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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 28, 2013
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204-516
Applicant	Noven Therapeutics, LLC
Date of Submission	August 28, 2012
PDUFA Goal Date	June 28, 2013
Proprietary Name / Established (USAN) names	Brisdelle Paroxetine
Dosage forms / Strength	Capsules; 7.5 mg (9.69 mg paroxetine mesylate)
Proposed Indication(s)	Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause
Recommendation:	***Approval***

1. Introduction

This NDA seeks marketing approval of a new indication (treatment of menopausal vasomotor symptoms or VMS) for a lower dose of an approved product, paroxetine mesylate, which is marketed under the tradename Pexeva. Pexeva was approved for the indication of major depressive disorder (MDD) and several other psychiatric indications in 2003 under NDA 21-299; the approved dose for MDD is 10-60 mg daily, depending on the indication. If approved, paroxetine would potentially be the first and only non-hormonal product approved for treatment of VMS.

VMS, or hot flushes/flashes, are symptoms of warmth and sweating that are very common (occurring in up to 75% of women) in the menopausal transition. Moderate VMS is defined as a sensation of heat with sweating that does not disrupt the woman's activities, while severe VMS is defined as a sensation of heat with sweating that causes transient cessation of activities. While VMS can be very bothersome, causing discomfort, embarrassment, and disruption of sleep, it is not a life-threatening condition. VMS may persist up to five years, or even longer in a minority of women, but is ultimately a self-limited condition.

There are a variety of hormonal drug products in different formulations (tablet, transdermal system, vaginal ring) approved for treatment of menopausal symptoms. In general, the efficacy of these hormone therapy (HT) products is very good, with a mean reduction of hot flushes by 2-7 events/day better than placebo. Most approved VMS products demonstrate a statistically significant and clinically meaningful reduction in the frequency of hot flushes by Week 4 of treatment, with the treatment effect maintained through at least 12 weeks of use (the duration of most HT clinical trials). The Division has generally considered that a reduction of at least two hot flushes per day better than placebo constitutes a clinically meaningful treatment effect. In addition, HT products (aside from some of the lower-dose products) are typically also approved for vulvovaginal atrophy, another bothersome symptom of menopause. Paroxetine has not sought this indication, and there is no physiological reason to believe it would ameliorate these symptoms.

All HT products contain either estrogen alone (used only in women without a uterus) or estrogen plus a progestin. The estrogen-only products have long carried a Boxed Warning about the risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen; this risk is mitigated by addition of a progestin. In 2002, safety data on HT from the Women's Health Initiative (WHI) study was published, showing increased risks of venous thromboembolism, stroke, myocardial infarction, invasive breast cancer and probable dementia. Since that time, HT labeling has included a Boxed Warning describing findings from the WHI and has recommended the use of "the lowest dose and for the shortest duration consistent with treatment goals and risks for the individual woman." A variety of lower dose products have been approved since the WHI study was published. The efficacy of the lower dose products is generally less than that of higher dose products, but, as most HT products have a range of dose options, women can start at the lowest dose and titrate up as needed to manage their symptoms. More recent data following the initial WHI publications suggest that risks of coronary heart disease and stroke are not increased in HT users aged 50-59, and that overall mortality is reduced in HT users.

In addition, both estrogen-alone and estrogen/progestin products are contraindicated in women with known, suspected, or history of breast cancer. Other labeled contraindications include other known or suspected estrogen-dependent neoplasia, active or history of DVT or PE, active or history of arterial thromboembolic disease (such as stroke or MI), known liver dysfunction or disease and known thrombophilic disorders. Therefore, there are significant subgroups of women, particularly those with current or a history of breast cancer, who may be symptomatic during menopause but unable to use the hormonal preparations. Many women who do not have absolute contraindications to use of HT are reluctant or unwilling to use HT due to publicity about the WHI findings. There is therefore both an absolute unmet need (in women with contraindications to HT) and a relative unmet need (in women who prefer not to use HT) for a non-hormonal VMS treatment.

Although the Applicant requested a priority review of this NDA per the criterion of an unmet medical need on the grounds that no satisfactory alternative non-hormonal therapy exists for this indication, the Division determined that a standard review was appropriate.

2. Background

2.1 DESCRIPTION OF PRODUCT

Paroxetine mesylate is a selective serotonin reuptake inhibitor (SSRI). Paroxetine was first marketed commercially in the US in 1992 as paroxetine hydrochloride under the brand name Paxil, which is indicated for MDD, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder and posttraumatic stress disorder.

Paroxetine mesylate has a chemical structure similar to paroxetine hydrochloride, the only difference being the associated salt. Paroxetine mesylate capsules are currently marketed as Pexeva (NDA 21-299, approved as a 505(b)(2) submission in 2003) for the indications of MDD, obsessive compulsive disorder, panic disorder and generalized anxiety disorder. Dosing ranges from an initial dose of 10 mg to a maximum of 60 mg/day, and vary by indication.

Current Pexeva labeling describes the following important safety issues:

- A boxed warning about risk of suicidality (class labeling for antidepressants)
- Serotonin syndrome (class labeling)
- Teratogenicity, particularly cardiovascular malformations, with first trimester exposure
- Precautions relating to a risk of seizures, potential reduction in efficacy of tamoxifen due to irreversible inhibition of CYP2D6, akathisia (psychomotor restlessness), hyponatremia, increased risk of bleeding events, bone fracture, and need for caution in patients with certain concomitant illnesses (e.g., narrow angle glaucoma)

Paroxetine mesylate has not been approved in any country for treatment of VMS, but is one of a number of non-hormonal treatments (including other antidepressants, herbal and soy products) that are sometimes used off-label to treat VMS symptoms. However, rigorous evidence of the safety and efficacy of such treatments is lacking.

2.2 REGULATORY HISTORY

The Division issued a draft guidance for clinical evaluation of hormonal products for menopausal symptoms in 2003, and has generally provided guidance based on this document for both hormonal and non-hormonal products intended to treat VMS. This document states that the VMS indication is to treat "moderate to severe vasomotor symptoms associated with the menopause." Clinical definitions of mild, moderate and severe VMS are provided, with moderate hot flushes defined as "sensation of heat with sweating, able to continue activity" and severe hot flushes defined as "sensation of heat with sweating, causing cessation of activity." Recommended entry criteria include postmenopausal women (defined as 12 months of spontaneous amenorrhea, 6 months of spontaneous amenorrhea with serum FSH > 40 mIU/mL, or six weeks post-surgical bilateral oophorectomy) who have a minimum of 7-8 moderate to severe hot flushes per day or 50-60 per week at baseline. Four co-primary endpoints are recommended:

- Mean change from baseline in frequency of moderate to severe hot flushes at Week 4
- Mean change from baseline in frequency of moderate to severe hot flushes at Week 12
- Mean change from baseline in severity of moderate to severe hot flushes at Week 4
- Mean change from baseline in severity of moderate to severe hot flushes at Week 12

The primary efficacy analyses are intended to show a clinically and statistically significant reduction of both frequency and severity at Week 4 that is maintained at Week 12. Daily diary entries can be used as the basis of the co-primary endpoints.

Paroxetine mesylate for VMS was developed under IND 76,636, and the Division and the Applicant had a number of discussions about the drug development program, study protocols and statistical analysis plans. At the April 2007 preIND meeting, the Division recommended that two adequate and well-controlled phase 3 studies would be needed to support the proposed indication, at least one of which should be conducted in the US. The Applicant agreed to follow the 2003 draft Guidance regarding co-primary endpoints.

In further advice provided in 2008 following review of the protocol for Study 003, the Division stated that a placebo-corrected reduction from baseline in the number of daily moderate to severe hot flushes of two hot flushes per day would meet the definition of a "clinically significant" reduction. It would not be acceptable to demonstrate statistically significant frequency and severity reductions at Week 4 but not at Week 12. An ANCOVA

analysis was acceptable to Division, but the Division did not agree to a responder analysis of the percent of women who experience moderate to severe hot flushes as a co-primary endpoint, in lieu of the Guidance-defined severity endpoint. The Division also requested the Applicant to evaluate the persistence of treatment benefit to 24 weeks of treatment.

An End-of-Phase 2 meeting was held in September 2010; at this time the Division and the Applicant discussed the demonstration of clinical meaningfulness that would be needed if the placebo-corrected VMS reduction was less than two hot flushes per day. A responder analysis based on a cutoff value identified using an anchoring global subject satisfaction questionnaire was recommended. The Division stated that "a product with a clinically meaningful treatment effect would have a statically significantly greater response rate in the treatment arm than in the placebo arm." Because the first trial (Study 004) was underway at the time of this meeting, the Division agreed that the Applicant could address the evaluation of clinical meaningfulness using an appropriate anchoring questionnaire in the planned second phase 3 study (Study 003). The Applicant agreed to evaluate the persistence of benefit to 24 weeks of treatment in one of the phase 3 studies. The Division informed the Applicant that it must conduct a formal evaluation of suicidality in the clinical trials according to current FDA guidelines for antidepressants.

The Applicant submitted a Special Protocol Assessment (SPA) for the Study 003 protocol and the Division issued a No Agreement letter in December 2010. Areas of disagreement included the planned evaluation of whether the treatment effect was clinically meaningful, a proposed key secondary endpoint of "awakening from sleep," and other issued relating to data collection and statistical methods. In a post-SPA meeting in February 2011, the Division stated that it was generally in agreement with revisions made by the Applicant and that a new SPA request should be submitted when the revised protocol was submitted for review. The Division requested that the cutoff used on the global satisfaction questionnaire dichotomize subjects with much improvement or better vs. a little improvement or worse. An SPA Agreement letter was issued for the Study 003 protocol in May 2011, following review of the revised protocol.

The Division provided further guidance on Study 004 in October 2011, including agreement to the proposed responder analysis to evaluate the persistence of benefit, with classification of subjects who prematurely discontinued as non-responders. An SPA was not requested for the Study 004 protocol.

A pre-NDA meeting was held in May 2012. The Division agreed to pooling safety data from the phase 3 and the phase 2 studies.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Ronald Orleans, stated in his review, dated May 29, 2013:

> *Based on the data submitted in Noven Therapeutics Inc. (the Applicant's) NDA submission, I recommend that NDA 204516 be approved for the treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause. This recommendation is based on the Applicant having demonstrated an acceptable safety and efficacy profile for this product.*

Team Leader Comment:
I concur with Dr. Orleans' recommendation for approval of paroxetine for treatment of VMS.

Dr. Orleans did not recommend any postmarketing risk management strategies, commitments or requirements.

3. CMC/Device

3.1 CMC

The drug substance is the same as that used to manufacture the approved Pexeva tablet and the manufacturing and specifications are the same with minor modifications.

The drug product is an immediate-release oral capsule that contains 9.69 mg of paroxetine mesylate, equivalent to 7.5 mg of paroxetine base. (b) (4) .

(b) (4). The requested 36 month expiry was granted, based on 18 months of registration stability data and 36 months of supportive stability data. The product should be stored at room temperature and protected from light and humidity.

The Office of Compliance found two sites involved in testing and the finished dose packaging site acceptable based on profile and three drug substance/drug product manufacturing, packaging and testing sites acceptable based on district recommendation; however, one of the drug product manufacturing sites had a pending regulatory action. For this reason, the overall recommendation was pending at the time of the initial chemistry review.

The primary Chemistry Reviewer, Caroline Strasinger, Ph.D., made the following recommendations in her review dated May 1, 2013:

> *This NDA has **not** provided sufficient information to assure identity, strength, purity and quality of the drug product.*
>
> *An overall "Acceptable" recommendation has **not** been made by the Office of Compliance.*
>
> *Labels and labeling (Description and How Supplied sections) are adequate.*
>
> *Therefore, from the ONDQA perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(1) ad 21 CFR 314.125(b)(13).*

On June 26, 2013, the Applicant withdrew the site with inspectional issues as a drug product manufacturer; its sole manufacturing facility is now a site that received an acceptable recommendation. Based on this action by the Applicant, the Office of Compliance issued an overall "ACCEPTABLE" recommendation on June 27, 2013. Dr. Strasinger amended her review on June 27, 2013 to reflect the Compliance recommendation and the Applicant's agreement to use the recommended dissolution specification. Her current recommendation is:

> *The specification for the drug product is now adequate. Additionally, the Office of Compliance has issued an overall "ACCEPTABLE" recommendation for all facilities involved.*
>
> *From the ONDQA perspective, this Application is now recommended for APPROVAL.*

No risk management strategies or phase 4 commitments/requirements were recommended.

3.2 Biopharmaceutics

The biopharmaceutics reviewer, Deepika Lakhani, Ph.D., reviewed the Applicant's proposed dissolution method and acceptance criteria and the use of dissolution to support two drug product manufacturing sites. The proposed dissolution method detected photo-unstable drug product and was found acceptable, but the dissolution criteria needed to be (b) (4) Q= (b) (4) at 20 minutes). The dissolution profile and f2 calculations supported the similarity of drug product manufactured at the two facilities. In her review dated April 26, 2013, Dr. Lakhani concluded that

> *From the Biopharmaceutics perspective an APPROVAL recommendation for NDA 204-516…cannot be granted as of April 26, 2013 due to the following pending information/agreement:*
>
> *- Agreement upon the recommended dissolution acceptance criterion*

Dr. Lakhani submitted an amendment to her review on May 24, 2013, in which she noted that the Applicant had agreed to the recommended dissolution acceptance criterion of Q= (b) (4) at 20 minutes. She made the following recommendation:

> *The ONDQA/Biopharmaceutics team has reviewed the amendment submitted on 8-MAY-2013. The following dissolution method for paroxetine mesylate capsules is deemed acceptable:*

Drug Name	***Dosage Form***	***USP Apparatus***	***Speed (rpm)***	***Medium***	***Volume (mL)***
Paroxetine Mesylate	*Capsule*	*II (paddle) with wire sinkers*	*75*	*simulated gastric fluid (pH 1.20 ± 0.05)*	*900 mL*

> *The following dissolution acceptance criterion has been recommended for paroxetine mesylate capsules and accepted by the Applicant:*
>
> ***Q= (b) (4) at 20 minutes***
>
> *From the Biopharmaceutics perspective, NDA 204-516 … (paroxetine mesylate) Capsules is recommended for APPROVAL.*

4. Nonclinical Pharmacology/Toxicology

The Applicant cross-referenced approved NDA 21-299 (Pexeva) for nonclinical toxicity testing of the drug product. There were no nonclinical studies submitted to support the new indication of treatment of VMS associated with menopause; none were needed because the proposed dose is lower than that approved for other indications.

Paroxetine binds to serotonin transporters in the synaptic membrane and inhibits reuptake of serotonin following its release from the nerve terminal. Because the physiological basis of VMS has not been established, the mechanism of action of paroxetine mesylate in potentially regulating VMS is not known.

The primary Toxicology Reviewer, Leslie McKinney, Ph.D., made the following recommendations in her review dated February 4, 2013:

> ***Recommendations on approvability:*** *This is a 505(b)(2) application. Noven Pharmaceuticals is relying on previous findings of safety for the active ingredient paroxetine from NDA 20-031 (Paxil®) and is cross-referencing its own NDA 21-299 and IND 76636 for paroxetine mesylate (Pexeva®) for support of this NDA.*
>
> *There were no nonclinical safety concerns identified for use of paroxetine for the new indication of treatment of vasomotor symptoms (VMS) in postmenopausal women. Based on previous approval of paroxetine at a dose greater than the proposed dose for treatment of VMS (7.5 mg/day), Pharm/Tox finds NDA 204516 approvable.*
>
> ***Recommendations for nonclinical studies:*** *None*
>
> ***Recommendations on labeling:*** *It should be noted that current labels for paroxetine drug products (Paxil®, Pexeva®) do not contain the pharmacologic class in the* ***Indications and Usage*** *section. Paroxetine has a designated established pharmacologic class (EPC) of 'serotonin reuptake inhibitor,' with recommended text for the label of 'selective serotonin reuptake inhibitor (SSRI).'*

The secondary pharmacology/toxicology reviewer, Alex Jordan, Ph.D., filed a memo on May 14, 2013, in which he concurred in Dr. McKinney's recommendation for approval.

Dr. McKinney also provided specific labeling recommendations that were conveyed to the Applicant.

5. Clinical Pharmacology

The Applicant submitted a single phase 1 single- and multiple dose pharmacokinetic (PK) study, a phase 2 proof-of-concept study, and cross-referenced NDA 20-031 (Paxil) and its own NDA 21-299 (Pexeva). The clinical trial formulation was the same as that to be marketed.

Brisdelle is an immediate release capsule that is completely absorbed after oral dosing. Although no food effect study was done with Brisdelle, based on information from the Paxil label, bioavailability is not expected to be affected by concomitant food intake. The proposed dosing is 7.5 mg once daily, at bedtime, with or without food. The phase 3 trials did not restrict dosing with respect to food intake. No justification of bedtime dosing was provided, and this is in distinction to Paxil and Pexeva labeling, which call for morning dosing. However, the safety and efficacy data from the phase 3 trials support acceptability of bedtime dosing.

The Applicant determined the PK profile of Brisdelle after single and repeated oral dosing in Study N30-005. In this study of 24 subjects taking paroxetine mesylate 7.5 mg once daily for 19 days, peak concentration (Tmax) was attained after about six hours, and steady-state was achieved by about 18 days. The steady-state maximum plasma concentration of paroxetine (Cmax) was 13.1 ng/mL and the total exposure (AUC) of paroxetine was more than nine times higher than that observed after a single dose, although variability of paroxetine PK parameters is very high. The excess accumulation is a consequence of the saturation of a major metabolizing enzyme (CYP2D6) of paroxetine at the clinical dose. Paroxetine distributes throughout the body including the central nervous system (CNS), with only 1% remaining in

the plasma. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. The mean elimination half-life of paroxetine is about 17 hours after a single 7.5 mg dose. Excretion is mainly through the urine (64%) and feces (probably via bile, 36%), mostly as metabolites.

Paroxetine systemic exposure (AUC and Cmax) doubled in patients with hepatic impairment or in patients with creatinine clearance of 30 to 60 mL/min compared to healthy subjects. In patients with creatinine clearance below 30 mL/min, there was a four-fold increase in paroxetine AUC. No dose adjustment is considered necessary for 7.5 mg paroxetine in patients with renal or hepatic impairment considering the relative low dose compared to the approved paroxetine doses.

There was insufficient information in the clinical studies to determine whether women aged 65 and over responded differently; this group comprised only about 6% of the phase 3 study population. Based on the Paxil label, Cmin concentrations in these older subjects may be 70-80% higher than those in younger subjects; however, again, dose adjustment is not needed given the low proposed dose relative to the higher doses approved for other indications.

No new drug-drug interaction (DDI) studies were conducted for Brisdelle; the Applicant proposes to use the information in the Paxil and Pexeva labels for its product. Labeling states that concomitant use with other drugs that alter CYP enzymes, including CYP2D6, may affect the plasma concentration of paroxetine. In addition, paroxetine irreversibly inhibits CYP2D6; concomitant use with other drugs metabolized by this enzyme may result in substantially increased systemic exposure to these drugs. Most of the DDI studies underlying labeling were based on doses of 20 mg or higher. The Sponsor justified reliance on these higher dose studies on the grounds that other data show that doses as low as 10 mg cause prolonged inhibition of CYP2D6, and that the nonlinear PK following multiple dosing of the 7.5 mg dose reflects auto-inhibition of CYP2D6 even at this lower dose.

However, tamoxifen is metabolized in several steps mediated by CYP2D6 to endoxifen, a metabolite responsible for a significant part of the pharmacologic effect of tamoxifen. There is concern that the CYP2D6 inhibitory effect of paroxetine reduces endoxifen concentration and thereby might reduce tamoxifen efficacy. Because studies evaluating the impact of CYP2D6 inhibition (some of which addressed the impact of CYP2D6 polymorphism) on breast cancer relapse/mortality have had conflicting results, the Division sought consultation from the Division of Oncology Products 1 for advice on labeling this potential concern (see Section 12).

In addition, paroxetine is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days after discontinuing MAOI therapy.

There were no explorations for dose response in this submission. The only dose studied was the 7.5 mg dosage form. At the End-of-Phase 2 meeting, the Sponsor noted that it had selected the 7.5 mg dose based on published literature showing efficacy for VMS symptoms for 10-25 mg doses of the approved paroxetine mesylate product. There did not appear to be a dose-response in the published literature, so the Sponsor selected a dose lower than that approved for psychiatric indications in order to have a dose that would likely show efficacy while also being safe and well-tolerated.

The primary Clinical Pharmacology Reviewer, Li Li, Ph.D., stated the following in her review dated May 17, 2013:

> *The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 (OCP/DCP3), finds NDA 204516 acceptable provided that agreement is reached between the Sponsor and the Division regarding the language in the package insert.*

No postmarketing requirements or commitments were recommended.

6. Clinical Microbiology

As the product is an oral capsule, no clinical microbiology review was warranted.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The development program for paroxetine mesylate for the VMS indication consisted of one phase 1 single and multiple dose PK study, a phase 2 placebo-controlled proof-of-concept study, and two phase 3 randomized, double-blind, placebo-controlled safety and efficacy trials. An overview of the clinical studies is presented in Table 1.

Table 1 Clinical Studies for Paroxetine Mesylate for VMS

Phase/ Study ID	Enrollment/ Centers/ Location/ Started-Completed	Study Design	Subjects Entered/ Subjects Completed	Study Duration
Phase 1 Study N30-005	N=24 healthy, postmenopausal women, ages 45-72 1 US center 7/15/11-8/12/11	Uncontrolled single and 14-day repeat dose pharmacokinetic study Paroxetine mesylate 7.5 mg capsule	Paroxetine mesylate: 24/24	3 week screening, 1 day treatment (followed by 5 non-treatment days), 14 days treatment
Phase 2 Study N30-002	N=102 postmenopausal women, ages 40-67 10 US centers 10/29/08-5/26/09	8-week double blind, placebo controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	Paroxetine mesylate: 49*/45 Placebo: 52/51	1 week placebo run-in period 8 week tx period
Phase 3 Study N30-003	N=614 postmenopausal women, ages 40-79 70 US centers 6/6/11-1/3/12	12 week double blind, placebo-controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	Paroxetine mesylate: 306/271 Placebo: 308/278	7 day screening, 12-day placebo run-in period, 12 week tx period
Phase 3 Study N30-004	N=570 postmenopausal women, ages 40-74 65 US centers 3/30/10-9/12/11	24-week double-blind, placebo-controlled Paroxetine mesylate 7.5 mg capsule daily vs. placebo	Paroxetine mesylate: 285/235 Placebo: 284**/218	7 day screening, 12-day placebo run-in period, 24 week tx period

***One subject randomized to paroxetine did not receive study drug**
**** One subject randomized to placebo did not receive study drug**
Source: Adapted from Applicant's Listing of Clinical Studies, Module 2.7.6 and Module 5.2

The clinical review focuses on the two phase 3 studies for efficacy. Efficacy data from Study N30-002 were not pooled with the phase 3 studies due to differences in the definition of the modified intent-to-treat (MITT) population and because the treatment duration for the phase 2 study was limited to eight weeks.

The two phase 3 studies enrolled a total of 1,174 postmenopausal women who had a mean total frequency of ≥ 56 moderate to severe vasomotor symptoms per week (≥ 7-8 per day on average) for 30 days prior to receiving study drug. Study N30-003 (hereafter referred to as Study 003) was a 12-week clinical trial, with a total of 614 postmenopausal women randomized 1:1 to receive paroxetine mesylate or placebo; this trial also evaluated the clinical meaningfulness of the change from baseline in VMS frequency. Study N30-004 (hereafter referred to as Study 004) was a 24-week clinical trial, with a total of 570 postmenopausal

women randomized 1:1 to receive paroxetine mesylate or placebo, and also evaluated the persistence of benefit over 24 weeks of treatment. Both studies included women with either natural or surgical menopause and both trials were conducted entirely in the US.

Following Screening, eligible subjects entered a 12-day single-blind placebo Run-in Period. During the Run-in Period, all subjects were dispensed single-blind placebo capsules (subjects were blinded to capsule content), which they took once daily at bedtime. Subjects were also asked to complete hot flush and sleep diaries each day using the Interactive Voice Response System/Interactive web Response System (IVRS/IWRS), recording the number of hot flushes daily, the severity of each episode of hot flush and total number of awakenings due to hot flushes.

Following completion of the Run-in Period, subjects who were compliant with diary entry and dosing and who continued to meet hot flush eligibility criteria (i.e., having more than 7 to 8 moderate to severe hot flushes per day or 50 to 60 moderate to severe hot flushes per week) were randomized into the Double-blind Treatment Period in a 1:1 ratio to receive either paroxetine mesylate (7.5 mg capsule) or placebo. Study treatment was taken orally once daily at bedtime beginning on Day 1 (day of randomization) and continuing up to Day 84 (Study 003) or Day 168 (Study 004). Subjects continued to fill out the daily hot flush and sleep diaries each day.

Daily Diaries

Both phase 3 studies used an electronic diary using the IVRS/IWRS for daily entry of hot flush data. This electronic diary was the only source document for the four co-primary endpoints. The diary was available to the subject throughout the day or night. To minimize recall, subjects were encouraged to enter hot flush data as soon as they experienced a hot flush, or at least once daily. Subjects were also provided with definitions of mild, moderate, and severe hot flushes, which conformed to those specified in the VMS Guidance.

Inclusion criteria specified postmenopausal women with 7-8 daily (or 50-60 weekly) moderate to severe VMS and were identical in the phase 3 studies. Subjects were to discontinue any psychotropic drugs or hormone therapy prior to starting the study and additional entry criteria specified discontinuation periods for psychotropic drugs and for estrogen alone or estrogen/progestin containing products prior to the Run-in Visit.

Exclusion criteria were generally similar across the phase 3 studies. Both phase 3 studies disallowed enrollment of subjects who were non-responders to previous SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) treatment for VMS, had evidence of impaired liver or kidney function, or with any clinically significant abnormality noted during screening. Excluded medical conditions in the phase 3 studies included psychiatric disorders (either lifetime history or more recently prior to screening), hypertension (unless on a stable dose of anti-hypertensive medication), clinically unstable cardiac disease, biliary tract disease, and thyroid disease (unless stable).

Two exclusion criteria were used in only a single study:

- Study 003 excluded subjects taking MAOIs, thioridazine, or pimozide (MAOIs were to be discontinued for at least four weeks prior to the Run-in Visit per the inclusion criteria)
- Study 004 excluded subjects with a body mass index (BMI) $\geq$40 kg/m^2.

In both phase 3 studies, subjects were re-qualified for participation after the 12-day placebo Run-in period.

Team Leader Comments:

- **The Division agreed to the plan to minimize "placebo responders" by requiring subjects to re-qualify on the basis of VMS frequency and severity after the placebo Run-in period.**
- **Although the risk of suicidal behavior and ideation is a concern for this class of drugs, the entry criteria excluded women with current or historical psychiatric disorders. Thus, the impact of paroxetine mesylate on such women, who may be particularly vulnerable, cannot be assessed in the clinical trials.**
- **Women with a history of cancer were not excluded from the trials; this will aid in generalizability of results to breast cancer survivors who are an important part of the target population for non-hormonal VMS therapy. Over the two studies, five subjects had a history of breast cancer and two of bilateral breast cancer; however, all happened to be randomized to placebo. It does not appear that any of the women in the studies used tamoxifen concomitantly with paroxetine.**

7.2 DEMOGRAPHICS

Demographic and baseline characteristics for all treated subjects are presented in Table 2 and Table 3. Across both studies, more than 60% of subjects were white. The mean age of subjects was 54-55 years. At baseline, the mean BMI was 28-29 kg/m^2. More than 80% of subjects were naturally menopausal in each study.

Table 2 Study 003: Demographics and Baseline Characteristics (MITT Population)

Parameter		Paroxetine N=301	Placebo N=305	Total N=606
Age (years)	Mean	54.9	54.5	54.7
	Median	54.0	53.0	54.0
	Min-Max	40-73	40-79	40-79
Race, n (%)	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)
	Other	2 (0.7)	8 (2.6)	10 (1.7)
Ethnicity, n (%)	Hispanic/Latina	27 (9.0)	37 (12.1)	64 (10.6)
Height (in)	Mean	64.5	64.4	64.4
	Min-Max	56-72	57-73	56-73
Weight (lb)	Mean	173	175	174
	Min-Max	80-389	98-338	80-389
BMI (kg/m^2)	Mean	29.3	29.7	29.5
	Min-Max	16.8-60.7	19.0-56.5	16.8-60.7
Daily # of mod-severe hot flushes	Mean	11.8	11.7	11.7
	Median	10.4	10.4	10.4
Daily hot flush severity score	Mean	2.5	2.5	2.5
	Median	2.5	2.5	2.5
Menopause type, n (%)	Natural	242 (80.4)	253 (83.0)	495 (81.7)
	Surgical	59 (19.6)	52 (17.0)	111 (18.3)

Source: Adapted from Applicant's Summary of Clinical Efficacy (SCE), Table 8, p 43

Table 3 Study 004: Demographics and Baseline Characteristics (MITT Population)

Parameter		Paroxetine mesylate N=284	Placebo N=284	Total N=568
Age (years)	Mean	54.2	54.5	54.4
	Median	54.0	54.0	54.0
	Min-Max	40-70	40-74	40-74
Race, n (%)	Caucasian	205 (72.2)	224 (78.9)	429 (75.5)
	Black	64 (24.3)	53 (18.7)	122 (21.5)
	Asian	3 (1.1)	6 (2.1)	9 (1.6)
	Other	7 (2.5)	1 (0.4)	8 (1.4)
Ethnicity, n (%)	Hispanic/Latina	16 (5.6)	21 (7.4)	37 (6.5)
Height (in)	Mean	64.9	64.3	64.6
	Min-Max	54-72	53-72	53-72
Weight (lb)	Mean	166.5	166.4	166.5
	Min-Max	107-263	100-274	100-274
BMI (kg/m^2)	Mean	28.0	28.3	28.1
	Min-Max	18.3-40.6	18.7-39.6	18.3-40.6
Daily number of mod-severe hot flushes	Mean	10.8	10.9	10.9
	Median	9.9	9.6	9.7
Daily hot flush severity score	Mean	2.5	2.5	2.5
	Median	2.5	2.5	2.5
Menopause type, n (%)	Natural	227 (79.9)	230 (81.0)	457 (80.5)
	Surgical	57 (20.1)	54 (19.0)	111 (19.5)

Source: Adapted from Applicant's SCE, Table 9, p 44

Team Leader Comments

- **The demographics for Study 004 are comparable to those of Study 003 with the exceptions that Study 004 was slightly more homogeneous racially (75% Caucasian) and had a lower mean and range for BMI.**
- **The Applicant did not clearly delineate the average time since onset of menopause in these studies.**
- **Baseline VMS frequency was slightly greater in Study 003, while baseline VMS severity scores were identical (2.5), representing an equal distribution between moderate and severe.**

7.3 DISPOSITION OF SUBJECTS

A total of 1,184 subjects were enrolled in the two phase 3 trials, 591 of whom used paroxetine mesylate.

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 4.

Table 4 Study 003: Disposition of 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)
Discontinued from study	35 (11.4)	30 (9.7)	65 (10.6)
Reasons for Discontinuation			
• Adverse Event/Serious Adverse Event	8 (2.6)	4 (1.3)	12 (2.0)
• Subject request	8 (2.6)	12 (3.9)	20 (3.3)
• Columbia Suicide Severity Rating Scale – Baseline	5 (1.6)	2 (0.6)	7 (1.1)
• Investigator opinion that study would be detrimental to well-being	2 (0.7)	1 (0.3)	3 (0.5)
• Non-compliance to 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: non-compliance	1 (0.3)	0	1 (0.2)
• Other: withdrew consent	1 (0.3)	1 (0.3)	2 (0.3)

*** According to the Applicant's response on 01/07/2013, drug intake was unknown for 4 subjects in the paroxetine mesylate group and 3 subjects in the placebo group. They were counted as having received at least one dose of study medication by the Division.**
Source: Applicant's CSR for Study N30-003, Table 7, p 72

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 5.

Table 5 Study 004: Disposition of Subjects

Disposition	Paroxetine mesylate n (%)	Placebo n (%)	Total n (%)
Number randomized	285	285	570
Received ≥ 1 dose of study drug	285 (100)	284 (99.6)	569 (99.8)
Completed study	235 (82.5)	218 (76.5)	453 (79.5)
Discontinued from study	50 (17.5)	67 (23.5)	117 (20.5)
Reasons for Discontinuation			
• Adverse Event/Serious Adverse Event	15 (5.3)	15 (5.3)	30 (5.3)
• Subject request	15 (5.3)	35 (12.3)	50 (8.8)
• Suicidality Tracking Scale	3 (1.1)	1 (0.4)	4 (0.7)
• Investigator opinion that study would be detrimental to well-being	0 (0.0)	2 (0.7)	2 (0.4)
• Non-compliance to 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: non-compliance	1 (0.4)	1 (0.4)	2 (0.4)
• Withdrew consent	2 (0.7)	0 (0.0)	2 (0.4)
• Relocation	2 (0.7)	1 (0.4)	3 (0.5)

Source: Applicant's CSR, Study N30-004, Table 8, p 69

Team Leader Comments

- **Overall, study completion rates were very good, with the expected finding of a higher discontinuation rate in the longer study, 004.**
- **There was no overall trend for higher discontinuation in a particular treatment arm. In Study 003, paroxetine subjects discontinued at a slightly higher rate, and reasons for differential discontinuation appear to be related to tolerability. In Study 004, the placebo subjects had a greater rate of discontinuations, with reasons for differential discontinuation that suggest dissatisfaction with efficacy.**
- **The Applicant did not provide further specification about why subjects discontinued due to "subject request;" line listings merely said "at their own request." Similarly, "withdrew consent" is not further detailed in the line listings. Aside from this, the Applicant provided a good level of granularity in identifying reasons for premature discontinuation.**

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

7.4.1.1 Analysis Population

The primary efficacy analyses were conducted on the MITT population, which was pre-defined by the Applicant as

- all consented and randomized subjects who had valid baseline hot flush diary data, received at least one dose of their randomized treatment, and had at least one day of on-treatment daily diary data

The MITT and Safety populations are shown in Table 6.

Table 6 Summary of Analysis Populations, Phase 3 Studies

Analysis Population	Paroxetine mesylate n (%)	Placebo n (%)	Total n (%)
Study N30-003 (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 N30-004 (N)	285	285	570
MITT	284 (99.6)	284 (99.6)	568 (99.6)
Safety	285 (100)	284 (99.6)	569 (99.8)

Source: Complete Study Report (CSR) for Study 003, Table 9 and for Study 004, Table 10

Team Leader Comments:

- **The Division agreed upon the definition of the MITT population during the drug development discussions.**
- **The numbers of subjects in the MITT and safety populations were very similar to the numbers of subjects randomized, indicating little early loss of subjects.**

7.4.1.2 Co-primary Endpoints

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

- 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 score of moderate to severe VMS per day from baseline to Week 4
- change in severity score of moderate to severe VMS per day from baseline to Week 12

The severity 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 average daily severity was defined as the mean of daily severity scores over reported days during a specific treatment week, and the daily severity score was calculated as the sum of (2 x the number of moderate hot flushes, plus 3 x the number of severe hot flushes), divided by the total number of moderate and severe hot flushes in that day. The average daily frequency during the treatment period for a specific week was calculated as the total number of moderate to severe hot flushes from self-reported diaries in that week divided by 7.

Team Leader Comment:

The draft VMS guidance does not discuss calculation of the severity score; however, the Division has also accepted a version that includes mild VMS on treatment (the number of mild hot flushes is added to both the numerator and the denominator). It is unclear which calculation provides a better representation of the treatment effect, as the severity score ultimately provides a measure only of the ratio of moderate to severe hot flushes (or of mild to moderate to severe hot flushes). A woman could experience a significant reduction in both moderate and severe hot flushes on treatment without changing her severity score if the ratio is unchanged (e.g., from 10 moderate and 10 severe at baseline to 1 moderate and 1 severe at Week 12), although the severity score would decrease if the ratio of severe:moderate hot flushes dropped. In addition, because the severity score reflects changes in both severity and frequency from baseline, it is not an independent endpoint from the frequency endpoint.

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

7.4.1.3 Additional Analyses Requested by FDA

Persistence of Benefit

In Study 004, a secondary 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 hot flush frequency at Week 24.

Persistence of benefit would be demonstrated by showing a statistically significant difference in the responder rate between the active and the placebo treatment groups. The logit model was used to analyze the proportion of 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 non-responders, along with those who achieved <50% reduction from baseline.

Team Leader Comment
The Division agreed to this plan of analysis.

Clinical Meaningfulness of the Change in VMS frequency

As lower estrogen dose hormonal products for VMS and non-hormonal treatments have been evaluated, the Division has observed that the magnitude of the treatment effect on VMS frequency is often less than that observed for "standard" dose HT. In order to ensure that such treatment effects are still of clinical benefit to women, the Division 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 VMS frequency from baseline of at least two moderate to severe hot flushes per day. Although these analyses are typically not specified as primary analyses in the statistical analysis plan, the Division does consider the results in its evaluation of whether acceptable efficacy has been demonstrated.

Team Leader Comment:
The responder analysis was not controlled for type 1 error.

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. The analysis was conducted based on data obtained at Weeks 4 and 12.

a) First, all MITT subjects in the study, 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 more conservative 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 the Division had recommended, as it is 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 not satisfied as the dependent variable, a logit model was fit to perform a receiver operating characteristic (ROC) analysis in order to determine the cutoff point for a clinically meaningful reduction in VMS frequency.

d) Based on the cutoff point 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 cutoff-point and non-responders were defined as those subjects whose mean daily hot flush frequency reduction was less than or equal to the established cutoff-point.

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.

7.4.1.4 Primary Analysis

Per protocol, to support this indication, efficacy needed to be demonstrated with respect to all four co-primary endpoints. In addition, the Applicant agreed to conduct secondary supportive analyses on the clinical meaningfulness of the reduction in VMS frequency if the placebo-adjusted change from baseline in the daily hot flushes was < 2, and to demonstrate the persistence of efficacy at Week 24 in at least one study.

The Applicant had pre-specified an alternate analysis in case the data were not determined to be normally distributed. Due to the violation of the normality assumption for the data for each co-primary endpoint, the Applicant and the FDA statistical reviewer analyzed each endpoint by this pre-specified alternative method, the rank-ANCOVA; 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 used for hypothesis testing. The Applicant's comparison for hypothesis testing was based on the least square (LS) mean difference of the rank-transformed endpoint. However, the FDA statistical reviewer included graphical presentation of the medians of change in the average daily frequency and severity over time and reported the difference between medians as a more appropriate estimate for the treatment effect of paroxetine mesylate relative to placebo in the case of skewed (non-normally distributed) data.

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 used the mixed model for repeated measurements (MMRM), which relies on observed case data, with no imputation of missing data. For sensitivity assessment, the last observation carried forward (LOCF) method was used to impute the missing data of each co-primary endpoint for the subjects who withdrew prematurely.

7.4.1.5 Subgroup Analyses

The Division conducted routine subgroup analyses on the basis of race (White vs. Non-White), BMI (< 32 vs. ≥ 32) and menopausal status (surgical vs. natural). In both studies, analysis of each co-primary efficacy endpoint by subgroups was performed using the same rank-ANCOVA model described previously with additional terms for subgroups and treatment by subgroup interaction. The descriptive statistics and estimated median difference between treatment groups were reported for the co-primary efficacy endpoint by subgroups.

7.4.2 Efficacy Results

7.4.2.1 Statistical Issues in Efficacy Analysis

Per protocol and per the Statistical Analysis Plan, the primary efficacy analysis was to be the change in daily VMS frequency and severity at Weeks 4 and 12. However, the Applicant's study reports provided results based on weekly change in VMS frequency and severity. The Applicant was requested to submit the planned analysis, and did so.

Also, the evaluation of clinical meaningfulness was not conducted as pre-specified and agreed to by the Division. Again, the Sponsor provided the appropriate analysis upon request.

7.4.2.2 Primary Efficacy Analysis

The FDA statistical reviewer confirmed the Applicant's results using the same pre-specified statistical methods. Results are summarized in Table 7 and depicted in Figure 1 and Figure 2. Subjects had a median of about 10 daily moderate to severe hot flushes at baseline. The placebo-subtracted reduction from baseline in VMS frequency was statistically significant at both Weeks 4 and 12 in both studies. Overall, the placebo-subtracted median reduction of average daily frequency of hot flushes was consistent across the two studies at Week 4 (estimated 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 (estimated median difference: 0.9), while efficacy was maintained in Study 004 (estimated median difference: 1.7).

Subjects had a median hot flush severity score of about 2.5. The comparisons between paroxetine mesylate and placebo on the reduction from baseline in the average daily severity of hot flushes achieved statistical significance at Week 4 in both studies, but at Week 12 in Study 004 only. The placebo-subtracted median reduction of average daily severity of hot flushes was small in both studies at Weeks 4 and 12, ranging from 0.03 to 0.05.

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 this analysis were consistent and similar to the primary analysis results using the observed data only.

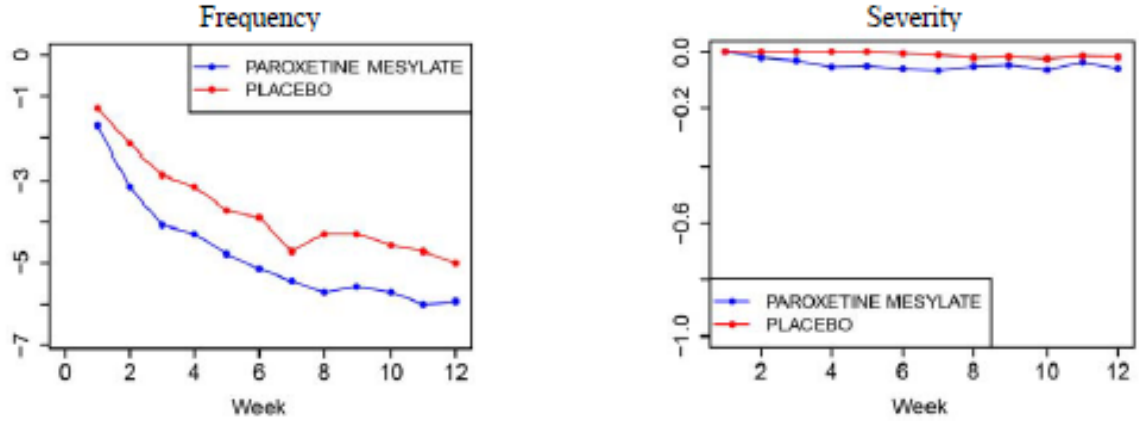
Table 7 Changes in Daily Frequency and Severity of Moderate to Severe Hot Flushes at Weeks 4 and 12 (MITT Population)

Study	Frequency			Severity		
	Paroxetine mesylate	Placebo	Treatment Difference	Paroxetine mesylate	Placebo	Treatment Difference
Study N30-003						
Baseline						
N	301	305		301	305	
Median	10.4	10.4		2.54	2.54	
Change from baseline						
Week 4 - N	289	293		281	289	
Median	-4.3	-3.1	-1.2	-0.05	0.00	-0.05
p-value#			**<0.0001**			**0.002**
Week 12 - N	264	274		236	253	
Median	-5.9	-5.0	-0.9	-0.06	-0.02	-0.04
p-value#			**0.009**			0.166
Study N30-004						
Baseline						
N	284	284		284	284	
Median	9.9	9.6		2.53	2.52	
Change from baseline						
Week 4 - N	276	274		268	271	
Median	-3.8	-2.5	-1.3	-0.04	-0.01	-0.03
p-value#			**<0.0001**			**0.037**
Week 12 - N	257	244		245	236	
Median	-5.6	-3.9	-1.7	-0.05	0.00	-0.05
p-value#			**0.0001**			**0.006**

*** Treatment Difference is the observed difference between medians.**
 # p-value is obtained from rank-ANCOVA model.
Source: Tables 5 & 6, Statistical review by Jia Guo, Ph.D., dated May 22, 2013

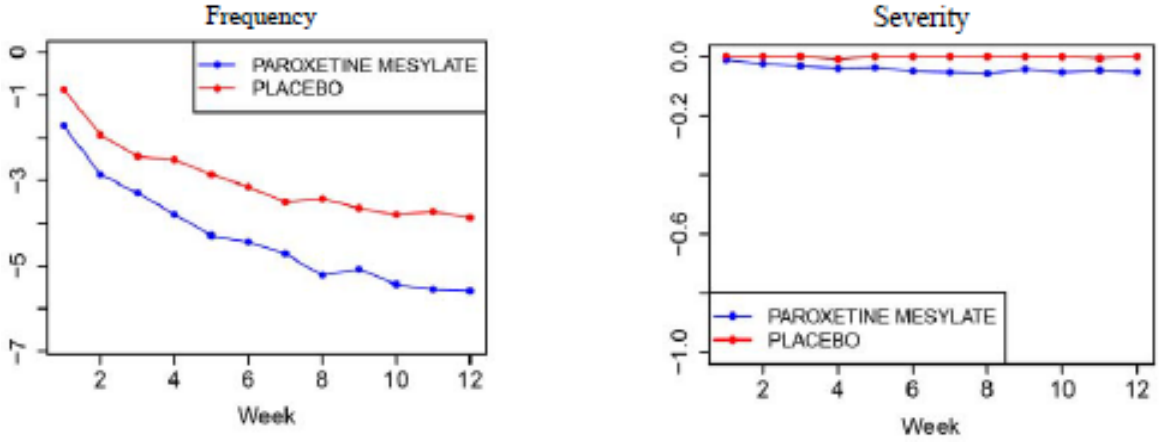
The median changes from baseline in daily frequency and severity of moderate to severe hot flushes over weeks by treatment groups are displayed in Figure 1 and Figure 2.

Figure 1 Study 003: Median Change from Baseline in Daily Frequency and Severity of Moderate to Severe Hot Flushes



Source: Figure 1, Statistical review by Jia Guo, Ph.D., dated May 22, 2013

Figure 2 Study 004: Median Change from Baseline in Daily Frequency and Severity of Moderate to Severe Hot Flushes



Source: Figure 2, Statistical review by Jia Guo, Ph.D., dated May 22, 2013

7.4.2.3 Additional Analyses Requested by FDA

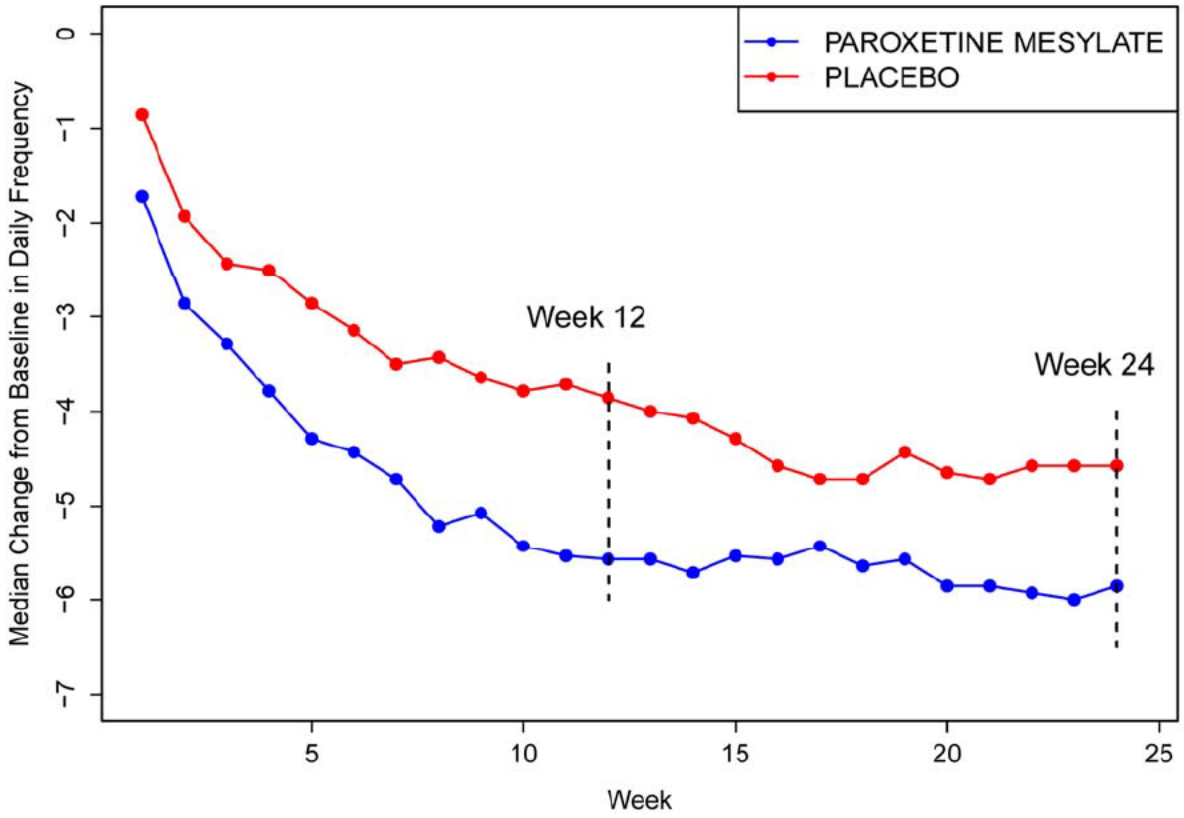
Persistence of Benefit

Treatment benefit for reduction of VMS frequency was explored descriptively in Study 004 by plotting the medians and median changes in average daily frequency of moderate to severe hot flushes over time and was analyzed more formally at Week 24 as a secondary endpoint, using a responder analysis. In this analysis, responders were defined as subjects who achieved ≥ 50% reduction from baseline in the frequency of moderate to severe hot flushes at Week 24. Non-responders were defined as those who had < 50% reduction at Week 24 or who prematurely discontinued the study (or otherwise did not have Week 24 data).

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 hot flushes compared to 36.3% of placebo-treated subjects (nominal p-value 0.007, logit model).

Figure 3 shows the median change from baseline in VMS frequency over treatment weeks.

Figure 3 Study 004: Median Change from Baseline in Daily Frequency of Moderate to Severe VMS



Source: Figure 5, Statistical review by Jia Guo, Ph.D., dated May 22, 2013

Team Leader Comments:

- **The numeric change in VMS frequency from baseline to Week 24 was not the prespecified analysis to support persistence of benefit, but is presented here for consistency with the presentation of data at Weeks 4 and 12 (the Applicant did not provide medians for daily values):**

Study	Frequency		
	Paroxetine mesylate	Placebo	Treatment Difference
Study N30-004			
Baseline			
N	284	284	
Daily Mean	10.8	10.9	
Change from baseline			
Week 24 - N	234	215	
Daily Mean	-5.7	-4.0	-1.7
p-value			**0.002**

Source: Study N30-004 Report, Table 14.2.2.02A1, p 287-291

- **I concur that the Applicant has demonstrated, according to the agreed-upon statistical analysis, that the treatment benefit of paroxetine on VMS frequency is maintained through 24 weeks of treatment.**

Clinical Meaningfulness of Change in VMS Frequency

As shown above, the estimated median difference on frequency reduction of moderate to severe hot flushes between paroxetine mesylate and placebo was < 2 hot flushes per day. Therefore, the analysis to evaluate whether this improvement is clinically meaningful according to the subject's overall assessment of the treatment benefit based on a "patient global improvement" anchoring question as described in Section 7.4.1.3 was conducted in Study 003 (Study 004 had already been initiated at the time the Division and the Applicant discussed the specifics of the desired evaluation).

For this analysis, the subjects in the MITT population, irrespective of treatment assignment, were categorized as satisfied vs. non-satisfied based on the PGI questionnaire results at Weeks 4 and 12, respectively. The satisfied subjects were defined as those whose PGI response was ≤ 2, and unsatisfied subjects were defined as those whose PGI response was > 2. Next, a ROC analysis was conducted by fitting a logistic regression model with "satisfied vs. unsatisfied" as the response variable and change from baseline in daily frequency of moderate and severe hot flushes as the covariate at Weeks 4 and 12, respectively.

Selected to maximize the sum of sensitivity and specificity, the cutoff values for change from baseline in daily frequency of moderate to severe hot flushes were -4.0 and -5.3 at Weeks 4 and 12, respectively. Subjects were classified as responders if the reduction from baseline was better than -4.0 at Week 4; or better than -5.3 at Week 12. Otherwise, subjects (including those with missing data) were classified as non-responders. At Week 4, 50% of subjects in the paroxetine group and 37% of subjects in the placebo group were responders (nominal p-value 0.001). At Week 12, 51% of subjects in the paroxetine group and 43% of subjects in the placebo group were responders (nominal p-value 0.055) (see Table 8).

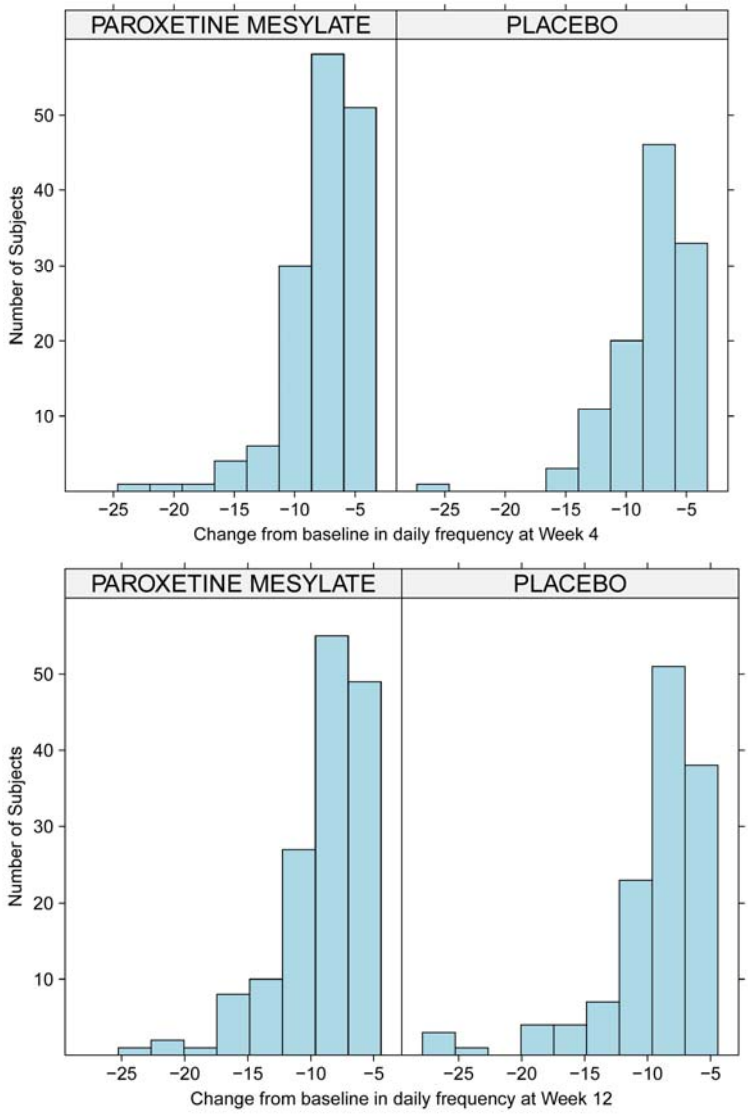
Table 8 Study 003: Percent of responders based on ROC cut-off (PGI ≤ 2 definition) MITT population

Visit	Cutoff	Statistics	Paroxetine mesylate n/N (%)	Placebo n/N (%)	Nominal p-value*
Week 4	-4.0	Responder	152/301 (50%)	114/305 (37%)	0.001
Week 12	-5.3	Responder	153/301 (51%)	131/305 (43%)	0.055

***p-value is obtained from a logit model adjusting for baseline average daily frequency.**
Source: Table 8, Statistical review by Jia Guo, Ph.D., dated May 22, 2013

Regardless of treatment assignment, the median change from baseline in daily frequency was -6.9 in the responders and -1.6 in the non-responders at Week 4. At Week 12, the mean change from baseline in daily frequency was -8.3 in the responders and -2.6 in the non-responders. Figure 4 presents the histograms of change from baseline in daily frequency of hot flushes in 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 hot flushes were similar for the two treatment groups at both weeks, although at both weeks, a higher proportion of paroxetine subjects experienced a reduction in VMS frequency.

Figure 4 Study 003: Change from Baseline in VMS Frequency among Responders, by Treatment Arm



Team Leader Comments

- **The majority of responders experienced VMS reductions of about 5-10 hot flushes/day.**
- **The median baseline frequency of VMS was higher in responders (11.4 hot flushes/day) than in non-responders (9.9 hot flushes/day). Within responders, the median baseline frequency was slightly higher among placebo subjects (11.6) than paroxetine subjects (11.0). Baseline frequency was not considered in the selection of cutoff values, but was accounted for in comparing the response rates between treatment arms.**
- **The number of subjects experiencing large reductions in VMS frequency (e.g., -15 or greater) appears similar across treatment arms.**

7.4.2.4 Post Hoc Subgroup Analyses

Subgroups based on race/ethnicity, BMI and menopausal etiology were evaluated by the FDA statistical reviewer; the first two of these are routine exploratory analyses. Gender and region subgroups were not conducted due to the all-female, all-US population enrolled in each study.

In Study 003, the race by treatment interaction was not significant; non-Caucasian women treated with paroxetine had numerically greater placebo-subtracted reductions in VMS frequency and severity at both Weeks 4 and 12 compared to Caucasian women. However, the race by treatment interaction was significant in Study 004 for change in frequency at Week 12 and change in severity at Week 4. In this study, non-Caucasian women treated with paroxetine had numerically lower placebo-subtracted reductions in VMS frequency and severity at both Weeks 4 and 12 compared to Caucasian women. The treatment effects were statistically significant only in the Caucasian subgroup, but this may reflect the low power to detect a difference in the small subgroup of non-Caucasians.

The BMI by treatment interaction was not significant in either study. In general, lower-BMI women on paroxetine experienced numerically greater placebo-subtracted reductions in VMS frequency and severity.

The type of menopause by treatment interaction was not significant in either study. Differences between the two subgroups (natural vs. surgical menopause) for change in VMS frequency and severity at both Weeks 4 and 12 were minimal in Study 003. In Study 004, naturally menopausal women treated with paroxetine had numerically greater placebo-subtracted reductions in VMS frequency and severity at both Weeks 4 and 12 compared to surgically menopausal women.

Team Leader Comments:

- **The inconsistent findings with respect to a race by treatment interaction may reflect the low enrollment of non-Caucasian women in these two trials. Overall, it is not clear that paroxetine has a differential treatment impact by race.**
- **Subgroup analyses by BMI and type of menopause also failed to identify a significant interaction with treatment. Where the magnitude of the treatment effect was numerically different, the larger subgroups (lower BMI and naturally menopausal women) generally had more favorable treatment effects.**

7.4.3 Overall Assessment of Efficacy

The data from the two phase 3 studies showed that

1. Paroxetine demonstrated statistically significant reductions from baseline in the daily frequency of moderate to severe hot flushes at Week 4 and Week 12 compared to placebo in both studies.
2. Paroxetine demonstrated statistically significant reductions from baseline in the daily severity of moderate to severe hot flushes at Week 4 in both studies, but failed to meet criteria for statistical significance at Week 12 in Study 003.
3. In Study 003, a clinically meaningful improvement in VMS frequency was demonstrated at Week 4 based on the comparison of responder rates in the paroxetine mesylate and placebo groups (50% vs. 37%, respectively). The difference in responder rates (51% vs. 43%, respectively) was less compelling at Week 12. Because Type 1 error was not accounted for in this secondary analysis, interpretation of p-values is not appropriate.

4. In Study 004, maintenance of the pre-specified treatment effect on VMS frequency was demonstrated at Week 24.

Overall, the studies succeeded on most of the demonstrations of efficacy requested by the Division. The aspects on which efficacy was not clearly shown were the failure of one study to show a treatment benefit for severity at Week 12, and the small differential in the proportions of women in each treatment arm who found the reduction in VMS frequency at Week 12 to be clinically meaningful. In addition, despite the statistical significance observed generally, the placebo-subtracted reductions in the VMS severity score were very small.

As discussed previously, I have reservations about the utility of the severity score. It does not truly assess the change in severity of hot flushes; rather, it calculates the ratio of moderate:severe hot flushes. In a woman who has a notable reduction in VMS frequency, but maintains the same ratio (e.g., 10:10 dropping to 1:1) this score will falsely indicate no reduction in VMS severity. For this reason, I place more weight on the reduction in VMS frequency as the more appropriate measure of the treatment effect of paroxetine.

I believe that the data show that paroxetine has a beneficial impact on the frequency of moderate to severe VMS, that the onset of this treatment benefit is rapid, and the effect is maintained through 24 weeks of treatment. In the absence of other approved non-hormonal treatments for VMS, I believe paroxetine offers a useful option to women who are unable to use hormonal medications.

Statistician's Conclusion

The Statistical Reviewer, Jia Guo, Ph.D., stated the following in her review dated May 22, 2013:

> *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. *In study -003, a clinically meaningful improvement in VMS frequency reduction was demonstrated at Week 4 based on the comparison of responder rates in the paroxetine mesylate and placebo groups. Although the responder rate at Week 12 was numerically in favor of paroxetine mesylate, was only marginally significant.*
> 4. *In study -004, a treatment effect on the daily VMS frequency was demonstrated at Week 24.*

Dr. Guo's overall conclusion was:

> *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.*

Team Leader Comment:
I concur with Dr. Guo's conclusion that the Applicant has provided appropriate evidence of the efficacy of paroxetine in the treatment of VMS, including demonstration that the treatment effect is clinically meaningful to women and that the treatment effect persisted to Week 24 of treatment.

8. Safety

In addition to postmarketing safety information on the approved Pexeva product, evaluation of paroxetine mesylate safety is based on the current NDA's clinical development program that includes data from one phase 1, one phase 2 study, and two phase 3 studies. A total of 1,300 subjects were treated in the paroxetine mesylate clinical program, of which 659 subjects received at least one dose of paroxetine; with the remainder receiving at least one dose of placebo. Of these, 235 subjects in the paroxetine group and 218 in the placebo group completed 24 weeks of treatment in Study 004.

Used for most evaluations, the "pooled safety dataset" includes the phase 2 study as well as the phase 3 studies, because all three studies enrolled very similar subject populations. The phase 2 study was only eight weeks in duration, compared to 12 to 24 weeks for the phase 3 studies. Safety evaluations were done on the safety population, which was pre-defined by the Applicant as

- all randomized subjects who received at least one dose of their randomized treatment and had at least one post-treatment safety assessment

The number of subjects and duration of exposure for the safety database is shown in Table 9.

Table 9 Drug Exposure by Duration, Pooled Safety Dataset

Category	Paroxetine mesylate N=635 n (%)	Placebo N=641 n (%)
≥1 day to ≤4 weeks	27 (4.3)	28 (4.4)
>4 weeks to ≤12 weeks	224 (35.3)	249 (38.8)
>12 weeks to ≤24 weeks	357 (56.2)	343 (53.5)
>24 weeks	14 (2.2)	13 (2.0)

Source: Applicant's Summary of Clinical Safety (SCS), Page 34, Table 6

Team Leader Comments:

- **The Division agreed to pooling of the safety data from the two phase 3 trials and from the supporting phase 2 trial.**
- **Safety data from the phase 1 pharmacokinetic study (Study N30-005) was not integrated into the data set. This study population enrolled basically healthy women and a placebo/comparator was not used in this study.**

8.1 Deaths and Serious Adverse Events

A total of two deaths (one on paroxetine and one on placebo) occurred in the overall clinical development program. The death in a paroxetine-treated subject occurred in a 55 year old African-American female who experienced a cardiorespiratory arrest 68 days after starting treatment with paroxetine mesylate. She died one day later, and was listed as having two serious adverse events (SAEs): coronary artery arteriosclerosis and cardiorespiratory arrest. She had a medical history of hypertension and had been taking an antihypertensive for about 15 years. She was diagnosed with hypercholesterolemia about one year before the event. At

the Screening Visit, her height was 64 inches and her weight was 184 lbs. Her blood pressure at Screening was 146/86 mm Hg with a pulse of 68 beats/min. Her screening electrocardiogram (ECG) was read as "abnormal and not clinically significant." Both SAEs were not considered by the Investigator to be related to study drug.

Team Leader Comment
Given the limited information currently available, it is not possible to determine whether or not this was a drug-related death.

Serious adverse events (SAEs) were reported in 14 subjects (2.2%) in the paroxetine group and nine subjects (1.4%) in the placebo group in the pooled safety database. Aside from the single death in Study 003, the SAEs in the remaining 13 paroxetine subjects were all reported in the 24-week Study 004, while the SAEs in the nine subjects in the placebo group were reported across the phase 2 (1 subject) and phase 3 (8 subjects; 1 in Study 003 and 7 in Study 004) studies.

The most common SAEs reported in the paroxetine mesylate group were suicidal ideation (three subjects) and appendicitis (two subjects). All nonfatal SAEs in the paroxetine group resolved without sequelae. SAEs that occurred in either treatment arm are listed in Table 10.

Table 10 Serious Adverse Events, Pooled Safety Dataset

System Organ Class (SOC) Preferred Term	Treatment Arm*	Action Taken (paroxetine arm only)
Psychiatric disorders		
Suicidal ideation	Paroxetine	Drug withdrawn
	Paroxetine	Drug continued
	Paroxetine	Drug continued
Suicide attempt	Paroxetine	Drug withdrawn
Cardiac disorders		
Arteriosclerosis coronary artery	Paroxetine	Subject died
Cardio-respiratory arrest		
Respiratory, thoracic and mediastinal disorders		
Asthma	Paroxetine	Drug continued
Infections and Infestations		
Appendicitis	Paroxetine	Drug interrupted
	Paroxetine	Drug interrupted
Sinusitis	Paroxetine	Drug interrupted
Clostridium difficile colitis	Placebo**	
Hepatobiliary disorders		
Cholecystitis	Paroxetine	Drug continued
Biliary dyskinesia	Paroxetine	Drug withdrawn
Cholecystitis	Placebo**	
Musculoskeletal and connective tissue disorders		
Arthritis	Paroxetine**	Drug continued
Osteoarthritis	Placebo	
Gastrointestinal disorders		
Abdominal pain	Paroxetine	Drug withdrawn
Dysphagia	Paroxetine**	Drug continued
Abdominal distension	Placebo**	
Colitis	Placebo**	
Gastrointestinal hemorrhage	Placebo	
Injury, poisoning and procedural complications		
Acetabulum fracture	Placebo	
Femur fracture		
Upper limb fracture	Placebo	
General disorders and administration site conditions		
Chest pain	Placebo	
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Endometrial cancer	Placebo	
Squamous cell carcinoma of the chest	Placebo	

*** Each row indicates a unique subject**
**** Subject also recorded for an SAE in a different SOC**
Source: SCS, Tables 20 & 21, pp 54-5

Team Leader Comment:
The main SAEs of concern based on this listing are suicidal ideation/suicide attempt, which occurred exclusively in the paroxetine group, and are further discussed in Section 8.1.1.1.

8.1.1 Other Adverse Events of Interest

The following events were pre-specified by the Applicant in the Statistical Analysis Plan as being of specific interest, based on AEs commonly reported for the drug classes of SSRIs and/or SNRIs:

- Suicidality
- Cardiovascular events
- Hepatic events
- Gastrointestinal or other bleeding events

In addition, AEs suggestive of serotonin syndrome, hyponatremia, bone fracture, activation of mania/hypomania, seizures, akathisia, hallucinations, and sexual dysfunction (events noted as Precautions in current labeling) were evaluated. None were reported in ≥ 1% of paroxetine subjects and with at least twice the incidence of placebo.

8.1.1.1 Suicidality

Suicidality was prospectively assessed in all four clinical studies. In Studies 002 and 004, the Suicidality Tracking Scale (STS) was used, and was administered at baseline as well as on-treatment. The Division subsequently recommended the use of the Columbia Suicide Severity Rating Scale (C-SSRS) in a Guidance (Suicidality: Prospective Assessment of Occurrence in Clinical Trials, September 2010), so in Studies 003 and 005, the C-SSRS was used, and was administered at baseline and on-treatment. For data pooling, STS scores were to be mapped using the domains defined in the Columbia Classification Algorithm for Suicide Assessment (C-CASA).

The Applicant used the following categories to assess suicidality in the phase 3 studies (the number of subjects in each treatment arm who fell into one or more of these categories is displayed in Table 11):

1. **Completed suicides**
2. **Suicide attempts**
3. **Spontaneous treatment-emergent suicidal ideation/behavior** reported as an AE/SAE leading to study discontinuation
4. **Suicidality events (suicidal behavior and/or ideation)** reported as an AE/SAE as a result of the completion of the:
   - C-SSRS suicidal behavior/ideation:
   - STS suicidal behavior/ideation: Based on a total STS score > 0 at any time point during the study
5. **Early discontinuations** due to meeting the pre-specified STS or C-SSRS score discontinuation criteria

Table 11 Assessment of Suicidality

Criterion for Suicidality	Phase 1 Study 005 24 paroxetine	Phase 2 Study 002 49 paroxetine 52 placebo	Phase 3 Study 003 306 paroxetine 308 placebo	Phase 3 Study 004 285 paroxetine 285 placebo
Completed suicide	0	0	0	0
Suicide attempt	0	0	0	1 paroxetine 0 placebo
Treatment-emergent suicidal ideation, reported as AE/SAE	0	0	0	4 paroxetine 0 placebo
C-SSRS-reported suicidal behavior	0	NA	0	NA
C-SSRS-reported suicidal ideation	0	NA	0	NA
STS-reported suicidal behavior	NA	0 paroxetine 1 placebo	NA	3 paroxetine 2 placebo
STS-reported suicidal ideation	NA	2 paroxetine 3 placebo	NA	4 paroxetine 8 placebo
Met C-SSRS criteria for discontinuation	0	NA	0*	NA
Met STS criteria for discontinuation	NA	0	0	1** paroxetine 1 placebo

***Two subjects, one in each arm, met C-SSRS criteria for exclusion at baseline, but were inadvertently enrolled, then discontinued shortly after starting study drug. They are not counted in this table, but are included in the safety population.**
**** One paroxetine subject met STS criteria for exclusion at baseline, but was inadvertently enrolled, then discontinued shortly after starting study drug. She is not counted in this table, but is included in the safety population.**
NA = not applicable; instrument not used
Source: Dr. Orleans' tabulation

Team Leader Comments:

- **The Applicant identified "suicidality" (used here to encompass suicide attempts/suicidal behavior and suicidal ideation) both on the basis of AEs/SAEs and on the basis of responses to the suicidality instruments. Some of these suicidality events were detected both as an AE/SAE and based on the subject's response and some were detected only when the subject provided a triggering response on the suicidality instrument. It is likely that relying only on AE/SAE reporting would result in under-detection of suicidality, but it is unclear to what extent relying on the screening instruments results in "false positive" reports of suicidality.**
- **The Applicant's reporting of suicidality was very confusing; subjects with STS scores indicating suicidality only at baseline were included in their counts of subjects who experienced suicidality and subjects who fell into more than one of the categories listed in the table above were counted in each category. In order to avoid such duplicate counts, the categories in Table 11 are mutually exclusive. If all treatment-emergent suicidality events are counted across all four studies, there are 15 in the paroxetine arms and 14 in the placebo arms.**

In phase 1 Study 005, there were no completed suicides or suicide attempts. There was also no spontaneous treatment-emergent suicidal behavior and/or ideation that led to premature

discontinuation from the study and no reported C-SSRS-emergent events of suicidal behavior or ideation.

In phase 2 Study 002, which used the STS, discontinuation criteria based on STS score were not pre-specified. There were no completed or attempted suicides in this study. There were no events of STS-emergent suicidal behavior in the paroxetine group (0/49) and one event in the placebo group (1/52; 1.9%). There were a total of six events of STS-emergent suicidal ideation in six subjects, of whom two subjects (2/49; 4.1%) were in the paroxetine group and four subjects (4/52; 7.7%) were in the placebo group. There was no STS-emergent suicidal behavior and/or suicidal ideation that led to a premature discontinuation in this study.

There were no cases of suicide attempt, C-SSRS-emergent suicidal ideation or suicidal behavior in either treatment arm in Study 003.

In Study 004, based on an STS total score > 0 at any point during the study, there were a total of five post-baseline reports of STS-emergent suicidal behavior (three in paroxetine subjects and two in placebo subjects) and 12 post-baseline reports of STS-emergent suicidal ideation (which were not also reported as STS-emergent suicidal behavior, AEs or SAEs or as meeting STS criteria for discontinuation), of which four events were in the paroxetine group and eight were in the placebo group. There were four paroxetine subjects who reported SAEs of suicide attempt/suicidal ideation and one who reported an AE of suicidal ideation (see Table 12). In the placebo arms, no subjects had AEs or SAEs of suicide attempt/suicidal ideation.

Subject medical/psychiatric history data was not summarized in the submission. Exclusion criteria for both phase 3 studies included a history of self-injurious behavior, suicidal ideation, depression, generalized anxiety, psychotic disorders, borderline personality disorders and Post Traumatic Stress Disorder.

Table 12 Cases of Suicide Attempt/Ideation and Suicidal Ideation Reported as AEs/SAEs, Pooled Phase 3 Dataset

Study #/ Subject ID	Suicide Ideation/Attempt	Age (years) Race	Day of Onset	Reported AE/SAE	Drug/ Outcome
Suicide Attempt Reported as an SAE					
N30-004/ 4-23-014	Suicide attempt with multiple non-study drug overdose; she reported suicidal thoughts; had past history of overusing prescription drugs & past mental health hospitalization, but had 0 scores on STS at baseline and early termination	50 Caucasian	54	**-SAE** -Suicide attempt	**Paroxetine** Discontinued
STS-Emergent Suicidal Ideation Reported as an SAE					
N30-004/ 4-05-013*	STS-emergent suicidal ideation: indicated taking active steps to prepare for suicide attempt and intentional injury. When contacted, stated she thought about suicide "a little" but did not have specific plan. (Also met pre-specified STS discontinuation criteria: at baseline indicated wish to be dead)	61 Asian	166	**-SAE** -Suicidal ideation	**Paroxetine** Discontinued - Recovered without sequelae
N30-004/ 4-22-004	STS-emergent suicidal ideation: indicated wish to be dead, think about suicide, plan for suicide and taking active steps to prepare for suicide attempt	53 Caucasian	174	**-SAE** -Suicidal ideation -	**Paroxetine** Not discontinued - Recovered without sequelae
N30-004/ 4-23-023	STS-emergent suicidal ideation: indicated wish to be dead, and think about suicide. Subject also had dx of metastatic cancer.	67 Caucasian	168	**-SAE** -Suicidal ideation	**Paroxetine** Not discontinued– Recovered without sequelae
STS-Emergent Suicidal Ideation Reported as an AE					
N30-004/ 4-48-022	STS-emergent suicidal ideation: indicated wish to be dead and think about suicide	50 African-American	83	**-AE** -Suicidal ideation	**Paroxetine** Discontinued

***Subject 4-05-013 was discontinued from the study due to an SAE of suicidal ideation and also due to pre-specified discontinuation criteria based on STS score; the subject is counted here as an SAE**
Source: SCS, Adapted from section on suicidality, page 63

Team Leader Comment:
It is notable that all cases of suicidality reported in the phase 3 trials occurred in Study 004. Study 004 was of longer duration, but four of the seven events in paroxetine subjects occurred in the first 12 weeks of the trial, so it is not clear that duration of exposure is a relevant factor.

The Applicant also provided a report from an expert consultant that concluded that "rates of suicidal ideation and behavior are in line with, or actually below, what may be expected in the general population of women of this age group over a period of nearly 6-months." A consult was requested of the Division of Psychiatry Products (DPP) during the review cycle to evaluate the suicidality data. Lucas Kempf, M.D., of DPP provided a consultative review, addressing the Division's three questions as shown in the following excerpts:

1. Comment on the appropriateness of the Applicant's evaluation of suicidality, including choice of instruments and mapping approach.

   The applicant, instead of mapping to the C-CASA preferred terms, mapped both scales to dichotomous terms of yes or no for 2 categories of suicidal ideation and suicidal behavior…

   The applicant did not follow the advice and mapped the STS to determinations of suicidal ideation and suicidal behavior for accounting purposes. They did not differentiate between a history of suicidality and treatment emergent suicidality, as is done in the C-SSRS. They erroneously report a high level of discontinuations due to suicidality rather than a "history of suicidality."

   After reading the narratives and correcting for this error, there does not appear to be a higher rate of discontinuations due to treatment emergent suicidality.

2. Comment on whether you agree with the Applicant's expert's conclusion that there does not appear to be a significant risk of suicidal ideation or behavior associated with use of paroxetine mesylate.

   We agree that these studies do not demonstrate an increased risk of suicidal ideation or behavior for drug vs. placebo in these study populations. However, these populations excluded patients with a history of suicidal ideation, and investigators discontinued any patients whose STS became even mildly elevated. Additionally, as evidenced by study N30-003's frequent discontinuation of higher risk patients after the inclusion criteria were changed to exclude patients with history of suicidal ideation or behaviors, these studies are not a fully representative population. In conclusion, the one episode of suicidal behavior happened in the treatment arm so we agree with the need for ongoing surveillance.

3. Comment on whether you believe labeling beyond class labeling about suicidality (including a boxed warning) is warranted to address the risk of suicidality associated with this drug.

   We suggest that the labeling for this product should include the verbatim class language for the suicidality boxed warning and warnings in Section 5…as presented in the submitted labeling.

   We believe the language in Section 14 should reflect the fact that the study population excluded with a history of suicidal ideation or behavior. There is a high likelihood that physicians will use this product in patients that have co-morbid depression and other psychiatric disorders because of paroxetine's other indications. It should be clear in labeling that this low dose has not been studied for depression, (b) (4) *Labeling should also state that these studies excluded any high risk patients. Therefore, the studies are not informative regarding patients with depression or other psychiatric disorders.*

We do not believe that there needs to be additional language in the Adverse Reactions section of labeling in regard to suicidality beyond the language they propose.

Team Leader Comment
Following extensive discussion, the Division and DPP agreed that the current class labeling for suicidality (which focuses on risk of suicidality in children and young adults) would be modified somewhat to be more appropriate to this postmenopausal population. However, general warnings about the potential risk of suicidality and need for monitoring subjects upon treatment initiation were maintained. In addition, a Limitation of Use was added stating that Brisdelle is not indicated for treatment of any psychiatric condition.

8.1.1.2 Cardiovascular Events

Cardiovascular AEs are reported in Table 13. These were evaluated due to the reported association of cardiovascular AEs with serotonin-norepinephrine reuptake inhibitors.

Table 13 Cardiovascular AEs, Pooled Safety Dataset

MedDRA Preferred Term	Paroxetine N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥ 1 TEAE	27 (4.3)	17 (2.7)
Hypertension*	7 (1.1)	3 (0.5)
Chest pain	4 (0.6)	1 (0.2)
Peripheral edema	4 (0.6)	1 (0.2)
Palpitations	3 (0.5)	2 (0.3)
EKG abnormal	3 (0.5)	1 (0.2)
Increased blood pressure*	1 (0.2)	7 (1.1)
Arrhythmia	1 (0.2)	0 (0.0)
Arteriosclerosis coronary artery	1 (0.2)	0 (0.0)
Cardio-respiratory arrest	1 (0.2)	0 (0.0)
Ventricular dysfunction	1 (0.2)	0 (0.0)
Chest discomfort	1 (0.2)	0 (0.0)
Cardiac murmur	1 (0.2)	0 (0.0)
Prolonged QT interval	1 (0.2)	0 (0.0)
Heart rate increased	1 (0.2)	0 (0.0)
Heart rate irregular	1 (0.2)	0 (0.0)

*** "Hypertension" was reported as an AE based on a diagnosis, while "blood pressure increased" was reported based on the subject's blood pressure measurement**
Source: Applicant's SCS, Page 60, Table 23

Team Leader Comments:

- **Although the incidence of reported hypertension was numerically higher with paroxetine, objective blood pressure data were similar in the two treatment groups (see Section 8.3).**
- **Other than the one reported death in a paroxetine subject in Study 003, there were no cardiovascular events reported as SAEs.**
- **Chest discomfort (one subject in the paroxetine group) was the only cardiovascular event resulting in discontinuation of study drug.**

8.1.1.3 Hepatic Events

The rate of hepatic AEs (reported as abnormal liver function test, increased transaminases, increased ALT and increased hepatic enzymes) was higher in the pooled placebo arms (0.9%) than the pooled paroxetine arms (0.5%) over the pooled safety dataset. There were no hepatic SAEs or AEs that led to discontinuation.

Team Leader Comment:
The Applicant stated that hepatic events were pre-specified mainly due to safety signals observed with the SNRI desvenlafaxine. In concert with the lack of laboratory signals relating to liver enzymes, paroxetine does not appear to have an adverse impact on the liver in this database. However, the postmarketing safety section of labeling, based on other doses/formulations of paroxetine, does include drug-induced liver injury and hepatic failure.

8.1.1.4 Gastrointestinal and Other Bleeding Events

SSRIs are associated with an increased risk of gastrointestinal (GI) bleeds as well as bleeding at other sites, likely due to reduced platelet serotonin. Table 14 displays the incidence of GI and other bleeding events that occurred more frequently in paroxetine subjects. In addition, one placebo subject had an SAE of GI hemorrhage; two paroxetine and three placebo subjects discontinued due to one of these events.

Table 14 GI or Other Bleeding Events Occurring with Higher Incidence in Paroxetine Arm, Pooled Safety Dataset

MedDRA Preferred Term	Paroxetine N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥ 1 TEAE	12 (1.9)	10 (1.6)
Vaginal hemorrhage or postmenopausal hemorrhage	6 (0.9)	6 (0.9)
Vitreous hemorrhage	1 (0.2)	0 (0.0)
Gingival bleeding	1 (0.2)	0 (0.0)
Rectal hemorrhage	1 (0.2)	0 (0.0)
Periorbital hematoma	1 (0.2)	0 (0.0)
Breast hematoma	1 (0.2)	0 (0.0)
Epistaxis	1 (0.2)	0 (0.0)

Source: Applicant's SCS, Page 63, Table 25

Team Leader Comments:

- **There was no signal of an increased risk of GI or other abnormal bleeding events. However, class labeling warning of this possibility will be retained.**
- **The categories of "vaginal hemorrhage" and "postmenopausal hemorrhage" warrant further investigation, as vaginal/uterine bleeding is abnormal in postmenopausal women not using hormones. However, it is a fairly common observation in newly menopausal women (i.e., shortly after the first 12 months of amenorrhea), declining substantially in women further out from the menopause.**

8.1.1.5 Events Associated with Discontinuation of Paroxetine

In the clinical trials, subjects were started on paroxetine mesylate without titration, and were discontinued from the drug without tapering. A Discontinuation-Emergent Signs and Symptoms (DESS) checklist was administered seven days after the last dose of study drug. This checklist is a 27-item instrument that queries for signs and symptoms associated with

SSRI discontinuation. "Old symptoms" were defined as symptoms that appeared before the seven days prior to the administration of the DESS, were present while taking study drug, and continued into the seven-day period. "New symptoms" were those that appeared after discontinuation of study drug and within the seven days prior to administration of the DESS. The results from the phase 3 trials are shown in Table 15.

Table 15 Summary of DESS, Pooled Safety Dataset

DESS Category	Paroxetine N=635 n (%)	Placebo N=641 n (%)
Subjects with old symptoms present	405 (100)	414 (100)
Subjects with old symptoms worsened	102 (25.2%)	73 (17.6%)
Subjects without new symptoms	394 (62.0)	429 (66.9)
Subjects with one or more new symptoms	112 (17.6)	88 (13.7)
Most commonly occurring new symptoms		
Increased dreaming or nightmares	4.9%	3.1%
Muscle cramps, spasms or twitching	3.5%	1.4%
Headache	3.1%	2.3%
Muscle aches or pains	2.7%	2.2%
Nervousness or anxiety	2.7%	1.9%
Fatigue, tiredness	2.5%	1.4%
Restless feeling in the legs	2.5%	1.1%
Trouble sleeping, insomnia	2.4%	1.1%

Source: SCS, Table 42, p 99

Team Leader Comments:

- **The subject's checking of symptoms on the checklist did not necessarily correlate with an AE report.**
- **About 15% of subjects developed new symptoms during the week after discontinuation, and the incidence of new symptoms did not differ much between paroxetine and placebo subjects. Certain symptoms, such as muscle cramps/spasms/ twitching, restless feeling in the legs, and trouble sleeping/insomnia were reported in the paroxetine group at twice the incidence of the placebo group; these may warrant inclusion in labeling.**
- **Overall, there does not appear to be a need for titration or tapering when initiating or discontinuing dosing, respectively.**

8.1.1.6 Other AEs Associated with SSRIs

The Applicant evaluated the following additional AEs commonly associated with the SSRI drug class:

- Sexual dysfunction – similar incidence of preferred terms of decreased libido, anorgasmia, sexual dysfunction and loss of libido
- Hyponatremia – no relevant AEs or sodium values < 130 mEq/L reported
- Bone fracture – AEs reported only in placebo group
- Activation of mania/hypomania – no relevant AEs reported
- Seizures – no relevant AEs reported
- Akathisia – three reports in paroxetine vs. one in placebo
- Hallucinations – no relevant AEs reported

8.2 Other Adverse Events

8.2.1 AEs leading to Discontinuation

A total of 28 subjects (4.4%) in the paroxetine mesylate group and 21 subjects (3.3%) in the placebo group had adverse events (AEs) leading to study drug discontinuation. The most frequently reported AEs (abdominal pain, herpes zoster, disturbance in attention, headache, anxiety and suicidal ideation) resulting in discontinuation each occurred in only two subjects. AEs leading to discontinuation that occurred more frequently in the paroxetine group are listed in Table 16.

Table 16 Adverse Events Leading to Study Drug Discontinuation that Occurred More Frequently in the Paroxetine Group, Pooled Safety Dataset

MedDRA Preferred Term	Paroxetine mesylate N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥ 1 AE	30 (4.7)	24 (3.7)
Abdominal pain	2 (0.3)	0
Herpes Zoster	2 (0.3)	0
Disturbance in attention	2 (0.3)	1 (0.2)
Headache	2 (0.3)	1 (0.2)
Suicidal ideation	2 (0.3)	0
Abdominal distension	1 (0.2)	0
Chest discomfort	1 (0.2)	0
Depressed mood	1 (0.2)	0
Elevated mood	1 (0.2)	0
Inability to think clearly, fatigue	1 (0.2)	0
Gingival bleeding	1 (0.2)	0
Sleep disorder	1 (0.2)	0
Suicide attempt	1 (0.2)	0

Source: Adapted from SCS, Table 22, p 57 and text on p 56

Team Leader Comments:

- **AEs plausibly related to study drug that led to discontinuation clustered around CNS effects (disturbance in attention in two paroxetine subjects and one placebo subject) and mood effects (suicidal ideation, depressed mood, elevated mood and suicide attempt, collectively, in five paroxetine subjects and no placebo subjects). However, anxiety led to discontinuation more often in placebo subjects than paroxetine subjects.**
- **The Applicant noted that two additional paroxetine subjects and three placebo subjects discontinued due to an AE but were not captured in its table of AE discontinuations. They are reported in the table above.**

8.2.2 Common Adverse Events

The most common AEs for the safety dataset are reported in Table 17, based on AEs that occurred in at least 1% of subjects and were more common among subjects in the paroxetine arms. Overall, 50% of subjects in the paroxetine group and 47% of subjects in the placebo group reported at least one adverse event. Results were similar when only the phase 3 safety dataset was evaluated.

Table 17 Selected Common Adverse Events (Safety Population)

System Organ Class (SOC) Preferred Term*	Paroxetine (N = 635) Frequency n (%)	Placebo (N = 641) Frequency n (%)
Nervous system disorders		
Headache, migraine, sinus headache, tension headache	40 (6.3)	31 (4.8)
Dizziness	12 (1.9)	5 (0.8)
Hypersomnia, sedation, somnolence	8 (1.3)	1 (0.2)
Hypoasthesia, paresthesia	8 (1.3)	3 (0.5)
Gastrointestinal disorders		
Nausea, vomiting	27 (4.3)	15 (2.3)
Diarrhea	17 (2.7)	16 (2.5)
Dry mouth	9 (1.4)	7 (1.1)
General disorders and administration site conditions		
Fatigue, malaise, lethargy	31 (4.9)	18 (2.8)
Infections and infestations		
Bronchitis	11 (1.7)	3 (0.5)
Urinary tract infection	10 (1.7)	8 (1.2)
Influenza	9 (1.4)	8 (1.2)
Musculoskeletal and connective tissue disorders		
Back pain	10 (1.6)	9 (1.4)
Fibromyalgia, myalgia	8 (1.3)	3 (0.5)
Psychiatric disorders		
Abnormal dreams, nightmare	9 (1.4)	8 (1.2)
Mood altered, mood swings	7 (1.1)	4 (0.6)
Respiratory, thoracic and mediastinal disorders		
Cough	7 (1.1)	2 (0.3)
Oropharyngeal pain	7 (1.1)	4 (0.6)
Vascular disorders		
Hypertension	7 (1.1)	3 (0.5)

*** Preferred terms representing similar events are grouped, even if they cross SOCs**
Source: Applicant's Integrated Summary of Safety, Table 4.1b, pp 355-372

Team Leader Comments:

- **AEs that occurred at a notably higher incidence in paroxetine subjects and are plausibly drug-related include headaches, fatigue complaints, nausea/vomiting, muscle complaints and dizziness.**
- **Overall, there do not appear to be major differences in the incidence of common AEs between treatment arms.**

8.3 Vital Signs

There were no clinically relevant differences in vital signs between the paroxetine and placebo groups in the pooled safety database. The proportion of subjects with clinically significant blood pressure results at screening and end of study is shown in Table 18 and did not suggest any adverse impact of paroxetine on blood pressure.

Table 18 Subjects with Clinically Significant Blood Pressure Values (Safety Population)

Parameter	Paroxetine N=635 n (%)		Placebo N=641 n (%)	
	Screening	End of Study	Screening	End of Study
Systolic BP	6 (0.9)	7 (1.1)	6 (0.9)	9 (1.4)
Diastolic BP	6 (0.9)	7 (1.1)	0	5 (0.8)

Source: Applicant's SCS, Table 36, p 88

8.4 Laboratory Testing

Assessment of mean hematological values over time showed no clinically relevant differences between the paroxetine and placebo groups. In general, the mean values for the various parameters remained within their normal ranges from baseline to the end of the study.

Clinical chemistries included albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine kinase, creatinine, plasma glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, and uric acid. Shift tables for chemistry parameters for the paroxetine group showed no clinically meaningful changes over time.

8.5 Electrocardiograms

All three studies evaluated routinely conducted ECGs as "normal," "abnormal, not clinically significant (ABN, NCS)," and "abnormal, clinically significant (ABN, CS)" based on the investigator's assessment. Shifts in readings from baseline to on-treatment are shown in Table 19.

Table 19 Shift Table of ECG Results, Pooled Safety Dataset

	Paroxetine mesylate N=635 n (%)			Placebo N=641 n (%)		
Baseline Category	ABN, CS	ABN, NCS	Normal	ABN, CS	ABN, NCS	Normal
ABN, CS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
ABN, NCS	1 (0.2)	154 (24.3)	84 (13.2)	1 (0.2)	155 (24.2)	82 (12.8)
Normal	2 (0.3)	66 (10.4)	297 (46.8)	1 (0.2)	71 (11.1)	301 (47.0)

Source: Applicant's ISS, Page 125, Table 75

No clinically relevant changes were observed between the groups. Three subjects (0.5%) in the paroxetine group and two (0.3%) subjects in the placebo group shifted from a normal or not clinically significant reading at baseline to a clinically significant abnormal ECG at the end of the study. No trends were apparent based on these findings.

8.6 Postmarketing Safety Findings

Although Brisdelle (or the paroxetine mesylate dose used in Brisdelle) is not marketed anywhere in the world, the Applicant submitted postmarketing safety data on Pexeva in the NDA. The submission included both the then-current Periodic Adverse Drug Experience Report (PADER) for Pexeva, covering the period from July 2010 through July 2011, and a literature search. The PADER included 37 initial serious unlisted reports (six in the US) and 9 follow-up reports (one in the US). The SOCs that included the greatest numbers of reports were Psychiatric Disorders (30, which included six reports of aggression, three each of

impulsive behavior and suicide attempt, and two each of completed suicide, disorientation, and intentional self-injury), Congenital, Familial and Genetic Disorders (11), Nervous System Disorders (9, including two reports of loss of consciousness). There were six fatalities among paroxetine users, including the two suicides; the other deaths included a possible overdose/possible serotonin syndrome, lung cancer, coronary heart disease and fatal hyponatremia in a polydrug user.

No new safety communications were issued during this reporting period, and no foreign actions taken. Labeling was submitted in response to an FDA request to harmonize labeling between Paxil and Pexeva.

The Applicant concluded that no significant change in the safety profile of Pexeva was observed. The literature search did not identify any new AEs reported with paroxetine treatment.

Pexeva was approved at a time when products did not undergo a 915 postmarketing safety review. There are no pending Tracked Safety Issues for Pexeva.

Team Leader Comment
I concur that the postmarketing safety data are consistent with the safety profile evidenced in this NDA submission.

8.7 Safety Update

The Applicant submitted a safety update on December 17, 2012, which consisted of the most recent PADER for Pexeva, and a new literature review. The Applicant stated that there are no ongoing or completed studies subsequent to the initial NDA submission. The PADER, which covered the period of July 2011 through July 2012, included 29 initial serious unlisted reports (two in the US) and 8 follow-up reports. The SOCs that included the greatest numbers of reports were Nervous System Disorders (which contained two reports each of neuroleptic malignant syndrome, parasthesia ["electric shock sensation"], and balance disorder), Psychiatric Disorders (which detailed multiple reports of aggression, anger, intentional self-injury, suicide attempts, sleep disorder and nightmare), and Social Circumstances (which detailed homicide [2 cases] and attempted murder). There were no fatalities among paroxetine users.

No new safety communications were issued during this reporting period, and no foreign actions taken. Labeling was submitted in response to FDA requests to add information on the potential drug interactions with methylene blue and linezolid and on the potential adverse effects on the newborn of SSRI exposure during pregnancy.

The literature search identified four reports involving paroxetine:

- Idiopathic thrombocytopenic purpura and alveolar hemorrhage following 10 year use of an unknown formulation of paroxetine; although initially resistant to treatment, the platelet count recovered after paroxetine was discontinued and ritixumab was started
- A fatal case of multiple drug overdose, including paroxetine, in a male with bipolar disorder; the death was ruled a suicide

- A male with a history of "hypersexuality" who had functional MRI changes in thalamic activity in response to an image of a girl in a swimsuit following discontinuation of paroxetine
- Five case reports of early treatment discontinuation due to side effects or lack of efficacy, including one completed suicide three weeks after discontinuation of his antidepressant (unspecified whether it was paroxetine or fluvoxamine)

The Applicant concluded that no new safety signals were identified.

Team Leader Comment
I concur that the safety update did not alter the safety profile.

8.8 Overall Assessment of Safety Findings

An overview of safety findings in the pooled safety dataset is presented in Table 20.

Table 20 Summary of AEs, Pooled Safety Dataset

Category	Paroxetine mesylate N=635[2] n (%)	Placebo N=641[2] n (%)
Subjects with any TEAE[1]	320 (50.4)	301 (47.0)
Deaths	1 (0.2)	0 (0)
Subjects with SAEs	14 (2.2)	9 (1.4)
Subjects with study drug discontinuations due to a TEAE	28 (4.4)	21 (3.3)
Subjects with suicidality[3]	6 (0.9)	1 (0.2)
Subjects with a cardiovascular TEAE	27 (4.3)	17 (2.7)
Subjects with a hepatic TEAE	3 (0.5)	6 (0.9)
Subjects with gastrointestinal or bleeding TEAE	12 (1.9)	10 (1.6)

[1] TEAE: Any AE that started or worsened on or after the day of first dose
[2] A subject is counted only once within each category
[3] includes subjects in the following categories: "Suicide attempt," "treatment-emergent suicidal ideation, reported as an SAE/AE" and "Met STS criteria for discontinuation"
Source: SCS, Page 43, Table 12

Overall, the incidence of SAEs, TEAEs generally and AEs of specific interest did not differ much by treatment arm. CNS and mood-related AEs occurred more frequently among subjects on paroxetine, as did suicidality-related events, albeit at a low rate. Current labeling addresses the risk of suicidality and of interference with cognitive and motor performance.

Death and SAEs were slightly more common in the paroxetine arm; but it is unclear the extent to which these were drug-related. Notable SAEs that occurred solely in the paroxetine arm were one suicide attempt and three cases of suicidal ideation.

SSRIs, including paroxetine, carry suicidality warnings, but these warnings report an increased risk in children, adolescents and young adults. Although the DPP consultant did not believe suicidality events overall were increased in the paroxetine arms of the clinical studies in this NDA, I am concerned that the class labeling may lead to minimization of the potential risk in this older population. I recommend that the SAEs be reported in the Adverse Reactions section of labeling. The remainder of class labeling, which recommends close monitoring for

signs of suicidality, mania or unusual changes in behavior, should be included in Brisdelle's warnings.

Other AEs that have been associated with other SSRIs or SNRIs, such as cardiovascular, hepatic or bleeding problems, did not show an increased incidence in these paroxetine trials.

There was no increase overall in discontinuation-related symptoms, and I concur that a tapering regimen does not appear necessary when stopping Brisdelle. Certain symptoms such as muscle spasms/twitching and sleep problems did occur more frequently among women discontinuing paroxetine compared to those who had been treated with placebo, but the incidence of these events was low.

Among the AEs leading to premature study termination, the most common were CNS symptoms (attention disturbance) and mood effects (including suicidality and depression); however, anxiety was more commonly associated with discontinuation in placebo subjects. Common AEs that occurred more frequently among paroxetine-treated women were headaches, nausea, fatigue and dizziness.

Based on the overall body of safety data, the major safety concern relates to the potential for an increase in suicidal ideation and behavior; while the body of evidence for SSRIs generally does not support an increased risk in this age group, the clinical trial data reviewed here lead me to recommend that this should be described in labeling.

9. Advisory Committee Meeting

A meeting of the Reproductive Health Drugs Advisory Committee was held on March 4, 2013 to discuss the efficacy findings and overall risk/benefit profile of paroxetine mesylate for treatment of VMS. The meeting was requested both because this application represents a potential first-in-class for this indication and because of the mixed efficacy findings. The Committee was asked to vote on the following questions; votes and discussion are summarized below each question:

1. **(VOTE)** Based on the pre-specified analyses, is there sufficient evidence to conclude that paroxetine mesylate is effective in treating moderate to severe vasomotor symptoms (VMS) associated with menopause?

   Yes: 7 No: 7 Abstain: 0

   a. Please provide a rationale for your vote and, if applicable, any additional recommendations.

   Discussion: The majority of members who voted against there being sufficient evidence of efficacy cited concerns about the magnitude of reductions, particularly with respect to severity and the high placebo response, which made it difficult to interpret the treatment benefit.

   Those who voted that there was sufficient evidence of efficacy generally cited a modest but real treatment benefit, and noted that they considered reductions in VMS frequency to be more clinically important than reductions in severity. One member noted that it appears to be very difficult for a non-hormonal product to meet the efficacy endpoints

established in the draft Guidance for hormonal products and that the guidance should be revisited.

2. **(VOTE)** Based on the pre-specified analyses, is there sufficient evidence to conclude that the change from baseline in VMS frequency is clinically meaningful to women?

   Yes: 4 ***No: 10*** ***Abstain: 0***

   a. Please provide a rationale for your vote and, if applicable, any additional recommendations.

   Discussion: Members who voted that the change in frequency did not appear to be clinically meaningful stated that the ROC-derived response rate in the paroxetine mesylate arm was minimally higher than that in the placebo arm. Others again noted the small treatment difference between paroxetine and placebo arms and several were concerned about the apparent reduction in benefit from Weeks 4 to 12.

   Those who voted that the change in frequency was clinically meaningful cited the higher responder rates in the paroxetine arm at both Weeks 4 and 12, and the persistence of benefit at Week 24, noting that women want a treatment benefit that is rapid in onset and durable.

3. **(VOTE)** Is the overall risk/benefit profile of paroxetine mesylate acceptable to support approval of this product for the proposed indication?

   Yes: 4 ***No: 10*** ***Abstain: 0***

   a. Please provide a rationale for your vote and, if applicable, any additional recommendations.

   Discussion: Members who voted that the risk/benefit profile was unacceptable were generally swayed by the small magnitude of the treatment effect and the majority was not concerned about safety. However, several members expressed concerns about suicidal ideation and one about a potential impact on bone safety. One member noted that the Sponsor may not have identified the optimal dose.

   Those who felt the risk/benefit was favorable to support approval noted minimal concerns about safety given the wide experience with paroxetine and the current off-label use for this indication, and also valued the small but real benefit, particularly given the need for a non-hormonal product. One member noted that approval would "legitimize" off-label use and allow for better safety surveillance.

Team Leader Comments

The vote on the demonstration of efficacy was evenly split, with those voting "no" generally expressing concern about the minimal reduction in severity and the placebo response, while those voting "yes" placed more weight on the frequency metric. As discussed previously, I side with this latter group in believing that reduction in frequency is the more relevant parameter by which to assess the treatment effect. I also agree with those who favored the clinical meaningfulness of the treatment effect that the rapid onset and persistent treatment benefit shown for paroxetine is important to women with VMS. Although, as discussed at the Advisory Committee meeting, there was not a strong statistical demonstration of clinical meaningfulness at Week 12, I am not convinced that this supportive analysis should rely upon statistical hypothesis testing, particularly because type 1 error was not controlled in this analysis. The

relative proportions of women in each treatment arm who found the change in VMS frequency to be clinically meaningful favored paroxetine at both Weeks 4 and 12.

Overall, despite the majority of members voting against approval, there were few concerns about safety; those who felt the risk/benefit profile was unacceptable were mainly responding to the small magnitude of the treatment effect. The two identified concerns, suicidality and possible impact on bone, will be addressed in labeling.

10. Pediatrics

The Applicant requested a full waiver of pediatric studies, and the Division concurred. The Pediatric Review Committee (PeRC) considered this application on May 22, 2013, and agreed with a full waiver because the condition of menopausal vasomotor symptoms does not exist in this population.

11. Other Relevant Regulatory Issues

The Applicant certified that it did not use any debarred investigators. The Applicant submitted financial disclosure information for investigators in the phase 2 and phase 3 studies, none of whom reported disclosable information.

The Office of Scientific Investigation (OSI) inspected three sites, each of which participated in both Studies 003 and 004. The sites were chosen based on considerations that included the number of subjects enrolled and lack of prior inspections, as well as their involvement in both studies.

Dr. Campbell's site (Study 003, Site 338; Study 004, Site 438) screened 29 subjects, randomized 17 subjects, and all 17 completed the study for Study 003; she screened 21 subjects and randomized 12 with all completing in Study 004. Records of all enrolled subjects were reviewed by OSI. OSI issued a No Action Indicated (NAI) evaluation and concluded that the studies appeared to have been conducted adequately and that the data may be used in support of the application.

Dr. Kalafer's site (Study 003, Site 323; Study 004, Site 423) screened 16 subjects, with six enrolled and all completing Study 003; he also screened 34 subjects with 17 enrolled and 15 completing Study 004. Records of four subjects in Study 003 and five in Study 004 were reviewed by OSI. Findings included a lack of timely review of sleep diaries, lack of documentation of appropriate subject compensation and inadequate test article reconciliation in that it could not be determined if all unused study drug was returned to the Applicant for disposal. Minor discrepancies in the time of reporting of hot flushes (by seconds to almost one hour) were noted for one subject in Study 004. OSI issued a Form 483 and a Voluntary Action Indicated (VAI) evaluation, but noted that these findings did not affect subject safety or efficacy results. Overall, OSI concluded that the studies appeared to have been conducted adequately and that the data appear acceptable in support of the application.

Dr. Blank's site (Study 003, Site 314; Study 004, Site 414) screened 23 subjects, enrolled 12 subjects, and 11 completed the study for Study 003; for Study 004, he screened 29 subjects, enrolled 15 and 11 completed the study. Records of all completing subjects were reviewed by OSI. OSI issued a NAI evaluation and concluded that the study appeared to have been conducted adequately and that the data appear acceptable in support of the application.

Roy Blay, Ph.D. from OSI made the following overall assessment and general recommendations in his review dated May 28, 2013:

> *The clinical investigator sites of Drs. Campbell, Blank, and Kalafer were inspected in support of this NDA. Drs. Campbell and Blank were not issued Form FDA 483s. The final classification for these inspections is No Action Indicated (NAI). Dr. Kalafer was issued a Form FDA 483. Review of the EIR for Dr. Kalafer's site indicated that the test article reconciliation and documentation of subject compensation was inadequate. The preliminary classification for the inspection of Dr. Kalafer is Voluntary Action Indicated (VAI). Other than these deficiencies at Dr. Kalafer's site, the data generated by these three clinical sites and submitted by the sponsor appear adequate in support of the respective indication.*

12. Labeling

The proprietary name Brisdelle was found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) during the review of this NDA.

Carton and container labeling was reviewed, revised and ultimately found to be acceptable by DMEPA, the Office of Prescription Drug Promotion (OPDP) and the CMC reviewer. Labeling proposed by the Applicant was reviewed and revised by the Division in consultation with DMEPA, OPDP, the Study Endpoints and Labeling Development team, the Pediatric and Maternal Health team and DPP (due to the extensive class labeling in SSRI products).

The potential decrease in tamoxifen efficacy attributable to paroxetine's irreversible inhibition of CYP2D6 was of particular concern because one of the major target populations for a non-hormonal VMS therapy is women with a history of or a high risk of breast cancer, who are contraindicated from using hormonal therapy. Interestingly, the tamoxifen label does not discuss concomitant use with paroxetine, while the Paxil and Pexeva labels recommend using "an alternative antidepressant with little or no CYP2D6 inhibition" in women on tamoxifen. Due to concern about this potential impact the Division consulted the Division of Oncology Products 1 (DOP1). Laleh Amiri-Kordestani, M.D. and Elimika Pfuma, Pharm.D., Ph.D., provided a consultative review, addressing the Division's two questions as shown in the following excerpts:

1. Do you anticipate any clinical impact on the effectiveness of tamoxifen if women with a history of or at high risk of breast cancer who are taking tamoxifen were to use paroxetine 7.5 mg concomitantly for VMS? It is anticipated that most women will continue their VMS treatment for several years.

   No, the current evidence does not support the negative impact on the efficacy of tamoxifen. There are several clinical studies looking into the association of CYP2D6 and clinical outcome in patients with breast cancer. Unfortunately, data from randomized controlled trials are lacking… Ahern et al. investigated 15 drugs inhibiting CYP2D6, and reported no association with breast cancer recurrence in the patients treated with tamoxifen; however, patients coadministrated paroxetine showed a higher odds ratio without statistical significance because of smaller sample size [PMID: 19690182]. In the report by Kelly et al. using 2430 patients treated with tamoxifen and a single SSRI, they reported that absolute increases of the period of overlapping use of paroxetine and tamoxifen were significantly associated with increases in the risk of

death from breast cancer [PMID: 20142325]. By contrast, Azoulay et al. reported that concurrent use of strong CYP2D6 inhibitors was not associated with an increased incidence of breast cancer recurrence [PMID: 20848186]. There are some limitations to these studies, and the questions remain regarding the contribution of CYP2D6 inhibitors vs. the genotype to the observed results.

Further investigation considering these issues is required.

2. Do you agree that the proposed labeling is appropriate and sufficient? If not, what language would you propose?

   We recommend that this information should not be included in the highlights section.

   DOP1 further recommended that language in Sections 5.2 and 7.7 expressing uncertainty about whether co-administration had a significant adverse effect be retained and that prescribers "may consider using an alternative treatment for VMS with little or no CYP2D6 inhibition."

The Division did not feel this advice abut "alternative treatment" was useful because there is no alternative VMS treatment for such women who have contraindications to hormonal therapy. Following discussion with the Clinical Pharmacology reviewer, the Division retained the Applicant's proposed language regarding uncertainty about the impact of co-administration, but revised the recommendation to state:

When tamoxifen is used for the treatment or prevention of breast cancer, weigh the likely benefit of paroxetine for treating VMS vs. the risk of possible decreased tamoxifen effectiveness, and consider avoiding the concomitant use of paroxetine for VMS treatment.

In addition, the Division retained the warning in the Highlights section, as well as in Warnings & Precautions and Drug Interactions sections of the Full Package Insert.

Other specific issues discussed during labeling negotiations included the Applicant's proposals to (b) (4) (both of which the Division denied, as these were claims that had not been agreed-upon in advance and were not based on endpoints that were properly accounted for in the statistical plan), and the inclusion of postmarketing data based on Pexeva and other paroxetine formulations. In order to report adverse reactions, rather than AEs, in the postmarketing section, the Applicant used an algorithm to evaluate causality, to which the Division agreed. The clinical pharmacology sections of labeling were also extensively revised. Agreement on labeling was reached on June 28, 2013.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that Brisdelle be approved for the indication "treatment of moderate to severe vasomotor symptoms associated with menopause."

13.2 Risk Benefit Assessment

Overall, I conclude that the Applicant has submitted an acceptable demonstration of efficacy of paroxetine for moderate to severe VMS. Over two trials, only a single co-primary endpoint

(of eight) failed to show statistical significance. The failure was on the severity score endpoint at Week 12, a parameter I believe is less relevant to the actual treatment benefit for women, because the score depends on the ratio of moderate:severe hot flushes, not the actual reduction in severity. While the magnitude of the changes in frequency and severity are not large, the change in frequency does appear to be clinically meaningful to the majority of women treated with paroxetine. The effect has also been demonstrated to be maintained through 24 weeks of treatment. In the absence of an approved non-hormonal VMS therapy, I find these results to be acceptable in support of approval.

On the risk side, the Brisdelle clinical trial findings have not demonstrated serious safety findings or safety concerns not previously identified for paroxetine or other SSRIs. My major concern is the small number of SAEs relating to suicidality, which were reported only among paroxetine-treated women. I believe this warrants description in labeling of this finding. SSRI class labeling otherwise appropriately discusses monitoring for such untoward effects.

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk management activities beyond labeling are recommended.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

I have no recommendations regarding postmarketing requirements or commitments.

13.5 Recommended Comments to Applicant

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M SOULE
06/28/2013

HYLTON V JOFFE
06/28/2013

I agree with approval of Brisdelle for the treatment of moderate to severe vasomotor symptoms associated with menopause. See the Division Director decisional memorandum.