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APPLICATION NUMBER:

204516Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204516
Priority or Standard	Standard
Submit Date(s)	August 28, 2012
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Division / Office	Bone, Reproductive and Urologic Products/Office of Drug Evaluation III
Reviewer Name(s)	Ronald J. Orleans, M.D.
Review Completion Date	May 21, 2013
Established Name	Paroxetine mesylate
(Proposed) Trade Name	Brisdelle
Therapeutic Class	Serotonin reuptake inhibitor
Applicant	Noven Therapeutics, LLC
Formulation(s)	Oral capsule
Dosing Regimen	One 7.5 mg capsule daily
Indication(s)	Treatment of moderate to severe vasomotor symptoms associated with the menopause
Intended Population(s)	Menopausal females

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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.

1.2 Risk Benefit Assessment

This application seeks approval for paroxetine mesylate (PM) capsules 7.5 mg for the treatment of moderate to severe VMS associated with the menopause. The tradename for this product is Brisdelle. Brisdelle is a serotonin reuptake inhibitor for the treatment of moderate to severe VMS.

Currently, hormonal therapy is the only FDA-approved treatment for VMS associated with menopause. However, hormone therapy is not appropriate for every patient. Some women are unwilling or unable to take hormones based on their medical history or based on perceived risks. For these women, there are currently no FDA-approved alternative products. Therefore, there is an unmet medical need for nonhormonal treatment of VMS.

Two adequate and well-controlled phase 3 studies of PM (N30-003 and N30-004) and one supporting phase 2 study (N30-002), all conducted in the US, support the efficacy of PM 7.5 mg for the indication sought. For Study N30-003, 614 subjects were randomized across 70 US study sites: 306 subjects in the paroxetine group and 308 subjects in the placebo group. In Study N30-004, 570 subjects were randomized across 65 US study sites: 285 subjects in both the paroxetine and placebo groups. In study N30-002, 101 subjects were randomized across 10 US study sites: 49 subjects in the paroxetine group and 52 subjects in the placebo group.

Efficacy was demonstrated by the following:

- The reduction in frequency of moderate to severe hot flashes was statistically significantly greater in the PM group than in the placebo group at both Week 4 and Week 12 in both phase 3 studies.
- The reduction in severity of moderate to severe hot flashes was statistically significantly greater in the PM group than in the placebo group at Week 4 in both phase 3 studies and at Week 12 in Study N30-004.
- In Study N30-003, PM was modestly more effective than placebo in reducing hot flash frequency (the placebo-subtracted reduction was less than 2 hot

flashes/day). However, even this modest reduction was demonstrated to be clinically meaningful to a majority of patients. A greater proportion of subjects in the paroxetine group (50-51%) than in the placebo group (37-43%) met the definition of a responder in the analysis of clinical meaningfulness at Week 4 and Week 12, respectively.

- In Study N30-004, persistence of benefit of PM treatment was demonstrated by a responder analysis that demonstrated that a significantly greater proportion of PM- treated subjects (47.5%) achieved a ≥ 50% reduction in frequency of moderate to severe hot flashes from Baseline to Week 24 than the placebo-treated group (36.2%).

The safety dataset consisted of 586 PM-treated subjects in the two phase pivotal 3 trials and 49 subjects in the single phase 2 trial. This review did not reveal any new or unlabeled safety issues relating to PM. The conclusions regarding product safety are these:

- The overall incidence of serious adverse events, treatment-emergent adverse events and adverse events of specific interest did not differ much in the PM and placebo groups.
- Central nervous system and mood-related adverse events occurred more frequently among subjects on paroxetine, as did suicidality-related events, although at a low rate.
- Current labeling addresses the risk of suicidality.

This reviewer concludes (1) that the treatment effect of PM 7.5 mg is indeed modest but clinically meaningful to patients and (2) that the use of PM 7.5 mg in the menopausal population has been demonstrated to be safe. Therefore, based on the data from the single phase 2 clinical trial and the two phase 3 clinical trials submitted to this NDA, PM has been demonstrated to be safe and effective for this indication and supports marketing approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Based on the clinical trials data submitted to this NDA, standard post-marketing surveillance is recommended to further monitor the safety and efficacy of PM. The Applicant plans to conduct enhanced pharmacovigilance for suicidality. No other specific risk management steps are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Hormone therapy (HT) (estrogen or estrogen progestin drugs) is the only FDA-approved treatment of vasomotor symptoms (VMS) associated with the menopause. However, not all women can take or choose to take HT. Therefore, there currently is a medical need for safe and effective nonhormonal treatment options to treat moderate to severe hot flushes in women with contraindications or intolerance to HT.

Selective serotonin reuptake inhibitors (SSRIs) have been investigated as a centrally acting, nonhormonal treatment for vasomotor symptoms associated with the menopause. The subject of this review, paroxetine mesylate (PM) is a potent SSRI.

Paroxetine was first marketed commercially in the US in 1992 as paroxetine hydrochloride under the brand name Paxil®. Paxil was approved at doses ranging from 10 to 60 mg/day, depending on the indication. Paroxetine hydrochloride is approved for the treatment of major depressive disorder (MDD), obsessive-compulsive disorder (OCD), panic disorder with or without agoraphobia, social anxiety disorder, generalized anxiety disorder (GAD), and posttraumatic stress disorder.
PM has a chemical structure that is similar to paroxetine hydrochloride, the only difference being the associated salt. Paroxetine mesylate is marketed commercially under the brand name Pexeva®. Pexeva was first approved for use in the US in 2003 at doses ranging from 10 to 60 mg/day, depending on indication. Paroxetine mesylate is approved for the treatment of MDD, OCD, panic disorder with or without agoraphobia, and GAD.

Noven (the Applicant) has developed PM 7.5 mg as an orally administered capsule for the treatment of moderate to severe vasomotor symptoms associated with menopause. The tradename of this product is Brisdelle.

Brisdelle is a nonhormonal therapy for VMS. It should be taken once daily, at bedtime, with or without food. Brisdelle was specifically developed to provide a lower dose of paroxetine than the doses used to treat depression, obsessive compulsive disorder, panic disorder, generalized anxiety disorder, social anxiety disorder, and post-traumatic stress disorder.

Medical Reviewer's Comments

- *In this review, the abbreviation of "PM" will be used to refer to the 7.5 mg paroxetine mesylate capsule.*
- *Currently, paroxetine is not approved in any country for the VMS treatment indication.*

2.2 Currently Available Treatments for Proposed Indications

While there are a variety of drug products in different formulations (tablet, transdermal system, vaginal ring) approved for the treatment of menopausal symptoms (including both VMS and symptoms related to vulvar/vaginal atrophy), all contain either estrogen alone or estrogen plus a progestin.

The estrogen-only products carry 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. The estrogen and estrogen/progestin products have a Boxed Warning describing findings from the Women's Health Initiative that reported increased risks of stroke, myocardial infarction (MI; associated only with use of estrogen/progestin), deep vein thrombosis (DVT), pulmonary embolism (PE; associated only with use of estrogen/progestin), invasive breast cancer (associated only with use of estrogen/progestin) and probable dementia in women ≥ 65 years old. Both estrogen-alone and estrogen/progestin products are contraindicated in women with known, suspected, or history of breast cancer. Other 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 other products are used off-label to treat VMS, such as antidepressants (Including paroxetine in higher doses), herbal and soy products; however, rigorous evidence of the safety and efficacy of these treatments is lacking.

As noted above, there are no nonhormonal products currently approved for the proposed indication.

2.3 Availability of Proposed Active Ingredient in the United States

Paroxetine, the active ingredient, was first marketed in the US in 1992 as paroxetine hydrochloride, Paxil, for psychiatric indications. Pexeva, which is the Applicant's product in tablet form and substitutes mesylate for hydrochloride as the associated salt, was approved for similar psychiatric indications in 1993. The current approved dosing for both products ranges from 10 mg/day to a maximum of 60 mg/day.

Medical Reviewer's Comment

- *The proposed dose to treat VMS is 7.5 mg daily, which is lower than the approved psychiatric doses.*

2.4 Important Safety Issues with Consideration to Related Drugs

Important safety issues described in the current Pexeva labeling include:

- 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)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The FDA 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 nonhormonal 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 FDA 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 N30-003, the FDA 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. In addition, 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 FDA, but FDA 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. FDA 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 FDA 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. FDA 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 was underway at the time of this meeting, the FDA agreed that the Applicant could address the evaluation of clinical meaningfulness using an appropriate anchoring questionnaire in the planned second phase 3 study. The Applicant agreed to evaluate the persistence of benefit to 24 weeks of treatment in one of the phase 3 studies. FDA informed the Applicant that it must conduct a formal evaluation of suicidality in the clinical trials according to current FDA guidelines.

The Applicant submitted a Special Protocol Assessment (SPA) for the Study N30-003 protocol and FDA 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, FDA 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. FDA 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 N30-003 protocol in May 2011, following review of the revised protocol.

FDA provided further guidance on Study N30-004 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 N30-004 protocol.

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

2.6 Other Relevant Background Information

2.6.1 Information Requests

No specific information requests from this reviewer were submitted to the Applicant for this review.

2.6.2 Division of Medication Error Prevention and Analysis (DMEPA)

Noven submitted a request for proprietary name review of Brisdelle (paroxetine), NDA 204516 on December 26, 2012. The Applicant also markets the active ingredient, paroxetine mesylate, under the proprietary name, Pexeva. In the review dated March 14, 2013, DMEPA concluded that the proposed proprietary name is acceptable from both a promotional and safety perspective.

2.6.3 Good Clinical Practice Assessment Branch, Office of Scientific Investigations

On October 26, 2012, the Division requested the Office of Scientific Investigations to audit 3 preselected sites to insure data integrity. Study sites 14 (Dr. Blank), 23 (Dr. Kalafer) and 38 (Dr. Campbell) all participated in both pivotal clinical trials. All study sites for both pivotal trials were located in the US. Based on an email from Roy Blay dated April 15, 2013, the three OSI inspections for this application have been completed; however, the inspection reports have not been reviewed yet. Only the inspection report for Dr. Kalafer has been received and it is tentatively classified VAI (Voluntary Action Indicated). The inspection reports for Drs. Blank and Campbell have not been received yet but are tentatively classified NAI (No Action Indicated). Therefore, based on these inspections, the study data for Protocols N30-003 and N30-004 submitted by the Applicant appear reliable in support of this NDA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant states that phase 2 and phase 3 clinical trials were conducted in accordance with the International Conference on Harmonization, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed. The protocols and protocol amendments were reviewed and approved by Independent Ethics Committees or Institutional Review Boards.

3.2 Compliance with Good Clinical Practices

The Applicant attests that the pivotal phase 3 clinical trial and the supportive phase 2 clinical trial were conducted in compliance with Good Clinical Practice.

3.3 Financial Disclosures

Form FDA 3454 ("Certification: Financial Interests and Arrangements of Clinical Investigators") was submitted in the NDA. On this form, Noven certified that they have not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. Noven also certified that the listed investigators did not disclose any proprietary interest in the product or in the company and that no investigator received significant payments of other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (ONDQA)

CMC
PM is an immediate-release, oral capsule which contains 9.69 mg of paroxetine mesylate, which is equivalent to 7.5 mg of paroxetine base. The drug product is manufactured at two sites; Norwich Pharmaceuticals in North Norwich, NY and (b) (4) Several additional companies have been listed as excipient testing and packaging facilities.

Paroxetine mesylate was previously approved as 10, 20, 30, and 40 mg paroxetine mesylate tablets (Pexeva) under NDA 21299. (b) (4) .

Medical Reviewer's Comments

- *The capsule actually contains 9.69 mg of paroxetine mesylate which is equivalent to 7.5 mg of paroxetine. The CMC reviewer stated that the presentation of the strength and the established name, as proposed by the applicant,* (b) (4) *is in violation of the USP Nomenclature Policy for Salt Drug Substances in Drug Products, effective May 1, 2013. The established name for this drug product should be paroxetine* (b) (4) *. All instances of* (b) (4) *must change to "paroxetine" so that the label should read "BRISDELLE (paroxetine), 7.5 mg.*
- *Per her review of May 1, 2013, the CMC reviewer also stated the following:*

  - *This NDA has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. The specification for the drug product was not deemed adequate due to the dissolution acceptance criterion for the drug product. Therefore, the quality of the drug product could not be assured.*
  - *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.*

Biopharmaceutics
Based on the Biopharmaceutics review dated April 26, 2013, approval cannot be granted until agreement is reached regarding the appropriate dissolution acceptance criterion.

Medical Reviewer's Comment

- *The Biopharmaceutics reviewer expects that an agreement will be reached during this review cycle. Once an agreement is reached, the reviewer will recommend approval of this NDA.*

4.2 Clinical Microbiology

A Clinical Microbiology review was not requested for this oral capsule.

4.3 Preclinical Pharmacology/Toxicology

NDA 204516 was submitted as a 505(b)(2) application. The Applicant is relying on previous findings of safety for the active ingredient paroxetine from NDA 20031 (Paxil) and is cross-referencing its own NDA 21299 and IND 76636 for paroxetine mesylate (Pexeva) to support the nonclinical toxicity testing for this NDA.

Medical Reviewer's Comment

- *In her review dated 2/1/134, the Pharmacology/Toxicology Reviewer stated that there were no nonclinical safety concerns identified for the use of paroxetine for the treatment of VMS in postmenopausal women. This was based on previous approval of paroxetine at a dose greater than the proposed dose for treatment of VMS (7.5 mg/day). Therefore, Pharm/Tox finds NDA 204516 approvable.*

4.4 Clinical Pharmacology

Paroxetine is completed absorbed after oral dosing and bioavailability is not affected by concomitant food intake. Paroxetine distributes throughout the body. including the

central nervous system, with only 1% remaining in the plasma. None of the metabolites contribute to the pharmacological effect of paroxetine

Medical Reviewer's Comment

- *NDA 204515 was found to be acceptable from a Clinical Pharmacology perspective.*

Paroxetine is a known CYP2D6 inhibitor. CYP2D6 is believed to be the major enzyme involved in the formation of the tamoxifen active metabolite, endoxifen. Endoxifen is believed to have a 100-fold greater affinity for the estrogen receptor and 30-100 fold greater potency than tamoxifen, *in vitro*. The clinical impact of the CYP2D6 inhibition on patients taking Tamoxifen for breast cancer prevention is uncertain.

To help us answer this question, a consult was obtained from the Division of Oncology Products 1 (DOP1). The following questions were asked:

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

DOP1 responded:

1. 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.
2. Labeling changes were suggested based on the current evidence. The statement that "(b) (4) should be replaced with "It is uncertain whether the co-administration of paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen."

Medical Reviewer's Comment

- *The changes recommended by DOP1 will be incorporated into labeling.*

4.4.1 Mechanism of Action

The mechanism of action of PM with respect to treatment of VMS is unknown.

4.4.2 Pharmacodynamics

The selection of the 7.5 mg/day dose that was used in both phase 3 studies was based on published literature showing no dose-response with regard to efficacy for VMS treatment in doses ranging from 10 to 25 mg but a dose relationship for tolerability. Therefore, a dose lower than the doses used to treat psychiatric disorders was chosen in order to achieve better patient tolerability.

4.4.3 Pharmacokinetics

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. Following a single oral dose of PM on Day 1, mean plasma concentrations of paroxetine reached a peak concentration at a median of 6 hours after dosing and started to decline exponentially with a mean half-life of 17.3 hours to less than 8% of the mean peak plasma concentration by 120 hours after dosing. The peak exposure, measured as maximum observed plasma concentration (Cmax), increased from 2.77 ng/mL after a single dose to 13.1 ng/mL at steady-state after 2 weeks of once-a-day dosing (Study Day 19), which is approximately 5-fold.

In a study of 24 subjects taking PM 7.5 mg once daily for 19 days, the steady-state maximum plasma concentration of paroxetine (Cmax) was 13.1 ng/mL and the total exposure (AUC) of paroxetine is eight times higher than that observed after a single dose. The excess accumulation is a consequence of the saturation of CYP2D6, which is discussed above.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Clinical studies with PM included:

1. Study N30-005: A phase 1, single center, single and multiple dose, open-label PK study in healthy postmenopausal women to support the use of PM in that population. All subjects received PM 7.5 mg capsules as a single dose and then, following a 5-day washout period, once daily for 14 days.

2. Study N30-002: A phase 2, 8-week, multicenter, double-blind, placebo-controlled proof-of-concept study using the to-be-marketed formulation of PM 7.5 mg daily for 8 weeks.

3. Studies N30-003 and N30-004: These were the two pivotal phase 3 clinical trials.

A summary of these studies is presented below.

Table 1 Paroxetine Mesylate Clinical Studies

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 -PM 7.5 mg capsule	-PM: 24/24	-3 weeks Screening, 1 day treatment (followed by 5 nontreatment days), then 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 -PM 7.5 mg capsule daily vs. placebo	-PM: 49*/45 -Placebo: 52/51	-1 week placebo run-in period -8 week treatment 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 -PM 7.5 mg capsule daily vs. placebo	-PM: 306/271 -Placebo: 308/278	-7 days screening, -12-day placebo run-in period, -12 week treatment 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 -PM 7.5 mg capsule daily vs. placebo	-PM: 285/235 -Placebo: 284**/218	-7 days screening, -12-day placebo run-in period, -24 week Treatment period

*One subject randomized to PM did not receive study drug
** One subject randomized to placebo did not receive study drug
Source: Medical Reviewer

Medical Reviewer's Comments

- *Data from the phase 2 Study N30-002 was not used for the efficacy analysis because it was only an 8- week study. However, data from this study was used in the safety analysis.*
- *The phase 3 pivotal studies were very similar in design. Both studies were randomized, double-blind, placebo-controlled, multicenter studies in women with either natural or surgical menopause.*
- *Both trials were conducted entirely in the US.*
- *Both trials utilized an electronic diary that was available throughout the day or night and used for daily entry of hot flush data.*

5.2 Review Strategy

The primary phase 3 clinical trials, as well as the supportive phase 1 and phase 2 clinical trials were reviewed to assess the safety and efficacy of PM. Efficacy was assessed from the two phase 3 trials. Safety was assessed using the pooled data from both these studies.

5.3 Discussion of Individual Studies/Clinical Trials

The following are general observations relating to the above phase 3 clinical trials.

Enrollment
All studies submitted to this NDA were conducted in postmenopausal women in the US. A total of 1,184 subjects were enrolled in the two phase 3 trials, 591 of whom used PM. A total of 614 subjects were enrolled in Study 003 (306 on PM and 308 on placebo) and 570 subjects were enrolled in Study 004 (285 in each arm).

Inclusion-Exclusion Criteria
Inclusion criteria were identical in the phase 2 and phase 3 studies and consisted of 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 2 and phase 3 studies. All phase 2 and 3 studies disallowed enrollment of subjects who were nonresponders 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 2 and 3 studies included psychiatric disorders (either lifetime history or more recently prior to screening, hypertension (unless on stable dose of antihypertensives), clinically unstable cardiac disease, biliary tract disease, and thyroid disease (unless stable).

Two exclusion criteria were used in a single study.

- Study N30-003 excluded subjects taking monoamine oxidase inhibitors (MAOIs), thioridazine, or pimozide (MAOIs were to be discontinued for at least 4 weeks prior to the Run-in Visit per the inclusion criteria).
- Study N30-004 excluded subjects with a body mass index (BMI) ≥ 40 kg/m^2.

Placebo Run-In Period
In both trials, subjects were requalified for participation after the 12-day Placebo Run-in period. Inclusion criteria following Run-in were also identical in both studies. Both studies had similar subject populations and both utilized the same definitions for the modified intent-to-treat (MITT) and per protocol (PP) populations.

Medical Reviewer's Comments

- *The Division agreed to the use of a 12-day Placebo Run-in period for the phase 3 trials. This would eliminate the placebo responders and also eliminate subjects who had difficulty completing the electronic diary.*
- *Hot flush frequency and severity inclusion criteria (7-8 moderate to severe hot flushes daily or 50-60 hot flushes weekly for at least 30 days prior to screening) conformed to the entry criteria in the VMS draft Guidance.*
- *The phase 3 study subjects were generally free of any history of significant psychiatric disorders. Exclusion criteria for Study N30-004 were initially more liberal regarding timeframes for a past history of psychiatric illness. The protocol was later amended and tightened to exclude subjects who had a lifetime history of psychiatric illness. Approximately 75% of subjects in Study N30-004 were enrolled under the original protocol that only excluded subjects with a major depressive episode within 2 weeks prior to enrollment, whereas 25% of the subjects were enrolled under the modified version that excluded subjects with a history of major depressive disorder anytime in their life, similar to Study N30-003.*
- *A personal history of cancer was not an exclusion criterion in either phase 3 study.*

Daily Diaries

The phase 2 study and both phase 3 studies used an electronic diary using the Interactive Voice Response System/Interactive web Response System (IVRS/IWRS) for daily entry of hot flash data. This electronic diary was the only source document for the 4 co-primary endpoints. The diary was available to the subject throughout the day or night (24/7). To minimize recall, subjects were encouraged to enter hot flash data as soon as they experienced a hot flash or at least once daily. Subjects were also provided with a Quick Reference Guide which included the definitions of mild, moderate, and severe hot flashes

The system generated daily compliance reports for each subject. The compliance reports tabulated the date and time of each hot flash entry and the number of hot flashes entered at each time point. Investigators were required to print these compliance reports daily and to review the data for compliance and completeness. Non-compliant subjects were contacted by study personnel and retrained.

Table 2 Daily Hot Flash Diary

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Number of today's hot flashes that were mild, moderate or severe	_mild _moderate _severe	_mild _moderate _severe	_mild _moderate _severe	_mild _moderate _severe	_mild _moderate _severe	_mild _moderate _severe	_mild _moderate _severe
Total number of moderate to severe hot flashes							
Total number of hot flashes							

Source: CSR N30-003, Page 38, Figure 1; CSR N30-004, Page 38, Figure 1

5.3.1 Phase 3 Study N30-003

Study Title
"A Phase 3, Twelve-Week, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause" (Protocol N30-003)

Study Objectives
The primary objective of this trial was to assess the safety and efficacy of PM for treatment of VMS associated with menopause.

The Applicant listed numerous secondary objectives which included assessment of:

- Mean number of hot flashes per day
- Mean weekly change from Baseline in hot flash frequency
- Mean weekly change from Baseline in hot flash severity
- Effects of PM compared with placebo on total number of awakenings due to hot flashes per day
- Mean change in frequency from Baseline to Week 4 for body mass index (BMI) <32 and ≥32 groups
- Mean change in frequency from Baseline to Week 12 for BMI <32 and ≥32 groups
- Mean change in severity from Baseline to Week 4 for BMI <32 and ≥32 groups
- Mean change in severity from Baseline to Week 12 for BMI <32 and ≥32 groups
- Change from Baseline in climacteric symptoms
- Daily interference of hot flashes
- The number of responders (based on ≥ 50% reduction in hot flash
- frequency)
- Summary of Patient Satisfaction Questionnaire (PSQ)

- Proportion of Patient Global Improvement (PGI) Responders
- Proportion of Clinical Global Impression (CGI) Responders
- Proportion of Numerical Rating Scale (NRS) Responders
- Sexual functioning
- Anxiety and depression
- Mood
- Effect on BMI

Clinical Trial Design

This was a multicenter, randomized, double-blind, placebo-controlled, 12-week study of 7.5 mg paroxetine mesylate capsules versus placebo in postmenopausal female subjects with moderate to severe VMS associated with menopause. Moderate and severe VMS were defined as follows:

- Moderate VMS: Sensation of heat with sweating, able to continue activity
- Severe VMS: Sensation of heat with sweating, causing cessation of activity

Enrollment

A total of 614 subjects were randomized into the study across 70 US study sites; 306 subjects in the PM group and 308 subjects in the placebo group. Of these, 297 subjects (97.1%) in the PM group and 302 subjects (98.1%) in the placebo group received at least one dose of study drug. A similar percentage of subjects in both groups completed the study; 271 of the 306 randomized in the PM group (88.6%) and 278 of the 308 subjects randomized in the placebo group (90.3%).

Clinical Trial Sites

The study utilized 70 study sites in the US.

Inclusion Criteria

1. Female, ≥ 40 years of age at Screening (inclusive)
2. Reported more than 7 to 8 moderate to severe hot flashes per day (average) or 50 to 60 moderate to severe hot flashes per week for at least 30 days prior to the Screening Visit
3. Willing and able to have been compliant with the protocol and provide a voluntary written informed consent
4. Must have met one of the following criteria:
    - Spontaneous amenorrhea for at least 12 consecutive months
    - Amenorrhea for at least 6 months and meet the biochemical criteria for menopause (FSH ≥ 40 mIU/mL)
    - Bilateral salpingo-oophorectomy ≥ 6 weeks with or without hysterectomy
5. Subjects must have:
    - Discontinued all psychotropic drugs as follows:
        - Two weeks prior to Run-in Visit for thioridazine, pimozide, tricyclic

antidepressants (TCAs), SSRIs (except for fluoxetine), SNRIs, lithium and oral narcoleptics, and all sedatives and hypnotics (with the exception of zolpidem, zaleplon, eszopiclone, and Benadryl)
    - Four weeks prior to Run-in Visit for fluoxetine, Saint John's Wort and monoamine oxidase inhibitors (MAOIs)
    - Twelve weeks prior to Run-in Visit for depot narcoleptics
- Discontinued estrogen alone- or estrogen/progestin-containing products as follows:
    - One week prior to Run-in Visit for vaginal hormonal products (rings, creams, gels)
    - Four weeks prior to Run-in Visit for transdermal estrogen alone or estrogen/progestin products
    - Eight weeks prior to Run-in Visit for oral estrogen and/or progestin therapy
    - Eight weeks prior to Run-in Visit for intrauterine progestin therapy
    - Three months prior to Run-in Visit for progestin implants and estrogen alone injectable drug therapy
    - Six months prior to Run-in Visit for estrogen pellet therapy or progestin injectable drug therapy

Medical Reviewer's Comment

- *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.*

Exclusion Criteria

1. History of hypersensitivity or adverse reaction to paroxetine or any of the inactive ingredients in PM capsules
2. Known non-response to previous SSRI or SNRI treatment for VMS
3. History of self-injurious behavior
4. Lifetime history of clinical diagnosis of depression; or treatment for depression
5. History of clinical diagnosis of border-line personality disorder
6. Presence of any of the following psychiatric disorders within the timeframes specified below:
    - Major Depressive Disorder — Life-time
    - Dysthymia — Past 2 Years
    - Bipolar Disorder — Life-time
    - Panic Disorder — Life-time
    - Agoraphobia — Past Month

- Social Phobia — Past Month
- Obsessive Compulsive Disorder — Past Month
- Generalized Anxiety — Life-time
- Alcohol Disorders — Past 12 months
- Drugs (Substance Abuse) — Past 12 months
- Psychotic Disorders — Life-time
- Anorexia Nervosa — Past 10 years
- Bulimia — Past 10 years
- Suicidality/Suicidal Ideation — Life-time
- Post Traumatic Stress Disorder — Life-time

7. History of hypertension in women who are not on a stable dose of antihypertensives for at least 30 days prior to Screening
8. Subjects taking MAOIs, thioridazine, or pimozide
9. Evidence of impaired liver function upon entry into the study (values ≥ 2 times the upper limit of normal [ULN] for aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin ≥ 1.3 mg/dL) or who, in the Investigator's opinion, exhibit liver function impairment to the extent that the subject should not participate in this study
10. Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia
11. Evidence of impaired kidney function upon entry into the study (i.e., serum creatinine >1.5 mg/dL or known renal stricture)
12. Biliary tract disease, adrenal cortical insufficiency, or any other medical condition that, in the Investigator's opinion, is inadequately treated and precludes entry into the study
13. Thyroid disease, unless subject is clinically stable with normal thyroid indices and is on maintenance thyroid medication (e.g., Synthroid or Cytomel) for ≥ 6 months prior to Screening
14. Positive urine pregnancy test result at run-in or at any time during study participation; females who are not at least 2 years postmenopausal must use adequate nonhormonal contraception (e.g., barrier methods) during study participation
15. Clinically significant abnormality at the Screening physical examination, ECG, laboratory tests or urine drug screen
16. Use of an investigational study medication within 30 days prior to Screening or during the study
17. Concurrent participation in another clinical study or previous participation in this study
18. Family of investigational site staff

Scheduled Visits
The Schedule of Events for this study is displayed in Section 9.4.

Screening
Screening procedures were performed within 7 days prior to the start of the single-blind placebo Run-in Period of the study.

- Review of inclusion/exclusion criteria
- Medical and psychiatric history
- General physical examination
- Vital sign measurements, including systolic and diastolic blood pressure, heart rate and body temperature
- Weight and height
- Standard 12-lead electrocardiogram (ECG)
- The following laboratory tests were performed during Screening:
    - Hematology
    - Serum chemistry
    - Urine drug screen
    - Follicle stimulating hormone (FSH)
- Record concomitant therapies
- Record AEs

Placebo Run-in Visit
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 flash and sleep diaries each day using IVRS/IWRS, recording the number of hot flashes daily, the severity of each episode of hot flash and total number of awakenings due to hot flashes.

Placebo Run-in Period

- Administration of study drug: once daily at bedtime
- Subject completed daily hot flash diary using the IVRS/IWRS
- Subject completed the daily sleep diary using the IVRS/IWRS
- Recorded concomitant therapies
- Recorded AEs

End of Run-in Visit
The End of Run-in Visit occurred within 3 days of completing the Run-in Period.

Run-in failures, defined as follows, were discontinued from the study:

- All subjects who did not have 7–8 moderate to severe hot flashes per day [average] or 50–60 hot flashes per week) at the end of the Run-in Period

- Subjects, who were noncompliant with completing the daily hot flash diaries (i.e., did not have at least 9 days of diary data) and who missed 3 or more doses of the study drug during the Run-in Period

Medical Reviewer's Comment

- *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.*

Following completion of the Run-in Period, subjects who were compliant with diary entry (had at least 9 days of diary data) and dosing (had not missed 3 or more doses of the study drug during the Run-in Period), and who continued to meet hot flash eligibility criteria (i.e., having more than 7 to 8 moderate to severe hot flashes per day or 50 to 60 moderate to severe hot flashes per week) were randomized into the Double-blind Treatment Period in a 1:1 ratio to receive either PM (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. Subjects continued to fill out the daily hot flash and sleep diaries each day using IVRS/IWRS.

Baseline Visit
The Baseline Visit took place within 3 days of completing the Run-in Period.

The following study evaluations were performed during the Baseline visit:

- Completion of the Columbia Suicide Severity Rating Scale (C-SSRS) at the clinic during the clinic visit
- If the subject answered "YES" to questions 1 and/or 2 for suicidal ideation or to any question for suicidal behavior, then the subject was discontinued.
- Subjects who were discontinued from the study due to the above criteria were referred to a mental health professional/psychiatrist.

Subject completion of the following on IWRS:

- Hospital Anxiety and Depression Scale (HADS): self-assessment scale designed to detect states of depression and anxiety
- Profile of Mood States (POMS): instrument that assesses 6 dimensions of affect or mood
- Greene Climacteric Scale (GCS): a self-assessment tool measuring menopause symptomatology
- Hot Flash Related Daily Interference Scale (HFRDIS): a 10-item scale designed to measure the degree which hot flashes interfered with daily activities
- Arizona Sexual Experience Scale (ASEX): used to quantify the subject's sexually related symptoms

- Numerical Rating Scale (NRS): measured how bothered the subject was by her VMS on a 0 (not bothered) to 10 (very much bothered) scale
- Investigator completion of the Clinical Global Impression Scale (CGI): the final patient-reported outcome instrument in which subjects were asked to respond to the following question: “Compared to before starting study medication, how would you describe your hot flushes now?”
- Urine pregnancy performed at the clinic for all females who had were not at least 2 years postmenopausal
- Randomization
- Subjects were instructed to take their study medication once daily at bedtime and to comply with the study drug dosing regimen

Double-blind Treatment Period (Day 1 to Day 84)
Administration of study medication began on Day 1 and continued up to the day before their Final Study Visit. Subjects returned to the clinic for evaluations on Day 14 (+3 days), Day 28 (+3 days), and Day 85 (+3 days), or upon early discontinuation.

Site personnel contacted subjects by telephone on Day 7 (+3 days), Day 21 (+3 days), Day 42 (+3 days) and Day 56 (+3 days). Symptom assessment questionnaires were administered at Baseline and on Day 28 and Day 85 Visits. Subjects were asked to complete a Discontinuation-emergent Signs and Symptoms (DESS) Scale within 7±3 days after the last dose of study medication.

On Day 28 and Day 85 or upon early discontinuation, subjects completed the following questionnaires on IWRS. Subjects completed these questionnaires at home up to 3 days before or after the clinic visit or at the clinic during their clinic visit.

- HADS
- POMS
- GCS
- HFRDIS
- ASEX
- NRS
- PSQ : patient satisfaction questionnaire asking “Are you satisfied with your treatment?” answered with a yes/no

On Day 14 and Day 28, subjects completed the C-SSRS at the clinic during the clinic visit

- If the subject answered “YES” to questions 1 and/or 2 for suicidal ideation or to any question for suicidal behavior, then the subject was discontinued.
- Subjects who were discontinued from the study due to the above criteria were referred to a mental health professional/psychiatrist.

On Day 28 and Day 85 or upon early discontinuation, the following instruments were completed:

- The Clinical Global Impression (CGI), which assessed the global severity of illness and the improvement from Baseline.
- The Patient Global Improvement (PGI) scale, which assessed improvement in VMS based on a 7-point scale. The PGI was also used as an anchor to evaluate Clinical Meaningfulness. (See Section 6.1.6 Other Endpoints)

The following evaluations were performed at the Day 85 Visit or upon early discontinuation from the study:

- Completion of the C-SSRS at the clinic during the clinic visit
- Hematology
- Serum chemistry
- General physical examination
- Standard 12-lead ECG

The following additional evaluations were performed 7±3 days after last dose of study drug:

- Subject completion of DESS on IWRS
- Review concomitant therapies and record new information
- Review AEs and record new information. AEs were recorded up to 7 days following the last dose of study medication.

Protocol Amendments

The original protocol was dated August 11, 2010; there were 4 clinically significant revisions.

Amendment 1, dated October 27, 2010:

- The definition of a Responder (a subject who achieved a ≥ 50% reduction from mean Baseline hot flash frequency) was added; this analysis was used to evaluate persistence of benefit in reducing VMS frequency at Week 24.
- The assessment of suicidality using the C-SSRS was added per the FDA draft guidance on suicidality
- Based on FDA feedback, the amendment stated that if the difference in change from baseline between LDMP and placebo was <2 hot flashes per day, a responder analysis would be conducted.

Amendment 2, dated January 13, 2011:

- The effects of PM compared to placebo on the total number of awakening due to hot flashes per day was deleted as a key secondary objective and became the fourth of 19 secondary objectives

- "Change from Baseline in total number of awakenings due to hot flashes per day: A Sleep Diary will be used to assess the number of awakenings due to hot flashes." was deleted as the key secondary efficacy variable and became the fourth of 19 secondary efficacy variables.
- Subjects taking MAOIs, thioridazine or pimozide were added to the Exclusion Criteria.
- The PGI Scale, which was used in the assessment of Clinical Meaningfulness in this study (See Section 6.1.6 Other Endpoints), was also added to the assessments on Day 28 and Day 85.

Amendment 3, dated March 7, 2011:

- The following exclusion criteria were added:
  (1) history of self-injurious behavior; (2) history of clinical diagnosis of depression; or treatment for depression; (3) history of clinical diagnosis of border-line personality disorder.
- Day 14 was made a clinic visit rather than a telephone visit and the C-SSRS was to be administered at Day 14 as well as Day 28 and Day 85.
- In addition, the timeframes for psychiatric disorders were changed to the following:
  - Major Depressive Disorder — Lifetime
  - Dysthymia — Past 2 Years
  - Bipolar Disorder — Lifetime
  - Panic Disorder — Lifetime
  - Agoraphobia — Past Month
  - Social Phobia — Past Month
  - Obsessive Compulsive Disorder — Past Month
  - Generalized Anxiety — Lifetime
  - Alcohol disorders — Past 12 months
  - Drugs (Substance Abuse) — Past 12 months
  - Psychotic Disorders — Life-time
  - Anorexia Nervosa — Past 10 years
  - Bulimia — Past 10 years
  - Suicidality/Suicidal Ideation — Lifetime
  - Post Traumatic Stress Disorder — Lifetime

Medical Reviewer's Comment

- *The timeframes for exclusion for many of these psychiatric disorders were significantly extended from 2 months to lifetime.*

Amendment 4, dated March 29, 2011:

- For the Responder Analysis to demonstrate Clinical Meaningfulness, the

cutoff point was established using the ROC analysis with all subjects, regardless of treatment assignment and whether or not they indicated satisfaction (as assessed by the PGI score) with their treatment.

Medical Reviewer's Comment

- *All prospectively defined analyses were conducted according to the approved Statistical Analysis Plan.*

5.3.2 Phase 3 Study N30-004

Study Title

"A Phase 3, Twenty-Four Week, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause" (Protocol N30-004)

Study Objectives

The primary objective was to assess the safety and efficacy of paroxetine mesylate for the treatment of VMS.

The secondary objectives were to assess:

- Mean number of hot flashes per day
- Mean weekly change from baseline in hot flash frequency
- Mean weekly change from baseline in hot flash severity
- The effects on total number of awakenings due to hot flashes per day
- Mean change in frequency from baseline to week 4 for BMI <32 and ≥ 32 groups
- Mean change in frequency from baseline to week 12 for BMI <32 and ≥ 32 groups
- Mean change in frequency from baseline to week 24 for BMI <32 and ≥ 32 groups
- Mean change in severity from baseline to week 4 for BMI <32 and ≥ 32 groups
- Mean change in severity from baseline to week 12 for BMI <32 and ≥ 32 groups
- Mean change in severity from baseline to week 24 for BMI <32 and ≥ 32 groups
- Change from baseline in climacteric symptoms
- Daily interference of hot flashes
- Number of responders (based on ≥50% reduction in hot flash frequency)
- Proportion of Clinical Global Impression (CGI) responders
- Proportion of Numerical Rating Scale (NRS) responders
- Sexual functioning
- Anxiety and depression
- Mood
- Effects on body mass index

- Persistence of efficacy at 24 weeks

Medical Reviewer's Comment

- *The FDA was particularly interested in the evaluation of the clinical meaningfulness of the treatment effect on VMS frequency and of the persistence of benefit to 24 weeks of treatment.*

Clinical Trial Design

This was a 24-week, multicenter, double-blind, randomized, placebo-controlled study of 7.5 mg paroxetine mesylate capsules versus placebo in female subjects with moderate to severe postmenopausal hot flashes. The definitions of moderate and severe hot flashes and the 2 oral study treatments (PM 7.5 mg capsule and placebo capsule) were the same as in Study N30-003.

Enrollment

A total of 570 subjects were randomized into the study across 65 US study sites. Subjects were evenly distributed between the PM and placebo groups (each treatment group had 285 subjects). All but 1 of the randomized subjects (99.8%) received at least 1 dose of study drug; Placebo Subject 4-53-008 did not receive any study drug.

Clinical Trial Sites

The study utilized 65 study sites in the US.

Inclusion Criteria

1. Female > 40 years of age at screening
2. Reported more than 7-8 moderate to severe hot flashes per day or 50-60 per week for at least 30 days prior to the screening visit of sufficient severity to cause desire for therapeutic intervention
3. Must meet one of the following criteria:
    a. Spontaneous amenorrhea for at least 12 consecutive months
    b. Amenorrhea for at least 6 months and meet the biochemical criteria for menopause (follicle-stimulating hormone ≥ 40 mIU/mL)
    c. Bilateral salpingo-oophorectomy ≥ 6 weeks prior to enrollment with or without hysterectomy
4. Willing and able to be compliant with the protocol and provide a voluntary written informed consent
5. Subjects must have:
    a) Discontinued all psychotropic drugs as follows:
        - Two weeks prior to Run-In Visit for thioridizine, pimozide, TCAs, SSRIs (except for fluoxetine), SNRIs, lithium and oral neuroleptics, and all sedatives and hypnotics (with the exception of zolpidem, zaleplon, eszopiclone and benadryl)

- Four weeks prior to Run-In Visit for fluoxetine, Saint John's Wort and monoamine oxidase inhibitors (MAOIs)
- Twelve weeks prior to Run-In Visit for depot neuroleptics

b) Discontinued estrogen alone or estrogen/progestin containing products as follows:

- One week prior to Run-In Period for vaginal hormonal products (rings, creams, gels)
- Four weeks prior to Run-In Period for transdermal estrogen and/or estrogen/progestin products
- Eight weeks prior to Run-In Period for oral estrogen and/or progestin therapy
- Eight weeks prior to Run-In Period for intrauterine progestin therapy
- Three months prior to Run-In Period for progestin implants and estrogen alone injectable drug therapy
- Six months prior to Run-In Period for estrogen pellet therapy or progestin injectable drug therapy

Exclusion Criteria

1. History of hypersensitivity or adverse reaction to paroxetine
2. Known non-responder to previous SSRI or SNRI treatment for VMS
3. Presence of any of the following psychiatric disorders within the timeframes specified below as ascertained by the Mini-International Neuropsychiatric Interview (MINI):

Major Depressive Episode	Past 2 weeks
Dysthymia	Past 2 weeks
(Hypo) Manic Episode	Lifetime
Panic Disorder	Past Month
Agoraphobia	Past Month
Social Phobia	Past Month
Obsessive Compulsive Disorder	Past Month
Generalized Anxiety	Past 6 months
Alcohol disorders	Past 12 months
Drugs (Substance Abuse)	Past 12 months
Psychotic Disorders	Lifetime
Anorexia Nervosa	Past 3 months
Bulimia	Past 3 months
Suicidality	Past month
Post Traumatic Stress Disorder	Past month

4. BMI ≥ 40 kg/m²

5. History of hypertension in subjects who are not on a stable dose of antihypertensives for at least 30 days prior to screening
6. Evidence of impaired liver function upon entry into the study (values ≥ 2 times the upper limit of normal for aspartate transaminase (AST), alanine transaminase (ALT), or bilirubin ≥ 1.3 mg/dL) or who, in the investigator's opinion, exhibit liver function impairment to the extent that the subject should not participate in the study
7. Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia
8. Evidence of impaired kidney function upon entry into the study (i.e., serum creatinine > 1.5 mg/dL) or known renal stricture
9. Biliary tract disease, adrenal cortical insufficiency, or any other medical condition that, in the investigator's opinion, is inadequately treated and precludes entry into the study
10. Thyroid disease, unless subject is clinically stable with normal thyroid indices and is on maintenance thyroid medication (e.g., Synthroid or Cytomel) for ≥ 6 months prior to screening.
11. Positive urine pregnancy test result at screening or at any time during study participation; females who are not at least 2 years post-menopausal must use adequate nonhormonal contraception (e.g., barrier methods) during study participation
12. Clinically significant abnormality at the screening physical examination, ECG, laboratory tests, or urine drug screen
13. Use of an investigational study medication within 30 days prior to screening or during the study
14. Concurrent participation in another clinical trial or previous participation in this trial
15. Family of investigational-site staff

Medical Reviewer's Comments

- *These inclusion/exclusion criteria are extensive but appropriate for this study.*
- *Washout periods for prior hormone use and the criteria used to determine menopausal status are consistent with the draft Guidance on Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms.*
- *Although the Division generally prefers no BMI restrictions in these types of studies to better reflect the general population of patients who may potentially use this drug, the restriction of a BMI of 40 or greater (i.e., morbid obesity) did not seem unusually restrictive.*

Scheduled Visits
The Schedule of Events for this study is displayed in Section 9.4.

Placebo Run-In Period
Subjects were screened, and eligible subjects entered a 12-day Run-in Period. During the Run-in Period, all subjects were dispensed single-blind placebo capsules (i.e., subjects were blinded to capsule content), which they took once daily at bedtime. They were also asked to complete daily hot flash and sleep diaries each day, recording the number of hot flashes daily, the severity of each episode of hot flash, and the total number of awakenings due to hot flashes. Following completion of the Run-in Period, subjects who were compliant with diary entry and dosing and who continued to meet hot flash eligibility criteria (i.e., having more than 7 to 8 moderate to severe hot flashes per day or 50 to 60 moderate to severe hot flashes per week) were randomized in a 1:1 ratio to receive either PM (7.5 mg capsule) or placebo. The treatment was taken once daily at bedtime beginning on Day 1 and continuing up to Day 168, and subjects also continued to fill out the daily hot flash and sleep diaries throughout this period.

Run-In Visit and Run-in Period
After the initial screening period, eligible subjects were entered into a 12-day run-in period. During the run-in period, subjects were not advised they were receiving placebo capsules in a single-blinded fashion. Subjects took the study medication once daily at bedtime and were instructed to complete the daily hot flash diary and the daily sleep diary recording the number of hot flashes daily, the severity of each episode of hot flash, daily hours of sleep, and number of awakenings.

Baseline Visit
The baseline visit occurred within 3 days of completing the run-in period. Subjects who recorded more than 7–8 moderate to severe hot flashes per day (average) or 50–60 moderate to severe hot flashes per week and who were compliant with diary entry and dosing were randomized in a double-blind manner to receive either PM 7.5 mg capsules or placebo capsules in a 1:1 ratio. Subjects were instructed to take the study medication once daily at bedtime. Subjects were also instructed to continue completing their hot flash diary and sleep diary cards.

During the Baseline Visit, all randomized subjects were asked to complete symptom assessment questionnaires which included the:

- HADS
- POMS
- GCS
- HFRDS
- ASEX
- NRS
- Suicidality Tracking Scale (STS)

The investigator completed the CGI – Investigator impression of severity and improvement of VMS.

A urine pregnancy test for all subjects who were not at least 2 years postmenopausal was repeated and a Month 1 blister card was dispensed.

Double-Blind Treatment Period (Day 1 to Day 169)
The randomized study treatment was self-administered once daily, at bedtime, beginning on Day 1 and continuing up to Day 168 (end of Week 24). During the treatment period, subjects continued to record the number of hot flashes and the severity of each hot flash in the daily diary and daily sleep diary.

Subjects returned to the clinic for evaluations on Day 28 + 3 days (Week 4), Day 84 + 3 days (Week 12), and Day 169 + 3 days (Week 24) or upon early discontinuation.

Site personnel contacted subjects by telephone on Day 7 + 3 days (Week 1), Day 14 + 3 days (Week 2), Day 21 + 3 days (Week 3), Day 42 + 3 days (Week 6), Day 56 + 3 days (Week 8), Day 112 + 3 days (Week 16) and Day 140 + 3 days (Week 20) as well as on post-treatment Day 7 + 3 days. Symptom assessment questionnaires were administered at the baseline (Day 1), at the Day 28, Day 84 and Day 169 visits. Subjects were asked to complete a Discontinuation Emergent Signs and Symptoms Scale (DESS) 7 days after last dose of study drug.

The end-of-study visit was on Day 169 (Week 24). At this visit a physical examination was done and ECG, CBC and repeat chemistries were obtained. These procedures were also done for subjects who discontinued the study prior to completion.

A telephone Post Treatment Visit was scheduled 7 days after the last dose of study medication. At this visit, a Discontinuation Emergent Signs and Symptoms Scale (DESS) was completed.

Protocol Amendments
The original protocol was dated February 18, 2010; there were several significant clinical amendments to the protocol.

Amendment 1, dated November 10, 2010:

- The synopsis was modified to define responder as subjects who had achieved a ≥ 50% reduction in mean hot flash frequency from baseline
- Assessment of suicidality was detailed to include additional information regarding the suicidal tracking scale per FDA's suicidality guidance document

Amendment 2, dated January 31, 2011:

- Additional exclusion criteria regarding self-injurious behavior and depression or

borderline personality disorder

- Modified the exclusion criteria regarding psychiatric disorders to the following: presence of any of the following psychiatric disorders within the timeframes specified:

Table 3 Modified Psychiatric Disorders Exclusion Criteria

Original Exclusions		Modified Exclusions (changes in bolded font)	
Disorder	**Timeframe**	**Disorder**	**Timeframe**
Major Depressive Episode	Past 2 weeks	Major Depressive **Disorder**	**Life-time**
Dysthymia	Past 2 years	Dysthymia	Past 2 years
(Hypo) Manic Episode	Life-time	**Bipolar Disorder**	Life-time
Panic Disorder	Past month	Panic Disorder	**Life-time**
Agoraphobia	Past month	Agoraphobia	Past month
Social Phobia	Past month	Social Phobia	Past month
Obsessive Compulsive Disorder	Past month	Obsessive Compulsive Disorder	Past month
Generalized Anxiety	Past 6 month	Generalized Anxiety	**Life-time**
Alcohol disorders	Past 12 months	Alcohol disorders	Past 12 months
Drugs (Substance Abuse)	Past 12 months	Drugs (Substance Abuse)	Past 12 months
Psychotic Disorders	Life-time	Psychotic Disorders	Life-time
Anorexia Nervosa	Past 3 months	Anorexia Nervosa	**Past 10 years**
Bulimia	Past 3 months	Bulimia	**Past 10 years**
Suicidality/Suicidal Ideation	Past month	Suicidality/Suicidal Ideation	**Life-time**
Post Traumatic Stress Disorder	Past month	Post Traumatic Stress Disorder	**Life-time**

Source: CSR, Page 66, Table 7

Medical Reviewer's Comment

- *The N30-004 protocol exclusion criteria were amended to broaden timeframes for past history of psychiatric disorders. More than 3 quarters of patients in Study N30-004 were enrolled under the original protocol that only excluded a major depressive episode in the past 2 weeks, whereas a quarter were enrolled under the modified version that excluded a lifetime history of major depressive disorder.*

Amendment 3, dated February 4, 2011:

- Modified the administration of the STS associated with the Day 14, Day 28, and Day 84 clinic visits to remove the option of completing it prior to the visit; i.e., making completion of it a mandatory portion of the clinic visit and specifying the following response criteria:
  - If the sum of STS scores from items 2, 3, and 4 is ≥ 2, then the subject will be discontinued.

  - If the sum of STS scores from items 5, 6, 7a, and 8 is > 0, then the subject will be discontinued.
  - If the subject's answer is "Yes" to item 1b or item 7, then the subject will be discontinued.
  - Subjects who are discontinued from the study due to the above STS criteria will be referred to a mental health professional/psychiatrist.
- Additional information was added in the safety monitoring plan addressing the creation of a Safety Monitoring Committee.

Medical Reviewer's Comments

- *Items 1b, 2, 3, 4, 5, 6, 7a and 8 in the STS were:*

Item 1b. Over the past week did you suffer any accident? Did you intend to die as a result of this accident? Score as yes or no

Item 2. Over the past week, how much did you think that you would be better off dead or wish you were dead? Score as 0 1 2 3 4

Item 3. Over the past week, how much did you want to harm yourself or to hurt or to injure yourself? Score as 0 1 2 3 4

Item 4. Over the past week, how much did you think about suicide? Score as 0 1 2 3 4

Item 5. Over the past week, how much did you plan for a suicide? Score as 0 1 2 3 4

Item 6. Over the past week, how much did you take active steps to prepare for a suicide attempt in which you expected or intended to die? Score as 0 1 2 3 4

Item 7.Over the past week, did you injure yourself intentionally? Score as yes or no

Item 7a. Over the past week how seriously did you intentionally injure yourself without suicidal intent? Score as 0 1 2 3 4

Item 8. Over the past week, how much did you attempt suicide? Score as 0 1 2 3 4

- *No adverse events occurred in the study that required the Safety Monitoring Committee to meet.*

Amendment 4, dated May 18, 2011:

- The original "Key Secondary Objective" to assess the effects of PM compared with placebo on total number of awakenings due to hot flashes was deleted and moved to a secondary objective.

6 Review of Efficacy

Efficacy Summary

- *PM 7.5 mg 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.*
- *The reduction in the hot flash severity score was statistically significant compared to placebo at Week 4 in both studies and at Week 12 in Study N30-004. The*

reduction in the hot flash severity score at Week 12 in Study N30-003 did not achieve statistical significance.

- *In Study N30-003, approximately 50% of subjects taking PM achieved a clinically meaningful improvement in hot flash frequency both at 4 weeks (p-value = 0.001 compared to placebo) and at 12 weeks (p-value = 0.055 compared to placebo).*
- *In Study N30-004, a significantly greater proportion of subjects taking PM achieved a 50% reduction in hot flash frequency from baseline compared to placebo at Week 24 demonstrating a persistence of benefit.*

6.1 Indication

The Applicant's proposed indication for PM is the treatment of moderate to severe hot flushes associated with the menopause.

6.1.1 Methods

The efficacy of PM as a treatment for VMS associated with menopause was studied in two phase 3 studies (at a dose of 7.5 mg once daily at bedtime) in 1,174 postmenopausal women with 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.

Patients with a presence or history of previous psychiatric disorders were excluded from both studies. Additionally subjects discontinued all psychotropic drugs and hormone therapy prior to treatment.

N30-003 was the 12-week clinical trial with a total of 614 postmenopausal women randomized 1:1 to receive at least one dose of PM 7.5 mg or placebo, and who had valid baseline and at least one day of on-treatment hot flash daily diary data.

N30-004 was the 24-week clinical trial with a total of 570 postmenopausal women randomized 1:1 to receive at least one dose of PM 7.5 mg or placebo, and who had valid baseline and at least one day of on-treatment hot flash daily diary data.

The primary efficacy analysis population in Studies N30-003 and N30-004 was the MITT population defined as "all randomized subjects with valid baseline daily hot flash diary data and who took at least one dose of study medication and who had at least one day of on-treatment daily hot flash diary data." The last observation carried forward LOCF principle was used to handle missing data. If a subject entered fewer than 4 days of diary data in a 1-week treatment interval, the average of the hot flash diary data over the most recent 7 days' entries was imputed even if this interval spanned 2 weeks.

In Study N30-003, eight subjects were excluded from the MITT population because they did not receive study drug. These included 5 subjects in the PM arm and 3 subjects in the placebo arm.

In Study N30-004, the MITT population consisted of 284 in each group. Of the 2 subjects excluded from the MITT group, 1 subject in the PM group had invalid diary data and 1 subject did not receive any study drug.

In the pooled phase 3 studies, a total of 591 subjects were randomized to PM and 593 subjects were randomized to placebo. The MITT population consisted of 585 subjects in the PM group and 589 subjects in the placebo group.

Table 4 Phase 3 Studies: Efficacy (MITT[1]) and Safety[2] Analysis Populations

Studies	PM N (%)	Placebo N (%)	Total
Study N30-003			
-Randomized	306 (100)	308 (100)	614
-MITT	301 (98)	305 (99)	606
-Safety	301 (98)	305 (99)	606
Study N30-004			
-Randomized	285 (100)	285 (100)	570
-MITT	284 (99.6)	284 (99.6)	568
-Safety	285 (100)	284 (99.6)	569
Total Randomized	591	593	1184
Total MITT Population	585 (99.0)	589 (99.3)	1174

[1] The MITT population included all randomized subjects with a valid baseline daily hot flash diary who had taken at least 1 dose of study medication and had at least 1 day of on-treatment daily hot flash diary data.
[2] The Safety population included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-treatment safety assessment.
Source: Medical Reviewer

Medical Reviewer's Comment

- *The FDA agreed upon the definition of the MITT population during the drug development discussions.*

Efficacy was determined as a statistically and clinically significant reduction in hot flush frequency and statistically significant reduction in hot flush severity for PM versus placebo. The total number of moderate and severe hot flashes recorded in the daily diary was used to evaluate the change from Baseline to Week 4 and Week 12 in the number of moderate and severe hot flashes per day. Severity of hot flashes for each subject was scored as the sum of (2 times the number of moderate hot flashes plus 3 times the number of severe hot flashes) divided by the total number of moderate to severe hot flashes.

6.1.2 Demographics

Across both studies, 60% of subjects were Caucasian. 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. Demographics for each study are displayed in the following tables.

Study N30-003

Table 5 Demographics and Baseline Characteristics, MITT Population, N30-003

Parameter		PM 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/Latino	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	172.8	174.7	173.7
	Min-Max	80-389	98-338	80-389
BMI (kg/m^2)	Mean	29.25	29.68	29.47
	Min-Max	16.8-60.7	19.0-56.5	16.8-60.7
Daily number of mod-severe hot flashes	Mean	11.79	11.65	11.72
	Median	10.43	10.43	10.43
Daily hot flash severity score	Mean	2.53	2.53	2.53
	Median	2.54	2.54	2.54
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 Summary of Clinical Efficacy (SCE), Page 43, Table 8

Study N30-004

Table 6 Demographics and Baseline Characteristics, MITT Population, N30-004

Parameter		PM 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/Latino	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	27.95	28.33	28.14
	Min-Max	18.3-40.6	18.7-39.6	18.3-40.6
Daily number of mod-severe hot flashes	Mean	10.83	10.90	10.87
	Median	9.86	9.57	9.71
Daily hot flash severity score	Mean	2.53	2.53	2.53
	Median	2.53	2.52	2.53
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 SCE, Page 44, Table 9

6.1.3 Subject Disposition

Study N30-003

In Study N30-003, a total of 614 subjects were randomized into the study (306 subjects to the PM 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 PM group (88.6%) and 278 of the 308 subjects randomized in the placebo group (90.3%). Details of subject disposition in Study 003 are summarized below

Table 7 Subject Disposition, All Randomized Subjects, Study N30-003

Disposition	PM 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			
• AE/SAE	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 to an Information Request on 01/07/2013, drug intake was unknown for 4 subjects in paroxetine mesylate group and 3 subjects in placebo group. They were counted as having received at least one dose of study medication by FDA.
Source: CSR, Study N30-003, Page 72, Table 7

Protocol Deviations
One major protocol deviation was identified in this study. The major protocol deviation was "subject did not satisfy entrance criteria," and this incidence of this deviation was low (0.8% of subjects overall) and similar between groups. The only other deviation reported was "subject received prohibited medication," reported at a higher percentage in the PM group than in the Placebo group (9.4% and 4.5%, respectively).

Medical Reviewer's Comments

- Study subjects were not allowed to take certain medications during the trial. These included tamoxifen, psychotropic drugs, estrogen and/or progestin products and off-label medications known to possibly ameliorate hot flashes.
- The submission was not clear about which of these medications were used more commonly by the subjects.

A summary of the major protocol violations for Study N30-003 is shown below.

Table 8 Summary of Major Protocol Deviations, All Randomized Subjects, Study N30-003

Major Deviation	PM N=306 n (%)	Placebo N=308 n (%)	Total N=614 n (%)
Subject did not satisfy entrance criteria	3 (1.0)	2 (0.6)	5 (0.8)
Subject received prohibited medication	29 (9.4)	14 (4.5)	43 (7.0)

Source: CSR, Page 73, Table 8

Study N30-004

In Study N30-004, a total of 570 subjects were randomized (285 subjects to the PM group and 285 subjects to the placebo group) into the study. All but one of the randomized subjects (99.8%) received at least 1 dose of study drug. (Placebo subject 53-008 did not receive any study drug.) More subjects randomized to the PM group (235/285 [82.5%]) than randomized to the placebo group (218/285 [76.5%]) completed the study.

Details of subject disposition in Study N30-004 are summarized below in Table 9.

Table 9 Subject Disposition, All Randomized Subjects, Study N30-004

Disposition	PM 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			
• AE/SAE	15 (5.3)	15 (5.3)	30 (5.3)
• Subject request	15 (5.3)	35 (12.3)	50 (8.8)
• Suicide 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: CSR, Study N30-004, Page 69, Table 8

Medical Reviewer's Comments

- *Subject disposition was similar across both arms of the phase 3 studies.*
- *For Study 003, the 12 week study, a similar percentage of subjects in both groups completed the study.*
- *The percentage of subjects who discontinued due to adverse events or serious adverse advents was higher in the paroxetine group (2.6% vs.1.3%).*
- *In Study 004, which was 24 weeks, a similar percentage in each arm completed the study.*
- *The percentage of discontinuations caused by AEs/SAEs was the same in both groups in Study 004, but certainly higher than Study 003, perhaps because it was a longer study.*

Protocol Deviations

Three subjects who were randomized to the PM treatment group were unblinded in this trial (Subjects 4-05-013, 4-22-004, and 4-23-014). No subjects from the Placebo treatment group were unblinded.

Table 10 Summary of Major Protocol Deviations, All Randomized Subjects, Study N30-004

Major Deviation	PM N=285 n (%)	Placebo N=285 n (%)	Total N=570 n (%)
Subject unblinded	3 (1.1)	0	3 (0.5)
Subject did not satisfy entrance criteria	1 (0.4)	2 (0.7)	3 (0.5)
Subject received excluded concomitant medication	1 (0.4)	4 (1.4)	5 (0.9)

Source: CSR, Page 70, Table 9

Medical Reviewer's Comment

- None of these deviations are believed to have affected the outcome or conclusions of this study.

6.1.4 Analysis of Primary Endpoint(s)

Primary Endpoints

Studies N30-003 and N30-004

Four co-primary efficacy endpoints were pre-specified in the two phase 3 trials. They were:

- Mean change from baseline in frequency of moderate to severe VMS per day at Week 4,
- Mean change from baseline in frequency of moderate to severe VMS per day at Week 12,
- Mean change from baseline in severity of moderate to severe VMS per day at Week 4,
- Mean change from baseline in severity of moderate to severe VMS per day at Week 12

The average daily frequency during the treatment period for a specific week was calculated as the total number of moderate to severe hot flashes from self-reported diaries in that week divided by 7.

The daily severity score was calculated as the sum of 2 times the number of moderate hot flashes, plus 3 times the number of severe hot flashes, divided by the total number of moderate and severe hot flashes in that day. The score always ranges from 2 to 3 and the score becomes indeterminate if the subject has zero hot flashes.

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 flash diary data over the most recent previous seven days' entries, even if this interval spanned two treatment weeks.

Medical Reviewer's Comments

- *As per the protocol, to support this indication, efficacy needed to be demonstrated with respect to all four co-primary endpoints.*
- *The FDA statistical reviewer reported the difference between medians as a more appropriate estimate for the treatment effect of PM relative to placebo as the data were skewed (non-normally distributed).*

Study N30-003: Clinical Meaningfulness

Because the magnitude of effect for PM on VMS frequency was anticipated to be less than for currently approved hormonal products, the FDA wanted to ensure that the treatment effect would still be of clinical benefit to women. For this reason, the FDA requested an analysis of the "clinical meaningfulness" of the change in VMS frequency for those products that do not demonstrate a placebo-adjusted reduction in moderate to severe VMS frequency from baseline of at least two hot flushes per day. Although these analyses are typically not specified as primary analyses in the statistical analysis plan, the FDA considered the results in its evaluation of whether acceptable efficacy has been demonstrated. This analysis of clinical meaningfulness of the hot flash frequency reduction in this study is found in Section 6.1.6.

Study N30-004: Persistence of Benefit

Study N30-004 evaluated the persistence of benefit over 24 weeks of treatment. Persistence of benefit was demonstrated by showing a statistically significant difference in the responder rate between the active and the placebo treatment groups. In this analysis, subjects who dropped out before Week 24 were considered non-responders, along with those who achieved <50% reduction from baseline. This analysis is discussed in Section 6.1.6.

Primary Endpoint Analysis

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

Descriptive statistics were reported for each endpoint. Graphical presentation of the change in frequency and severity from baseline to Week 12 were also provided. For sensitivity assessment, LOCF method was used to impute the missing data of each co-primary endpoint for the subjects who withdrew prematurely.

The table below shows the mean daily change in hot flash frequency from baseline to Week 4 and baseline to Week 12 in the 2 co-primary efficacy endpoints for each pivotal study.

Table 11 Mean Change in Median Daily Frequency of Moderate to Severe Hot Flashes, Studies N30-003 and N30-004, MITT

	Study N30-003			Study N30-004		
	PM N=301	Placebo N=305	Treatment Difference p-value	PM N=284	Placebo N=284	Treatment Difference p-value
			Baseline			
N	301	305		284	284	
Mean (SD)	11.8 (4.9)	11.7 (4.4)		10.8 (3.9)	10.9 (4.0)	
Median	10.4	10.4		9.86	9.57	
			Change from Baseline at Week 4			
n	289	293		276	274	
Mean (SD)	-4.7 (4.0)	-3.4 (4.7)		-4.1 (4.0)	-2.7 (4.3)	
Median	-4.29	-3.14		-3.79	-2.50	
Placebo-subtracted median*	-1.15		**<0.0001****	-1.29		**<0.0001****
			Change from Baseline at Week 12			
n	264	274		257	244	
Mean (SD)	-6.22 (4.5)	-5.33 (5.3)		-5.31 (4.7)	-3.94 (5.1)	
Median	-5.93	-5.00		-5.57	-3.86	
Placebo-subtracted median*	-0.93		**0.0090****	-1.71		**0.0001****

* Treatment Difference is the observed difference between medians.
** P-value is obtained from rank-ANCOVA model.
Source: Adapted from FDA Statistician's Review

Medical Reviewer's Comments

- *Subjects had a median of about 11-12 daily moderate to severe hot flashes at baseline.*
- *The median placebo subtracted reduction in hot flash frequency in Study 003 was -1.2 at Week 4 and -0.9 at Week 12.*
- *The median placebo subtracted reduction in hot flash frequency in Study 004 was -1.3 at Week 4 and -1.7 at Week 12.*
- *Although the magnitude of these reductions in hot flash frequency was not large, all were statistically significant (p-values <0.05).*

Table 12 below shows the mean daily change in the severity score from baseline to Week 4 and baseline to Week 12 in the 2 co-primary efficacy endpoints for each pivotal study.

Table 12 Mean Change in Median Daily Severity Score of Moderate to Severe Hot Flashes per Study, MITT

	Study N30-003			Study N30-004		
	PM N=301	Placebo N=305	Treatment Difference p-value	PM N=284	Placebo N=284	Treatment Difference p-value
			Baseline			
N	301	305		284	284	
Mean (SD)	2.53 (0.30)	2.53 (0.31)		2.53 (0.30)	2.53 (0.32)	
Median	2.537	2.538		2.535	2.523	
			Change from Baseline at Week 4			
n	281	289		268	271	
Mean (SD)	-0.09 (0.25)	-0.05 (0.23)		-0.09 (0.24)	-0.06 (0.22)	
Median	-0.052	0.000		-0.040	-0.008	
Placebo-subtracted median*	-0.052		**0.0017****	-0.032		**0.0368****
			Change from Baseline at Week 12			
n	236	253		245	236	
Mean (SD)	-0.104 (0.29)	-0.084 (0.29)		-0.126 (0.32)	-0.066 (0.26)	
Median	-0.058	-0.018		-0.051	0.000	
Placebo-subtracted median*	-0.040		**0.1658****	-0.051		**0.0064****

* Treatment Difference is the observed difference between medians.
** P-value is obtained from rank-ANCOVA model.
Source: Adapted from FDA Statistician's Review

Medical Reviewer's Comments

- *Subjects had a median hot flash severity score at baseline of about 2.5.*
- *The average weighted severity score gives a possible range in the change from baseline of -1 to +1. The difference between PM and placebo on the median reduction of average daily severity of VMS at Weeks 4 and 12 ranged from 0.03 to 0.05. The magnitude of these reductions was very small but did achieve statistical significance at Week 4 in both pivotal studies, but only at Week 12 in Study N30-004.*
- *The frequency co-primary endpoint is a fair representation of patient burden. The severity score co-primary endpoint is somewhat flawed because it is not a stand-alone score, but depends on frequency, which is already evaluated as the other*

co-primary endpoint. The severity score is not an absolute reduction in the severity of moderate or severe hot flashes but is only a weighted average dependent on frequency. It also becomes indeterminate if the subject has all her hot flushes reduced to mild hot flashes or has zero hot flashes.

- *A subject with an equal number of moderate to severe hot flashes (e.g. 5 severe and 5 moderate) will have a severity score of 2.5. If the number of severe flashes remain the same but the moderate flashes increase (e.g., 5 severe and 10 moderate), the severity score improves to 2.3. The patient is clinically worse despite her improved hot flash severity score.*
- *Because of these limitations in the severity scoring, the Applicant has suggested an alternative calculation to analyze decrease in the severity of hot flashes. An alternative calculation would be a reduction in "hot flash composite score" (consisting of the frequency of moderate hot flashes x 2 + the frequency of severe hot flashes x 3). This score is actually just the numerator of the weighted average score. The range for this calculation would be 0 - 250+. The Applicant believes this calculation is more representative of the overall patient burden than the weighted severity score. However, this method of calculating hot flash severity is post hoc and was not prespecified in the SAP. Therefore, the Division is not considering the "hot flash composite score" in our evaluation of efficacy.*

Table 13 summarizes the co-primary endpoint analyses over the two studies.

Table 13 Summary Analysis of Co-Primary Endpoints

Endpoint	Study	Visit	Median Change from Baseline		
			PM	Placebo	Treatment Difference (p-value)
Reduction in Hot Flash Frequency	N30-003	Week 4	-4.3	-3.1	-1.2 **(<0.001)***
		Week 12	-5.9	-5.0	-0.9 **(0.009)***
	N30-004	Week 4	-3.8	-2.5	-1.3 **(<0.001)***
		Week 12	-5.6	-3.9	-1.7 **(<0.001)***
Reduction in Hot Flash Severity	N30-003	Week 4	-0.05	0.00	-0.05 **(0.002)***
		Week 12	-0.06	-0.02	-0.04 (0.166)
	N30-004	Week 4	-0.04	-0.01	-0.3 **(0.037)***
		Week 12	-0.05	0.00	-0.05 **(0.006)***

*Achieves statistical significance
Source: FDA Statistician

Medical Reviewer's Comment

- *Over the two studies, the reduction in hot flash severity score at 12 weeks was the only co-primary endpoint (of the eight co-primary endpoints) that did not achieve statistical significance.*

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant listed as many as 20 secondary endpoints for each phase 3 trial. Included in these were an analysis to evaluate clinical meaningfulness in Study N30-003 and an analysis to assess persistence of efficacy in Study N30-004. A subgroup analysis of women on the basis of BMI (< 32 kg/m^2 vs. ≥ 32 kg/m^2) was also included. Other secondary endpoint analyses were not prespecified in the SAP and are not discussed in this review.

6.1.6 Other Endpoints

Supportive Endpoints

Study N30-003: Analysis to Evaluate Clinical Meaningfulness

Study N30-004 was initiated in March of 2010 prior to the initiation of Study N30-003. The Division noted that the placebo-subtracted reduction in hot flash frequency in Study N30-004 was less then 2 per day, so was concerned regarding the clinical benefit of this decrease. Therefore for Study N30-003, based on the FDA request, the Applicant pre-specified an analysis to evaluate whether the observed treatment effect is clinically meaningful if the difference between PM and placebo in the change of average daily frequency of moderate to severe hot flashes were less than 2 hot flashes per day.

To address whether the reduction of < 2 daily hot flashes per day was clinically meaningful to subjects, a responder analysis anchored to patient satisfaction was conducted.

1. All MITT subjects in the study, regardless of treatment assignment, were categorized by the Applicant into two groups (i.e., satisfied or unsatisfied) based on their responses to the 7 point PGI questionnaire, which assessed the subject's impression of her 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 (1) 'Very much better' or (2) 'Much better' or (3) 'A little better' and were considered unsatisfied if the response to the same question was (4) 'No change' or (5) 'A little worse' or (6) 'Much worse' or (7) 'Very much worse'. The LOCF principle was used to handle any missing PGI score for this analysis.

2. The FDA requested that the subjects should be considered as "satisfied" based on a cutoff on the PGI responses of (1) = 'Very much better' or (2) = 'Much better' and be considered as "unsatisfied" if their response was between 3 to 7. The FDA requested this as it was more conservative to consider that women who experienced only a "little" improvement might not find this satisfactory, particularly if the drug also had unpleasant side effects.

3. Using this category of satisfied and unsatisfied, a receiver operating characteristic (ROC) analysis was conducted in order to determine the threshold cutoff point for a clinically meaningful reduction in VMS frequency using "satisfied versus 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. The cutoff point was the value that maximized the sensitivity and specificity of the ROC.

4. Based on the cutoff point established above, a responder analysis was performed by categorizing women in the PM and placebo groups as responders or non-responders. Responders were defined as those subjects who achieved 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.

5. The proportion of responders between the treatment groups was compared adjusting for the baseline number of hot flushes as a covariate in the model.

Given the cutoff values established in the ROC, subjects were classified as responders if the change from baseline was < -4.0 at Week 4; or < -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 PM group and 37% of subjects in the placebo group were responders (p-value 0.001). At Week 12, 51% of subjects in the PM group and 43% of subjects in the placebo group were responders (p-value 0.055). See Table 14 below.

Table 14 Percent of Responders Based on the ROC Threshold, N30-003, MITT

Visit	Cut-off	Statistics	PM N=301 n (%)	Placebo N=305 n (%)	p-value
Week 4	-4.0	Responder	152 (50)	114 (37)	**0.001**
		Non-responder	149 (50)	191 (63)	
Week 12	-5.3	Responder	153 (51)	131 (43)	**0.055**
		Non-responder	148 (49)	174 (57)	

Source: FDA Statistician

Study N30-004: Persistence of Efficacy at Week 24

In Study N30-004, a secondary analysis was planned to assess the persistence of the reduction in VMS frequency at Week 24 using a responder analysis. Responders were defined as those subjects who achieved ≥ 50% reduction from baseline in moderate to severe hot-flash frequency at Week 24. Non-responders were defined as those who had

a < 50% reduction at Week 24 or who prematurely discontinued the study. Percent reduction at Week 24 was defined as follows:

- The number of moderate to severe hot flashes at baseline minus the number of moderate to severe hot flashes at Week 24 divided by the number of moderate to severe hot flashes at baseline.

Based on the MITT population, 47.5% of the PM-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 (p-value 0.0066).

Table 15 Percentage of Responders at Week 24, N30-004, MITT

Visit	Statistics	PM N=284 n (%)	Placebo N=284 n (%)	p-value
Week 24	**Responder**	135 (47.5)	103 (36.3)	**0.0066**
	Non-responder	149 (52.5)	181 (63.7)	

Source: FDA Statistician

Medical Reviewer's Comments

- *Treatment with PM through Week 24 resulted in a greater percentage of subjects with a ≥ 50% reduction from baseline in moderate to severe hot flash frequency than placebo-treated subjects (48% versus 36%). This difference in responder rates achieved statistical significance.*
- *Conclusion: Subjects taking PM at Week 24 showed a significantly higher response rate for VMS frequency than subjects taking placebo, so persistence of efficacy in reducing VMS was demonstrated to Week 24.*

6.1.7 Subpopulations

The phase 3 studies were not powered to test for subgroup differences. The Applicant conducted analyses on subgroups with at least 20 subjects.

Body Mass Index, Pooled phase 3 Studies

The mean change in hot flash frequency and severity was stratified by BMI (<32 kg/m^2, ≥ 32 kg/m^2) in the pooled phase 3 studies. The total number of moderate to severe hot flashes recorded in the daily diary was used to evaluate the change from Baseline to Week 4 and Baseline to Week 12.

In both of the BMI subgroups <32 kg/m^2 and ≥ 32 kg/m^2, the mean reduction in frequency of moderate to severe hot flashes at Week 4 and Week 12 was greater in the PM group than in the placebo group. Differences between the treatment groups were statistically significant (p≤ 0.0018), with the exception of the Week 12 endpoint in BMI subgroup ≥ 32 kg/m^2.

In the BMI category ≥ 30.0 kg/m^2 (obese), the mean reduction in severity of moderate to severe hot flashes was greater in the PM group than in the placebo group at Week 4 and was greater in the placebo group than in the PM group at Week 12. Neither of these differences was statistically significant.

Age, Pooled phase 3 Studies
In the age categories ≥ 40 to < 65 and ≥ 65 years, the mean reduction in frequency of moderate to severe hot flashes at Week 4 and Week 12 was greater in the PM group than in the placebo group. Differences between the treatment groups were statistically significant (p≤ 0.0062), with the exception of the Week 12 endpoint in age category ≥ 65 years.

In the age (decades) subgroups ≥ 40 to < 50, ≥ 50 to < 60, and ≥ 60 to < 70 years, the mean reduction in frequency of moderate to severe hot flashes at Week 4 and Week 12 was greater in the PM group than in the placebo group. Differences between the treatment groups were statistically significant (p ≤ 0.01), with the exception of the Week 12 endpoint in the age category ≥ 40 to < 50 years.

Natural or Surgical Menopause
In the pooled phase 3 studies, there were 469 subjects in the PM group and 483 subjects in the placebo group with a natural onset of menopause. The mean reduction in the frequency of moderate to severe hot flashes was significantly greater in the PM group compared with the placebo group at both Week 4 and Week 12 (p=0.0001). The mean reduction in the severity of moderate to severe hot flashes was significantly greater in the PM group compared with the placebo group at both Week 4 (p=0.0028) and Week 12 (p=0.0118).

There were 116 subjects in the PM group and 106 subjects in the placebo group who had a surgical onset of menopause. For these subjects, the difference in mean reduction of hot flash frequency between the PM and placebo groups was not significant at Week 4 or Week 12. The mean reduction of hot flash severity between the PM and placebo groups was not significant at Week 4 or Week 12.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Published clinical studies for the use of paroxetine in the treatment of hot flashes provided the Applicant with initial suggestions of its efficacy and safety for this indication. Early studies assessed 2 doses of paroxetine controlled-release (at doses of 12.5 mg/day and 25 mg/day) for the relief of hot flash frequency and severity in a population of menopausal women. Both doses of paroxetine were more effective than placebo with regard to the change from Baseline to Week 6 in daily hot flash composite score, and both doses were associated with a similar magnitude of hot flash reduction. Though the 12.5 mg and 25 mg doses did not differ in efficacy, they did differ in safety with fewer AEs reported at the lower dose.

The results of the proof-of-concept phase 2, 8-week, double-blind, placebo-controlled study of PM 7.5 mg per day for the treatment of VMS associated with menopause conducted by the Applicant (Study N30-002) provided further evidence to take the 7.5 mg dose into the phase 3 clinical trials.

Medical Reviewer's Comment

- *The Applicant did not do any formal dose-ranging studies but depended on previous published literature to determine what they considered to be an appropriate dose for this indication.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See Section 6.1.6 Other Endpoints

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues were addressed.

7 Review of Safety

Safety Summary

This review did not reveal any new or unlabeled safety issues relating to paroxetine mesylate. In summary, the conclusions regarding safety are these:

- *The overall incidence of serious adverse events, treatment-emergent adverse events and adverse events of specific interest did not differ much by treatment arm.*
- *Central nervous system and mood-related adverse events occurred more frequently among subjects on paroxetine, as did suicidality-related events, although at a low rate.*
- *Current labeling addresses the risk of suicidality.*

The overall incidence of AEs in the safety dataset was similar was across the two treatment groups. A total of 54% of subjects in the PM group and 47% of subjects in the placebo group reported at least 1 AE.

A similar incidence of drug-related AEs (defined as definitely, possibly or remotely related to study drug based on the investigator's assessment) were reported in the PM and placebo group (19.5% and 17.6%). The incidence of any AE reported as severe (PM 3.9%; placebo 3.6%) were also similar across both treatment groups.

Table 16 is a summary of deaths, SAEs and AEs across treatment groups.

Table 16 Summary of Adverse Events and Deaths, Safety Dataset

Category	PM N=635[3] n (%)	Placebo N=641[3] n (%)
Subjects with any TEAE[1]	320 (50.4)	301 (47.0)
-Subjects with drug-related[2] TEAE	124 (19.5)	113 (17.6)
Subjects with any severe TEAE	25 (3.9)	23 (3.6)
-Subjects with drug-related severe TEAE	6 (0.9)	9 (1.4)
Deaths	1 (0.2)	0 (00)
Subjects with SAEs	14 (2.2)	9 (1.4)
-Subjects with drug-related SAEs	3 (0.5)	0 (00)
Subjects with study drug discontinuations due to a TEAE	28 (4.4)	21 (3.3)
-Subjects with study drug discontinuations due to a drug-related TEAE	18 (2.8)	15 (2.3)
Subjects with suicidality[4]	6 (0.9)	1 (0.2)
Subjects with a cardiovascular TEAE	27 (4.3)	17 (2.7)
-Subjects with a drug-related cardiovascular TEAE	8 (1.3)	5 (0.8)
Subjects with a hepatic TEAE	3 (0.5)	6 (0.9)
-Subjects with a drug-related hepatic TEAE	1 (0.2)	6 (0.9)
Subjects with gastrointestinal or bleeding TEAE	12 (1.9)	10 (1.6)
-Subjects with a drug-related gastrointestinal or bleeding TEAE	2 (0.3)	2 (0.3)

[1] TEAE: Any AE that started or worsened on or after the day of first dose
[2] Related AEs include possibly, probably or definitely related based on the investigator
[3] A subject is counted only once within each category
[4] Includes "Suicide attempt," "treatment-emergent suicidal ideation, reported as an SAE/AE" and "Met STS criteria for discontinuation"
Source: SCS, Page 43, Table 12

7.1 Methods

The evaluation of paroxetine safety was based on the database from the clinical development program and the postmarketing safety information from the approved Pexeva product.

The labeled safety issues associated with paroxetine include:

- 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:
  -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
  -need for caution in patients with certain concomitant illnesses (e.g., narrow angle glaucoma)

Medical Reviewer's Comments

- *Regarding suicidality, the Pexeva label states that all patients being treated with antidepressants for any indication should be monitored appropriately.*
- *Serotonin syndrome has been reported with both SSRIs and SNRIs*
- *Teratogenic effects occurring in the first trimester of pregnancy have been reported from epidemiological studies.*

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This NDA includes 3 clinical studies to evaluate the safety of PM in postmenopausal women. These studies are listed below. All studies included a single dose level of PM administered orally once daily in the evening as a 7.5 mg capsule.

A total of 1,276 subjects were treated in the PM clinical program, of which 635 subjects received at least 1 dose of PM and 641 subjects received at least 1 dose of placebo. Of these, 235 subjects in the PM group and 218 in the placebo group completed 24 weeks of treatment in Study N30-004.

The safety analysis set was defined as all subjects who took at least one dose of study drug and had at least 1 postdose safety assessment.

Datasets for the safety population are summarized in Table 17 below.

Table 17 Safety Population[1], Safety Dataset

Study	PM	Placebo	Total
		Phase 3 Studies	
-Study N30-003	301	305	606
-Study N30-004	285	284	569
Phase 3 Studies Pool	**586**	**589**	**1,175**
		Phase 2 Study	
-Study N30-002	49	52	101
Safety Dataset	**635**	**641**	**1,276**

[1]The Safety population included all randomized subjects who received at least 1 dose of study medication and had at least 1 post-treatment safety assessment.
Source: Adapted from the Summary of Clinical Safety (SCS), Page 15, Table 1

Medical Reviewer's Comments

- *The FDA agreed upon the definition of the safety population during the drug development discussions.*
- *At the Pre-NDA Meeting of May 29, 2012, the Division stated that pooling the safety data from the two phase 3 trials and from the supporting phase 2 trial was acceptable.*
- *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.*

7.1.2 Categorization of Adverse Events

Adverse events (AEs) for Studies N30-003 and N30-004 were coded based on Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. Study N30-002 was originally coded using MedDRA version 11.1 and had to be recoded to version 13.1 for pooling purposes. Study N30-005 was coded using MedDRA version 14.0.

Subjects were instructed to take the study drug at bedtime everyday beginning on the day of randomization. Treatment-emergent adverse events (TEAEs) were defied as AEs for which the onset is on or after the date of randomization. AEs were followed up to 7 days post-dose or up to 30 days for AEs that were ongoing at the end of the study. SAEs were collected up to 30 days post-dose.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The primary pool for the evaluation of safety included all 3 controlled studies termed by the Applicant as the "All Controlled Studies Pool," referred to hereafter as the safety dataset. This pool includes data from the two phase 3 clinical trials and the one phase 2 clinical trial. All of these studies were placebo-controlled, had a similar subject population, and used the PM 7.5 mg capsule administered daily dosage form.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Double-blind treatment duration was 8 weeks in Study N30-002, 12 weeks in Study N30-003, and 24 weeks in Study N30-004. Mean exposure in the safety dataset was 110.9 days (range 2 to 180 days) in the PM group and 107.6 days (range 2 to 177 days) in the placebo group.

Most subjects in this study received study drug for >4 weeks (93.7% in the PM group). A total of 58.4% of subjects in the PM group received treatment for >12 weeks.

Drug exposure is summarized in Table 18.

Table 18 Drug Exposure by Duration, Safety Dataset

Category	PM 7.5 mg 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: SCS, Page 34, Table 6

7.2.2 Explorations for Dose Response

There were no explorations for dose-response in this submission. The only dose studied was the 7.5 mg capsule.

The Applicant noted that it had selected the 7.5 mg dose based on published literature showing efficacy for VMS symptoms using 10-25 mg doses of the approved paroxetine mesylate product. There does not appear to be a dose-response in the published literature, so the Applicant 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.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or *in vitro* testing was performed.

7.2.4 Routine Clinical Testing

Routine clinical testing included hematology, a chemistry screen, FSH, pregnancy testing, and an electrocardiogram; see Section 9.4 Schedule of Assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolic, clearance and interaction are discussed in the Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Four potential adverse events of special interest for similar drugs were:

- Cardiovascular events
- Hepatic events
- GI or bleeding events
- Suicidality

The determination of suicidality was based on the TEAEs as well as data from two suicidality scales. For pooling purposes, the Suicidality Tracking Scale (STS) used in Studies N30-002 and N30-004 was mapped to the Columbia Suicide Severity Rating Scale (C-SSRS) used in N30-003 and N30-005 using the Columbia Classification Algorithm for Suicide Assessment (C-CASA).

Medical Reviewer's Comments

- *The STS is an 8-item prospective scale. Each item is scored on a 5-point scale. The scale is administered either by the clinician or self-reported by the subject.*
- *The C-SSRS is also a prospective study for monitoring for emergence of suicidality.*
- *Further information regarding these scales is found in Section 7.3.5 under Suicidality*

7.3 Major Safety Results

7.3.1 Deaths

One death occurred in the PM clinical program. This death occurred in Study N30-003. Subject 3-47-020 was a 55 year old African-American female who experienced a cardiorespiratory arrest and coronary artery arteriosclerosis 68 days after starting treatment with LDMP. These SAEs led to her death. She had a medical history of hypertension and hypercholesterolemia and had been taking Benazepril, an antihypertensive, for about 15 years. She was noted to be hypertensive at the Screening visit with a BP of 146/86 mm Hg. Both SAEs were considered by the Investigator to be not related to study drug.

Medical Reviewer's Comment

- *Given the limited information, it was not possible for the Division to determine if this death was drug-related or not.*

7.3.2 Nonfatal Serious Adverse Events

SAEs were reported in 14 subjects (2.2%) in the PM group and 9 subjects (1.4%) in the placebo group in the safety dataset. With the exception of the single death in the N30-003 study, the remaining 13 subjects in the PM group with SAEs were all reported in the 24-week study, N30-004, while the 9 subjects in the placebo group were reported across the phase 2 (1 subject) and phase 3 (8 subjects; 1 in N30-003 and 7 in N30-004) studies. However, the greater number of SAEs in the PM group in Study N30-004 is not attributable merely to the longer 24-week treatment period in Study N30-004 compared to the 12-week treatment period in Study N30-003. Similar number of subjects in Study 004 had an SAE in the first 12 weeks of treatment compared to Weeks 13-24.

The most common SAEs reported in the PM group were suicidal ideation (3 subjects) and appendicitis (2 subjects). All nonfatal SAEs in the PM group resolved without sequelae. Nonfatal SAEs occurring in the PM arm are listed in Table 19.

Table 19 Nonfatal Serious Adverse Events, Safety Dataset

MedDRA Preferred Term	PM N=635 N (%)	Age, Race, Day of Onset	Drug Action Taken
Subjects with ≥1 SAE	**13 (2.0)**		
Suicidal ideation	1	60, Asian, Day 167	Withdrawn
Suicidal ideation	1	53, Cauc. Day 175	Continued
Suicidal ideation	1	67, Cauc. Day 169	Continued
Suicide attempt	1	50, Cauc. Day 55	Withdrawn
Appendicitis	1	46, AA Day 119	Interrupted
Appendicitis	1	49, AA Day 73	Interrupted
Abdominal pain	1	59, AA Day 10	Withdrawn
Dysphagia	1	52, AA Day 161	Continued
Biliary dyskinesia	1	47, AA Day 122	Withdrawn
Cholecystitis	1	51, AA Day 1	Continued
Asthma	1	55, AA Day 114	Continued

Sinusitis	1	53, Cauc. Day 6	Interrupted
Arthritis	1	68, Cauc. Day 72	Continued

Source: SCS, Page 54, Table 20

Medical Reviewer's Comments

- *A total of 10 nonfatal SAEs were reported in 13 subjects (2%) in the paroxetine group. Nine subjects in the placebo group (1.4%) reported nonfatal SAEs.*
- *There were two subjects with suicidal ideation who continued on PM therapy. One of the subjects (the 67 year old Caucasian) had a concurrent medical diagnosis of metastatic cancer so the suicidal ideation was assessed as not related to study drug. The SAE in the other subject (the 53 year old Caucasian) was considered by the investigator to be moderate in intensity and she was continued on PM. Both subjects recovered without sequelae.*

7.3.3 Dropouts and/or Discontinuations

The percentage of subjects who completed the study was similar across both treatment groups. A total of 84 subjects (13.2%) in the PM group and 94 subjects (14.7%) in the placebo group discontinued the study.

Table 20 Subject Disposition, Safety Dataset

	PM 7.5 mg n (%)	Placebo n (%)
Safety Population	635	641
Completed the study	551 (86.8)	547 (85.3)
Discontinued	84 (13.2)	94 (14.7)
Reason for Discontinuation		
• AE/SAE	24 (3.8)	20 (3.1)
• At own request	25 (3.9)	46 (7.2)
• C-SSRS rating scale/STS	4 (0.6)	2 (0.3)
• Investigator's discretion relating to subject well being	2 (0.3)	3 (0.5)
• Noncompliant with study requirements	2 (0.3)	6 (0.9)
• Not specified	0	1 (0.2)
• Elective surgery	1 (0.2)	0
• Eligibility criteria not met	3 (0.5)	4 (0.6)
• Lack of efficacy	2 (0.3)	2 (0.3)
• Lost to follow-up	14 (2.2)	7 (1.1)
• Non-compliance	2 (0.3)	1 (0.2)
• Relocation	2 (0.3)	1 (0.2)
• Withdrew consent	3 (0.5)	1 (0.2)

Source: SCS, Page 35, Table 7

A total of 28 subjects (4.4%) in the PM group and 21 subjects (3.3%) in the placebo group had AEs leading to study drug discontinuation. The most frequently reported AE's (abdominal pain, herpes zoster, disturbance in attention, headache, anxiety and suicidal ideation) resulting in discontinuation in the PM group occurred in only 2 subjects. Table 21 lists the AEs leading to discontinuation of study drug.

Table 21 Adverse Events Leading to Study Drug Discontinuation, Safety Dataset

MedDRA Preferred Term	PM 7.5 mg N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥ 1 AE	28 (4.4)	21(3.3)
Abdominal pain	2 (0.3)	0 (0.0)
Herpes Zoster	2 (0.3)	0 (0.0)
Disturbance in attention	2 (0.3)	1 (0.2)
Headache	2 (0.3)	1 (0.2)
Anxiety	2 (0.3)	4 (0.6)
Suicidal ideation	2 (0.3)	0 (0.0)
Abdominal distension	1 (0.2)	0 (0.0)
Gingival bleeding	1 (0.2)	0 (0.0)
Chest discomfort	1 (0.2)	0 (0.0)
Depressed mood	1 (0.2)	0 (0.0)
Elevated mood	1 (0.2)	0 (0.0)
Suicide attempt	1 (0.2)	0 (0.0)
Vaginal hemorrhage	1 (0.2)	1 (0.2)
Gastrointestinal hemorrhage	0 (0.0)	1 (0.2)
Bloody discharge	0 (0.0)	1 (0.2)
Agitation	0 (0.0)	1 (0.2)
Depression	0 (0.0)	2 (0.3)
Mood swings	0 (0.0)	2 (0.3)
Nervousness	0 (0.0)	1 (0.2)
Panic attack	0 (0.0)	1 (0.2)

Source: Adapted from SCS, Page 57, Table 22

Medical Reviewer's Comments

- *The most frequently reported adverse events resulting in drug discontinuation only occurred in two subjects.*
- *It is interesting to note that anxiety led to discontinuation more often in placebo subjects (4, 0.6%) than paroxetine subjects (2, 0.3%).*
- *Suicide attempt, depressed mood and suicidal ideation lead to study drug discontinuation only in the PM group.*

7.3.4 Significant Adverse Events

Four categories of AEs of special interest were prespecified for analysis based on known class effects of SSRIs (bleeding, suicidality) and the CV events and hepatic events associated with the SNRI, desvenlafaxine. Other labeled adverse events of interest were evaluated and generally no signals detected. These AEs are discussed in 7.3.5. Submission Specific Primary Safety Concerns

Medical Reviewer's Comments

- *The term "Suicidality" is defined to include suicide attempts, suicidal behavior and suicidal ideation.*
- *No safety signals were detected regarding cardiovascular, hepatic gastrointestinal or bleeding events. The only event of some concern was suicidality, which was prospectively assessed in all four clinical studies.*

7.3.5 Submission Specific Primary Safety Concerns

Suicidality

Suicidality was assessed in all 4 clinical studies. Suicidality in these studies was determined in three ways:

(1) Using the STS scale used in Study N30-004
(2) Using the C-SSRS scale used in Study N30-003 and
(3) Through adverse event or serious adverse event reporting.

Suicidality detection overlapped as some events were identified both because they were reported as an AE/SAE and were detected by subject responses to the suicidality instruments.

In Studies N30-002 and N30-004, the STS was used. The FDA subsequently recommended the use of the C-SSRS in a Guidance (Suicidality: Prospective Assessment of Occurrence in Clinical Trials, September 2010) so in Study N30-003, the C-SSRS was used. For data pooling, STS scores were mapped using the domains defined in the C-CASA.

The Applicant used the following categories to assess suicidality in the phase 3 studies; summary results for each category are reported.

1. **Completed suicides**: There were no completed suicides in the clinical development program.

2. **Suicide attempts**: In the safety dataset, there was 1 suicide attempt in the PM group (1/635=0.2%) and none in the placebo group.

3. **Treatment-emergent suicidal ideation/behavior reported as an AE/SAE leading to study discontinuation**: None

4. **Suicidality events (suicidal behavior and/or ideation) reported as an AE/SAE as a result of responses to the**:

- C-SSRS suicidal behavior/ideation: None
- STS suicidal behavior: Based on a total STS score > 0 at any time point during the study, there were a total of 11 events of STS-emergent suicidal behavior (6 events in the PM group and 5 events in the placebo group). None were reported as an AE/SAE and none led to premature discontinuation
- STS suicidal ideation: Based on a total STS score > 0 at any time point during the study, there were a total of 55 events of STS-emergent suicidal ideation (23 events in the PM group and 32 events in the placebo group).

5. **Early discontinuations due to meeting the pre-specified STS score discontinuation criteria**

The Safety Dataset includes the one phase 2 and the two phase 3 trials. Table 22 is a summary of the suicidality events occurring in this dataset. The categories in each row of the table are mutually exclusive so that subjects are not counted twice.

Table 22 Summary of Suicidality, Safety Dataset

Parameter	Safety Dataset	
	PM (N=635)	Placebo (N=641)
Completed suicide	0	0
Suicide attempt (Study N30-004, Subject 4-23-014)	1	0
Treatment-emergent suicidal behavior and/or ideation solely reported as an AE/SAE	4	0
C-SSRS-reported suicidal behavior	0	0
C-SSRS-reported suicidal ideation	0	0
STS-reported suicidal behavior	6	5
STS-reported suicidal ideation	23	32
Met C-SSRS criteria for discontinuation	0*	0
Met STS criteria for discontinuation	1**	1

*Two subjects, one in each arm, met C-SSRS criteria for exclusion at baseline, but were inadvertently enrolled, then were discontinued shortly after starting study drug. They are not counted in this table, but are included in the safety population.
**An additional PM 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: SCS, Adapted from Page 66, Table 26

Medical Reviewer's Comments

- *Suicidality was determined both on the basis of AEs/SAEs and on the basis of responses to the suicidality instruments.*
- *There was 1 suicide attempt in 1 subject in the PM group (1/635; 0.2%) and none in the placebo group.*
- *In the controlled studies, there were 3 SAEs of suicidal ideation (3/635, 0.5%), all occurring in Study N30-004 and none in the placebo group.*

Summary of Individual Studies (Evaluation Instrument)

1. Phase 1 Study N30-005 (C-SSRS)

- 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-reported events of suicidal behavior or ideation.

2. Phase 2 Study N30-002 (STS)

- In Study N30-002, subjects completed the STS at Baseline and Day 57 or Early Termination. Discontinuation criteria based on STS score were not prespecified. If the Investigator did not consider the STS response an AE or reason for discontinuing the subject, then the scores were not reported as such.
- There were no completed or attempted suicides in this study.
- There was no spontaneous treatment-emergent suicidal behavior and/or suicidal ideation events reported as an SAE/AE that led to premature discontinuation.
- There were no events of STS- reported suicidal behavior in the PM group (0/49; 0%) and 1 event in the placebo group (1/52; 1.9%).
- There were a total of 6 events of STS- reported suicidal ideation in 6 subjects of which 2 subjects (2/49; 4.1%) were in the PM group and 4 subjects (4/52; 7.7%) were in the placebo group.
- There was no STS-reported suicidal behavior and/or suicidal ideation events that led to a premature discontinuation in this study.

3. Phase 3 Study N30-004 (STS)

- In Study N30-004, subjects completed the STS using the Interactive Web Response System (IWRS) at Baseline and Day 169 or Early Termination. The protocol frequency of testing was later amended on January 31, 2011 to Baseline, Day 28, Day 84 and Day 169 or Early Termination. The protocol was again amended on February 4, 2011 to add Day 14 for STS testing.
- In the original protocol dated February 18, 2010, STS scores were not pre-specified for discontinuation. If the Investigator did not consider the STS score as an AE or reason for discontinuation, they were not recorded as such. The protocol was amended on January 31, 2011 with pre-specified discontinuation criteria based on STS score.

- There was one suicide attempt in one subject in the PM group (1/285; 0.4%) and none in the placebo group (0/284).
- Based on STS total score > 0 at any point during the study, there were a total of 55 events of STS-emergent suicide ideation, of which 23 events were in the PM group and 32 events were in the placebo group.
- There were also 6 STS-reported suicidal behavior events in the PM group and 4 STS-reported behavior events in the placebo group in this study.
- One subject in the PM group had STS-reported suicidal ideation at baseline that met pre-specified discontinuation criteria defined in the protocol; however, this subject was inadvertently not discontinued at baseline.

4. Phase 3 Study N30-003 (C-SSRS)

- In Study N30-003, the C-SSRS was administered at Baseline, Day 14, Day 28, and Day 84 or Early Termination.
- There were no completed suicides, suicide attempts, spontaneous treatment-emergent suicidal behavior and/or suicidal ideation, or C-SSRS-reported suicidal ideation or behavior.
- One subject in the PM group and 1 subject in the placebo group had C-SSRS-reported suicidal ideation at baseline that met pre-specified discontinuation criteria defined in the protocol; however, these subjects were inadvertently not discontinued at baseline.

For the PM cohort in the safety dataset, there were a total of 4 subjects reporting SAEs of suicide attempt/ideation and 1 subject reporting an AE of suicidal ideation. In the placebo cohort, there were no SAEs of suicide attempt/ideation and 1 AE of suicidal ideation. See Table 23 below.

Table 23 Subject Listing-Suicidal Ideation/Suicide Attempt, Safety Dataset

Study #/ Subject ID	Suicide Ideation/Attempt	Age (years)/ Race	Day of Onset	Reported AE/SAE	Drug/ Outcome
Suicide Attempt Resulting in an SAE					
N30-004/ 4-23-014	-Suicide attempt with multiple non- study medication overdose	50/Caucasion	54	**-SAE** -Suicide attempt	**PM** Discontinued
STS-Reported Suicidal Ideation Resulting in an SAE					
N30-004/ 4-05-013*	-STS-emergent suicidal ideation (Also met pre-specified STS discontinuation criteria)	61/Asian	166	**-SAE** -Suicidal ideation -STS total score = 22	**PM** Discontinued - Recovered without sequelae
N30-004/ 4-22-004	STS-emergent suicidal ideation	53/Caucasion	174	**-SAE** -Suicidal ideation -STS total score = 5	**PM** -Not discontinued - Recovered without sequelae
N30-004/ 4-23-023	STS-emergent suicidal ideation	67/Caucasion	168	**-SAE** -Suicidal ideation -STS total score = 3	**PM** -Not discontinued -Recovered without sequelae
STS–Reported Suicidal Ideation Resulting in an AE					
N30-004/ 4-48-022	STS-emergent suicidal ideation	50/African-American	83	**-AE** -Suicidal ideation -STS total score = 2	**PM** -Discontinued

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

Medical Reviewer's Comments

- *All treatment-emergent cases of suicidality reported in the phase 3 trials occurred in Study N30-004, which was of 24 weeks duration. However, four of the seven events (1 suicide attempt + 6 STS-reported behaviors) in PM subjects occurred in the first 12 weeks of the trial, so it is not clear that duration of exposure is a relevant factor.*
- *One suicide attempt occurred. This was in a 50 year old Caucasian woman who took an overdose of nonstudy medication in the setting of increased anxiety and depressed mood. This occurred on Day 54 of the study. She was rushed to the hospital, treated and released.*

- *The incidence of suicidality, while low, is greater in women treated with PM. Such an effect is described in class labeling for all antidepressant drugs. The Division of Psychiatry Products (DPP) was consulted to advise us whether (1) class labeling was appropriate in postmenopausal women with moderate to severe vasomotor symptoms and (2) whether actions beyond class labeling are warranted to address this effect.*

Division of Psychiatric Products Consultation
On January 4, 2013, the Division sought consultation regarding the suicidality risk from the Division of Psychiatric Products. The following questions were submitted:

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

Summary of DPP Response
- The Applicant did not map the STS to the C-CASA preferred terms, as recommended, but instead mapped the STS to determinations of suicidal ideation and suicidal behavior "for accounting purposes." The result was that 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." 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."

Summary of DPP Response
- DPP agreed that the clinical studies submitted to the NDA did not demonstrate an increased risk of suicidal ideation or behavior for drug vs. placebo in these study populations. However, they noted that the study populations excluded patients with a history of suicidal ideation, and investigators discontinued any patients whose STS became even mildly elevated. Therefore, these studies are not fully representative of the population who may use this drug.
- It was noted that the one episode of suicidal behavior happened in the treatment arm, so DPP agreed with the need for ongoing surveillance.

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

Summary of DPP Response
DPP suggested the following regarding labeling:

- The labeling for this product should include the verbatim class language for the suicidality boxed warning and warnings in Section 5. Warning and Precautions as presented in the submitted labeling.
- The language in Section 14 should reflect the fact that the study population excluded patients with a history of suicidal ideation or suicidal behavior as there is a high likelihood that physicians will use this product in patients that have comorbid depression and other psychiatric disorders.
- It should be clear in labeling that this low dose has not been studied for depression, as indicated in their proposed labeling.
- Labeling should also state that these studies excluded any high risk patients, and therefore were are not informative regarding patients with depression or other psychiatric disorders.
- DPP 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.

Medical Reviewer's Comments

- *I generally agree with the DPP evaluation.*
- *If the drug is approved for VMS treatment, ongoing surveillance should be advised. The Applicant has proposed routine pharmacovigilance and appropriate labeling to mitigate potential risks of suicidality.*
- *The Applicant is also planning to conduct enhanced pharmacovigilance for suicidality. New cases will be queried for relevant medical history, current symptoms, concomitant medication, duration of PM therapy and clinical outcomes. All this information will be reviewed for potential safety signals and shared with the FDA on an ongoing basis.*
- *In my opinion, the pharmacovigilance program proposed by the Applicant is sufficient.*

Cardiovascular Events

Cardiovascular TEAEs are listed below in Table 24.

Table 24 Cardiovascular Events, Safety Dataset

MedDRA Preferred Term	PM 7.5 mg 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: SCS, Page 60, Table 23

A total of 14 of 27 subjects in the PM group and of the 17 subjects in the placebo group had a CV medical history. Most of the subjects with hypertension events had a history of hypertension (5/7 subjects in the PM group and 2/3 subjects in the placebo group).

Medical Reviewer's Comments

- *Other than the one reported death in Study N30-003, there were no CV events reported as SAEs.*
- *Chest discomfort (Subject 4-22-014) in the PM group was the only CV event resulting in discontinuation of study drug.*

Hepatic Events

Hepatic TEAEs are listed below in Table 25.

Table 25 Hepatic Events, Safety Dataset

MedDRA Preferred Term	PM 7.5 mg N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥1 TEAE	3 (0.5)	6 (0.9)
Abnormal liver function test	2 (0.3)	0 (0.0)
Transaminases increased	1 (0.2)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	4 (0.6)
Hepatic enzyme increased	0 (0.0)	2 (0.3)

Source: SCS, Page 62, Table 24

Medical Reviewer's Comment

- *None of the hepatic events were reported as SAEs or led to discontinuation of study drug.*

Gastrointestinal or Bleeding Events

The incidence of GI or bleeding AEs was similar in both treatment groups. Vaginal hemorrhage was the most commonly reported bleeding event in both groups, as shown in Table 26.

Table 26 Gastrointestinal or Bleeding Events, All Controlled Studies

MedDRA Preferred Term	PM 7.5 mg N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥1 TEAE	12 (1.9)	10 (1.6)
Vaginal hemorrhage	6 (0.9)	3 (0.5)
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)
Postmenopausal hemorrhage	0 (0.0)	3 (0.5)

Source: SCS, Page 63, Table 25

Medical Reviewer's Comments

- *One GI or bleeding event (GI hemorrhage) was reported as an SAE in the placebo group.*
- *GI or bleeding events led to discontinuation of study drug in 2 subjects in the PM group and 3 subjects in the placebo group.*
- *Based on the cardiovascular, hepatic, or gastrointestinal/bleeding safety data in this application, I do not believe any additional specific postmarketing surveillance is indicated for these areas.*

Known Adverse Events with SSRIs:

Sexual Dysfunction

- Preferred Terms use to monitor sexual dysfunction were decreased libido, anorgasmia, sexual dysfunction, and loss of libido. The incidence of each of these AEs was similar in both the PM and placebo groups.

Hyponatremia

- No Preferred Terms suggestive of hyponatremia or sodium values below the lower limit of normal (130 mEq/L) were reported.

Bone Fracture

- There were no reported Preferred Terms for femur or upper limb fractures in the PM group. One subject reported 2 femur fractures in the placebo group. Another subject in the placebo group reported an upper limb fracture.

Activation of Mania/hypomania

- No Preferred Terms suggestive of mania/hypomania were reported.

Seizures

- No Preferred Terms suggestive of seizures were reported.

Akathisia (Restless Leg Syndrome)

- Preferred Term reported by three subjects in the PM group and 1 subject in the placebo group.

Hallucinations

- No Preferred Terms suggestive of hallucinations were reported.

Medical Reviewer's Comments

- *None of the AEs suggestive of serotonin syndrome, hyponatremia, bone fracture, activation of mania/hypomania, seizures, akathisia, hallucinations, and sexual dysfunction) were reported in ≥1% of subjects in the PM group and with at least twice the incidence of placebo.*
- *No safety signals were found regarding these concerns.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The data described below reflect exposure to PM in the two phase 3 clinical trials.

Overall, 50% of subjects in the PM group and 47% of subjects in the placebo group reported at least 1 adverse event. The most commonly observed AEs (≥ 2% and with at least twice the incidence in the placebo group) reported in these studies were nausea (3.8% PM, 1.4% placebo), fatigue (3.4% PM, 1.5% placebo), and dizziness (2.0% PM, 0.8% placebo).

Table 27 Frequency of Adverse Reactions (≥ 2% of Subjects and at a higher incidence than placebo) in the PM group in Pooled Phase 3 Studies

System Organ Class Preferred Term	PM (n = 586) Frequency n (%)	Placebo (n = 589) Frequency n (%)
Subjects with ≥ 1 AE	**295 (50.3)**	**275 (46.7)**
Infections and infestations		
Nasopharyngitis	30 (5.1)	29 (4.9)
Bronchitis	11 (1.9)	3 (0.5)
Urinary tract infection	10 (1.7)	8 (1.4)
Influenza	9 (1.5)	8 (1.4)
Nervous system disorders		
Headache	25 (4.3)	22 (3.7)
Dizziness	12 (2.0)	5 (0.8)
Gastrointestinal disorders		
Nausea	22 (3.8)	8 (1.4)
Diarrhea	17 (2.9)	15 (2.5)
Dry mouth	9 (1.5)	7 (1.2)
Musculoskeletal and connective tissue disorders		
Back pain	10 (1.7)	9 (1.5)
General disorders and administration site conditions		
Fatigue	20 (3.4)	9 (1.5)
Psychiatric disorders		
Abnormal dreams	6 (1.0)	4 (0.7)
Mood swings	6 (1.0)	3 (0.5)
Respiratory, thoracic and mediastinal disorders		
Cough	7 (1.2)	2 (0.3)
Oropharyngeal pain	6 (1.0)	3 (0.5)
Skin and subcutaneous tissue disorders		
Rash	6 (1.0)	3 (0.5)
Reproductive system and breast disorders		
Vaginal hemorrhage	6 (1.0)	3 (0.5)
Vascular disorders		
Hypertension	6 (1.0)	3 (0.5)

Source: SCS, Page 47, Table 16

Medical Reviewer's Comment

- *Overall, there doesn't appear to be any major differences in the incidence of common AEs between the treatment arms.*

The commonly reported AEs in the safety dataset are shown below. Of these events, only fatigue and nausea were reported with an incidence in the PM group of at least twice that reported in the placebo group.

Table 28 Adverse Events by Preferred Term in at Least 2% of Subjects, Safety Dataset

System Organ Class Preferred Term	PM 7.5 mg N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥1 TEAE	320 (50.4)	301 (47.0)
• Nasopharyngitis	33 (5.2)	33 (5.1)
• Headache	29 (4.6)	27 (4.2)
• **Fatigue**	**24 (3.8)**	**11 (1.7)**
• **Nausea**	**23 (3.6)**	**9 (1.4)**
• Sinusitis	19 (3.0)	26 (4.1)
• Upper respirator tract infection	18 (2.8)	28 (4.4)
• Diarrhea	17 (2.7)	16 (2.5)
• Insomnia	10 (1.6)	13 (2.0)

Source: SCS, Page 46, Table 15

Adverse Event by Time of Onset

Of these commonly reported AEs, fatigue occurred primarily within the first week of treatment. Headache, nausea, and diarrhea primarily occurred within the first 4 weeks of treatment. Insomnia, dizziness, nasopharyngitis, sinusitis, and upper respiratory tract infection tended to occur throughout the study. None of the AEs increased in frequency with longer exposure to study drug.

AEs in only one SOC (Respiratory, thoracic and mediastinal disorders) were reported in the PM group (6.1%) with an incidence of at least twice that reported in the placebo group (2.4%).

Medical Reviewer's Comments

- *AEs in the Respiratory, thoracic and mediastinal disorders SOC included cough (PM 1.2%; placebo 0.3%) and oropharyngeal pain (PM 1.0%; placebo 0.5%).*
- *There is no signal here that these events were drug-related.*

A similar incidence of drug related adverse events (per the investigator's assessment) was reported in the PM group (19.5%) and the placebo group (17.6%). See Table 29.

Table 29 Drug Related Adverse Events* by Preferred Term in at Least 1% of Subjects, Safety Dataset

System Organ Class Preferred Term	PM 7.5 mg N=635 n (%)	Placebo N=641 n (%)
Subjects with ≥1 TEAE	124 (19.5)	113 (17.6)
• Headache	18 (2.8)	17 (2.7)
• Fatigue	18 (2.8)	6 (0.9)
• Nausea	15 (2.4)	4 (0.6)
• Dizziness	10 (1.6)	4 (0.6)
• Insomnia	8 (1.3)	9 (1.4)
• Dry mouth	8 (1.3)	5 (0.8)
• Diarrhea	7 (1.1)	3 (0.5)
• Anxiety	5 (0.8)	8 (1.2)
• Irritability	4 (0.6)	10 (1.6)

* As judged by the investigator
Source: SCS, Page 50, Table 18

7.4.2 Laboratory Findings

Hematology
Assessment of mean hematological values over time showed no clinical differences between the PM 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 Chemistry
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. Assessment of mean clinical chemistry values over time showed no clinical differences between the PM and placebo groups.

7.4.3 Vital Signs

There were no clinically relevant differences in vital signs between the PM and placebo groups in the Safety Dataset.

7.4.4 Electrocardiograms (ECGs)

All 4 studies (including the phase 1 study) evaluated ECGs per the Investigator's assessment. No clinically relevant changes were observed between the groups. Three subjects (0.5%) in the PM group and 2 (0.3%) subjects in the placebo group who were assessed at Baseline as "normal" or "abnormal, but not clinically significant" had an

"abnormal, clinically significant" ECG at the end of the study. No trends were apparent based on these findings.

Medical Reviewer's Comments

- *The ECG assessments of "normal" or "abnormal but not clinically significant" or "clinically significant" were not clearly defined in the submission.*
- *Three PM subjects had initial ECGs deemed by the investigator as not clinically significant but had abnormal, clinically significant ECGs at the end of the study. One subject (4-05-013) developed hypertension during the study which may have affected the ECG. The hypertension was determined by the investigator to be possibly related to study drug. Subject 4-22-015 had an initial ECG read as abnormal but not clinically significant. She developed an abnormal clinically significant ECG with AEs of anxiety, chest discomfort and irregular heartbeat. The AEs were all determined by the Investigator to be possibly related to study drug. The third subject (3-48-010) had a history of hypertension and was on antihypertensive medication. She developed a supraventricular arrhythmia that was determined by the Investigator not to be related to study drug.*
- *The ECG findings in this study do not raise any specific safety concerns.*

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed for this submission.

7.4.6 Immunogenicity

Not applicable for this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not applicable, as the Applicant is seeking approval of only one dose of PM.

7.5.2 Time Dependency for Adverse Events

See Section 7.4.1 Time of Onset

7.5.3 Drug-Demographic Interactions

This product is indicated for use only in postmenopausal women. No other special populations were studied.

7.5.4 Drug-Disease Interactions

No drug-disease interaction studies were performed for this NDA application.

7.5.5 Drug-Drug Interactions

See Section 4.4 Clinical Pharmacology

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity trials were indicated or performed.

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction data were indicated or performed.

7.6.3 Pediatrics and Assessment of Effects on Growth

In accordance with PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant has requested a waiver of pediatric study requirements. This waiver request was made for all pediatric age groups, neonates through adolescents. The indication sought for PM for the treatment of VMS associated with menopause is an adult-related condition. The Applicant maintains that conducting studies in pediatric age groups would be highly impractical as so very few pediatric females experience menopause symptoms. They believe that the statutory reasons for waiver have been met so PM qualifies for waiver of pediatric assessment requirements.

Medical Reviewer's Comments

- *The Division concurs with the Applicant's waiver request.*
- *The Pediatric Review Committee has routinely waived pediatric studies for VMS products.*

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Drug Discontinuation

In the clinical trials, subjects were started on PM 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.

A “Prior symptom” was defined as a symptom that was present while taking study drug and that continued into the post-drug 7-day period. Prior symptoms persisted in relatively the same number of subjects in each treatment arm (405 and 414) in the pooled phase 3 dataset. In both treatment arms, the symptoms were most likely to remain unchanged; however, prior symptoms worsened in about 25% of the subjects who stopped paroxetine and 18% of those who discontinued placebo.

Based on this checklist, about 18% of the subjects on PM and 14% on placebo developed new symptoms during the week after discontinuation. Certain new symptoms, such as muscle cramps or spasm, restless feeling in the legs, and trouble sleeping or insomnia were reported in the paroxetine group at twice the incidence of the placebo group.

Table 30 Adverse Events after Drug Discontinuation, Safety Dataset

Category	Paroxetine N=635 n (%)	Placebo N=641 n (%)
Prior symptom persisted	405 (100)	414 (100)
Prior symptom worsened	102/405 (25)	73/414 (18)
New symptom:	112/635 (18)	88/641 (14)
-Dreaming/nightmares	31/635 (4.9)	20/641 (3.1)
-Muscle cramps, spasm	3.5%	1.4%
-Headache	3.1%	2.3%
-Muscle aches/pains	2.7%	2.2%
-Nervousness/anxiety	2.7%	1.9%
-Restless legs	2.5%	1.1%
-Fatigue, tiredness	2.5%	1.4%
-Insomnia	2.4%	1.1%

Source: Adapted from SCS, Page 99, Table 42

Medical Reviewer's Comment

- *Based on the above data, there doesn't seem to be a need to taper the dose of PM when the drug is discontinued.*

7.7 Additional Submissions / Safety Issues

7.7.1 The 4-Month Safety Update Report

PADER

A Postmarketing Adverse Drug Experiences Report (PADER) for NDA 21-299 (Pexeva) was previously submitted to the FDA on August 23, 2012. This report covered the period from July 4, 2011 to July 3, 2012.

A total of 252 adverse events were reported in patients who were taking Pexeva. The most frequently reported System Organ Classes (SOCs) with non-expedited adverse events were: psychiatric disorders (n=49), nervous system disorders (n=30), general disorders and administrative site conditions (n=23), gastrointestinal disorders (n=16). The most frequently reported non-expedited events included Vision blurred (3), Drug interaction (3), Drug withdrawal syndrome (3), Toxicity to various agents (3), Dizziness (3), Hyponatremia (3), Agitation (3), Anxiety (3), Insomnia (3), Syncope (3), Mania (3), Restlessness (3), Suicidal ideation (7), and Hyperhidrosis (4).

The most frequently reported SOCs with expedited adverse events were: psychiatric disorders (28), nervous system disorders (n=15), general disorders and administrative site conditions (n=5), gastrointestinal disorders (n=4). The most reported expedited events included Contusion (2), Balance disorder (2), Neuroleptic malignant syndrome (2), Paresthesia (2), Aggression (3), Anger (2), Intentional self-injury (2), Nightmare (3), Suicide attempt (3), and Homicide (2).

Medical Reviewer's Comment

- *If the Applicant/Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Applicant/Sponsor for expedited reporting.*

There were no reports with a fatal outcome during the reporting period. No new safety information or "Dear Health Care Professional" letters were distributed and there were no foreign actions related to paroxetine mesylate. The submitted reports did not warrant any significant change in the safety profile of Pexeva relative to previous reporting periods.

The 4-Month Safety Update
The 4-Month Safety Update was submitted to the NDA on December 17, 2012 as Amendment 6. The report contained an updated literature search. This search generated 4 cases where paroxetine was involved. These cases were idiopathic thrombocytopenic purpura and alveolar hemorrhage, an intentional multiple drug overdose, a man with right hippocampal agenesis and sexual crimes (hypersexuality) and lack of energy. A review of these four 4 cases did not alter the safety profile of Pexeva.

There have not been any new studies or any ongoing or completed studies with PM 7.5 mg since the August 28, 2012 submission of the NDA.

8 Postmarket Experience

PM 7.5 mg is not currently commercially available in any part of the world, and there are no pending applications for foreign registration. PM 7.5 mg is a lower dose than the doses currently approved for Paxil (paroxetine hydrochloride) and Pexeva (paroxetine mesylate). Both Pexeva and Paxil are approved at doses ranging from 10 to 60 mg/day for long-term use.

9 Appendices

9.1 Literature Review/References

Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine-controlled release in the treatment of menopausal hot flashes, a randomized controlled trial, JAMA. (2003) 289:2827-34.

9.2 Labeling Recommendations

Labeling is currently under review.

9.3 Advisory Committee Meeting

On March 4, 2013, an Advisory Committee was convened regarding PM. The following discussion is largely based on the "Quick Minutes" documentation of the Advisory Committee proceedings.

The FDA requested the Committee to respond to three questions:

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

The Committee voted: Yes- 7 No- 7 Abstain- 0

- *Half of the committee voted "yes" to this question. Those who voted "yes" noted that there was some moderate effectiveness even though it barely met the criteria. Of those who voted yes, it was noted that frequency may be easier to measure than severity and that frequency may be valued over severity.*
- *Those who voted "no" noted that the results were mixed based on the inconsistent results for severity at Week 12 in Study N30-003. It was also felt that the magnitude of effect was minimal.*

2. 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?

The Committee voted: Yes- 4 No- 10 Abstain- 0

- *Those who voted "yes" noted that based on frequency and personal assessment, it was felt that the effect was clinically meaningful.*

- *Those who voted "no" felt it difficult to differentiate between placebo effect and drug effect. It was also noted that there was a decline in placebo-subtracted effect between Weeks 4 and 12.*

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

The Committee voted: Yes- 4 No-10 Abstain- 0

- *Those who voted "yes" noted that the side effects are recognized for this medication and the lower dose was recognized as possibly more tolerable for women. It was also noted that this drug had a small beneficial effect.*
- *Those who voted "no" noted that the treatment effect was small. Some felt the side effect profile acceptable while others were concerned in regards to suicidal ideation for a new population of users. Overall, those who voted "no" felt that the clinical meaningfulness did not meet expectation and the risk outweighed the potential benefits.*

Medical Reviewer's Comments

- *Regarding Question 1, the Committee was divided regarding approval. There seemed to be some agreement, though, that the measurement of hot flash frequency may be valued over severity because the measurement of severity was problematic. I agree with this.*
- *Regarding Question 2, the criteria for achieving what was "clinically meaningful" was unclear. In my opinion, the responder rate of 50% PM vs. 37% placebo at Week 4 was both statistically significant and clinically meaningful. The responder rate of 51% PM versus 43% placebo at Week 12 barely missed statistical significance, but, in my opinion, still showed that the reduction in VMS frequency was clinically meaningful to a majority of PM subjects.*
- *I was surprised by the Committee's vote on Question 3. Although the treatment effect with PM was modest, to expect more with a nonhormonal medication, in my opinion, was unrealistic. No unusual safety issues were documented with this product. In my opinion, the risk-benefit profile supports marketing approval for this indication. It was of interest to me that the 4 "yes" votes on Question 3 (supporting approval) came from clinicians. The two statisticians on the panel both voted "no" to this question.*

9.4 Schedule of Assessments

Study N30-003 Schedule of Evaluations

Study Schedule	**Screening Period**	**Run-in Visit**	Run-in Period	**End Of Run-in**	**Baseline**	**Double-blind Treatment Period**								**Post Treatment**
Duration	**Up to 7 days**	**1 day**	**12 days**	**1 day**	**1 day**	**85 days**								**1 day**
Visit Name	**Screen**	Run-in		End Of Run-in	Baseline	Day 1 to 84	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	End Of Study Day 85	7 Days After Last Dose
Week								**2**		**4**			**12**	
Clinic Visit	Yes	Yes		Yes	Yes			Yes		Yes			Yes	
Telephone Visit							Yes		Yes		Yes	Yes		Yes
Hot Flash Eligibility Criteria (IVRS/IWRS)	X				X									
Medical and Psychiatric History	X													
Physical Examination	X												X	
Vital Signs	X				X			X		X			X	
Weight and Height	X				X			X		X			X	
Electrocardiogram	X												X	
Hematology[1]	X												X	
Chem 20[2]	X												X	
FSH	X													
Urine Pregnancy Test (all females who are not at least 2 years postmenopausal)		X			X			X		X			X	
Record Concomitant Therapies and AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGI										X			X	
CGI					X					X			X	
C-SSRS					X			X		X			X	
DESS														X

[1] Hematology included hemoglobin, hematocrit, platelets, total white blood cell count, neutrophils, lymphocytes , and eosinophils

[2] Chem 20 panel included sodium, potassium, chloride, total carbon dioxide (bicarbonate), creatinine, glucose, urea nitrogen, albumin, total calcium, total magnesium, phosphorus, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, direct bilirubin, lactate dehydrogenase, total protein, total creatine kinase, and uric acid.

Study N30-004 Schedule of Evaluations

Study Schedule	Screening /Baseline	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	Day 84	Day 112	Day 140	End of Study Day 169	Post-treatment
Week			Week 2		Week 4			Week 12			Week 24	
Clinic Visit	Yes		Yes		Yes			Yes			Yes	
Telephone Visit		Yes		Yes		Yes	Yes		Yes	Yes		Yes
Hot Flash Eligibility Criteria (IVRS/IWRS)	X											
Medical and Psychiatric History	X											
Physical Examination	X										X	
Vital Signs	X		X		X			X			X	
Weight and Height	X		X		X			X			X	
Electrocardiogram	X										X	
Hematology[1]	X										X	
Chem 20[2]	X										X	
FSH	X											
Urine Pregnancy Test (all females who are not at least 2 years postmenopausal)			X		X			X			X	
PGI												
Investigator completion of CGI	X				X			X			X	
Subject completion of STS	X		X		X			X			X	
DESS												X

[1]Hematology included hemoglobin, hematocrit, platelets, total white blood cell count, neutrophils, lymphocytes , and eosinophils

[2]Chem 20 panel included sodium, potassium, chloride, total carbon dioxide (bicarbonate), creatinine, glucose, urea nitrogen, albumin, total calcium, total magnesium, phosphorus, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, direct bilirubin, lactate dehydrogenase, total protein, total creatine kinase, and uric acid.

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

/s/

RONALD J ORLEANS
05/21/2013

LISA M SOULE
05/21/2013
I concur with Dr. Orleans' conclusions and recommendation for approval of NDA 204516 for treatment of VMS.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204516 **Applicant: Noven** **Stamp Date: 8.28.12**

Drug Name: Paroxetine mesylate 7.5 mg capsules **NDA Type: 505(b)(2) Standard Review** **PDUFA Date: 6.28.13**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD with Global Submit Review enabled
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			Well organized
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			Module 1.14
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2) Reference listed drug is Paxil® (paroxetine hydrochloride)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			Stearns et al. JAMA, June 4, 2003, Vol. 289, No 21, 2827-2834 was included in the submission.
EFFICACY					

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: N30-003 Indication: VMS Pivotal Study #2: N30-004 Indication: VMS	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 13.1
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data			X	

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during the pre-submission discussions with the sponsor?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA 204516 Filing Meeting
10/23/2012

General

LDMP (low dose mesylate of paroxetine) is an SSRI being developed for the treatment of moderate to severe VMS associated with menopause. The product contains 7.5 mg of paroxetine mesylate and is formulated as a capsule. Higher doses (10 to 60 mg) of paroxetine (Paxil® or Pexeva®) are approved for psychiatric indications and have been in use in the US since the initial approval of Paxil (paroxetine hydrochloride) in 1992. Generally, antidepressant doses of paroxetine are in the range of 20 to 60 mg/day.

Pexeva (paroxetine mesylate) has a chemical structure similar to paroxetine hydrochloride, the only difference being the associated salt. Pexeva was first approved for use in the US in 2003 at doses ranging from 10 to 60 mg/day, depending on the psychiatric indication.

There are no nonhormonal therapies currently approved for the treatment of VMS. LDMP is not approved and has no pending marketing applications outside of the United States.

Reference Listed Drug for 505(b)(2)

- NDA 20-031: Paroxetine Hydrochloride (Paxil)
- Route of administration Oral tablets
- Strength 10mg, 20mg, 30mg, 40mg
- GlaxoSmithKline

Clinical Studies (Individual)

1. Supportive Study N30-002: "A Phase 2, Exploratory, Eight- Week, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Efficacy and Safety Study of Mesafem (paroxetine mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause."
    - 101 subjects randomized
    - 49 randomized to LDMP
    - 52 randomized to placebo

2. **Pivotal Study N30-003:** "A Phase 3, Twelve-Week, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause."

- 12 week study = 84 days
- N=606 subjects
- Inclusion criterion of 7-8 moderate or severe hot flashes per day and 50-60 moderate to severe hot flashes per week
- 4 co-primary endpoints (Mean change in frequency and severity relative to placebo at 4 weeks and 12 weeks)

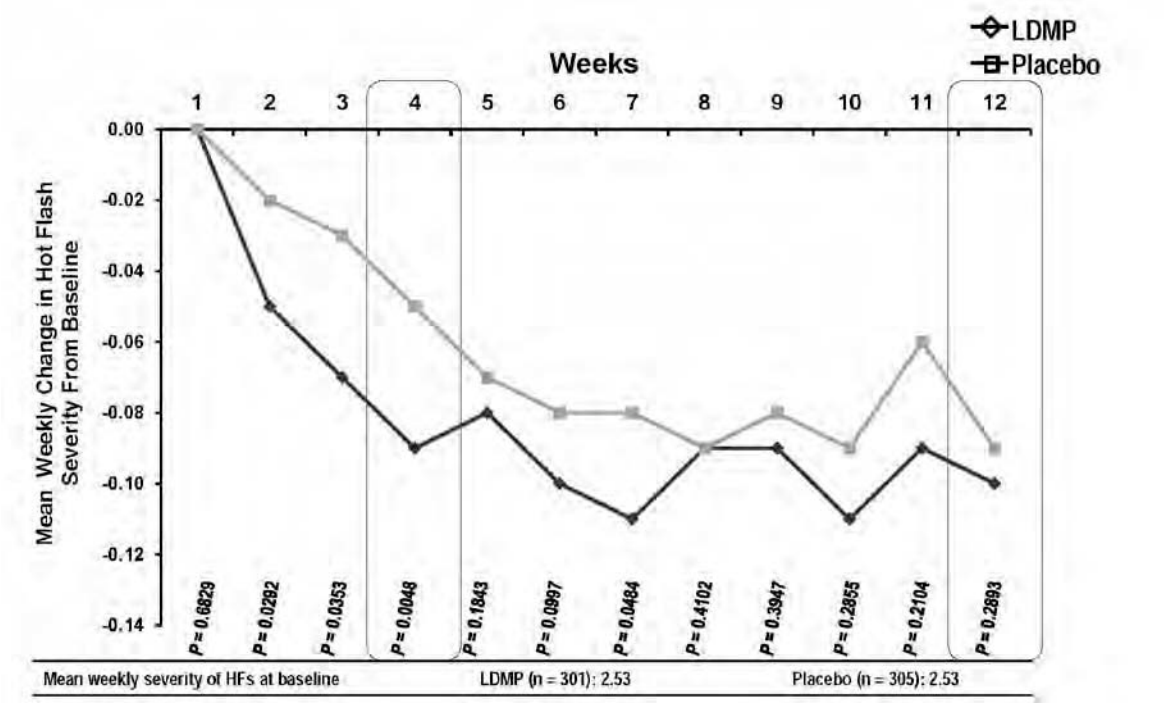
- If the frequency difference were less than 2 moderate or severe hot flashes per day, a responder analysis was required to determine a clinical meaningful response.
- 12-day Placebo Run-in period

N30-003: Reduction in Frequency and Severity of Hot Flashes

	Entered/ Completed	Baseline	Week 4	Week 12
Frequency (Mean Weekly Mod to Severe)				
LDMP	306/271	82.55	-32.96	-43.52
Placebo	308/278	81.54	-23.52	-37.33
P-value			p<0.0001	p=0.0090
Severity				
LDMP	306/271	2.53	-0.09	-0.10
Placebo	308/278	2.53	-0.05	-0.09
P-value			p=0.0048	**p=0.2893**

The weekly mean reduction in severity of moderate to severe hot flashes at Week 12 in Study N30-003 demonstrated a statistically significant difference from the placebo response.

Mean weekly change in severity of hot flashes, Week 1 to Week 12, Study N30-003, MITT population



Source: ISE

Responder Analysis:

- Based on the percentage of satisfied subjects (based on the Patient Global Improvement {PGI} questionnaire) regardless of treatment
- The question asked was: "Compared to before starting the study medication, how would you describe your hot flushes now?"
- Possible responses were:
    1. Very much better
    2. Much better
    3. A little better
    4. No change
- A sensitivity analysis of satisfied subjects with a PGI score ≤2, showing a greater proportion of responders in the LDMP group at Week 4 and Week 12 that reached significance at Week 4 (p=0.0037) but not at Week 12 (LDMP, 61%; Placebo, 55%). This analysis which was based on the percentage of responders in each group was not consistent with the protocol specified agreement.

3. **Pivotal Study N30-004:** "A Phase 3, Twenty-Four Week, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Efficacy and Safety Study of Mesafem (Paroxetine Mesylate) Capsules in the Treatment of Vasomotor Symptoms Associated with Menopause."

- 24 week study (168 days)
- N=570
- Four co-primary Endpoints as in N30-003

- A patient satisfaction anchored responder analysis was used to determine if these reductions in hot flash frequency were clinically meaningful. This analysis was based on the percentage of responders in each treatment group.
- In addition, a co-primary endpoint of persistence of benefit to Week 24 was assessed using a responder analysis. A responder was defined as a subject whose frequency of moderate to severe hot flashes was reduced by 50% or more from baseline to Week 24. The proportion of subjects classified as responders was significantly greater in the LDMP group (48%) than in the Placebo group (36%; p=0.0066).

N30-004: Reduction in Frequency and Severity of Hot Flashes

	Entered/ Completed	**Baseline**	**Week 4**	**Week 12**
Frequency (Mean Weekly Mod to Severe)				
LDMP	285/235	75.79	-28.9	-37.2
Placebo	285/218	76.33	-19.0	-27.6
P-value			p<0.0001	p=0.0001
Severity				
LDMP	285/235	2.53	-0.09	-0.12
Placebo	285/218	2.53	-0.06	-0.07
P-value			p=0.0452	p=0.0114

Safety

- A total of 1300 subjects were treated in the LDMP clinical program, of which 659 subjects received at least 1 dose of LDMP.
- Of these, 235 subjects in the LDMP group (218 in the Placebo group) completed 24 weeks (6 months) of treatment in Study N30-004
- The percentage of subjects who completed the study was similar across treatment groups (86.8% and 85.3% in the LDMP and Placebo groups, respectively). A total of 84 subjects (13.2%) and 94 subjects (14.7%) discontinued the study in the LDMP and Placebo groups, respectively.

Suicidality

- There were no completed suicides reported in the LDMP clinical development program. There was 1 suicide attempt in 1 subject in the LDMP group (1/635; 0.2%) and none in the Placebo group (0/641; 0.0%).
- One death occurred in a 55-year-old woman who experienced SAEs of cardiorespiratory arrest and coronary artery arteriosclerosis that led to death 68

days after starting treatment with LDMP 7.5 mg. Neither event was considered by the Investigator to be related to study drug.

Potential Review Issues:

The Applicant failed to make all primary efficacy endpoints (failed on severity of hot flushes at Week 12 in Study 003) and failed on the "clinical meaningfulness" analysis at Week 12 in Study 003. This will be a review issue.

Analysis issues regarding the Applicant's responder analysis calculations to demonstrate clinical meaningfulness were noted by the Statistician. (See Statistics Filing Checklist). The response variable used in the Applicants ROC analysis in Study N30-003 was not consistent with the protocol specified agreement. The Applicant will be asked to reconduct the responder analysis to resolve these issues.

Ronald J. Orleans, M.D.	10/23/2012
Reviewing Medical Officer	Date
Lisa Soule, M.D.	11/06/2012
Clinical Team Leader	Date

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

/s/

RONALD J ORLEANS
11/08/2012

LISA M SOULE
11/08/2012
I concur with Dr. Orleans that NDA 204-516 is fileable from a clinical perspective.