CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 209863	Submission Dates: 3/29/2018 and 4/16/2018
Proposed Brand Name	XYOSTED
Generic Name	Testosterone enanthate (TE)
Clinical Pharmacology Primary Reviewer	Chongwoo Yu, PhD
Clinical Pharmacology Secondary Reviewer	Doanh Tran, PhD
OCP Division	Division of Clinical Pharmacology 3 (DCP3)
OND Division	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Applicant	Antares Pharma Inc.
Submission Type	Resubmission / 505(b)(2)
Relevant IND	IND 116022
Formulation, Strength, and Dosing Regimen	Subcutaneous (SC) injection. The starting dose is 75 mg administered SC into the abdomen once a week (QW). The dose can be adjusted based upon total testosterone (T) trough concentrations (C_{trough}) that are obtained following 6 weeks of treatment as below: • Decrease dose to 50 mg if T $C_{trough} \geq 650$ ng/dL • Increase dose to 100 mg if T $C_{trough} < 350$ ng/dL • Maintain dose at current dose if T $C_{trough} \geq 350$ ng/dL and < 650 ng/dL
Indication	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous T

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1 EXECUTIVE SUMMARY

Antares Pharma Inc. submitted 505(b)(2) New Drug Application (NDA) 209863 for testosterone enanthate (TE) subcutaneous (SC) injection (XYOSTED) on December 20, 2016 to seek an approval of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (T). This NDA also relied on prior findings of nonclinical safety from literature.

XYOSTED is supplied as an auto-injector device intended for SC injection of 50 mg/0.5 mL, 75 mg/0.5 mL, or 100 mg/0.5 mL TE into the abdomen. XYOSTED contains a sterile, nonpyrogenic clear colorless to yellow solution to yield a final delivered TE dose of 50 mg, 75 mg, or 100 mg. The starting dose is 75 mg TE once a week. The dose can be adjusted based upon total T trough concentrations (C_{trough}) that are obtained following 6 weeks of treatment as below:

- Decrease dose to 50 mg if total T $C_{trough} \geq 650$ ng/dL
- Increase dose to 100 mg if total T $C_{trough} < 350$ ng/dL
- Maintain dose at current dose if total T $C_{trough} \geq 350$ ng/dL and < 650 ng/dL

The Division took a Complete Response (CR) action on October 20, 2017. There were no Clinical Pharmacology related deficiencies found for the original NDA. Reference is made to Dr. Chongwoo Yu's Clinical Pharmacology review for NDA 209863 dated September 25, 2017 and the Division's CR letter dated October 20, 2017 under NDA 209863 in DARRTS.

The Applicant submitted a resubmission for this NDA on March 29, 2018 and April 16, 2018. Applicant proposes a Boxed Warning to maximize risk communication for blood pressure elevation, as well other changes to labeling that were discussed in its briefing book and meeting presentation of the February 21, 2018, Type A, post-action meeting. The Applicant also proposes a risk evaluation and mitigation strategy (REMS) consisting of Medication Guide and Communication Plan (i.e., health care provider [HCP] Letter, HCP email, Professional Society Letter, Professional Society email, Website). The Applicant considers its proposed strategies as the appropriate method to communicate the risk of blood pressure elevations with XYOSTED. The Applicant has also concluded that Boxed Warning and REMS consisting of Medication Guide and Communication Plan provide adequate risk mitigation for an appropriate benefit-risk balance, and has therefore considers them as Complete Response to the October 20, 2017 CR letter.

In addition, per the Division's request, the Applicant submitted additional information to address the potential cross-reactivity of TE with T immunoassays.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) reviewed the resubmission for NDA 209863 submitted on March 29, 2018 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.

1.2 Post-marketing Requirements or Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Type A, Post-Action Meeting Discussion and Information Request (IR)

As a part of discussion at the February 21, 2018, Type A, post-action Meeting the Division conveyed the following IR to the Applicant:

"Provide information to address the potential of cross reactivity of testosterone enanthate (TE) present in patients treated with TE injection and immunoassays commonly used to measure T concentration in clinical practice. Provide rationale on whether the cross reactivity (if any) would impact the safe and effective use of TE injection."

In addition, the Division requested that the Applicant provide a correlation analysis (including graphs) at individual sample level of samples analyzed using different assays (e.g., liquid chromatography-tandem mass spectrometry [LC-MS/MS] and immunoassay).

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.

Dosing of XYOSTED in QST-13-003 and QST-15-005 was managed with Roche immunoassay reagents on the electrochemiluminescent immunoassay platform Elecsys-El 70. Cross reactivity to TE of the Roche electrochemiluminesce system (ECLIA) was not quantified by the manufacturer, but cross-reactivity to a similar ester, testosterone propionate (TP) was less than or equal to 2.56% (510(k) Number: k093421). The Roche ECLIA was used to manage all dose selection during the clinical trial program, and the studies met their C_{avg} and C_{max} endpoints as determined by LC-MS/MS. Further, in study QST-15-005, trough T was quantified both by LC-MS/MS as well as ECLIA. Following trough monitoring and dose adjustment at Week 6, the percentage of patients in the trough concentration range of 350-650 ng/dL (the prescribed range for XYOSTED) as determined by ECLIA was 82.4% at Week 12 (Table 14.2.1.1). This agreed precisely with the determination of 82.4% by LC-MS/MS (Table 14.2.2.1).

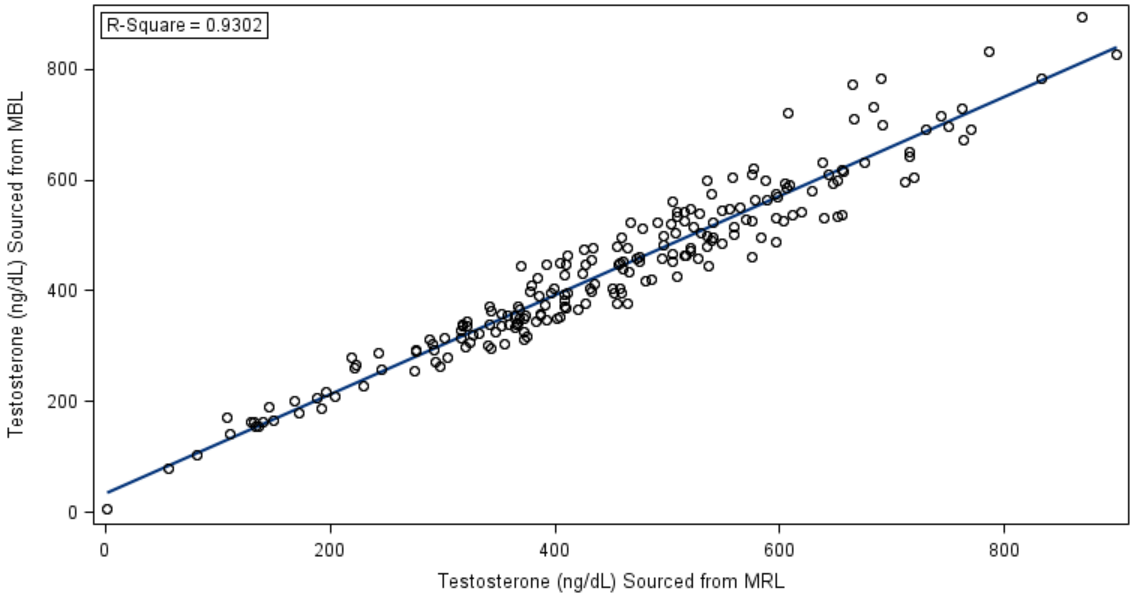
Information about T ester cross-reactivity is available from some manufacturers. The Diasorin Liason 510(k) number K122793 indicates < 7.48% cross reactivity with TP. Siemens Dimension Vista LOCI Total T Flex reagent cartridge for the Dimension Vista System 510(k) number K151529 indicates 0% cross-reactivity with TP. The BioMerieux VIDAS T II is indicated to have cross-reactivity to TP of less than or equal to 5.82% (Cosin, et al. IFCC Worldlab 2014 poster 1092).

The Sponsor has concluded that T concentration measurements using all of these platforms will yield accurate results that will be clinically useful. It is the Sponsor's plan to include the above justification and assessment in our re-submission to address the Agency's response."

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.*

In addition, based on the Applicant's submitted data, there appears to be a high correlation (R^2 = 93-97%) and the slope is close to unity for total T concentrations obtained between LC-MS/MS and ECLIA for individual patients across different time points and different studies (Figure 1 and data for individual studies QST-13-003 and QST-15-005 [not shown]). Therefore, it appears that the use of an immunoassay will not affect the effective use of TE.

Figure 1: Correlation of Trough Total T Concentration for Safety Population (Studies QST-13-003 and QST-15-005)



x-axis: T concentration obtained using ECLIA (b) (4)
y-axis: T concentration obtained using LC-MS/MS (b) (4)

Inter-Center Consult to the Center for Devices and Radiological Health (CDRH)

On May 9, 2018, the Clinical Pharmacology review team sent the following consult questions to CDRH and received the responses below on August 4, 2018:

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. The following table summarizes the data:*

Assay	510(k) Number	Highest TP conc tested	% Cross-reactivity*
Siemens ADVIA Centaur Testosterone II	k151986	10,000 ng/mL	2.94%
Siemens Dimension Vista LOCI Total Testosterone	k151529	100 ng/mL	0.00%
Abbott ARCHITECT 2nd Generation Testosterone	k120009	100 ng/mL	<10%
Diasorin LIASON Testosterone	k122793	50 ng/mL	7.48%
Roche Elecsys® Testosterone II Immunoassay	k093421	100 ng/mL	2.46%

* % Cross-reactivity = 100 x ((measured value – true value)/concentration of cross-reactant).

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, 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.*

In its consult review, CDRH recommended the Applicant to design a robust study and provide data demonstrating the rate of TE cross-reactivity with commonly-used immunoassays. The CDRH reviewer noted that the Applicant may find the *Clinical Laboratory Standards Institute's document EP07-A2 Interference Testing in Clinical Chemistry*, helpful in designing and evaluating TE potential cross-reactivity.

Reference is made to Dr. Marianela Perez-Torres's inter-center consult review dated August 4, 2018 in DARRTS for more detailed information.

Reviewer's Comments: *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.*

Conclusion & Recommendation

Based on the following reasons, this reviewer concludes that potential of TE cross-reaction with T immunoassays will not affect the safe and effective use of XYOSTED and no further information is needed for approval of this NDA.

1. The mean TE/T ratio is approximately 20% and even with an unlikely 100% cross-reactivity the overestimation of T concentrations it will not be a safety concern as it will reduce the dose based on the titration scheme in place.

2. It was confirmed that TP had a less than 10% cross-reactivity with 5 FDA-cleared T immunoassays. Considering that TE has longer side chain compared to TP, it is unlikely that a higher than 10% cross-reactivity would be expected.

3. The correlation analysis between T concentrations obtained using a LC-MS/MS method developed [redacted] (b) (4) and a ELICA which employed the Roche E-170 Modular analyzer revealed a high correlation (R^2 = 93-97%) and the slope is close to unity for total T trough concentrations obtained in human serum for individual patients across different time points and different studies (i.e., Studies QST-13-003 and QST-15-005). The trough T concentrations obtained at Week 12 from both studies using the LC-MS/MS method and the ELICA method were 132-900 ng/dL and 186-894 ng/dL, respectively. It should be noted that these concentrations cover the intended therapeutic T concentration range and the high correlation between the two methods indicate that at least the Roche ELICA (which was used in these Phase 3 studies) did not show a significant cross-reactivity to be concerned about the reliability of data obtained via immunoassays.

2 PROPOSED PRODUCT LABEL

The following Clinical Pharmacology related parts of the Applicant's proposed label were submitted in this NDA. The double underlined text is recommended to be inserted and the strikethrough text is recommended to be deleted by the Clinical Pharmacology review team upon completion of reviewing the Applicant's proposed product label.

It should be noted that the Applicant's proposed labeling language is acceptable for all other sections not listed below from the Clinical Pharmacology standpoint. Please note that Sections illustrated below does not necessarily reflect the entire corresponding Section of the product label.

Highlights

----------DOSAGE AND ADMINISTRATION----------

- **Prior to initiating XYOSTED**: Ceonfirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2.1).
- **Starting dose:** (b) (4) (2.2, 2.3).
- **Dose Adjustment:** (b) (4)
- (b) (4)

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION

2.1 Confirmation of Hypogonadism Before Initiation of XYOSTED

Prior to initiating XYOSTED, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

2.2 Starting Dose and Dose Adjustment

The starting dose of XYOSTED is 75 mg (b) (4) administered subcutaneously into the abdomen once a week.

Dose adjustment

(b) (4)

(b) (4)

The trough testosterone concentration should then be checked periodically thereafter.

2.3 (b) (4)

(b) (4)

Instruct patients on the proper use of the XYOSTED injection autoinjector and direct them to use the proper injection site. Refer to Instruction for USE for proper use of XYOSTED.

Visually inspect XYOSTED for particulate matter and discoloration prior to administration. Do not use XYOSTED if the seal is broken.

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with corticosteroids may result in increased fluid retention and requires careful monitoring, particularly in patients with cardiac, renal or hepatic disease.

7.4 Medications that May Also Increase Blood Pressure

Some prescription medications and (b) (4) analgesic and cold medications contain drugs known to increase blood pressure. Concomitant administration with XYOSTED may lead to additional increase in blood pressure *[see Warnings and Precautions (5.5)]*.

Reviewer's Comment: *Section 7.4 is newly proposed by the Applicant.*

(b) (4)

Reviewer's Comment: *Recommend deleting Section* (b) (4) *to be consistent with the current practice* (b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2. Pharmacodynamics

No specific pharmacodynamic studies were conducted using XYOSTED.

12.3 Pharmacokinetics

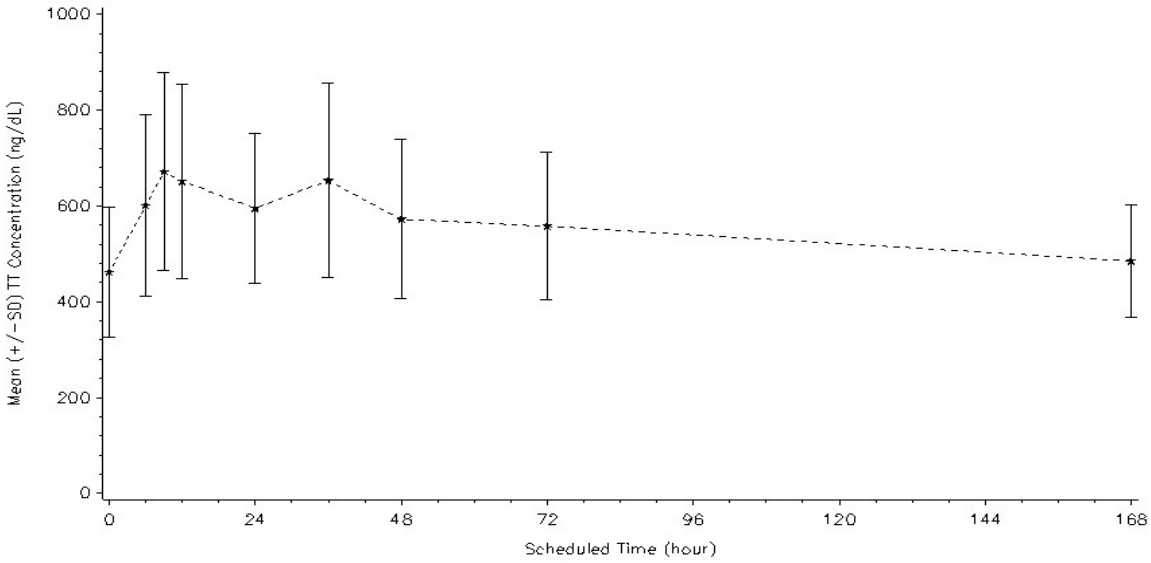
Absorption and Bioavailability

XYOSTED delivers physiologic amounts of testosterone, producing circulation testosterone concentrations that approximate normal concentrations (300-1,100 ng/dL) seen in healthy men.

Following weekly subcutaneous injection of XYOSTED for 12 weeks, serum testosterone concentrations reach a maximum after a median of 11.9 hours (range: 5.8-168.7 hours) then slowly decline (see figure 1). The starting dose of XYOSTED was 75 mg weekly. XYOSTED dose was adjusted based upon total testosterone trough concentrations that were obtained following 6 weeks of dosing *[See Dosage and Administration (2.2)]*. Steady state serum testosterone concentration was achieved by Week 6.

(b) (4)

Figure 1. Mean (±SD) of Total Testosterone (TT) Concentration (ng/dL) Following Weekly Administration of XYOSTED for 12 Weeks (N=137)



(b) (4)

Reviewer's Comment: *The following information regarding the achievement of steady state is already stated above: "Steady state serum testosterone concentration was achieved by Week 6."* (b) (4)

At Week 12, blood samples for pharmacokinetic (PK) analysis were obtained from all patients before and at specified times up to 168 hours after (b) (4) XYOSTED administration. (b) (4) (Table 2)

Table 2. Arithmetic Mean (SD) and Range Total Testosterone Pharmacokinetic Parameters Following Administration of 50 mg, 75 mg, or 100 mg XYOSTED at Week 12 of Weekly Treatment (N=137)

	$C_{avg.0\text{-}168\ hr}$ (ng/dL)	C_{max} (ng/dL)	T_{max} (hr)[a]	C_{min} (ng/dL)	AUC (0-168 hr) (ng·hr/dL)
Mean (SD)	553 (127)	790 (215)	~~23(24)~~11.9	436 (109)	92,955 (21,385)
Min - Max	276 – 1,036	389 - 1,410	6 - 168	166 - 788	46,432 - 173,987

[a] Reported in median

Distribution
Circulating testosterone is primarily bound in serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free), and the rest is loosely bound to albumin and other proteins.

Elimination
Metabolism
Testosterone enanthate is metabolized to testosterone via ester cleavage of the enanthate group. The mean (SD) maximum concentration of testosterone enanthate was 169.2 (67.8) ng/dL at Week 12 following weekly administration of XYOSTED.

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT). At pre-dose of Week 12 treatment, the mean DHT/testosterone ratio was 0.07 which was within the normal range.

Excretion
About 90% of a testosterone dose given intramuscularly is excreted in the urine as glucuronic and sulfuric acid-conjugates of testosterone or as metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

14 CLINICAL STUDIES
XYOSTED was evaluated in a 52-week (b) (4)

Patients were trained on proper use of the device to self-administer the initial dose of 75 mg (b) (4) on the same day of the week and at approximately the same time (7:00 am ±2 hours). (b) (4)

(b) (4)

Reviewer's Comment: *Table 3 was deleted as it was redundant information with Table 2 in Section 12.3.*

(b) (4)

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

/s/

CHONGWOO YU
08/24/2018

DOANH C TRAN
08/24/2018

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 209863	Submission Dates: 12/20/2016, 4/7/2017, 6/19/2017, 7/20/2017, and 8/31/2017
Proposed Brand Name	XYOSTED
Generic Name	Testosterone enanthate (TE)
Clinical Pharmacology Primary Reviewer	Chongwoo Yu, PhD
Clinical Pharmacology Secondary Reviewer	Doanh Tran, PhD
OCP Division	Division of Clinical Pharmacology 3 (DCP3)
OND Division	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor	Antares Pharma Inc.
Submission Type	Original / 505(b)(2)
Relevant IND	IND 116022
Formulation, Strength, and Dosing Regimen	Subcutaneous (SC) injection. The starting dose is 75 mg administered SC into the abdomen once a week (QW). The dose can be adjusted based upon total testosterone (T) trough concentrations (C_{trough}) that are obtained following 6 weeks of treatment as below: • Decrease dose to 50 mg if T $C_{trough} \geq 650$ ng/dL • Increase dose to 100 mg if T $C_{trough} < 350$ ng/dL • Maintain dose at current dose if T $C_{trough} \geq 350$ ng/dL and < 650 ng/dL
Indication	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous T

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1 EXECUTIVE SUMMARY

Antares Pharma Inc. submitted 505(b)(2) New Drug Application (NDA) 209863 for testosterone enanthate (TE) subcutaneous (SC) injection (XYOSTED) on December 20, 2016 to seek an approval of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (T). This NDA also relies on prior findings of nonclinical safety from literature.

XYOSTED is supplied as an auto-injector device intended for SC injection of 50 mg/0.5 mL, 75 mg/0.5 mL, or 100 mg/0.5 mL TE into the abdomen. XYOSTED contains a sterile, nonpyrogenic clear colorless to yellow solution to yield a final delivered TE dose of 50 mg, 75 mg, or 100 mg. The starting dose is 75 mg TE once a week. The dose can be adjusted based upon total T trough concentrations (C_{trough}) that are obtained following 6 weeks of treatment as below:

- Decrease dose to 50 mg if total T $C_{trough} \geq 650$ ng/dL
- Increase dose to 100 mg if total T $C_{trough} < 350$ ng/dL
- Maintain dose at current dose if total T $C_{trough} \geq 350$ ng/dL and < 650 ng/dL

To support the approval of XYOSTED, the Sponsor submitted 4 Clinical Pharmacology/ Biopharmaceutics/Clinical studies which included 2 Phase 3 studies. All 4 studies used the to-be-marketed (TBM) formulation. Study QST-13-003 was the pivotal Phase 3 efficacy and safety study and included a pharmacokinetic (PK) sub-study. Study QST-15-005 was a Phase 3 safety study, including a PK sub-study, but no efficacy assessments were included. Other clinical studies included a single dose PK study (QST-14-004) in healthy males and a relative bioavailability (BA) study (QST-13-002). In addition, 7 human factor and usability studies were also submitted. As the efficacy, safety, and PK data supporting this application were mainly obtained from the pivotal Phase 3 study, QST-13-003, this review focuses on the review of Study QST-13-003. Studies QST-15-005, QST-13-002, and QST-14-004 were not reviewed in detail.

For the pivotal Phase 3 study, QST-13-003, a formal consult to the Office of Study Integrity and Surveillance (OSIS) was made on February 6, 2017 for inspections of the bioanalytical study sites. An OSIS memorandum was issued on June 19, 2017 with a recommendation to accept the bioanalytical data for further FDA review. There are no pending bioanalytical or clinical site inspection issues.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) reviewed NDA 209863 submitted on December 20, 2016, April 7, 2017, June 19, 2017, July 20, 2017, and August 31, 2017. The overall Clinical Pharmacology information submitted to support this NDA is **acceptable** and XYOSTED is **recommended for approval** from the Clinical Pharmacology standpoint.

1.2 Post-marketing Requirements or Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Overall Efficacy and Safety Conclusion

The efficacy of XYOSTED was successfully demonstrated in hypogonadal males with the TBM dosing regimen. In addition, all of the following pre-specified criteria for the key safety endpoint

(i.e., 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:

- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Less than 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- At least 85% of subjects with a serum total T $C_{max} \leq$ 1,500 ng/dL

Primary Efficacy Endpoint Analysis

The Sponsor conducted a pivotal Phase 3 study, QST-13-003 to demonstrate the clinical efficacy and safety of XYOSTED. Study QST-13-003 was a multiple-dose, 52-week study conducted in 150 hypogonadal males to evaluate the efficacy and safety of XYOSTED administered SC once each week. The study included a screening phase, a 12-week treatment with titration phase, and an extended treatment phase for evaluation of long-term safety.

Participants who met all eligibility criteria were assigned to receive XYOSTED 75 mg weekly as the starting dose. XYOSTED was self-administered once each week on the same day of the week and at approximately the same time (7:00 am $\pm$ 2 hours). Adjustments to dose may have been made at Week 7 based upon the Week 6 serum total T concentration at the end of the dosing interval (C_{trough}) value.

The primary **efficacy analysis showed a responder rate of 90.0%** (135 responders out 150 subjects; 95% confidence interval (CI): 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 300-1,100 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 to be ≥ 65%.

Key Safety Endpoint Analysis

Table 1 presents the number and percentage of subjects in the safety population with a serum total T C_{max} in each range at Week 12.

Table 1: Number (Percentage) of Subjects by Serum Total T C_{max} in Selected Ranges at Week 12 of the Safety Population (Study QST-13-003; N=150)

Ranges	Number of Subjects
Total number of participants	150
C_{max} < 1,500 ng/dL	137 (91.3)
1,500 ng/dL ≤ C_{max} ≤ 1,800 ng/dL	0 (0)
1,800 ng/dL < C_{max} ≤ 2,500 ng/dL	0 (0)
C_{max} > 2,500 ng/dL	0 (0)

Week 12 Completers = 137 subjects

As shown in Table 1, all of the following criteria for the key safety endpoint, total T C_{max} at Week 12 were met in the pivotal Phase 3 study, QST-13-003:

- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Less than 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- At least 85% of subjects with a serum total T $C_{max} \leq$ 1,500 ng/dL

Formulation

XYOSTED is a SC drug/medical device combination product. Each single-use prefilled XYOSTED auto-injector contains sterile, preservative-free TE in nonpyrogenic clear colorless to yellow solution for SC administration of a fixed volume of 0.5 mL yielding final delivered doses of 50 mg, 75 mg, or 100 mg TE. TE is contained within a single-dose syringe with a 27-gauge, ½-inch needle with a soft needle shield within an auto-injector, which is equipped with a needle safety guard and safety cap. Each XYOSTED device provided a single dose as a single injection.

Dose Titration Scheme

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.

Absorption

Table 2 summarizes the arithmetic mean (SD) steady state PK parameters of serum total T at Week 12 obtained from the pivotal Phase 3 study, QST-13-003. It should be noted that the starting dose of XYOSTED was 75 mg TE weekly and the dose of XYOSTED was titrated at Week 7 based on the total T $C_{trough\ 168h}$ at Week 6. All subjects were on their current dose at Week 12 since Week 7 or earlier. Steady state for total T was reached before or by Week 6.

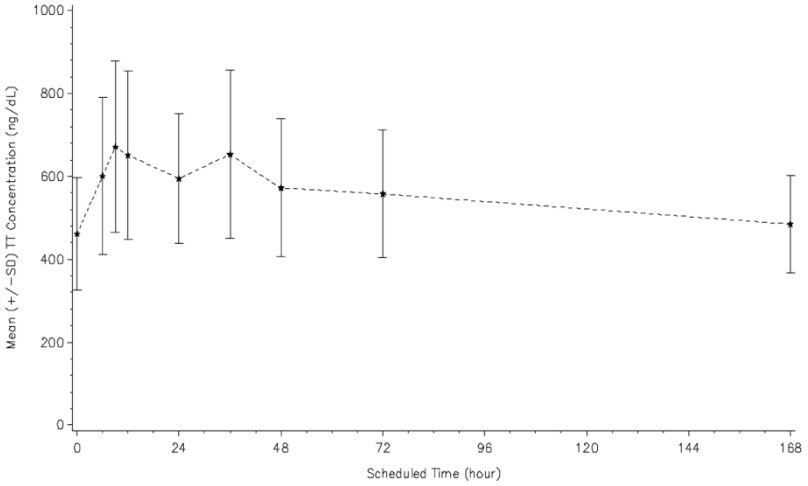
Table 2: Arithmetic Mean (SD) Total T PK Parameters at Week 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (Study QST-13-003)

TE Dose (mg)	N	$C_{avg\ 168h}$ (ng/dL)	C_{max} (ng/dL)	T_{max} (hr)[a]	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)

[a] Reported in median (range)

Figure 1 presents mean (±SD) total T PK concentrations at Week 12.

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 TE (Study QST-13-003; N=137)



Distribution, Metabolism, and Excretion

Specific studies describing the distribution, metabolism, or excretion of T absorbed from XYOSTED have not been conducted.

Distribution: Circulating T is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of T in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

Metabolism: TE is metabolized to T via ester cleavage of the enanthate group. The mean (SD) maximum concentration of TE was 169.2 (67.8) ng/dL at Week 12 following weekly administration of XYOSTED.

T is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of T are 17β-estradiol (E2) and dihydrotestosterone (DHT). At pre-dose of Week 12 treatment, the mean DHT/T ratio was 0.07 which was within the normal range.

Excretion: About 90% of a dose of T given IM is excreted in the urine as glucuronic and sulfuric acid conjugates of T and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of T occurs primarily in the liver.

Reviewer's Comment: *This information listed under Excretion comes from the Delatestryl® (NDA 009165; approved on December 23, 1953) product label and is listed in the product labels of other T replacement therapy as a class labeling language.*

Drug-Drug Interaction (DDI)
No DDI studies were conducted with XYOSTED. The following information is available in the labeling of other T replacement therapy drugs:

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication. Changes in anticoagulant activity may be seen with androgens. Therefore, more frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy. The concurrent use of T with corticosteroids may result in increased fluid retention and requires monitoring particularly in patients with cardiac, renal, or hepatic disease.

Use in Specific Populations
Geriatric Use: There have not been sufficient numbers of geriatric patients in controlled clinical studies with XYOSTED to determine whether efficacy or safety in those over 65 years of age differs from younger subjects. Of the 283 patients enrolled in the 6 month and one year efficacy and safety clinical study utilizing XYOSTED, 49 (17.0%) were over 65 years of age.

Renal or Hepatic Impaired Patients: No studies were conducted in patients with renal or hepatic impairments.

Pediatric Use: No pediatric studies were conducted with XYOSTED. The Sponsor submitted a pediatric waiver request under investigational new drug (IND) application 116022 on December 11, 2014. The Division agreed to waive all studies in all children and adolescents ages 0 to < 17 years, because these studies would be impossible or highly impractical and there are too few children with the disease/condition to study. Reference is made to the Advice letter sent to the Sponsor on February 9, 2015 (IND 116022).

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.

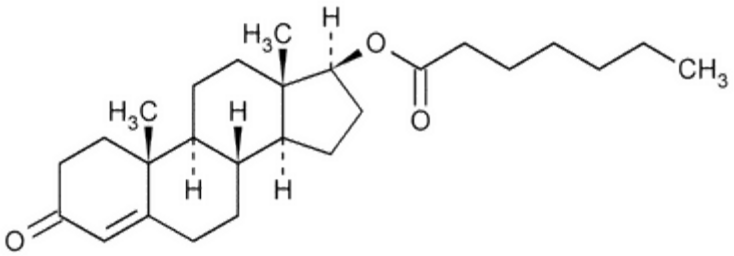
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is XYOSTED and what is its active pharmacological ingredient?

XYOSTED is a SC drug/medical device combination product. Each single-use prefilled XYOSTED auto-injector contains TE, an ester derivative of an endogenous androgen, T. TE is a white to creamy white crystalline powder described by the chemical name (17β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one. TE has the molecular formula $C_{26}H_{40}O_3$, the molecular weight 400.59, and the molecular structure the chemical formula:

Figure 2: Structural Formula of TE



XYOSTED contains TE in sterile, preservative-free, and nonpyrogenic colorless to pale yellow solution supplied in a single-dose syringe assembled in a pressure-assisted auto-injector for SC administration. Each XYOSTED auto-injector contains 50 mg, 75mg, or 100 mg of TE dissolved in 0.5mL of sesame oil providing three product strengths of 50mg/0.5mL, 75mg/0.5mL, and 100mg/0.5mL.

2.1.2 What is the regulatory history of XYOSTED?

The following meetings were held between the Division of Bone, Reproductive, and Urologic Products (DBRUP) and the Sponsor under IND 116022:

- Type B, pre-IND meeting: December 5, 2012
- Type C, guidance meeting: May 1, 2014
- Type B, pre-NDA meeting: November 2, 2016

Reference is made to the official minutes of each meeting in DARRTS for the meeting outcome.

2.1.3 What are the relevant clinical data submitted to support the approval of XYOSTED?

This NDA contains the following:

- Draft product label in physician labeling rule (PLR) format
- Information on the composition of drug products used in the clinical studies
- Full clinical study reports of 4 Clinical Pharmacology/Biopharmaceutical/Clinical studies
- Bioanalytical study reports and method validation reports
- Request of waiver for pediatric studies (copy of the initial pediatric study plan [iPSP] Agreement letter)

To support the approval of XYOSTED, the Sponsor submitted 4 Clinical Pharmacology/ Biopharmaceutics/Clinical studies, which included two Phase 3 studies. All 4 studies used the TBM formulation. Study QST-13-003 was the pivotal Phase 3 efficacy and safety study, and included a PK sub-study. Study QST-15-005 was a Phase 3 safety study, including a PK sub-study, but no efficacy assessments were included. Other clinical studies included a single dose PK study (QST-14-004) in healthy males and a relative BA study (QST-13-002). In addition, 7 human factor and usability studies were also submitted.

The Clinical Pharmacology/Biopharmaceutics/Clinical studies submitted to this NDA are summarized in the Table 3 below.

Table 3: Summary of Clinical Pharmacology/Biopharmaceutics/Clinical Studies Submitted to NDA 209863

Study	Objective	Population	Dosing Regimen	Design
QST-13-003 TBM formulation	Pivotal Efficacy/Safety	150 hypogonadal males	Starting dose: 75 mg TE QW (XYOSTED) Dose titration up to 100 mg TE QW or down to 50 mg TE QW at Week 7 based on Week 6 total T C_{trough} as necessary	Phase 3, Open label, double blind (to dose strength), multiple dose, 52-week study (including a PK sub-study)
QST-15-005 TBM formulation	Safety	133 hypogonadal males	Starting dose: 75 mg TE QW (XYOSTED) *General study population*: Dose titration up to 100 mg TE QW or down to 50 mg TE QW at Week 7 based on Week 6 total T C_{trough} as necessary *PK sub-study population*: Dose titration allowed only after 12 weeks	Phase 3, Open label, uncontrolled, multiple dose, 26-week study (including a PK sub-study)
QST-13-002 TBM formulation	Relative BA	39 hypogonadal males	Treatment A: 100 mg TE QW for 6 weeks (XYOSTED)) Treatment B: 50 mg TE QW for 6 weeks (XYOSTED) Treatment C: Single dose of 200 mg TE (IM injection of DELATESTRYL)	Phase 2, open-label, 3-srm, randomized, multiple dose, parallel study
QST-14-004 TBM formulation	Single dose PK	12 healthy males	Treatment A: Single dose of 50 mg TE (XYOSTED) Treatment B: Two consecutive dose of 100 mg TE (XYOSTED)	Phase 1, Open label, single dose study

As the efficacy, safety, and PK data supporting this application were mainly obtained from the pivotal Phase 3 study, QST-13-003, this review focuses on the review of Study QST-13-003.

2.2 General Clinical Pharmacology

2.2.1 What is the proposed mechanism of action?

TE is metabolized to T via ester cleavage of the enanthate group. Endogenous androgens, including T and DHT are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution.

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

XYOSTED was developed with an aim to ensure that the desired serum total T concentrations (i.e., 300-1,100 ng/dL) are achieved in hypogonadal men following treatment with XYOSTED.

2.2.2 What are the proposed dosing regimen and administration instructions?

The proposed starting dose of XYOSTED is 75 mg of TE (i.e., one device) administered once a week. The dose should be adjusted based upon total T trough concentrations obtained following 6 weeks of XYOSTED treatment. See Section 2.2.6 of this review for the detailed dose titration scheme. XYOSTED should be injected into the abdomen. IM or intravascular delivery must be avoided.

2.2.3 What are the steady state PK parameters of total T following the administration of XYOSTED?

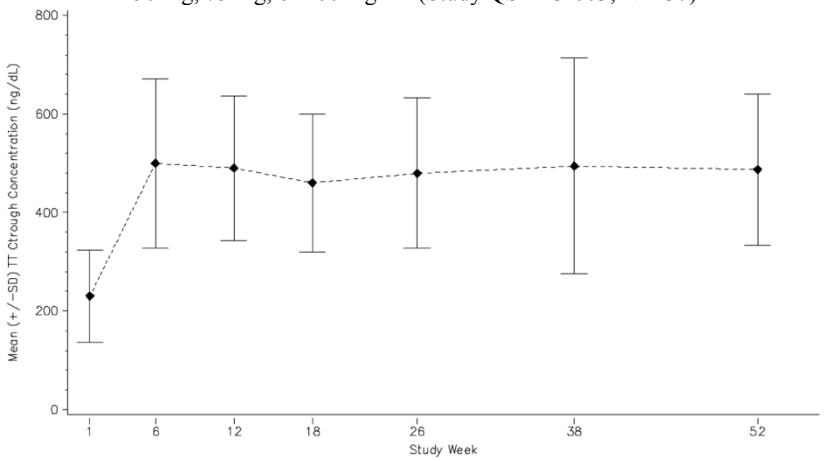
Steady state PK parameters of total T were characterized in the pivotal Phase 3 study (QST-13-003). Study QST-13-003 was a multiple-dose, 52-week study conducted in 150 hypogonadal males (i.e., 25-78 yrs. of age; body mass index [BMI] of 19.4-39.9 kg/m^2). The study included a 12-week treatment with titration phase and a total of 137 (91.3%) subjects completed the 12-week treatment with titration phase

Participants who met all eligibility criteria were assigned to receive XYOSTED 75 mg TE as the starting dose. XYOSTED 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 serum total T concentration at the end of the dosing interval (C_{trough}) value.

In Study QST-13-003, the PK Population was defined as all subjects among those participants who received at least 1 dose of XYOSTED and had at least 1 blood sample drawn post-dose for the PK analysis (142 subjects). The PK Sub-study population consisted of all patients who participated in the sub-study with at least one Week 1 blood sample drawn post-dose for the PK analysis were included in the PK Sub-study population. The PK Sub-study population consisted of 21 patients.

Figure 3 presents mean (± SD) of total T C_{trough} PK concentration by study week. The total T C_{trough} remains constant from Week 6 throughout Week 52.

Figure 3: Plot of Mean (±SD) Total T C_{trough} PK Concentration (ng/dL) Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (Study QST-13-003; N=137)



Reviewer's Comment: *The mean total T C_{trough} at Week 1 (pre-dose) was 231.6 ng/dL and the total T C_{trough} ranged between 460.3 ng/dL (Week 18) and 501.9 ng/dL (Week 6) from Week 6 through Week 52. It appears that steady state for total T was reached before or by Week 6.*

Table 4 summarizes the arithmetic mean (SD) steady state PK parameters of serum total T at Weeks 1 (single dose) and 12 (multiple dose) obtained from the pivotal Phase 3 study (QST-13-003). It should be noted that the starting dose of XYOSTED was 75 mg TE weekly and the dose of XYOSTED was titrated at Week 7 based on the total T $C_{trough\ 168h}$ at Week 6. All subjects were on their current dose at Week 12 since Week 7 or earlier.

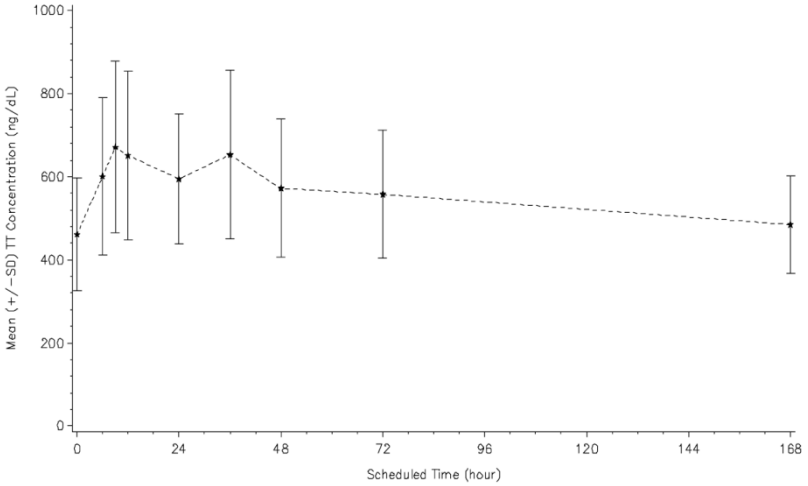
Table 4: Arithmetic Mean (SD) Total T PK Parameters at Weeks 1 and 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (Study QST-13-003)

TE Dose (mg)	N	$C_{avg\ 168h}$ (ng/dL)	C_{max} (ng/dL)	T_{max} (hr)[a]	C_{min} (ng/dL)	AUC(0-168 hr) (ng·hr/dL)
Week 1 (Single dose; PK sub-study population)						
75	21	357 (76)	487 (123)	35.0 (9.0-167.7)	235 (71)	60,028 (12,773)
Week 12 (Multiple dose; PK sub-study population)						
50	4	484 (95)	667 (210)	30.0 (9.0-72.6)	374 (125)	81,350 (15,948)
75	13	515 (98)	765 (187)	9.1 (5.9-71.8)	419 (82)	86,525 (16,420)
100	2	670 (231)	1,070 (0)	22.0 (9.0-35.0)	197 (88)	112,477 (38,846)
Week 12 (Multiple dose; PK population)						
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)

[a] Reported in median (range)

Figure 4 presents mean (±SD) total T PK concentrations at Week 12.

Figure 4: 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 TE (N=137; Study QST-13-003)



2.2.4 How was the dose of XYOSTED for the pivotal Phase 3 trial determined?

The doses selected for evaluation in the pivotal Phase 3 study (QST-13-003) were 50, 75, and 100 mg TE administered as SC injections using the XYOSTED auto-injector. Since the intended frequency of dosing was weekly, the nominal doses selected spanned a range of half the 100 mg to 200 mg doses of TE used when every other week IM dosing of TE was employed. Sponsor believed that their experience with SC TE administered via needle and syringe also supported the utility of these doses. Therefore, 100 and 50 mg dose strengths were selected for evaluation in the Phase 2 study of the PK, safety, and tolerability of XYOSTED (Study QST-13-002). Sponsor believes that results of that study showed that overall SC T was well tolerated and provided consistent measures of exposure week to week. On average, both the 100 mg and 50 mg doses

provided average total T concentrations within the normal range, but some participants receiving 50 mg TE demonstrated low concentrations just prior to their next dose, and some participants on 100 mg TE had instances of peak total T concentrations above 1,500 ng/dL. Modeling and simulation demonstrated that an intermediate dose of 75 mg TE had a projected incidence of subnormal trough concentrations of 20%, and an incidence of 0% of C_{max} values above 1,500 ng/dL. For this reason, an intermediate dose of 75 mg TE was evaluated as the starting dose in Study QST-13-003.

Reviewer's Comment: *It should be noted that the Phase 2 study, QST-13-002 was not reviewed in detail as it did not contain any critical information needed to make a regulatory decision on this NDA.*

2.2.5 How was the efficacy and safety of XYOSTED assessed and what were the results?

The Sponsor conducted a pivotal Phase 3 study (QST-13-003) to demonstrate the clinical efficacy and safety of XYOSTED. Study QST-13-003 was a multiple-dose, 52-week study conducted in 150 hypogonadal males (i.e., 25-78 yrs. of age; body mass index [BMI] of 19.4-39.9 kg/m^2) to evaluate the efficacy and safety of XYOSTED administered SC once each week. The study included a screening phase, a 12-week treatment with titration phase, and an extended treatment phase for evaluation of long-term safety. In total, 150 participants received XYOSTED. A total of 137 (91.3%) subjects completed the 12-week treatment with titration phase and 97 (64.7%) subjects completed the full study (through the Follow-up Visit).

Participants who met all eligibility criteria were assigned to receive XYOSTED 75 mg TE as the starting dose. XYOSTED was self-administered once each week on the same day of the week and at approximately the same time (7:00 am $\pm$ 2 hours). Adjustments to dose may have been made at Week 7 based upon the Week 6 serum total T concentration at the end of the dosing interval (C_{trough}) value.

Primary Efficacy Analysis

Table 5 summarizes the number of patients with Week 12 total T $C_{avg\ 168h}$ within the normal total T range (i.e., 300-1,100 ng/dL) for those subjects who received at least 1 dose of XYOSTED (i.e., Safety Population; N=150) that were used for the primary efficacy analysis. If a subject did not have a valid $C_{avg\ 168h}$, the subject was included in the analysis as not having achieved a total T $C_{avg\ 168h}$ within the pre-specified normal range of 300-1,100 ng/dL. Overall, 135 (90.0%) subjects had total T $C_{avg\ 168h}$ values within the normal total T concentration range at Week 12: 25 (100.0%) patients on the 50 mg dose, 91 (87.5%) patients on the 75 mg dose, and 19 (90.5%) patients on the 100 mg dose.

Table 5: Number (%) of Patients with Week 12 Total T $C_{avg\ 168h}$ in the Normal Total T Concentration (300-1,100 ng/dL) – Primary Efficacy Analysis (N=150)

	Dose at Week 12			Overall (N=150)
	50 mg TE (N=25)	75 mg TE (N=104)	100 mg TE (N=21)	
N (%)	25 (100)	91 (87.5)	19 (90.5)	135 (90.0)
95% CI	(86.3, 100.0)	(79.6, 93.2)	(69.6, 98.8)	(84.0, 94.3)

The primary **efficacy analysis showed a responder rate of 90.0%** (135 responders out 150 subjects; 95% CI: 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 300-1,100 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 to be ≥ 65%.

Key Safety Endpoint Analysis: Total T C_{max}

The key safety endpoint, total T C_{max}, had the following pre-specified criteria that were expected to be met at Week 12:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Having a serum total T $C_{max} \leq$ 1,500 ng/dL in at least 85% of subjects

Table 6 presents the number and percentage of subjects with a serum total T C_{max} in each range at Week 12.

Table 6: Number (Percentage) of Subjects by Serum Total T C_{max} in Selected Ranges at Week 12 (Study QST-13-003; N=150)

Ranges	Week 12
Number of subjects[a]	150
C_{max} < 1,500 ng/dL	137 (91.3)
1,500 ng/dL ≤ C_{max} ≤ 1,800 ng/dL	0 (0)
1,800 ng/dL < C_{max} ≤ 2,500 ng/dL	0 (0)
C_{max} > 2,500 ng/dL	0 (0)

Week 12 Completers = 137 subjects

[a] Subjects who received at least 1 dose of XYOSTED

As shown in Table 6, all of the key safety criteria regarding total T C_{max} at Week 12 were met in the pivotal Phase 3 study (QST-13-003).

Reviewer's Comment: *On February 8, 2017, the review team requested the Office of Scientific Investigations (OSI) for inspections on clinical study sites. As a result, 3 clinical study sites were inspected between March 13 – April 4, 2017 and the inspection report was issued on June 19, 2017. A copy of the inspection report can be found in DARRTS under NDA 209863.*

After evaluation of inspectional observations and the responses from the clinical study sites, the OSI inspector recommended that the clinical portions of the audited study be accepted for further FDA review.

DHT/T Ratio

Table 7 summarizes the DHT/T ratio (%) at Week 12 (Week 12 completers = 137 subjects).

Table 7: Summary of Week 12 Pre-dose and Week 12 DHT/T Parameter Ratios (%) (Study QST-13-003)

	Week 12 Pre-dose	AUC(0-168h)	AUC(0-∞)	$C_{avg\ 168h}$	C_{min}	C_{max}
N	139	137	14	137	137	137
Mean (SD)	7.36 (2.68)	6.54 (2.31)	10.12 (7.27)	6.54 (2.31)	6.44 (2.47)	5.72 (2.38)

Note: AUC(0-∞) was not calculated when the constant lambda was not assigned, which occurred if the terminal elimination phase was not linear, if the T_{max} was 1 of the last 3 data points, or if the regression coefficient was < 0.8.

Reviewer's Comment: *The serum DHT/T $C_{avg.168h}$ ratio for XYOSTED was approximately 0.07 and did not exceed the normal limit reported in literature (i.e., 0.05-0.33 reported by Diver et al., 2003). The mean serum DHT/T $C_{avg.168h}$ ratio of 0.07 was comparable with the reported values of 0.05-0.11 from most of the other approved T replacement products. It should be noted that Weeks 1 and 12 pre-dose DHT/T ratios were comparable (data not shown).*

2.2.6 What dose titration scheme did the Sponsor use in the pivotal Phase 3 study?

In the pivotal Phase 3 study (QST-13-003), the starting dose of XYOSTED was 75 mg TE weekly. XYOSTED was self-administered once weekly 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 serum total T C_{trough} value. 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 dose strength.

Additional adjustments to dose were also made at Weeks 13, 19, 27, and 39 as necessary.

Patients who were receiving XYOSTED 100 mg TE and required a dose increase remained on the 100 mg TE dose with no adjustment. Patients who were receiving XYOSTED 50 mg TE and required a dose reduction remained on the 50 mg dose with no adjustment unless the total T C_{trough} was ≥ 650 ng/dL; in this case, the site was instructed to discontinue the patient.

For labeling, the Sponsor is proposing to utilize the dose titration scheme used in the pivotal Phase 3 trial (Study QST-13-003).

2.3 Intrinsic Factors

2.3.1 Was there any age effect observed in the efficacy and safety of XYOSTED?

There have not been sufficient numbers of geriatric patients in controlled clinical studies with XYOSTED to determine whether efficacy or safety in those over 65 years of age differs from younger subjects. Of the 283 patients enrolled in the 6 month and one year efficacy and safety clinical study utilizing XYOSTED, 49 (17.0%) were over 65 years of age.

2.3.2 Did the Sponsor conduct any pediatric studies during the development of XYOSTED?

No pediatric studies with XYOSTED were conducted. In accordance with the Pediatric Research Equity Act (PREA) (21 USC 355c), the Sponsor submitted a request for a full waiver of pediatric studies under IND 116022 on December 11, 2014.

The Division agreed to waive all studies in all children and adolescents ages 0 to < 17 years, because these studies would be impossible or highly impractical and there are too few children with the disease/condition to study. Reference is made to the Advice letter sent to the Sponsor on February 9, 2015 (IND 116022).

The Sponsor acknowledged and agreed with the agreed iPSP included with the Agency's Advice Letter on March 20, 2015.

2.3.3 Did the Sponsor conduct PK studies in population with renal or hepatic impairment?

No. The Sponsor did not conduct any studies in patients with renal or hepatic impairments. No additional information is available in the labeling of other T replacement therapy (e.g., Testim®, AndroGel®, or Axiron®) regarding this aspect.

2.4 Extrinsic Factors

2.4.1 Did the Sponsor conduct any DDI studies?

No DDI studies were conducted with XYOSTED. The following information is available in the labeling of other T replacement therapy drugs: Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication. Changes in anticoagulant activity may be seen with androgens. Therefore, more frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy. The concurrent use of T with corticosteroids may result in increased fluid retention and requires monitoring particularly in patients with cardiac, renal, or hepatic disease.

2.5 General Biopharmaceutics

2.5.1 What is the quantitative composition of the drug products used in the clinical trials of this application?

XYOSTED is a SC drug/medical device combination product. Each single-use prefilled XYOSTED auto-injector contains sterile, preservative-free TE in nonpyrogenic clear colorless to yellow solution for SC administration of a fixed volume of 0.5 mL yielding final delivered doses of 50 mg, 75 mg, or 100 mg TE. TE is contained within a single-dose syringe with a 27-gauge, ½-inch needle with a soft needle shield within an auto-injector, which is equipped with a needle safety guard and safety cap. Each XYOSTED device provided a single dose as a single injection. The unit composition of XYOSTED is provided in Table 8.

Table 8: Unit Composition of XYOSTED

Ingredients	Quality Standard	Function of Components	Dose Strength		
			50 mg /0.5 mL	75 mg/ 0.5 mL	100 mg/ 0.5 mL
Testosterone Enanthate	USP	Active Pharmaceutical Ingredient	50 mg	75 mg	100 mg
Sesame Oil	NF	Solvent	q.s. to 0.5 mL	q.s. to 0.5 mL	q.s. to 0.5 mL

Reviewer's Comment: *The TBM formulation of XYOSTED was used in the pivotal Phase 3 study (QST-13-003).*

2.6 Bioanalytical Methods

2.6.1 Did the Sponsor use validated bioanalytical methods to generate the study data?

Yes. Serum samples were analyzed for T, DHT, TE, dihydrotestosterone enanthate (DHTE), and 17β-estradiol (E2) using validated liquid chromatography - tandem mass spectrometry (LC-MS/MS) methods (b) (4) It should be noted that this review is focused on T and DHT concentrations that are relevant to the primary and secondary endpoints. The dynamic ranges for total T and DHT were both 2-1,000 ng/dL. More details about the bioanalytical methods can be found in Section 4.1.1 of this review.

A formal consult to the OSIS was made for the bioanalytical study site inspection and there are no unresolved inspection findings. Reference is made to Dr. Kara Scheibner's OSIS Memorandum dated June 19, 2017 under NDA 209863 in DARRTS.

The acceptance criteria and performance of the total T and DHT bioanalytical methods are in compliance with the Agency's *Bioanalytical Method Validation Guidance*. In summary, the method validation and performance of the bioanalytical methods used for this application are acceptable.

3 PROPOSED PRODUCT LABEL

The following Clinical Pharmacology related parts of the Sponsor's proposed label were submitted in this NDA. The double underlined text is recommended to be inserted and the ~~strikethrough~~ text is recommended to be deleted by the Clinical Pharmacology review team upon completion of reviewing the Sponsor's proposed product label.

It should be noted that the Sponsor's proposed labeling language is acceptable for all other sections not listed below from the Clinical Pharmacology standpoint. Please note that Sections illustrated below does not necessarily reflect the entire corresponding Section of the product label.

Highlights

----------DOSAGE AND ADMINISTRATION----------

- Prior to initiating XYOSTED, confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2).

(b) (4)

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION

Prior to initiating XYOSTED, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using XYOSTED.

Reviewer's Comment: *Inserted Section 12.2 to be compliant with the Agency's Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format: Guidance for Industry (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf).*

12.3 Pharmacokinetics

Absorption and Bioavailability

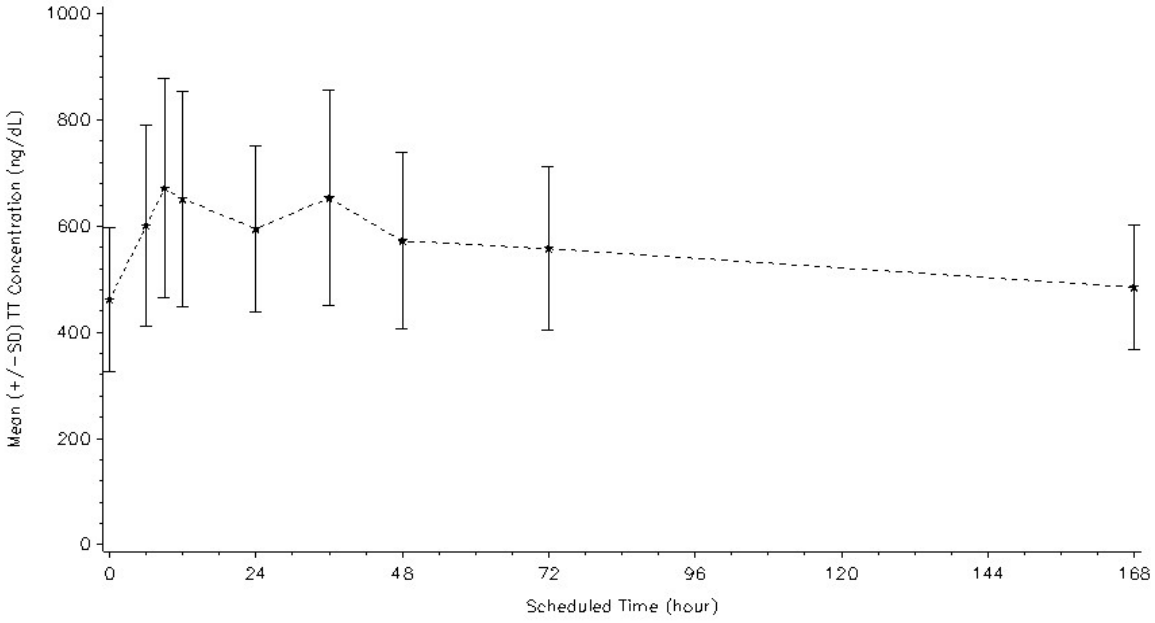
XYOSTED delivers physiologic amounts of testosterone, producing circulation testosterone concentrations that approximate normal concentrations (300-(b) (4) ng/dL) seen in healthy men.

Following weekly subcutaneous injection of XYOSTED for 12 weeks, serum testosterone concentrations reach a maximum after a median of 11(b) (4)9 hours (b) (4) XYOSTED dose was adjusted based upon total testosterone trough concentrations that were obtained following 6 weeks of dosing *[See Dose and Administration (2.2)]*. Steady state serum testosterone concentration was achieved (b) by Week 6. (b) (4)

Reviewer's Comment: *Added information regarding the starting dose and dosage regimen.*

(b) (4)

Figure 1. (b) (4)-Mean (±SD) of (b) (4) Total Testosterone (TT) (b) (4)-Concentration (ng/dL) Following Weekly Administration of XYOSTED for 12 Weeks (b) (4) (N=137)



(b) (4)

Reviewer's Comment: *The following information regarding the achievement of steady state is already stated above: "Steady state serum testosterone concentration was achieved at 6 weeks."*

(b) (4)

(b) (4)

Reviewer's Comment: *The information regarding PK parameters were relocated from Section 14 and Table 2 was reconstructed using this reviewer's PK analysis results.*

(b) (4)

Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free), and the rest is loosely bound to albumin and other proteins.

Reviewer's Comment: *Edited to make it consistent with other T replacement therapy product labels (e.g., NATESTO and AVEED) on Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/).*

Elimination

Metabolism

Testosterone enanthate is metabolized to testosterone via ester cleavage of the enanthate group. The mean (SD) maximum concentration of testosterone enanthate was 169.2 (67.8) ng/dL at Week 12 following weekly administration of XYOSTED.

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestostoerone (DHT). (b) (4) At pre-dose of Week 12 treatment, the mean DHT/testosterone ratio was 0.07 which was within the normal range.

Elimination
About 90% of a testosterone dose is excreted in the urine as glucuronic and sulfuric acid-conjugates of testosterone or as metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

Reviewer's Comment: *Sub-section title "Elimination" was added to make product label in compliance with the Agency's Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format: Guidance for Industry (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf).*

Metabolism information regarding TE was added to make this product label consistent with the product label of AVEED (i.e., testosterone undecanoate). Other parts of the Metabolism sub-section were deleted to make the labeling language consistent with other T replacement product labels.

14 CLINICAL STUDIES
XYOSTED was evaluated in a 52-week (b) (4)

Patients were trained on proper use of (b) (4) to self-administer the initial dose of 75 mg (b) (4) on the same day of the week and at approximately the same time (7:00 am ±2 hours). (b) (4)

(b) (4)

Reviewer's Comment: *Information regarding PK parameters was deleted and relocated to Section 12.3 Pharmacokinetics*.

Reviewer Comment: *Primary efficacy results in Table 3 were corrected to reflect the Division's primary efficacy analysis results.*

Reviewer's Comment: *Table 4 and its related text were deleted as it was redundant information with Table 2 in Section 12.3.*

4 APPENDICES

4.1 Individual Study Reviews

4.1.1 Phase 3 Trial (Study QST-13-003): Efficacy and Safety Study

Title: A Double-Blind, Multiple-Dose, 52-Week Study to Evaluate the Efficacy and Safety of XYOSTED Testosterone Administered Subcutaneously Once Each Week to Adult Males with Hypogonadism

Primary Objective: To demonstrate the efficacy and safety of XYOSTED in adult hypogonadal males

Clinical Study Centers: 30 sites in the U.S.
Clinical Study Period: July 7, 2014 – October 30, 2015

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: October 27, 2014 – September 12, 2015

Study Design, Treatments, Drug Administration, and Dose Titration Scheme:
This was a Phase 3, multiple-dose, 52-week study to evaluate the efficacy and safety of XYOSTED (TE) administered SC once each week to adult males with hypogonadism. The study included a screening phase, a treatment with titration phase, and an extended treatment phase for evaluation of long-term safety.

All participants must have had 2 total T concentration values < 300 ng/dL obtained in the morning during the Screening Phase. Qualifying total T concentrations must have been obtained on 2 separate occasions no less than 7 and no more than 9 days apart after completion of washout, if required.

XYOSTED administered in this study was provided in 3 blinded dose strengths of 50, 75, and 100 mg TE. Each XYOSTED device provided a single dose as a single injection. The injection volume for XYOSTED was 0.5 mL (for all 3 dose strengths). The XYOSTED device is an auto-injector containing TE solution in sesame oil contained in a glass syringe fitted with a thin-walled, 27-gauge needle within the device. The device is activated by firmly pressing and holding the un-capped device against the skin for a minimum of 10 seconds, allowing delivery of the SC TE dose to the patient. Once the device is removed from the surface of the skin, a lockout feature prevents depression of the needle guard and re-exposure to the needle as a sharps injury prevention feature.

Participants who met all eligibility criteria were assigned to receive XYOSTED 75 mg as the starting dose. Participants were trained by designated site staff on proper use of the XYOSTED device. XYOSTED was self-administered once each week on the same day of the week and at approximately the same time (7:00 am $\pm$ 2 hours). Adjustments to dose may have been made at Week 7 based upon the Week 6 serum total T C_{trough} value. 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 dose strength.

Additional adjustments to dose were also made at Weeks 13, 19, 27, and 39 as necessary.

Patients who were receiving XYOSTED 100 mg and required a dose increase remained on the 100 mg dose with no adjustment. Patients who were receiving XYOSTED 50 mg and required a dose reduction remained on the 50 mg dose with no adjustment unless the total T C_{trough} was ≥ 650 ng/dL; in this case, the site was instructed to discontinue the patient.

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

As a part of this study, a single-dose (first dose) PK sub-study was completed at approximately 4 clinical sites and included 21 participants. Participants included in the PK sub-study had blood samples for PK analysis of TT, DHT, TE, DHTE, and E2 obtained before and at specified times up to 168 hours after the first XYOSTED 75 mg dose administration. PK parameters to characterize total T exposure following a single 75 mg dose of XYOSTED were derived.

Safety and tolerability assessments, including laboratory assessments, adverse events (AEs), injection site assessments, and participant-reported questionnaires were conducted for all participants at scheduled intervals during the treatment with/titration phase of the study. The participant's use of the XYOSTED to self-administer injections was observed and evaluated by designated site staff. The treatment with/titration phase was 12 weeks in duration.

Participants were followed and safety data was collected for an additional 40 weeks following the treatment with titration phase. Safety and tolerability assessments, including laboratory assessments, AEs, and injection site assessments were conducted at scheduled intervals during this study phase. Final study evaluations were completed at the 52nd week of treatment, or at the point of early withdrawal, with follow-up visits completed as necessary to resolve out-of-reference-range assessments and ongoing AEs.

Blood sampling for PK characterization took place according to the pre-defined sampling schedule (see the *PK Sampling and Characterization* section below for details).

Reviewer's Comment: *It should be noted that while the Division conveyed the following recommendation on January 7, 2015, the Sponsor did not characterize full PK profiles at Week 6: "Full PK profiles for total T, DHT, E2, TE, and DHT should be characterized on Weeks 1 (i.e., in the PK sub-study), 6, and 12."*

Therefore, the evaluation of dose titration scheme based on Week 6 data (i.e., correlation analysis between Week 6 total T C_{trough} and $C_{avg.168h}$) could not be performed.

Sponsor's Dose Selection Rationale

The doses selected for evaluation in this study were 50, 75, and 100 mg TE administered as SC injections using the XYOSTED auto-injector. Since the intended frequency of dosing was weekly, the nominal doses selected spanned a range of half the 100 mg to 200 mg doses of TE used when every other week IM dosing of TE was employed. Sponsor's experience with SC TE administered via needle and syringe also supported the utility of these doses. Therefore, 100 and 50 mg dose strengths were selected for evaluation in the Phase 2 study of the PK, safety, and tolerability of XYOSTED (Study QST-13-002). Sponsor believes that results of that study showed that overall SC T was well tolerated and provided consistent measures of exposure week to week. On average, both the 100 mg and 50 mg doses provided average total T concentrations

within the normal range, but some participants receiving 50 mg demonstrated low concentrations just prior to their next dose, and some participants on 100 mg had instances of peak total T concentrations above 1,500 ng/dL. Modeling and simulation demonstrated that an intermediate dose of 75 mg had a projected incidence of subnormal trough levels of 20%, and an incidence of 0% of C_{max} values above 1,500 ng/dL. For this reason, an intermediate dose of 75 mg was evaluated as the primary dose in this Phase 3 study.

Reviewer's Comment: *It should be noted that the Phase 2 study, QST-13-002 was not reviewed in detail as it did not contain any critical information needed to make a regulatory decision on this NDA.*

Inclusion Criteria:

- Adult males of ≥ 18 years of age with a documented diagnosis of hypogonadism. Documentation of consistent signs and symptoms of androgen deficiency was required.
- Had two fasting morning (i.e., before 10 am) serum total T concentrations < 300 ng/dL, at least 3 days apart within 60 days of the initial treatment
- Participants must have had 2 morning total T concentrations < 300 ng/dL during the Screening Phase:
    - The first total T concentration was obtained after completion of washout from current T therapy, if applicable.
    - Morning total T concentrations had to be obtained on separate occasions (visits) and spaced no less than 7 and no more than 9 days apart.
    - One repeat total T concentration was allowed if 1 of the 2 morning total T concentrations was ≥300 ng/dL. The repeat total T concentration was required to be obtained no less than 7 and no more than 9 days after the second total T concentration was obtained.
- All participants were required to agree to practice effective contraception throughout the duration of the study and for 30 days after receiving the last dose of XYOSTED. Acceptable methods of birth control included condom with spermicide, vasectomy, or monogamous relations with a female partner who was of non-childbearing potential (post-menopausal, surgical or congenital sterility) or was of child-bearing potential and practiced a reliable method of contraception (hormonal contraception, double-barrier methods with spermicide, or intrauterine device).

Exclusion Criteria:

Participants who met any of the following criteria were excluded from the study:

- Individuals who had an allergic reaction or idiosyncratic reaction to sesame seeds, sesame products, or sesame oil.
- History of food anaphylaxis.
- History of intolerance, allergy, or idiosyncratic reaction to testosterone products.
- Body mass index (BMI) ≥40 kg/m^2.
- Hematocrit ≥52% at the initial Screening Visit.
- Individual history or current evidence of breast or prostate cancer.
- Other malignancy diagnosed or treated within 5 years of the date of Screening with the exception of non-melanoma carcinoma of the skin.
- Elevated prostate specific antigen (PSA) for age. Prostate specific antigen > 2.5 ng/mL in men 18 to 60 years and > 4 ng/mL in men 61 years and older was exclusionary.
- Presence of prostate nodule or induration upon digital rectal exam (DRE).
- Obstructive uropathy of prostatic origin and of a severity that, in the opinion of the Investigator, contraindicated the use of T.

- Participants with poorly controlled diabetes. Participants on a stable dose and regimen of anti-diabetic medications for a minimum of 4 weeks and who had a hemoglobin A1c level at ≤7.5% were permitted to participate in the study.
- Participants with New York Heart Association Class III or IV congestive heart failure.
- Within 6 months of the Screening Visit had myocardial infarction, unstable angina leading to hospitalization, percutaneous coronary intervention, coronary artery bypass graft, uncontrolled cardiac arrhythmia, stroke, transient ischemia attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease.
- History or current treatment for thromboembolic disease or use of anti-thromboembolic medications. Use of low-dose aspirin was permitted.
- Participants taking adrenocorticotropic hormone or oral or depot corticosteroids.
- History of severe, untreated sleep apnea.
- Historical or current evidence of any clinically significant disease or disorder that, in the opinion of the Investigator, may have caused participation in the study to be detrimental to the participant or which may have influenced the results of the study. This included cardiovascular, renal, hepatic, hematological, neuropsychological, endocrine, gastrointestinal, and pulmonary disease.
- Positive serology for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (HCVAb) at the Screening Visit.
- Current evidence of alcohol or drug abuse. A positive drug screen was exclusionary without documentation of a prescription and medical condition requiring treatment with the drug for which the screen was positive. Exception for tetrahydrocannabinol was allowed in states where recreational use of marijuana was legal.
- Any skin condition in the injection site area that could confound injection site assessments (e.g., dermatographism, urticaria, atopic dermatitis, tattoos, scarring, psoriasis, etc.).
- Administration of any other investigational compound within 1 month prior to Screening or 5 half-lives of the XYOSTED (whichever was longer).
- Within 12 months of the Screening Visit, the participant had taken estrogen, gonadotropin-releasing hormone agonists, or growth hormone.
- Participants who had taken other androgens (e.g., dehydroepiandrosterone [DHEA]), anabolic steroids, other sex hormones, or other substances/medications, including dietary supplements, known to affect the PK of TE.
    - Discontinuation of these substances/medications was allowed at the initial Screening Visit provided that the half-life of the substance/medication allowed complete washout (minimum of 5 half-lives) during the washout section of the Screening Phase. Washout must have been completed before the Qualification (Qual) Visit.
    - DHEA was required to be washed out for a minimum of 4 weeks.
    - Participants who would require the use of these substances/medications during the duration of the study were excluded.
- Participants who were considering or had scheduled any major surgical or dental procedure anticipated to be associated with significant blood loss (≥500 mL) during the study.
- Participants who donated plasma or blood within 56 days of the Screening Visit or had a history of donation of more than 500 mL of blood or plasma within 3 months of Screening. Blood and plasma donation was further prohibited during the duration of the study.

- Unable to understand verbal or written English or any other language in which a certified translation of the informed consent was available.

Removal of Subjects from the Study:
Participants may have withdrawn consent and/or may have been discontinued by the Investigator for any reason at any time during the study. A participant may have been withdrawn from the study for any of the following reasons:

- Participant withdrew consent,
- Sponsor (Antares Pharma, Inc.) or Investigator requested the participant be withdrawn,
- Protocol violation/non-compliance,
- Lost to follow-up/failure to return,
- Adverse event (AE),
- Met stopping criteria, or
- Study completion.

Stopping criteria were developed to assure participant safety. If any of the criteria listed below were met, XYOSTED was stopped and the participant was withdrawn from the study.

- Increase in PSA $\geq$1.4 ng/mL above the Baseline value at study entry;
- Elevated hematocrit >55% during the Treatment with Titration or Extended Treatment Phases of the study;
- Occurrence of any of the following cardiovascular events: myocardial infarction, new onset angina, unstable angina, cardiac revascularization (bypass, stenting, or endarterectomy), transient ischemic attack, or cerebrovascular accident;
- Anaphylaxis; or
- Participants receiving XYOSTED 50 mg who required a dose reduction and who had a total T C_{trough} $\geq$650 ng/dL.

If a participant was prematurely discontinued from participation in the study for any reason, the Investigator was required to make every effort to complete final study procedures and to ensure return of all XYOSTED supplies. Participants who prematurely discontinued the study for any reason were not allowed to re-enter the study. If a participant was lost to follow-up (failed to return for study visits), a reasonable effort was to be made to determine why the participant failed to return; this information was documented in source documents. Participants who withdrew, were discontinued, or were lost to follow-up were not replaced. The date a participant was withdrawn from the study, and the reason for discontinuation, was recorded in the electronic case report form (eCRF). If there were multiple reasons for early discontinuation, all reasons were recorded. All final study procedures and evaluations were to be performed for participants who were withdrawn from the study, regardless of the cause of withdrawal. If a participant was withdrawn because of an AE, the event was followed until the medical condition returned to Baseline or was considered stable or chronic. Participants who were discontinued due to elevated PSA or elevated hematocrit were advised to follow up with their urologist or primary care physician. Discontinuation of participants due to AEs, including those due to abnormal laboratory results, was reported promptly to the Sponsor.

Study Investigators:

Table A-1-1: Study Investigators of Study QST-13-003

Site 001 Gary Bedel, MD 333 Conover Drive, Suite D Franklin, OH 45005	*Site 002* Bradley Block, MD 2441 West State Road 426, Suite 2011 Oviedo, FL 32765
Site 003 James Borders, MD Central Kentucky Research Associates, Inc. 3475 Richmond Road, 3rd Floor Lexington, KY 40509	*Site 004* E. Clark Cullen, MD Sunstone Medical Research, LLC 1700 East Barnett Road Medford, OR 97504
Site 005 Matthew Davis, MD Rochester Clinical Research, Inc. 500 Helendale Road, Suite L20 Rochester, NY 14609	*Site 006* Douglas Denham, DO Clinical Trials of Texas, Inc. 7940 Floyd Curl Drive, Suite 700 San Antonio, TX 78229
Site 007 Stephen Devenport, MD Granger Medical Clinic-Riverton 12391 South 4000 West Riverton, UT 84065	*Site 008* John Ervin, MD The Center for Pharmaceutical Research 1010 Carondelet Drive, Suite 426 Kansas City, MO 64114
Site 009 Gregory Flippo, MD Alabama Clinical Therapeutics, LLC 52 Medical Park East Drive, Suite 203 Birmingham, AL 35235	*Site 010* Nicole Gullick, MD 2055 West Hospital Drive, Suite 145 Tucson, AZ 85704 Note: Dr. Gullick replaced Dr. Gordon as Principal Investigator for Site 010.
Site 010 James Gordon, MD 2055 West Hospital Drive, Suite 145 Tucson, AZ 85704 Note: Dr. Gordon was replaced by Dr. Gullick as Principal Investigator for Site 010.	*Site 011* Yogesh Paliwal, MD 1060 East Foothill Boulevard, Suite 204 Upland, CA 91786

Site 012 John Scott, MD 2809 Emerywood Parkway, Suite 140 Richmond, VA 23294	*Site 013* Kathleen Hwang, MD Omega Medical Research 400 Bald Hill Road Warwick, RI 02886
Site 014 Jed Kaminetsky, MD 215 Lexington Avenue, 21st Floor New York, NY 10016	*Site 015* Gary Karlin, MD 2 Princess Road, Suite J Lawrenceville, NJ 08648
Site 017 Barry Lubin, MD Health Research of Hampton Roads – Norfolk, Inc. 885 Kempsville Road, Suite 221 Norfolk, VA 23502	*Site 018* Michael McCartney, MD ActiveMed Practices & Research, Inc. 421 Merrimack Street, Suite 203 Methuen, MA 01844
Site 019 Andrew McCullough, MD Community Care Physicians, PC The Urological Institute of NENY 23 Hackett Boulevard Albany, NY 12208	*Site 020* John McGettigan, Jr., MD Quality of Life Medical & Research Centers, LLC 5390 East Erickson Drive Tucson, AZ 85712
Site 021 James McMurray, MD Medical Affiliated Research Center, Inc. 303 Williams Avenue, Suite 512 Huntsville, AL 35801	*Site 022* Roger Miller, Jr., MD 2950 Halcyon Lane, Suite 706 Jacksonville, FL 32223
Site 023 Tommy Mook, MD Regional Urology, LLC 255 Bert Kouns Shreveport, LA 71106	*Site 024* Abraham Morgentaler, MD 1 Brookline Place, Suite 624 Brookline, MA 02445
Site 025 Alan Reichman, MD 7080 Southwest Freeway Houston, TX 77074	*Site 026* Stephan Sharp, MD 1500 Church Street, Suite 100 Nashville, TN 37203
Site 027 Teresa Sligh, MD 6400 Laurel Canyon Boulevard, Suite 300A North Hollywood, CA 91606	*Site 028* Cynthia Strout, MD 1156 Bowman Road, Suite 102 Mt. Pleasant, SC 29464
Site 029 Ronald Swerdloff, MD 1124 West Carson Street Building CDCRC, Room 101 1000 West Carson Street Torrance, CA 90502	*Site 030* Duane Wombolt, MD 400 Gresham Drive 402 Medical Tower Norfolk, VA 23507
Site 034 Allen Sussman, MD 723 Southwest 10th Street, Suite 100 Renton, WA 98057	

Prior and Concomitant Medications:
Medications (including vitamins, herbal supplements, and over-the-counter [OTC] medications and therapies) used within 30 days before the initial Screening Visit were recorded in the electronic case report form (eCRF). The use of medications with a specified washout period of

longer than 30 days was also recorded to ensure completion of the required washout period. For participants receiving T replacement therapy at the Screening Visit, the drug name, dose, regimen, and length of time on regimen was recorded in the eCRF, along with the date of the last T dose administration.

The administration of any additional medication (including OTC and vitamins) above that specified in the protocol was clearly documented both in the source documents and the eCRF. Medications, other than XYOSTED, were not to be taken during the study. This excluded medications that were approved by the Medical Monitor and Sponsor; such approved medications were documented in the source documents and recorded in the eCRF. Exceptions to this rule applied to medications needed to treat AEs. Such administration was clearly documented and cross-referenced with the AE in the eCRF, and may have required discontinuation of XYOSTED and withdrawal of the patient from the study, if the medication was prohibited. All other therapies prohibited by the protocol must have been discontinued prior to study participation, according to the protocol-specified periods. These medications were only discontinued if the Investigator decided that discontinuing therapy was the best course of action for the patient. Investigators were instructed not to discontinue medications and therapies for the sole purpose of making a patient eligible for enrollment into the study. Prohibited or restricted medications/substances and the minimum required washout period for each are provided in Table A-1-2.

Table A-1-2: Prohibited and Restricted Medications for Study QST-13-003

Medication/Substance	Required Washout Period
Opiates [1]	24 hours
Anti-thromboembolic medications [2]	2 weeks
Adrenocorticotropic hormone	1 week
Corticosteroids (oral or depot)	4 weeks
Estrogen	12 months
Gonadotropin-releasing hormone agonist	12 months
Growth hormone	12 months
Androgens (dehydroepiandrosterone and androstenedione)	4 weeks
Anabolic substances (clomiphene, human chorionic gonadotropin, human menopausal gonadotropin, etc.)	4 weeks
Substances that interfere with androgen metabolism (anastrozole, dutasteride, flutamide, testolactone, spironolactone, finasteride, and ketoconazole)	2 weeks
Saw palmetto, phytoestrogens	4 weeks
Investigational compounds	30 days or 5 half-lives, whichever is longer

1. Daily use of opiates in patients with a valid prescription and stable dose and regimen was allowed. As needed use was discouraged, and discontinuation was required at least 24 hours before Screening and any visits where qualifying TT or C_{trough} blood samples were obtained.
2. Patients on anti-thromboembolic medications at Screening were excluded from the study; however, patients using these medications for temporary indications (eg, following cardiac ablation, hip or knee surgery, etc.) were allowed to enroll in the study following the required washout for anti-thromboembolic medication.

C_{trough} = blood concentration at end of dosing interval; TT = total testosterone.
Source: Study Protocol (Appendix 16.1.1)

In addition, patients were required to comply with the following food, beverage, and activity limitations:

- No consumption of alcohol for 48 hours before study visits;
- No strenuous resistance exercise 72 hours before the initial Screening Visit, Week 13, 26, 38, and 52 Visits, and any visit where clinical laboratory assessments were obtained, such as at Early Withdrawals;
- Patients were required to fast for a minimum of 8 hours before all study visits when blood samples were obtained, and on days when the Quantose IR panel was obtained; and

- All patients were required to remain at the clinical site for a minimum of 12 hours after dose administration on Day 1 of Week 12 of the Treatment with Titration Phase. Patient activity during this time was limited to light recreational activities; strenuous exercise was prohibited.

Treatment Compliance:
Designated site staff assessed patient compliance with dose administration by review of the diary, including review of any injection reactions, AEs, or difficulties. If a patient had indicated injection reactions, AEs, or difficulties, the site contacted the patient for follow-up. Noncompliant patients were counseled and provided additional training as appropriate.

PK Sampling and Characterization:
Blood samples for PK characterization were obtained at scheduled times for quantitation of total T, DHT, E2, TE, and DHTE.

- Week 1 (PK sub-study participants only): Pre-dose, 0.5, 1, 3, 6, 9, 12, 24, 36, 48, 72, and 168 hrs post-dose
- Week 12 (all participants): Pre-dose, 6, 9, 12, 24, 36, 48, 72, and 168 hrs post-dose
- C_{trough} samples: Trough total T blood samples were obtained within 15 minutes before dose administration on Day 1 of Week 1, 6, 12, 18, 26, 38, and 52 Visits for all patients.

Concentrations obtained from these samples were utilized in derivation of PK parameters (C_{max}, C_{min}, $C_{avg\ 168h}$, and area under the curve [AUC]) to support primary and key secondary PK endpoints.

Actual collection times were used in all calculations. The Linear/Linear method (equivalent to the Linear Trapezoidal Linear Interpolation option in WinNonlin® Professional), which employs the linear trapezoidal method for any area, was used in the computation of AUCs. Interpolation of concentration values was conducted using the linear interpolation rule for any time point.

Missing or non-quantifiable (NQ) data were handled based on the current knowledge of drug PK measures. For different scenarios of not measureable or undetectable concentrations, the following rules were applied:

- If 1 or more NQ values occurred in the PK profile before the first measurable concentration, they were assigned a value of 0. For linear plots, 0 concentration value(s) before the first measurable concentration were included in the plot;
- If any post-dose NQ data occurred between measurable concentrations in a profile or at early post-dose time points prior to the first measurable concentration, the NQ was generally omitted (set to missing) in the derivation of PK parameters, statistical analysis, and the individual patient plots; NQ data which occurred after the last measurable concentration were omitted (set to missing) in the derivation of PK parameters and from the individual patient plots; and
- If the concentration for the last scheduled time point (i.e., 168 hr) was below limits of quantification (BLQ), then it was imputed for the calculation of AUC(0-168h):
    - If there was an obvious first-order terminal elimination observed, then λ_z was estimated with linear regression of concentration in logarithm scale vs. time using at least 3 data points. Uniform weighting was selected to perform the regression analysis. The constant λ_z was not assigned if the terminal elimination phase was not linear (as appears in a semi-logarithmic scale), if the T_{max} was 1 of the 3 last data points, or if the regression coefficient was less than 0.8. Once a valid λ_z was determined, the concentration at the scheduled post-dose time point

needed for AUC(0-168h) calculation was estimated. If the value estimated based on λz was less than the lower limit of quantitation (LLOQ), the LLOQ value was used.

- If the constant λ_z could not be assigned, then the last 2 measureable concentrations in the Week 12 profile were used to extend the concentration line to the 168 hr time point needed for the AUC(0-168h) calculation. If the value estimated from this extension line was less than LLOQ, the LLOQ value was used.

Sample Size Determination:
With a minimum of 125 evaluable patients and exactly 75% of the safety population meeting the success criteria for the primary endpoint with a Week 12 total T concentration within the pre-specified normal range, the lower bound of the 2-sided 95% CI was to equal or exceed 65%. Approximately 150 patients were to be enrolled in this study to ensure completion of the treatment titration phase by approximately 125 patients. Additionally, a minimum of 100 patients needed to complete collection of 26 weeks of safety data, and a minimum of 50 patients needed to complete collection of 52 weeks of safety data. Safety data collection was inclusive of safety data collected during the treatment titration phase and during the extended treatment phase.

Efficacy and Safety Variables and Assessments
The primary efficacy endpoint: The number and percentage of subjects with a serum total T $C_{avg\ 168h}$ within the normal range of 300 - 1,100 ng/dL on Day 120.

The primary efficacy endpoint, $C_{avg\ 168h}$, was calculated from the AUC using the following formula:

$$C_{avg\ 168h} = AUC(0\text{-}168\ h) / 168$$

Actual collection times were used in the calculation. The study was considered to have met its efficacy criteria if the percentage was ≥ 75% and the lower bound of the 95% CI was ≥ 65%.

Key Safety Endpoint:
The key safety endpoint, total T C_{max}, had the following criteria that were expected to be met on Day 120:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Having a serum total T C_{max} ≤ 1,500 ng/dL in at least 85% of subjects

Other Secondary efficacy/safety variables:

- The serum DHT, TE, DHTE, and E2 PK profiles (including AUC(0-168 h), AUC(0-inf), C_{avg}, C_{min}, C_{max}, and T_{max}) on Day 120

Other Safety Assessments:
Safety data included treatment emergent adverse events (TEAEs), biomarkers, vital signs, physical examinations, and investigation of injection site reactions (ISRs), self-injection assessment questionnaire (SIAQ), psychosexual daily questionnaire (PDQ), 12-lead electrocardiogram (ECG), and clinical laboratory assessments (e.g., FSH, LH, and sex hormone binding globulin [SHBG]).

The schedule of procedures of this study is presented in Table A-1-3 below.

Table A-1-3: Schedule of Assessment – Screening and Treatment Titration Phases (Study QST-13-003)

Study Phase	Screening Phase					Treatment Titration Phase								
Visit	Initial Screen	WO[1]	TT[2] Qual 1	TT[2] Qual 2	TT[2] Qual 3	Week 1[3]		Week 6	Week 7	Week 12				
Individual Visit Days	1		1	1	1	1	2	1	1	1	2	3	4	8[10]
Study Day						1	2	36	43	78	79	80	81	85
Informed consent	X													
Medical/surgical history	X													
Medication history	X													
Physical examination including DRE	X													
Height and weight (BMI)	X													
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments including PSA[4]	X													
Endocrine function assessment[4]	X					X								
Biomarkers[4]	X					X								
Serology[4]	X													
Qualifying TT levels[4]			X	X	X									
ECG				X										
Urine drug screen				X										
Verification of all eligibility criteria						X								
Quantose™ *IR* panel[5]						X								
QST device training						X								
Register patient in IWRS	X													
IP dispensing via IWRS[6]						X	X	X	X	X				
Dose administration[7]						X		X	X	X				
Injection site assessment[8]						X	X	X	X	X	X			
TT C_{trough} blood sample[9]						X		X		X				
PK profile blood collection (TT, DHT, DHTE, E2, and TE)										X[11]	X[11]	X[11]	X[11]	X[11]
Titrate dose via IWRS, if required									X					
IP accountability and compliance								X		X				
Administer SIAQ						X				X				
Administer PDQ[12]				X	X			X		X				
Site review of PDQ entries						X			X					
Assessment of self-administration essential tasks						X		X	X	X				

Study Phase	Screening Phase					Treatment Titration Phase								
Visit	Initial Screen	WO[1]	TT[2] Qual 1	TT[2] Qual 2	TT[2] Qual 3	Week 1[3]		Week 6	Week 7	Week 12				
Individual Visit Days	1		1	1	1	1	2	1	1	1	2	3	4	8[10]
Study Day						1	2	36	43	78	79	80	81	85
Progress to Extended Treatment Phase														X
Concomitant medication review	X		X	X	X	X	X	X	X	X	X	X	X	X
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Washout period was dependent on patient's testosterone therapy at time of Screening. Patients who were naïve to treatment or who had discontinued testosterone therapy with adequate WO before the initial screen, were permitted to proceed to TT Qualification Visit 1 (TT Qual 1), and this visit was combined with the initial Screening Visit.
   a. Buccal, transdermal, and topical WO was a minimum of 2 weeks from last application.
   b. Intramuscular WO was a minimum of 4 weeks from last application.
   c. Testopel® washout was considered complete at the end of the dosing interval.
2. The TT Qual 1 Visit was completed as soon as the WO period was complete. All TT Qual Visits were completed a minimum of 7 and maximum of 9 days apart. A minimum of 2 TT <300 ng/dL were required for study participation. If 1 of the TT values from TT Qual 1 or TT Qual 2 Visits was ≥300 ng/dL, 1 retest was allowed at TT Qual 3 Visit, which occurred a minimum of 7 and a maximum of 9 days after TT Qual 2 Visit.
3. Week 1 Visit assessments for patients included in the PK sub-study are provided in Table 5.
4. Patients were required to fast a minimum of 8 hours prior to clinical laboratory, endocrine function, biomarker, and qualifying TT blood sampling.
5. Quantose™ *IR* panel included insulin, 2-hydroxybutyric acid, oleic acid, and linoleoylglycerophosphocholine. Patients were required to fast for a minimum of 8 hours prior to obtaining these blood sample(s).
6. Investigational Product Dispensing schedule: Week 1 – dispensed 1 device for use in clinic and 4 devices for patient administration at home. Week 6 – dispensed 1 device for use in clinic. Week 7 – dispensed 1 device for use in clinic and 4 devices for patient administration at home. Week 12 – dispensed 1 device for use in clinic.
7. QuickShot™ Testosterone was self-administered once each week on the same day of each week and at approximately the same time (7:00 am ±2 hr). When dose administration coincided with a study visit (Weeks 1, 6, 7, and 12), the patient administered the dose at the clinical study site, allowing coordination of study evaluations and assessments that were timed relative to dose administration.
8. Injection site assessments completed pre-dose and at 30 minutes, 1, and 24 hours after dose administration. At Weeks 6 and 7, ISA reactions present at 1 hour after dose administration were evaluated 24 hours after dose administration during an unscheduled visit. Unscheduled ISAs were completed as deemed necessary by the Investigator.
9. C_{trough} blood samples were obtained before QST dose administration.
10. Day 8 of Week 12 corresponded to the Week 13 Visit for the Extended Treatment Follow-up Phase. The 168h post-dose PK sample was obtained on this day and refer to Table 6 for remaining assessments completed at the Week 13 Visit.
11. Pharmacokinetic profile obtained for all patients at Week 12.
12. Psychosexual Daily Questionnaire was completed daily beginning at TT Qual Visit 2 and continuing until the first day of Treatment Titration Week 1 Visit and during Treatment Titration Weeks 6 and 12.

BMI = body mass index; C_{trough} = blood concentration at the end of dosing interval; DHT = dihydrotestosterone; DHTE = dihydrotestosterone enanthate; DRE = digital rectal exam; E2 = estradiol; ECG = electrocardiogram; IP = investigational product; IR = insulin resistance; ISA = injection site assessment; IWRS = Interactive Web Response System; PDQ = Psychosexual Daily Questionnaire; PK = pharmacokinetic; PSA = prostate specific antigen; QST = QuickShot™ Testosterone; Qual = qualification; SIAQ = Self-injection Assessment Questionnaire; TE = testosterone enanthate; TT = total testosterone; WO = washout.
Source: Study Protocol (Appendix 16.1.1)

Table A-1-4: Schedule of Assessment – Visit 1 PK Sub Study (Study QST-13-003)

Study Phase	Treatment Titration Phase				
Visit	Week 1 (PK Sub-Study Patients Only)				
Individual Visit Day	1	2	3	4	8
Study Day	1	2	3	4	8
Vital signs	X	X	X	X	X
Endocrine function assessments[1]	X				
Biomarkers[1]	X				
Verification of all eligibility criteria	X				
Quantose™ *IR* panel[2]	X				
QST device training	X				
IP dispensing via IWRS[3]	X				
Dose administration[4]	X				
Injection site assessment[5]	X	X			
PK sampling[6]	X	X	X	X	X
Administer SIAQ	X				
Site review of PDQ entries	X				
Assessment of self-administration essential tasks	X				
Concomitant medication review	X	X	X	X	X
Adverse event collection	X	X	X	X	X

1. Patients were required to fast a minimum of 8 hours prior to endocrine function and biomarker blood sampling.
2. Quantose™ *IR* panel included insulin, 2-hydroxybutyric acid, oleic acid, and linoleoylglycerophosphocholine. Patients were required to fast for a minimum of 8 hours prior to obtaining these blood sample(s).
3. Investigational product dispensing schedule: Week 1 – dispensed 1 device for use in clinic and 4 devices for patient administration at home.
4. QuickShot™ Testosterone was self-administered once each week on the same day of each week and at approximately the same time (7:00 am ±2 hr). When dose administration coincided with a study visit (Week 1), the patient administered the dose at the clinical study site, allowing coordination of study evaluations and assessments that were timed relative to dose administration.
5. Injection site assessments completed pre-dose and at 30 minutes, 1, and 24 hours after dose administration. Unscheduled ISAs were completed as deemed necessary by the Investigator.
6. Pharmacokinetic profile obtained for all patients in the PK sub-study at Week 1.

IP = investigational product; IR = insulin resistance; ISA = injection site assessment; IWRS = Interactive Web Response System; PDQ = Psychosexual Daily Questionnaire; PK = pharmacokinetic; QST = QuickShot™ Testosterone; SIAQ = Self-injection Assessment Questionnaire.
Source: Study Protocol (Appendix 16.1.1)

Table A-1-5: Schedule of Assessment – Extended Treatment and Follow-up Phases (Study QST-13-003)

Study Phase	Extended Treatment Phase								Follow-up Phase[1]	
Visit	Week 13	Week 18	Week 19	Week 26	Week 27	Week 38	Week 39	Week 52	Early Withdrawal	Follow-Up Visit
Individual Visit Days	1	1	1	1	1	1	1	1		1
Study Day	85	120	127	176	183	260	267	358	Point of exit	7-14
Physical examination including DRE	X			X		X		X	X	
Weight (BMI)	X			X		X		X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments including PSA[2]	X			X		X		X	X	
Endocrine function assessment[2]	X			X		X		X	X	
Biomarkers[2]	X			X		X		X	X	
ECG	X			X		X		X	X	
Quantose™ *IR* panel[3]	X			X				X	X	
IP dispensing via IWRS[4]	X	X	X	X	X	X	X	X		
Dose administration[5]	X	X	X	X	X	X	X	X		
Injection site assessment[6]	X	X	X	X	X	X	X	X		
TT Ctrough blood sample[7]		X		X		X		X	X	
Titrate dose via IWRS, if required	X		X		X		X			
IP accountability and compliance		X		X		X		X	X	
Administer SIAQ				X				X		
Administer PDQ[8]				X						
Site review of PDQ entries	X				X					
Assessment of self-administration essential tasks	X	X	X	X	X	X	X	X		
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Adverse event collection	X	X	X	X	X	X	X	X	X	X
Register completion in IWRS									X	X

1. End of study assessment completed at Week 52 or at the point the patient withdrew from the study. Follow-Up Visit was completed 7 to 14 days after completion of the final assessments.
2. Patients were required to fast a minimum of 8 hours prior to clinical laboratory, endocrine function, biomarker, and qualifying TT blood sampling.
3. Quantose™ *IR* panel included insulin, 2-hydroxybutyric acid, oleic acid, and linoleoylglycerophosphocholine. Patients were required to fast for a minimum of 8 hours prior to Quantose *IR* panel.
4. Investigational product dispensing schedule: Week 13 – dispensed 1 device for use in clinic and 4 devices for patient administration at home. Week 18 – dispensed 1 device for use in the clinic. Week 19 – dispensed 1 device for use in clinic and 6 devices for patient administration at home. Week 26 – dispensed 1 device for use in clinic. Week 27 – dispensed 1 device for use in clinic and 10 devices for patient administration at home. Week 38 – dispensed 1 device for use in clinic. Week 39 – dispensed 1 device for use in clinic and 12 devices for patient administration at home. Week 52 – dispensed 1 device for use in clinic.
5. QuickShot™ Testosterone was self-administered once each week on the same day of each week and at approximately the same time (7:00 am ±2 hr). When dose administration coincided with a study visit (Weeks 13, 18, 19, 26, 27, 38, 39, and 52), the patient administered the dose at the clinical study site, allowing coordination of study evaluations and assessments that were timed relative to dose administration.
6. Injection site assessments completed pre-dose and at 30 minutes and 1 hour after dose administration. ISA reactions present at 1 hour after dose administration were evaluated at 24 hours after dose administration. Unscheduled ISAs were completed as deemed necessary by the Investigator.
7. C_{trough} blood samples were obtained before QST dose administration.
8. Psychosexual Daily Questionnaire was completed daily during Week 26.

BMI = body mass index; C_{trough} = blood concentration at the end of dosing interval; DRE = digital rectal exam; ECG = electrocardiogram; IP = investigational product; IR = insulin resistance; ISA = injection site assessment; IWRS = Interactive Web Response System; PDQ = Psychosexual Daily Questionnaire; PSA = prostate specific antigen; QST = QuickShot™ Testosterone; SIAQ = Self-injection Assessment Questionnaire; TT = total testosterone.
Source: Study Protocol (Appendix 16.1.1)

Bioanalytical Methods:

Reviewer's Comment: *While concentrations of TE, DHTE, and E2 were also measured, it should be noted that this review is focused on T and DHT concentrations that are relevant to the primary and secondary endpoints. However, the method validation and performance of the bioanalytical methods for TE, DHTE, and E2 were reviewed and considered acceptable*

Bioanalysis for total T and DHT was conducted at (b) (4) (b) (4) Human serum samples were analyzed using LC-MS/MS methods for the determination of total T and DHT concentrations. Serum samples were stored in the freezer at -20°C until sample analysis.

T and DHT were extracted from 0.2 mL of serum by a liquid-liquid extraction (LLE) using methyl *tert*-butyl ether (MTBE). The extracted samples were dried under a stream of nitrogen, the residue was reconstituted and the supernatant was transferred to a 96-well plate for LC-MS/MS analysis.

Reconstituted sample extracts (10 µL) were analyzed using a Shimadzu high performance liquid chromatography (HPLC) System equipped with an Applied Biosystems Sciex 5500 QTRAP mass spectrometer. Chromatographic separation was performed on a Phenomenex HyperClone, C18, 50 x 2.0 mm, 5 µm-column for T and DHT using gradient elution. Positive ions generated from the electrospray ion source were detected using the multiple reaction monitoring (MRM) mode. Quantitation was performed using a weighted linear regression ($1/concentration^2$) of the determined peak area ratios for T, DHT, T-d_3 (internal standard [IS]), and DHT-d_4 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 0.02-10 ng/mL (2-1,000 ng/dL) for both total T and DHT.

Due to the presence of endogenous T and DHT, calibration standards and quality control (QC) samples for T and DHT were prepared in charcoal treated human serum (i.e., add 50 mg charcoal to 1 mL human serum, vortex well, and store in a refrigerator for 24 hours. Then centrifuge to get supernatant. Repeat the procedure again using another 50 mg charcoal to get charcoal treated human serum) except for high QC samples. For high T and DHT QC samples, regular human serum was used.

Accuracy of the calibration standards and QC samples during sample analysis was expressed as percent difference from theoretical concentration (i.e., % RE). For serum total T, the %RE ranged from -1.6% to 2.0% for the 8 calibration standards in the range of 2-1,000 ng/dL and -1.4% to 2.8% for low, medium, high, and 10-times dilution QCs (i.e., 6, 40, 800, and 5,000 ng/dL, respectively). For serum DHT, the % RE ranged from -1.8% to 2.0% for the 8 calibration standards in the range of 2-100 ng/dL and -2.3% to 3.7% for low, medium, high, and 10-times dilution QCs (i.e., 6, 40, 800, and 5,000 ng/dL, respectively).

Precision of the calibration standards and QC samples during sample analysis was expressed as the percent % CV. For serum total T, the % CV ranged from 1.6% to 6.0% for the 8 calibration standards in the range of 2-1,000 ng/dL and 2.3% to 7.1% for low, medium, high, and 10-times dilution QCs (i.e., 6, 40, 800, and 5,000 ng/dL, respectively). For serum DHT, the % CV ranged from 2.3% to 9.6% for the 8 calibration standards in the range of 2-100 ng/dL and 3.4% to 11.1% for low, medium, high, and 10-times dilution QCs (i.e., 6, 40, 800, and 5,000 ng/dL, respectively).

Long-term storage stability for both T and DHT in human serum at -20°C and -70°C was established for 31 days and 184 days, respectively, and samples were processed and analyzed within the established period for long-term storage stability.

Stability (i.e., accuracy of ≤ 15%) of T and DHT in human serum was confirmed for 3 freeze/thaw cycles at -20°C and -70°C, respectively.

After 53 hours of storage in the auto-sampler at room temperature, the % REs of the replicate analyses of T and DHT Low and High QC samples were always ≤ 15%.

After 4 hours of storage in human serum on the bench-top at room temperature, the % REs of the replicate analyses of T and DHT Low and High QC samples were always ≤ 15%.

Incurred sample reanalysis (ISR) was conducted on 104 samples (7.1%) for total T and 112 samples (8.6%) for DHT out of a total of 1,474 study samples. All 104 ISR samples (100%) were within ± 20% of the original results for both total T and DHT. These ISR results confirmed the reproducibility of the bioanalytical method.

Potential hydrolysis from TE to T

The Division conveyed the following information request (IR) comment to the Sponsor via the Filing Communication letter dated February 24, 2017 to address the potential TE to T conversion during blood sample preparation.

"*Refer to our January 7, 2015, Advice/Information Request (AD/IR) letter to your IND 116022 in which we discussed the potential for conversion of testosterone enanthate (TE) to testosterone (T) during blood sample preparation. As we mentioned, it has been reported that testosterone esters, such as testosterone enanthate (TE), may be easily hydrolyzed to testosterone (T) due to nonspecific esterases in blood during blood collection, resulting in overestimation of the T concentration. Therefore, caution is needed in sample preparation (Wang et al., 2008; Lachance et al., 2015). This will be a review issue. Submit data and information on how you assessed the potential and extent of TE to T conversion during sample collection and preparation. This information should describe how you accounted for any potential overestimation of T concentration in your bioanalysis of clinical trial samples.*"

On April 7, 2017, the Sponsor submitted their response to the Division's comment in the Filing Communication letter. Upon the completion of review of the Sponsor's response, the Division conveyed the following comment via the IR letter dated June 1, 2017.

"*We received your response dated April 7, 2017 to the Division's Filing Communication dated February 24, 2017 regarding the potential conversion of testosterone enanthate (TE) to testosterone (T) during blood sample preparation.*

Your response refers to published literature that may have used different sample collection and bioanalytical methods from your studies. You have not provided any information regarding your collection and bioanalytical method addressing the potential conversion of TE to T during blood sample collection/preparation. Therefore, you did not adequately address our concerns.

We remind you that bioanalytical method validation involves documenting, through the use of specific laboratory investigations, that the performance characteristics of a method are suitable and reliable for the intended analytical applications. Reference is made to Guidance for Industry: Bioanalytical Method Validation

(https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf).

In order to address our outstanding concern of potential TE to T conversion, submit data/information that you have generated in assessing the potential and extent of TE to T conversion during your sample collection and preparation and explain how it is relevant to your phase 3 trials. This information should describe in detail how you accounted for any potential overestimation of T concentration in your bioanalysis of clinical trial samples.

If you do not have data addressing this issue, you should use the same sample collection/preparation method and condition (e.g., type of blood collection tube, additives, temperature, and time) and bioanalytical method at the bioanalytical laboratory used in your Phase 3 studies and assess the potential of conversion from TE to T during blood sample collection/preparation to demonstrate that it does not affect the measurement of total T concentrations from your Phase 3 studies."

On June 19, 2017, the Sponsor submitted an amendment with their response to the Division's IR dated June 1, 2017. Upon the completion of the Division's review, the following IR comment was conveyed to the Sponsor via the IR letter dated July 13, 2017.

"*While we do not endorse any particular method, study or publication, we note that the two publications that we previously referenced (Wang et al., 2008 and Lachance et al., 2015) made reasonable attempts to address the potential conversion of testosterone enanthate (TE) to testosterone (T) during blood sample collection and preparation and provided potentially useful information.*

In light of those publications, we seek further information concerning the approach that you took to address and to prevent the potential conversion of TE to T. We seek this information to provide assurance that the total T concentrations reported in your Phase 3 studies are reliable.

While you did assess the stability of TE during freeze-thaw cycles and at benchtop, the stability of TE in blood from the moment of blood collection until your "zero" hour sample (e.g., about 25 minutes post-blood collection) was not assessed and is unknown. This specific information can be generated by collecting fresh blood samples, spiking a known amount of TE into the blood samples (with and without additives) immediately after blood collection, processing the samples at various timepoints (the timepoints should cover the range permitted in your sample processing protocol used to process the clinical study samples) and comparing the total T concentrations of the TE spiked samples with fresh blood samples without TE spiked in. The comparison of these three types of samples (e.g., TE spiked into blood with additives added, TE spiked into blood without additives added, and fresh blood without anything added) will provide necessary information about the stability of TE during the entire sample collection and preparation process.

We further recommend that the spiked TE concentration(s) include a level similar to the expected TE C_{max} in your clinical samples and that you provide a rationale supporting the clinical relevance of the spiked TE concentration(s).

In addition, the effects of different blood collection tubes, temperature of blood collection, and spiking solvents, etc., were also assessed in the two referenced publications and you should consider evaluating the effects of those factors."

On July 20, 2017, the Sponsor responded to the Division's IR with additional information and has adequately addressed the Division's IR. Briefly, per the Division's request, the stability of TE in human whole blood during the serum sample collection process and its potential conversion to T was assessed. The assessment was conducted by spiking TE into whole blood at blood TE concentrations of 1 ng/mL and 5 ng/mL, which were the estimated average and C_{max} concentrations of TE in serum samples from Study QST 13-003 per Sponsor. Fresh blood from two individuals was collected and spiked with TE immediately after collection accordingly before processing to generate the corresponding serum samples. For each subject, one control blood sample was obtained for the measurement of baseline serum total T concentration. Additionally, 4 blood draws were spiked with TE immediately after collection and used for the assessment of TE stability at two concentrations and two time points. At 45 minutes post blood collection, the blank sample and a sample at each concentration were centrifuged at 4ºC and 1800×g for 15 minutes to separate the serum and cells. Serum samples were aliquoted to 2-mL polypropylene tubes. At 60 minutes, the remaining blood samples were centrifuged and serum samples aliquoted. Samples from each time point were compared to control blood for total T and samples from 60 minutes are compared to sample at 45 minutes for TE since a true zero sample for the TE spiked sample could not be established. The serum samples were then processed and analyzed in triplicate each using the corresponding validated bioanalytical method for total T or TE. The results were compared within the individual subject only.

Baseline (blank control) serum and serum samples derived from TE-spiked blood from different processing times (i.e., 45 min and 60 min) processed in triplicate and analyzed for total T. The results were shown in Table A-1-6.

Table A-1-6: Total T Concentrations (ng/mL) in Serum Samples from TE Spiked Human Blood and Controls

Subject 1

		Conc. Low (1 ng/mL for TE)		Conc. High (5ng/mL for TE)	
	Control Blood	45min	60min	45min	60min
Replicate					
1	3.96	3.62	3.61	3.94	3.51
2	3.92	3.70	3.29	3.85	3.54
3	4.03	3.75	3.52	3.78	3.57
n	3	3	3	3	3
Mean	3.97	3.69	3.47	3.86	3.54
SD (n-1)	0.06	0.07	0.17	0.08	0.03
CV (%)	1.5	1.9	4.9	2.1	0.8
Relative to Control (%)	—	93.0	87.4	97.2	89.2

Subject 2

		Conc. Low (1 ng/mL for TE)		Conc. High (5ng/mL for TE)	
	Control Blood	45min	60min	45min	60min
Replicate					
1	5.82	5.72	5.86	5.99	5.76
2	5.88	5.71	5.70	5.76	5.87
3	5.81	5.71	5.86	5.88	5.88
n	3	3	3	3	3
Mean	5.84	5.71	5.81	5.88	5.84
SD (n-1)	0.04	0.01	0.09	0.12	0.07
CV (%)	0.7	0.2	1.5	2.0	1.2
Relative to Control (%)	—	97.8	99.5	100.7	100.0

Run 1.

Table A-1-7: TE Concentrations (ng/mL) in Serum Samples from TE Spiked Human Blood AT Different Processing Times

Subject 1

Replicate	Conc. Low (1 ng/mL for TE)		Conc. High (5ng/mL for TE)	
	45min	60min	45min	60min
1	1.18	1.03	4.94	4.19
2	1.16	1.02	6.00	5.49
3	1.06	1.07	6.10	5.28
n	3	3	3	3
Mean	1.13	1.04	5.68	4.99
SD (n-1)	0.06	0.03	0.64	0.70
CV (%)	5.3	2.9	11.3	14.0
Remaining (%)	—	92.0	—	87.9

Subject 2

Replicate	Conc. Low (1 ng/mL for TE)		Conc. High (5ng/mL for TE)	
	45min	60min	45min	60min
1	1.25	1.13	5.70	5.66
2	1.30	1.20	4.73	4.93
3	1.27	1.09	5.79	5.17
n	3	3	3	3
Mean	1.27	1.14	5.41	5.25
SD (n-1)	0.03	0.06	0.59	0.37
CV (%)	2.4	5.3	10.9	7.0
Remaining (%)	—	89.8	—	97.0

While there was a small TE concentration decrease (Table A-1-7) in the blood at different processing times, the results suggest that TE was unlikely converted to T in the blood during the time frame of the clinical blood collection and processing time.

OSIS Inspection of the bioanalytical study site:
The Clinical Pharmacology review team requested inspections on clinical study sites on February 6, 2017. As a result, [redacted] (b) (4) were inspected during [redacted] (b) (4) and the inspection report was issued on June 19, 2017. A copy of the inspection report can be found in DARRTS under NDA 209863.

After evaluation of inspectional observations and the responses from the bioanalytical study site, the OSIS inspector recommended that the bioanalytical data of the audited study be accepted for further FDA review.

Reviewer's Comment: *The acceptance criteria and performance of the total T and DHT bioanalytical methods are in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods in clinical studies are acceptable and there are no unresolved bioanalytical issues related to the approvability of XYOSTED.*

Disposition of Subjects:
In total, 150 participants received XYOSTED. A total of 137 (91.3%) subjects completed the 12-week treatment and titration phase and 97 (64.7%) subjects completed the full study (through the Follow-up Visit): 13 (52.0%) patients on the 50 mg dose at Week 12, 69 (66.3%) patients on the 75 mg dose at Week 12, and 15 (71.4%) patients on the 100 mg dose at Week 12. In total, 52 (34.7%) patients prematurely withdrew from the study: 12 (48.0%) patients on the 50 mg dose at Week 12, 34 (32.7%) patients on the 75 mg dose at Week 12, and 6 (28.6%) patients on the 100 mg dose at Week 12. The most common reasons for early withdrawal were withdrawal of consent (9 [6.0%] patients) and adverse events (5 [3.3%] patients). Twenty-nine (19.3%) patients

cited multiple reasons for withdrawal. Table A-1-8 summarizes patient disposition by treatment dose at Week 12 for all enrolled patients.

Table A-1-8: Participant Disposition by Treatment – Enrolled Participants (Study QST-13-003)

Characteristics	Dose at Week 12			Overall
	SC QST 50 mg	SC QST 75 mg	SC QST 100 mg	
Enrolled – n	-	150	-	150
Dosed patients [1] – 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 staus – 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)

Note: For the dose at Week 12 columns, a patient was counted in the 75 mg column if he discontinued prior to Week 7 titration.
1. 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.
Source: Post-text Table 14.1.1.1

Data Sets Analyzed:

- Safety population: Consisted of all participants who received at least 1 dose of XYOSTED (150 patients). The safety population was used to examine the primary efficacy results in patients who completed Week 12 and had a calculable C_{avg}(0-168h).
- Per-protocol population: Consisted of all patients who followed the study protocol and did not have any significant protocol deviations that had the potential to impact response. Patients who did not dose on the correct day prior to the collection of Week 12 PK samples were excluded. The per-protocol population was finalized prior to database lock and contained 129 patients.
- PK population: All patients in the Safety Population with at least 1 blood sample drawn post-dose for the PK analysis were included in the PK Population. The PK Population contained 142 patients.
- PK Sub-study population: All patients who participated in the sub-study with at least 1 Week 1 blood sample drawn post-dose for the PK analysis were included in the PK sub-study Population. The PK sub-study population contained 21 patients.

Table A-1-9 presents the number of patients in each analysis population according to treatment dose at Week 12.

Table A-1-9: Population Analyzed by Treatment (Study QST-13-003)

Population	Dose at Week 12			Overall
	SC QST 50 mg n (%)	SC QST 75 mg n (%)	SC QST 100 mg n (%)	n (%)
Safety Population [1]	25 (100.0)	104 (100.0)	21 (100.0)	150 (100.0)
Per-Protocol Population [2]	22 (88.0)	89 (85.6)	18 (85.7)	129 (86.0)
PK Population [3]	25 (100.0)	96 (92.3)	21 (100.0)	142 (94.7)
PK Sub-Study Population [4]	4 (16.0)	14 (13.5)	3 (14.3)	21 (14.0)

Note: For the dose at Week 12 columns, a patient was counted in the 75 mg column if he discontinued prior to Week 7 titration.
1. The Safety Population consisted of all patients who received at least 1 dose of the investigational product. The Safety Population was used as the denominator in all percentage calculations.
2. The Per-Protocol Population consisted of all patients who followed the study protocol, did not have any significant protocol deviations that may have impacted response, completed Week 12, and had a calculable $C_{avg168h}$.
3. The PK Population consisted of all patients in the Safety Population with at least 1 blood sample drawn post-dose for the PK analysis.
4. The PK Sub-Study Population consisted of all patients who participated in the sub-study with at least 1 Week 1 blood sample drawn post-dose for the PK analysis.

$C_{avg168h}$ = average concentration over the 7-day dosing interval (0-168 hours); PK = pharmacokinetic; QST = QuickShot™ Testosterone; SC = subcutaneous.
Source: Post-text Table 14.1.1.3

Demographics of Subjects:
The mean age of subjects was 53.4 (range: 25-78) years old. The majority of subjects were Caucasian (88.7%). The mean BMI was 31.2 (range: 19.4-39.9) kg/m^2. Demographics are summarized in Table A-1-10.

Table A-1-10: Demographics and Baseline Characteristics of Safety Population by Treatment

Demographic/Characteristic Category/Statistic	Dose at Week 12: SC QST 50 mg (N=25)	SC QST 75 mg (N=104) [1]	SC QST 100 mg (N=21)	Overall (N=150)
Age at Informed Consent (years)				
n	25	104	21	150
Mean	60.2	52.6	49.1	53.4
Standard deviation	10.44	12.07	10.84	12.04
Median	63.0	53.0	49.0	54.0
Minimum	30	25	26	25
Maximum	78	76	75	78
Ethnicity - n (%)				
Hispanic or Latino	2 (8.0)	4 (3.8)	2 (9.5)	8 (5.3)
Not Hispanic or Latino	23 (92.0)	100 (96.2)	19 (90.5)	142 (94.7)
Race - n (%)				
White	21 (84.0)	93 (89.4)	19 (90.5)	133 (88.7)
Black or African American	1 (4.0)	8 (7.7)	2 (9.5)	11 (7.3)
Asian	3 (12.0)	1 (1.0)	0 (0.0)	4 (2.7)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.7)
Other	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.7)
Currently receiving testosterone (T) therapy?				
No	24 (96.0)	85 (81.7)	20 (95.2)	129 (86.0)
Yes, type:	1 (4.0)	19 (18.3)	1 (4.8)	21 (14.0)
Buccal T therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IM or SC T injection	0 (0.0)	8 (7.7)	0 (0.0)	8 (5.3)
Topical or transdermal T therapy	1 (4.0)	10 (9.6)	1 (4.8)	12 (8.0)
Testopel	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.7)

Demographic/Characteristic Category/Statistic	Dose at Week 12: SC QST 50 mg (N=25)	SC QST 75 mg (N=104) [1]	SC QST 100 mg (N=21)	Overall (N=150)
Body Weight at Screening (kg)				
n	25	104	21	150
Mean	84.38	101.76	108.99	99.87
Standard deviation	21.356	15.269	19.224	18.403
Median	81.60	99.90	110.70	98.35
Minimum	49.9	68.0	78.0	49.9
Maximum	146.5	136.7	145.1	146.5
Body Height at Screening (cm)				
n	25	104	21	150
Mean	175.39	178.78	181.31	178.57
Standard deviation	8.759	6.112	9.699	7.321
Median	174.00	178.50	181.00	178.00
Minimum	160.0	163.0	162.6	160.0
Maximum	192.0	198.1	207.0	207.0
Body Mass Index (BMI) at Screening (kg/m^2)				
n	25	104	21	150
Mean	27.19	31.78	33.01	31.19
Standard deviation	5.197	4.102	4.164	4.659
Median	27.40	31.60	32.40	31.05
Minimum	19.4	22.2	23.8	19.4
Maximum	39.7	39.9	39.0	39.9

Demographic/Characteristic Category/Statistic	Dose at Week 12: SC QST 50 mg (N=25)	SC QST 75 mg (N=104) [1]	SC QST 100 mg (N=21)	Overall (N=150)
Baseline Total Testosterone (TT) (ng/dL)				
n	24	93	20	137
Mean	234.3	232.0	218.3	230.4
Standard deviation	121.44	88.74	84.22	94.01
Median	239.0	228.0	225.5	229.0
Minimum	2	22	39	2
Maximum	548	531	372	548
Baseline TT Category - n (%)				
<300 ng/dL	18 (72.0)	75 (72.1)	18 (85.7)	111 (74.0)
>=300 ng/dL	6 (24.0)	18 (17.3)	2 (9.5)	26 (17.3)
Baseline SHBG - (nmol/L)				
n	25	104	21	150
Mean	49.0	22.8	17.1	26.4
Standard deviation	30.07	7.97	7.78	17.44
Median	44.8	22.0	13.5	22.6
Minimum	11	9	7	7
Maximum	135	43	34	135
Baseline FSH Category - n (%)				
<=1xULN	16 (64.0)	82 (78.8)	19 (90.5)	117 (78.0)
>1xULN	9 (36.0)	22 (21.2)	2 (9.5)	33 (22.0)
Baseline LH Category - n (%)				
<=1xULN	17 (68.0)	88 (84.6)	20 (95.2)	125 (83.3)
>1xULN	8 (32.0)	16 (15.4)	1 (4.8)	25 (16.7)

[1] For the dose at week 12 columns, a subject is counted in the 75 mg column if they discontinue prior to week 7 titration.
Note: Baseline is defined as the measurement collected pre-dose on Week 1 Day 1.

Protocol Deviations:
There were no significant protocol deviations that would result in an exclusion from efficacy and safety analysis.

Withdrawal of Study Site 010
Study Site 010 (WG Clinical Research, 2055 West Hospital Drive, Suite 145, Tucson, AZ 85704) was a privately owned research site where investigators and sub-investigators work as employees at the site. Site 010 ceased participation and was terminated from the study after the Investigator resigned and was not replaced by the site. The site had enrolled 5 patients, 2 of which (Patient (b) (6) and Patient (b) (6)) were ongoing at the time of the site's termination from the study. The termination of study-related activities by the site impacted a portion of data cleaning activities, as some queries went unanswered. The nature of the incomplete data was varied and included missing clock-times around the performance of study activities and assessments, missed study procedures, missed entries in the study drug eCRF, and failure to reconfirm the Investigator's assessment of relatedness of AEs. Protocol deviations that went unreported in the deviation eCRF included performing study procedures outside of the protocol-specified time window and witness of informed consent by site staff not included on the delegation log for this activity. In addition, the final visits (unscheduled and early termination visits) for Patient (b) (6) (b) (6) and Patient (b) (6) which occurred just prior to the site's termination, were documented in source documents, but were not entered into the eCRF. The Sponsor states that review of the source documents for these visits did not reveal any additional safety events that should have been transcribed to the eCRF. Overall, these types of missing data and deviations did not impact the interpretation of the primary efficacy endpoints or safety summaries.

Treatment Compliance Results:
Per Sponsor, mean patient compliance, as determined by reconciliation of dispensed and returned IP, was 100.9% during the Treatment with Titration phase (Weeks 1-12). Compliance remained high during the Extended Treatment Phase: overall compliance was 98.2%. During the overall study, mean compliance was 98.5%. The compliance data were supported by additional data, including diary completion data, the high frequency of normal trough total T concentrations, and the detection of TE in the blood.

Reviewer's Comment: *While it is unknown of how the Sponsor derived the compliance rates, there were no significant findings or concerns identified to question the reliability of the study.*

Concomitant Medication Results:

Table A-1-11 summarizes concomitant medications taken by > 10 patients overall in the safety population. In total, 138 (92.0%) patients in the Safety Population took concomitant medications. The most common classes of concomitant medications were 3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors (49 [32.7%] patients); platelet aggregation inhibitors, excluding heparin (42 [28.0%] patients); other lipid modifying agents (32 [21.3%] patients); and plain angiotensin-converting-enzyme inhibitors (30 [20.0%] patients). A total of 27 (18.0%) patients took opium-derived medications during the study: 21 (14.0%) patients took natural opium alkaloids; 3 (2.0%) patients took opium alkaloids and derivatives; and 3 (2.0%) patients took opium derivatives and expectorants. Daily use of opiates in patients with a valid prescription and stable dose and regimen was allowed; however, as needed use was discouraged and discontinuation was required at least 24 hours before screening and before any visits where qualifying total T or C_{trough} blood samples were obtained.

Table A-1-11: Summary of Concomitant Medications (Taken by >10 Patients) – Safety Population

ATC Term	Overall (N=150) n (%)
Patients with any concomitant medication	138 (92.0)
HMG-CoA reductase inhibitors	49 (32.7)
Platelet aggregation inhibitors, excluding heparin	42 (28.0)
Other lipid modifying agents	32 (21.3)
ACE inhibitors, plain	30 (20.0)
Multivitamins, plain	28 (18.7)
Propionic acid derivatives	27 (18.0)
Proton pump inhibitors	26 (17.3)
Vitamin D and analogues	26 (17.3)
Drugs used in erectile dysfunction	22 (14.7)
Natural opium alkaloids	21 (14.0)
Anilides	20 (13.3)
Selective serotonin reuptake inhibitors	19 (12.7)
Biguanides	18 (12.0)
Dihydropyridine derivatives	18 (12.0)
Angiotensin II antagonists, plain	17 (11.3)
Glucocorticoids	17 (11.3)
Beta blocking agents, selective	16 (10.7)
Other antidepressants	15 (10.0)
Other antihistamines for systemic use	15 (10.0)
Benzodiazepine derivatives	13 (8.7)
Fibrates	13 (8.7)
Influenza vaccine	13 (8.7)
Acetic acid derivatives and related substances	12 (8.0)
Other anti-inflammatory and anti-rheumatic agents, non-steroids	11 (7.3)

Note: Concomitant medications were defined as any medication taken after the first dose administration of IP.
ACE = angiotensin-converting-enzyme; ATC = anatomical therapeutic chemical;
HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; IP = investigational product.
Source: Post-text Table 14.1.3

Office of Scientific Investigations (OSI) inspection of the clinical study sites:

The Clinical review team requested inspections on clinical study sites on February 8, 2017. As a result, 3 clinical study sites (Table A-1-12) were inspected between March 13 – April 4, 2017 and the inspection report was issued on June 19, 2017. A copy of the inspection report can be found in DARRTS under NDA 209863.

Table A-1-12: Clinical Sites Inspected

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Jed Kaminetsky 215 Lexington Avenue, 21st Floor New York, NY 10016	QST-13-003/ (14 enrolled) and QST-15-005/ (14 enrolled)	22-29 Mar 2017	VAI
Tommy Mook Regional Urology, LLC 255 Bert Kouns Industrial Loop Shreveport, LA 71106	M51810-US003/ (12 enrolled) and QST-15-005/ (18 enrolled)	13-16 March 2017	NAI
Marc Gittelman 21150 Biscayne Boulevard, #300 Aventura, FL 33180	QST-15-005/ (15 enrolled)	28 Mar-4 Apr 2017	NAI

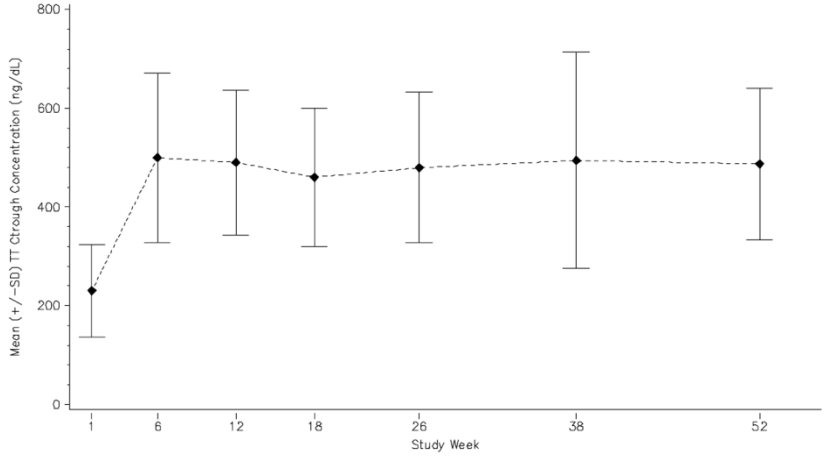
After evaluation of inspectional observations and the responses from the clinical study sites, the OSIS inspector recommended that the clinical portions of the audited study be accepted for further FDA review.

Serum total T PK

The PK Population was defined as all patients in the Safety Population with at least 1 blood sample drawn post-dose for the PK analysis (142 subjects). The PK Sub-study population consisted of all patients who participated in the sub-study with at least 1 Week 1 blood sample drawn post-dose for the PK analysis were included in the PK Sub-study Population. The PK sub-study population contained 21 patients.

Figure A-1-1 presents mean (± SD) of total T C_{trough} PK concentration by study week. The total T C_{trough} remains constant from Week 6 throughout Week 52.

Figure A-1-1: Plot of Mean (±SD) Total T C_{trough} PK Concentration (ng/dL) Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (N=137; Study QST-13-003)



Reviewer's Comment: *The mean total T C_{trough} was 231.6 ng/dL at Week 1 (pre-dose) and the total T C_{trough} ranged between 460.3 ng/dL (Week 18) and 501.9 ng/dL (Week 6) from Week 6 through Week 52. It appears that steady state for total T was reached before or by Week 6.*

Table A-1-13 summarizes the total T PK parameters for Weeks 1 and 12 of the PK Sub-study Population and for Week 12 of the PK population.

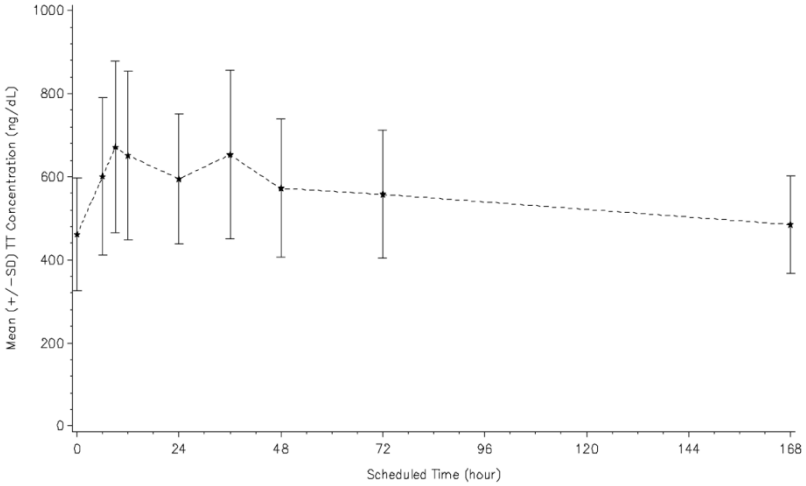
Table A-1-13: Arithmetic Mean (SD) Total T PK Parameters at Weeks 1 and 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (Study QST-13-003)

TE Dose (mg)	N	$C_{avg\ 168\ hr}$ (ng/dL)	C_{max} (ng/dL)	T_{max} (hr)[a]	C_{min} (ng/dL)	AUC(0-168 hr) (ng·hr/dL)
Week 1 (PK sub-study)						
75	21	357 (76)	487 (123)	35.0 (9.0-167.7)	235 (71)	60,028 (12,773)
Week 12 (PK sub-study)						
50	4	484 (95)	667 (210)	30.0 (9.0-72.6)	374 (125)	81,350 (15,948)
75	13	515 (98)	765 (187)	9.1 (5.9-71.8)	419 (82)	86,525 (16,420)
100	2	670 (231)	1,070 (0)	22.0 (9.0-35.0)	197 (88)	112,477 (38,846)
Week 12 (PK population)						
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)

[a] Reported in median (range)

Figure A-1-2 presents mean (±SD) Week 12 total T PK concentrations by treatment at Week 12 for the PK Population.

Figure A-1-2: 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 TE (N=137; Study QST-13-003)



Serum DHT PK

Table A-1-14 summarizes the DHT PK parameters for Weeks 1 and 12 of the PK Sub-study Population and for Week 12 of the PK population.

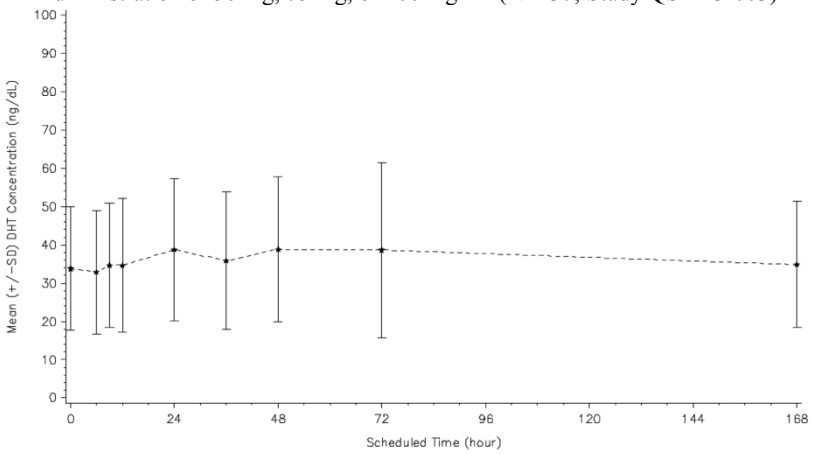
Table A-1-14: Arithmetic Mean (SD) DHT PK Parameters at Weeks 1 and 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (Study QST-13-003)

TE Dose (mg)	N	$C_{avg\ 168\ hr}$ (ng/dL)	C_{max} (ng/dL)	T_{max} (hr)[a]	C_{min} (ng/dL)	AUC(0-168 hr) (ng·hr/dL)
Week 1 (PK sub-study)						
75	21	25 (10)	31 (12)	35.1 (2.9-168.5)	17 (8)	4,210 (1,626)
Week 12 (PK sub-study)						
50	4	41 (19)	47 (22)	47.9 (9.0-72.6)	30 (17)	6,810 (3,165)
75	13	34 (14)	41 (18)	35.3 (6.0-71.9)	26 (11)	5,709 (2,423)
100	2	45 (20)	58 (12)	42.5 (12.1-73.0)	35 (12)	7,478 (3,384)
Week 12 (PK population)						
50	25	48 (26)	61 (38)	47.3 (6.0-167.7)	35 (17)	8,042 (4,339)
75	93	34 (13)	41 (16)	35.7 (5.9-169.3)	27 (11)	5,725 (2,252)
100	19	34 (19)	43 (22)	24.2 (5.8-167.8)	27 (17)	5,749 (3,137)
Overall	137	37 (18)	45 (24)	35.3 (5.8-169.3)	28 (14)	6,151 (2,977)

[a] Reported in median (range)

Figure A-1-3 presents mean (±SD) Week 12 DHT PK concentrations by planned treatment at Week 12 for the PK Population.

Figure A-1-3: Plot of Mean (±SD) of Serum DHT Concentration-Time Curve at Week 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (N=137; Study QST-13-003)



Serum TE PK

Table A-1-15 summarizes the total T PK parameters for Weeks 1 and 12 of the PK Sub-study Population and for Week 12 for the PK Population.

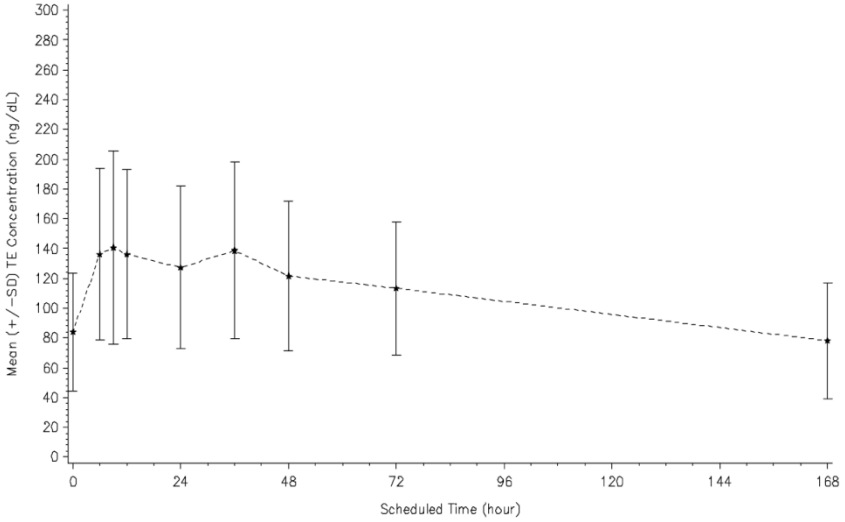
Table A-1-15: Arithmetic Mean (SD) TE PK Parameters at Week 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (N=137; Study QST-13-003)

TE Dose (mg)	N	$C_{avg\ 168\ hr}$ (ng/dL)	C_{max} (ng/dL)	T_{max} (hr)[a]	C_{min} (ng/dL)	AUC(0-168 hr) (ng·hr/dL)
Week 1 (PK sub-study)						
75	21	69 (23)	98 (46)	71.0 (9.0-168.5)	23 (12)	11,552 (3,914)
Week 12 (PK sub-study)						
50	4	98 (9)	163 (33)	17.9 (9.0-72.6)	71 (7)	16,537 (1,482)
75	13	111 (26)	167 (30)	9.1 (5.9-71.4)	167 (30)	18,676 (4,314)
100	2	209 (49)	361 (157)	22.0 (9.0-35.0)	122 (40)	35,024 (8,227)
Week 12 (PK population)						
50	25	96 (35)	147 (55)	24.0 (5.9-72.6)	59 (23)	16,067 (5,808)
75	93	106 (34)	163 (56)	11.9 (5.9-194.4)	71 (27)	17,717 (5,735)
100	19	148 (50)	228 (101)	24.1 (5.8-72.2)	104 (37)	24,898 (8,375)
Overall	137	110 (40)	169 (68)	12.2 (5.8-194.4)	73.2 (31)	18,422 (6,686)

[a] Reported in median (range)

Figure A-1-4 presents mean (±SD) Week 12 TE PK concentrations by planned treatment at Week 12 for the PK Population. Overall, TE concentrations increased at all scheduled time points from pre-dose to 72 hours post-dose for all XYOSTED treatment groups. TE concentrations then decreased at 168 hours post-dose for all 3 XYOSTED treatment groups.

Figure A-1-4: Plot of Mean (±SD) of Serum TE Concentration-Time Curve at Week 12 Following Weekly Administration of 50 mg, 75 mg, or 100 mg TE (N=137; Study QST-13-003)



Reviewer's Comment: *It should be noted that while the Division conveyed the following recommendation on January 7, 2015, the Sponsor did not characterize full PK profiles at Week 6: "Full PK profiles for total T, DHT, E2, TE, and DHT should be characterized on Weeks 1 (i.e., in the PK sub-study), 6, and 12"*

Overall, DHT, E2, and TE concentrations increased from pre-dose to post-dose at the scheduled Week 12 time points. DHT remained within normal ranges during dosing with TE.

Only 16 patients had DHTE concentrations > LLOQ, and for most of these patients, only a few time points were > LLOQ. Due to the low numbers, the PK profile summaries for DHTE were not presented by the Sponsor.

Efficacy Evaluation Results:

Primary Efficacy:

The primary efficacy endpoint was the responder rate, which was calculated based on the percentage of subjects whose serum total T $C_{avg\ 168h}$ was between 300 and 1,100 ng/dL (i.e., total T normal concentration range) at Week 12. The primary efficacy endpoint would be met if the responder rate was ≥75%. The primary efficacy analysis compared the lower bound of the 2-sided 95% exact binomial confidence interval (CI) of the number of patients in the Safety Population that had a $C_{avg\ 168h}$ value at Week 12 for total T within the defined range. If the lower bound of 2-sided 95% exact binomial CI was ≥65%, the primary efficacy goal for this clinical study would be met.

Table A-1-16 summarizes the Sponsor's analysis of the number and percentage of patients with Week 12 total T $C_{avg\ 168h}$ within the defined range (300-1,100 ng/dL) for the Safety Population.

Table A-1-16: Number (%) of Patients with Week 12 Total T $C_{avg\ 168h}$ in the Normal T Concentration Range – Safety Population

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) [1]	SC QST 100 mg (N=21)	
300 to 1100 ng/dL				
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.
1. 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 14.2.1.1.1

The Sponsor's analysis reports that 139 (92.7%) patients had total T $C_{avg\ 168h}$ values within the defined normal range at Week 12: 25 (100.0%) patients on the 50 mg dose, 94 (90.4%) patients on the 75 mg dose, and 20 (95.2%) patients on the 100 mg dose.

Reviewer's Comment: *In the Sponsor's primary efficacy analysis, they used the last recorded post-dose total T concentration value if the patient did not have calculable Week 12 $C_{avg.168h}$ value. A single total T concentration would not be relevant nor appropriate to use instead of C_{avg} values in the efficacy analysis.*

Efficacy Sensitivity Analysis:
In the Sponsor's primary efficacy sensitivity analysis, if a subject did not have a valid $C_{avg\ 168h}$, the subject was included in the analysis as not having achieved a total T $C_{avg\ 168h}$ within the pre-specified normal range of 300-1,100 ng/dL.

Table A-1-17 summarizes the number of patients with Week 12 total T $C_{avg\ 168h}$ within the normal T range (i.e., 300-1,100 ng/dL) for the Safety Population sensitivity analysis. Overall, 135 (90.0%) subjects had total T $C_{avg\ 168h}$ values within the normal T concentration range at Week 12: 25 (100.0%) patients on the 50 mg dose, 91 (87.5%) patients on the 75 mg dose, and 19 (90.5%) patients on the 100 mg dose.

Table A-1-17: Number (%) of Patients with Week 12 Total T $C_{avg\ 168h}$ in the Normal T Concentration – Sensitivity Analysis - Safety Population

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) [1]	SC QST 100 mg (N=21)	
300 to 1100 ng/dL				
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.
1. 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

Reviewer's Comment: *As indicated above, using a single total T concentration value instead of a $C_{avg.168h}$ value is inappropriate. Therefore,* ***the Clinical Pharmacology review team considers the Sponsor's primary efficacy sensitivity analysis results to be the appropriate primary efficacy outcome.*** *Per the Biostatistics reviewer, Dr. Sonia Castillo, the Biostatistics review team agrees to the results of the Sponsor's sensitivity analysis presented above.*

Safety Evaluation Results:

Key Safety Endpoint (Serum total T C_{max} at Week 12)

The following criteria were expected to be met for the key safety endpoint, total T C_{max} at Week 12:

- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Less than 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- At least 85% of subjects with a serum total T $C_{max} \leq$ 1,500 ng/dL

Table A-1-18 presents the number and percentage of subjects in the Safety Population with a serum total T C_{max} in each C_{max} category at Week 12. All Week 12 completers (N=137; see Table A-1-7) had a C_{max} < 1,500 ng/dL.

Table A-1-18: Number (Percentage) of Subjects by Serum Total T C_{max} in Selected Ranges at Week 12 of Safety Population (N=150)

Ranges	50 mg	75 mg	100 mg	Overall
Number of subjects	25	104	21	150
C_{max} < 1,500 ng/dL	25 (100)	93 (89.4)	19 (90.5)	137 (91.3)
1,500 ng/dL ≤ C_{max} ≤ 1,800 ng/dL	0 (0)	0 (0)	0 (0)	0 (0)
1,800 ng/dL < C_{max} ≤ 2,500 ng/dL	0 (0)	0 (0)	0 (0)	0 (0)
C_{max} > 2,500 ng/dL	0 (0)	0 (0)	0 (0)	0 (0)
Missing Week 12 C_{max}	0 (0)	11 (10.6)	2 (9.5)	13 (8.7)

Reviewer's Comment: *There were no subjects with measured total T C_{max} >1,500 ng/dL, 1,800-2,500 ng/dL, or > 2,500 ng/dL at Week 12. Therefore, the key safety endpoint regarding serum total T C_{max} was met.*

DHT/T, E2/T, and TE/T Ratios

Table A-1-19 summarizes the DHT/TT, E2/TT, and TE/TT ratios at Week 1 pre-dose (Baseline) and Week 12 for the PK Sub-study Population. Table A-1-20 summarizes the DHT/TT, E2/TT, and TE/TT ratios (%) derived based on concentrations (i.e., ng/dL) at Week 12 for the PK Population

Table A-1-19: Summary of Weeks 1 and 12 Pre-dose and Week 12 DHT/TT, E2/TT, and TE/TT Parameter Ratios (%) – PK Sub-study Population

Ratio (%) Statistic	Week 1 Pre-Dose	Week 12 Pre-Dose	$AUC_{(0\text{-}168h)}$	$AUC_{(0\text{-}\infty)}$	$C_{avg168h}$	C_{min}	C_{max}
DHT/TT							
n	21	19	19	1	19	19	19
Mean (SD)	7.63 (3.120)	7.61 (2.795)	6.88 (2.291)	5.99	6.88 (2.291)	6.56 (2.027)	5.74 (1.848)
E2/TT							
n	21	19	19	1	19	19	19
Mean (SD)	0.71 (0.393)	0.95 (0.380)	0.81 (0.246)	0.81	0.81 (0.246)	0.66 (0.269)	0.81 (0.262)
TE/TT							
n	21	19	19	5	19	19	19
Mean (SD)	0.00 (0.000)	21.90 (8.512)	23.23 (7.914)	12.97 (4.593)	23.23 (7.914)	19.84 (6.946)	24.36 (6.690)

Note: $AUC_{(0\text{-}\infty)}$ was not calculated when the constant lambda z was not assigned, which occurred if the terminal elimination phase was not linear, if the T_{max} was 1 of the last 3 data points, or if the regression coefficient was <0.8.
$AUC_{(0\text{-}168h)}$ = area under the concentration-time curve from time 0 to Day 8 (1 week); $AUC_{(0\text{-}\infty)}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $C_{avg168h}$ = average concentration over the 7-day dosing interval (0-168 hours); C_{max} = maximum (peak) blood concentration; C_{min} = minimum blood concentration;
DHT/TT = dihydrotestosterone/total testosterone ratio; E2/TT = estradiol/total testosterone ratio; SD = standard deviation;
TE/TT = testosterone enanthate/total testosterone ratio; T_{max} = time to reach maximum blood concentration.
Source: Post-text Table 14.2.2.6

Table A-1-20: Summary of Week 12 Pre-dose and Week 12 DHT/TT, E2/TT, and TE/TT Parameter Ratios (%) - PK Population

Ratio (%) Statistic	Week 12 Pre-Dose	$AUC_{(0\text{-}168h)}$	$AUC_{(0\text{-}\infty)}$	$C_{avg168h}$	C_{min}	C_{max}
DHT/TT						
n	139	137	14	137	137	137
Mean (SD)	7.36 (2.676)	6.54 (2.312)	10.12 (7.267)	6.54 (2.312)	6.44 (2.466)	5.72 (2.380)
E2/TT						
n	139	137	13	137	137	137
Mean (SD)	0.93 (0.416)	0.85 (0.315)	0.72 (0.477)	0.85 (0.315)	0.70 (0.266)	0.84 (0.337)
TE/TT						
n	139	137	33	137	137	137
Mean (SD)	18.88 (8.662)	20.32 (7.338)	11.86 (6.238)	20.32 (7.338)	17.44 (7.265)	21.89 (7.375)

Note: $AUC_{(0\text{-}\infty)}$ was not calculated when the constant lambda z was not assigned, which occurred if the terminal elimination phase was not linear, if the T_{max} was 1 of the last 3 data points, or if the regression coefficient was <0.8.
$AUC_{(0\text{-}168h)}$ = area under the concentration-time curve from time 0 to Day 8 (1 week); $AUC_{(0\text{-}\infty)}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $C_{avg168h}$ = average concentration over the 7-day dosing interval (0-168 hours); C_{max} = maximum (peak) blood concentration; C_{min} = minimum blood concentration; DHT/TT = dihydrotestosterone/total testosterone ratio; E2/TT = estradiol/total testosterone ratio; SD = standard deviation; TE/TT = testosterone enanthate/total testosterone ratio; T_{max} = time to reach maximum blood concentration.
Source: Post-text Table 14.2.2.5

Reviewer's Comment: *The serum DHT/T $C_{avg.168h}$ ratio for XYOSTED was approximately 0.07 and did not exceed the normal limit reported in literature (i.e., 0.05-0.33 reported by Diver et al., 2003). The mean serum DHT/T $C_{avg.168h}$ ratio of 0.07 is comparable with the reported values of 0.05-0.11 from most of the other approved T replacement products. It should be noted that Weeks 1 and 12 pre-dose DHT/T ratios are comparable.*

Other Safety Assessments

Based on the evaluation of AEs, clinical laboratory variables, vital signs, and physical examination findings, treatment with XYOSTED was generally well tolerated. Less than 8% of patients had injection site observations of induration, bleeding, hematoma, ecchymosis, itching, or pain. However, treatment emergent adverse events (TEAEs) of hypertension and increased hematocrit and PSA levels were regularly reported.

Briefly, the Sponsor reported that in total, 125 (83.3%) patients had TEAEs during the study and 75 (50.0%) patients had a TEAE during the active treatment period. The most frequently reported TEAEs were increased hematocrit (21 [14.0%] patients), hypertension (19 [12.7%] patients), and increased PSA (18 [12.0%] patients). Hematocrit and PSA AEs were defined by the protocol and required XYOSTED discontinuation. Hypertension was part of the medical history in roughly half (49.3%) of study patients. Hypertension TEAEs were predominantly reported in patients with a history of hypertension. In addition, 16 of 19 (84.2%) patients with a TEAE of hypertension also had 1 or more hypertensive blood pressure readings (systolic $\geq$ 140 mmHg and/or diastolic $\geq$ 90 mmHg) during the Screening Period (prior to receiving the first dose of XYOSTED).

Per the Clinical reviewer, Dr. Debuene Chang, the percentage of subjects with hematocrit increase (defined as shift from normal range to above normal range) was 11.3% in the Phase 3 studies (Studies QST-13-003 and QST-15-005). Approximately 5% of study subjects in this study (Study QST-13-003) met the pre-defined study discontinuation criterion of hematocrit > 55%. The rate of PSA increase was 7.8% in the Phase 3 studies. The increase in hematocrit and PSA are not unexpected for T replacement therapy and it appears that these data are generally comparable to other approved products.

Overall, 30 (20.0%) patients had TEAEs that led to discontinuation from the study; the most frequently reported TEAEs that led to discontinuation were increased PSA and increased hematocrit, both of which were defined by the protocol, were considered related to and required discontinuation of XYOSTED.

Reviewer's Comment: *Confirmed increases from baseline to Week 12 in mean systolic blood pressure (SBP) (i.e., 4 mm Hg) and diastolic (DBP) (i.e., 2 mm Hg) remains an unresolved Safety issue for the review team. The Agency's Division of Cardiovascular and Renal Products (DCRP) consultants confirmed these mean increases from baseline. DCRP cautioned that "…as the mean baseline blood pressure increases, there could be a modest increase in cardiovascular risk."*

Conclusions:
Overall, 135 (90.0%) subjects had total T $C_{avg\ 168h}$ values within the normal T concentration range at Week 12 of weekly treatment of XYOSTED and the primary efficacy endpoint was met. In addition, there were no subjects with measured total T C_{max} >1,500 ng/dL, 1,800-2,500 ng/dL, or > 2,500 ng/dL at Week 12. Therefore, the key secondary safety endpoint regarding serum total T C_{max} was also met.

Based on the evaluation of AEs, clinical laboratory variables, vital signs, and physical examination findings, treatment with XYOSTED was generally well tolerated. However, treatment emergent adverse events (TEAEs) of hypertension and increased hematocrit and PSA levels were regularly reported. These safety concerns will be addressed by the Clinical review team.

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/s/

CHONGWOO YU
09/25/2017

DOANH C TRAN
09/25/2017