CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-256

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Addendum to Summary Review for Regulatory Action

Date	January 13, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	22-256
Applicant Name	Forest Laboratories, Inc.
Date of Submission	December 18, 2007
PDUFA Goal Date	October 18, 2008
Proprietary Name / **Established (USAN) Name**	Savella Milnacipran HCl
Dosage Forms / Strength	Tablet, 12.5 mg, 25 mg, 50 mg, 100 mg
Proposed Indication	For the management of fibromyalgia
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Jane Filie, M.D.
Statistical Review	Joan Buenconsejo, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Asoke Mukherjee, Ph.D.; Elizabeth Bolan, Ph.D.; Mohammed Atiar Rahman; Ph.D. (statistics); Karl Lin, Ph.D. (statistics); R. Daniel Mellon, Ph.D.; Paul Brown, Ph.D.
CMC Review	Craig Berta, Ph.D.; Elsbeth G. Chikhale, Ph.D.; Ali H. Al Hakim, Ph.D.
Clinical Pharmacology Review	Sayed Al-Habet, Ph.D.; Suresh Doddapneni, Ph.D.
DDMAC	Michelle Safarik, PA-C
DSI	Roy Blay, Ph.D.; Constance Lewin, M.D., M.P.H.; Dawn Wydner, B.S.N., R. N.; Michelle Chuen, M.D.; Leslie Ball, M.D.
CDTL Review	Mwango Kashoki, M.D., M.P.H.
OSE/DMEPA	Denise V. Baugh, Pharm.D.; Lunda Y. Kim-Jung, Pharm.D.; Denise P. Toyer, Pharm.D.; Carol A. Holquist, R.Ph.
OSE/DAEA	N/A
OSE/DRISK	N/A
DEPI	N/A
CSS	Katherine Bonson, Ph.D.; Michael Klein, Ph.D.
Division of Cardiorenal Products	Norman Stockbridge, M.D., Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
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DEPI= Division of Epidmiology
CSS=Controlled Substances Staff

In my review dated October 16, 2008, I recommended a Complete Response based on two outstanding issues, the need for a MedGuide, and thus a REMS, and the need to reach agreement on the PMRs listed in that review. However, while those requirements had actually been met by the PDUFA date (October 18th), an additional concern developed at the end of the review period which precluded our taking an approval action at that time. This new concern, as noted in my earlier review, was the receipt of a letter from the Government Accountability Project (GAP) on October 7th which documented a whistleblower's allegations regarding the integrity of the data submitted to the application.

It was immediately apparent to the review team and to the signatory authority, Dr. Curtis Rosebraugh, that a for-cause inspection would be required to fully assess these allegations and DSI was contacted to initiate the process. While a Complete Response action was an alternative possibility to missing the PDUFA goal date, it seemed more appropriate to attempt to resolve this new issue as quickly as possible and not to have to wait for a resubmission which would have initiated an additional review cycle.

A DSI for-cause investigation was performed on site at Forest Research Institute by the members of the DSI inspection team, Ms. Dawn Wydner and Dr. Michelle Chuen, and including Dr. Thomas Permutt, Director of the Division of Biometrics II. Dr. Permutt was included because of his expertise in statistical issues associated with products in this division based on his many years of work with DAARP, and because of his familiarity with this particular application. The inspection took place between December 1, 2008 and December 3, 2008. Dr. Permutt met with staff from Forest and reviewed the conduct of protocol FMS-031 entitled, "A Phase III Pivotal, Multi-center, Double-Blind, Randomized, Placebo-Controlled Mono-therapy Study of Milnacipran for Treatment of Fibromyalgia," and protocol MLN-MD-02 entitled, "A Phase III Pivotal, Multicenter, Double-Blind, Randomized, Placebo-Controlled Monotherapy Study of Milnacipran for Treatment of Fibromyalgia."

According to the informant, 57 study participants did not have personal electronic device (PED) data at the three-month primary study endpoint. While the study personnel made a decision to make every effort to retrieve all the missing PED data, the informant asserted that only the PED data of the 23 patients known to be positive responders were recovered and that this would have introduced bias favoring the study drug.

Based on the inspection, Drs. Chuen and Lewin were satisfied that there were no regulatory violations and that the data integrity was acceptable, as long as the misclassifications due to PED malfunctions did not adversely impact the efficacy results. The following has been reproduced from Dr. Permutt's memo of January 8, 2009, which documents his findings and conclusions:

> …The primary measure of outcome was a "responder analysis" in which patients could be classified as responders only if they *both* reported a good global outcome (PGIC 1 or 2) and recorded a good pain score in their electronic diary. The 23 patients in question were those who had PGIC 1 or 2 and therefore might be classified as responders if they had good pain scores. The other 34 of the 57 patients would be nonresponders regardless of their pain scores. Thus, it was entirely appropriate to try to retrieve pain data for the 23 patients in case some truly were responders; it was less important to retrieve pain data for the 34 who would be classified as nonresponders regardless of the pain data. Note that these 34 were not left out of the analysis, but correctly classified as nonresponders.
>
> It also appears from electronic data submitted in the application and reviewed by Joan Buenconsejo, Ph.D. that 22 of the 23 patients were ultimately classified as nonresponders anyway, either because pain data could not be retrieved or because it did not meet the responder criterion. Furthermore, the one patient classified as a responder was in the placebo group.

I believe [GAP] misunderstood the protocol and the documents [they] passed on. The 23 patients were not "known to be positive responders to milnacipran." They were possible responders based on the other component of the primary endpoint, whereas the other 34 were known not to be responders regardless of the pain score. Furthermore, there is no suggestion that any of this discussion took place after unblinding the treatment allocations, so that the patients in question are possible responders to *treatment,* whether with milnacipran or placebo.

I believe the handling of missing data in this study was in keeping with good practice.

Based on this inspection and the conclusions drawn by Dr. Permutt and the DSI team, I am confident that the missing data was handled in accordance with good practices and that this matter may be put to a close. Therefore, I am now able to recommend approval of this application.

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

/s/

Bob Rappaport
1/13/2009 11:45:14 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

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Recommended Action:	Complete Response

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1. Introduction

Milnacipran is a selective norepinephrine and serotonin reuptake inhibitor. It was originally developed and manufactured by Pierre Fabre Medicament in France, and was approved in that country as an antidepressant in 1997. It has since been approved and marketed for that indication in multiple countries. Cypress Bioscience and Forest Laboratories partnered with Pierre Fabre in the development of milnacipran for the treatment of fibromyalgia. Their requested trade name is Savella.

Fibromyalgia (FM) is a chronic condition characterized by diffuse musculoskeletal pain, fatigue and disordered sleep. It is also frequently associated with depression and other

psychiatric conditions, cognitive difficulties and headaches. While it primarily affects women between the ages of 30 and 50, it is also seen in younger and older women, and in men as well as adolescents and, in rare cases, younger children. There are two recently approved products for the management of FM, Lyrica and Cymbalta.

2. Background

During much of the development of Savella, drugs to treat FM were reviewed by the former Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products (DAAODP). (b) (4) In 2005, as part of an overall reorganization of the Office of New Drugs, DAAODP merged with the former Division of Anesthetic, Critical Care and Addiction Drug Products to form the current Division of Anesthesia, Analgesia and Rheumatology Products (DAARP). After extensive internal discussion, as well as discussion with the Director of the Office of Drug Evaluation II, the supervisory office for DAARP, and in the interest of simplifying product labeling, it was decided that we would only approve a single indication for products intended to treat any of the features of FM. That indication would be "For the management of FM." As pain was considered to be the primary and outstanding feature of FM, the indication would require only a demonstration of a treatment effect on an agreed upon pain measure. However, in order to encourage study of a product's effect on the other aspects of the FM syndrome, the Division provided an incentive to do so such that data demonstrating treatment effects on function, disturbed sleep or other domains specific to FM, when confirmed in an appropriately designed trial with an acceptable statistical analysis plan (SAP), would be included in the Clinical Trials section of the product label.

An additional change in DAARP's requirements for studies to support the efficacy of a product intended to manage FM was instituted late in the course of this product's clinical development plan. This change reduced the required length of pivotal efficacy trials from six to three months. When informed of this change in policy, the sponsor requested that they be permitted to truncate their second Phase 3 efficacy study at three months and this request was granted. In addition, as the Division's change regarding allowable (b) (4) was not finalized until shortly after the sponsor had submitted this application, (b) (4) . However, the sponsor was informed of this change in policy as soon as it occurred and did not express any concerns regarding its impact on their application.

The primary concern that arose during the review of this application was in regard to whether the sponsor had provided adequate evidence of efficacy. Drs. Filie, Buenconsejo, Price and Kashoki undertook extensive and in depth analyses of the data from the two pivotal efficacy studies and have concluded that, in spite of their initial concerns, there is adequate evidence to support the indication of "For the management of FM." The safety profile of this product is

not dissimilar to others in its class, and an approved label would have to include a boxed warning for suicide and suicidality as part of the class labeling for antidepressant medications.

On October 7, 2008, we received a letter from the Government Accountability Project which stated that a whistleblower had reported that certain improprieties had occurred in regard to the data collected for one of the pivotal studies submitted in this application. While our initial review of this allegation did not appear to raise concerns regarding the integrity of the data from the study, it is necessary for FDA to complete a thorough investigation. The Division of Scientific Investigation is currently working to complete that investigation.

3. CMC

As per Dr. Bertha's and Dr. Chikhale's reviews, there are no outstanding CMC concerns for this application. While the to-be-marketed product is formulated as 12.5-mg, 25-mg, 50-mg and 100-mg tablets, a capsule formulation was employed during the Phase 1 and Phase 3 studies. The sponsor requested a waiver to conduct in vivo bioequivalence studies between the two formulations. Based on the fact that the drug substance is highly soluble and highly permeable, and because the in vitro dissolution data demonstrate that the milnacipran capsules and the Savella tablets are both rapidly dissolving formulations, a biowaiver was granted. There are no concerns regarding drug substance purity or drug product degradants, or novel or uncharacterized excipients. The stability data support a 24-month expiry for the product.

Five facilities required inspection by the Office of Compliance. These facilities have been inspected and found acceptable.

4. Nonclinical Pharmacology/Toxicology

I concur with Drs. Bolan, Mukherjee and Mellon that there are no outstanding concerns related to the pharmacology or toxicology of Savella that would preclude its approval. Drs. Mukherjee and Mellon have concluded that the sponsor should repeat the Ames bacterial reverse mutation assay, as they were unable to provide adequate documentation regarding the certificate of analysis for the drug substance batch used in the study submitted in support of this application. However, Dr. Brown has concluded that a repeat study is not necessary as no concerns were noted in the available study data, the drug tested negative in the other mutagenicity studies and, most significantly, the negative carcinogenicity studies should mitigate any concerns regarding mutagenicity.

While Dr. Mukherjee recommends a specific monitoring plan for liver toxicity in the clinical setting based on the finding of hepatic cell vacuolation in male rats at doses that would be equivalent to doses in the proposed clinical range, I concur with Dr. Mellon that, based on an absence of any signal of hepatotoxicity during the extensive clinical experience with this drug in other countries and the minimal transaminase elevations noted in the FM clinical studies, routine medical monitoring should be adequate to detect any signs of liver toxicity. I also concur with Dr. Mellon that, although recommended by Dr. Mukherjee, specific monitoring

for keratitis is unnecessary as the ocular effects of this class of drugs are well understood and are clearly delineated in the product label.

I concur with Drs. Mellon and Mukherjee that the findings of embryofetal lethality and reduced pup weights and viability appear to be treatment related, and the labeling for Savella should clearly discourage the use of this drug during pregnancy and in breast feeding women. I also concur that, given the adverse effects noted in the reproductive toxicology studies, a juvenile animal study should be conducted prior to the initiation of pediatric clinical studies.

5. Clinical Pharmacology/Biopharmaceutics

I concur with Drs. Al-Habet and Doddapaneni that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application. The clinical pharmacology has been thoroughly described in their reviews, and Dr. Kashoki has included a substantial summary of the findings in her CDTL review. I will briefly summarize the more important findings. Savella has high bioavailability in the range of 85 to 90%. Plasma protein binding is low (~13%), independent of drug concentration. T_{max} is approximately 2 to 4 hours. The product is dose proportional after single and multiple dose administration. The elimination half-life is 6 to 8 hours. There is no food effect on the pharmacokinetics of the product, but food does appear to increase tolerability. Milnacipran is primarily excreted in the urine, with minimal metabolism by the CYP450 system. It is expected that other drugs that increase heart rate or blood pressure would be likely to result in a pharmacodynamic interaction with Savella.

Exposure was increased in patients with severe renal impairment and a dose adjustment will be necessary for these patients. Drs. Al-Habet and Doddapaneni have recommend use with caution in patients with moderate renal impairment and that patients with severe renal impairment be treated with half of the generally recommended dose. They also recommend caution in administration to patients with severe liver impairment. Exposure was also increased in older subjects, though this would be expected as the prevalence of varying degrees of renal dysfunction increases with age.

The sponsor performed a Thorough QT Study which was reviewed by the QT Inter-Disciplinary Review Team (QT-IRT). The QT-IRT found several deficiencies in the design and conduct of this study and initially recommended that the sponsor repeat the study. Their comments were shared with Forest in a Discipline Review Letter and the sponsor responded with a rebuttal. The QT-IRT reviewed the sponsor's response and concluded that, while the sponsor's chosen correction for heart rate is not the most appropriate method, based on the actual data it is unlikely that the drug will have a clinically relevant effect on QT at therapeutic exposures. Therefore, they recommended that the results using the more appropriate correction methodology be included in the label and, if the sponsor would like to include the data using their chosen correction methodology, they would need to repeat the study. They also recommended a repeat study be considered should the clinical review team find reports of QT prolongation in the clinical database. As this was not the case, and as there has been no signal of a QT effect in the foreign post-marketing database, a repeat study has not been

recommended by the clinical review team as a requirement for approval. I concur with these recommendations.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The sponsor submitted two Phase 3 efficacy trials, Study FMS-031 (Study 031) and Study MLN-MD-02 (Study 02). Both studies were randomized, double-blind, placebo-controlled, parallel-arm, fixed-dose trials that enrolled subjects 18 to 70 years of age with a diagnosis of FM as defined by the American College of Rheumatology criteria. Each study compared the efficacy of Savella 50 mg BID and 100 mg BID to placebo. Study drug was titrated to the targeted fixed dose over three weeks beginning at 12.5 mg BID, increased to 50 mg BID by the end of the first week, and then doubled each week thereafter. Hydrocodone up to 60 mg/day (formulated as hydrocodone/APAP or hydrocodone/ibuprofen) was employed as rescue analgesia, with use limited to a total of 10 days. Rescue medication was not permitted within 48 hours of a scheduled study visit.

Study 031:

Study 031 was a six-month trial and enrolled subjects with a baseline pain score of at least 50 mm on a 100-mm Visual Analogue Scale (VAS). Subjects were excluded if they had refractory FM (i.e., had failed at least two courses of treatment with either tricyclic antidepressants or SNRI agents) or if they had evidence of severe psychiatric illness including suicidal ideation or a current major depressive episode. The primary efficacy outcome measures were: 1) pain intensity measured on a 100-mm VAS; 2) patient function measured with the FIQ and the SF-36 Physical Component Summary (SF-36 PCS): and, 3) patient global impression of improvement measured with a FM-specific patient global impression of change (PGIC) question. The original protocol for Study 031 was submitted as a Special Protocol Assessment (SPA). It specified the primary efficacy analysis endpoint to support the indication of "the treatment of FM syndrome" as the percentage of patients who were responders based on the following criteria:

- Greater than or equal to 30% improvement in pain from baseline to endpoint, and
- PGIC rating of "improved" (i.e., a score of 1, 2 or 3 on a 1 to 7 point scale) at endpoint, and
- Improvement in at least one of the following measures of function:
    - Greater than or equal to 20% improvement in FIQ-PF score form baseline to endpoint
    - Greater than or equal to 5 units of improvement in the SF-36 PCS score from baseline to endpoint

This outcome measure was to be analyzed at six months and the Last Observation Carried Forward (LOCF) imputation methodology for missing data was to be employed. DDAODP failed to reach agreement with the sponsor on this SPA. Subsequent modifications to the protocol included:

- Efficacy for an additional indication of "the treatment of the pain of FM" would be explored using a responder analysis that included the responder criteria for pain and the patient global.

- For the FM syndrome indication, the function outcome would be measured using a greater than or equal to 30% improvement in FIQ-PF, with the SF-36 PCS changed to a secondary outcome.

A final agreement on the SPA was not achieved, however. An additional recommendation that was provided by DAARP was the use of more conservative imputation strategies for imputation of missing data which were to be employed as sensitivity analyses. A "step-down" procedure was employed in the statistical analysis to control the overall type 1 error due to multiple comparisons.

The sponsor's analysis using the protocol specified SAP found no statistically significant treatment effect for either the FM Pain or FM Syndrome primary outcome results. Forest hypothesized that this was due to the inclusion of subjects with moderately severe depression and to the use of an "unresponsive" function measure, the FIQ-PF. They amended the then ongoing Study 02 to exclude subjects with a Beck Depression Inventory (BDI) score of greater than 25 and to employ the SF-36 PCS as the function metric. As these changes resulted in successful outcomes for Study 02, Forest proposed reanalyzing Study 031 using these criteria. This analysis is referred to as the Uniform Program Analysis (UPA). The Division agreed to this proposal.

The following tables reproduced from page 27 of Dr. Kashoki's review summarize the results of the primary efficacy analyses (b) (4) at both the three-month and six-month landmarks:

Appears This Way On Original

(Adapted) Statistical Reviewer's Tables 29 and 30: Primary Efficacy Analyses: Composite Responder Rates for Milnacipran versus Placebo at the 3-Month Landmark – UPA Analysis (Study FMS-031)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
		N=223	N=224	N=441
Three-Month Landmark				
Composite Pain Responders				
	BOCF†	43 (19%)	61 (27%) 1.55 (<1.0, 2.4) p=0.0554	118 (27%) 1.54 (1.0, 2.3) p=0.0323
	BOCF‡	43 (19%)	61 (27%) 1.57 (1.0, 2.4) p=0.0477	118 (27%) 1.54 (1.0, 2.3) p=0.0329
Composite Syndrome Responders				
	BOCF†	27 (12%)	44 (20%) 1.84 (1.1, 3.2) p=0.0277	85 (19%) 1.80 (1.1, 2.9) p=0.0175
	BOCF‡	27 (12%)	44 (20%) 1.75 (1.0, 3.0) p=0.0351	85 (19%) 1.75 (1.1, 2.8) p=0.0197
Six-month landmark				
Composite Pain Responders				
	BOCF†	39 (17%)	53 (24%) 1.41 (0.9, 2.3) p=0.1511	104 (24%) 1.49 (<1.0, 2.3) p=0.0605
	BOCF‡	39 (17%)	53 (24%) 1.46 (0.9, 2.3) p=0.1079	104 (24%) 1.46 (<1.0, 2.2) p=0.0704
Composite Syndrome Responders				
	BOCF†	27 (12%)	40 (18%) 1.46 (0.8, 2.5) p=0.1751	73 (17%) 1.47 (0.9, 2.4) p=0.1244
	BOCF‡	27 (12%)	40 (18%) 1.56 (0.9, 2.7) p=0.0999	73 (17%) 1.45 (0.9, 2.3) p=0.1299

BOCF implies subjects who dropped out are considered nonresponders

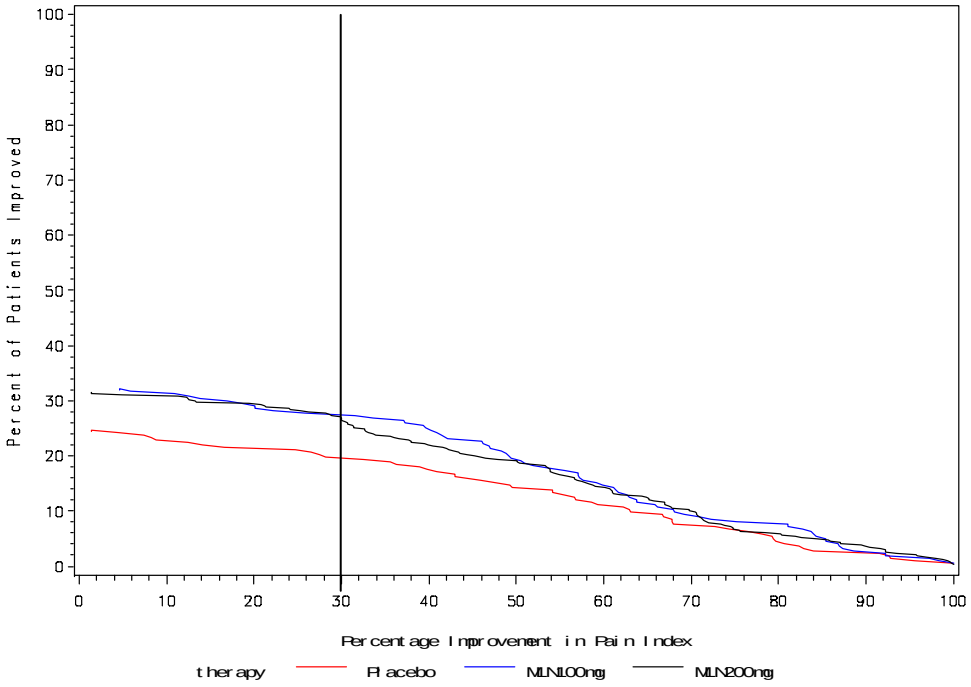
†For Composite Pain and Pain only domain – Sponsor-pre-specified logistic regression model with treatment group, baseline pain, and baseline pain by treatment interaction as explanatory variables. The superiority of milnacipran over placebo was tested at the overall median value of baseline pain score for patients included in the model.

‡ logistic regression model with treatment group and baseline pain as explanatory variable.. This is the same as MLN-MD-02

Based on the sponsor's step-down procedure to adjust for multiplicity (see Dr. Kashoki's review, page 25, for a summary of this procedure), the statistically significant results for the 200-mg per day Savella dose for both the FM pain and FM syndrome endpoints at three months are acceptable; but because the results for the 200-mg per day Savella dose for the FM pain endpoint at six months were not statistically significant, no further comparisons should be allowed, including the 100-mg per day three month outcome for both the FM pain and FM syndrome endpoints.

The review team further explored the data to assess the role of the pain outcome alone as pain is considered the dominant feature of FM. The following graph, reproduced from page 28 of Dr. Kashoki's review, demonstrates that, for subjects who reported that they were "much improved" or "very much improved" on the PGIC, there were consistently more Savella-treated subjects than placebo-treated subjects at each level of improvement in their pain scores from 0 to 100%, although this difference was relatively small and particularly less noticeable at the highest levels of response.

Statistical Reviewer's Figure 1: Pain Response Profile for Patients with PGI =1 or PGI=2 (i.e. Composite Pain) – Study FMS-031 (UPA Analysis)



The team performed an extensive battery of additional analyses to explore the outcomes for the individual domains included in the composite outcomes. Dr. Kashoki provides a thorough discussion of these explorations in her review and the reader is referred to that discussion for detail. It is important to note, however, that these analyses did demonstrate that the treatment effect for Savella found in the composite outcomes does not appear to be driven by the patient global response outcome, the pain outcome or the function outcome. In fact, when studied in

isolation, no statistically significant treatment effect for the global response, the pain endpoint or the function endpoint were demonstrated for Savella compared to placebo.

This raised the question of whether a treatment effect on depression was driving the overall positive outcome for Savella. Therefore, the team performed an additional analysis which assessed whether the proportions of treatment responders varied by depression status. The results of this analysis demonstrated that there were similar numbers of treatment responders among the less and more depressed patients, suggesting that the favorable composite outcomes were also not due to an antidepressant effect of Savella.

Study 02:

Study 02 was similar in design to Study 031. However, the study enrolled subjects with a baseline pain score of at least 40 mm on a 100-mm VAS and a score of greater than or equal to 4 on the physical function component of the FIQ. As noted above, an amended reanalysis plan for Study 02 was agreed to by the Division during the course of the study, and that amended plan forms the basis for the analyses described below.

The following tables reproduced from page 14 of Dr. Kashoki's review summarize the results of the primary efficacy analyses (b) (4) :

Primary Efficacy Analyses: Composite "FM Pain" Responder Rates at the 3-Month Landmark (ITT population) – Study MLN-MD-02

		Placebo	Milnacipran	
Endpoint	Imputation		100 mg/d	200 mg/d
Composite "FM Pain" responders		N=401	N=399	N=396
	BOCF	**66 (16%)**	**91 (23%)** **1.50 (1.1, 2.1)** **p=0.0252**	**98 (25%)** **1.68 (1.2, 2.4)** **p=0.0037**

(Derived from the statistical reviewer's Table 17)

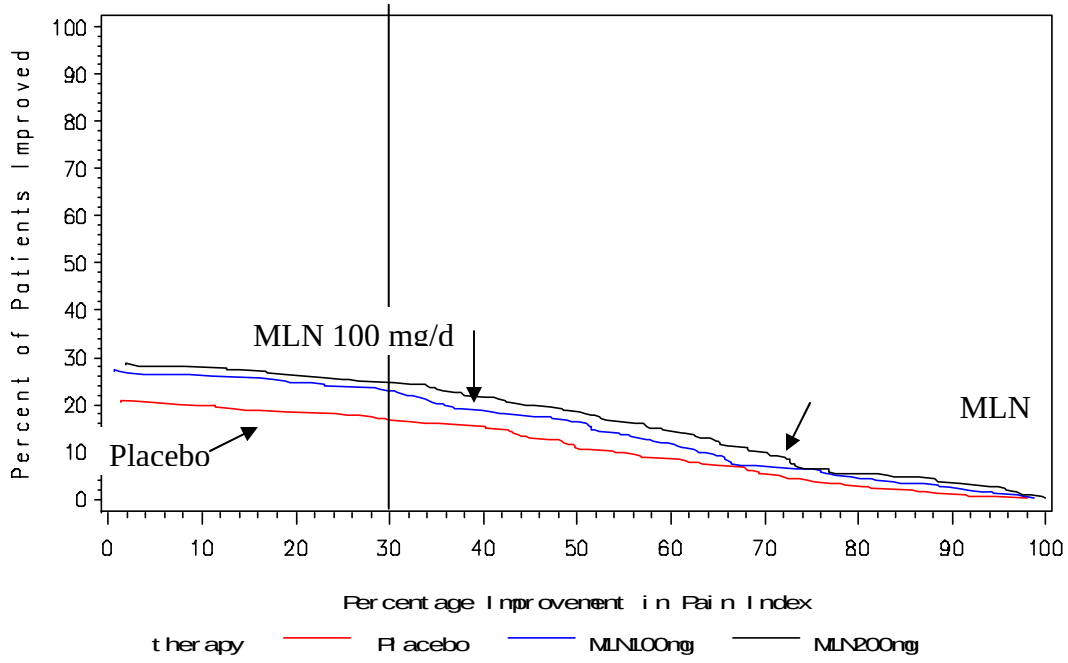
Primary Efficacy Analyses: Composite "FM syndrome" Responder Rates at the 3-Month Landmark (ITT population) – Study MLN-MD-02

		Placebo	Milnacipran	
Endpoint	Imputation		100 mg/d	200 mg/d
Composite "FM syndrome" responders		N=401	N=399	N=396
	BOCF	**35 (9%)**	**58 (15%)** **1.79 (1.1, 2.8)** **p=0.011**	**55 (14%)** **1.75 (1.1, 2.8)** **p=0.015**

(Derived from the statistical reviewer's Table 25)

The cumulative response curve for the pain outcome alone for Study 02 is similar to that seen for Study 031. The following graph is reproduced from page 15 of Dr. Kashoki's review:

Statistical Reviewer's Figure 2: Composite Pain Response Profile – Study MLN-MD-02



The team again performed an extensive battery of additional analyses to explore the outcomes for the individual domains included in the composite outcomes. It is important to note that, in this study, these analyses did demonstrate that the treatment effect for Savella found in the composite outcomes appears to be driven by the patient global response outcome rather than the pain or function outcomes. When studied in isolation, statistically significant treatment effects for pain and function were not demonstrated for Savella compared to placebo.

Again, an additional important analysis performed by the review team assessed whether the proportions of treatment responders varied by depression status. For this study, the results of this analysis demonstrated that there were more treatment responders among the less depressed patients than among the more depressed patients. This again suggests that the favorable composite outcomes were not due to an antidepressant effect of Savella.

8. Safety

Overall, there were 2596 subjects exposed to Savella in the clinical studies. Of these 2596, 1824 were patients with FM, 1109 were treated with 200 mg/day and 354 were treated for at least one year. Two subjects died during the completed FM studies. One died due to pneumonia and the other due to renal cell carcinoma. I concur with the Drs. Filie and Kashoki that neither of these deaths is likely to be due to exposure to Savella. In the 120-Day Safety

Update, a 46 year old, female patient in an ongoing European Phase 3 FM study was reported to have committed suicide. It is possible that this death was related to treatment with Savella.

The serious adverse events (SAEs) that were considered by the review team to be most likely related to treatment with Savella were primarily cardiac in nature. Indeed, cardiac disorders were the SAEs that occurred with the greatest frequency and they occurred with greater frequency in Savella-treated subjects compared to placebo-treated subjects. However, in general, they all occurred infrequently. The following tables, reproduced from pages 39 and 40 of Dr. Kashoki's review, summarize the most common SAEs:

MLN 100 mg	MLN 200 mg
Chest pain (0.1%) Palpitations (0.1%) Angina unstable (0.1%) Atrial fibrillation (0.1%) Atrial flutter (0.1%) Ventricular extrasystoles (0.1%) Chest discomfort (0.1%)	Chest pain (0.3%) Palpitations (0.1%) Myocardial infarction (0.1%) Fecaloma (0.1%) Nausea (0.1%) Heart rate increased (0.1%) Blood pressure increased (0.1%)

MLN 100 mg	MLN 200 mg
Deep vein thrombosis (0.1%)	Ischemic stroke (0.1%) TIA (0.1%) Headache (0.1%) Migraine (0.1%) Presyncope (0.1%) Abortion spontaneous (0.1%) Suicidal ideation (0.1%)

Discontinuations due to adverse events (AEs) from the two Phase 3 trials occurred most frequently in the Savella 200-mg/day group (24%), followed by the Savella 100-mg/day group (19%), and then the placebo group (9%). The AEs that most frequently resulted in discontinuation in the Savella-treatment arms and which occurred at a higher rate than in the placebo-treatment arms were: nausea, palpitations, depression, increased heart rate, constipation, headache, insomnia, hyperhidrosis, vomiting, dizziness and fatigue.

The most common AEs occurring in Savella-treated subjects in the placebo-controlled FM trials were: nausea, headache, constipation, insomnia, hot flush and dizziness. Of note, nausea and vomiting occurred at very high frequencies in the Phase 1 studies when titration was not employed.

While increases in the total platelet counts were noted in the Savella-treated subjects in the clinical studies, these increases were not considered to be clinically relevant by the review team, being in the 6% range, with mean changes of 12.4 ± 52.3 for the Savella 100-mg arm and 16.1 ± 50.8 for the Savella 200-mg arm. No thrombotic or other possibly platelet-related events were noted in the clinical studies. The foreign labels for milnacipran products describe risks of abnormal bleeding, however. Mild elevations in transaminase levels were noted in the Savella-treated subjects in an apparent dose dependent pattern. However, there were no elevations greater than 3 x ULN and no bilirubin elevations greater than 1.5 x ULN.

The following table, reproduced from page 45 of Dr. Kashoki's review, summarizes the incidence of cardiovascular-related AEs in the FM safety database:

MedDRA coding	Frequency of Cardiovascular-Related AEs (% patients)		
SOC HLGT PT	Placebo	MLN 100 mg/day	MLN 200 mg/day
Cardiac disorders	4.1	10.6	9.6
Cardiac arrhythmias	1.8	3.4	2.9
Palpitations	2.3	7.9	6.6
Tachycardia	0.6	2.7	2.2
Vascular disorders	1.8	6.9	4.3
Hypertension	1.8	6.6	4.3
General disorders and administration site conditions			
Chest pain	1.8	2.9	2.1
Chest discomfort	0.9	1.6	1.0
Investigations			
Heart rate increased	1.1	5.5	5.9
Blood pressure increased	0.8	3.2	2.6

SOC: system organ class; HLGT: high level group term; PT: preferred term

While relatively mild, more elevations in BP occurred in the Savella-treated subjects compared to the placebo-treated subjects. The mean increases in SBP were 3.1 mmHg in the 100-mg/day arm and 3 mmHg in the 200-mg/day arm. The mean increases in DBP were 3.1 mmHg in the 100-mg/day arm and 2.6 mmHg in the 200-mg/day arm. The mean SBP change in the placebo-arm was -0.1 mmHg and the mean change in DBP in the placebo-arm was 0.4 mmHg. Shift data demonstrated that, for subjects with a SBP less than or equal to 120 mmHg at baseline, more Savella 100-mg and 200-mg treated subjects, 55% and 57%, respectively, than placebo-treated subjects, 47%, developed pre-hypertension, defined as a maximal SBP of greater than 120-140 mmHg. Shifts to higher SBP values were low without a clear difference across treatment groups. Patients who were pre-hypertensive at baseline again appeared to have a greater risk of worsened blood pressure when treated with Savella compared to placebo, and similar findings occurred in regard to DBP changes. Subjects who were normotensive at baseline also appeared to incur a greater risk of developing hypertension when treated with

Savella compared to placebo, although the effect appears to be, oddly, inversely related to dose. These findings are summarized in the following table, reproduced from page 46 of Dr. Kashoki's review:

Clinical Reviewer's Table 43: Incidence of hypertension in the placebo-controlled FM trials

Normotensive at Baseline N (%)	End-of-Treatment				
	TEAE report of HTN	Change in HTN Meds	TEAE or meds subtotal	HTN by BP	HTN Total
Placebo 391 (62.7%)	6 (1.5%)	5 (1.3%)	7 (1.8%)	28 (7.2%)	34 (8.7%)
MLN 100mg/day 369 (59.2%)	13 (3.5%)	12 (3.3%)	15 (4.1%)	72 (19.5%)	75 (20.3%)
MLN 200 mg/day 507 (60.6%)	13 (2.6%)	12 (2.4%)	18 (3.6%)	84 (16.6%)	89 (17.6%)

HTN: hypertension

There also appeared to be a mean increase in heart rate in the Savella-treated subjects compared to the placebo-treated subjects in the placebo-controlled FM trials. While these increases were small, 6.6 bpm in the 100-mg/day arm and 7.1 bpm in the 200-mg/day arm (compared to -0.3 bpm in the placebo arm), a shift analysis did demonstrate that 14.5% of subjects in the 100-mg/day arm and 11.8% of subjects in the 200-mg/day arm had increases in HR from normal to greater than 100 bpm, compared to only 0.8% of subjects in the placebo arm.

On page 3 of the consult provided to DAARP from the Division of Cardiorenal Products, Dr. Stockbridge concludes:

> The effects of milnacipran on blood pressure and heart rate have not been well characterized, but they appear to be modest. However, if the effects were present throughout the interdosing interval and persist during chronic treatment, they can be expected to have an appreciable --perhaps 50% -- increase in risk of death, MI, and stroke, like any corresponding natural pressor effect. A 50% increase in mortal-morbid events may still be small if the baseline risk is small--young people, no hypertension, no diabetes, no hyperlipidemia. One should also not expect that monitoring will mitigate against the risk because clinicians are unlikely to detect effects of this magnitude.

On page 54 of her review, Dr. Kashoki states the following:

> Dr. Stockbridge based the 50% estimate upon epidemiological data with essential hypertension and the large body of controlled studies of antihypertensive agents. All of these data support a doubling of cardiovascular risk for every ~6 mmHg change in blood pressure. It is Dr. Stockbridge's opinion that even if milnacipran were used in a high-risk population (with elevated blood pressure and other cardiovascular risk factors), it is unlikely that post-marketing data could detect the incremental mortality/morbidity risk. Dr. Stockbridge also opined that the blood pressure increase observed with MLN is not large enough to be reliably detected (and treated), even in carefully monitored patients.
>
> As previously noted, the magnitude of the effects of MLN on blood pressure and heart rate are in the range of those for other NSRIs that are approved for chronic conditions.

> Therefore it appears that the possibility of an increased cardiovascular risk with the observed degree of blood pressure and heart rate increase is not, in and of itself, sufficient to preclude approval of these products.

The following comments from page 99 of Dr. Filie's review summarize Savella's effects on mood in the clinical studies:

> Altogether, 28-29% of milnacipran-treated patients with depression [at baseline] had a psychiatric adverse event, compared to 25% of placebo patients with depression at baseline. Among patients without depression at baseline, 22% of placebo patients had a psychiatric adverse event during the studies, compared to 19-22% of milnacipran patients. Thus, the risk of a psychiatric AE appeared greater for patients with depression at baseline.
>
> In the patients with depression at baseline, the following psychiatric events were more frequent in the milnacipran-treated patients than in the placebo-treated patients: anxiety (6-7% vs. 4%) and insomnia (14% of MLN 200 mg/day patients vs. 11% of placebo patients).
>
> In patients without depression at baseline, insomnia occurred with greater frequency in the milnacipran groups (12% of patients) compared to the placebo grout (10% of patients).
>
> With respect to the incidence of depression specifically, the analyses showed that among the patients with depression at baseline, 26% of placebo-treated patients experienced depression during the study, compared to 5% and 8% of MLN 100 mg/day and MLN 200 mg/day patients, respectively. This suggests that milnacipran exerted an antidepressant effect. Among patients without depression at baseline, the effect was less: 5% of placebo patients reported an episode of depression, compared to 3% of MLN 100 mg/day patients and 2% of MLN 200 mg/day patients.
>
> Among patients with depression at baseline, the incidence of suidical ideation was highest in the MLN 200mg/day group (1.3%) compared to the placebo (0.5%) and MLN 100 mg/day groups. In the patients without depression at baseline, suicidal ideation occurred slightly more frequently in placebo-treated patients (0.5%) than in MLN-treated patients (0%). The data suggest that among patients with depression, treatment with milnacipran – particularly at the higher dose - could increase the risk of suicidal ideation.
>
> There was no evidence of a drug effect with respect to suicide attempt.

While discontinuation of milnacipran has been documented to result in withdrawal symptoms in some patients with major depressive disorder, the AE profile of Savella did not suggest the emergence of withdrawal symptoms in the FM study patients. However, a formal assessment for withdrawal symptoms was not incorporated into the studies.

The CSS conclude the following regarding Savella's potential to induce a withdrawal syndrome (from page 1 of first CSS consult):

> …based on the presence of a withdrawal syndrome in non-fibromyalgia patients following milnacipran discontinuation (as cited in the proposed drug label), CSS concludes that milnacipran can induce physical dependence.

In addition, the CSS provide the following recommendations regarding the abuse liability of Savella on pages 4-5 of their first consult (my italics):

> As noted above, insufficient information was submitted for the adequate assessment of the abuse potential of milnacipran. In order for milnacipran to be assessed for abuse potential, *CSS recommends that the studies listed below be conducted in the post-marketing period*, dependent on concurrence by the Office of Surveillance and Epidemiology. CSS is available to review protocols prior to study initiation, if desired.
>
> 1) A receptor binding study should be conducted with F-2800, the N-desethyl metabolite of milnacipran. If the receptor binding study should show significant binding at sites associated with abuse potential, animal abuse studies may need to be conducted with the metabolite.
>
> 2) An appropriately-designed self-administration study with milnacipran should be conducted in rats or monkeys. Animals should be trained to lever-press in response to food reward prior to introduction of drugs. A positive control drug with known abuse potential should be used in order to validate the study.
>
> 3) Depending on the results of the self-administration study and the metabolite study, a human abuse potential study may be necessary.
>
> 4) A prospective human physical dependence study should be conducted in fibromyalgia patients to characterize the withdrawal syndrome that occurs following milnacipran discontinuation. The results from this study will provide information to health care professionals and patients on the incidence and duration of adverse events that occur upon withdrawal.

9. Advisory Committee Meeting

This application was not presented to an advisory committee meeting as the product is not the first in its class and as no major safety concerns were found during our review that would bring into question the approvability of the product based on its risk:benefit profile.

10. Pediatrics

The applicant has requested deferral of pediatric studies until the safety and efficacy of Savella have been established in adults. Their proposed pediatric plan includes the following two studies:

- Study MLN-PK-18 is intended to evaluate the pharmacokinetic profile of oral milnacipran in patients with JPFS ages 13-17.
- Study MLN-MD-14 will be an open-label, flexible-dose study of approximately 3-month treatment duration. The primary objective of Study MLN-MD-14 is to evaluate the safety, tolerability, and preliminary efficacy of oral milnacipran in JPFS patients aged 13-17.

The clinical review team agrees that a deferral is indicated, but notes that a randomized, double-blind, controlled study will be necessary to establish the efficacy of Savella in pediatric patients. I concur with their conclusions.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The review team proposed a number of labeling changes to the package insert and the patient package insert which have been agreed to by the sponsor.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action

  Complete Response

- Risk Benefit Assessment

  The sponsor has provided adequate evidence of the efficacy and safety of Savella to support the indication of "For the management of FM." An unusual finding in this application is that, while the product appears to be effective when measured according to a prespecified responder definition, the results on the individual components of that responder definition, pain, function and a patient global evaluation, were not consistently statistically significant in the post-hoc analyses performed by the clinical/statistical review team. In particular, the dominant feature of FM is pain and the results of the team's analyses of the individual pain endpoints did not demonstrate a statistically significant treatment effect for Savella on the pain endpoint in either of the clinical trials. However, there was a clear trend in the direction of a treatment effect for pain and these were, of course, post hoc analyses. It is certainly possible that some other factor than an improvement in pain or function is the primary driver for Savella's overall positive effect in FM. Nevertheless, FM is a poorly understood condition with no clear physiological or structural cause; and it may well be that an unknown factor is pivotal to providing relief from the basically symptomatic effects of FM that often result in devastating outcomes for patients suffering from the disorder.

  The clinical/statistical team did rule out the possibility that the positive treatment effect was simply an antidepressant effect. This was an essential component to the analysis of this application as many patients with FM do suffer from concomitant depression and an effect on this domain alone would not necessarily imply an effect on the syndrome of FM. Overall, the results of

the studies submitted in this application show that Savella is effective in treating the symptoms of FM in some patients, and that the safety profile of the product is similar to the class of NSRI antidepressants and supports a reasonable risk in the face of the product's benefit in treating this debilitating disorder. Standard monitoring and standard labeling statements should be adequate to address the relatively mild cardiovascular and liver toxicities noted in the clinical study database.

As noted above under **Background**, on October 7, 2008, the Agency received a letter from the Government Accountability Project which stated that a whistleblower had reported that certain improprieties had occurred in regard to the data collected for one of the pivotal Phase 3 studies intended to support the efficacy of Savella. While our initial review of this allegation did not appear to raise concerns regarding the integrity of the data from this study, it is necessary for FDA to complete a thorough investigation. The Division of Scientific Investigation is currently working to complete that investigation. Therefore, until this investigation has been completed, this application should not be approved.

- Recommendation for Postmarketing Risk Management Activities

  A Medication Guide will be necessary due to the risk of suicide and depression associated with NSRI antidepressant drugs. Therefore, a REMS will be required in order for Savella to be approved for marketing.

  Dr. Kashoki has also recommended that the following studies be performed as post-marketing risk management requirements:

  - Pediatric studies, as noted above in 10. Pediatrics.

  - A prospective, controlled, observational pregnancy registry study and an open-label, single-dose, pharmacokinetic study in healthy lactating women. These recommendations are based on the fact that FM is primarily a disorder seen in women of child bearing potential, and on the preclinical findings documented in the reproductive toxicology studies.

  I concur with Dr. Kashoki's recommendations for PMRs.