CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

NDA #:	209863 (Supporting Document 032 / eCTD # 0032)
Product Name:	Xyosted (Testosterone Enanthate) 50 mg, 75 mg, and 100 mg injection
Indication(s):	Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency of absence of endogenous testosterone – primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired)
Applicant:	Antares Pharma, Inc.
Dates:	Letter Date: March 29, 2018 PDUFA Date: September 29, 2018
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Sonia Castillo, Ph.D.
Concurring Reviewer:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Clinical Reviewer: Debuene Chang, M.D. Clinical Team Leader: Mark Hirsch, M.D.
Project Manager:	Jeannie Roule

This memo closes the NDA assignment in DARRTS for the statistical review team. This Class 2 complete response resubmission addresses the two issues outlined in the Complete Response Letter conveyed to the Applicant on October 20, 2017. These issues were: 1) that this testosterone enanthate product could cause a clinically meaningful increase in blood pressure, 2) that the Agency is unable to exclude drug causality for two cases of suicide attempt (including one completed suicide) and two cases of depression in the sponsor's development program. There are no statistical efficacy issues outlined in the Complete Response Letter that would preclude approval.

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/s/

SONIA CASTILLO
08/01/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Supporting Doc. #:	209863 / 0001
Drug Name:	Xyosted (Testosterone Enanthate) 50 mg, 75 mg, and 100 mg injection
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Date(s):	Letter Date: December 20, 20146 PDUFA Date: October 20, 2017
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Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Sonia Castillo, Ph.D.
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Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Debuene Chang, M.D., Clinical Reviewer Mark Hirsch, M.D., Clinical Team Leader
Project Manager:	Jeanie Roule
Key Words:	Clinical studies, NDA review

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1. EXECUTIVE SUMMARY

The one submitted study provides evidence demonstrating the efficacy of Xyosted (testosterone enanthate) injection for the treatment of adult male hypogonadism based on the percentage of men who achieved total serum testosterone levels within the normal range.

The evidence is based on achieving total serum testosterone levels within the normal range, defined as ≥ 300 ng/dL and ≤ 1100 ng/dL, after 12 weeks of treatment in at least 75% of men with the lower bound of the 95% confidence interval for the estimate of the percentage of achieving the total serum testosterone levels within the normal range no less than 65%.

2. INTRODUCTION

2.1 Overview

This submission consists of one open-label, single-arm, multicenter, dose titration study submitted to evaluate the efficacy and safety of Xyosted (testosterone ethanate) injection for the treatment of adult male hypogonadism. Table 2.1 presents a brief study summary.

Table 2.1
Brief Summary of Clinical Study for Testosterone Undecanoate (TU)

Study Number (Country / #) Dates of Study Conduct	Subject Population	Treatment	ITT[1] Population	Design[2]
QST-13-003 (United States / 27) July 2014 to Nov. 2015	Men aged 18 years or older with clinically verified hypogonadism (total testosterone levels < 300 ng/dL for each of one morning sample taken on two different days)	50 to 100 mg of testosterone ethanate weekly **Total**	150 **150**	OL,SA, DT, MC, 52-week

Source: Statistical Reviewer's listing.
[1] ITT = Intent to Treat, received investigational product
[2] OL = Open-label, SA = Single Arm, DT = Dose Titration, MC = Multicenter

The proposed indication is:

> *Xyosted (testosterone enanthate) injection is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.*
>
> - *Primary hypogonadism (congenital or acquired)*
> - *Hypogonadotropic hypogonadism (congenital or acquired.*

The proposed dose of testosterone enanthate is 50 mg to 100 mg injected once weekly.

Testosterone replacement is used to treat the symptoms of hypogonadism and according to the Applicant:

> Hypogonadism in men is a clinical syndrome in which low levels of serum testosterone are found in association with specific signs and symptoms. Failure of the testes to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa may be primary (i.e., due to disorders of the testes), or secondary (i.e., due to disruption at 1 or more levels of the hypothalamic-pituitary-testicular [HPT] axis). ...
>
> The impact of hypogonadism on the adult male is well understood. Lowering of testosterone concentrations in adult males is associated with rapid and marked loss of bone mineral density, increase in fat mass, and a loss of muscle mass and strength. Lowering of testosterone concentrations also results in hot flashes and a decrease in overall sexual activity, thoughts, and fantasies, and is linked to metabolic syndrome and depression. …
>
> As the decades-old standard of care for hypogonadism, testosterone enanthate (TE) is most frequently administered as an intramuscular (IM) bolus injection every 2 to 4 weeks. The limitations of this treatment are the need for frequent visits to a healthcare provider for injections and the fluctuations of testosterone levels experienced by patients due to the intermittent dosing schedules, which contribute to periods of hormone overexposure and underexposure, occurring early and late after injection, respectively. ...
>
> [Xyosted] is a new single-use, pressure-assisted, autoinjector prefilled with TE solution and is designed for subcutaneous (SC) self-administration for the treatment of hypogonadism in adult males. The doses administered subcutaneously by the [Xyosted] device are 50, 75, and 100 mg of TE weekly. [Xyosted] is expected to extend the therapeutic dosing potential of TE by improving its usability and avoiding fluctuating serum testosterone levels that could lead to variable effects. (*Source: Clinical Study Report QST-13-003, section 7, pages 31and 32*)

The study is designed to demonstrate the efficacy of testosterone enanthate for the treatment of adult male hypogonadism.

2.2 Data Sources

The application was submitted electronically. The submitted SAS data sets were complete and well documented. The following review items are located in the CDER Electronic Document Room as described below:

- The complete study report was submitted under submission date 12-20-2017 (eCTD Sequence Number 0001) which is located at \\CDSESUB1\evsprod\NDA209863\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hypogonadism\5351-stud-rep-contr\qst-13-003 and responses to information requests are located at \\Cdsesub1\evsprod\NDA209863\0004 , \\Cdsesub1\evsprod\NDA209863\0010 , and \\Cdsesub1\evsprod\NDA209863\0019 under submission dates 1-24-2017 (eCTD Sequence Number 0004), 4-7-2017 (eCTD Sequence Number 0010), and 6-29-2017 (eCTD Sequence Number 0019), respectively.
- Raw and derived data sets used for analysis and the data set define and program files are located at \\CDSESUB1\evsprod\NDA209863\0001\m5\datasets\qst-13-003 under submission date 12-20-2017 (eCTD Sequence Number 0001)

3. STATISTICAL EVALUATION

This section describes the study design, data and analysis quality, evaluation of efficacy, and study results.

3.1 Data and Analysis Quality

The submitted datasets were well documented and easily accessible. The derived efficacy datasets used for the primary efficacy analysis can be created from the raw datasets. I was able to reproduce the primary efficacy results as presented in the study report from the derived efficacy dataset based on frequency of events. The final statistical analysis plan was submitted prior to unblinding and there were no changes to the pre-specified primary analyses as presented in the protocol.

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

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

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

3.2 Evaluation of Efficacy

The Applicant has submitted one pivotal clinical study (QST-13-003) designed to demonstrate the efficacy and safety of testosterone ethanate (TE) injection for the treatment of adult male hypogonadism. This review will focus on the primary endpoint of percentage of men who achieve a normal total testosterone level.

3.2.1 Study QST-13-003: Design and Endpoints

Study QST-13-003 was a 52-week, open label, multiple-dose,dose-titration, multicenter, Phase 3 study to evaluate the efficacy and safety of TE administered subcutaneously once each week to adult males with hypogonadism. The study included a screening phase, a 12-week treatment titration phase, and an extended treatment phase to evaluate long-term safety. A pharmacokinetics profiles substudy at week 1 was also conducted in a subgroup of subjects but this review will not focus on the substudy.

Eligible subjects were adult men ≥18 years of age, in good health, with a documented diagnosis of hypogonadism (consistent signs and symptoms of androgen deficiency), and who had 2 morning serum total testosterone (TT) values <300 ng/dL during screening. Qualifying TT samples were collected as follows:

- Subjects were required to fast a minimum of 8 hours prior to TT blood sampling.
- The first TT level was obtained after completion of washout from current testosterone therapy, if applicable.
- Morning TT levels had to be obtained on separate visits and spaced no less than 7 and no more than 9 days apart.
- One repeat TT level was allowed if 1 of the 2 morning TT levels was ≥300 ng/dL. The repeat TT was required to be obtained no less than 7 and no more than 9 days after the second TT level was obtained.

Main exclusion criteria included: body mass index ≥40 kg/m^2, elevated hematocrit, elevated prostate specific antigen, untreated sleep apnea, and presence of a prostate nodule at the baseline physical examination.

Eligible subjects received the starting dose of Xyosted 75 mg and were trained on proper use of the Xyosted device, which was self-administered once each week on the same day of the week and at approximately the same time. Xyosted was provided in three blinded dose strengths of 50 mg/0.5 mL, 75 mg/0.5 mL, and 100 mg/0.5 mL. Each Xyosted device provided a single dose as a single injection.

Dose adjustments were made at week 7 based upon the week 6 blood TT concentration at the end of the 6-week dosing interval (C_{trough}) value. Dose titration criteria were as follows: decrease dose by 25 mg if TT $C_{trough} \geq 650$ ng/dL; increase dose by 25 mg if TT $C_{trough} < 350$ ng/dL; or maintain dose if TT 350 ng/dL $\leq C_{trough} < 650$ ng/dL.

At week 12, blood samples for pharmacokinetic analysis of TT were obtained from subjects at pre-dose and at specified times up to 168 hours after TE administration. The PK parameters listed below were calculated from the individual TT time data collected during the treatment titration phase week 12 profiles:

- $AUC_{(0\text{-}168h)}$: Area under the concentration-time curve from week 12/time 0 to week 12/Day 8 (1 week). The time points from pre-dose to 168 hours post-dose were used;
- $C_{avg168h}$: Average weekly concentration from week 12/time 0 to week 12/Day 8, calculated as $AUC_{(0\text{-}168h)} \div 168$ hrs

Upon completion of the 12-week treatment titration phase, patients remained on their Xyosted dose with adjustments to dose based on TT C_{trough} values implemented at scheduled intervals, if required. Subjects were followed and safety data was collected for an additional 40 weeks. Final study evaluations were completed at the 52nd week of treatment or at the point of early withdrawal.

Primary Efficacy Endpoint

The primary objective was to evaluate the efficacy of testosterone ethanate (TE) injection in adult men with hypogonadism based on the percentage of treated subjects that had a 168-hr average total testosterone concentration over the 7-day dosing interval (0-168 hours) ($C_{avg168h}$) in the normal range (≥ 300 ng/dL and ≤ 1100 ng/dL) after 12 weeks of therapy.

The primary efficacy variable was the percentage of treated subjects with a total T $C_{avg168h}$ value within the normal range at week 12. Success was defined as at least 75% of subjects had a TT $C_{avg168h}$ within the normal range (≥ 300 ng/dL and ≤ 1100 ng/dL) at week 12 and the lower bound of the associated 2-sided 95% confidence interval was at least 65%.

3.2.2 Study QST-13-003: Statistical Methodologies

The primary efficacy analysis population is defined as all subjects who received at least 1 dose of test product.

Primary Efficacy Endpoint

The pre-specified primary efficacy analysis is the percentage of subjects who attain a serum total T C_{avg} value within the normal range at week 12 in the efficacy population. This percentage is summarized descriptively and the 95% confidence interval is approximated by a binomial distribution.

The pre-specified primary efficacy analysis accounted for missing week 12 endpoint data as follows:

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

The primary efficacy sensitivity analysis accounted for missing week 12 data endpoint data as follows:

> If a subject did not have a valid $C_{avg168\ h}$, that is, if the subject discontinued before week 12 visit or the subject had a week 12 visit but the $C_{avg168\ h}$ was not calculable, the subject was included in the analysis as not having achieved TT $C_{avg168\ h}$ within the range.

Sample Size

The chosen sample size of 125 subjects fulfills the requirements that at least 75% of subjects meet the success criteria of a week 12 TT $C_{avg168h}$ within the pre-specified normal range ($\geq$ 300 ng/dL and $\leq$ 1100 ng/dL) and a lower bound for the 95% confidence interval of at least 65% (Values calculated using exact binomial methods). To account for drop outs, total of 150 subjects were enrolled so that 125 subjects complete through week 12.

3.2.3 Study QST-13-003: Subject Disposition and Baseline Characteristics

Table 3.2 presents the subject disposition for study QST-13-003. A total of 150 subjects were enrolled at 27 centers in the U.S. All 150 subjects took at least one dose of study drug and they all make up the efficacy population. Of these 150 subjects, 15 did not have a TT $C_{avg168h}$ at week 12. The discontinuation rate was 34.7% (52 subjects). Reasons for premature discontinuation from study in these 52 subjects included multiple reasons (19.3% or 29 subjects), withdrawal of consent (6% or 9 subjects), and adverse event (3.3% or 5 subjects).

Table 3.2
Study QST-13-003: Enrollment and Disposition of Subjects
(Efficacy Population: All Subjects Had at Least One Dose of Study Product)

	Xyosted (all doses)
Number of Enrolled	150
Number Who Took Study Product (Efficacy Population)	150
Completed Week 12 n (%)*	139 (92.7)
Completed Study n (%)	97 (64.7)
Discontinued n (%)*	52 (34.7)
Missing Study Completion Status n (%)	1 (0.7)
Primary Reason for Discontinuation n (%)*:	
Adverse Event	5 (3.3)
Non-Compliance	2 (1.3)
Withdrawal of Consent	9 (6.0)
Lost to Follow-Up	1 (0.7)
Sponsor's Request	2 (1.3)
Met Stopping Criteria	3 (2.0)
Other	1 (0.7)
Multiple	29 (19.3)

Source: Table 9 on page 70, Study QST-13-003 report and Statistical Reviewer's listing.
* With respect to number of subjects who took study product.

As noted above, 29 (19.3%) subjects were classified as having multiple reasons for study withdrawal. An information request was sent to the Applicant by the Division on June 19, 2017 for a revised summary of the "reasons for withdrawal" which was received on June 29, 2017. Table 3.3 presents a summary of the revised reasons for early withdrawal is presented in Table 3.3.

The majority of subjects were Caucasian (88.7%) and less than 65 years of age (81.3%). Subjects had a mean age of 53.4 years and a mean screening serum total testosterone concentration of 230.4 ng/dL. All subjects had hypogonadism but the type of hypogonadism (primary or secondary) was not specified.

Table 3.3
Study QST-13-003: Revised Disposition of Subjects
(Efficacy Population: All Subjects Had at Least One Dose of Study Product)

Reason for Early Withdrawal (subjects may be counted in more than 1 reason)	n (%)*
Adverse Event (not related to elevated PSA or HCT)	16 (10.7)
Elevated PSA	14 (9.3)
Elevated Hematocrit	7 (4.7)
Elevated PSA and Hematocrit	2 (1.3)
Elevated Testosterone (after on TE 50 mg and C_{trough} > 650 ng/dL)	6 (4.0)
Non-Compliance	
Withdrawal of Consent or Withdrawal by Subject	12 (8.0)
Lost to Follow-up	1 (0.7)
Other: All	11 (7.3)
Other: Met Stopping Criteria	5 (3.3)

Source: Table 6 from Clinical review; based on Sponsor IR response dated June 29, 2017 (eCTD Sequence Number 0019).
PSA- prostate specific antigen, HCT- hematocrit
Subjects could have been counted in >1 reason for early withdrawal.

3.2.4 Study QST-13-003: Results and Conclusions

Primary Efficacy Endpoint

This reviewer has verified the Applicant's pre-specified primary efficacy results, presented in Table 3.4, based on the percentage of subjects with a serum total testosterone $C_{avg168h}$ in the normal range at week 12. Efficacy was demonstrated with the percentage of subjects with a serum total testosterone $C_{avg168h}$ level within the normal range at week 12 of 92.7% (139 of 150 subjects) with 95% CI of 87.3% to 96.3%.

Table 3.4
Study QST-13-003: Percentage of Subjects with Serum Total Testosterone Level in the Normal Range [300 ng/dL ≤ $C_{avg168h}$ ≤ 1100 ng/dL] at Week 12
(Efficacy Population*)

Treatment Group	n	Normal Level	Percentage (95% C.I.)
Testosterone Enanthate	150	139	92.7 (87.3, 96.3)

Source: Table 14 on page 80 of Study QST-13-003 clinical study report and statistical reviewer's calculations.
* Efficacy population includes all subjects who took at least one dose of study product.

Primary Efficacy Sensitivity Analysis

The results of the sensitivity analysis are presented in Table 3.5. Efficacy was demonstrated for the sensitivity analysis with the percentage of subjects with a serum total testosterone $C_{avg168h}$ level within the normal range at week 12 of 90.0% (135 of 150 subjects) with 95% CI of 84.0% to 94.3%.

Table 3.5
Study QST-13-003: Sensitivity Analysis - Percentage of Subjects with Serum Total Testosterone Level in the Normal Range [300 ng/dL ≤ $C_{avg168h}$ ≤ 1100 ng/dL] at Week 12
(Efficacy Population*)

Treatment Group	n	Normal Level	Percentage (95% C.I.)
Testosterone Enanthate	150	135	90.0 (84.0, 94.3)

Source: Table 15 on page 80 of Study QST-13-003 clinical study report and statistical reviewer's calculations
* Efficacy population includes all subjects who took at least one dose of study product.

Of the 4 extra subjects with a normal serum TT level that are included in Table 3.4 but not included in Table 3.5, two subjects had a single TT concentration value at 168h post-dose at week 12 (552 ng/dL and 501 ng/dL) and two subjects had valid TT C_{avg168} values at week 1 from the pharmacokinetics substudy (449 ng/dL and 312

ng/dL). The two single TT concentration values and the two week 1 substudy TT $C_{avg168h}$ values were used to classify each subject as having a normal TT value per the pre-specified method to account for missing data (see the *Primary Efficacy Endpoint* section at the top of page 6).

3.3 Evaluation of Safety

For information about the evaluation of safety, refer to the clinical evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

No subgroup analyses by gender or geographic region were necessary because all subjects were men and the study was conducted in the United States. There were too few non-Caucasian subjects (< 12%) and too few subjects 65 years or older (< 20%) to conclude if the efficacy endpoint was similar by race or age group. The clinical reviewer did not identify any additional subgroup of interest for statistical review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

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

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

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

5.2 Collective Evidence

The one submitted study provides evidence demonstrating the efficacy of Xyosted (testosterone ethanate) injection for the treatment of adult male hypogonadism based on the percentage of men in the safety population who achieved total serum testosterone levels within the normal range.

The evidence is based on achieving total testosterone $C_{avg168h}$ levels within the normal range, defined as $\geq$ 300 ng/dL and $\leq$ 1100 ng/dL, after 12 weeks of treatment in at least 75% of men and with the lower bound of the 95% confidence interval for the estimate of the percentage of men achieving the total serum testosterone levels within the normal range no less than 65%. The percentage of men with a serum total T $C_{avg168h}$ level within the normal range at week 12 was 90.0% (135 of 150 subjects) with 95% CI of 84.0% to 94.3%.

5.2 Conclusions and Recommendations

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

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/s/

SONIA CASTILLO
09/13/2017

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