CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Memo

Date	September 28, 2018
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA# /Supplement#	209863
Applicant	Antares Pharma, Inc
Date of Submission	March 29, 2018
PDUFA Goal Date	September 29, 2018
Proprietary Name / Established (USAN) names	Xyosted testosterone enanthate
Dosage forms / Strength	50 mg, 75 mg, 100 mg weekly subcutaneous injection via autoinjector
Proposed Indication(s)	Replacement of testosterone in adult men with deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism
Recommended:	***Approval***

1. Introduction/Executive Summary

Xyosted, formerly known as QuickShot Testosterone (QST), is proposed for use as a new testosterone replacement therapy (TRT). Each dose of Xyosted contains 50 mg, 75 mg or 100 mg of testosterone enanthate (TE) in sesame oil. Xyosted is a parenteral formulation for subcutaneous administration by an incorporated autoinjector. The testosterone dose is administered by the patient himself once weekly using the autoinjector. The principal benefit of this new approach is patient convenience.

TRT is the current standard of care for hypogonadal men with primary or secondary hypogonadism due to conditions associated with a genetic or structural disorder. Nonetheless, despite a drug class Limitation of Use (LOU) in approved product labeling, TRT products are often prescribed to older men with "low T" for the treatment of "age-related hypogonadism". There are a host of FDA-approved TRT products available, including a variety of formulation types. Xyosted would be another therapeutic option in the armamentarium for TRT.

The original NDA for Xyosted was supported by results from 5 clinical studies, including

- Three (3), short-term (one to six doses) Phase 1 and Phase 2 studies: those were Studies QST 13- 002, QST 14-004 and QST 16-006, and
- Two (2), long-term, Phase 3 studies: those were Studies QST 13-003 (1-year) and QST 15-005 (6 months).

Consistent with the Division's expectations for TRT studies, the Phase 3 studies had no concurrent controls and were open-label (except for a double-blind to dosage strength in the 1-year Study QST 13-003).

Study QST 13-003, the single, "pivotal", Phase 3 efficacy and safety study, included a total of 150 hypogonadal men (97 completed) who received treatment for up to 52 weeks. Study QST

15-005, a Phase 3 safety study, included another 133 hypogonadal men (113 completed) who received treatment for up to 26 weeks.

In brief, the Efficacy data from the Phase 3 pivotal Study QST-13-003, along with supporting data from the other clinical studies, supports the Sponsor's contention that QST provides testosterone replacement in adult men with hypogonadism.

For Safety, the overall NDA database consists of:

- 116 hypogonadal adult male patients who were randomized to receive one (QST 14-004), two (QST 16-006), or six (QST 13-002) doses of Xyosted in the short-term studies,
- 150 hypogonadal adult male patients who received Xyosted for up to 52 weeks in Study QST 13-003, and
- 133 hypogonadal adult male patients who received Xyosted for up to 26 weeks in Study QST 15-005.

Thus, a total of 283 patients received Xyosted in the long-term studies. A total of 380 patients received at least 1 dose, a total of 242 received at least 24 doses (approximately 6 months of treatment), and a total of 99 received at least 52 doses (approximately 12 months of treatment). The overall mean age of the Phase 3 subjects was 53.9 years, with the majority of patients (82.7%) younger than 65 years of age. The overall mean body weight was 99.8 kg.

In general, the safety profile for QST TE was consistent with the known safety profile for TRT, except for:

- *Increases in blood pressure (BP)* were observed in some patients in both Phase 3 studies. In the 6-month study QST 15-005, Xyosted increased systolic BP (SBP) within the first 12 weeks of treatment by an average of 4 mmHg based on ambulatory blood pressure monitoring (ABPM) measurements. In the 1-year study QST 13-003, Xyosted increased SBP from baseline also by an average of 4 mmHg based on BP cuff measurements - and 10% of Xyosted-treated patients were either started on antihypertensive (anti-HTN) medications or required changes to their existing anti-HTN medication regimen.
- *Four total cases of depression and suicidal ideation and behavior*, including one case of completed suicide, were reported during the long-term Xyosted studies. Depression requiring discontinuation was reported in 2 of the 283 patients in the two Phase 3 studies, and suicide attempts (one complete and one incomplete) were reported in 2 additional patients, comprising a total of 4 patients, representing 1.4% of patients who received Xyosted for up to one year. While each of these 4 cases included possibly confounding factors, and there was no clear evidence to support an increased risk of suicidality and depression with Xyosted compared to other forms of TRT, the occurrence of 4 depression/suicide events among 283 long-term study patients was notable.

Additionally, the incidence of *increased hematocrit, including cases of polycythemia*, in the long-term studies appeared somewhat greater than has been generally reported for TRT.

Based on these Clinical safety concerns, the Clinical review team recommended a Complete Response (CR) action for the original application, and on October 20, 2017 a CR letter, containing two Clinical deficiencies (the increased BP and depression/suicide issues) was issued to Antares.

On February 21, 2018, the Division met with Antares in a Type A meeting to discuss pathways to resolve the Clinical deficiencies listed in the CR letter and to identify any remaining issues that might preclude NDA approval. The reader is referred to the final Type A meeting minutes in DARRTS.

On March 29, 2018, the Sponsor provided a CR NDA re-submission to the NDA. Other than a "Hypertension Discussion" White Paper that had already been submitted by Sponsor to the IND and reviewed by FDA in the context of a Type A meeting, no new data or data analyses were submitted in the re-submission. In response to the CR deficiencies, the re-submission contained substantially revised product labeling, including a Medication Guide, and a proposal for a Communication Plan Risk Evaluation and Mitigation Strategy (REMS). The Sponsor asserted that the two Clinical CR deficiencies, and any other Clinical safety-related concerns (e.g., increased hematocrit, safe patient handling of the autoinjector, etc.) could be addressed through the substantially improved prescriber and patient labeling; and if necessary, through a communication to prescribers.

As part of this CR re-submission (second cycle) review, the NDA review team re-considered the the key clinical safety issues and CR deficiencies and discussed the issues extensively within FDA. Ultimately, the Division and review team determined that each of these issues could be addressed through substantive labeling, supplemented by a postmarketing requirement study for one of the issues, and with pharmacovigilance for another.

For the "*increased BP*" CR deficiency, the Sponsor agreed to resolve this issue through new substantive labeling, including:

- A Boxed Warning,
- A new Contraindication that limits use of Xyosted to the indicated patient population, and
- A comprehensive Medication Guide.

For this issue, the Sponsor also agreed to conduct a post marketing requirement (PMR) study to assess patients' comprehension of key risk messages in the Medication Guide.

For the "*depression/suicide*" CR deficiency, the Sponsor also agreed to resolve this issue through substantive new labeling, including a new Warning and additional information in the Adverse Reactions and Patient Counseling sections, and in the Medication Guide. For this issue, the Sponsor also agreed to provide a separate report concerning depression and suicide case reports in each quarterly NDA Periodic Adverse Event Report (PADER) for the first three years of Xyosted marketing. The Sponsor will propose changes to the Xyosted labeling, if needed, based on the findings from these quarterly reports.

For the "*increased hematocrit/polycythemia*" issue, the Sponsor agreed to resolve this issue through substantive new labeling to reflect these findings. For example, the labeling will recommend monitoring of hematocrit approximately every 3 months while patients are on Xyosted.

Concerns previously expressed by the Division of Medication Error Prevention and Analysis (DMEPA) in regard to the Instructions for Use (IFU) document were remedied through labeling discussions with the Sponsor.

There are now no deficiencies from any review discipline, including Clinical, Chemistry, or DMEPA, that preclude approval.

Therefore, based on successful resolution of the CR deficiencies, and with acceptable agreed-upon labeling, a postmarketing requirement study for one safety issue, and pharmacovigilance with special reporting requirements for another safety issue, I concur with the Clinical reviewer and the rest of the NDA review team that this NDA should be ***Approved***.

2. Background

2.1 DESCRIPTION OF PRODUCT

The proposed product, testosterone enanthate injection USP, 50 mg, 75 mg, or 100 mg in sesame oil solvent, will be supplied as single-use, pre-filled, disposable, mini-needle autoinjectors that deliver 0.5 mL volume for once-a-week administration into the subcutaneous tissue of the abdomen region.

Currently, parenteral testosterone via intramuscular injection employs testosterone esters, including testosterone enanthate (TE) and testosterone cypionate. Testosterone esters are readily soluble in common oils, which are suitable as vehicles for drug administration. This type of drug-vehicle combination has a depot-like effect, resulting in longer periods of systemic exposure. As the testosterone ester is hydrolyzed, testosterone is released into the circulation, and provides for relatively constant systemic testosterone exposure with intermittent dosing.

2.2 REGULATORY HISTORY

For details related to the regulatory history of the original NDA, the reader is referred to my October 19, 2017, CDTL memo concerning the original NDA.

In brief, three IND milestone meetings were held between the Division and the Sponsor:

On December 5, 2012, the Division met with the Sponsor for a Type B, Pre-IND meeting.

On May 1, 2014, the Division met with the Sponsor for a Type C Guidance meeting. The Guidance meeting included discussion of efficacy and safety results from completed Phase 1 and 2 clinical studies, plans for Phase 3 and human factor studies, and plans for an NDA submission.

On October 31, 2016, the Division conveyed preliminary FDA responses to the Sponsor's Questions in preparation for a Type B pre-NDA meeting. Following receipt of the preliminary FDA responses, and following the Division's response to two clarifying Sponsor questions, the Sponsor informed the Division that the pre-NDA meeting was no longer necessary. The meeting was cancelled.

On November 28, 2016, final Pre-NDA meeting minutes were conveyed to the Sponsor.

On December 20, 2016, the original NDA was submitted.

On October 20, 2017, the Division issued a CR letter containing two Clinical deficiencies (the increased BP and depression/suicide issues) for the original NDA.

On February 21, 2018, the Division met with Antares at a Type A meeting to discuss pathways to resolve the deficiencies listed in the CR letter and to identify any remaining issues.

On March 22, 2018, the final Type A meeting minutes were conveyed to Antares.

On March 29, 2018, Antares submitted a Complete Response NDA re-submission. No new data or data analyses were submitted in the re-submission. In response to the CR deficiencies, the Sponsor provided revised product labeling, including a Medication Guide, as well as a proposal for a Communication Plan Risk Evaluation and Mitigation Strategy (REMS).

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary Clinical reviewer, Debuene Chang, stated in her final review, dated September 24, 2018:

> *"Recommendation on Regulatory Action: The* Clinical *review team recommends* ***Approval*** *for this new drug application (NDA), for the following reasons:*
>
> *Efficacy: The efficacy data from the Phase 3 pivotal study QST-13-003, along with supporting data from the Phase 3 study QST-15-005, supports the Sponsor's contention that Xyosted provides testosterone replacement in adult men with hypogonadism.*
>
> *Safety: The safety profile for Xyosted is consistent with the known safety profile for TRT, as demonstrated by the data submitted in the original NDA, except for the following three serious safety issues which are now considered to be resolved:*
>
> 1. *Identification of the potential for Xyosted to raise average systolic blood pressure (SBP) by approximately 4 mm Hg, a clinically meaningful amount. Specifically, ABPM measurements in Study QST-15-005 showed that treatment with Xyosted was associated with mean systolic/diastolic BP increases of 4/2 mm Hg. The Sponsor agrees to resolve this deficiency through the following:*
>
>   a. *Substantive labeling revisions, including the following elements:*
>
>   - *A Boxed Warning*
>   - *A new Contraindications that limits use of Xyosted to the indicated patient population*
>   - *A comprehensive Medication Guide (Med Guide)*
>
>   b. *A Post marketing requirement (PMR) study to assess patients' comprehension (of key risk messages) in the Med Guide*
>
> 2. *Reporting of two cases of suicide attempt (including one completed suicide) and two cases of severe depression in a rather small safety database.*
>
>   *The Sponsor proposes substantive labeling revisions, including a new Warning for Depression and Suicide that will describe these 4 cases, including the attempted and completed suicides. The Sponsor also agrees to provide quarterly Periodic Adverse Event Reports (PADER) for the first three years of marketing that will contain a section dedicated to this key safety issue. The Sponsor will propose changes to the Xyosted*

labeling, if needed, based on their findings for this issue. At this time, while the labeling describes the 4 cases (prominently)….the available data does not support that this product has an increased risk for depression and suicide as compared to other TRT products. By agreeing to a new Warning and to report any new cases in quarterly PADERs for 3 years, in the opinion of the Clinical review team, the Sponsor has sufficiently addressed this issue.

3. *Reporting of high rates of erythropoietic adverse events (AEs), such as increased hematocrit and polycythemia, in the phase 3 studies. The Sponsor agrees to substantive labeling revisions to reflect these findings and the labeling will recommend monitoring of hematocrit every 3 months while on patients are on Xyosted, which resolves this deficiency.*

***Risk Benefit Assessment**: The Clinical review team concludes that Xyosted is safe and effective as labeled. The risk/ benefit ratio for Xyosted for TRT in men with hypogonadism is now considered acceptable for approval of this NDA.*

3. CMC

The Chemistry review team, including Hamid Shafiei, Ben Stevens, James Norman, Christine Craig, Alison Aldridge, Thao Vu, and Mark Seggel, had the following recommendation in their final review dated September 24, 2018:

"*Antares Pharma's 505(b)(2) New Drug Application #209863, for Xyosted (testosterone enanthate) Injection), 50 mg/0.5 mL, 75 mg/0.5 mL and 100 mg/0.5 mL, as resubmitted in response to the October 20, 2017 Complete Response Letter, is now recommended for APPROVAL from the OPQ perspective.*

Agreement has been reached on the drug product aspects of the labeling (package insert, container/carton). The labeling now complies with the requirements under 21 CFR 201.

This NDA does contain adequate drug substance, drug product, manufacturing process, product quality microbiology, and device (auto-injector) engineering data and information to support approval of this drug-device combination product.

The commercial drug substance and drug-device product manufacturing, packaging and testing facilities have acceptable CBPM status.

The claimed categorical exclusion from the environmental assessment requirements is granted."

4. Nonclinical Pharmacology/Toxicology

In their final review dated August 20, 2018, the Pharmacology/Toxicology (PharmTox) review team of Miyun Tsai-Turton and Kimberly Hatfield had the following final recommendation:

"*Approvability: Pharm/tox recommends approval*".

The PharmTox review team stated that the NDA contained no nonclinical studies. Instead, published literature was provided under Module 4. The PharmTox review team noted that the

Sponsor referred to the Agency's previous findings for Delatestryl (under NDA 009165) for the nonclinical pharmacology, pharmacokinetics and toxicology. There were no additional nonclinical comments.

In their final labeling-specific memo dated September 24, 2018, the same team (Miyun Tsai-Turton and Kimberly Hatfield) provided a thorough outline of the nonclinical labeling discussions and final agreed-upon nonclinical labeling text. The reader is referred to this memo for details of the nonclinical labeling text. In summary, the PharmTox review team concurred with the Sponsor on final nonclinical labeling text. The final text complies fully with the Pregnancy and Lactation Labeling Rule (PLLR).

5. Clinical Pharmacology/Biopharmaceutics

In their final review dated August 24, 2018, the Clinical Pharmacology review team of Chongwoo Yu and Donny Tran had the following Recommendation:

> *"The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed the resubmission for NDA 209863 submitted on March 29, 2019 and April 16, 2018. The overall Clinical Pharmacology information submitted to support this NDA is acceptable and XYOSTED is recommended for approval from the Clinical Pharmacology standpoint".*

The final Clinical Pharmacology review had the following comments of note:

- "*As per the Division's request, the Applicant submitted information (in the re-submission) to address the potential cross-reactivity of TE with T immunoassays.*"
- The February 21, 2018, Type A meeting included a discussion of the cross-reactivity issue, summarized as:

  "*The Applicant submitted the following response via email to the regulatory project manager and reiterated it at the February 21, 2018 Type A, post-action meeting:*

  "TE and testosterone cypionate are the most widely prescribed T esters, and dosing these agents is usually managed with standard T assays, which are often immunoassays. In the case of XYOSTED, TE appears in the serum at a fraction of the total T content. At pre-dose trough, when XYOSTED concentrations will be monitored, the TE/T ratio is 20%. If there were an immunoassay with 100% cross-reactivity, that would equate to 20% overestimation of T concentrations. As reported in the study report for QST-13-003 the average T C_{min} concentration (T concentration at steady state 7 days after a dose) determined by LC-MS/MS was 417.9 ng/dL. A 20% overestimate of this level, at approximately 499 ng/dL, would result in no change in dose in the average patient, though some patients with true concentrations of 650 ng/dL would have estimated T trough concentrations above 650 ng/dL and resultant dose reductions".
- In regard to the Sponsor's response above, the Clinical Pharmacology team stated:

  "Reviewer's Comment: Based on Table A-1-20 (page 48) of Dr. Chongwoo Yu's Clinical Pharmacology review of the original NDA 209863 dated September 25, 2017, the mean TE/T ratio appears to be 20%. This reviewer agrees to the Applicant's safety assessment

that it would not be a safety concern even at the unlikely case of 100% cross-reactivity as in the event of overestimation, it will reduce the dose"

- For the cross-reactivity issue, ClinPharm requested a consult from the Center for Devices and Radiological Health (CDRH). In their final consult review dated August 4, 2018, CDRH offered the following responses to two specific ClinPharm consult questions (the CDRH responses are abbreviated for brevity):

  1. *Do you agree that cross-reactivity of TP to testosterone (T) immunoassays is expected to be <10%?*

     CDRH Response: We have reviewed the data of recently cleared T immunoassays and confirmed that we observed that % of TP cross-reactivity has been below 10%. However, we note that each company have tested different concentrations of TP, thus the data is not necessarily equivalent.

  2. *Based on the observed data for TP, what range of cross-reactivity may be expected for TE?*

     CDRH Response: It is difficult to anticipate the level of interference or cross-reactivity that a new drug will have, since even the smallest differences in chemical structure could have a different impact on antibody recognition. And, as noted in the table above (Table not shown here for brevity), *each assay may present different levels of cross-reactivity when testing the same substance. In general, less than 10% cross-reactivity is considered to be non-significant.*

- The following reflects the Clinical Pharmacology response to the two CDRH responses:

  Reviewer's Comment: Based on CDRH's review of data from 5 cleared T immunoassays, it was confirmed that the % of TP cross-reactivity is below 10% which is considered to be non- significant. As TP has a smaller side chain compared to TE, it appears that it is unlikely that TE will have more than a 10% cross-reactivity.

- It should be noted that in their final consult review, CDRH recommended that the Applicant "*design a robust study and provide data demonstrating the rate of TE cross-reactivity with commonly-used immunoassays*". Concerning this recommendation for the Sponsor to conduct another study, in addition to the comments provided above, ClinPharm noted that a correlation analysis between T concentrations using a LC-MS/MS method developed (b) (4) and T concentrations using a ECLIA which employed the Roche E-170 Modular analyzer revealed a high correlation (R^2 = 93-97%) and the slope was close to unity for total T trough concentrations obtained in human serum for individual patients across different time points and different studies. ClinPharm noted that these concentrations covered the intended therapeutic T concentration range and the very high correlation between the two methods indicated that at least the Roche ECLIA (which was used in the Xyosted Phase 3 studies) did not show a significant cross-reactivity that would raise concerns about the reliability of data obtained via immunoassays. Thus, ClinPharm did not concur with CDRH as to the need for another study to demonstrate the rate of TE cross-reactivity with commonly-used immunoassays.

The original Clinical Pharmacology review, authored by the same team, and dated September 25, 2017, had the following comments of note:

In regard to Efficacy:

- *"The efficacy of XYOSTED was successfully demonstrated in hypogonadal males with the TBM dosing regimen. The primary efficacy analysis showed a responder rate of 90.0% (135 responders out 150 subjects; 95% confidence interval: 84.0%-94.3%) at Week 12. Responders were defined as subjects who had a total T $C_{avg.168h}$ in the normal range of 300-1100 ng/dL at Week 12. The study results met the pre-specified efficacy criteria of responder rate ≥75% and the lower bound of the 95% CI ≥ 65%.*

- *In addition, all of the following pre-specified criteria for the key (secondary) endpoints (e.g., total T C_{max} at Week 12) were met in the pivotal Phase 3 study, QST-13-003, as there was no subject with a serum total T C_{max} of > 1,500 ng/dL, as follows:*
  - *No subjects with a serum total T C_{max} > 2500 ng/dL*
  - *Less than 5% of subjects with a serum total T C_{max} in the range of 1800- 2500 ng/dL*
  - *At least 85% of subjects with a serum total T C_{max} ≤ 1500 ng/dL*

In regard to Dose Titration:

- *"In the pivotal Phase 3 study, QST 13-003, the starting dose of XYOSTED was 75 mg TE and the dose of XYOSTED was titrated at Week 7 based on the serum total T concentration at the end of the dosing interval (C_{trough}) value at Week 6. XYOSTED dose titration criteria were as follows:*
  - *If total T C_{trough} ≥650 ng/dL, decrease dose by 25 mg;*
  - *If total T C_{trough} < 350 ng/dL, increase dose by 25 mg; or*
  - *If total T C_{trough} ≥350 ng/dL and < 650 ng/dL, maintain current dose strength.*

  Additional adjustments to dose were also made at Weeks 13, 19, 27, and 39, as necessary. The TBM dose titration scheme in the product label should follow the Phase 3 study dose titration scheme".

In regard to Bioanalytical Methods:

- *"Serum samples were analyzed for total T and DHT using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The method validation and performance of the total T and DHT bioanalytical methods are in compliance with the Agency's Bioanalytical Method Validation Guidance. The method validation and performance of the bioanalytical methods are acceptable".*

- *"A formal consult was made (to the Office of Study Integrity and Surveillance[OSIS]) for the bioanalytical site inspection and there were no unresolved inspection findings".*

6. Clinical Microbiology

The final determination by Microbiology was that the information in the application was acceptable, and in this regard, the final Chemistry review for the original NDA (first cycle review) stated:

"The Applicant has met also regulatory expectations with regards to the test methods, acceptance criteria and verification of the suitability of use of the tests for bacterial endotoxins and sterility."

7. Clinical/Statistical – Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for Xyosted consisted of 5 clinical studies, including three (3), short-term, PK and tolerability studies (Studies QST 13-002, QST 14-004 and QST 16-006); one, 52-week, uncontrolled, "pivotal", Phase 3 efficacy and safety study that was blinded only to dosage strength (Study QST 13-003); and one, 26-week, uncontrolled, open- label, safety study (Study QST 15-005). Except for healthy adult male volunteers in Study QST 14-004, all subjects were hypogonadal adult males.

A tabular listing of the clinical studies is shown in Table 1 below.

Table 1: Overview of Clinical Studies in the Xyosted Clinical Development Program

Study	Study Design	Number of Subjects	Population Enrolled	Duration of Treatment
QST-13-003	Phase 3, double-blind for dosage strength only, multiple-dose, efficacy and safety study	Randomized: N = 150 Completed: N = 97	Hypogonadal males	52 weeks (12 months)
QST-15-005	Phase 3, uncontrolled, multiple-dose, safety study	Randomized: N = 133 Completed: N = 113	Hypogonadal males	26 weeks (6 months)
QST-13-002	Phase 2, three-arm, open-label, randomized, multiple-dose, comparative bioavailability study	Randomized: N = 39 Completed: N = 38	Hypogonadal males	Arms A&B: 6 weeks Arm C: Single dose
QST-16-006	Phase 2, open-label safety and tolerability study	Randomized: N = 65 Completed: N = 59	Hypogonadal males	Two injections separated by 1 week
QST-14-004	Phase 1, open-label, single-dose study	Completed: N = 12	Healthy male subjects	Single dose
Source: NDA submission Section 2.5 Clinical Overview Table 1				

7.2 DEMOGRAPHICS

Table 2 below shows the demographic profile for subjects in the Phase 3 studies:

Table 2: Demographic and Baseline Characteristics in Studies QST-13-003 and QST-15-005.

Characteristic	Study QST 13-003 N = 150	Study QST 15-005 N = 133
Age, years		
Mean (SD)	53.4 (12.0)	54.5 (10.3)
Median	54.0	55.0
Min – Max	25-78	27-74
Ethnicity, n (%)		
Hispanic or Latino	8 (5.3)	17 (12.8)
Not Hispanic or Latino	142 (94.7)	116 (87.2)
Race, n (%)		
White	133 (88.7)	113 (85.0)
Black or African American	11 (7.3)	18 (13.5)
Asian	4 (2.7)	1 (0.8)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
Multiple	1 (0.7)	0 (0.0)
Other	1 (0.7)	1 (0.8)
Currently receiving testosterone therapy?		
No	129 (86.0)	102 (76.7)
Yes, type:	21 (14.0)	31 (23.3)
Buccal TRT	0 (0.0)	0 (0.0)
IM or SC TRT	8 (5.3)	23 (17.3)
Topical or transdermal TRT	12 (8.0)	8 (6.0)
Testopel	1 (0.7)	0 (0.0)
Baseline body mass index, kg/m^2		
Mean (SD)	31.2 (4.66)	31.5 (4.43)
Median	31.1	31.3
Min – Max	19.4-39.9	23.5-40.0
Baseline total testosterone, ng/dL		
N	137	133
Mean (SD)	230.4 (94.0)	214.9 (102.4)
Median	229.0	213.0
Min – Max	2-548	4-690
Testosterone category at baseline visit, n (%)		
<300 ng/dL	111 (74.0)	109 (82.0)
≥300 ng/dL	26 (17.3)	24 (18.0)
Source: QST-13-003 CSR Table 14.1.2; QST-15-005 CSR Table 14.1.2		

Table 2 shows that the Phase 3 study subjects were predominately obese, middle-aged, white males (White 85 – 88.7%; median age 54-55 years; mean BMI 31.2-31.5 kg/m^2).

7.3 DISPOSITION OF SUBJECTS

Table 3 shows the disposition of all subjects in the "pivotal" phase 3 study QST 13-003 with reasons for subjects' early withdrawal shown.

Table 3: Patient Disposition with Reasons for Early Withdrawal in Study QST-13-003

Characteristics	**Overall n (%)**
Enrolled – n	150
Dosed subjects – n (%)	150 (100.0%)
Completed Week 12 – n (%)	137 (91.3%)
Completed study – n (%)	97 (64.7%)
Early withdrawal – n (%)	52 (34.7%)
Missing completion status - n (%)	1 (0.7%)
Reasons for early withdrawal (subjects may have been counted in >1 category)	
Clinical adverse event (not related to elevated PSA or increased HCT)	16 (10.7%)
Elevated PSA	14 (9.3%)
Increased HCT	7 (4.7%)
Elevated PSA and increased HCT	2 (1.3%)
Elevated testosterone (while on lowest dose and $C_{trough} \geq 650$ ng/dL)	6 (4%)
Non-compliance	3 (2.0)
Withdrawal of consent or withdrawal by subject	12 (8.0)
Lost to follow-up	1 (0.7)
Other: All "other" reasons combined	11 (7.3)
Other: Met a stopping criterion	5 (3.3)
PSA- prostate specific antigen, HCT- hematocrit ***Source: Sponsor IR response dated June 29, 2017***	

Over the 52-week treatment period in Study QST 13-003, approximately 35% (52/ 150) of subjects withdrew prematurely, which included approximately 9% (14/ 150 subjects) of subjects for protocol-defined elevated PSA; 5% (7/ 150 subjects) for protocol-defined increased HCT; and 1.3% (2/150 subjects) for both protocol-defined elevated PSA and protocol-defined increased HCT. In addition, 4% (6/150 subjects) also withdrew for elevated testosterone (defined as $C_{trough} > 650$ ng/ dL despite being on the lowest dose).

In Study QST 13-003, subject disposition at an earlier timepoint (Week 12) is clinically meaningful because Week 12 was the primary timepoint for assessment of efficacy. Table 4 below provides an overview of subject disposition at Week 12 in Study QST 13-003, also showing dosage strengths that were being used by subjects at Week 12.

Table 4: Patient Disposition by Treatment at Week 12 in Study QST 13-003

Characteristics	Dose at Week 12			Overall
	SC QST 50 mg	SC QST 75 mg	SC QST 100 mg	
Enrollment (All start at 75 mg) – n	-	150	-	150
Dosed patients – n (%)	25 (100.0)	104 (100.0)	21 (100.0)	150 (100.0)
Completed Week 12– n (%)	25 (100.0)	93 (89.4)	19 (90.5)	137 (91.3)
Completed the study – n (%)	13 (52.0)	69 (66.3)	15 (71.4)	97 (64.7)
Early withdrawal – n (%)	12 (48.0)	34 (32.7)	6 (28.6)	52 (34.7)
Missing completion status – n (%)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.7)
Reasons for early withdrawal – n (%)				
Adverse event	2 (8.0)	3 (2.9)	0 (0.0)	5 (3.3)
Non-compliance	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.3)
Patient withdrew consent	1 (4.0)	7 (6.7)	1 (4.8)	9 (6.0)
Lost to follow-up	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.7)
Sponsor's request	0 (0.0)	1 (1.0)	1 (4.8)	2 (1.3)
Met stopping criteria	2 (8.0)	1 (1.0)	0 (0.0)	3 (2.0)
Other	0 (0.0)	0 (0.0)	1 (4.8)	1 (0.7)
Multiple	7 (28.0)	19 (18.3)	3 (14.3)	29 (19.3)

Notes: For the Dose at Week 12 columns, a patient was counted in the 75 mg column if he discontinued prior to the Week 7 titration opportunity.
Includes all patients who received at least 1 dose of the investigational product. The number of dosed patients was used as the denominator in all percentage calculations unless otherwise specified.
QST = QuickShot™ Testosterone; SC = subcutaneous.

7.4 EFFICACY RESULTS

7.4.1 Assessment of Efficacy

The assessment of efficacy in this NDA was consistent with efficacy assessments conducted for TRT products in prior NDAs as well as with the Division's expectations and requirements for TRT studies.

In Study QST 13-003, the "pivotal" study, all subjects who met the study eligibility criteria were assigned to receive QST 75 mg. Patients were trained by designated site staff on proper use of the QST device. QST TE was self-administered once each week on the same day of the week and at approximately the same time (7:00 am ±2 hours). Adjustments to dose may have been made at Week 7 based upon the Week 6 blood concentration at the end of the dosing interval (C_{trough}) value. Dose titration criteria were as follows:

- Decrease dose by 25 mg if TT $C_{trough} \geq 650$ ng/dL
- Increase dose by 25 mg if TT $C_{trough} < 350$ ng/dL
- Maintain dose strength if TT $C_{trough} \geq 350$ ng/dL and < 650 ng/dL.

At Week 12, blood samples for pharmacokinetic (PK) analysis of total testosterone (TT), dihydrotestosterone (DHT), dihydrotestosterone enanthate (DHTE), estradiol (E2), and testosterone enanthate (TE) were obtained from all patients before and at specified times up to 168 hours after QST dose administration. Pharmacokinetic parameters to characterize TT exposure over the dosing interval were derived.

7.4.1.1 Primary Efficacy Analysis

The primary efficacy endpoint in Study QST 13-003 was the percentage of patients with serum TT average concentration over the 7-day dosing interval (0-168 hours) ($C_{avg168h}$) within the defined range (300 to 1100 ng/dL). The primary endpoint would be considered to have been met if ≥ 75% of patients had TT $C_{avg168h}$ within the range at Week 12, with a lower bound of the 95% confidence interval (CI) ≥ 65%.

Overall, the Sponsor calculated that 139 (92.7%) patients had TT $C_{avg168h}$ values within the defined range at Week 12.

Table 5 shows the Sponsor's analysis of the number and percentage of patients with Week 12 TT $C_{avg168h}$ within the defined range (300 to 1100 ng/dL) for the safety population in study QST 13-003.

Table 5: Sponsor's Analysis of the Number (%) of Patients with Week 12 TT $C_{ave168h}$ 300 to 1100 ng/dL in Study QST-13-003

Week 12 $C_{avg168h}$ Category Statistic	Dose at Week 12			Overall (N=150)
	SC QST 50 mg (N=25)	SC QST 75 mg (N=104)*	SC QST 100 mg (N=21)	
n (%)	25 (100.0)	94 (90.4)	20 (95.2)	139 (92.7)
95% Exact Binomial CI	(86.3, 100.0)	(83.0, 95.3)	(76.2, 99.9)	(87.3, 96.3)

Note: The Safety Population consisted of all patients who received at least 1 dose of the investigational product. Percentage was calculated using the number of patients in the column heading as the denominator. If the patient did not have calculable Week 12 $C_{avg168h}$, the last recorded post-dose TT was used in the analysis. If the patient did not have a post-dose TT determination, the patient was included in the analysis as not having achieved TT $C_{avg168h}$ within 300 to 1100 ng/dL.
* For the dose at Week 12 columns, a patient was counted in the 75 mg column if he discontinued prior to Week 7 titration.
Abbreviations: $C_{avg168h}$ = average concentration over the 7-day dosing interval (0-168 hours); CI = confidence interval; QST = QuickShot™ Testosterone; SC = subcutaneous; TT = total testosterone.
Source: 5.3.5.1 Study Report QST-13-003, p. 80

In the analysis shown in Table 5, the Sponsor included subjects with missing calculable Week 12 $C_{avg168h}$ by using the last recorded post-dose TT to derive the result for the primary efficacy endpoint. Table 6 below provides an analysis of the primary efficacy endpoint using only those subjects with calculable data for Week 12 $C_{avg168h}$, as recommended by FDA's Statistical Review team. This analysis shows that the primary efficacy endpoint and study objective was met again, whereby Study QST-13-003 met the prospectively planned primary efficacy endpoint overall with 135/150 subjects (90.0%) responding, with the 95% CI (84.0, 94.3) showing a lower bound well above the 65% lower limit for trial success.

Table 6: FDA Analysis of Number (%) of Patients with Week 12 TT $C_{ave168h}$ Values 300 to 1100 ng/dL – Primary Efficacy Endpoint for Study QST 13-003

Week 12 $C_{avg168h}$ Category Statistic	Dose at Week 12			Overall (N=150)
	SC QST 50mg (N=25)	SC QST 75 mg (N=104) [1]	SC QST 100mg (N=21)	
n (%)	25 (100.0)	91 (87.5)	19 (90.5)	135 (90.0)
95% Exact Binomial CI	(86.3, 100.0)	(79.6, 93.2)	(69.6, 98.8)	(84.0, 94.3)

Note: The Safety Population consisted of all patients who received at least 1 dose of the investigational product. Percentage was calculated using the number of patients in the column heading as the denominator. If the patient did not have calculable Week 12 $C_{avg168h}$, the patient was included in the analysis as not having achieved TT $C_{avg168h}$ within 300 to 1100 ng/dL.
For the dose at Week 12 columns, a patient was counted in the 75 mg column if he discontinued prior to Week 7 titration.
$C_{avg168h}$ = average concentration over the 7-day dosing interval (0-168 hours); CI = confidence interval; QST = QuickShot™ Testosterone; SC = subcutaneous; TT = total testosterone.
Source: Post-text Table 14.2.1.1.2.

7.4.1.2 Secondary Efficacy Analysis

The "key" secondary efficacy endpoints in Study QST 13-003 (sometimes referred to as "safety" endpoints in these studies), were the same as for all prior TRT studies, and included:

- Percentage of patients with TT maximum (peak) blood concentration (C_{max}) <1500 ng/dL. This endpoint would be considered to have been met if ≥ 85% of patients had TT C_{max} in this range at Week 12 of treatment;
- Percentage of patients with TT C_{max} 1800 to 2500 ng/dL, inclusive. This endpoint would be considered to have been met if <5% of patients had TT C_{max} in this range at Week 12 of treatment;
- Number of patients with TT C_{max} >2500 ng/dL. This endpoint would be considered to have been met if no patients had TT C_{max} in this range at Week 12 of treatment;

Overall, 137 of 150 randomized (91.3%) patients had TT C_{max} <1500 ng/dL at Week 12: with 25 (100.0%) patients achieving this endpoint while taking the 50 mg dose, 93 (89.4%) while taking the 75 mg dose, and 19 (90.5%) while taking on the 100 mg dose.

There were no patients with TT C_{max} >1500 ng/dL, 1800 to 2500 ng/dL, or >2500 ng/dL at Week 12.

In total, 13 (8.7%) patients had missing TT C_{max} values at Week 12: 11 (10.6%) patients while taking the 75 mg dose and 2 (9.5%) patients while taking the 100 mg dose. After excluding those patients with missing Week 12 C_{max} values, all patients still had TT C_{max} <1500 ng/dL at Week 12.

Table 7 shows the results for this "key" secondary endpoint at Week 12 of treatment in Study QST 13-003.

Table 7: Results for Key Secondary Endpoint at Week 12 in Study QST-13-003.

Week 12 C_{max} Category	Dose at Week 12			Overall (N=150) n (%)
	SC QST 50 mg (N=25) n (%)	SC QST 75 mg (N=104)* n (%)	SC QST 100 mg (N=21) n (%)	
<1500 ng/dL	25 (100.0)	93 (89.4)	19 (90.5)	137 (91.3)
1800 to 2500 ng/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>2500 ng/dL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing Week 12	0 (0.0)	11 (10.6)	2 (9.5)	13 (8.7)

Note: The Safety Population consisted of all patients who received at least 1 dose of the investigational product. Percentage was calculated using the number of patients in the column heading as the denominator.
* For the dose at Week 12 columns, a patient was counted in the 75 mg column if he discontinued prior to Week 7 titration.
Abbreviations: C_{max} = maximum (peak) blood concentration; QST = QuickShot™ Testosterone; SC = subcutaneous; TT = total testosterone.
Source: 5.3.5.1 Study Report QST-13-003, p. 81.

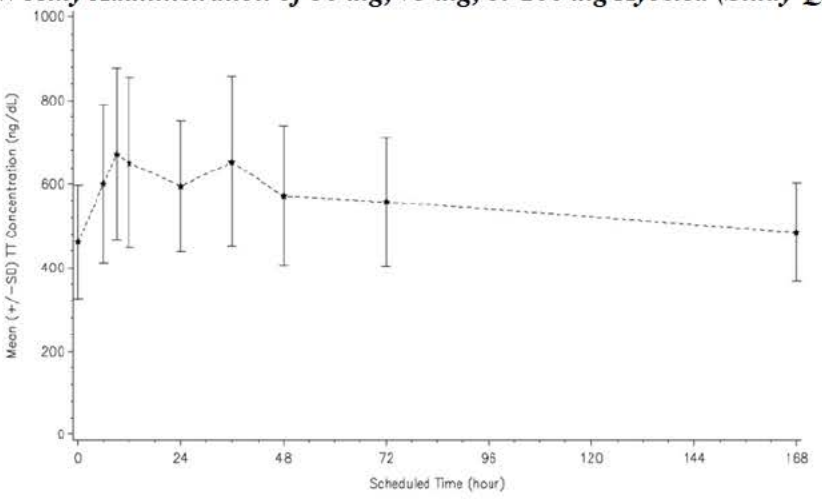
Table 8 provides a summary of the arithmetic means (with standard deviations) of the steady-state PK of serum total TT concentrations at Week 12 obtained from patients in study QST 13-003

Table 8: Arithmetic Mean (SD) Total T PK Parameters at Week 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg Xyosted (Study QST-13-003)

TE Dose	N	$C_{avg,168h}$ (ng/dL	C_{max} (ng/dL)	T_{max}	C_{min} (ng/dL)	AUC(0-168 hr) (ng·hr/dL)
50	25	598 (178)	850 (275)	12.0 (5.8-72.6)	458 (140)	100,500 (29,859)
75	93	538 (108)	758 (186)	11.9 (5.9-168.2)	431 (97)	90,317 (18,159)
100	19	571 (127)	866 (239)	24.1 (5.8-168.7)	428 (121)	95,940 (21,374)
Overall	137	553 (127)	790 (215)	11.9 (5.8-168.7)	436 (109)	92,955 (21,385)

Figure 1 below, showing average total testosterone concentrations over a full week at Week 12, provides a graphical representation of the testosterone replacement associated with Xyosted.

Figure 1: Plot of Mean (±SD) of Serum Total T Concentration-Time Curve at Week 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg Xyosted (Study QST-13-003; N=137)



For details in regard to other secondary and exploratory endpoints in Study QST 13-003, the reader is referred to the medical officer's final Clinical review of the original NDA.

Statistician's Conclusion

In their final memo dated September 13, 2018, Sonia Castillo of the Division of Biometrics following statement:

> "*There are no statistical efficacy issues outline in the Complete Response Letter that would preclude approval.*"

In their September 13, 2017, final review of the original NDA, Dr. Castillo and the Statistical Team Leader Mahboob Sobhan had the following overall conclusion:

> "*The one submitted study provides evidence demonstrating the efficacy of Xyosted (testosterone enanthate) injection for the treatment of adult male hypogonadism.*"

One comment of note from the Statistical review was as follows:

- "*One statistical issue was identified that affected the quality of the analysis. The pre-specified primary efficacy analysis accounted for missing week 12 endpoint data as follows:*

  > *If a subject does not have a valid testosterone $C_{avg168h}$, the last recorded post-baseline total testosterone (TT) concentration is used in the primary analysis. If the subject discontinued prior to a post-baseline TT collection, the subject is included in the analysis as not having achieved a TT $C_{avg168\ h}$ within the normal range.*

  If the last post-baseline total testosterone (TT) value is to be used for analysis, it should be the last recorded TT $C_{avg168h}$ value after a sufficient amount of time has passed for an effect to be seen. The Applicant included (in the analysis) four subjects without a TT $C_{avg168h}$ at Week 12 but they (the 4 subjects) had other TT values. Two subjects had a single TT concentration value at the single time point of 168h post-dose at Week 12 and two subjects had a TT C_{avg168} value at Week 1. Using the last single TT concentration value from one time point or from a Week 1 TT $C_{avg168h}$ value from the pharmacokinetic substudy is not (considered) *adequate. Other than the Week 1 $C_{avg168h}$ value from the pharmacokinetic substudy, the study did not include an additional TT $C_{avg168h}$ evaluation after a sufficient amount of time had passed to reach an effect prior to the Week 12 evaluation. Without any appropriate prior TT $C_{avg168h}$ values to rely upon to use to account for an invalid TT $C_{avg168h}$ at Week 12, the* (Biometrics review team has determined that the) *subject should be considered as having no post-baseline TT $C_{avg168h}$ value. This subject should be included in the analysis as not having achieved a TT $C_{avg168h}$ within the normal range. To address this issue, this reviewer considers the Applicant's sensitivity analysis, which included the subject in the analysis as having not achieved TT $C_{avg168h}$ within the normal range, as the primary efficacy result for labeling".*

  The results of the sensitivity analysis are presented in the Statistical Review Table 3.5. The Statistical review team stated, "*Efficacy was demonstrated for the sensitivity*

analysis with the percentage of subjects with a serum total testosterone $C_{avg168h}$ level within the normal range at Week 12 of 90.0% (135 of 150 subjects) with 95% CI of 84.0% to 94.3%".

7.4.2 Overall Assessment of Efficacy

The efficacy data from the Phase 3 pivotal study QST-13-003, along with supporting data from the other clinical studies, supports the Sponsor's contention that QST provides testosterone replacement in adult men with hypogonadism.

8. Safety

8.1 SAFETY RESULTS

The Clinical safety review of the original NDA encompassed pooled safety data from three short-term Phase 1/Phase 2 studies (Studies QST 13- 002, QST 14-004 and QST 16-006) and the two "long-term" Phase 3 studies (Studies QST 13-003 and 15-005). All but one of these studies were conducted in adult hypogonadal men.

The overall NDA database consists of

- 116 hypogonadal adult male patients who received up to 6 doses in the three "short-term" studies,
- 133 hypogonadal adult male patients who received up to 26 weeks of treatment in the Phase 3 safety Study QST 15-005, and
- 150 hypogonadal adult male patients who received up to 52 weeks of treatment in the Phase 3 safety Study QST 13-003.

Thus, the total number of patients who received treatment in the two, long- term studies is 283. A total of 380 patients received at least 1 dose, 242 received at least 24 treatments (approximately 6 months of treatment), and 99 received at least 52 treatments (approximately 12 months of treatment).

The following sections provide an overview description of the NDA safety results, focusing on the results from the long-term, Phase 3 studies. For additional details, the reader is referred to the medical officer's final Clinical review of the original NDA.

8.1.1 Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events

Deaths

One death was reported in the clinical development program. Patient (b) (6) in the pivotal Phase 3 Study QST 13-003 had an SAE of "completed suicide" that resulted in death. The Sponsor considered the event as possibly related to Xyosted, stating that depression has been described as an adverse event in the labels of other testosterone products, and suicide is associated with depression. The Sponsor provided the following abbreviated narrative of this case:

Patient (b) (6) – suicide, method unknown

(b) (6) a 72 year-old male with hypogonadism, experienced an SAE of suicide, method unknown. After providing Informed Consent, the patient was enrolled and received his first dose

(b) (6) *The patient had been on study treatment for over 6 months (75mg weekly self-injections) before the event was reported following his last dose of study medication on Study Day 169.*

On Study Day 176, the patient failed to report to his scheduled Week 26 study visit. The investigative site reported they were informed by voicemail that the patient wished to discontinue from the study due to "personal reasons." On Study Day 178, the investigative site contacted the patient and scheduled an Early Termination (ET) study visit. This was the last contact the investigative site had with the patient. The patient failed to report to the scheduled ET study visit. The investigative site continued to attempt to contact the patient for follow-up. The patient's stepson subsequently contacted the investigative site and informed the site that the patient had committed suicide on Study Day 182. The method of suicide was not reported and further details were not provided.

The patient's medical history included: benign prostatic hypertrophy, erectile dysfunction, type 2 diabetes mellitus, gastroesophageal reflux disorder, cholecystitis, cholecystectomy, and detached retina. The site reported there was no known history of mental health disorders.

Concomitant medications included metformin, aspirin, gamma-aminobutyric acid, kelp, L-arginine, vitamin B, vitamin B6, vitamin B12, multi-B vitamin, chromium picolinate, St John's wort, 5-hydroxytryptophan, valerian, melatonin, glyburide, sildenafil citrate, tadalafil and omeprazole.

The Sponsor considered the event of suicide, method unknown, as possibly related to underlying depression, stating that depression is a labeled adverse event for other testosterone products and suicide can be an adverse outcome of depression, and therefore the event of suicide is possibly related to study medication.

In response to a request for information, the Sponsor provided all the serum T concentrations for this subject and the list of values demonstrated that none were out of normal range.

CDTL Comment**: **I concur with the Clinical reviewer that the data for this case is insufficient to draw the conclusion that suicide in this patient was a direct result of study treatment. While suicide has been very rarely reported in patients taking TRT in the postmarketing period, a relationship between suicide and TRT has not been established. It is notable, however, that to our knowledge, this is the first reported completed suicide in a clinical study of TRT. While the information for this case, as well as for another case of suicidal ideation in this NDA, does raise concerns, it does not clearly support a unique risk for this product compared to others in the class, largely because the relevant data is very limited and the patients' medical histories confound the ability to draw a conclusion of drug causality in the individual cases. A decision was reached to describe this case, and 3 others, in the approved labeling for Xyosted.

Serious Adverse Events (SAEs)

Overall, a total of 7 patients (2.5%) experienced a total of 12 SAEs in the Xyosted clinical development program. All reported SAEs were reported in the two long-term studies QST-13-003 and QST-15-005. A total of 3 patients reported a total of 3 SAEs in Study QST-13-003 and a total of 4 patients reported a total of 9 SAEs in Study QST-15-005.

The following table lists the 12 SAEs, including actions taken in response to the SAEs and the SAE outcomes. The table also includes the fatal SAE that was discussed previously under "Deaths".

Table 9: SAEs in Studies QST-13-003 and QST-15-005.

Study Patient Number	Race/ Age	Study day when SAE started	SAE – Preferred term	Severity	Withdrawn from study?	Action taken and outcome
QST-13-003						
(b) (6)	*W/62*	6	Depression	Severe	Yes	Medication required Recovered/resolved with continued outpatient care
	W/71	182	Completed suicide	Severe	Yes	None Fatal event
	W/67	207	Vertigo	Moderate	No	Medication required Recovered/resolved
QST-15-005						
(b) (6)	*W/68*	59	Visual impairment	Severe	No	Medication required Recovered/resolved
	B/63	99	Coronary artery disease	Severe	No	Medication required Recovered/resolved with sequelae
		133	Arthritis bacterial	Severe	No	Medication required Recovered/resolved
		147	Prinzmetal's angina	Severe	Yes	Medication required Recovered/resolved with sequelae
		159	Acute myocardial infarction	Severe	Already Withdrawn	Recovered/resolved with sequelae
		159	Ventricular tachycardia	Severe	Already Withdrawn	Recovered/resolved
		160	Respiratory failure	Severe	Already Withdrawn	Recovered/resolved
	W/58	37	Appendicitis	Moderate	No	Medication required Recovered/resolved
	W/52	96	Deep vein thrombosis	Mild	Yes	Medication required Recovered/resolved

Race: W = White; B = Black or African American.
SAE = serious adverse event
Source: ISS Table 35.5.7

Of the 7 patients who reported SAEs in the two Phase 3 studies, four discontinued the study due to their SAE.

Patient (b) (6), also in Study QST 13-003, had an SAE of depression (severe) and he discontinued the study after receiving a single dose of study drug. The patient reported a baseline history of depressive disorder with worsening of this condition at 6 days after his first dose. The event included suicidal ideation requiring hospitalization. Based on the clinical event, the study medication was discontinued. An abbreviated case narrative is provided here:

Patient (b) (6) – worsening depressive disorder
Patient (b) (6) a 63 year old male with hypogonadism and depressive disorder, experienced an SAE of worsened depressive disorder. After providing Informed Consent, the patient received his first dose, 75 mg (b) (6) This was the patient's most recent dose prior to the onset of the AE.

On Study Day 6, after an argument with his spouse, the patient intentionally ingested 20 to 25 tablets of tramadol 50 mg which had not been prescribed to him. Emergency medical services were summoned and the patient was transported to the Emergency Department. A review of systems revealed suicidal thoughts and ideations. Physical examination revealed the patient to be alert and oriented x3 with calm affect, coherent speech, appropriate mood, rational thought, and normal perceptions. The patient was subsequently admitted to the hospital on Study Day 7 for evaluation and treatment of worsening depressive disorder. Treatment included venlafaxine and observation. On Study Day 12, the patient was discharged from the hospital and the event of worsened depressive disorder resolved with ongoing outpatient psychiatric care. The study medication was discontinued due to the event and the patient was withdrawn from the study on Study Day 31.

The patient's medical history also included gallstones, erectile dysfunction, cholecystectomy, hypercholesterolemia, acid reflux, backache, urinary retention, and seasonal allergies.

Concomitant medications included aspirin, pantoprazole, simvastatin, and fenofibrate.

At the Division's request, the Sponsor provided serum TT concentrations during the study for this patient, with results as follows.

The Sponsor reported that the subject met the study eligibility criteria with at least two AM total testosterone concentrations less than 300 ng/ dL. His baseline serum testosterone concentrations were 120 ng/dL, 190 ng/dL, and 140 ng/dL (b) (6) respectively. His SAE was reported on Day 6 after his first injection on Day 1 and he received no further study medication. Repeat TT concentrations were not checked until Day 31 when the subject was withdrawn from the study. At that time, the subject's TT concentration was 190 ng/dL, consistent with his baseline TT concentrations.

CDTL Comment: The Sponsor reported that the patient had a past medical history of major depressive disorder, diagnosed in 1998. The status of this condition was described as "ongoing" during the study enrollment period. The subject had been treated for his depressive disorder with Paxil (b) (6) The reason for discontinuation of Paxil was not provided.

The subject's last serum testosterone concentration was obtained 31 days after his single QST TE dose and at that time, his serum T was back to its baseline, pre-treatment value. A testosterone concentration was not available from the patient's hospitalization.

From the patient's history, he had an untreated major depressive disorder when he enrolled in the study. He had been treated for 8 years with an antidepressant medication, which had been discontinued less than 6 months prior to the study Screening period. Based on this confounding history, and the lack of a serum

testosterone concentration prior to Day 31, it is not possible to establish a causal relationship between the AE of worsened depressive disorder to study medication. Nonetheless, a decision was made to describe this case, and other similar cases, in the approved product labeling.

In regard to other notable SAEs, in Study QST-15-005, one patient (Patient (b) (6)) reported 6 different SAEs (coronary artery disease, arthritis bacterial, Prinzmetal's angina, acute myocardial infarction, ventricular tachycardia, and respiratory failure) and discontinued study medication due to the SAE of Prinzmetal's angina. In addition, Patient (b) (6) had an SAE of deep vein thrombosis (DVT) that resolved, but treatment was discontinued as the investigator assessed the SAE as related to the study drug.

CDTL Comment: Both acute MI and DVT have been reported in patients on TRT, but the relationship between these serious cardiovascular events and TRT remains unclear. The data for these two events in this NDA is too limited to establish causality between these two serious CV events and the study medication.

Discontinuations Due to Adverse Events (AEs)

A total of 38 subjects (13.4%) discontinued from one of the clinical studies due to an AE, including 30 subjects in Study QST-13-003 and 8 subjects in Study QST-15-005. Two of the withdrawals due to AEs were due to SAEs. The vast majority of subjects who withdrew due to an AE did so for meeting a protocol-defined, laboratory-based, stopping criterion (n=31).

The protocol-defined, laboratory-based, stopping criteria in the Phase 3 studies included:

- Increase in serum prostate specific antigen (PSA) ≥1.4 ng/mL above the Screening value;
- Hematocrit >55% during the Treatment Titration or Extended Treatment phases of the study;
- Patients receiving QST TE 50 mg who had a C_{trough} ≥650 ng/dL.

In Study QST 13-005, the pivotal Phase 3 study, a total of 30 patients withdrew due to a total of 37 AEs. The AEs that led to discontinuation in this study were: PSA increased (13 reports), hematocrit increased (7 reports), blood testosterone increased (3 reports), polycythemia (2 reports), and depression, right bundle branch block, prostatitis, fatigue, hyperhidrosis, dyspnea, heart rate increased, blurred vision, hyper-sexuality, prostate neoplasm, hypertension, and drug concentration changed (1 report each).

In Study QST 15-005, the other Phase 3 study, a total of 8 patients withdrew due to a total of 8 AEs. The AEs that led to discontinuation in this study were: depression (2 reports), hematocrit increased (2 reports), and polycythemia, DVT, insomnia, and Prinzmetal's angina (1 report each).

8.1.2 Other Adverse Events

Commonly Reported Adverse Events

In the pooled Phase 3 studies QST 13-003 and QST 15-005, the System Organ Classes (SOCs) with the greatest number of subjects reporting TEAEs were: Infections and Infestations (79 subjects, 27.9%), Investigations (76 subjects, 26.9%), General Disorders and Administrative Site Conditions (56 subjects, 19.8%), and Musculoskeletal and Connective Tissue Disorders (33 subjects, 11.7%).

In the pooled Phase 3 studies, a total of 212 patients (74.9%) experienced at least 1 TEAE. The majority of TEAEs were judged by the investigator as being mild (35.7% of patients) or moderate (35.3% of patients) in severity. A total of 11 patients (3.9%) had TEAEs that were judged by the investigator as being severe.

In the pooled Phase 3 studies, the most commonly reported TEAEs by Preferred Term (PT) were: hematocrit increased (32 subjects, 11.3%), PSA increased (22 subjects, 7.8%), upper respiratory tract infection (22 subjects, 7.8%), hypertension (22 subjects, 7.8%), injection site bruising (15 subjects, 5.3%), injection site hemorrhage (13 subjects, 4.6%), sinusitis (13 subjects, 4.6%), nasopharyngitis (11 subjects, 3.9%), headache (10 subjects, 3.5%), and CPK increased (10 subjects, 3.5%).

The following Table summarizes the TEAEs by SOC and PT in the pooled Phase 3 studies.

Table 10: Number (%) Patients with TEAEs by SOC and PT in Pooled Studies QST 13-003 and QST 15-005

System Organ Class Preferred Term	Studies 003/005 Overall N=283 n (%)
Patients with any TEAE	*212 (74.9)*
Blood and Lymphatic System Disorders	*9 (3.2)*
Polycythemia	5 (1.8)
Eye Disorders	*9 (3.2)*
Vision blurred	3 (1.1)
Gastrointestinal Disorders	26 (9.2)
Hemorrhoids	4 (1.4)
Nausea	4 (1.4)
Abdominal pain	3 (1.1)
Diarrhea	3 (1.1)
Gastroesophageal reflux disease	3 (1.1)
Large intestinal polyp	3 (1.1)
General Disorders and Administration Site Conditions	*56 (19.8)*
Injection site bruising	15 (5.3)
Injection site hemorrhage	13 (4.6)
Fatigue	6 (2.1)
Injection site erythema	5 (1.8)
Edema peripheral	5 (1.8)
Injection site induration	3 (1.1)
Non-cardiac chest pain	3 (1.1)
Immune System Disorders	*4 (1.4)*
Seasonal allergy	3 (1.1)
Infections and Infestations	79 (27.9)

Upper respiratory tract infection	22 (7.8)
Sinusitis	13 (4.6)
Nasopharyngitis	11 (3.9)
Urinary Tract Infection	8 (2.8)
Bronchitis	7 (2.5)
Gastroenteritis	4 (1.4)
Influenza	4 (1.4)
Pneumonia	4 (1.4)
Acute sinusitis	3 (1.1)
Viral infection	3 (1.1)
Injury, Poisoning and procedural complications	***21 (7.4)***
Muscle strain	3 (1.1)
Investigations	***76 (26.9)***
Hematocrit increased	32 (11.3)
Prostatic specific antigen increased	22 (7.8)
Blood creatinine phosphokinase increased	10 (3.5)
Blood testosterone increased	4 (1.4)
Metabolism and Nutrition Disorders	***12 (4.2)***
Hyperlipidemia	3 (1.1)
Musculoskeletal and Connective Tissue Disorders	***33 (11.7)***
Back pain	7 (2.5)
Arthralgia	5 (1.8)
Bursitis	3 (1.1)
Musculoskeletal pain	3 (1.1)
Osteoarthritis	3 (1.1)
Pain in extremity	3 (1.1)
Nervous System Disorders	***20 (7.1)***
Headache	10 (3.5)
Dizziness	3 (1.1)
Sciatica	3 (1.1)
Psychiatric Disorders	***14 (4.9)***
Anxiety	4 (1.4)
Insomnia	4 (1.4)
Depression	3 (1.1)
Renal and Urinary Disorders	***11 (3.9)***
Hematuria	4 (1.4)
Reproductive System and Breast Disorders	***22 (7.8)***
Prostatitis	8 (2.8)
Testicular atrophy	3 (1.1)
Respiratory, Thoracic and Mediastinal Disorders	***21 (7.4)***
Cough	6 (2.1)
Sinus congestion	4 (1.4)
Dyspnea	3 (1.1)
Sleep apnea syndrome	3 (1.1)
Skin and Subcutaneous Tissue Disorders	***28 (9.9)***
Acne	4 (1.4)
Dermatitis contact	3 (1.1)
Eczema	3 (1.1)

Vascular Disorders	***27 (9.5)***
Hypertension	22 (7.8)
Flushing	3 (1.1)

Although a subject may have had two or more TEAEs, the subject is counted only once within a SOC category. The same subject may contribute to two or more preferred term categories.
PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Source: ISS Table 35.5.2.1

CDTL Comment: The incidences of increased hematocrit (11.3%), polycythemia (1.8%), and hypertension (7.8%) are notable.

As part of agreed-upon final product labeling, the commonly reported adverse events from the phase 3 studies will be shown in two separate Adverse Reactions tables, one for the 1-year study QST 13-003 and one for the 6-month study QST 15—005, as follows;

Table 1 (of the agreed-upon final product labeling): Number (%) of Patients with Adverse Reactions ≥2% in a 1 Year study with XYOSTED

Preferred Term	**Overall (N=150) n (%)**
Hematocrit increased	21 (14.0)
Hypertension	19 (12.7)
Prostatic specific antigen (PSA) increased	18 (12.0)
Injection site bruising	10 (6.7)
Headache	8 (5.3)
Back pain	5 (3.3)
Blood creatine phosphokinase increased	5 (3.3)
Injection site hemorrhage	5 (3.3)
Acne	4 (2.7)
Blood testosterone increased	4 (2.7)
Cough	4 (2.7)
Edema peripheral	4 (2.7)
Injection site erythema	4 (2.7)
Prostatitis	4 (2.7)
Urinary tract infection	4 (2.7)
Abdominal pain	3 (2.0)
Arthralgia	3 (2.0)
Fatigue	3 (2.0)
Hematuria	3 (2.0)
Polycythemia	3 (2.0)
Sleep apnea syndrome	3 (2.0)

Note: Includes events that started on or after the first dosing, or existed prior to the first dose and worsened in severity or relatedness after dosing. Percentage was calculated using the number of patients in the column heading as the denominator.

Table 2 (of the agreed-upon final product labeling): Number (%) of Patients with Adverse Reactions **≥2%** in a 6-Month Study with XYOSTED

Preferred Term	**Overall (N = 133) n (%)**
Hematocrit increased	11 (8.3)
Injection site hemorrhage	8 (6.0)
Blood creatine phosphokinase increased	5 (3.8)
Injection site bruising	5 (3.8)
Prostatitis	4 (3.0)
Prostatic specific antigen (PSA) increased	4 (3.0)
Urinary tract infection	4 (3.0)
Fatigue	3 (2.3)
Hypertension	3 (2.3)
Insomnia	3 (2.3)
Nausea	3 (2.3)
Note: Includes events that started on or after the first dosing, or existed prior to the first dose and worsened in severity or relatedness after dosing. Percentage was calculated using the number of patients in the column heading as the denominator.	

In regard to the reported incidence of AEs by patient age, when comparing younger men (<65 years of age) to older men (≥ 65 years of age), a greater percentage of subjects in the ≥65 years subgroup compared to the <65 years subgroup reported an SAE (6.1% vs 1.7%), a TEAE that was moderate in severity (59.2% vs 30.3%), or a TEAE that lead to study discontinuation (24.5% vs 11.1%).

The following Table summarizes AEs by the two age subgroups.

Table 11: TEAEs by Age Subgroup in Studies QST 13-003 and QST 15-005

Category	<65 Years N=234 n (%)	**≥65** years N=49 n (%)
Patients with any TEAE	169 (72.2)	43 (87.8)
Patients with any TEAE by maximum severity		
Mild	90 (38.5)	11 (22.4)
Moderate	71 (30.3)	29 (59.2)
Severe	8 (3.4)	3 (6.1)
Patients with any SAE	4 (1.7)	3 (6.1)
Patients with any treatment-emergent SAE	4 (1.7)	3 (6.1)
Patients with TEAE leading to discontinuation	26 (11.1)	12 (24.5)
Patients with any adverse event involving death	0 (0)	1 (2.0)
SAE = serious adverse event; TEAE = treatment-emergent adverse event. *Source: ISS Table 35.5.1.1*		

CDTL Comment: Higher rates of all TEAEs, TEAEs of moderate and severe intensities, and TEAEs leading to study discontinuation were observed in the ≥ 65 years age group compared to the < 65 years age group. Though the data are limited, they do support the approved drug class labeling concerning cautious use of TRT in the geriatric population, and also not to use

TRT for the treatment of conditions such as "age-related hypogonadism", that are not associated with a structural or genetic disorder.

8.1.3 Routine Laboratories, Vital Signs and Electrocardiograms (ECGs)

Routine Laboratories

In the Phase 3 studies QST 13-003 and QST 15-005, routine safety laboratory tests included: biochemistry, hematology, urinalysis, coagulation, serum PSA, and serum lipids. The Sponsor provided a summary of routine lab test results at baseline and at all scheduled post-dose visits.

There were no notable changes from baseline in routine biochemistry, urinalysis, or coagulation tests. Increases in hematocrit and PSA are discussed below.

Increases in Hematocrit

Results from hematology testing demonstrated a clinically significant increase from baseline in hematocrit. In the pooled Safety population from Studies QST 13-003 and QST 15-005, the group mean hematocrit increased from baseline by 2.5% at Week 13, by 3.8% at Week 26, and by 5.4% at Week 52. The following Table summarizes the hematocrit changes from baseline in the Phase 3 studies.

Table 12: Summary of Mean Hematocrit Changes in Studies QST 13-003 and QST 15-005)

Parameter (unit) Statistic	Baseline	Week 13	Change from Baseline to Week 13	Week 26	Change from Baseline to Week 26	Week 52	Change from Baseline to Week 52
Hematocrit (%)							
n	283	258	258	236	236	96	96
Mean (SD)	45.1 (3.34)	47.7 (3.77)	2.5 (2.95)	49.1 (4.05)	3.8 (3.40)	50.1 (3.73)	5.4 (3.42)

SD = standard deviation.
Source: ISS Table 35.7.2.1

A total of 32 subjects (11.3%) experienced "increased HCT", defined as an increase in HCT from baseline HCT, in the combined Phase 3 studies QST 13-003 and 15-005.

A total of 12 subjects (9 subjects in QST-13-003 and 3 subjects in QST-15-005) experienced an "elevated hematocrit", defined as a HCT of ≥55%. A total of 4 of the total 283 subjects (1.4%) experienced this degree of hematocrit elevation after 3 months of Xyosted treatment (on Day 90), while a total of 8 of the 283 subjects (4.5%) experienced this degree of hematocrit elevation after 6 months of Xyosted treatment (on Day 180). The Table below summarizes these patients.

Table 13: Summary of Patients in Studies QST 13-003 and QST 15-005 With Hematocrit ≥55%

QST-13-003	Pt ID	Age	Baseline Weight	Baseline BMI	BL Hct	Baseline C_{trough}	Wk 12 C_{trough}	Week 12 QST dose	Threshold visit
	(b) (6)	56	96.40	36.50	46	303	731	100 mg	38 wks
		49	112.8	36	45	165	322	100 mg	38 wks
		54	111.5	31.5	47	223	304	100 mg	26 wks
		50	136.2	39.8	49	198	521	75 mg	12 wks
		34	103.4	32.6	46	217	246	75(12)/100(13)	38 wks
		63	110.2	36.8	47	208	606	75 mg	26 wks
		61	73.9	24.7	48	289	455	75 mg	13 wks
		57	102.6	33.9	45	213	900	75(12)/50(13)	26 wks
		66	111	38	49	225	192	75(12)/100(13)	26 wks
QST-15-005		61	77.6	26.9	46	82	399	75 mg	18 wks
		57	110	39.2	51	205	706	75(12)/50(13)	13 wks
		53	97	32	45	141	349	100 mg	13 wks

BL = Baseline, Hct = hematocrit; Pt = patient
Source: QST-13-003 Listing 16.2.1.2; Listing 16.2.4.1; Listing 16.2.6.1; Listing 16.2.8.2; Listing 16.2.9.3
QST-15-005 Listing 16.2.1.2; Listing 16.2.4.1; Listing 16.2.6.1; Listing 16.2.8.2; Listing 16.2.9.3

CDTL Comment: Xyosted is associated with a clinically meaningful, and potentially serious or even life-threatening, increase in hematocrit.

Decreases in Serum High Density Lipoprotein (HDL) Cholesterol

Serum lipid parameters were evaluated in the phase 3 studies QST 13-003 and QST 15-005. Mean decreases from Baseline to Week 52 were observed for all serum lipid parameters, including HDL-cholesterol. Mean cholesterol and triglyceride concentrations decreased by 17.3 mg/dL and 16.5 mg/dL, respectively, and mean LDL-C and HDL-C concentrations decreased by 8.5 mg/dL and 4.5 mg/dL, respectively. The following table summarizes the results of serum lipid concentrations for Studies QST 13-003 and QST 15-005.

Table 14: Summary of Serum Lipid Evaluations in Studies QST 13-003 and QST 15-005

Parameter (unit) Statistic	Baseline	Week 13	Change from Baseline to Week 13	Week 26	Change from Baseline to Week 26	Week 52	Change from Baseline to Week 52
Cholesterol (mg/dL)							
N	282	261	260	240	239	97	97
Mean (SD)	188.5 (40.12)	172.5 (37.69)	- 15.8 (27.34)	175.5 (42.06)	- 14.1 (27.86)	178.8 (41.14)	- 17.3 (27.99)
HDL Cholesterol (mg/dL)							
N	282	261	260	240	239	97	97
Mean (SD)	44.3 (14.20)	38.9 (12.88)	- 5.6 (6.64)	38.9 (12.95)	- 5.5 (7.34)	41.2 (14.10)	- 4.5 (8.53)
LDL Cholesterol (mg/dL)							
N	271	251	242	233	224	95	90

Mean (SD)	111.4 (35.41)	102.9 (32.65)	- 8.7 (22.92)	104.7 (34.45)	- 7.3 (23.65)	105.1 (36.38)	- 8.5 (23.38)
Triglycerides (mg/dL)							
N	282	261	260	240	239	97	97
Mean (SD)	168.4 (101.29)	159.8 (106.94)	- 8.4 (98.52)	164.0 (130.03)	- 6.2 (124.40)	171.9 (152.99)	- 16.5 (139.24)

HDL Cholesterol = high-density lipoprotein cholesterol; LDL Cholesterol = low-density lipoprotein cholesterol; SD = standard deviation; ***Source: ISS Table 35.7.5.1***

CDTL Comment: While total cholesterol, triglycerides and LDL cholesterol concentrations fell while patients were on Xyosted, there was actually an average decrease in serum HDL-cholesterol that may be clinically meaningful.

Increases in Serum Prostate Specific Antigen (PSA)

Increases from baseline were observed in serum PSA concentrations in Studies QST 13-003 and QST 15-005. Mean serum PSA concentrations were 1.05 µg/L at Baseline and increased to 1.32 µg/L, 1.27 µg/L and 1.33 µg/L at Weeks 13, 26, and 52, respectively. The following Table summarizes the mean PSA values at Baseline and the changes from baseline in mean PSA during the phase 3 studies.

Table 15: Summary of Changes in Serum PSA in Studies QST 13-003 and QST 15-005

Parameter (unit) Statistic	Baseline	Week 13	Change from Baseline to Week 13	Week 26	Change from Baseline to Week 26	Week 52	Change from Baseline to Week 52
PSA (µg/L)							
n	283	262	262	239	239	97	97
Mean (SD)	1.05 (0.69)	1.32 (0.91)	0.26 (0.49)	1.27 (0.83)	0.24 (0.43)	1.33 (0.82)	0.36 (0.48)

SD = standard deviation; ***Source: ISS Table 35.7.4.1***

In studies QST 13-003 and 15-005, patients with serum PSA increase of ≥ 1.4 ng/mL, or with an absolute serum PSA >4.0 ug/L, were to discontinue study medication. A total of 13 patients (4.6%) reached these thresholds. None of the patients had progressive increases in serum PSA after discontinuing Xyosted.

A TEAE of "Elevated PSA" was reported when the patient's serum PSA rose by >0.75 ug/L, or when the patient's total serum PSA was > 4.0 ug/L. Overall 22 patients (7.8%) experienced an AE of "Elevated PSA" in Studies QST 13-003 and QST 15-005.

There were 5 patients with serum PSA greater than the upper limit of normal (>ULN) at Week 13, 3 patients with PSA concentrations >ULN at Week 26, and 2 patients with values >ULN at Week 38. There were no patients with PSA values >ULN at Week 52.

CDTL Comment: Increases in PSA are a known class effect of TRT and Xyosted labeling will describe these results with a recommendation to monitor PSA in men on Xyosted.

Vital Signs

Vital signs, including systolic and diastolic blood pressures (SBP/DBP) by sphygmomanometric cuff, heart rate (HR), respiratory rate (RR), and body temperature, were collected in both Phase 3 studies, and the data were analyzed at Baseline and at all scheduled post-dose visits with presentation of the data as mean changes from Baseline.

Based on increases from Baseline observed in mean cuff BPs in Study QST-13-003, ambulatory blood pressure monitoring (ABPM) was requested by the Division and conducted by the Sponsor at Baseline, at Week 6 and at Week 12 in the Phase 3 study QST-15-005. The ABPM data was collected and analyzed by the Sponsor and this data also demonstrates mean increases from Baseline in SBP and DBP.

In the pooled Phase 3 studies QST 13-003 and QST 15-005 using cuff data, both SBP and DBP increased from baseline, with average SBP increases ranging from 2.6 to 4.4 mmHg and average DBP increases ranging from 0.5 to 1.6 mmHg. The following Table summarizes the mean BP increases.

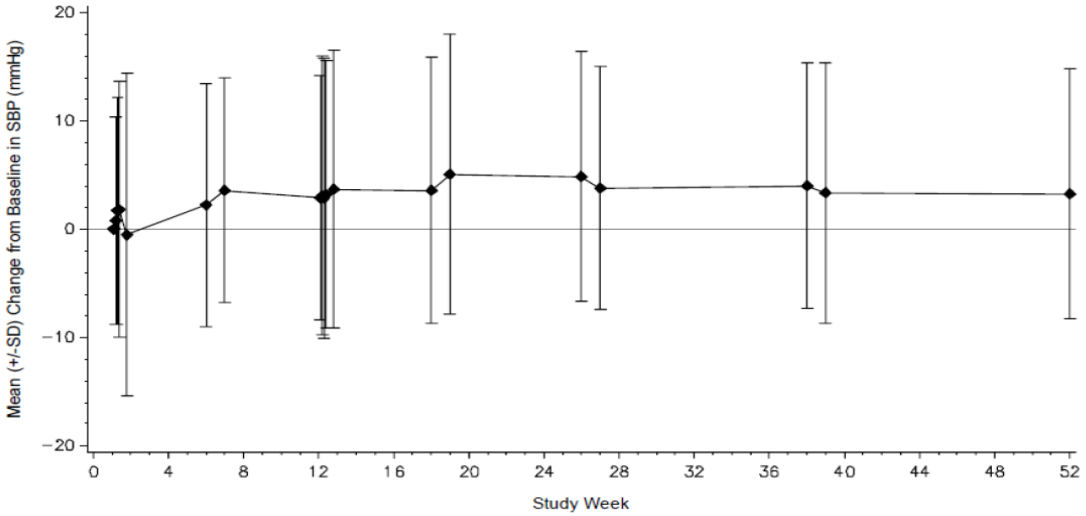
Table 16: Mean SBP and DBP by Visit in Studies QST 13-003 and QST 15-005

Parameter (unit) Statistic	Baseline	Week 6 (Day 1)	Change from BL to Week 6 (Day 1)	Week 12 (Day 1)	Change from BL to Week 12 (Day 1)	Week 26 (Day 1)	Change from BL to Week 26 (Day 1)	Week 52 (Day 1)	Change from BL to Week 52 (Day 1)
Systolic Blood Pressure (mmHg)									
n	283	276	276	263	263	240	240	98	98
Mean (SD)	126.2 (11.2)	128.8 (12.4)	2.6 (11.4)	129.4 (12.2)	3.2 (11.5)	130.5 (11.6)	4.4 (11.3)	130.6 (10.6)	3.3 (11.5)
Diastolic Blood Pressure (mmHg)									
n	283	276	276	263	263	240	240	98	98
Mean (SD)	79.1 (8.2)	80.3 (8.6)	1.2 (6.8)	80.9 (9.0)	1.6 (8.1)	80.7 (9.4)	1.3 (8.3)	81.2 (9.2)	0.5 (9.1)

SD = standard deviation; *Source: ISS Table 35.8.1*

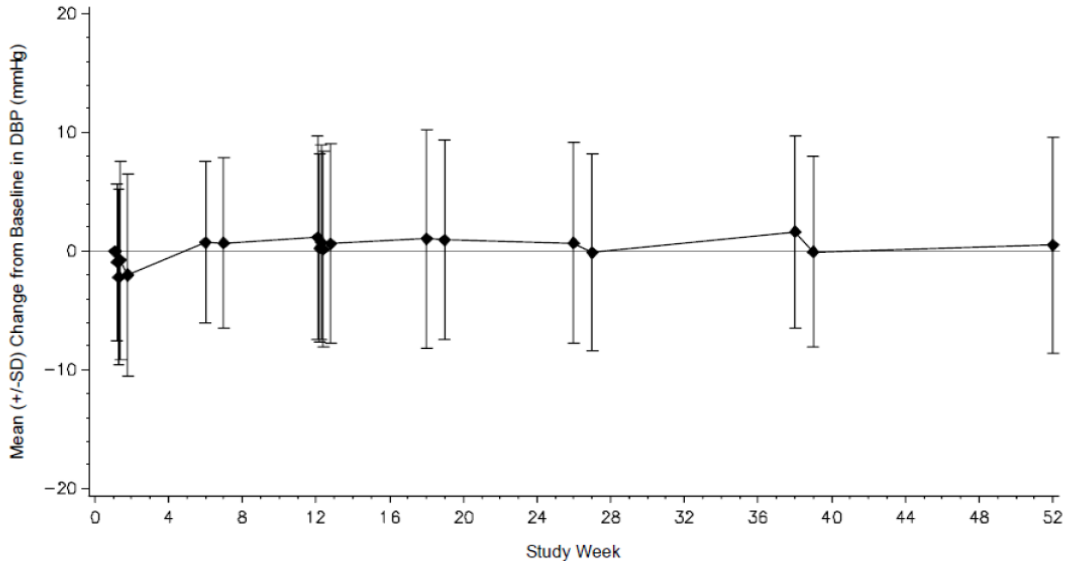
The following two figures graphically depict the mean changes from Baseline in cuff SBP and DBP, respectively, for Study QST 13-003.

Figure 2: Mean Change from Baseline in SBP (via Cuff) in Study QST-13-003



Note: Baseline was defined as the Week 1 pre-dose value. If missing, the last measurement prior to first dose was used. SBP=systolic blood pressure; SD = standard deviation
Source: QST 13-003 CSR, section 12.6.1

Figure 3: Mean Change from Baseline in DBP (via Cuff) in Study QST-13-003

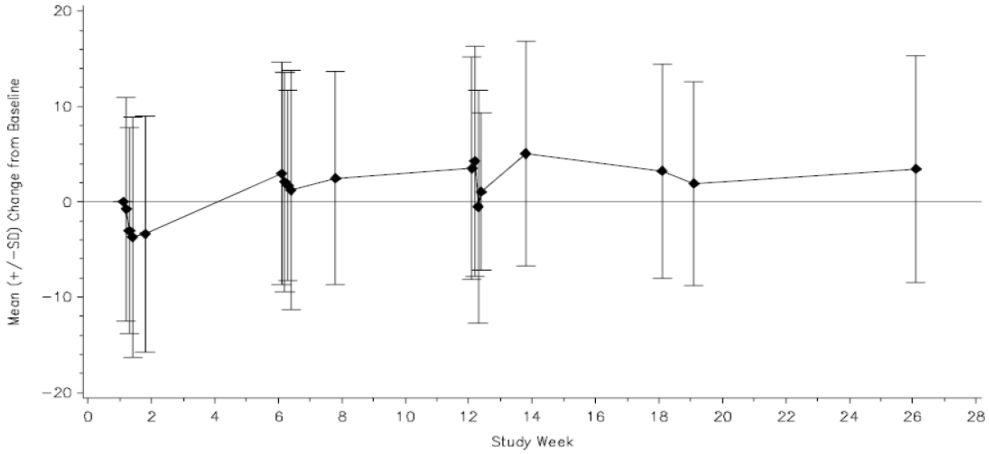


Note: Baseline was defined as the Week 1 pre-dose value. If missing, the last measurement prior to first dose was used. DBP=diastolic blood pressure; SD = standard deviation
Source: QST 13-003 CSR, section 12.6.1

In the second phase 3 study QST-15-005, ambulatory BP monitoring was performed in all patients in the study and patients with BP above the normal range (SBP ≥ 140 mmHg and/ or

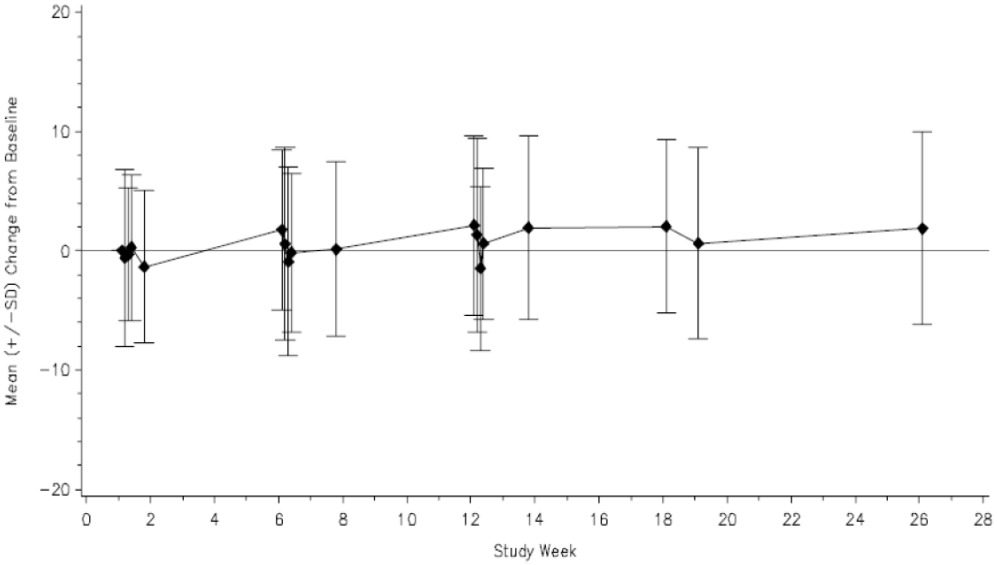
DBP ≥ 90 mmHg) were excluded from the study. The following two figures depict the mean SBP and DBP changes from baseline, respectively, in Study 15-005, as measured by ABPM, in subjects with at least 18 hours of ABPM tracing.

Figure 4: Mean Change from Baseline in SBP (via ABPM) in Study QST-15-005



Note: Baseline was defined as the Week 1 pre-dose value. If missing, the last measurement prior to first dose was used. DBP=diastolic blood pressure; SD=standard deviation; ***Source: QST 13-003 CSR, section 12.6.1***

Figure 5: Mean Change from Baseline in DBP (via ABPM) in Study QST-15-005



Note: Baseline was defined as the Week 1 pre-dose value. If missing, the last measurement prior to first dose was used. DBP=diastolic blood pressure; SD=standard deviation; Source: QST 13-003 CSR, section 12.6.1

A formal consultation was requested from the Division of Cardiovascular and Renal Products (DCRP) to assist in the review of the vital signs information, including the evidence for increased

BP. The reader is referred to Section 11.7 of this Memo for details concerning the DCRP consult. To summarize the consult briefly here, DCRP concluded that evidence was clear concerning the approximate mean 4/2 mHg increase from Baseline in SBP/DBP.

To summarize the ABPM data, in the 6-month clinical study 15-005, 24-hour ambulatory blood pressure monitoring (ABPM) was conducted in 133 patients, 113 of whom completed the study. ABPM was conducted at 3 distinct 24-hour time periods: at Baseline and following 6 and 12 weeks of XYOSTED therapy. A total of 78 patients had acceptable ABPM recordings at all three time periods. In that group, the mean change in systolic BP from baseline to Week 12 (n=62) was + 3.9 mmHg (90% CI 1.8-6.0) and the mean change in diastolic BP was 1.5 mmHg (95% CI 0.5- 2.5). These ABPM results from study 15-005 were consistent with the BP results obtained by cuff measurement in study 13-003.

CDTL Comment: The vital signs data from the phase 3 studies demonstrates a clinically meaningful group mean increase in SBP of approximately 4 mmHg. This level of increase in BP can increase the risk of major adverse cardiovascular events, including myocardial infarction, stroke and cardiac death. For this reason, the product labeling will contain a Boxed Warning for this issue, as well as new Contraindication to gear use towards men with certain medical conditions, a new Warning related to increased BP, a new section in Adverse Reactions, and prominently displayed information about increased BP in the Medication Guide.

ECGs

Results from routine ECGs conducted during the phase 3 studies showed a small number of ECG abnormalities that appeared consistent with the range of ECG abnormalities that might be observed in the background in this patient population. Aside from one case of atrial fibrillation in the Phase 2 study QST 16-006, one case each of paroxysmal atrial tachycardia and right bundle branch block in Study QST 13-003, and one case each of anteroseptal infarct and left bundle branch block in Study QST 15-005, there were no other clinically significant changes from baseline in ECG.

CDTL Comment: Testosterone is not known to alter the QT interval or other ECG parameters. In the case of the patient with anteroseptal infarct, the patient did not disclose his new-onset angina to the investigator during the Screening Period.

8.2 Postmarketing Safety Findings

Currently, there is no postmarketing experience for Xyosted. There is also very little published information concerning chronic subcutaneous administration of testosterone to hypogonadal men. Delatestryl, the intramuscular (IM) form of testosterone enanthate, has been marketed since 1953. The risks of Delatestryl are likely comparable to the known risks of TRT products, with the possible exception of mood changes that may be associated with the peaks and declines in serum testosterone that are associated with the pharmacokinetics of the IM injection. The risks of TRT are generally known and they include a variety of adverse androgenic effects, including potential adverse effects on spermatogenesis, the prostate (enlarged prostate, BPH symptoms), skin (acne), the hematologic system (e.g., increased hematocrit), the respiratory

system (sleep apnea), the peripheral circulation (peripheral edema), and on mood. Whether TRT directly causes serious cardiovascular events in older men is currently unknown.

8.3 Overall Assessment of Safety Findings

In general, the safety profile for Xyosted was consistent with the known safety profile for TRT products, except for:

1) ABPM measurements in study QST 15-005 showed that treatment with Xyosted was associated with a mean systolic/diastolic BP increases of 4/2 mmHg. 9.5% of patients in that study required initiation or adjustment of antihypertensive medications. Similar increases in BP were also observed by routine cuff measurement in study QST 13-003. Increases in BP of this magnitude can increase the risk of having a heart attack, stroke or cardiac death. The risk of increased BP that can increase the risk of MACE will be described prominently in labeling with recommendations provided to lower the risk. The labeling for increased BP has been broached previously in this memo and is summarized again in the Labeling section later in this memo.

2) Two cases of suicide attempt (including one completed suicide) and two cases of depression (total of 4 distinct cases) were reported among 283 phase 3 clinical study subjects. It should be noted that each of these 4 cases included possibly confounding variables. Further, there is no clear evidence that Xyosted poses more of a risk to patients than other TRT formulation for disturbances of mood. Nonetheless, reporting of two cases of suicide attempt in a relatively small NDA is notable and this potential risk will be described prominently in labeling. Labeling for depression and suicide has been broached previously in this memo and is summarized again in the Labeling section later in this memo.

Finally, increased hematocrit (including polycythemia) was reported in a significant percentage of patients in the phase 3 studies, and labeling will prominently describe this risk and will provide recommendations for lowering the risk. Labeling for increased hematocrit/ polycythemia and depression/ suicide has been broached previously in this memo and is summarized again in the Labeling section later in this memo.

9. Advisory Committee Meeting

An Advisory Committee was not held for the Xyosted new drug application. All safety issues were clearly identified and these issues were discussed widely within FDA. It was determined that robust labeling, a PMR study (for the increased BP issue) and special pharmacovigilance (for the depression/suicide issue) satisfactorily address these issues. There were no unresolved questions to pose to an Advisory Committee.

10. Pediatrics

On February 9, 2015, the Division issued to Antares an "Agreed iPSP", providing concurrence with the Sponsor's proposal for a full waiver of pediatric assessment

requirements for all pediatric age groups based on the rationale that pediatric studies would be impossible as studies would be impossible or highly impractical.

This decision was consistent with prior agreements from the Division and from the Pediatric Review Committee (PeRC) for the Antares application, as well as for all prior Division determinations for PREA for TRT products approved since 2002.

On September 20, 2017, the Division met with PeRC again concerning Antares, to receive final PeRC advice/agreement on the Agreed iPSP. At the September 2017, PeRC meeting, the Division of Metabolism and Endocrinology Products (DMEP) expressed that pediatric studies in TRT, including for Xyosted, were neither impossible nor highly impractical, and in fact, were needed. Based on this assertion, the PeRC rescinded their previous agreement for the Antares application of a full waiver of pediatric studies (as previously conveyed to Antares by the Division in the Agreed iPSP), and instead, PeRC recommended a partial waiver of required pediatric studies in pediatric patients younger than 14 years of age, and a deferred required pediatric study in adolescent males with permanent hypogonadism (not constitutional delay of puberty).

On October 2, 2017, DMEP completed a consult review for the Antares NDA. In brief, the consult describes 1) the possible numbers of potential pediatric study subjects based on the specific conditions and diseases that result in "true" hypogonadism in pediatric patients, and 2) the study design intricacies and uncertainties associated with conducting a study in pediatric patients with permanent hypogonadism. DMEP concluded that it was beyond the scope of the current consult, especially given the limited time remaining before the PDUFA action date for the original NDA (first cycle), to determine a final study(ies) design, efficacy or safety endpoints, duration of treatment, or sample size for the recommended study in adolescent patients with permanent hypogonadism.

On October 16, 2017, the Division of Pediatric and Maternal Health (DPMH) completed a final consult review, providing the following final recommendation on pediatric study requirements:

1. A partial waiver of pediatric study requirement for all TRT programs in patients less than 14 years of age is reasonable on the basis that studies are impossible and highly impractical.
2. Further discussion is warranted with internal stakeholders regarding the optimal studies to be conducted (b) (4) and whether such studies are feasible.
3. Pending further internal discussion, DPMH recommends issuing a PREA PMR for deferred studies in adolescent males, 14 years to less than 17 years of age (see Discussion above). If, based on follow-up discussion, there is internal consensus that studies are infeasible in this age group, then the applicant may be release from any PMR in the future."

On October 20, 2017, a Complete Response (CR) letter was issued. Pediatric issues were not described in the CR letter.

On September 24, 2017, in an email to DBRUP, Lynne Yao of PeRC stated her agreement with

DBRUP to convene a panel of experts sometime in the future to discuss the issue of required pediatric studies of TRT. In the meantime, Dr. Yao cautioned that from a regulatory perspective, despite pediatric TRT studies still being under discussion within FDA, if there was a chance that a panel would recommend a pediatric study(ies) of Xyosted, that DBRUP should proceed to make a request for a pediatric study(ies) in the upcoming Xyosted NDA action letter, because the lack of such a request in the NDA action letter would preclude a future request for a pediatric study for Xyosted. Therefore, the following request for deferred pediatric study was conveyed to the Sponsor. The Sponsor subsequently provided its concurrence. Information about the deferred study will appear in the action letter:

Please refer to the attached letter dated September 22, 2017, where we advised you of the Agency's reconsideration of the appropriateness of the partial waiver of PREA requirements for adolescent boys with pathological or genetic causes of hypogonadism who require chronic testosterone replacement. Our discussions are ongoing. Because we have not concluded that a partial waiver in this subgroup is appropriate, your pediatric study in this subgroup will be a deferred PREA requirement, as follows:

> A study of testosterone replacement therapy in pediatric males ages 14 years and older for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism.
>
> Final Protocol Submission: 04/2021
> Study/Trial Completion: 04/2026
> Final Report Submission: 10/2026

The proposed milestone of the final study protocol takes into account the time anticipated for the Agency to reach a decision about a study in adolescent boys requiring chronic testosterone replacement. We request your concurrence with the deferred PREA study and milestones by 9/26/18. Let us know if you have any questions.

11. Other Regulatory Issues Including Consultations

11.1 Consultation: Office of Scientific Investigations (OSI)

During the original review of the NDA, the Office of Scientific Investigations (OSI) was consulted to conduct inspections of three clinical sites that participated in the Xyosted Phase 3 studies. The three sites selected were: Jed Kaminetsky (New York, NY), Tommy Mook (Shreveport, L) and Marc Gittleman (Aventura, FL). No issues of clinical significance were identified at Dr. Kaminetsky's or Dr. Mook's sites.

However, at Dr. Gittelman's site, the inspector noted that some ABPM tracing were categorized as "*Not Good Quality*". The Division and OSI pursued this issue with the Sponsor and investigator and ultimately determined that some patients did not achieve at least 18 hours of ABPM recordings. Therefore, in conjunction with our consultants from the Division of Cardiovascular and Renal Products (DCRP), the Division required the Sponsor to submit a re-analysis of results from the 24-hour ABPM tracing, to include only those patients with at least

18 hours of tracings.

In their final conclusion of their Clinical Inspection Summary, Roy Blay, Phillip Kronstein, and Kassa Ayalew of OSI concluded:

> *"Other than the concerns regarding ABPMs as discussed above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of this respective application."*

OSI expressed no concerns about the conclusions from the data from Dr. Kaminetsky's and Dr. Mook's sites.

11.2 Consultation: Office of Surveillance and Epidemiology (OSE)/ Division of Medication Errors Prevention and Analysis (DMEPA)

11.2.1 DMEPA Tradename Review

In their final review dated May 23, 2018, Denise Baugh and Lolita White of DMEPA stated:

> *"The proposed proprietary name (Xyosted) is acceptable."*

11.2.1 DMEPA Container/Carton/Package Insert Labeling Review

In their final review dated September 22, 2018, Denise Baugh and Lolita White of DMEPA concluded:

> *"The revised container label and carton labeling for Xyosted is acceptable from a medication error perspective. We have no further recommendations at this time.*
>
> *Additionally, we find the revised Instructions for Use (IFU) is acceptable from a medication error perspective and we have determined that no further human factors validation study of the IFU labeling is required at this time."*

CDTL Comment: DMEPA's previous concern regarding the results of human factors studies and the IFU have been resolved through optimized labeling.

11.3 Consultation: Office of Surveillance and Epidemiology (OSE)/Division of Medical Policy Programs (DMPP)

In their final memo dated September 21, 2018, Kelly Jackson, Lynn Panholzer, Marcia Williams and LaShawn Griffiths of DMPP had the following conclusion

> *"The Medication Guide (MG) and IFU are acceptable with our recommended changes".*

CDTL Comment: All of DMPP's recommended changes to the Medication Guide and IFU were implemented.

11.4 Consultation: Office of Prescription Drug Promotion (OPDP)

In her final memo dated September 19, 2018, Lynn Panholzer of OPDP had the following conclusion

> *"In response to DBRUP's consult request dated April 2, 2018, OPDP has reviewed the*

proposed product labeling (PI), Medictaion Guide, Instructions for Use (IFU) and carton and container labeling for Xyosted.

OPDP's comments on the proposed PI…..are provided below.

A combined OPDP and DMPP review will be completed for the Medication Guide and IFU and comments will be sent under separate cover.

OPDP has reviewed the proposed carton and container labeling…and we do not have any comments".

CDTL Comment: OPDP participated in all labeling discussions. All OPDP comments were considered and the majority were implemented. Those few that were not implemented due to Clinical non-concurrence were discussed with OPDP. OPDP did not express major objection to not implementing those few recommendations.

11.5 Financial Disclosure

In compliance with 21 CFR Part 54, the Sponsor adequately disclosed the absence of any Investigator's proprietary interest in this product, and the absence of any special financial arrangements between themselves and any Investigator.

11.6 Consultation: Division of Metabolism and Endocrinology Products (DMEP)

In their final consult review dated October 2, 2017, Ovidiu Galescu, Mary Roberts and James Smith of DMEP provided advice and recommendations to DBRUP concerning possible requirements for pediatric studies of Xyosted for the treatment of adolescent pediatric patients with permanent hypogonadism (not for constitutional delay of puberty).

The reader is referred to Section 10 of this review ("***Pediatrics***"), for details concerning the DMEP consult and pediatric issues for this application.

11.7 Consultation: Division of Cardiovascular and Renal Products (DCRP)

In the CR re-submission, the Sponsor re-submitted a "White Paper" document entitled "*Hypertension Discussion*" that they had originally submitted as part of their February 21, 2018, Type A meeting package. DBRUP had also previously consulted the Division of Cardiovascular and Renal Products (DCRP) to review the Sponsor's "*Hypertension Discussion*" document as part of FDA's preparation for the Type A meeting. For purpose of this meeting, DCARP finalized their consult to DBRUP on January 15, 2018. The "*Hypertension Discussion*" document submitted in the CR is exactly the same document as the document submitted in the Type A meeting package. Therefore, DCARP's consult for the NDA re-submission is exactly the same as their consult completed on January 15, 2018 for the Type A meeting.

In their final consult review dated June 11, 2018, Fortunato (Fred) Senatore, Martin Rose and Norman Stockbridge of DCRP concluded:

- "*The administration of XYOSTED will cause an increase of blood pressure with a mean SBP/DBP effect of ~ 4/1 mmHg within 12 weeks of treatment. This increase will be larger*

in some individuals. The hypertensive effect of this drug will increase the risk of cardiovascular death, myocardial infarction, stroke, and heart failure, albeit modestly. The risk will increase when given to patients with higher baseline risk (i.e., established cardiovascular disease or multiple cardiac risk factors)"

- "*We confirm that the baseline characteristics of the patient population in the phase-3 program were representative of the type of patient likely to be encountered in clinical practice for the treatment of hypogonadism with testosterone*".
- "*We do not feel further clinical studies will provide additional useful information*".
- "*If DBRUP feels marketing of the product is desirable because the benefit outweighs the cardiovascular and any other risks, then we suggest appropriate language in the PI as suggested in previous consults*".

The rest of the DCARP consult contains a series of original FDA assertions, followed by Sponsor "rebuttals", followed by DCARP's opinions on the Sponsor's rebuttals. The reader is referred to the consult for details of these written interactions.

CDTL Comment: It is important to point out here that DCARP emphasized that the observed increase in BP can increase the risk of MACE, but probably only modestly, and that in their opinion, this risk could be handled in product labeling through description of the risk and monitoring as long as the risk/benefit ratio allowed.

For completeness, it is valuable to share DCARP's conclusions from their original consult for the original NDA. This consult, dated August 3, 2017, authored again by Fortunato (Fred) Senatore, Martin Rose and Norman Stockbridge of DCRP concluded:

"One can expect a 4 mmHg rise in SBP and a 2 mmHg rise in DBP when prescribed QuickShot Testosterone (QST). This elevation in blood pressure may not be detectable with respect to the usual variation in daily blood pressure and may be clinically irrelevant for those with low baseline blood pressures.

There is no distinguishable outlier group that drove the overall small increment in blood pressure following initiation of QST.

As the mean baseline blood pressure increases, there could be a modest increase in cardiovascular risk. Consider restricting the use of this product in patients diagnosed with an elevated mean blood pressure".

The DCARP original consult describes details of the re-analysis of ABPM data from study 15-005 based on data from only those subjects with at least 18 hours of measured recordings in the 24-hour recording period. The consult included tables and bar graphs that show the overall mean rises in blood pressure and the distribution of blood pressure changes at Weeks 6 and 12 in Study QST 15-005 (the reader is referred to the Figures and Tables in the DCRP consult Appendix).

Of key interest are the cumulative distribution function (CDF) curves that show changes in blood pressure for all subjects in study QST 15-005 (the reader is referred to Figures 1 -8 in the consult Appendix).

Several of these tables and figures are provided here as highlights from the original DCRP consult.

Table 17. Summary of Cuff Blood Pressures for Studies QST-13-003, QST-15-005, and the ISS

			SBP (mm Hg)			DBP (mmHg)		
Study	N	Duration	Baseline	Endpoint	Δ from Bl	Baseline	Endpoint	Δ from Bl
003	150	52 wks	127	131	4	80	81	1
005	133	26 wks	126	129	3	78	80	2
ISS	283	26 wks	126	131	4	79	81	2

Source: Study 003: Table 14.3.4.3.5 CSR; Study 005: Table 14.3.4.7.1 CSR; ISS: Table 35.8.1 ISS

Table 18: Mean Systolic and Diastolic Blood Pressure Obtained by ABPM in Study QST 15-005

Timepoint	N	Mean SBP (SD)	SBP mean Δ BL (SD)	Mean DBP (SD)	DBP mean Δ BL (SD)
Overall					
Baseline (BL)	110	124 (11)	---	78 (6)	---
Week 6	106	128 (11)	4 (10)	79 (6)	1 (5)
Week 12	98	128 (12)	4 (11)	80 (6)	1 (6)
Awake					
Baseline (BL)	106	126 (11)	---	79 (6)	---
Week 6	105	129 (12)	4 (10)*	80 (6)	1 (5)*
Week 12	98	130 (12)	4 (11)**	81 (6)	2 (6)**
Asleep					
Baseline (BL)	101	118 (18)	---	73 (9)	
Week 6	98	119 (16)	1 (17)***	74 (8)	0.4 (9)***
Week 12	95	120 (20)	2 (22)****	74 (9)	0 (10)****

*Δ BL = change from baseline, SD= standard deviation; SBP, DBP and Δ BL are in mmHg; *(n=102), ** (n=95), *** (n=92), **** (n=90)*

Source: Source: DCRP review compilation of data from Table 14.2.3.7 and 14.2.3.8 located in \\CDSESUB1\evsprod\NDA209863\209863.enx., SN # 0001/ module 5.3.5.1/ Study Body Report/ Expert ABPM Report

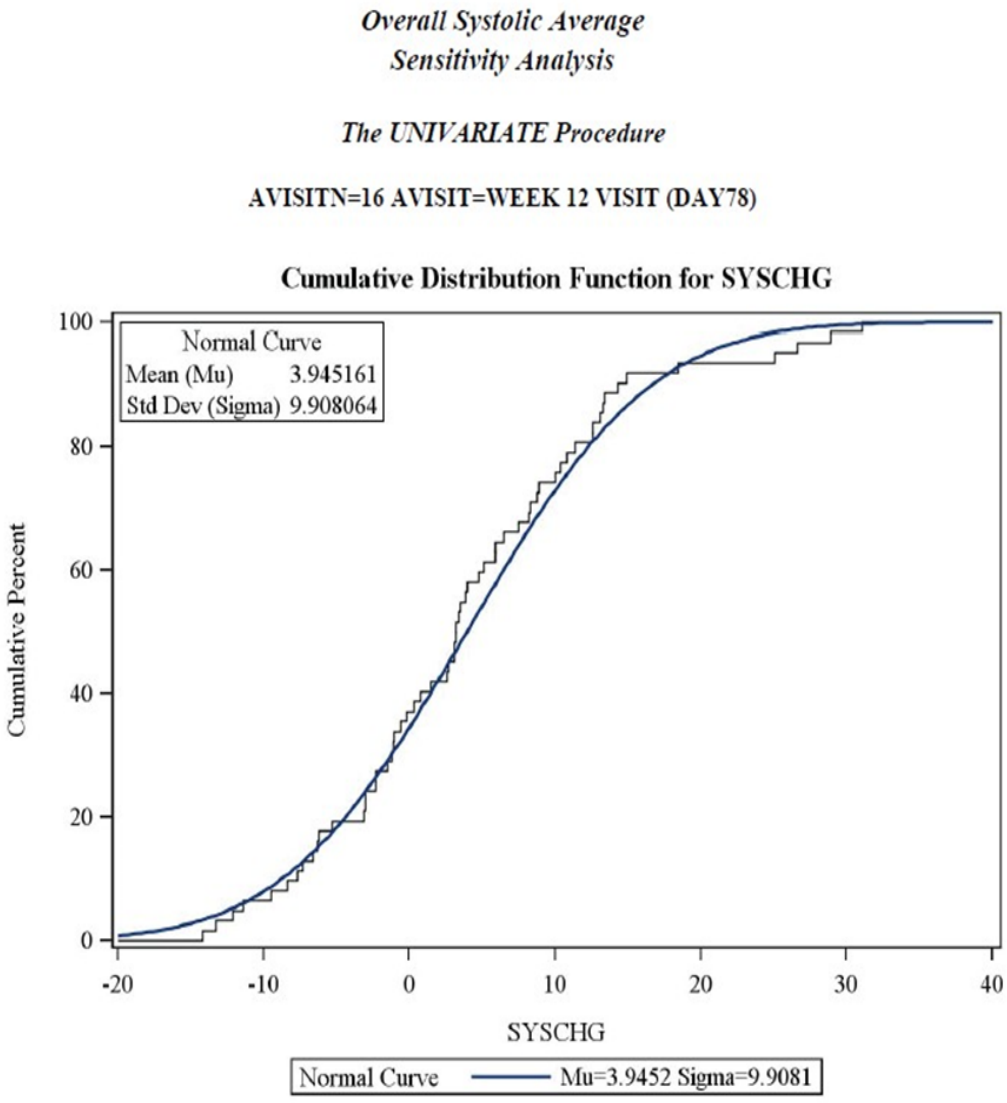
Table 19: Percentage of Subjects with Reductions/Increases in BP by ABPM in Study QST 15-005

Timepoint	N	Mean SBP Δ BL (SD) (mmHg)	% Subjects Reduced or No Change in SBP	% Subjects with 0-20 mmHg increase in SBP	Mean DBP Δ BL (SD) (mmHg)	% Subjects Reduced or No Change in DBP	% Subjects with 0-20 mmHg increase in DBP
	ITT Population						
Week 6	106	+ 3.5 (10)	35	60	+1.2 (5)	40	60*
Week 12	98	+ 3.7 (11)	40	55	+1.3 (6)	40	60
	Per Protocol (Subjects Compliant with 18-hour Rule)						

Week 6	67	+3.0 (8)	35	60	1.1 (3)	36	50**
Week 12	62	+3.9 (10)	35	60	1.5 (5)	37	60*

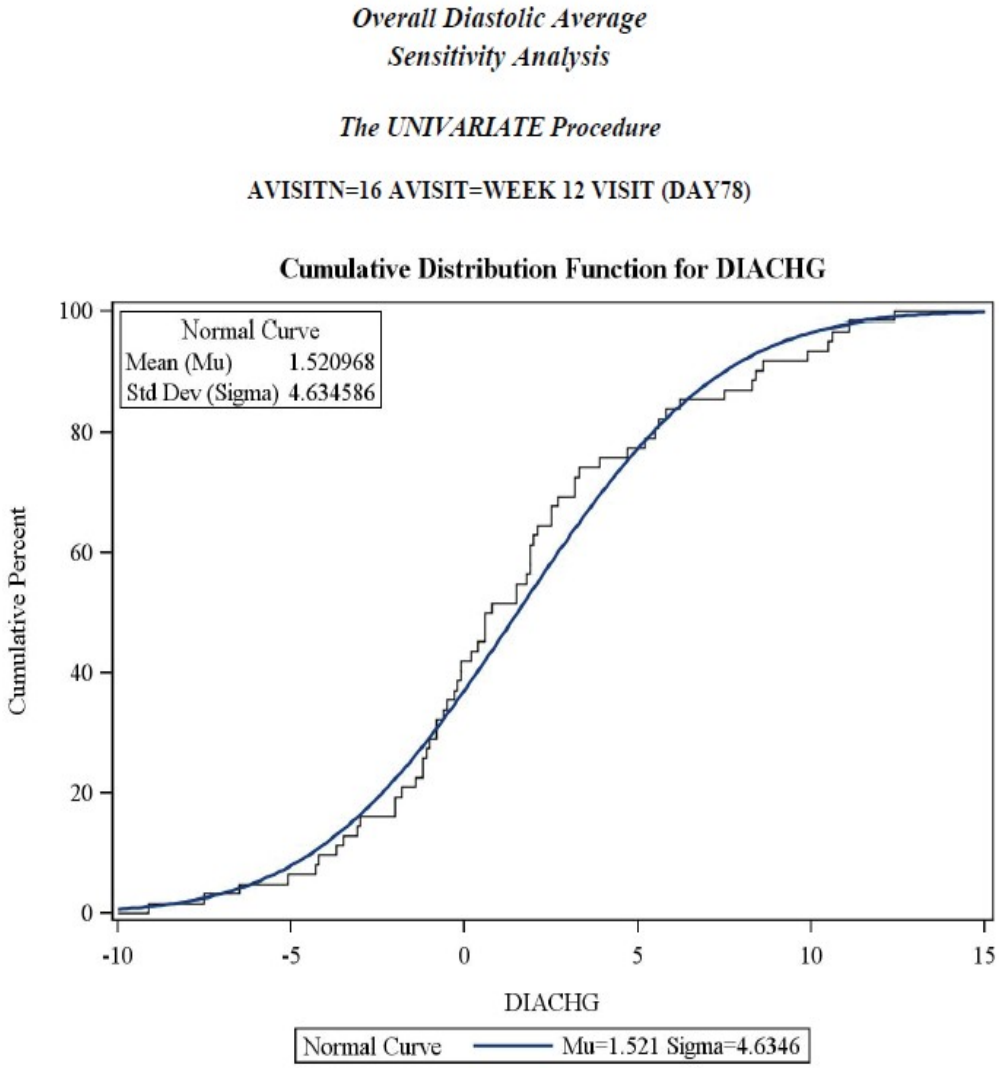
**Increase in DBP between 0—10 mmHg; **Increase in DBP between 0—5 mmHg*
Source: Sample size from Table 2 and Table 3 in the DCRP consult review; mean changes from baseline and standard deviation directly from the CDF curves; % subjects with reductions or increases in blood pressure manually estimated from the CDF curves.

Figure 8: CDF Curve for Systolic BP by ABPM at Week 12 in Study QST 15-005 (Sensitivity Analysis)



Source: Submission # 0017 Module 5.3.5.1

Figure 9: CDF Curve for Diastolic BP by ABPM at Week 12 in Study QST 15-005 (Sensitivity Analysis)



Source: Submission # 0017 Module 5.3.5.1

CDTL Comments: A clinically meaningful mean increase in BP was observed in normotensive hypogonadal male patients after 6 and 12 weeks of treatment with Xyosted in the phase 3 study QST 15-005. Results from ABPM assessments demonstrated group mean increases in systolic and diastolic BP (SBP and DBP) of approximately 4 mmHg and 2 mmHg, respectively. Further, 9.5% of patients in the study required initiation or adjustment of antihypertensive medications in order to maintain BP within the normal range. The observation of increased BP with Xyosted was also observed in cuff blood pressures.

11.8 Consultation: Office of Surveillance and Epidemiology (OSE)/ Division of Pharmacovigilance II (DPVII)

For this CR re-submission, DPVII was asked to opine on the utility of an enhanced pharmacovigilance (EPV) program, including expedited 15-day reporting to FDA, to monitor post-market reports of depression and suicide. DPVII considered whether EPV would be a useful tool for assessing the risk of depression and suicidality for Xyosted.

In their final consult review dated June 12, 2018, Rachna Kapoor, Lynda McCulley and Ida-Lina Diak of DPVII provided the following conclusion about ePV:

> "*In conclusion, although we do not believe that expedited reporting of cases describing depression and suicidality related events would help FDA gain a better understanding of this potential safety issue, we do request that the sponsor provide periodic and cumulative summaries and analyses of all reports of depression and suicidality-type events since approval of Xyosted as part of the quarterly PADER for the first three years of marketing of Xyosted. Additionally, we request that the sponsor discuss the effectiveness of its labeling regarding this safety issue in each PADER along with recommendation for changes in labeling, if needed, based on their findings."*

CDTL Comment: We agree with DPV's approach to postmarketing pharmacovigilance and reporting requirements for depression and suicide for Xyosted. The Sponsor will be asked to submit quarterly reports and analyses of the depression/suicide issue within their PADERS for the first 3 years and to continuously evaluate the need for labeling revisions based on the evidence.

As part of the original NDA review, DPVII was consulted to conduct a search of the FDA's Adverse Event Reporting System (FAERS) to identify postmarketing reports of suicide in hypogonadal men taking approved testosterone products for TRT and also to conduct a review and analysis of those cases.

In their final consult review for the original NDA dated August 30, 2017, Rachna Kapoor and Neha Gada of DPVII provided the following conclusion:

> "*We identified cases of suicidal attempt, completed suicide, and suicidal ideation reported with the use of testosterone. We are mindful that this memo is a high-level summary and the individual cases were not reviewed for drug-event causality given the rapid responses need by DBRUP. However, a vast majority of the cases do not provide necessary information regarding concomitant medications, past medical history, duration of therapy, time-to-onset of suicidal symptoms, and previous history of suicidal attempts to ascertain drug-event association. This is a limitation of spontaneous data. Additionally, we did not a specific trend.*"

The DPV search of FAERS identified a total of 74 relevant cases, including 13 cases of suicide attempt, 15 cases of completed suicide, and 46 cases of suicidal ideation (n=46) in men taking testosterone. The majority of these cases lacked sufficient information concerning the reason for product use, past medical history, concomitant medications, psychiatric history or concurrent psychiatric symptoms, and details of the case, including details of the suicide event. DPV also remarked that most cases of completed suicide described underlying depression and anxiety.

CDTL Comment: The suicide cases identified by DPVII almost uniformly lacked critical information necessary to allow for a meaningful assessment of causality between suicide and TRT.

11.9 Consultation: Controlled Substances Staff (CSS)

For the CR re-submission, the Controlled Substances Staff (CSS) was consulted to evaluate the Sponsor's proposals for the Abuse Potential and Dependence sections of product labeling. CSS also provided comments on other parts of labeling as well as on post-marketing pharmacovigilance for the depression/suicidality issue.

In their final consult review dated September 20, 2018, Alicja Lerner, Martin Rusinowitz and Dominic Chiapperino) offered the following Recommendations:

"*1. The Sponsor's proposed Pharmacovigilance plan for suicidality and depression is appropriate*…..(if expediting reported is ultimately requested by FDA*), CSS recommends expedited reporting also for "attempted suicide" and "suicidal ideation". Providing the suicidality AE data in quarterly PADER submissions is acceptable too, consistent with the approach proposed by DPV/OSE by Dr. R. Kapoor, June 12, 2016. However, expedited reporting….would be preferred….*

CDTL Comment: The Xyosted review team made a determination that quarterly reporting of the relevant cases (with analysis) in the PADERs would be acceptable and expedited reporting would not further assist FDA in its review of the issue.

"*2. CSS proposed consideration of a Boxed Warning for suicidality and the addition of suicidality as an AE in Section 9.3 Dependence.…..…While the currently proposed Warning (Section 5.16) is a valuable addition to labeling, it may not be prominent enough for such a serious adverse event, and might be overlooked….*" CSS proposed some text for a new Boxed Warning and for Section 9.3 for suicidality.

CDTL Comment: The Xyosted review team made a determination that a Boxed Warning of suicidality for Xyosted was not supported by the available evidence. The new Warning would appropriately describe the cases and issue.

For the original NDA, CSS was consulted to evaluate the Sponsor's proposals for the Abuse Potential and Dependence sections of product labeling. CSS also evaluated the Xyosted clinical study safety results that were potentially indicative of abuse, dependence or withdrawal. CSS also provided comments on the psychiatric AEs observed in the Xyosted clinical studies, including 1 case of completed suicide, 1 case of suicide attempt, and 2 cases of depression.

In their final consult review for the original NDA dated October 6, 2017, Alicja Lerner and Dominic Chiapperino (signing for Silvia Calderon and Martin Rusinowitz) offered the following Conclusions and Recommendations:

"*<u>Conclusions</u>*

1. *Testosterone and, thus, all testosterone containing products are controlled in Schedule III of the Controlled Substances Act (CSA) since 1990.*
2. *Testosterone products are known to form dependence resulting in a withdrawal syndrome upon drug*

discontinuation in healthy men and women (athletes, bodybuilders) who take it in supratherapeutic doses. However, the data on consequences of testosterone withdrawal in older men with hypogonadism after testosterone replacement therapy (TRT) are very sparse. Therefore, Sponsors should continue to acquire reports of adverse events (AEs) indicating these withdrawal signs and symptoms in future clinical studies, to further refine section 9.3 (Dependence) for testosterone products' labeling (see Recommendations).

3. *Review of the safety database for this NDA identified two cases related to suicidality; one of these cases was a "completed suicide," and the second one was coded as "depression" but was, in reality, a "suicide attempt." The risk of suicidality in testosterone and anabolic steroids abusers was noted already during testosterone TSI # 1351 (4 completed suicides, 6 suicide attempts, and 12 suicidal ideations).*
4. *Upon identification of the two "suicidality" cases under the current NDA for QST, CSS recommended that the Division consult OSE/DPV to evaluate further this issue, the Division followed up on this request and the corresponding review from OSE can be found in DARRTS. However, the review states that it is only "high level" review, and a detailed analysis of cases was not performed. However, CSS further reviewed the data and information provided in the OSE/DPV review, and presents some representative cases and provides further comments and recommendations.*
5. *Depression in older hypogonadal men has been observed (Barrett-Connor et al. 1999, Shores et al., 2004; Amore et al., 2008; Makhlouf et al., 2008). Also, depressed men with lower levels of testosterone were shown to be at higher risk of suicide (Sher, 2013). Treatment with testosterone may cause depression as an AE (see labeling). In the current NDA, 15-30% of subjects with the disease condition had a history of depression, and some subjects were discontinued due to AEs of depression. However, suicidality during TRT and upon withdrawal of testosterone has not been evaluated and, therefore, it is recommended in the future studies of TRT that depression and suicidality are evaluated with appropriate questionnaires (see Recommendations). These scales are in common use for other psychoactive drugs in patient populations with a history of depression, current depression, and for drugs known to precipitate depression.*
6. *Dependence was not systematically evaluated in any of the conducted studies and there is no data on dependence and withdrawal in this NDA. Information on withdrawal AEs were requested twice, in the 74-day letter and in an IR dated July 7, 2017. It appears though that the Sponsor is confusing the situation where subjects discontinue drug treatment due to AEs (discontinuation AEs) and the situation where drug discontinuation leads to AEs (withdrawal AEs).*
7. *There was a number of cases where drug accountability discrepancies were reported in the clinical studies QST-13-003 and QST-15-005 and showed that some subjects lost a number of devices, representing 60 % to 80 % of the total amount of devices received by these subjects. These cases may be indicative of drug misuse and/or diversion of the study drug (see Discussion, section on Diversion/Drug Accountability).*
8. *There were three cases of "above expected testosterone levels" that may be indicative of misuse. Two cases with levels above 1500 ng/dL and one case of 2300 ng/dL 3 hours post dose. As the submission's ISS states (page 18), the maximum Ctrough values were in the range of 900-1300 ng/dL, with mean values all below 500 ng/dL.*

<u>Recommendations</u>

1. *Since testosterone is known to be abused and misused, we recommend continuing post- marketing assessment of AEs suggestive of abuse-potential, dependence, and withdrawal. These assessments should be included in the Sponsor's standard Periodic Adverse Event Reports (PADERS).*

2. *If new clinical studies are conducted with QST, then CSS recommends evaluation of dependence and withdrawal at the end of the trial(s). In order to evaluate potential dependence and withdrawal after discontinuation of therapeutic doses of testosterone, it is recommended that all AEs be collected for at least 4 weeks from drug discontinuation, at weekly intervals. Additionally, we recommend that appropriate depression, suicidality, and insomnia scales be administered (see below).*

3. *CSS recommends addressing the need for studying the signs and symptoms following discontinuation of testosterone containing product, and we suggest including the following language for sponsors at the time of future Pre-IND or IND submissions:*

    - *A testosterone withdrawal syndrome may last for weeks or months and include the following withdrawal symptoms and signs: depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism. Although a testosterone withdrawal syndrome is known to occur after prolonged use of supra-therapeutic doses of testosterone, withdrawal adverse events after discontinuation of therapeutic doses of testosterone in hypogonadal men have not been evaluated.*
    - *In order to evaluate potential dependence and withdrawal after abrupt discontinuation of therapeutic doses of testosterone, it is recommended that all emerging AEs be collected for at least 4 weeks from drug discontinuation at weekly intervals and that depression, suicidality, and insomnia scales be administered (see below).*
        - *Columbia-Suicide Severity Rating Scale (C-SSRS)*
        - *Depression Scales (any of those listed below):*
            - *Hamilton Depression Rating Scale (HDRS)*
            - *Montgomery-Asberg Depression Rating Scale (MADRS)*
            - *Beck Depression Inventory*
            - *Hospital Anxiety and Depression Scale (HADS)*
        - *Insomnia Scales (any of those listed below):*
            - *Pittsburgh Sleep Quality Index (PSQI)*
            - *Leeds Sleep Evaluation Questionnaire (LSEQ)*
            - *Epworth Sleepiness Scale (ESS)*

4. *We have the following recommendations for the label changes for all testosterone drugs. Data generated by OSE-DPV and reviewed by CSS indicates there may be a causal relationship of testosterone treatment with: 1) suicidality, especially in patients with pre- existing depression; 2) resolution of suicidality upon testosterone discontinuation; and 3) emergence of withdrawal syndrome with the key adverse events of suicidality and depression. Because of importance of this major safety issue CSS would recommend that OSE-DPV proceeds with the full analysis of the data presented in the OSE-DPV review (Aug 30 2017). CSS recommends the following changes to testosterone product labeling:*

    - *Add "suicidality" as an adverse events, and possibly consider a Black Box Warning based on the outcome of further OSE review of the data*
    - *Add "suicidality and depression" as withdrawal adverse events in the section 9.3 Dependence (suggested language): After the discontinuation of treatment with testosterone emergence of suicidality and depression were observed.*

CDTL Comments: The Xyosted review team agreed with some of the CSS conclusions and recommendations and implemented many of their labeling recommendations. However, we did not agree with all of the CSS conclusions and not all of the CSS labeling recommendation were

implemented. For example, we did agree that the available evidence for Xyosted demonstrated unexpected or excessive serum testosterone concentrations. A multi-disciplinary FDA review team concluded that Xyosted achieved the primary efficacy and secondary safety TT concentration endpoints in Study QST 13-003.

Further, the amount of missing or unreturned drug product during the Xyosted clinical trials was not particularly notable for this NDA, in our opinion. Therefore, we did not view the information in the NDA as demonstrating evidence of misuse or abuse of Xyosted.

In addition, based on the limited available evidence and confounding factors, we did not agree with the CSS conclusion that TRT products, including Xyosted, has been shown to cause suicidal behavior or suicidal ideation in hypogonadal men taking TRT.

Since no additional clinical studies of Xyosted were planned, the CSS recommendations for monitoring in future clinical studies could not be implemented.

Finally, I advise that the CSS recommendations for class-related labeling and safety monitoring regarding use, abuse and withdrawal should be brought to the attention of our Safety Team in DBRUP for their follow-up management for the product as part of a class.

12. Labeling

For each of the major clinical safety risks (risks of increased BP, depression/suicide and increased hematocrit/polycythemia), this section provides key elements of the new Boxed Warning, new Contraindication, new Warnings & Precautions, new Adverse Reactions subsections, related parts of the Patient Counseling section, and related parts of the Medication Guide are described briefly here. These are not verbatim labeling texts. For verbatim text, the reader is referred to the final agreed-upon Xyosted product labeling.

Labeling for Risk of Increased BP

Boxed Warning

- XYOSTED can increase blood pressure (BP)
- Increased BP can increase the risk of having a major adverse cardiovascular event (MACE), including myocardial infarction, stroke and cardiac death, especially in men with a history of, or risk factors for, cardiovascular disease.
- Practitioners need to monitor for and treat new-onset hypertension as well as exacerbations of pre-existing hypertension while patients are on XYOSTED.
- Due to the risk of increased BP that can increase the risk of MACE, XYOSTED should not be used to treat men with low testosterone due to a condition that is not associated with a structural or genetic disorder.

Contraindications

Due to the risk of increased BP that can increase the risk of MACE, do not use XYOSTED for the treatment of men with low testosterone due to a condition that is not associated with a structural or genetic disorder. The Indications section of labeling provides examples of conditions that cause low testosterone and are associated with structural and genetic disorders.

Warnings & Precautions (as first Warning)

- In clinical trials, XYOSTED was shown to increase systolic BP in the first 12 weeks of treatment on average by 4 mmHg. Such an increase in BP can increase the risk of MACE, especially in patients with established cardiovascular disease or risk factors for cardiovascular disease.
- In a 1-year study of Xyosted, of 150 patients, 15 (10%) were started on antihypertensive medications or required changes to their antihypertensive medication regimen.
- Prescribers should be counseled to check BP as early as 6 weeks of initiating Xyosted and periodically thereafter and treat new-onset hypertension and exacerbations of pre-existing hypertension.
- Very small increases in blood pressure may not be detected but still can increase the risk of MACE.

Adverse Reactions

Adverse Reactions includes a subsection that provides additional summary details concerning Xyosted-related increases in BP.

Patient Counseling Information

Patient Counseling informs prescribers to inform patients about the Xyosted-related risk of increased BP that can increase the risk of MACE, as well as to have their blood pressure monitored while on Xyosted.

Medication Guide

The Medication Guide summarizes the key information concerning the risk of increased BP and conveys important recommendations to patients, as follows:

- Xyosted can increase your BP which could increase your risk of heart attack, stroke, or cardiac death
- Inform your Healthcare Providers if you have hypertension
- If your BP increases while you are on Xyosted, antihypertensive medications may need to be started, or if you are already taking antihypertensive medications, new antihypertensive medications may need to be added or the dosages of your current antihypertensive medications may need to be adjusted to control your BP
- Take your antihypertensive medications as instructed
- If your BP cannot be adequately managed, Xyosted may need to be discontinued

Labeling for Depression and Suicide

Warnings & Precautions

Despite insufficient evidence to conclude a causal relationship to Xyosted, a Warning & Precaution was added (as the final W&P) to describe the two cases of depression and two cases of suicide (one completed) that were reported during the Xyosted clinical studies. In addition, patients on Xyosted should report changes in mood to their health care providers.

Adverse Reactions

The Adverse Reactions section includes a Depression/Suicide subsection that provides additional summary details concerning the 2 cases of depression and 2 cases of suicide (one completed) in patients who were on Xyosted in clinical studies.

Additional labeling, including information to patients in Patient Counseling and the Medication Guide informs patients about possible changes in mood, including depressed mood and suicidal ideation, while on TRT, including Xyosted.

Labeling for Increased Hematocrit/Polycythemia

Warnings & Precautions

A Warning & Precaution was added (as the second W&P) to describe the observed increases in hematocrit and cases of polycythemia that were reported as adverse events in the clinical studies of Xyosted. The recommended frequency for monitoring for these events is provided in the Warning. Prescribers are reminded to monitor hematocrit approximately every 3 months in patients on Xyosted.

Adverse Reactions

In addition to two tables showing the types and frequencies of adverse reactions related to erythropoiesis reported in the two phase 3 clinical studies of Xyosted (showing data for each study separately), the Adverse Reactions section includes a subsection that provides additional summary details concerning the adverse events of increased hematocrit and polycythemia in the clinical studies.

Additional labeling, including information to patients in Patient Counseling Information and the Medication Guide informs patients about possible increases in hematocrit, the risks associated with these increases, and the need to monitor hematocrit and either temporarily or permanently discontinue Xyosted due to increases hematocrit.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend Approval for this application.

In the prior review cycle, a Complete Response (CR) action was recommend based on the Clinical safety deficiencies. However, since that time, the Sponsor has agreed to substantive labeling revisions for the product that have addressed the major Clinical safety issues, including agreeing to a robust new Boxed Warning, a new Contraindication, descriptions of the major clinical safety issues in various sections of the PI, and a comprehensive Medication Guide. The Sponsor has also agreed to conduct a PMR study that will assess patients' comprehension of the key increased BP risk message in the Med Guide; and to perform post marketing pharmacovigilance with special reporting requirements for cases of depression and suicide.

These changes address the clinical safety deficiencies identified in the original submission. For more detail, the reader is referred to the Section 12 of this memo - Labeling.

There are no unresolved issues from any other review discipline or other Division.

Xyosted is now considered safe and effective as labeled; and the risk/ benefit ratio for Xyosted for TRT in men with hypogonadism is deemed acceptable for NDA approval.

13.2 Risk Benefit Assessment

In my opinion, the risk/benefit assessment for Xyosted for testosterone replacement therapy in hypogonadal men is acceptable; and Xyosted is safe and effective as labeled, for the following reasons:

Efficacy: The efficacy data from the Phase 3 pivotal Study QST-13-003, along with supporting data from the Phase 3 Study QST-15-005, confirms the Sponsor's contention that Xyosted provides testosterone replacement in adult men with hypogonadism.

Safety: The safety profile for Xyosted is largely consistent with the known safety profile for TRT, as demonstrated by the data submitted in the original NDA, with three issues of note for Xyosted. These three issues, while notable for the product, are now considered to be resolved from the clinical regulatory perspective:

1. Identification of the potential for Xyosted to raise average systolic blood pressure (SBP) by approximately 4 mm Hg, a clinically meaningful amount. Specifically, ABPM measurements in Study QST-15-005 showed that treatment with Xyosted was associated with mean systolic/diastolic BP increases of 4/2 mm Hg. Cuff BP measurements in Study QST-13-003 showed a similar mean increase in SBP.

   The Sponsor agrees to resolve this deficiency through substantive labeling revisions as well as a post marketing requirement (PMR) study to assess patients' comprehension of the key increased BP risk message in the Medication Guide. The labeling for this issue will include the following elements:

   a. A new Boxed Warning
   b. A new Contraindications that limits use of Xyosted to the indicated patient population
   c. A comprehensive Medication Guide
   d. A Post marketing requirement (PMR) to assess patients' comprehension of the Med Guide

2. Reporting of two cases of suicide attempt (including one completed suicide) and two cases of severe depression in a rather small safety database. The Sponsor proposes substantive labeling revisions, including a new Warning for depression and suicide that will describe these 4 cases, including the attempted and completed suicides. The Sponsor also agrees to provide quarterly Periodic Adverse Event Reports (PADERs) for the first three years of marketing that will contain a section dedicated to this key safety issue. The Sponsor will propose changes to the Xyosted labeling, if needed, based on their findings for this issue. It should be noted that while the labeling describes the cases and contains a new Warning, the available data does not support that this product has an increased risk for depression and

suicide as compared to other TRT products.

3. Reporting of relatively high rates of erythropoietic adverse events (AEs), such as increased hematocrit and polycythemia, in the phase 3 studies. The Sponsor agrees to substantive labeling revisions to reflect these findings and the labeling will recommend monitoring of hematocrit approximately every 3 months while on patients are on Xyosted, which resolves this deficiency.

In the prior review cycle, the Clinical review team had recommended a Complete Response (CR) action based on the Clinical safety deficiencies provided above. However, the Sponsor now agrees to substantive labeling revisions including changes to the Boxed Warning, a new Contraindication, and a comprehensive Medication Guide, as well as to a PMR study that will assess patients' comprehension of the key increased BP risk message in the Med Guide. The sponsor also agrees to pharmacovigilance with special reporting requirements for cases of depression and suicide. These changes address the clinical safety deficiencies identified in the original submission. Given these changes, I find that Xyosted is safe and effective as labeled, and that the risk/ benefit ratio for Xyosted for TRT in men with hypogonadism is acceptable for NDA approval.

13.2 Recommendation for Postmarketing Risk Management Activities

The Sponsor agreed to provide periodic and cumulative summaries and analyses of all reports of depression and suicidality-type events since approval of Xyosted as part of the quarterly Periodic Adverse Drug Event Report (PADER) for the first three years of marketing of Xyosted. The Sponsor will evaluate the quarterly report information to determine whether labeling revisions are needed for this issue.

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

The Sponsor agreed to conduct a required postmarketing study that will assess patients' comprehension of the key increased BP-related risk information in the Medication Guide. We requested, and the Sponsor agreed to the following:

> "*Conduct an appropriately designed label comprehension study to assess patients' understanding of key risk messages in the Medication Guide for Xyosted. The primary objective of this study is to assess patient comprehension of materials related to increases in blood pressure and potential associated increased risk of major adverse cardiovascular events with Xyosted. The study population should 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 results of this study may result in revisions to the Medication Guide to optimize patient's understanding of important risks of Xyosted.*"

13.5 Recommended Additional Comments to Applicant

There are no Additional Clinical Comments to the Applicant at this time.

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/

MARK S HIRSCH
09/28/2018

HYLTON V JOFFE
09/28/2018
I concur. This document serves as the division's decisional memorandum on the application.