CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204516Orig1s000

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

NDA/BLA #:	204516
Supplement #:	
Drug Name:	Paroxetine Mesylate 7.5 mg capsule
Indication(s):	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
Applicant:	NOVEN Therapeutics, LLC
Date(s):	Submitted: 08/28/2012 PDUFA: 06/28/2013
Review Priority:	Standard
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Keywords: NDA review, analysis of covariance, multiple endpoints, ROC analysis

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1 EXECUTIVE SUMMARY

In this submission, the Applicant is seeking approval of paroxetine mesylate for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. To support this claim, the safety and efficacy data from two phase 3, double-blind, randomized, placebo-controlled clinical trials (N30-003 and N30-004) were submitted. This review evaluates to determine from a statistical perspective if the submitted information supports this claim.

In both studies (hereafter referred as studies -003 and -004), eligible subjects were randomized to receive either paroxetine mesylate (7.5 mg) or placebo in a 1:1 ratio, administered once daily at bedtime during the treatment period and were instructed to complete the daily hot flush diary during the treatment period. The duration of treatment period was 12 weeks in study -003 and 24 weeks in study -004. Study -004 was designed with a 24-week treatment period to assess the persistence of efficacy. Each treatment arm was planned to enroll 267 subjects to ensure the study had at least 85% and 95% power to detect a difference of 1.41 episodes in daily VMS frequency reduction and 0.08 in daily VMS severity reduction between paroxetine mesylate and placebo groups assuming 15% dropout rate.

In both studies, the following four co-primary efficacy endpoints were defined:

- change in frequency of moderate to severe VMS per day from baseline to Week 4;
- change in frequency of moderate to severe VMS per day from baseline to Week 12;
- change in severity of moderate to severe VMS per day from baseline to Week 4; and
- change in severity of moderate to severe VMS per day from baseline to Week 12.

In addition, the following two important secondary efficacy variables were also defined:

- clinical meaningfulness for the change from baseline in the VMS daily frequency if the placebo-adjusted reduction in moderate to severe VMS frequency from baseline is less than two hot flushes per day in study -003;
- persistence of efficacy at Week 24 in study -004.

In both studies, the Applicant analyzed each co-primary efficacy endpoint by the pre-specified rank-ANCOVA method i.e., an ANCOVA analysis on rank-transformed data. The comparison between paroxetine mesylate vs. placebo was based on the estimated least square (LS) mean difference of the rank transformed endpoint.

The reviewer confirmed the Applicant's analyses results using the same pre-specified statistical methods. Paroxetine mesylate reduced 1.2 and 1.3 more hot flushes per day at Week 4, and 0.9 and 1.7 more hot flushes per day at Week 12 compared to placebo, in studies -003 and -004, respectively. These reductions in frequency were statistically significant at both weeks compared to placebo in both studies. Paroxetine mesylate also reduced severity of hot flushes ranging from 0.03 to 0.05 compared to placebo at Weeks 4 and 12 in both studies. Although the reductions in severity were very small, they were statistically significant at Week 4 in both studies and significant only at week 12 in study -004.

The clinical meaningfulness of the placebo-adjusted reduction in daily VMS frequency was evaluated based on a "patient global improvement" anchoring question using ROC method in study -003. The results showed a clinically meaningful improvement in the reduction of VMS frequency in favor of paroxetine mesylate at Weeks 4 and 12 compared to placebo. The persistence of efficacy at Week 24, evaluated by a responder analysis, was also in favor of paroxetine mesylate treated subjects compared to placebo treated subjects.

From a statistical perspective, the results support the efficacy of paroxetine mesylate in the treatment of moderate to severe vasomotor symptoms in menopausal women.

2 INTRODUCTION

2.1 Overview

The Applicant, NOVEN Therapeutics LLC, seeks approval of paroxetine mesylate 7.5 mg capsules for treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

According to the Applicant, "paroxetine mesylate 7.5 mg is an orally administered selective serotonin reuptake inhibitor (SSRI) and is an alternative to hormone therapy for the treatment of moderate to severe VMS associated with menopause. Its efficacy is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxytryptamine, 5-HT)".

The Applicant has submitted two phase 3 clinical studies (-003 and -004) that were designed to demonstrate the safety and efficacy of paroxetine mesylate for the treatment of moderate to severe VMS associated with the menopause in postmenopausal women with more than 7 to 8 moderate to severe hot flushes per day or 50 to 60 per week. Table 1 presents a brief summary of each of the two studies addressed in this review.

Table 1 – List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
-003	Phase 3, double-blind, Randomized, multicenter, placebo-controlled	12-week	7 days	Randomized: Paroxetine mesylate: 306 Placebo: 308	Female >=40 years > 7 to 8 moderate to severe hot flushes per day (average) or 50 to 60 moderate to severe hot flushes per week for at least 30 days prior to the Screening Visit
-004	Phase 3, double-blind, Randomized, multicenter, placebo-controlled	24-week	7 days	Randomized: Paroxetine mesylate :285 Placebo: 285	Female >=40 years > 7 to 8 moderate to severe hot flushes per day (average) or 50 to 60 moderate to severe hot flushes per week for at least 30 days prior to the Screening Visit

Source: Reviewer's summary based on study reports.

The protocol for study -003 was submitted to the Division for special protocol assessment on 03/30/2011 and an agreement letter with minor comments was issued by the Division on 05/13/2011.

2.2 Data Sources

The study data, reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items are located in the Electronic Document Room at \\Cdsesub1\EVSPROD\NDA204516 under the submissions dated 08/28/2012, 12/08/2012, 01/07/2013 and 03/26/2013.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were two statistical analysis issues noted by the reviewer in the submission dated 08/28/2012, which are summarized as follows,

(1) Both the study protocols and statistical analysis plans pre-specified the primary efficacy analysis on the change from baseline in frequency and severity of VMS/day at Weeks 4 and 12. But the study reports provided analysis results on the weekly change from baseline in frequency and severity of VMS instead of daily as pre-specified.

A request to re-analyze the co-primary endpoints based on the average daily change was communicated to the Applicant on 11/29/2012 and the updated analysis results were submitted on 12/08/2012.

(2) For study -003, the analysis to demonstrate clinical meaningfulness was not conducted as pre-specified and agreed to by the Division. The response variable used in the Applicant's Receiver Operator Curve (ROC) analysis was not consistent with what was specified in the study protocol. Additionally, in the Applicant's submitted program "t14-2-1-1-5a.sas" for study -003, the approach used to find the threshold for change from baseline in VMS frequency by using [(b) (4) was not appropriate.

These issues in the ROC analysis were sent to the Applicant in a filing communication letter dated 11/ 09/2012. The Applicant was requested to re-conduct the ROC analysis for the binary outcome PGI satisfaction response ("satisfied" vs. unsatisfied") directly at Weeks 4 and 12 respectively. Sample SAS code for ROC analysis was sent to the Applicant in the filing communication letter. The updated analysis results were submitted on 12/08/2012.

Details on issue (2) and the Applicant's updated analysis were discussed and reviewed in section 3.2.4.2.1.

3.2 Evaluation of Efficacy

The efficacy evaluation of paroxetine mesylate is based on studies -003 and -004.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Both -003 and -004 were phase 3 multicenter, double-blind, randomized, placebo-controlled studies of paroxetine mesylate 7.5 mg capsules in female subjects with moderate to severe postmenopausal VMS. Each study was comprised of a screening period (up to 7 days), a placebo run-in period (12 days), a baseline visit, a double-blind treatment period and a post-treatment visit. After the initial screening period, eligible subjects entered into a 12-day run-in period. During the run-in period, subjects received placebo capsules in a single-blinded fashion and were instructed to complete hot flush diaries to record the number of hot flushes daily, the severity of each episode of hot flush. Following completion of the run-in period, subjects continuing to meet hot flush eligibility criteria were randomized to receive either

paroxetine mesylate (7.5mg) or placebo in a 1:1 ratio, administered once daily at bedtime during the treatment period and were instructed to continue completing the daily hot flush diary during the treatment period. The duration of treatment period was 12 weeks in study -003 and 24 weeks in study -004. Study -004 was designed with a 24-week treatment period to assess the persistence of efficacy at 24 weeks.

3.2.1.2 Endpoints

3.2.1.2.1 Primary Efficacy Endpoints

In both studies, the co-primary efficacy variables were defined as:

- change in frequency of moderate to severe VMS per day from baseline to Week 4;
- change in frequency of moderate to severe VMS per day from baseline to Week 12;
- change in severity of moderate to severe VMS per day from baseline to Week 4; and
- change in severity of moderate to severe VMS per day from baseline to Week 12.

The average daily frequency and severity of hot flushes for each subject during the run-in period were calculated as:

(b) (4)

(b) (4)

The severity (scoring) of hot flushes was defined as:

- Mild (1): sensation of heat without sweating
- Moderate (2): sensation of heat with sweating, able to continue activity
- Severe (3): sensation of heat with sweating, causing cessation of activity

The severity score for Day *i* was calculated as,

(b) (4)

The average daily severity score of hot flushes during the treatment period for a specific week was calculated as (b) (4)

In the event that a subject entered fewer than four days of diary data in a one week treatment interval, then the average of the hot flush diary data over the most recent previous seven days' entries was imputed, even if this interval spanned two treatment weeks.

3.2.1.2.2 Secondary Endpoints

Secondary endpoints were pre-defined by the Applicant in each study protocol. The following two were considered important by the Division

- clinical meaningfulness for the change from baseline in the VMS daily frequency if the placebo-adjusted reduction in moderate to severe VMS frequency from baseline is less than two hot flushes per day in study -003;
- persistence of efficacy at Week 24 in study -004.

When lower doses of estrogen products and nonhormonal treatments have been evaluated for the treatment of VMS, the FDA has observed that the magnitude of the treatment effect on VMS frequency is often less than that observed for "standard" dose hormonal therapies. In order to ensure that such treatment effects are still of clinical benefit to women, the FDA has requested that an analysis of the "clinical meaningfulness" of the change in VMS frequency be conducted for those products that do not demonstrate a placebo-adjusted reduction in moderate to severe VMS frequency from baseline of at least two hot flushes per day.

3.2.2 Statistical Methodologies

3.2.2.1 Analysis of Co-Primary Endpoints

For each co-primary endpoint, if the data was normally distributed, then the repeated measures analysis with baseline as covariate, treatment and week as factors and a random effect component (mixed model) would be used. If the normality assumption was not met then a rank-ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data with ranked baseline value of the endpoint as a covariate and treatment group as a factor would be used.

Descriptive statistics were reported for each endpoint. Graphical presentations of the change in frequency and severity from baseline to Week 12 were also provided. The primary analysis relied on the observed data with no imputation of missing values. For sensitivity assessment, the last observation carried forward (LOCF) method was used to impute the missing data of each co-primary endpoint for the subject who withdrew prematurely.

3.2.2.2 Analysis of Secondary Endpoints

3.2.2.2.1 Study -003: Clinical Meaningfulness

In study -003, the Applicant pre-specified an analysis to evaluate the clinically meaningfulness of the observed treatment effect, using the following steps if the difference between paroxetine mesylate and placebo in the change from baseline in average daily frequency of moderate to severe hot flushes was < 2 and statistically significant at Weeks 4 and 12.

a) First, all MITT subjects regardless of treatment assignment, were categorized into two groups (i.e., satisfied and unsatisfied) based on a 7-point Patient Global Impression (PGI) questionnaire administered at Weeks 4 and 12 that assessed the subject improvement in VMS. Subjects were considered "satisfied" with their treatment if their response to the question "Compared to before starting the study medication, how would you describe your hot flushes now?" was 'Very much better' (1), 'Much better' (2) or 'A little better' (3) and were considered unsatisfied if the response to the same question was

'No change' (4), 'A little worse' (5), 'Much worse' (6) or 'Very much worse' (7). LOCF was used to handle any missing PGI score for this analysis.

b) The Division requested that a second analysis be conducted using a different definition of satisfaction. For this analysis, subjects would be considered satisfied with their treatment if their response to the question were 'Very much better' (1) or 'Much better' (2). Subjects with responses of 'A little better' (3) or worse (4-7) were considered unsatisfied.

This was the definition that the Division had recommended, as it was more conservative to consider that women who experienced only a "little" improvement might not find this satisfactory, particularly if the drug also had unpleasant side effects.

c) Using this category of "satisfied" and "unsatisfied" as a dependent variable, a logit model was fit to perform a receiver operating characteristic (ROC) analysis in order to determine the threshold for a clinically meaningful reduction in VMS frequency.

d) Based on the threshold established above, a responder analysis was performed by categorizing women in the paroxetine mesylate and placebo groups as responders or non-responders. Responders were defined as those subjects who achieve a mean daily hot flush frequency reduction greater than the established threshold and non-responders were defined as those subjects whose daily hot flush frequency reduction was less than or equal to the established threshold.

e) A logit model was then used to compare the proportion of responders between the treatment groups adjusting for the baseline number of hot flushes as a covariate in the model.

This analysis was conducted at Weeks 4 and 12 respectively.

3.2.2.2.2 Study -004: Persistence of Efficacy at Week 24

In study -004, an analysis was planned to assess the persistence of efficacy at Week 24 using the following responder analysis. Responders were defined as those subjects who achieved ≥ 50% reduction from baseline in moderate to severe VMS frequency at Week 24, the percent change in VMS frequency was calculated using the formula:

Persistence would be demonstrated by showing a statistically significant difference in having 50% or more reduction at Week 24 compared to baseline between the active and the placebo treatment groups. A logit model was used to analyze the proportion of hot flush frequency reduction responders with baseline number of hot flushes as a covariate in the model. In this analysis subjects who dropped out before Week 24 were considered failures, along with those who achieved <50% reduction from baseline.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In study -003, a total of 614 subjects were randomized into the study (306 subjects to the paroxetine mesylate group and 308 subjects to the placebo group). A similar percentage of subjects in both groups completed the study; 271 of the 306 randomized in the paroxetine group (88.6%) and 278 of the 308 subjects randomized to placebo (90.3%). Details of subject disposition in study -003 are summarized in Table 2.

Table 2 – Study -003: Subjects Disposition

	Paroxetine mesylate n (%)	Placebo n (%)	Total n (%)
Number randomized	306	308	614
Received ≥1 dose of study drug*	301 (98.4)	305(99.0)	606 (98.7)
Completed study	271 (88.6)	278 (90.3)	549 (89.4)
Discontinues from study	35 (11.4)	30 (9.7)	65 (10.6)
Reasons for participation discontinuation			
AE/SAE	8 (2.6)	4 (1.3)	12 (2.0)
At their own request	8 (2.6)	12 (3.9)	20 (3.3)
Columbia Suicide Severity Rating Scale	5 (1.6)	2 (0.6)	7 (1.1)
In the Investigator's or Sponsor's opinion, continuation in the study would be detrimental to the subject's well-being	2 (0.7)	1 (0.3)	3 (0.5)
The subject not able to comply with study requirements	1 (0.3)	2 (0.6)	3 (0.5)
Other: Not specified	0	1 (0.3)	1 (0.2)
Other: Eligibility criteria not met	2 (0.7)	4 (1.3)	6 (1.0)
Other: Lack of efficacy	2 (0.7)	0	2 (0.3)
Other: Lost to follow-up	5 (1.6)	4 (1.3)	9 (1.5)
Other: Noncompliance	1 (0.3)	0	1 (0.2)
Other: Withdrew consent	1 (0.3)	1 (0.3)	2 (0.3)

Source: Table 7 in -003 study report.
According to the NOVEN's response on 01/07/2013, drug intake was unknown for 4 subjects in paroxetine mesylate group and 3 subjects in placebo group. They were counted as having received at least one dose of study medication by the reviewer.

In study -004, a total of 570 subjects were randomized into the study (285 subjects to the paroxetine group and 285 subjects to the placebo group). All but one of the randomized subjects (99.8%) received at least one dose of study drug. A total of 82.5% of the paroxetine group and 76.5% of the placebo group completed the study. Details of subject disposition in study -004 are summarized in Table 3.

For both studies, the most common reasons for study discontinuation were AE and subject's own request.

Table 3 – Study -004: Subjects Disposition

	Paroxetine mesylate n (%)	Placebo n (%)	Total n (%)
Number randomized	285	285	570
Received ≥1 dose of study drug	285 (100.0)	284 (99.6)	569 (99.8)
Completed study	235 (82.5)	218 (76.5)	453 (79.5)
Discontinues from study	50 (17.5)	67 (23.5)	117 (20.5)
Reasons for participation discontinuation			
AE/SAE	15 (5.3)	15 (5.3)	30 (5.3)
At their own request	15 (5.3)	35 (12.3)	50 (8.8)
Suicidality Tracking Scale	3 (1.1)	1 (0.4)	4 (0.7)
In the Investigator's or Sponsor's opinion, continuation in the study would be detrimental to the subject's well-being	0 (0.0)	2 (0.7)	2 (0.4)
The subject not able to comply with study requirements	1 (0.4)	4 (1.4)	5 (0.9)
Other: Not specified	0 (0.0)	1 (0.4)	1 (0.2)
Other: Elective surgery	1 (0.4)	0 (0.0)	1 (0.2)
Other: Eligibility criteria not met	1 (0.4)	2 (0.7)	3 (0.5)
Other: Lack of efficacy	0 (0.0)	2 (0.7)	2 (0.4)
Other: Lost to follow-up	9 (3.2)	3 (1.1)	12 (2.1)
Other: Noncompliance	1 (0.4)	1 (0.4)	2 (0.4)
Other: Relocation	2 (0.7)	1 (0.4)	3 (0.5)
Other: Withdrew consent	2 (0.7)	0 (0.0)	2 (0.4)

Source: Table 8 in -004 study report.

For primary efficacy and safety analyses, the Applicant pre-defined the following populations in both studies,

- MITT population: all consented and randomized subjects who had valid baseline hot flush diary data, received at least 1 dose of their randomized treatment, and had at least 1 day of on-treatment daily diary data.
- Safety population: all randomized subjects who received at least 1 dose of their randomized treatment and had at least 1 post-treatment safety assessment.

The numbers of subjects in each defined analysis populations were presented in Table 4. A total of 606 out of 614 (98.7%) subjects were included in MITT population in study -003, and 568 out of 570 (99.6%) subjects were included in MITT population in study -004.

Table 4 – Summary of Analysis Populations in studies -003 and -004

Study Analysis Population	Paroxetine mesylate n (%)	Placebo n (%)	Total n (%)
Study -003 (N)	306	308	614
MITT	301 (98.4)	305 (99.0)	606 (98.7)
Safety	301 (98.4)	305 (99.0)	606 (98.7)
Study -004 (N)	285	285	570
MITT	284 (99.6)	284 (99.6)	568 (99.6)
Safety	285 (100)	284 (99.6)	569 (99.8)

Source: Table 9 in -003 study report and Table 10 in -004 study report.

The demographics and baseline characteristics of the treatment groups are summarized in the Appendix (Tables 11-12) for studies -003 and -004 respectively. In both studies, more than 60% of subjects were white (64.7% in -003; 75.5% in -004). The mean age of subjects was 54.7 years in study -003 and was 54.4 years in -004. At baseline, the mean BMI was 29.47 kg/m^2 in study -003 and 28.14 kg/m^2 in -004. More than 80% of subjects had natural menopause onset in each study (study -003: 81.7%; study -004: 80.5%).

3.2.4 Results and Conclusions

3.2.4.1 Results for Co-Primary Efficacy Endpoints

The Applicant had pre-specified an alternative analysis in case the data were not determined to be normally distributed. Due to the violation of normal assumption (Kolmogorov-Smirnov, P-value<0.01) of the data for each co-primary endpoint, each endpoint was analyzed by the pre-specified rank-ANCOVA method.

Results are summarized in Tables 5-6, and depicted in Figures 1-2. Subjects had a median of about 10 daily moderate to severe hot flushes at baseline. Overall, the difference between paroxetine mesylate and placebo on the median reduction of average daily frequency of VMS was consistent across the two studies at Week 4 (median differences of 1.2 and 1.3 in study -003 and study -004, respectively). However, the improvement at Week 12 appeared to diminish by about one-fourth in study -003 (median difference: 0.9), while efficacy was maintained in study -004 (median difference: 1.7). The comparisons between paroxetine mesylate and placebo on the reduction of average daily frequency of VMS at both Weeks 4 and 12 achieved statistical significance in both studies (p-values <0.05).

At baseline, subjects had a median hot flush severity score of about 2.50 in both studies. The difference between paroxetine mesylate and placebo on the median reduction of average daily severity of VMS was small at Weeks 4 and 12, ranging from 0.03 to 0.05. The comparisons between paroxetine mesylate and placebo on the reduction of daily severity of VMS achieved statistical significance at Week 4 in both studies, but only at Week 12 in study -004.

Table 5 – Study -003: Changes in the Daily Frequency and Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 (MITT Population)

	Frequency		Severity	
	Paroxetine mesylate	**Placebo**	**Paroxetine mesylate**	**Placebo**
Baseline				
N	301	305	301	305
Mean (SD)	11.79 (4.87)	11.65 (4.39)	2.528 (0.304)	2.526 (0.306)
Median	10.43	10.43	2.537	2.538
Change from baseline at Week 4				
N	289	293	281	289
Mean (SD)	-4.71 (4.00)	-3.36(4.65)	-0.091(0.253)	-0.046 (0.227)
Median	-4.29	-3.14	-0.052	0.000
Median Difference	-1.15		-0.052	
P-value[#]	<0.0001		0.0017	
Change from baseline at Week 12				
N	264	274	236	253
Mean (SD)	-6.22 (4.53)	-5.33 (5.31)	-0.104 (0.294)	-0.084 (0.294)
Median	-5.93	-5.00	-0.058	-0.018
Median Difference	-0.93		-0.040	
P-value[#]	0.0090		0.1658	

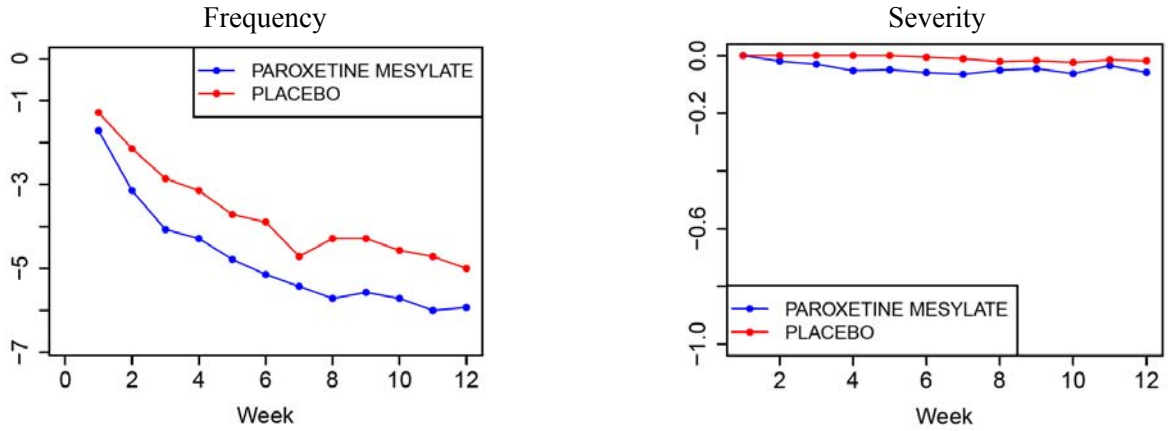
Source: Table 14.2.2.01A1 and Table 14.2.2.01_SEVA1 in -003-responsetables.pdf (dated 12/07/2012); Reviewer's analysis.
P-value is obtained from rank-ANCOVA model.

Table 6 – Study -004: Changes in the Daily Frequency and Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 (MITT Population)

	Frequency		Severity	
	Paroxetine mesylate	Placebo	Paroxetine mesylate	Placebo
Baseline				
N	284	284	284	284
Mean (SD)	10.83(3.86)	10.90 (3.96)	2.525 (0.299)	2.532(0.315)
Median	9.86	9.57	2.535	2.523
Change from baseline at Week 4				
N	276	274	268	271
Mean (SD)	-4.13 (4.02)	-2.71(4.31)	-0.092(0.243)	-0.059 (0.217)
Median	-3.79	-2.50	-0.040	-0.008
Median Difference	-1.29		-0.032	
P-value[#]	<0.0001		0.0368	
Change from baseline at Week 12				
N	257	244	245	236
Mean (SD)	-5.31 (4.67)	-3.94 (5.13)	-0.126 (0.315)	-0.066 (0.264)
Median	-5.57	-3.86	-0.051	0.000
Median Difference	-1.71		-0.051	
P-value[#]	0.0001		0.0064	

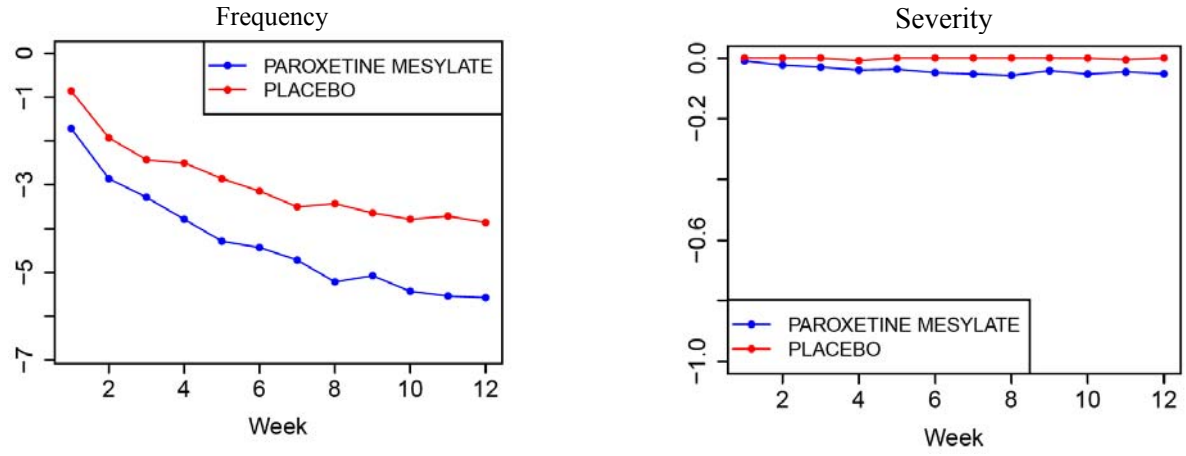
Source: Table 14.2.2.01A1 and Table 14.2.2.01_SEVA1 in -004-responsetables.pdf (dated 12/07/2012); Reviewer's analysis.
P-value is obtained from rank-ancova model.

Figure 1 – Study -003: Median Change from Baseline in the Daily Frequency and Severity of Moderate to Severe VMS



Source: Reviewer's analysis.

Figure 2 – Study -004: Median Change from Baseline in the Daily Frequency and Severity of Moderate to Severe VMS



Source: Reviewer's analysis.

Sensitivity analyses of the co-primary endpoints were conducted for the MITT population to evaluate the robustness of the data and the impact of subject withdrawal. These analyses used LOCF imputation for missing data points, (e.g., from subjects who were withdrawn prematurely or discontinued from the treatment). The results of the sensitivity analyses were consistent and similar to the primary analyses results using the observed data only.

3.2.4.2 Results for Secondary Efficacy Endpoints

3.2.4.2.1 Study -003: Clinical Meaningfulness of Change in VMS frequency

As seen from the efficacy analysis of change from baseline in daily frequency of moderate and severe VMS, the median difference was <2 per day. Therefore, the analysis to evaluate whether this improvement was clinically meaningful according to the subject's overall assessment of the treatment benefit based on a PGI anchoring question as described in section 3.2.2.2 was conducted in study -003.

Reviewer's comments on the analysis results submitted on 08/28/2012:

In the submission dated 08/28/2012, for study -003, the response variable used in the Applicant's Receiver Operator Curve (ROC) analysis was not consistent with what was specified in the -003 study protocol and agreed upon by the Division, which should be "satisfied" and "unsatisfied" based on answers to the PGI questionnaire at Weeks 4 and 12 for each subject, respectively.

(b) (4)

(b) (4)

which was not appropriate.

Also, the reviewer noticed that in the Applicant's submitted program 't14-2-1-1-5a.sas' for study -003, the approach to find the threshold for change from baseline in VMS frequency by using (b) (4) *was not appropriate. This was pointed out in the filing communication letter and the reviewer suggested the Applicant to use the following approach to find the threshold. The sample code for ROC analysis is*

(b) (4)

(b) (4)

Reviewer's comments on the Applicant's response submitted on 12/08/2012:

In the response dated 12/08/2012, the Applicant emphasized that (b) (4)

(b) (4)

" approach is not appropriate.

Results of analysis conducted as FDA requested:

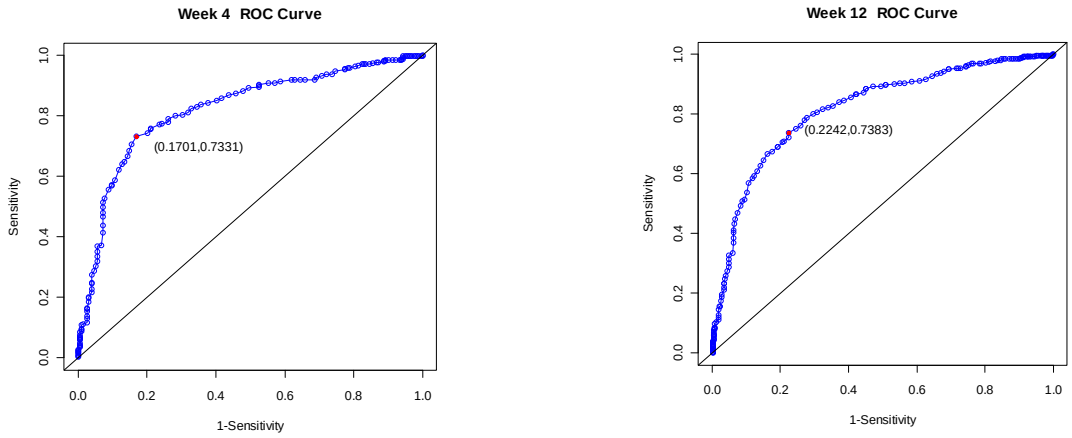
The Division requested the Applicant to re-conduct the responder analysis to demonstrate clinical meaningfulness to resolve the above two issues. In the logistic regression model that conducts the ROC analysis, use the binary variable defined by PGI, i.e. "satisfied" vs. "unsatisfied", as the response variable directly at Week 4 and Week 12 respectively.

In the submission made on 12/08/2012, the Applicant provided ROC analysis results as requested by the Division to address the above two issues.

For this analysis, the subjects in the MITT population, irrespective of treatment assignment, were categorized as "satisfied" vs. "unsatisfied" based on the PGI questionnaire results at Weeks 4 and 12, respectively. FDA recommended that the "satisfied" subjects were defined as those whose PGI response was ≤ 2, and "unsatisfied subjects" were defined as those whose PGI response was > 2.

After categorizing the subjects as "satisfied" and "unsatisfied", a ROC analysis was conducted by fitting a logistic regression model with satisfied vs. unsatisfied as the response and change from baseline in daily frequency of moderate and severe hot flushes as the covariate at Weeks 4 and 12 respectively. The ROC curves, i.e. sensitivity vs. 1-specificity for all possible covariate values are shown below.

Figure 3 – Study -003: ROC Curves at Weeks 4 and 12



Source: Reviewer's analysis.

The Applicant's analysis results did not report the threshold values for Weeks 4 and 12. The reviewer repeated the Applicant's analysis using the submitted program t14-2-1-1-6a.sas and dataset adroc.xpt submitted on 12/08/2012 to obtain these threshold values.

To maximize the sum of sensitivity and specificity, the threshold values at Weeks 4 and 12 were -4 (sensitivity=0.7331, specificity=0.8299), and -5.2857 (sensitivity=0.7383, specificity=0.7758) for change from baseline in daily frequency of VMS. Subjects were classified as responders if the change from baseline was not missing and < -4, at Week 4; < -5.2857 at Week 12. Otherwise, subjects were classified as non-responders. Subjects with missing change from baseline at either week were classified as non-responders. Table 7 shows at Week 4, a total of 266 over 606 subjects were responders. The median of change from baseline in daily frequency was -6.86 in the responders and -1.57 in the non-responders. At Week 12, 284 subjects were responders and the median change from baseline in daily frequency was -8.29 in the responders and -2.57 in the non-responders.

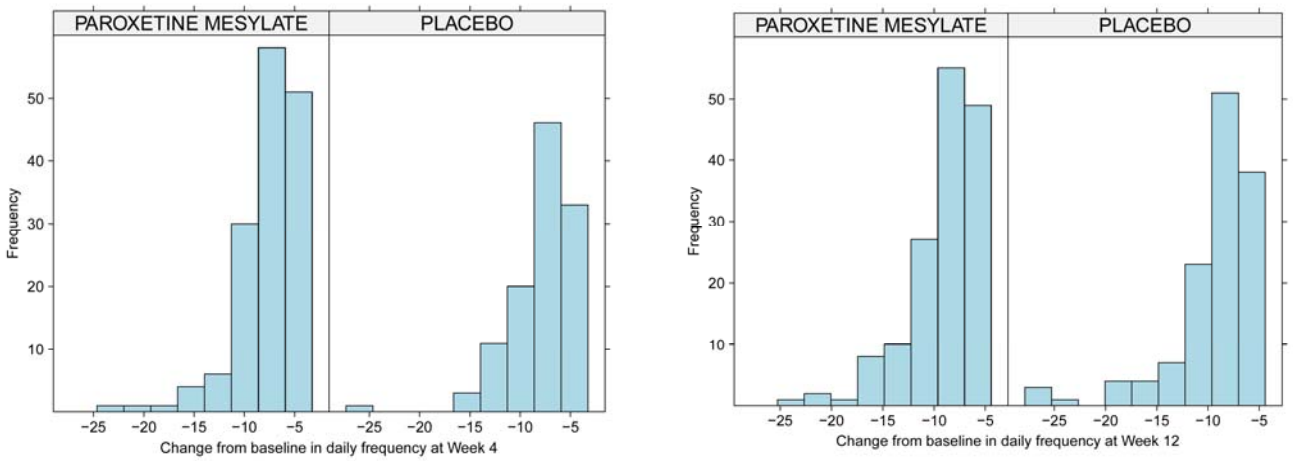
Table 7 – Study -003 Summary Statistics of Change from Baseline in the Daily Frequency of Moderate or Severe VMS by responders and non-responders based on the cut-off from ROC (PGI ≤ 2 as satisfied subjects)

Visit	Statistics	Responders	Non-Responders
Week 4	N	266	340
	Mean (SD)	-7.69 (3.12)	-0.95 (2.55)
	Median	-6.86	-1.57
Week 12	N	284	322
	Mean (SD)	-9.25 (3.74)	-1.87 (2.75)
	Median	-8.29	-2.57

Source: Reviewer's analysis.

Figure 4 presents the histograms of change from baseline in daily frequency of VMS among responders as defined above at Weeks 4 and 12 by treatment groups. As seen from the two histograms, the distributions of change from baseline in daily frequency of VMS were similar for the two treatment groups at both weeks.

Figure 4 – Study -003: Histogram of Change from Baseline in the Daily Frequency of Moderate or Severe VMS among Responders, by Treatment Arm



Source: Reviewer's analysis.

Table 8 shows that at Week 4, the responder rates were 50% vs. 37% in the paroxetine mesylate group and placebo group. The difference was statistically significant (p-value=0.0012) after adjusting for baseline daily frequency of VMS at 0.05 level. At Week 12, the responder rates were 51% vs. 43% in the paroxetine mesylate group and placebo group. The difference was not statistically significant (P-value=0.0550) after adjusting for baseline daily frequency of hot flushes at 0.05 level. No type I error control was done for this analysis.

Table 8 – Study -003 Percent of Responders based on the cut-off from ROC (PGI<=2 as satisfied subjects) MITT population

Visit	Cutoff	Statistics	Paroxetine mesylate n/N (%)	Placebo n/N (%)	p-value
Week 4*	-4.000	Responder	152/301 (50%)	114/305 (37%)	0.0012
		Non-responder	149/301 (50%)	191/305 (63%)	
Week 12	-5.2857	Responder	153/301 (51%)	131/305 (43%)	0.0550
		Non-responder	148/301 (49%)	174/305 (57%)	

Source: *Week 4 results are from the reviewer's analysis. Table 14.2.1.1.6A in -003-responsetables.pdf (dated 12/07/2012)

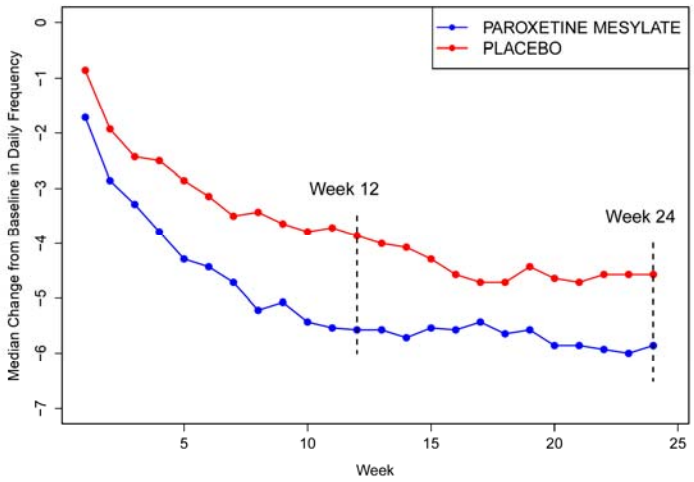
The Applicant also conducted the above analysis by defining "satisfied" and "unsatisfied" subjects as those whose PGI was ≤ 3 vs. >3 and the analysis results are presented in the Appendix.

3.2.4.2.2 Study -004: Assessment for Persistence of Efficacy at Week 24

Treatment benefit for reduction of VMS frequency at Week 24 was explored descriptively in study -004 by plotting the median changes in average daily frequency of moderate to severe VMS over time and analyzed using a responder analysis.

Figure 5 shows the median changes from baseline in daily frequency of VMS over treatment weeks.

Figure 5 – Study -004: Median Change from Baseline in the Daily Frequency of Moderate or Severe VMS to Week 24



Source: Reviewer's analysis.

In the responder analysis, responders were defined as subjects who achieved ≥ 50% reduction from baseline in the frequency of moderate to severe VMS at Week 24. Non-responders were defined as those who had < 50% reduction at Week 24 or who prematurely discontinued the study. Based on the MITT population, 47.5% of paroxetine mesylate treated subjects achieved ≥ 50% reduction from baseline at Week 24 in the frequency of moderate to severe VMS compared to 36.3% of placebo treated subjects (p-value 0.0066).

Table 9 – Study -004: Percentage of Responders at Week 24, MITT population

Visit	Statistics	Paroxetine mesylate n/N (%)	Placebo n/N (%)	p-value
Week 24	Responder	135/284 (47.54%)	103/284 (36.27%)	0.0066
	Non-responder	149/284 (52.46%)	181/284 (63.73%)	

Source: Table 14.2.2.16A in -004 study report.

3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Efficacy of paroxetine mesylate was also explored by subgroups defined by race (white and non-white), BMI (<32 kg/m^2, ≥32 kg/m^2) and menopause onset type (natural vs. surgical). In both studies, analyses of each co-primary efficacy endpoint by subgroups were performed using the same rank-ANCOVA model described previously in section 3.2.2.1 with additional terms for subgroup and treatment by subgroup interaction as appropriate.

4.1 Gender, Race, Age, and Geographic Region

Both phase 3 studies were conducted in the U.S. and enrolled female subjects only; therefore, analysis by gender and geographical region was not performed.

The efficacy results by race groups are shown in Tables 16-19. In study -003, the treatment by race group interaction for each co-primary endpoint was not statistically significant at the 0.10 level. The treatment effect of paroxetine mesylate on the change in average daily frequency and severity of VMS was smaller in white subjects compared to non-white subjects at both weeks. In study -004, the treatment by race group interaction was statistically significant at the 0.10 level for the change in daily frequency at Week 12 and change in daily severity at Week 4. The treatment effect of paroxetine mesylate on the change in average daily frequency and severity of VMS was shown in white subjects but not in non-white subjects.

Based on these results by race, studies -003 and -004 did not show consistent pattern of treatment effect of paroxetine mesylate relative to placebo in white and non-white subjects.

4.2 Other Special/Subgroup Populations

In both studies, analyses of each co-primary efficacy endpoint were also performed for subgroups of subjects based baseline BMI (<32 kg/m^2, ≥ 32 kg/m^2) and time of menopause (natural, surgical).

Subgroup analysis by baseline BMI:

The efficacy results by BMI defined groups are presented in Tables 20-23. In both studies, the treatment by BMI group interaction for each co-primary endpoint was not statistically significant at the 0.10 level.

Both studies showed that the treatment effect of paroxetine mesylate on the change in average daily frequency of VMS was similar in the BMI<32 subjects and BMI>=32 subjects at Week 4 and was numerically greater at Week 12 in the BMI<32 subjects. And the treatment effects on the change in average daily severity of VMS were numerically greater in the BMI<32 subjects compared with BMI>=32 subjects at both Weeks.

Subgroup analysis by type of menopause:

The clinical reviewer was interested in the efficacy of paroxetine mesylate by the type of menopause (natural vs. surgical). Post-hoc analysis was conducted by the reviewer and the analysis results are presented in Tables 24-27.

In study -003, the treatment by menopause onset type was statistically significant at the 0.10 level for the change in daily frequency at Weeks 4 and 12. The treatment effects of paroxetine mesylate on the change in average daily frequency and severity of VMS were similar in subjects with natural menopause compared with subjects with surgical menopause at Week 4 and smaller at Week 12.

In study -004, the treatment by menopause onset type was not statistically significant at the 0.10 level for each co-primary endpoint. The treatment effects of paroxetine mesylate on the change in average daily frequency and severity of VMS were numerically greater in subjects with natural menopause compared with subjects with surgical menopause at both weeks.

5 SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

The data from the two phase 3 studies showed that

1. Paroxetine mesylate 7.5 mg demonstrated statistically significant reductions from baseline in the daily frequency of moderate to severe VMS at Week 4 and Week 12 compared to placebo in both studies.
2. Paroxetine mesylate 7.5 mg demonstrated statistically significant reductions from baseline in the daily severity of moderate to severe VMS at Week 4 in both studies, but failed to meet criteria for statistical significance at Week 12 in study -003.
3. Paroxetine mesylate 7.5 mg demonstrated a clinically meaningful improvement in VMS frequency reduction at Week 4 based on the comparison of responder rates between the paroxetine mesylate and placebo groups. However, at Week 12 the responder rate was only marginally significant in favor of paroxetine mesylate.
4. Paroxetine mesylate 7.5 mg also demonstrated the persistence of treatment benefit on the daily VMS frequency reduction at Week 24.

From a statistical perspective, the totality of evidence supports the efficacy of paroxetine mesylate 7.5 mg in the treatment of moderate to severe vasomotor symptoms associated with menopause.

APPENDICES

Demographics

Table 10 – Study -003: Subject Demographics, MITT Population

Parameter		Paroxetine mesylate N=301	Placebo N=305	Total N=606
Age (years)	n	301	305	606
	Mean (SD)	54.9 (5.95)	54.5 (6.27)	54.7 (6.11)
	Median	54.0	53.0	54.0
	Min - Max	40 -73	40 -79	40 -79
Race, n (%)	White or Caucasian	190 (63.1)	202 (66.2)	392 (64.7)
	Black	106 (35.2)	93 (30.5)	199 (32.8)
	American Indian	2 (0.7)	1 (0.3)	3 (0.5)
	Asian	1 (0.3)	1 (0.3)	2 (0.3)
	European	0 (0.0)	1 (0.3)	1 (0.2)
	Other	2 (0.7)	7 (2.3)	9 (1.5)
Ethnicity, n (%)	Hispanic/Latino	27 (9.0)	37 (12.1)	64 (10.6)
	Not Hispanic/Latino	274 (91.0)	268 (87.9)	542 (89.4)
Height (in)	n	300	305	605
	Mean (SD)	64.5 (2.76)	64.4 (2.82)	64.4 (2.79)
	Median	64.2	64.2	64.2
	Min -max	56 -72	57 -73	56 -73
Weight (lb)	n	301	304	605
	Mean (SD)	172.8 (38.6)	174.7 (38.5)	173.7 (38.5)
	Median	166.7	169.7	168.0
	Min -max	80 -389	98 -338	80 -389
BMI (kg/m2)	n	300	305	605
	Mean (SD)	29.25 (6.21)	29.68 (5.94)	29.47 (6.07)
	Median	28.28	29.02	28.69
	Min -max	16.78 -60.67	19.02 -56.46	16.78 -60.67
Type of Menopause Onset, n (%)	Natural	242 (80.4)	253 (83.0)	495 (81.7)
	Surgical	59 (19.6)	52 (17.0)	111 (18.3)

Source: Table 10, 11 in the study -003 report.

Table 11 – Study -004: Subject Demographics, MITT Population

Parameter		Paroxetine mesylate N=284	Placebo N=284	Total N=568
Age (years)	n	284	284	568
	Mean (SD)	54.2 (5.47)	54.5 (5.74)	54.4 (5.60)
	Median	54.0	54.0	54.0
	Min -Max	41 -70	40 -74	40 -74
Race, n (%)	White or Caucasian	205 (72.2)	224 (78.9)	429 (75.5)
	Black	69 (24.3)	53 (18.7)	122 (21.5)
	Asian	3 (1.1)	6 (2.1)	9 (1.6)
	Native Hawaiian	1 (0.4)	-	1 (0.2)
	European	2 (0.7)	1 (0.4)	3 (0.5)
	Other	4 (1.4)	-	4 (0.7)
Ethnicity, n (%)	Hispanic/Latino	16 (5.6)	21 (7.4)	37 (6.5)
	Not Hispanic/Latino	268 (94.4)	263 (92.6)	531 (93.5)
Height (in)	n	284	284	568
	Mean (SD)	64.9 (2.48)	64.3 (2.75)	64.6 (2.63)
	Median	65.0	64.2	64.6
	Min -Max	54 -72	53 -72	53 -72
Weight (lb)	n	284	284	568
	Mean (SD)	166.5 (32.7)	166.4 (32.7)	166.5 (32.7)
	Median	162.0	161.2	161.5
	Min -Max	107 -263	100 -274	100 -274
BMI (kg/m2)	n	284	284	568
	Mean (SD)	27.95 (5.11)	28.33 (4.92)	28.14 (5.02)
	Median	27.43	27.74	27.49
	Min -Max	18.26 -40.6	18.67 -39.6	18.26 -40.6
Type of menopause onset (n [%])	Natural	227 (79.9)	230 (81.0)	457 (80.5)
	Surgical	57 (20.1)	54 (19.0)	111 (19.5)

Source: Table 11 in the study -004 report.

Table 12 – Study -003: Changes in the Daily Frequency and Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 (LOCF, MITT Population)

	Frequency		Severity	
	Paroxetine mesylate	Placebo	Paroxetine mesylate	Placebo
Baseline				
N	301	305	301	305
Mean (SD)	11.79 (4.87)	11.65 (4.39)	2.528 (0.304)	2.526 (0.306)
Median	10.43	10.43	2.537	2.538
Change from baseline at Week 4				
N	301	305	301	305
Mean (SD)	-4.70 (3.97)	-3.28 (4.74)	-0.091(0.255)	-0.042 (0.226)
Median	-4.29	-3.14	-0.047	0.000
Median Difference	-1.15		-0.047	
P-value#	<0.0001		0.0008	
Change from baseline at Week 12				
N	301	305	301	305
Mean (SD)	-6.10 (4.47)	-5.16 (5.31)	-0.117 (0.306)	-0.089 (0.307)
Median	-5.86	-5.00	-0.060	-0.017
Median Difference	-1.86		-0.043	
P-value#	0.0038		0.0728	

Source: Table 14.2.2.01_SevA1_LOCF and Table 14.2.2.01A1_LOCF in -003-locfresponsetables.pdf submitted on 01/07/2013.
P-value is obtained from rank-ANCOVA model.

Table 13 – Study -004: Changes in the Daily Frequency and Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 (LOCF, MITT Population)

	Frequency		Severity	
	Paroxetine mesylate	**Placebo**	**Paroxetine mesylate**	**Placebo**
Baseline				
N	284	284	284	284
Mean (SD)	10.83(3.86)	10.90 (3.96)	2.525 (0.299)	2.532(0.315)
Median	9.86	9.57	2.535	2.523
Change from baseline at Week 4				
N	284	284	284	284
Mean (SD)	-4.11 (4.00)	-2.72(4.25)	-0.100(0.243)	-0.057 (0.213)
Median	-3.71	-2.50	-0.040	-0.008
Median Difference	-1.21		-0.032	
P-value[#]	<0.0001		0.0084	
Change from baseline at Week 12				
N	284	284	284	284
Mean (SD)	-5.06 (4.72)	-3.60(5.05)	-0.125 (0.313)	-0.069 (0.272)
Median	-5.21	-3.36	-0.062	0.000
Median Difference	-1.85		-0.062	
P-value[#]	<0.0001		0.0020	

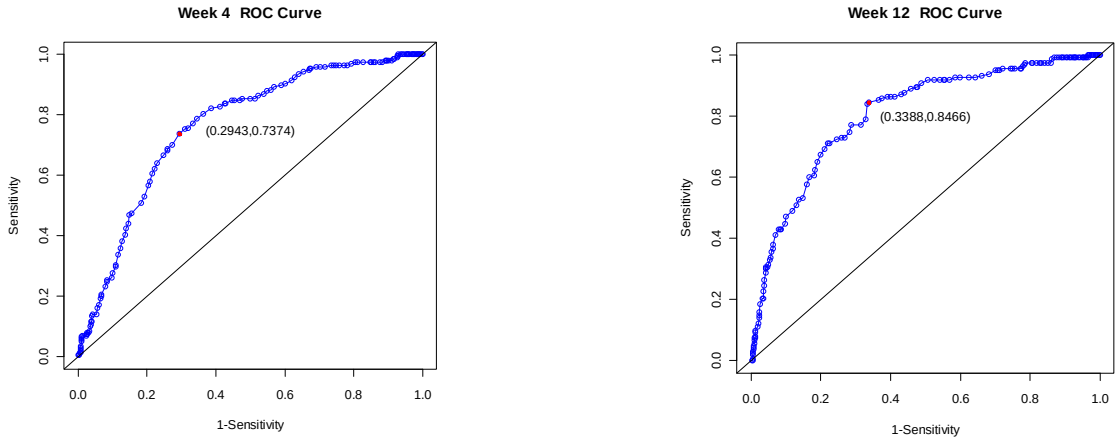
Source: Table 14.2.2.01_SevA1_LOCF and Table 14.2.2.01A1_LOCF in -004-locfresponsetables.pdf submitted on 01/07/2013.

P-value is obtained from rank-ancova model.

Study -003: Sensitivity analysis to demonstrate clinical meaningfulness

First, the satisfied subjects were defined as the subjects whose PGI <=3, and unsatisfied subjects were defined as those whose PGI>3. Second, a ROC analysis was conducted by fitting a logistic regression model with "satisfied" vs. "unsatisfied" as the response and change from baseline in daily frequency of moderate and severe hot flushes as the covariate at Weeks 4 and 12 respectively. The ROC curves, i.e. sensitivity vs. 1-specificity for all possible covariate values are shown below.

Figure 6 – Study -003: ROC Curves at Weeks 4 and 12 (sensitivity analysis)



Source: Reviewer's analysis.

The Applicant's analysis results did not report the cutoff values for Week 4 and Week 12. The reviewer repeated the Applicant's analysis using the submitted programs t14-2-1-1-5a.sas, t14-2-1-1-6a.sas and dataset adroc.xpt submitted on 12-08-2012.

To maximize the sum of sensitivity and specificity, the cutoff values at Week 4 and Week 12 were -3.1429 (sensitivity=0.7374, specificity=0.7057) and -5.4286 (sensitivity=0.8466, specificity=0.6612) for change from baseline in daily frequency of moderate and severe hot flushes. Subjects were classified as responders if the change from baseline was not missing and < -3.1429, at Week 4; < -5.4286 at Week 12. Otherwise, subjects were classified as non-responders. Subjects with missing change from baseline at either week were classified as non-responders. Table 14 shows at Week 4, a total of 320 out of 606 subjects were responders. The median of change from baseline in daily frequency was -6.36 in the responders and -0.86 in the non-responders. At Week 12, 271 subjects were responders. The median change from baseline in daily frequency was -8.43 in the responders and -2.71 in the non-responders.

Table 14 – Study -003 Summary Statistics of Change from Baseline in the Daily Frequency of Moderate or Severe VMS by responders and non-responders based on the cut-off from ROC (PGI<=3 as satisfied subjects)

Visit	Statistics	Responders	Non-Responders
Week 4	N (%)	320	284
	Mean (SD)	-7.02 (3.22)	-0.38 (2.43)
	Median	-6.36	-0.86
Week 12	N	271	335
	Mean (SD)	-9.44 (3.73)	-2.04 (2.78)
	Median	-8.43	-2.71

Source: Reviewer's analysis

Table 15 shows that at Week 4, the responder rates were 58% vs. 47% in the Paroxetine mesylate group and placebo group. The difference was statistically significant (P-value=0.0058) after adjusting for baseline daily frequency of hot flushes. At Week 12, the responder rates were 48% vs. 42% in the Paroxetine mesylate group and placebo group. The difference was not statistically significant (P-value=0.1332) after adjusting for baseline daily frequency of hot flushes.

Table 15 – Study -003 Percent of responders based on the cut-off from ROC (PGI<=3 as satisfied subjects) MITT population

Visit	Statistics	Paroxetine mesylate n/N (%)	Placebo n/N (%)	p-value
Week 4	Responder	176/301 (58%)	144/305 (47%)	0.0058
	Non-responder	125/301 (42%)	161/305 (53%)	
Week 12	Responder	144/301 (48%)	127/305 (42%)	0.1332
	Non-responder	157/301 (52%)	178/305 (58%)	

Source: Table 14.2.1.1.5A in -003-responsetables.pdf (dated 12/07/2012) and review's analysis.

Subgroup Analysis Results

Table 16 – Study -003 Changes in the Daily Frequency of Moderate to Severe VMS at Weeks 4 and 12 by Race (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline	
			Week 4	Week 12
White				
Placebo	n	202	195	185
	Mean (SD)	11.56 (4.19)	-3.60 (4.36)	-5.16 (5.31)
	Median	10.36	-3.57	-5.00
Paroxetine mesylate	n	190	185	176
	Mean (SD)	11.56 (4.54)	-4.75 (3.82)	-5.93 (4.37)
	Median	10.29	-4.43	-5.57
	Median Diff.		-0.86	-0.57
	P-value		0.0017	0.0357
Non-White				
Placebo	n	103	98	89
	Mean (SD)	11.82 (4.79)	-2.88 (5.17)	-5.69 (5.31)
	Median	10.57	-2.64	-5.14
Paroxetine mesylate	n	111	104	88
	Mean (SD)	12.20 (5.33)	-4.53 (4.32)	-6.80 (4.81)
	Median	10.86	-4.14	-6.79
	Median Diff.		-1.50	-1.65
	P-value		0.0062	0.1392
P-value for treatment by race group interaction term			0.7085	0.9163

Source: Reviewer's analysis.

Table 17 – Study -003 Changes in the Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 by Race (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
White				
Placebo	n	202	193	175
	Mean (SD)	2.516 (0.310)	-0.057 (0.229)	-0.086 (0.288)
	Median	2.531	-0.017	-0.020
Paroxetine mesylate	n	190	180	158
	Mean (SD)	2.549 (0.310)	-0.079 (0.239)	-0.095(0.278)
	Median	2.563	-0.033	-0.039
	Median Difference		-0.016	-0.019
	P-value		0.1010	0.6689
Non-White				
Placebo	n	103	96	78
	Mean (SD)	2.545 (0.298)	-0.023 (0.224)	-0.079 (0.311)
	Median	2.540	0.000	-0.013
Paroxetine mesylate	n	111	101	78
	Mean (SD)	2.491 (0.291)	-0.112 (0.276)	-0.122 (0.323)
	Median	2.520	-0.063	-0.091
	Median Difference		-0.063	-0.078
	P-value		0.0042	0.1048
P-value for treatment by race group interaction term			0.1342	0.2486

Source: Reviewer's analysis.

Table 18 – Study -004 Changes in the Daily Frequency of Moderate to Severe VMS at Weeks 4 and 12 by Race (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
White				
Placebo	n	224	216	190
	Mean (SD)	10.97 (4.06)	-2.78 (4.46)	-4.04 (5.21)
	Median	9.71	-2.57	-3.86
Paroxetine mesylate	n	205	200	188
	Mean (SD)	10.65 (3.60)	-4.46 (3.87)	-5.67 (4.62)
	Median	9.86	-4.43	-6.07
	Median Difference		-1.86	-2.19
	P-value		<.0001	<.0001
Non-White				
Placebo	n	60	58	54
	Mean (SD)	10.66 (3.59)	-2.47 (3.70)	-3.61 (4.87)
	Median	9.36	-2.43	-3.57
Paroxetine mesylate	n	79	76	69
	Mean (SD)	11.29 (4.46)	-3.26 (4.31)	-4.31 (4.69)
	Median	9.86	-2.36	-3.37
	Median Difference		0.07	0.20
	P-value		0.4050	0.8724
P-value for treatment by race group interaction term			0.1267	0.0330

Source: Reviewer's analysis.

Table 19 – Study -004 Changes in the Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 by Race (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
White				
Placebo	n	224	214	184
	Mean (SD)	2.528 (0.312)	-0.049 (0.215)	-0.061 (0.261)
	Median	2.514	0	0
Paroxetine mesylate	n	205	193	177
	Mean (SD)	2.522 (0.286)	-0.105(0.251)	-0.142 (0.332)
	Median	2.549	-0.048	-0.074
	Median difference		-0.048	-0.074
	P-value		0.0032	0.0024
Non-White				
Placebo	n	60	57	52
	Mean (SD)	2.546 (0.330)	-0.096 (0.221)	-0.083 (0.278)
	Median	2.570	-0.049	-0.016
Paroxetine mesylate	n	79	75	68
	Mean (SD)	2.533 (0.333)	-0.059 (0.219)	-0.083 (0.263)
	Median	2.485	-0.008	-0.032
	Median difference		0.041	-0.016
	P-value		0.2503	0.9975
P-value for treatment by race group interaction term			0.0153	0.1489

Source: Reviewer's analysis.

Table 20 – Study -003 Changes in the Daily Frequency of Moderate to Severe VMS at Weeks 4 and 12 by BMI groups (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
BMI <32				
Placebo	n	212	206	196
	Mean (SD)	11.72 (4.45)	-3.63 (4.61)	-5.29 (5.24)
	Median	10.64	-3.29	-5.00
Paroxetine mesylate	n	221	211	193
	Mean (SD)	11.90 (4.91)	-5.02 (4.17)	-6.43 (4.66)
	Median	10.57	-4.43	-6.57
	Median Difference		-1.14	-1.57
	P-value		0.0001	0.0034
BMI ≥32				
Placebo	n	93	87	78
	Mean (SD)	11.47 (4.29)	-2.71 (4.71)	-5.44 (5.51)
	Median	10.43	-2.71	-5.36
Paroxetine mesylate	n	79	77	70
	Mean (SD)	11.51 (4.80)	-3.90 (3.39)	-5.67 (4.14)
	Median	10.29	-4.00	-5.00
	Median Difference		-1.29	0.36
	P-value		0.1034	0.6971
P-value for treatment by BMI group interaction term			0.5056	0.2336

Source: Reviewer's analysis.

Table 21 – Study -003 Changes in the Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 by BMI groups (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
BMI <32				
Placebo	n	212	203	179
	Mean (SD)	2.541 (0.308)	-0.056 (0.233)	-0.077 (0.307)
	Median	2.564	0	-0.009
Paroxetine mesylate	n	221	206	170
	Mean (SD)	2.518 (0.305)	-0.107 (0.261)	-0.111 (0.298)
	Median	2.537	-0.060	-0.060
	Median Difference		-0.060	-0.051
	P-value		0.0026	0.0957
BMI ≥32				
Placebo	n	93	86	74
	Mean (SD)	2.491(0.299)	-0.022 (0.212)	-0.010 (0.265)
	Median	2.494	-0.011	-0.042
Paroxetine mesylate	n	79	74	65
	Mean (SD)	2.561 (0.300)	-0.046 (0.228)	-0.087 (0.286)
	Median	2.549	-0.016	-0.075
	Median Difference		-0.005	-0.033
	P-value		0.2976	0.9231
P-value for treatment by BMI group interaction term			0.4215	0.3389

Source: Reviewer's analysis.

Table 22 – Study -004: Changes in the Daily Frequency of Moderate to Severe VMS at Weeks 4 and 12 by BMI groups (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
BMI <32				
Placebo	n	214	205	179
	Mean (SD)	11.12 (4.16)	-2.90 (4.29)	-4.14 (5.43)
	Median	9.79	-2.57	-3.86
Paroxetine mesylate	n	219	212	197
	Mean (SD)	11.09 (4.08)	-4.23 (4.08)	-5.56 (4.72)
	Median	10.14	-4.07	-5.86
	Median Difference		-1.50	-2.00
	P-value		0.0005	0.0004
BMI≥32				
Placebo	n	70	69	65
	Mean (SD)	10.26 (3.24)	-2.14 (4.36)	-3.39 (4.19)
	Median	9.29	-2.43	-3.29
Paroxetine mesylate	n	65	64	60
	Mean (SD)	9.95 (2.86)	-3.82 (3.86)	-4.48 (4.43)
	Median	9.14	-3.14	-4.50
	Median Difference		-1.71	-1.21
	P-value		0.0218	0.1701
P-value for treatment by BMI group interaction term			0.8236	0.7026

Source: Reviewer's analysis.

Table 23 – Study -004: Changes in the Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 by BMI groups (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
BMI <32				
Placebo	n	214	204	173
	Mean (SD)	2.539 (0.320)	-0.058 (0.218)	-0.058 (0.252)
	Median	2.531	0	0
Paroxetine mesylate	n	219	205	187
	Mean (SD)	2.544 (0.289)	-0.097 (0.240)	-0.138 (0.323)
	Median	2.552	-0.037	-0.051
	Median Difference		-0.037	-0.051
	P-value		0.0342	0.0036
BMI ≥32				
Placebo	n	70	67	63
	Mean (SD)	2.509 (0.300)	-0.063 (0.216)	-0.089 (0.296)
	Median	2.498	-0.031	-0.031
Paroxetine mesylate	n	65	63	58
	Mean (SD)	2.463 (0.324)	-0.078 (0.254)	-0.086 (0.283)
	Median	2.441	-0.050	-0.054
	Median Difference		-0.019	-0.023
	P-value		0.5865	0.6994
P-value for treatment by BMI group interaction term			0.5726	0.2862

Source: Reviewer's analysis.

Table 24 – Study -003: Changes in the Daily Frequency of Moderate to Severe VMS at Weeks 4 and 12 by menopause onset groups (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
Natural				
Placebo	n	253	242	225
	Mean (SD)	11.77 (4.41)	-3.42 (4.67)	-5.38 (5.37)
	Median	10.71	-3.14	-5.14
Paroxetine mesylate	n	242	232	212
	Mean (SD)	11.67 (4.82)	-4.77 (3.80)	-6.08 (4.51)
	Median	10.29	-4.43	-5.86
	Median Difference		-1.29	-0.72
	P-value		<.0001	0.0222
Surgical				
Placebo	n	52	51	49
	Mean (SD)	11.06 (4.31)	-3.05 (4.61)	-5.11 (5.05)
	Median	9.86	-2.71	-4.71
Paroxetine mesylate	n	59	57	52
	Mean (SD)	12.28 (5.11)	-4.44 (4.76)	-6.76 (4.59)
	Median	10.71	-3.43	-6.71
	Median Difference		-0.72	-2.00
	P-value		0.4762	0.2402
P-value for treatment by menopause onset group interaction term			0.2370	0.9760

Source: Reviewer's analysis.

Table 25 – Study -003: Changes in the Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 by menopause onset groups (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
Natural				
Placebo	n	253	239	210
	Mean (SD)	2.524 (0.307)	-0.055 (0.238)	-0.077 (0.300)
	Median	2.555	-0.010	-0.014
Paroxetine mesylate	n	242	224	190
	Mean (SD)	2.530 (0.311)	-0.082 (0.252)	-1.02 (0.299)
	Median	2.546	-0.053	-0.056
	Median Difference		-0.043	-0.042
	P-value		0.0266	0.1683
Surgical				
Placebo	n	52	50	43
	Mean (SD)	2.536 (0.304)	-0.002 (0.162)	-0.115 (0.271)
	Median	2.515	0	-0.022
Paroxetine mesylate	n	59	57	46
	Mean (SD)	2.521 (0.278)	-0.123 (0.258)	-0.114 (0.271)
	Median	2.527	-0.048	-0.091
	Median Difference		-0.048	-0.069
	P-value		0.0086	0.8898
P-value for treatment by menopause onset group interaction term			0.1672	0.6487

Source: Reviewer's analysis.

Table 26 – Study -004: Changes in the Daily Frequency of Moderate to Severe VMS at Weeks 4 and 12 by menopause onset groups (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
Natural				
Placebo	n	230	222	196
	Mean (SD)	10.77 (3.70)	-2.49 (4.11)	-3.69 (4.85)
	Median	9.57	-2.36	-3.71
Paroxetine mesylate	n	227	220	206
	Mean (SD)	10.97 (4.13)	-4.21 (4.00)	-5.48 (4.60)
	Median	9.86	-4.00	-5.71
	Median Difference		-1.64	-2.00
	P-value		<.0001	<.0001
Surgical				
Placebo	n	54	52	48
	Mean (SD)	11.47 (4.93)	-3.68 (4.98)	-4.98 (6.11)
	Median	9.64	-3.07	-4.21
Paroxetine mesylate	n	57	56	51
	Mean (SD)	10.25 (2.45)	-3.81 (4.13)	-4.60 (4.93)
	Median	9.86	-3.71	-4.57
	Median Difference		-0.64	-0.36
	P-value		0.7604	0.8526
P-value for treatment by menopause onset group interaction term			0.0786	0.0846

Source: Reviewer's analysis.

Table 27 – Study -004: Changes in the Daily Severity of Moderate to Severe VMS at Weeks 4 and 12 by menopause onset groups (MITT Population)

Subgroup Treatment	Statistics	Baseline	Change from baseline Week 4	Change from baseline Week 12
Natural				
Placebo	n	230	220	190
	Mean (SD)	2.537 (0.316)	-0.061 (0.213)	-0.072 (0.260)
	Median	2.531	-0.008	-0.003
Paroxetine mesylate	n	227	215	197
	Mean (SD)	2.524 (0.298)	-0.103 (0.239)	-0.138 (0.320)
	Median	2.544	-0.048	-0.067
	Median Difference		-0.040	-0.064
	P-value		0.0221	0.0078
Surgical				
Placebo	n	54	51	46
	Mean (SD)	2.511 (0.316)	-0.049 (0.234)	-0.040 (0.282)
	Median	2.517	-0.009	0.000
Paroxetine mesylate	n	57	53	48
	Mean (SD)	2.530 (0.306)	-0.051 (0.258)	-0.078 (0.290)
	Median	2.516	-0.011	-0.019
	Median Difference		-0.002	-0.019
	P-value		0.9803	0.4521
P-value for treatment by menopause onset group interaction term			0.3187	0.6003

Source: Reviewer's analysis.

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/s/

JIA GUO
05/22/2013

MAHBOOB SOBHAN
05/22/2013