the rest of MRS-TU-2019EXT as is seen in Figure 7. T C_{max} vs. TU demonstrates a consistent non-drug effect seen for Site 104 subjects. Therefore, it is reasonable to conclude that T C_{max} outliers > 2.5X ULN are highly unlikely to result in a safety risk for patients using Kyzatrex and the benefit far outweighs the risks associated with this class of drugs. Kyzatrex will provide an additional benefit of being another orally administered drug which can be titrated to the optimal desired range and monitored periodically thereafter.
- It is of utmost importance to note that transient increase in Cmax in couple of subjects from Site 104 did not indicate any change in safety parameters such as hemoglobin, PSA or in the Lipids. Therefore, I do not have any safety concerns for use of Kyzatrex in hypogonadal patient population.

  Also, the Clinical Pharmacology Review team and their management agrees with the Applicant's observation of Kyzatrex being a safe and efficacious drug.

Discussion

I agree with the Applicant's observation as discussed above. It clearly indicates that the observed T C_{max} values at Site 104 demonstrate a substantial contribution from another effect, identified as PK blood sample mishandling.
This observation is also confirmed by the Clinical Pharmacology review team.

Therefore, in general the T C_{max} outliers > 2.5X ULN are highly unlikely a result of the drug effect at Site 104. Dr. Kaufman, in his review, points out that there are two subjects ((b) (6)), who have shown high T C_{max} values. For subject (b) (6), the observed T concentration is 4500ng/dL, and the predicted value is 1189 ng/dL. For subject (b) (6), the observed T concentration is 3999ng/dL, and the predicted value is 1041 ng/dL. In my clinical opinion, predicted values are generally assumptions that may not always happen to be true in the real world. In the case of subject # (b) (6), the highest C_{max} value was seen after the second dose (three hours post evening dose) which corresponds to TU T_{max}. There is a high likelihood that a high fat meal after the evening dose could have contributed to an unusually high C_{max} value which normalized by the next day. These increases were seen to be transient in nature, and therefore, any concern of a safety risk is very low. In addition, patients receiving Kyzatrex will be titrated until a stable Testosterone concentration is achieved. This will be followed by periodic monitoring thereafter. The overall benefit of oral Kyzatrex is very

high in comparison to the already established risks that are associated with testosterone drug products as a class. Therefore, I find that C_{max} excursions seen in these two subjects do not point to a safety risk and do not pose any safety concern to the hypogonadal patient population going to use Kyzatrex if approved.

The Applicant demonstrated and the Agency has acknowledged that there were process irregularities at clinical Site 104 that contributed to C_{max} outliers. It should be noted that any deviation from standard procedures of sample handling and processing may lead to unexpectedly higher T concentration from plasma compared to serum prepared from blood collected at the same timepoint from the same subject. Additionally, there were no subjects with C_{max} excursions above 2.5 X ULN seen at any other 18 clinical sites during the clinical trial MRS-TU-2019EXT. As such, the overall reliability and integrity of data from other 18 clinical sites are no longer in question when we exclude data from Site 104.

Safety Update

NDA 213953 was submitted on December 31st, 2020 and included a literature review for 5-year period 2015 through 2019. The current literature survey covers the time from the previous literature review to the DSUR cut-off date of March 17th, 2022. There were no reported safety issues. The effect of Kyzatrex on ambulatory blood pressure in hypogonadal men was reviewed by Dr. Jordan Dimitrakoff, clinical reviewer, DUOG during the first review cycle.

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.

Recommendation made by Dr. Jordan Dimitrakoff, Safety Reviewer, DUOG:
"From the safety perspective, an approval is recommended for the resubmission of NDA 213953".

Conclusion

On January 27, 2022, Marius submitted a class 2 resubmission. The resubmission included a reanalysis showing that there is a significant non-drug effect for the C_{max} outliers, and the reason for the outliers is not indicative of a safety concern or an issue with the data from 18 other clinical trial sites. Therefore, I recommend an approval action for Kyzatrex oral capsules.

Clinical-Pharmacology Review by Drs. Chongwoo Yu and Yanhui Lu

The Office of Clinical Pharmacology (OCP)/Division of Cardiometabolic and Endocrine Pharmacology (DCEP) reviewed the Applicant's resubmission for NDA 213953 submitted on January 27, 2022. The overall Clinical Pharmacology information submitted to support this NDA is acceptable and Kyzatrex® is recommended for approval as a TRT in adult males for

conditions associated with a deficiency or absence of endogenous T from the Clinical Pharmacology standpoint.

CDTL Comment
I concur with the recommendation made by OCP.

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

Dr. Chongwoo Yu notes in his review, that subjects from clinical study Site 104 had NaF/EDTA plasma T concentration results paradoxically higher than serum T concentrations obtained at the same time. As a result, the Applicant excluded all subjects from this site (N=16) for efficacy analysis. The primary efficacy endpoint was met regardless of the exclusion of Site 104. T C_{avg} within normal range after 90 Days, 95% Confidence Intervals ≥ 65% (Lower Bound) was 82.6 (n= 155) without excluding site 104 and 82.3 (n=139) with excluding site 104. The normal range for plasma T being 222-800 ng/dL.

The key secondary PK endpoints (i.e., T C_{max}) were not met when including all 155 subjects, However, the key secondary PK endpoints were met after excluding subjects from Site 104.
C_{max} <1200 ng/dL, (Target >85%), without excluding Site 104, (81.5%)
with excluding Site 104 was (87.7%)
C_{max} 1440 <2000ng/dL, (Target <5%), without excluding Site 104, (9%)
with excluding Site 104, (5%)
C_{max} > 2000ng/dL, (Target 0%), without excluding Site 104 (5%)
with excluding Site 104, (0%).

Drs. Chongwoo Yu and Yanhi Lu in their resubmission review state that all T exposures (i.e., AUC) observed in NaF/EDTA plasma and serum from Site 104 fell within the range of observed T AUC values from other study sites. *The distribution pattern of AUC values for NaF/EDTA plasma T, serum T, and NaF/EDTA plasma TU in each dose group appears to be similar between Site 104 and other sites except for NaF/EDTA plasma T AUC values at 600 mg and 800 mg doses. The 5 T C_{max} outliers subjects from Site 104 generally had higher NaF/EDTA plasma T exposure compared to other subjects in the respective dose groups of 600 mg and 800 mg. However, it should be noted that this was not the case for NaF/EDTA TU exposure.*

CDTL Comment
Generally, it is expected that higher TU concentrations (and AUCs) will result in higher T concentrations. This observation indicates that most of these 5 T C_{max} outliers were not expected to have so high NaF/EDTA plasma T exposure because their serum T exposures and NaF/EDTA plasma TU exposures were within the range of observed values from other sites.

Mean plasma over serum ratios

Drs. Chongwoo Yu and Yanhui Lu further in their review state that the mean concentrations of serum T were higher than that of NaF/EDTA plasm T at most of the time points. This was possibly due to factors including: (1) sample matrix (i.e., serum vs. plasma); (2) TU to T ex-vivo conversion (i.e., because sample preparation conditions including temperature and time are different) and (3) sample tube types (i.e., serum prepared from blood collected in plain tubes vs. plasma prepared from blood collected in NaF/EDTA tubes). Therefore, it is expected that serum T concentrations are generally higher than NaF/EDTA plasma T concentrations. However, as mentioned earlier, there were subjects from clinical study Site 104, who had NaF/EDTA plasma T concentrations paradoxically higher than serum T concentrations obtained at the same time.

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

Four out of five T C_{max} outliers participated in the serum sub-study (except for Subject (b) (6)) and had PK profiles obtained from NaF/EDTA plasma, EDTA plasma, and serum. All four of these subjects, paradoxically had higher T exposure from plasma than from serum. *It should be noted that the difference between plasma and serum exposure was larger around T_{max} than at other time points. TU T_{max} was 15 hours post-morning dose (i.e., 3 hours post-evening dose) for Subjects (b) (6), and (b) (6) while it was 3 hours post-morning dose for Subject (b) (6).*

CDTL Comment

This further reinforces the fact that high C_{max} values were seen approximately 3 hours post evening dose which is also post an evening meal. A high fat meal or a high fat breakfast could contribute to higher C_{max} values in addition to the ex-vivo TU to T conversion which was a result of sample mishandling at Site 104.

CDTL Comment

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

However, in some cases despite plasma TU exposures being similar, NaF/EDTA plasma T exposures were significantly different (e.g., Subject (b) (6) vs. Subject (b) (6); Subject (b) (6) vs. (b) (6) – in both these cases, one subject was from the 5 T C_{max} outliers while the other subject was not, and the cause of this is unknown). It should be noted that only one subject (i.e., Subject (b) (6)) among the NaF/EDTA plasma T C_{max} outliers (i.e., with T C_{max} value > 2.5x ULN of 2,000 ng/dL) also had the corresponding serum T C_{max} value > 2.5x ULN (i.e., > 2,500 ng/dL). The real reason for Cmax excursion in this case cannot be determined as pointed out by Dr. Chongwoo Yu in his review.

Discipline Reviews

CMC Recommendation – "Approval"

Dr. Hamid Shafiei, CMC Lead, notes that in this resubmission label deficiencies have been adequately addressed. There was sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance. The Office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended that the facilities involved in this application have remained adequate. Also, this application is recommended for an approval from the OPQ perspective. The applicant's request for the categorical exclusion from the preparation of environmental assessment has been granted.

CMC Recommendation by Subdiscipline:

Drug Substance	Adequate
Drug Product	Adequate
Quality Labeling	Adequate
Manufacturing	Adequate
Biopharmaceutics	Adequate
Microbiology	Adequate

Other disciplines including Non-Clinical (Pharm-Tox), and Biostatistics did not have any new information submitted to review during this review cycle. These disciplines recommended an approval for Kyzatrex in the last review cycle. For details see Unireview dated October 2021, in DARRTS.

Labeling negotiations were completed and a final Label and a medication guide for Kyzatrex that is consistent with other already approved oral testosterone drug products was formalized.

PMR's

The following two PMR's will be issued for this application:

PMR #1:

A trial of testosterone replacement therapy in pediatric males ages 12 years to less than 18 years of age for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism.

PMR Proposed Milestones	
Draft Protocol Submission:	04/2024
Final Protocol Submission:	08/2024
Trial Completion:	08/2029
Final Report Submission:	02/2030

PMR #2:

An appropriately designed label comprehension study that assesses patients' understanding of key risk messages in the Medication Guide for testosterone replacement therapy. The primary objective of this study is to assess patient comprehension of materials related to increase in

blood pressure that can increase the risk of major adverse cardiovascular events with testosterone replacement therapy. Include men representative of those who use prescription testosterone therapy with a range of cardiac risk factors, a range of education levels, and various literacy levels. The study findings may result in revisions to the Medication Guide to optimize patients' understanding of important risks of testosterone replacement therapy.

PMR Proposed Milestones
Draft Protocol Submission: 10/2022
Final Protocol Submission: 06/2023
Study Completion: 12/2023
Final Report Submission: 03/2024

Overall Conclusion and Recommendation

Based on the totality of data, I agree with the Applicant that the data from Site 104 should be excluded. The primary and key secondary efficacy endpoints of the study which are based on C_{avg} and C_{max}, respectively, and are derived from the PK data are met. The efficacy of Kyzatrex is established with a sufficient degree of certainty from the PK data of MRS-TU-2019EXT from its 18 clinical sites (excluding Site 104). The benefit of Kyzatrex oral capsules far exceeds than the risks that are established with TRT as a class.

While there were irregularities (such as mishandling of blood samples at clinical Site 104 that resulted in C_{max} excursions in at least two subjects), these high C_{max} values do not represent any safety risk to the hypogonadal population who take Kyzatrex oral capsules. There were no C_{max} excursions seen at any other 18 clinical sites for MRS-TU-2019EXT study. There was no drug effect seen that could have contributed to these high C_{max} values.

I recommend an *approval* for Kyzatrex oral capsules.

Deputy Division Director (Acting) Concurrence

Male hypogonadism is a serious medical condition resulting from insufficient/absent secretion of testosterone by the testis. Testosterone replacement therapy (TRT) is recommended for the treatment of men with testosterone deficiency from structural or genetic/congenital etiologies. There are currently multiple options for TRT, including injection, implants, transdermal, nasal gel and oral routes of administration.

Marius Pharmaceuticals, LLC submitted its original NDA for what would now be the third oral TRT option, Kyzatrex, on December 31, 2020. This application focused on MRS-TU-2019EXT an open-label, single arm phase 3 efficacy and safety study that included 24- hour ambulatory blood pressure monitoring (ABPM). Kyzatrex is a soft gelatin capsule containing (b) (4) testosterone undecanoate (TU), a prodrug of testosterone (T), (b) (4) . TU is converted to T by nonspecific esterases in the body. The proposed

starting dose is 200 mg orally twice daily and the dose can be adjusted to anywhere between 100 mg and 400 mg twice daily, based on serum T concentration. It is well known that when blood samples are collected in a plain tube (serum) without an esterase inhibitor, TU can be converted to T *ex vivo*, and an overestimation of T concentrations can occur. Other laboratory conditions which can also lead to increased *ex vivo* conversion are incubation temperature (lower temperature slows conversion) and incubation time (conversion is most rapid within the first 30 minutes, reduced incubation time allows for less overall conversion.) To minimize the impact of this *ex vivo* conversion in their study, the Applicant relied on plasma T concentrations, collected in NaF/EDTA tubes (with the esterase inhibitor). The Applicant also did a serum substudy, where blood was collected in plasma and serum tubes, to determine the correlation of T concentrations in the samples. It is expected that the serum T concentration will be higher than the plasma T concentration. At a pre-NDA meeting (for IND 118675, on July 22, 2020), the Applicant noted that multiple subjects at Site 104 had plasma T concentrations paradoxically higher than serum T concentrations and determined that there was sample mishandling at the site. The Applicant proposed to exclude Site 104 from the efficacy analysis, which would have allowed them to meet not only the primary efficacy endpoint, but also key secondary endpoints, most notably for Cmax outliers. This was flagged as a potential review issue to be undertaken during NDA review. During NDA review, an inspection by the Office of Scientific Integrity and Surveillance (OSIS) of Site 104 and subsequently Site 107 found that there was no documentation of PK sample handling and processing at several clinic visits, including at the timepoint for the primary efficacy evaluation. OSIS concluded that the conditions were likely present at other sites and that they could not 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 TU to T in blood samples. OSIS ultimately concluded that the Applicant did not adhere to the applicable statutory requirements and FDA regulations governing study conduct, but that their response to the Form 483 and proposed corrective actions appeared adequate to prevent the recurrence of these observations in any ongoing or future studies. The Applicant was asked to provide more information on sampling handling in MRS-TU-2019EXT for all of the other study sites in order for the clinical team to fully assess the impact of the inspection findings on data reliability. The Applicant could not provide documentation to address Agency concerns about the reliability of the data for the entire study, and therefore the application received a Complete Response action. The Applicant was advised to conduct a new phase 3 study. A Type A post-action meeting was held on January 21, 2022, at which time the Agency stated, while sample mishandling could have contributed to the excessive Cmax excursions, the applicant needed to provide evidence to exclude the possibility of drug effect. The Applicant submitted a supplement on January 27, 2022.

The current submission contains no new data or documentation. While it is intuitively consistent with good laboratory practice that there is adequate documentation of adherence to processes and it is unfortunate that the Applicant could not provide the requested information,

the language in 21 CFR 312.60 is very broad. It is clear that the Applicant's proposed corrective actions were found satisfactory by OSIS for future studies. For this particular submission, the Applicant did provide additional analyses for study MRS-TU-2019EXT, which the Applicant asserts (1) demonstrate that Site 104 is very different from other Sites in terms of sample handling, and (2) demonstrate that Cmax outliers (five at Site 104) are very unlikely to be due to drug effect and (3) support that Site 104 (16 subjects) should be excluded from the analysis. This submission was filed and reviewed.

The data presented show the following:

(1) Comparison of NaF/EDTA Plasma T Cmax and TU Concentrations, Site 104 vs. all other sites:
    a. Plasma TU concentrations at the T Tmax and at the TU Tmax, at Site 104 appear to be similar to the other 18 sites in Study MRS-TU-2019EXT. The median values from Site 104 and all other sites are within the inner quartiles for each other, and the lower and upper quartiles are similar in range. There were no TU Cmax outliers identified at Site 104.
    b. Plasma T Cmax values for Site 104 subjects (not only the five outliers) exhibit a different relationship with TU concentrations than for all other sites and were statistically different (higher) from that observed from other sites. The Applicant examined T exposure compared with dose, for Site 104 and other sites. Almost all T exposures (AUC) in plasma and serum from Site 104 are within the range of observed T AUC from other study sites. The AUC values for plasma T, serum T and plasma TU in each dose group are also similar between Site 104 and other sites, except for plasma T AUC values at 600 mg and 800 mg doses. The five T Cmax outliers from Site 104 generally had higher plasma T exposures compared to other subjects at other sites in the 600 mg and 800 mg dose groups, BUT they did not show higher plasma TU exposure as would be expected.
    c. In the serum substudy, multiple subjects from Site 104 had plasma T concentrations paradoxically higher than serum T concentrations obtained at the same time. This is different from the other sites. A further evaluation of the individual PK Profiles of the 5 T Cmax outliers, showed that 4 participated in the serum substudy and demonstrated the same paradoxically higher T exposure from plasma than from serum. The difference between plasma and serum exposure was larger around Tmax than at other timepoints.

    These findings support a conclusion that sample mishandling at Site 104 made a significant contribution to the T concentrations beyond the expected drug effect of TU.

(2) Plasma to Serum Ratios

a. The Applicant plotted the geometric mean of plasma to serum ratios and compared the geometric least squares means of plasma to serum T AUC ratio of Site 104 to all other sites and the p-value was <0.0001. The Applicant asserts that this indicates that Site 104 plasma to serum concentration ratios are statistically different from other sites' ratios. Mean plasma to serum ratios > 1 were observed from Site 104 subjects while mean plasma to serum ratios of < 1 were observed from subjects from other Sites (as would be expected).
b. Plasma to serum T were compared at various visits (Visits 8E, 10E, 12 E) and data suggest that execution of study procedures on day 90E (visit 12 E) at Site 104 differed from those at other visits at all sites.
c. Scatterplots of plasma T vs. TU concentrations from different time points (pre- and post-dose timepoints) show that samples from some Site 104 subjects had notably high T concentrations compared to other sites' subjects while they had comparable TU concentrations—most notably the 5 T Cmax outliers.

These findings support the conclusion that conditions were different at Site 104 than at other sites, which could have impacted measurements of T. An extrinsic effect appears more likely than drug effect.

(3) Evaluation of T, dihydrotestosterone and TU Exposures from Subjects at Site 104

The 5 T Cmax outliers were generally on higher doses of Kyzatrex (600 mg or 800 mg). Three of the five had higher plasma TU concentrations at T Tmax, which could be a contributing factor to the outlier T concentrations. But in some cases, the TU exposure did not explain the high plasma T exposure. When considering the available serum T data, Subject (b) (6) was the only subject with a high T Cmax value (i.e., > 2.5x ULN) both in serum and NaF/EDTA plasma. Therefore, it is not clear whether this subject is an outlier due to process mishandling solely or a combination of both ex-vivo TU to T conversion and some contributing drug effect.

(4) Subject level data

The applicant developed a linear regression model to predict T Cmax as a function of TU concentration. The model used observed plasma T Cmax and the associated plasma TU concentrations from all sites except Site 104, to predict what T Cmax would be expected to be at Site 104. 14/16 subjects at Site 104 had values above what the model predicted and almost all fell above the upper 90% CI limit of the predicted line. The model underpredicted the plasma T Cmax for Site 104 subjects, especially for the 5 outliers. This discordance between actual and predicted T Cmax at Site 104 may have been due to a combination of drug-related effect and sample mishandling. However, sample mishandling appears to range from 22% to 60% using the 90% CI upper limit, which is a conservative estimate. While the clinical reviewer has concerns that the model does not accurately predict T concentrations and may underestimate the drug

effect, this cannot be definitively determined. However, the primary culprit seems to be consistent sample mishandling at Site 104.

Deputy Division Director (Acting) Conclusion

It is clear from the totality of information submitted by the Applicant that plasma data from Site 104 are different from the other Sites, particular on Day 90E, the date for efficacy assessment. I find it reasonable to exclude data from Site 104, and the available data from the other sites provide sufficient evidence of effectiveness. A safety update encompassing a literature search for oral testosterone undecanoate revealed no new safety concerns—one paper described small increases in ambulatory blood pressure, which is a known risk with these products. The safety profile is consistent with testosterone replacement therapies as a class.

Therefore, because substantial evidence of effectiveness has been demonstrated and the safety profile is consistent with drugs in the class, I concur with the recommendation for approval of this efficacy supplement.

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

/s/

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07/20/2022 09:23:58 AM

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