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APPLICATION NUMBER:

22-256

CROSS DISCIPLINE TEAM LEADER REVIEW

9/14/08

Cross Discipline Team Leader Review
N 22-256 (Milnacipran Hydrochloride)

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Cross-Discipline Team Leader Review

Date	September 14, 2008
From	Mwango Kashoki, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	N 22-256
Supplement#	
Applicant	Cypress Bioscience, Inc. Forest Laboratories, Inc.
Date of Submission	
PDUFA Goal Date	
Proprietary Name / Established (USAN) names	Milnacipran hydrochloride
Dosage forms / Strength	12.5-mg, 25-mg, 50-mg, and 100-mg tablets
Proposed Indication(s)	1. Treatment of fibromyalgia syndrome 2. Treatment of the pain associated with fibromyalgia
Recommended:	Approval

APPEARS THIS WAY
ON ORIGINAL

1. Introduction

Forest Laboratories, Inc. has submitted NDA 22-256, a 505(b)(1) application, for milnacipran hydrochloride tablets.

Milnacipran (MLN) is a selective norepinephrine and serotonin reuptake inhibitor; it inhibits norepinephrine uptake with greater potency than serotonin. MLN was discovered and is manufactured by Pierre Fabre Medicament in France. Pierre Fabre conducted the initial non-clinical and clinical development of MLN, and obtained marketing approval for the drug as an antidepressant in France in 1997. Currently, MLN is approved in multiple countries in Europe, Asia and South America for depression ("depressed state," major depressive disorder (MDD)). Cypress Bioscience and Forest Laboratories are partnered with Pierre Fabre in the development of MLN for the treatment for fibromyalgia. For the rest of this review, the Applicant will be referred to as "Forest."

In the NDA, the Applicant sought approval for two indications: treatment of fibromyalgia syndrome, and treatment of the pain of fibromyalgia. These indications had been agreed upon over the course of the product's development. However, shortly after the NDA was submitted, this review division informed the Applicant that based on recent internal discussion, the regulatory requirements for studies of potential fibromyalgia treatments have been modified; currently the division considers the "treatment of fibromyalgia" to be the more appropriate indication. Nevertheless, although Forest's trials incorporated efficacy endpoints different from the currently preferred endpoints, the division was willing to review the already submitted NDA package and would assess efficacy based on the totality of the data. The Applicant agreed to the change in the proposed indication.

Overall, there is adequate evidence of efficacy of milnacipran, and the data show that the benefits of treatment outweigh the risks. I recommend that an approval regulatory action be taken for this application, pending satisfactory resolution of the outstanding abuse liability and labeling issues.

2. Background

Fibromyalgia (FM) is a chronic condition characterized by diffuse musculoskeletal pain, disordered sleep and fatigue. It affects primarily women, particularly between the ages of 30 to 50, but it is also seen in men as well as children and adolescents. It affects approximately 1-2% of the adult US population. FM varies in severity, but may be debilitating in a substantial proportion of patients. It is frequently associated with a variety of nonspecific complaints such as cognitive difficulties, depression, anxiety, and headaches.

The first product approved for the treatment of FM was Lyrica (pregabalin), a compound previously approved for the treatment of epilepsy, pain associated with diabetic peripheral neuropathy (DPN), and post-herpetic neuralgia (PHN). The other product approved for this indication is Cymbalta (duloxetine). Duloxetine is a selective serotonin and norepinephrine

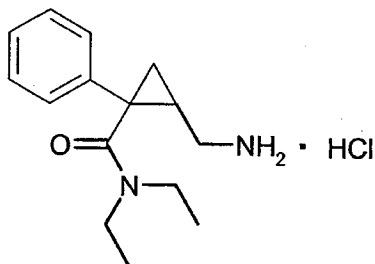
reuptake inhibitor (SSNRI) and, in addition to fibromyalgia, is approved for DPN, generalized anxiety disorder (GAD) and maintenance treatment of major depression.

3. Chemistry, Manufacturing, and Controls (CMC)/Device

Review of the CMC data was performed by Dr. Craig Bertha (drug product) and Dr. Elspeth Chikhale (drug substance). From the CMC perspective, there are no issues to preclude NDA approval.

Drug Substance

Milnacipran has the chemical name: (±)-[1R(S),2S(R)]-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride. Structurally, the drug exists as a racemic mixture with two racemic forms: cis-(dl) and racemate (Z form), composed of two (d- and l-) enantiomers (isomers). The structural formula is:



MLN is produced by chemical synthesis. It is a white to off-white powder and is a BCS class I drug (high solubility and high permeability). MLN is freely soluble in water, methanol, ethanol, chloroform, and methylene chloride and sparingly soluble in diethyl ether.

Review of the data for the drug substance identified no issues with respect to purity.

Drug Product

The to-be-marketed product comprises immediate-release (IR) film coated tablets in the following strengths: 12.5-mg, 25-mg, 50-mg, and 100-mg. The tablets are round and vary in color, depending on the dose strength: pink (12.5-mg), white (25-mg), 50-mg (green), and blue (100-mg). The tablets are compositionally proportional.

Milnacipran capsules were used in the Phase 1 and pivotal Phase 3 studies. On August 14, 2006, the Applicant requested a waiver to conduct *in vivo* bioequivalence studies between milnacipran HCl immediate release capsules and the proposed tablet formulation. Because milnacipran HCl is a highly soluble and highly permeable and because the *in vitro* dissolution data show that milnacipran capsules and tablets dosage forms are rapidly dissolving, a biowaiver was granted by FDA on December 13, 2006.

Review of the data identified no issues with respect to degradants, novel or uncharacterized excipients in the drug product. The data support a 24-month expiry for the drug product.

Inspection by the Office of Compliance of five facilities for the manufacturing/testing/packaging of the drug substance and drug product was requested. Four facilities (for the drug product) have been inspected and found acceptable. The recommendation for one facility (drug substance manufacturer) was still pending at the time of this review.

4. Nonclinical Pharmacology/Toxicology

Evaluation of the non-clinical data was conducted by Dr. Elizabeth Bolan and Dr. Asoke Mukherjee. Refer to their reviews for details regarding the non-clinical data.

Based upon her review of the general pharmacology and impurity data, as well as the acute toxicology, carcinogenicity studies, and mouse Tg rasH2 carcinogenicity study, Dr. Bolan did not identify any nonclinical safety issues that would preclude approval of the NDA. Dr. Bolan did note one drug product degradation impurity, [redacted], for which the levels exceeded ICHQ3B Qualification Threshold of no more than (NMT) 0.2%. However, Dr. Bolan considered that the Applicant's [redacted] impurity specification is acceptable because [redacted] is a [redacted] here are adequate toxicology and genotoxicity data to support its safety. Dr. Bolan did not recommend any additional non-clinical studies. b(4)

Dr. Mukherjee's review of the repeat-dose toxicology, genetic toxicology, reproductive toxicology, carcinogenicity, mouse bioassay, and rat bioassay data also did not find any safety issues that would preclude NDA approval.

Noteworthy findings from Dr. Mukherjee's review that can be addressed in the product labeling are:

- In male rats, liver vacuolation at doses higher than 15 mg/kg, which is in the range of the proposed human dosing. Dr. Mukherjee recommended that, depending on the clinical data, patients' transaminase levels be measured if use of MLN beyond one year is anticipated.
- Keratitis was noted in male and female rats after a chronic use which may be related to dry eye conditions.
- Administration of milnacipran at 5 mg/kg/day (4 times less than the maximum recommended human dose (MRHD) on an mg/m² basis) decreased fertility in rats.
- Administration of milnacipran in mice up to 125 mg/kg (3 times MRHD on an mg/m² basis) during the period organogenicity did not show teratogenicity. However, an embryocidal effect and an extra single rib were noted in pregnant rats and rabbits at 5 and 15 mg/kg, respectively. These doses are 0.25 and 1.5 times maximum recommended human doses on mg/m² in rats and rabbits, respectively.

Based on the findings of the fertility and reproductive safety studies, Dr. Mukherjee recommends Pregnancy Category C for milnacipran.

Phase 4 commitment

The mutagenicity studies showed milnacipran is not mutagenic. However, the Applicant did not provide certificate of analysis for the batch of drug used in the Ames assay. Therefore the results of this study cannot be considered definitively negative. Dr. Mukherjee recommends that the Ames assay be repeated as a Phase IV commitment using a clinical batch for milnacipran (should MLN be approved).

5. Clinical Pharmacology/Biopharmaceutics

Dr. Sayed Al Habet reviewed the Clinical Pharmacology data. Please refer to his review for details regarding the pharmacokinetic data for MLN. There were no Clinical Pharmacology issues that would preclude approval.

Pharmacokinetics

The absolute bioavailability of MLN is in the range of 85% to 90%. The plasma protein binding of milnacipran is approximately 13% and is independent of the concentration. C_{max} is attained within approximately 2 to 4 hours after oral administration.

Dose proportionality was observed after single and multiple dose administration. Notably, the dose proportionality studies were limited by high incidences of nausea and vomiting, as well as increases in heart rate that prevented the administration of the MLN beyond 300 mg.

The elimination half-life of racemic milnacipran is 6-8 hours. The d- enantiomer has a longer elimination half-life (8-10 hours) than l-milnacipran (4 to 6 hours). Steady state level is achieved within 36 to 48 hours and is approximately 70% higher than that achieved after a single dose.

Food effect has no effect on the kinetics of either the capsule or tablet dosage forms. However, food does increase the tolerability of MLN.

Metabolism and Excretion

Approximately 90% to 97% of milnacipran dose is excreted in the urine – 55% is excreted unchanged, and the rest as metabolites. The metabolites of MLN include l-milnacipran carbamoyl O-glucuronide (17%), d-milnacipran carbamoyl O-glucuronide (2%) and N-desethyl milnacipran (8%). N-desethyl milnacipran is considered to be inactive, based on pre-clinical data.

The CYP450 system is not a major route of metabolism for MLN. The inhibition and induction potential of milnacipran on CYP 450 isozymes was low. Based on the limited information of the interaction of MLN with digoxin, a known p-glycoprotein (P-gp) intestinal and renal substrate, the drug does not appear to be transported via P-gp.

Drug-drug interactions

As noted above, MLN does not significantly induce or inhibit CYP 450 isoenzymes. Also, co-administration of various drugs did not show a significant effect on the PK of milnacipran. As

such, the potential for interactions with drugs that are substrates, inhibitors or inducers of CYP450 enzymes is low.

The pharmacodynamic effects of co-administration of MLN with drugs that increase heart rate or blood pressure, including other norepinephrine or serotonin reuptake inhibitors, have not been extensively studied. It is reasonable to expect that concomitant use of these drugs could result in greater CV effects.

The European and Japanese labels for MLN either contraindicate or recommend cautious concomitant use of clonidine, digoxin, serotonin agonists, and alpha and beta sympathomimetics, due to their potential to worsen MLN's pharmacodynamic effects.

Special Populations

- Renal impairment

In patients with severe renal impairment, the exposure to MLN was increased (C_{max} ~60% and AUC ~200%) and clearance was markedly reduced (65%). The Applicant did not provide information regarding kinetics of MLN in patients with end-stage renal disease or on dialysis.

Overall, the data show that dose adjustment is necessary in patients with severe renal impairment. Based on the doubling of the AUC, it is recommended that half the MLN dose be used in patients with severe renal impairment. Dr. Al Habet recommends that MLN should be used with caution in patients with moderate renal impairment.

- Hepatic impairment

The two studies that were conducted in patients with hepatic impairment were limited in their ability to provide conclusive data regarding the effects of hepatic impairment. The studies showed inconsistent and variable results, and enrolled a relatively few number of subjects (refer to Dr. Al Habet's review for details). Nevertheless, the available data suggest that milnacipran should be administered with caution in patients with severe hepatic impairment.

- Older subjects

The MLN exposure in this population was generally higher than in younger subjects by approximately 35% to 65%. This is expected, given that older persons can have varying degrees of renal impairment. Based on these data, dose adjustment may be necessary in elderly patients, especially in those with renal impairment.

- Pediatric patients

MLN has not been studied in pediatric patients.

- Gender

There were no differences in the kinetics of MLN between males and females.

- Pregnancy and Lactation

The Applicant states that it is not known if MLN is excreted in human milk or transferred via the placenta in humans. Therefore, there is limited information in nursing mothers and

pregnant women. The Applicant has proposed that MLN be categorized as pregnancy Category C.

The foreign labels for MLN contain information regarding use during pregnancy and lactation. The Japanese label for MLN states the following:

6. Use during Pregnancy, Delivery or Lactation

(3) It is desirable not to administer this product to nursing mothers, but if its use is essential, mothers must be instructed not to breast-feed their baby. [It has been reported in a study on the oral administration of this product to rats that the drug transferred to milk (the concentration in milk was 3 times higher than that in plasma)].

The European label states:

4.6 Pregnancy and lactation

Because small amounts of Milnacipran are excreted in breast-milk, breast-feeding is contraindicated.

The foreign recommendations regarding pregnancy and lactation should be included in the US label.

- Race/Ethnicity

No information is available on the PK of drug in different ethnic groups.

Effect on QT interval

The Applicant conducted a thorough QT study (MLN-PK-10) of MLN. This study was reviewed by the QT Inter-Disciplinary Review Team (QT-IRT).

The QT-IRT noted several limitations to the study, namely:

1. The Applicant derived an individual-specific heart rate correction factor (QTcNi) using interval data collected at rest on day -1. The IRT did not consider this suitable to apply to a drug that increases heart rates outside the resting range because it assumes that the QT/RR relationship remains linear outside the resting range.
2. The study was not optimally designed to assess assay sensitivity. Moxifloxacin was administered to subjects on day 1 followed by dosing with placebo or milnacipran for 37 days. The moxifloxacin should be conducted concurrently with the other treatment arms in order to demonstrate that the study was designed and conducted to detect an effect on the QT/QTc interval.

The QT-IRT recommended that the sponsor perform a repeat TQT study incorporating the following elements:

- Use exercise or 24-h ambulatory ECG monitoring at baseline as a method to increase the range of heart rates to compute an individual-correction factor.
- Collection of additional ECGs during the titration of milnacipran to determine the dose/concentration-response relationship for QT prolongation.
- Conduct of the moxifloxacin control arm concurrently with the other arms.

- Use of a double-dummy blind, given that in this study, over-encapsulation of the moxifloxacin tablet may have caused a decrease in moxifloxacin exposure.

The IRT's comments were sent to the Applicant as a Discipline Review Letter (July 23, 2008). The company responded, providing explanations that rebutted the IRT's deficiencies. The IRT reviewed the Applicant's response and concluded that:

- While neither the applicant's QTcNi nor the IRT's QTcF is an appropriate heart rate correction method (because neither correction method completely removes the QT/RR relationship in all subjects), the QTcF corrects for the heart rate more sufficiently than QTcNi when pooling all treatment from all subjects and when the data are stratified by treatment group.

Based on QTcF, the study failed to exclude [an increase of 10 ms] with a supratherapeutic dose. Because the supradose is 3- to 4-fold higher than the clinical dose and exposure-response relationship is shallow, it is not expected that milnacipran will have a clinically relevant effect on QTcF at therapeutic exposures. In the absence of a repeat TQT study, [the IRT recommends] that [the QTcF results are described] in the label.

A repeat study will be necessary if the Applicant wants to include QTcI in the label. A repeat TQT study could also be considered if there are reports of QT prolongation in the clinical database which would be inconsistent with the TQT study results.

The safety data from the FM trials, from the MDD trials conducted for the European marketing application, and from the MDD postmarketing safety database do not suggest a QT effect of milnacipran.

On September 8, 2008, the Division discussed with the company its decision that the QTcF results best reflect the effects of MLN on the QT interval and should be included in the product label. Following approval, if the Applicant desires to include QTcNi data in the label, another QT study would be necessary.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The Division of Anti-Inflammatory, Analgesic and Ophthalmology Drug Products (DAAODP) was initially responsible for the review of the Investigational New Drug (IND) application for milnacipran as a therapy for fibromyalgia. DAAODP considered that efficacy of for new fibromyalgia therapies was to be supported by trials of at least 6 months' duration. Also, efficacy was to be on endpoints comprising three domains: patients' pain, function, and report

of global (overall) improvement. DAAODP allowed for two possible indications: “treatment of fibromyalgia syndrome” and “treatment of the pain of fibromyalgia.” Efficacy for the treatment of fibromyalgia syndrome would be supported by achieving simultaneous and clinically significant improvement in all three domains, and efficacy for the treatment of the pain of fibromyalgia indication was to be based on achieving simultaneous and clinically significant improvement of just the pain and patient global impression of improvement domains.

The company proposed a composite responder analysis, modeled after the American College of Rheumatology definition of improvement in rheumatoid arthritis. Patients would be defined as responders, based on specific magnitudes of improvement in pain, function, and global change. DAAODP agreed this type of endpoint, and required that patients demonstrate at least a 30% improvement in each component in order to be considered a treatment responder.

There was considerable discussion regarding which measure was appropriate for assessment of patient function. DAAODP recommended the Fibromyalgia Improvement Questionnaire – Physical Function (FIQ-PF) instrument, since this is a disease-specific measure, as opposed to the metric that the company proposed, the Short Form-36 Physical Component Score (SF-36 PCS), since this is a general, non-specific measure. Forrest opposed the FIQ-PF, because if patients entered the trials with scores of zero or near zero it would be challenging to demonstrate improvement in these patients and include them as “responders” for the FM Syndrome claim. Also, the FIQ-PF contains outdated and/or irrelevant questions for the patient population. The company argued that the SF-36 PCS does not have these issues. Forrest incorporated both the FIQ-PF and SF-36 PCS as primary and secondary function measures in the FMS-031 efficacy trial, and found that the latter measure was responsive to change. Therefore, in the subsequent efficacy trial, MLN-MD-02, the SF-36 PCS was the primary function measure, and the FIQ-PF was used as a secondary.

When the Office of New Drugs (OND) was reorganized, the Division of Anesthesia, Anesthesia, and Rheumatology Products (DAARP) assumed review responsibility for all fibromyalgia applications. DAARP reconsidered the efficacy requirements for these products and concluded that the treatment indication should be limited to “treatment (or management) of fibromyalgia.” DAARP considers that that pain is predominant feature of fibromyalgia. There are other prominent features of fibromyalgia that occur, such as decreased physical functioning, depression, disordered sleep and daytime fatigue. DAARP decided that distinction between that provision of indications based on treatment of the overall condition versus treatment of specific symptoms was not appropriate.

To support the “treatment of fibromyalgia” indication, at least two adequate and well-controlled studies of at least 3 months’ duration are required, using pain as the primary endpoint. The trials should also evaluate the effect of treatment on other domains as secondary outcomes, such as sleep, fatigue, and function. If the product is determined to be efficacious for any of the secondary domains, this information may be included in the Clinical Trials section of the label. The studies must use validated measures for its efficacy outcomes. With respect to measures of physical function, the Division has concluded that although the Fibromyalgia Impact Questionnaire (FIQ) is a validated measure, it may not be perform as

well as the physical function subscale of the Short-Form 36 Health Questionnaire (SF36-PF). Therefore the Division recommends that sponsors include both of these function scales in the efficacy trials.

Both DAAODP's and DAARP's policies regarding development of fibromyalgia treatments evolved over the course of the milnacipran (MLN) development program, and this impacted the design and endpoints of the key efficacy trials.

Efficacy studies:

Two Phase 3 studies were submitted in support of efficacy of milnacipran: studies FMS-031 and MLN-MD-02. Both studies can be considered adequate and well-controlled based on the study design. Each study was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trial that enrolled patients aged 18-70 years with a diagnosis of fibromyalgia (as defined by the American College of Rheumatology criteria), and compared the efficacy of milnacipran 50 mg BID and 100 mg BID compared to placebo. The dose of study drug was titrated to the target fixed dose over three weeks, beginning at 12.5 mg BID and increased to 50 mg BID by the end of the first week, and then doubled each week thereafter. Hydrocodone was permitted as rescue analgesia, with use limited to 10 days and not permitted within 48 hours of a scheduled clinic visit. However, the studies differed with respect to other characteristics, as described below.

(a) Study FMS-031

Study FMS-031 was a 6-month trial and enrolled patients with a baseline pain score of at least 50mm on a 100-mm Visual Analog Scale (VAS) and were excluded if they had refractory fibromyalgia (i.e. had failed at least two courses of tricyclic antidepressants or SNRI agents), or had evidence of severe psychiatric illness (including risk of suicide, current major depressive episode). The primary efficacy outcomes were (i) pain intensity (measured on a 100-mmVAS); (ii) patient function, patient function (measured by the FIQ and the SF-36 Physical Component Summary (SF-36 PCS); and (iii) the patient global impression of improvement (measured by a fibromyalgia-specific patient global impression of change (PGIC) question).

The original protocol for Study FMS-031 was submitted for Special Protocol Assessment (SPA). The protocol specified a single primary efficacy endpoint to support a "treatment of fibromyalgia syndrome" indication, namely the percentage of patients that were responders based on the following criteria:

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

Initially, the primary efficacy analysis was to use the last observation carried forward (LOCF) method to impute for missing data, and a closed testing procedure (Hochberg) to control for multiplicity (refer to the statistical review for details). The endpoint would be analyzed at study end (i.e. 6-months).

DAAODP failed to reach agreement with the sponsor on the protocol under a SPA. DAAODP recommended several revisions to the efficacy analysis (Advice Letter September 12, 2003 and Type A meeting, October 14, 2003). The protocol was subsequently modified to include the following:

- Efficacy for an additional possible indication, “**treatment of the pain of fibromyalgia**,” would be explored, based on a responder analysis using the responder criteria for pain and the patient global.
- For the “**treatment of fibromyalgia syndrome**” indication, function response would be measured using a $\geq 30\%$ improvement in FIQ-PF score, and the SF-36 PCS was changed to a secondary measure

Although DAAODP concurred with the amendments, the protocol revision was not submitted as a SPA, nor was a letter from DAAODP sent to the company stating that a SPA agreement had been reached. Forrest has previously stated that there was a SPA agreement but has not, even though asked by the Agency (Type C meeting, June 2, 2006), provided specific documentation that supports this contention.

DAARP also provided recommendations regarding the analysis of FMS-031. DAARP advised the sponsor to include other imputation methods as sensitivity analyses, due to the limitations of the LOCF strategy (Type C Guidance meeting, May 9, 2005). In chronic trials where pain is the primary outcome, a major issue is how to statistically handle missing data due to patient dropout. In these trials, there is often differential dropout across treatment groups: patients in the active group tend to discontinue due to adverse events, and patients treated with placebo tend to dropout because of lack of efficacy. Because the treatments confer a benefit (i.e. decrease pain) only during the period that they are taken, an effective chronic analgesic is considered to be one that relieves pain and can be used over a long period of time (i.e. has long-term tolerability). Thus, it is important to use imputation strategies for missing data that do not impute favorable pains scores for individuals who prematurely discontinue treatment, particularly those who discontinue due to an adverse effect of treatment.

Because FMS-031 was essentially complete when DAARP assumed review responsibility, DAARP agreed to the Applicant’s proposal to assess efficacy at both 3 months and 6 months. DAARP found the proposed efficacy endpoints for the “**pain of FM**” and “**FM syndrome**” indications acceptable, but advised Forrest that for the former indication, the patient global assessment need not be a co-primary endpoint; instead it could be analyzed separately as a secondary endpoint.

Forrest analyzed the results of FMS-031 using LOCF to impute missing data and the FIQ-PF as the function measure. The company found that for the “**FM pain**” indication, there was no statistical evidence of efficacy at 3 months for either MLN group. However, there was a statistically difference between placebo and MLN 200 mg/day when a more conservative imputation method, baseline observation carried forward (BOCF), was used. For the “**FM syndrome**” analysis using LOCF, BOCF and the FIQ-PF, there was no evidence of efficacy for either dose.

The company theorized that the lack of efficacy observed in FMS-031 was a result of the study population (inclusion of people with moderately severe depression) and use of an unresponsive function measure (FIQ-PF); post hoc analyses using this population and BOCF imputation supported this. Forrest amended the then ongoing study, MLN-MD-02, to exclude patients with a Beck Depression Inventory (BDI) score of > 25 , and incorporated the SF-36 PCS into the primary efficacy analysis. This protocol change resulted in favorable efficacy findings for MLN-MD-02 (see Efficacy Results section, below). Consequently, Forrest proposed to DAARP that study FMS-031 still be submitted as pivotal efficacy study but reanalyzed using the analyses and patient population criteria that were specified for MLN-MD-02. This analysis would be referred to as the Uniform Program Analysis (UPA), and would allow for comparison of efficacy results using the same time point, responder definition, imputation method, and population. DAARP agreed to this proposal.

(b) Study MLN-MD-02

Study MLN-MD-02 was initially designed as a 3-month trial. The study enrolled patients with a baseline pain score of at least 40mm on a 100-mm VAS and a score of ≥ 4 on the physical function component of the FIQ. The exclusion criteria and rescue medication were similar to those of study FMS-031, as were the primary efficacy outcomes (i.e. pain intensity, patient function and patient global impression of improvement).

Two primary efficacy analyses were to be performed for MLN-MD-02: (i) the proportion of patients who met the requirements for a “treatment of FMS,” and (ii) the proportion of patients who satisfied the definition of response for a “treatment of the pain of FM.” The criteria for response on the pain, function, and patient global domains, and the method for data imputation were similar from the criteria used in FMS-031. However, study MLN-MD-02 employed a different closed testing procedure to control for the multiple efficacy comparisons (refer to the statistical review for details).

Following review of the protocol by DAAODP, the study duration was extended to 6 months. This was because although the division had previously stated that one 6-month trial (FMS-031) and one 3-month trial (MLN-MD-02) would be sufficient to support efficacy, DAAODP later deemed that at least two 6-month trials would be more appropriate for a chronic condition such as fibromyalgia.

As described above, based on preliminary findings from study FMS-031, the protocol for MLN-MD-02 was amended to exclude patients with moderate-severe depression (with BDI > 25) and patients with a FIQ score < 4 . In the NDA, the Applicant refers to this subgroup of the ITT population as the “UPA population.” Additionally, the criterion for response on the function domain was changed to an improvement of 6 points or more on the SF-36 PCS at endpoint (from an improvement 5 points). Furthermore, the criterion for response PGIC was changed to a rating of “much or very much improved” (i.e. a PGIC score of 1 or 2 at endpoint). BOCF imputation was employed in the primary analysis.

Efficacy results:

The clinical review of the efficacy data was performed by Dr. Jane Filie and the statistical review was performed by Dr. Joan Buenconsejo. Refer to their reviews for details regarding the efficacy analyses.

Results: Study MLN-MD-02

Disposition

Of the 1196 patients in study MLN-MD-02, 68% completed 3 months of treatment. Among the 32% of patients who discontinued, AEs were the most common reason for discontinuation. Dropout due to AEs occurred more frequently in the MLN groups (20-24% of patients) than in the placebo group (10%). Dropout due to lack of efficacy was somewhat comparable across all three treatment groups (5-9%).

Patient Disposition – Study MLN-MD-02

		Milnacipran			
		Placebo N=401	100 mg/d N=399	200 mg/d N=396	Total N=1196
Tx15† (wk 15)	Completed	290 (72%)	264 (66%)	257 (65%)	811 (68%)
	Discontinued	111 (28%)	135 (34%)	139 (35%)	385 (32%)
	AE	38 (10%)	78 (20%)	94 (24%)	210 (18%)
	Lack of Efficacy	36 (9%)	28 (7%)	19 (5%)	83 (7%)
	Other	37 (9%)	29 (7%)	26 (7%)	92 (8%)

(Derived from the statistical reviewer's Table 8)

Primary efficacy analysis:

As previously discussed, the efficacy endpoint for the “FM pain” indication was the proportion of patients that met pain (pain intensity) and patient global (PGIC) responder definitions. The efficacy endpoint for the “FM syndrome” indication was the proportion of patients that met pain, function (SF-36 PCS) and patient global responder definitions. In order to control the overall type I error for comparisons of two dosages of milnacipran to placebo for two indications, the following sequential gate-keeping multiple comparison procedure was used:

1. Step 1: 100 mg versus placebo at 3 months for the “FM pain” indication and 200 mg versus placebo at 3-months for the “FM pain” indication.
2. Step 2: 100 mg versus placebo at 3-months for the “FM syndrome” indication and 200 mg versus placebo at 3-months for the “FM syndrome” indication.

a. Composite Responder Analysis: Pain of Fibromyalgia

Dr. Buenconsejo confirmed the Applicant's finding that there were statistically significantly more composite pain (Pain + PGIC) responders in the MLN 100 mg/day (23%) and MLN 200 mg/day (25%) groups than in the placebo group (16%). This difference was statistically significant.

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

Endpoint	Imputation	Placebo	Milnacipran	
			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)

b. Composite Responder Analysis: Fibromyalgia Syndrome

Again, similar to the Applicant, Dr. Buenconsejo found that there were more patients in the MLN 100 mg/day and 200 mg/day groups (15% and 14%, respectively) than in the placebo group (9%) that met the definition of composite “FM syndrome” responder. Although the absolute proportions in responders were relatively low, the differences in responder rates between the MLN and placebo groups did reach statistical significance.

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

Endpoint	Imputation	Placebo	Milnacipran	
			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

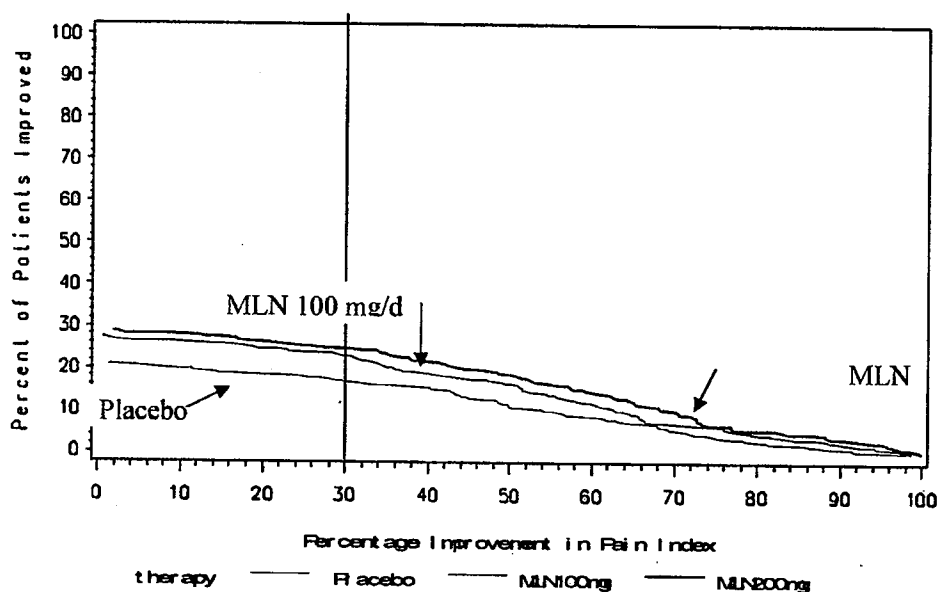
(Derived from the statistical reviewer’s Table 25)

Cumulative (continuous) Responder Analysis – Composite “FM pain” endpoint

The Applicant’s “FM pain” composite endpoint defined response based on a single level (cut-off) of pain improvement. Because pain is considered to be the dominant symptom of fibromyalgia, the data were explored to determine whether a difference between the MLN and placebo treatment arms was still observed when multiple levels of pain improvement were used to define treatment response (i.e. a cumulative (continuous) responder analysis). Of note, this is not an ITT analysis. Instead, this plots the proportion of patients who reported a PGIC score of “much improved” or “very much improved” who also experienced various degrees of pain relief.

The analysis showed that at each level of pain improvement (e.g. $\geq 10\%$ improvement, $\geq 20\%$ improvement, etc.), both doses of MLN had more treatment responders than the placebo group. The proportion of MLN 200 mg/day responders was slightly greater MLN 100 mg/day responders, but this difference was less apparent at higher definitions of pain response (i.e. $\geq 70\%$ pain improvement). Thus, more MLN-treated patients who report feeling “improved” or “very much improved” experience decreased pain than do placebo-treated patients, at all levels of pain improvement.

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



Additional FDA Exploratory Analyses:

As previously discussed, the Division currently considers that a “treatment of fibromyalgia” indication should be supported by efficacy trials that use pain as the primary endpoint, and that effects of treatment on other fibromyalgia domains (such as sleep, fatigue, and function) should be assessed as secondary outcomes.

A comparison of average (i.e. group mean) pain scores at study end or the change in mean pain scores at study end are commonly performed to evaluate effects of treatment on pain. Although a recognized limitation of a comparison of means is that average scores do not necessarily predict individual subject response, this analysis was still done to further assess minlacipran’s effects.

Also, even though the agreed-upon efficacy outcomes that were based on co-primary endpoints showed positive results, further exploration of the effects of MLN treatment on each

of the individual domains was conducted to assess whether there was still suggestion of efficacy when the results were analyzed based on the Division's currently preferred outcomes.

Change in mean pain from baseline to study end

Dr. Buenconsejo found that at study end, the placebo group had a mean change in pain of 10 mm (on a 100 mm VAS), compared to 12.4 mm and 12.9 mm for the MLN 100 mg/day and 200 mg/day groups, respectively. This corresponds to a difference in the change of mean pain scores of 2.4-2.9 mm. Based on p-values unadjusted for multiplicity, there is evidence of a treatment difference for the MLN 200 mg/day group. However, the clinical meaningfulness of the absolute difference in mean pain scores is not readily apparent.

(Adapted) Statistical Reviewer's Table 19: Average Pain Score Mean Change from Baseline to Endpoint – Study MLN-MD-02

Treatment Group	Pain Score (Using BOCF)		
	Baseline	LSMean Change*	p-value†
Placebo	65.8	10.0	
Milnacipran 100 mg/d	64.5	12.4	0.0833
Milnacipran 200 mg/d	64.3	12.9	0.0354

*ANCOVA with treatment and baseline score as explanatory variables; positive implies improvement
† unadjusted p-value

The results of the comparison of means are not consistent with the findings of the primary efficacy (composite responder) analyses. Whereas the primary analyses showed that more milnacipran-treated patients than placebo patients had good responses with respect to improvement in pain, function and global status, the comparison of means found that there was equivalent improvement of pain across the treatment groups. This suggests that it was improvement in patient function and or global status, more than improvement in pain that contributed to the favorable composite responder results.

To explore whether this was indeed the case, the proportions of "pain only" responders in each of the treatment groups were compared. For the composite "FM pain" and "FM syndrome" endpoints, the Applicant defined pain response as $\geq 30\%$ decrease in pain from baseline.

Responder Analysis: Pain responders

- a. Proportion of patients with $\geq 30\%$ improvement in pain from baseline

Dr. Buenconsejo found that there were numerically more "pain only" responders in the MLN 100 mg/day and 200 mg/day groups (31% and 30%, respectively) than in the placebo group (25%). There was no evidence of a dose response. The point estimates for the odds ratios were favorable for MLN, but based on the 95% confidence intervals there is insufficient evidence to show that the difference in "pain only" responders is statistically relevant.

(Adapted) Statistical Reviewer's Table 10: "Pain Only" Responder Rate for Milnacipran Versus Placebo at the 3-Month Landmark – Study MLN-MD-02

Endpoint/ Population		Placebo	Milnacipran	
			100 mg/d	200 mg/d
% patients with ≥ 30% ↓ in pain from baseline	Imputation	N=401	N=399	N=396
ITT	BOCF	101 (25%)	124 (31%) 1.34 (<1.0, 1.8)	119 (30%) 1.28 (0.9, 1.8)

This analysis also shows that there were more "pain only" responders than composite "FM pain" responders. This is not surprising, given that the latter group of patients had to demonstrate response on both the pain and patient global outcomes.

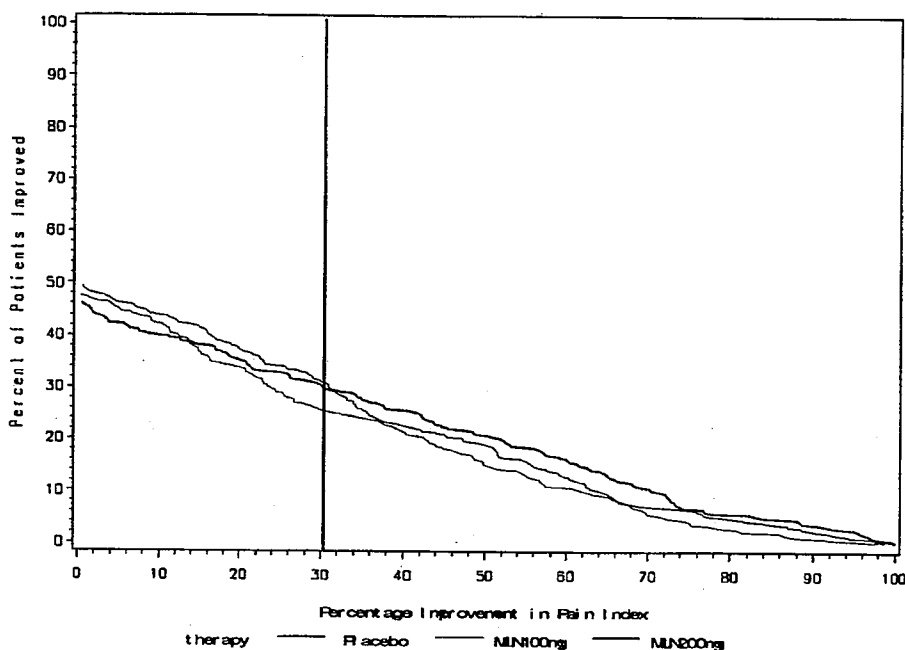
The lack of a considerable difference in the rates of "pain only" responders between the MLN and placebo groups is consistent with the findings of the comparison of mean pain scores at study end, and again suggests that the results of the composite responder analysis were more due to treatment differences in function or patient global response, than to differences in pain.

b. Cumulative (continuous) responder profile - Pain responders

As previously stated, the Applicant defined pain response based on a single cut-off for pain response. To determine whether a difference between the MLN and placebo treatment arms was observed when multiple levels of pain improvement were used to define treatment response, continuous responder curve was plotted for the proportion of patients in each group who achieved various levels of pain reduction or greater. This ITT analysis found that there was no separation between the curves for the MLN arms and the placebo curve. That is, across multiple levels of pain response, MLN did not show a difference from placebo. Again, this finding suggests that MLN did not have a clear analgesic effect for the fibromyalgia patients and indicated the need for exploration of treatment differences with respect to the function and patient global outcomes.

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Statistical Reviewer's Figure 4: Pain Response Profile – Study MLN-MD-02



Responder Analysis: Patient Global

The rates of “patient global only” responders in each of the groups were compared. The definition of response that was employed for the composite “FM pain” and “FM syndrome” endpoints, namely a PGIC score of 1 or 2 at study end, was used for this analysis.

There were numerically more “patient global only” responders in the MLN 100 mg/day and 200 mg groups (31% and 33%) than in the placebo group (23%). The confidence intervals for the odds ratios were supportive of the significance of these differences. Thus, compared to placebo-treated patients, more MLN-treated patients reported an overall improvement with treatment.

(Adapted) Statistical Reviewer's Table 21: Patient Global Improvement Only Responder Rate for Milnacipran Versus Placebo at the 3-Month Landmark – Study MLN-MD-02

Endpoint/ Population	Imputation	Placebo	Milnacipran	
			100 mg/d	200 mg/d
% patients with PGIC score of 1 or 2 at study end		N=401	N=399	N=396
ITT	BOCF	92 (23%)	125 (31%) 1.53 (1.1, 2.1)	129 (33%) 1.62 (1.2, 2.2)

Responder Analysis: Function

For the composite “FM pain” and “FM syndrome” endpoints, function response was defined as a decrease in SF-36 PCS score of at least 6 points from baseline. This definition was used to compare the rates of “function only” responders in each of the groups.

The difference in “function only” responders was greatest for the MLN 100 mg/day group (27% versus 21% in the placebo group). Based on the 95% CI and the unadjusted p-value, there is insufficient evidence that this difference is statistically significant. The MLN 200 mg/day group had a comparable proportion of “function only” responders to the placebo group.

Responder Analyses: “Function only” Responder Rates at the 3-Month Landmark (ITT population), based on the SF-36 PCS – Study MLN-MD-02

Endpoint		Placebo	Milnacipran	
			100 mg/d	200 mg/d
SF-36 PCS Score ↓ of ≥ 6 points	Imputation	N=401	N=399	N=396
	BOCF	86 (21%)	108 (27%) 1.37 (<1.0, 1.9) p=0.0628	89 (22%) 1.10 (0.8, 1.6) p=0.5777

(Adapted from the statistical reviewer’s Table 25)

As discussed in Section 7, DAARP currently recommends that the physical function subscale of the SF-36 (SF-36 PF) be used to measure physical function in fibromyalgia studies. The Applicant used the SF-36 physical component summary (SF-36 PCS) to assess function. Although the scoring is weighted to primarily include items for the Physical Functioning, Role-Physical, and Bodily Scales, the SF-36 PCS includes items from other non-physical domains (such as mental health and vitality). Thus the SF-36 is not an adequate measure of physical function. The Division therefore calculated the change in mean SF-36 PF score to determine if there was a difference in physical function. (A responder analysis is not feasible, since a responder definition for this endpoint is not currently defined.)

Responder Analyses: “Function only” Responder Rates at the 3-Month Landmark (ITT population), based on the SF-36 PF – Study MLN-MD-02

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=401	N=399	N=396
Mean Pain Score (Range) - BOCF			
Baseline	34 (15 - 57)	34 (15 - 57)	34 (15 - 53)
3-month landmark*	34 (15 - 57)	36 (17 - 57)	36 (15 - 57)
Change from Baseline†	-0.3 (-36 - 27)	-1.8 (-38 - 19)	-1.7 (-35 - 25)

This analysis showed that the MLN groups had a greater mean decrease in SF-36 PF score (approximately -1.8 points) than did the placebo group (-0.3 points). The clinical significance

of this relatively small difference in pain scores is not clear. Of note, the MLN and placebo groups were very similar with respect to the range of changes in SF-36 PF scores.

The results of the comparison of responder rates for each of the individual domains suggested that a favorable response on the “patient global” endpoint was the primary contributor towards the positive outcomes of the composite endpoints, rather than a favorable effect of MLN on patients’ pain and function. That is, for the composite endpoints, more MLN patients met “patient global” responder criteria than placebo patients (or, conversely, fewer MLN patients met “pain” or “function” responder criteria). To explore whether this was correct, the proportions of “pain but not global” and “global only” responders in each group were compared.

The table shows that among the “pain but not global” responders, slightly more placebo patients (9%) than MLN 100 mg/d and 200 mg/d patients (8% and 5%) did not also meet criteria for a good PGIC response. However, among the “patient global only” responders, approximately the same proportions of patients in the MLN and placebo groups did not have a favorable pain response. Thus inter-group differences in patient global vs. pain response by themselves do not account for the composite responder efficacy results.

Proportion of pain and patient global responders – Study MLN-MD-02

Responder definition	Placebo	MLN 100 mg/day	MLN 200 mg/day
<i>Composite pain responders</i> Pain/PGIC (yes/yes)	16%	23%	25%
<i>“Pain only” responders</i> Pain (yes)	25%	31%	30%
<i>“Patient global only” responders</i> PGIC (yes)	23%	31%	33%
<i>% pain responders who were not PGIC responders</i> Pain/PGIC (yes/no)	9%	8%	5%
<i>% patient global responders who were not pain responders</i> Pain/PGIC (no/yes)	7%	8%	8%

The finding of a difference between the MLN and placebo composite “FM pain” responder rates, but no difference between the groups with respect to the “pain only” responder rates was further explored. The data were examined for any differences with respect to the magnitude of change in pain intensity for the composite “FM pain” responders versus the “pain only” responders.

The mean change in pain score for the composite “FM pain” responders was 40 mm, compared to mean pain change of approximately 37 mm for the “pain only” responders. Thus, the “pain only” responders showed slightly less of an improvement in pain than did the composite “FM pain” responders. The magnitude of change in mean pain score for the patients who met the PGIC responder definition but not the pain responder definition was even less remarkable

(about 6.5 mm). Comparison of the range of pain intensity scores at study end, as well as the median pain scores at study end yielded similar results.

Thus it appears that the composite "FM pain" responders did have not better changes in absolute pain intensity than the "pain only" responders, which is consistent with the findings of the change in mean pain and "pain only" responder analyses. This suggests that the composite responders' report of an overall feeling of improvement in fibromyalgia (i.e. good PGIC score) may be due to effects on other aspects of the disease.

Because many patients with fibromyalgia also have co-morbid depression, and because milnacipran is an antidepressant, the data were explored to determine whether the positive composite responder results were due to a favorable effect of drug on depression.

Responder Analysis: Patients with depression vs. Patients without depression

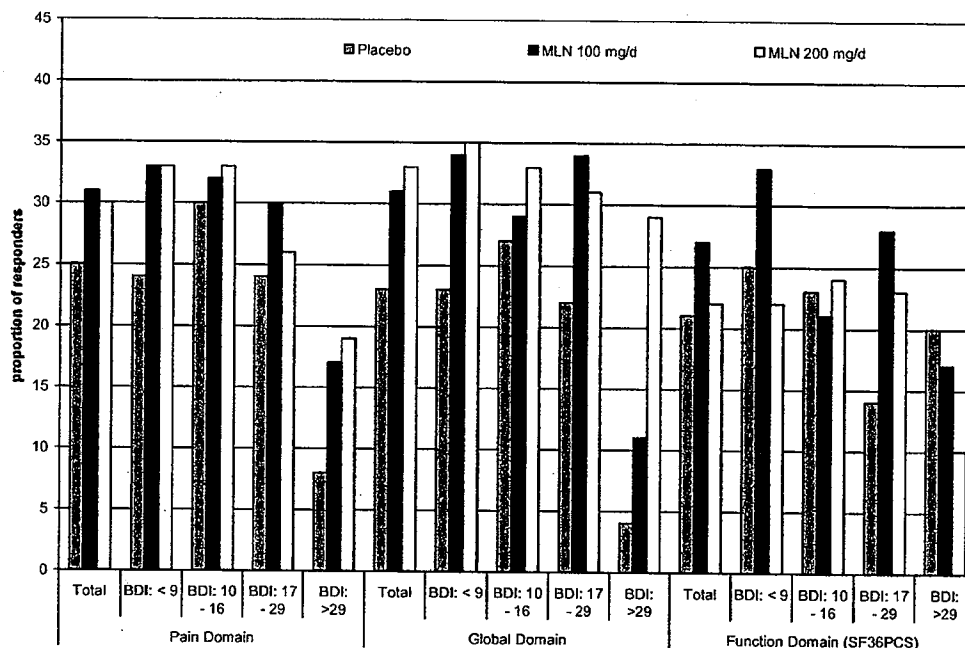
In study MLN-MD-02, patients with current major depressive episode were excluded using the MINI. Also, patients with moderately severe to severe depression, as defined by a Beck Depression Inventory (BDI) score of > 25 were excluded from the study.

To determine whether the proportions of treatment responders varied by depression status, Dr. Buenconsejo performed responder analyses for the composite "FM pain" and "FM syndrome" endpoints, as well as for each of the individual components (pain, function, and patient global).

At baseline, approximately 90% of patients had BDI scores ≤ 25 . For each responder definition, more patients with BDI scores ≤ 25 met responder criteria than did patients with BDI scores > 25 . That is, there was a greater number of treatment responders in the less depressed patients than in the more depressed patients, which suggests that the favorable composite "FM pain" and "FM syndrome" results were not due to an antidepressant effect of MLN. Notably, there was relatively fewer number of patients with BDI scores > 25 compared to ≤ 25 .

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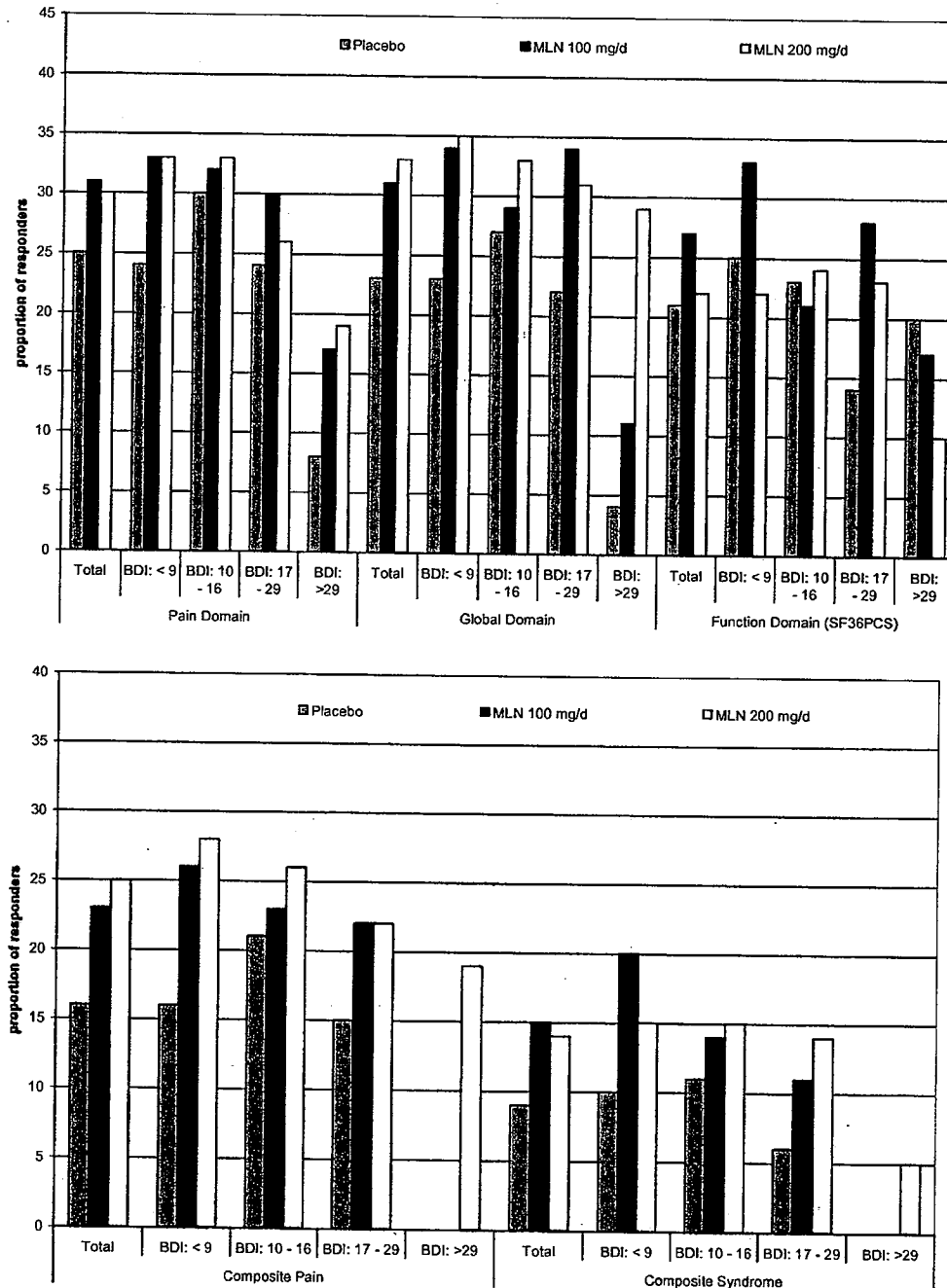
Statistical Reviewer's Figure 17: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study MLN-MD-02



The Applicant's definition of moderately severe to severe depression as a BDI score > 25 appears to have been arbitrarily selected. More commonly, depression severity is categorized as follows: a BDI score of 0 to 9 is considered normal to minimal depressive symptoms; scores of 10-16 indicate mild depression; scores of 17-29 reflect moderate depression, and scores of 30-63 indicate severe depression. Therefore the efficacy data were reanalyzed based on these baseline BDI sub-groups.

This analysis again showed that there were more MLN patients than placebo patients that met criteria for response, for both the composite responder definitions and the individual domain responder definitions. Also, the overall pattern of response showed that, overall, patients with lower BDI scores (i.e. less depressed patients) were more likely to be responders than persons with higher BDI scores (i.e. more depressed patients), across all definitions of response (pain, function, etc.). As can be concluded from the previous analysis, this finding does not support the theory that milnacipran's antidepressant effect was largely responsible for the positive primary efficacy findings.

Statistical Reviewer's Figure 40: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study MLN-MD-02



Efficacy Summary – MLN-MD-02:

Based on the applicant's primary efficacy endpoints, both MLN 100 mg/day and 200 mg/day demonstrated superior efficacy to placebo. That is, there were more treatment responders among patients treated with MLN than among placebo-treated patients, as based on the composite "FM pain" and "FM syndrome" responder criteria. However, *post hoc* analyses of effects of treatment on each of the individual domains of the composite endpoints (pain, function, and patient global), found that there were no differences in pain and function responder rates. There were treatment differences in the rates of patient global responders. Exploration of the data found that differences in baseline pain, duration of FM symptoms, distribution of pain scores at study end, mean pain scores at study end, and baseline depression level do not explain the statistical difference in composite responder rates but not "pain only" responder rates. Also, the differences in composite responder rates between the MLN and placebo groups do not appear to be due to an antidepressant effect. Overall, among patients who feel "improved" or "very much improved" after treatment, more MLN 100 mg/day and 200 mg/day patients than placebo patients experience decreased pain.

Results: Study FMS-031

Per agreement with the Agency, the Applicant reanalyzed study FMS-031 using the patient population criteria and efficacy analyses that were specified for study MLN-MD-02. Patients with FIQ-PF scores < 4 and BDI scores > 25 were excluded, and the resultant modified patient population was termed the Uniform Program Analysis (UPA) population. Also, the reanalysis method was referred to as the Uniform Program Analysis (UPA). The UPA is detailed in the table below:

Uniform Program Analysis Definitions – study FMS-031

	Domain Improvement Definition			Handling of Missing Data
	Pain	Global	Physical Function	
Treatment of Pain @ 3-Month Landmark (Tx15)	≥ 30% improvement from baseline to landmark on PED pain	Much improved, or very much improved at landmark (Score of 1 or 2 on PGIC)	None	BOCF to 3-month Landmark
Treatment of Pain @ 6-Month Landmark (Tx27)				BOCF to 3-month Landmark; LOCF from 3-month to 6-month Landmark
Treatment of Syndrome @ 3-Month Landmark (Tx15)			≥ 6-point improvement from baseline to landmark on SF-36-PCS score	BOCF to 3-month Landmark
Treatment of Syndrome @ 6-Month Landmark (Tx27)				BOCF to 3-month Landmark; LOCF from 3-month to 6-month Landmark

BOCF = baseline observation carried forward; LOCF = last observation carried forward; PED = Patient Experience Diary; PGIC = Patient Global Impression of Change; SF-36 = Short Form-36 Health Survey.

Source: Clinical Study Report FMS-031, page 65

In the UPA, patient response for the "FM pain" and "FM syndrome" endpoints was defined similar to MLN-MD-02. Because study FMS-031 was a 6-month study, these endpoints were assessed at both the 3-month and 6-month time points. BOCF was the imputation strategy for

the 3-month analyses, whereas a combination of BOCF and LOCF was used for the 6-month analyses.

Multiplicity adjustment

In order to control the overall experiment-wise error rate for comparing both the 200-mg/d and 100-mg/d milnacipran dosages with placebo, for both the treatment of pain of fibromyalgia and the treatment of FMS indications, at both Weeks 14-15 (i.e. weeks 11-12 of stable treatment) and Weeks 26-27, eight primary comparisons were performed using the following sequential gatekeeping multiple testing procedure:

1. 200 mg versus placebo on composite pain at Weeks 14-15
2. 200 mg versus placebo on composite syndrome at Weeks 14-15 and 200 mg versus placebo on composite Pain at Weeks 26-27
3. 200 mg versus placebo on composite syndrome at Weeks 26-27
4. 100 mg versus placebo on composite pain at Weeks 14-15
5. 100 mg versus placebo on composite syndrome at Weeks 14-15 and 100 mg versus placebo on composite pain at Weeks 26-27,
6. 100 mg versus placebo on composite Syndrome at Weeks 26-27

At each step, individual hypotheses were tested at the family-wise 5% level of significance only if all of the preceding individual hypotheses were tested and rejected via their closed family. At Step 2 and Step 5, Hochberg's step-up multiple testing procedure was used to test the individual hypothesis in that family at the family-wise 5% level of significance.

Because the Division currently requires analysis of efficacy of fibromyalgia treatments after only 3 months on drug, this memo will focus on the 3-month results. For details regarding the findings of the 6-month analyses, please refer to Dr. Buenconsejo's review.

Disposition

Altogether, 37% of the 888 patients in FMS-031 discontinued treatment prior to 3 months of stable therapy. This rate was slightly higher than that observed in study MLN-MD-02 (32%). Similar to MLN-MD-02, the major reason for discontinuation was adverse event, and this was more frequent in the MLN groups than in the placebo group: whereas 9% of placebo patients dropped out because of an AE, 17% and 25% of MLN 100 mg/day and MLN 200 mg/day patients dropped out because of an AE. Placebo patients were slightly more likely than MLN patients to discontinue because of lack of efficacy.

(Adapted) Statistical Reviewer's Table 14: Number (%) of Patients who reached different study visits – Study FMS-031

		Milnacipran			Total N=888
		Placebo N=223	100 mg/d N=224	200 mg/d N=441	
Tx15 Wk 15	Completed	161 (72%)	140 (63%)	264 (60%)	565 (64%)
	Discontinued	62 (28%)	84 (37%)	177 (40%)	323 (37%)
	Death	1 (0.4%)	0	0	1 (0.1%)
	AE	19 (9%)	39 (17%)	108 (25%)	166 (19%)
	Lack of Efficacy	28 (13%)	23 (10%)	41 (9%)	92 (10%)
	Others	14 (6%)	22 (10%)	28 (6%)	64 (7%)

Primary efficacy analysis

- a. Composite Responder Analysis: Pain of Fibromyalgia
- b. Composite Responder Analysis: Fibromyalgia Syndrome

Because of the nature of the Applicant's method to adjust for multiplicity, the results of the "FM pain" and "FM syndrome" composite responder analyses are presented together.

At 3 months, there were more composite "FM pain" (pain + PGIC) responders in the MLN 100 mg/day (27%) and MLN 200 mg/day (27%) groups than in the placebo group (19%). Similar response rates were observed at six months: 17% of placebo were composite "FM pain" responders compared to 24% of both the MLN 100- and 200-mg/day patients.

With respect to the composite "FM syndrome" (pain + function + PGIC) responders, at 3 months there were more responders in the MLN 100- and 200-mg/day groups (20% and 19%, respectively) than in the placebo group (12%). Similar differences were observed at 6 months, with 17-18% of MLN-treated patients meeting criteria for "FM syndrome" response versus 12% of placebo patients.

Based on the Applicant's step-down procedure for the UPA analysis, treatment with MLN 200 mg/day resulted in a statistically significant difference in "FM pain" and "FM syndrome" responders at 3 months. Because the difference in 6-month "FM pain" response rates for MLN 200 mg/day and placebo did not achieve statistical significance, none of the other comparisons could be tested for significance. This includes the MLN 100 mg/day response rates for both the "FM pain" and "FM syndrome" endpoints.

**(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

*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.

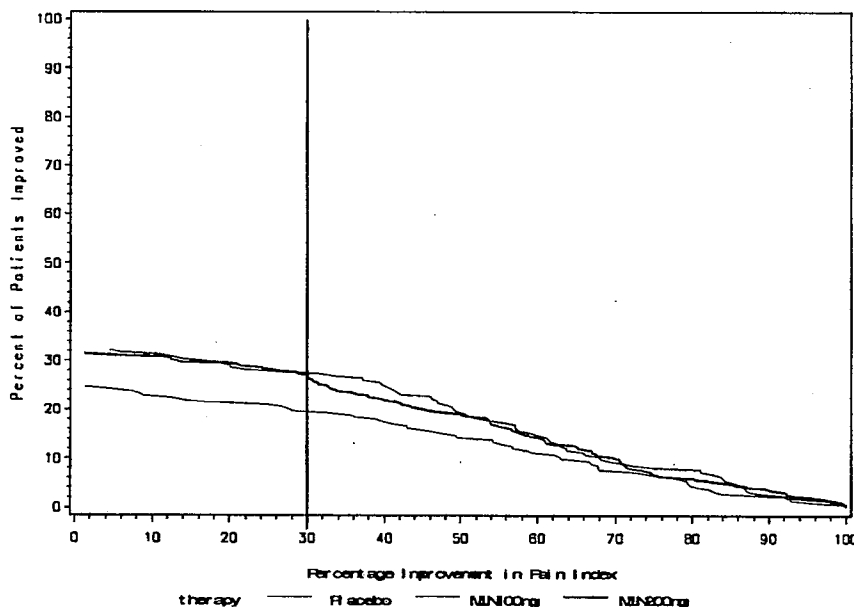
‡ logistic regression model with treatment group and baseline pain as explanatory variable.. This is the same as MLN-MD-02

Cumulative (continuous) Responder Analysis – Composite “FM pain” endpoint

The Applicant’s “FM pain” composite endpoint defined response based on a single level (cut-off) of pain improvement. The data were explored to determine whether a difference between the MLN and placebo treatment arms was still observed when multiple levels of pain improvement were used to define treatment response (i.e. a cumulative (continuous) responder analysis). In this analysis, the proportions of patients who reported a PGIC score of “improved” or “very much improved” and who also met specific levels of pain response were plotted.

The continuous responder curves showed that at each level of pain improvement (e.g. $\geq 10\%$ improvement, $\geq 20\%$ improvement, etc.), both MLN groups had numerically more treatment responders than the placebo group. There was no evidence of a difference in the proportion of responders between the MLN groups.

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



Additional FDA Exploratory Analyses:

The same exploratory analyses that were performed for study MLN-MD-02 were conducted for study FMS-031. Because the Division currently considers that efficacy trials intended to support a “treatment of fibromyalgia” indication should use pain as the primary endpoint and evaluate effects on other fibromyalgia domains (e.g. function) as secondary outcomes, these

types of analyses were conducted. Also, because a comparison of average (i.e. group mean) pain scores at study end is commonly performed in studies assessing effects of treatment on pain, this analysis was also performed.

Change in mean pain from baseline to study end

The results of this analysis were similar to those observed for study MLN-MD-02. At 3 months, the placebo group had a mean change in pain of 13 mm (on a 100 mm VAS), compared to 15 mm for the MLN 100 mg/day and 200 mg/day groups. This corresponds to a difference in the change of mean pain scores of approximately 2 mm. Based on p-values unadjusted for multiplicity, there is no evidence of a treatment difference for the MLN 200 mg/day group. The clinical meaningfulness of the absolute difference in mean pain scores is not readily apparent.

(Adapted) Statistical Reviewer's Table 31: Average Pain Score Mean Change from Baseline to the 3-month Endpoint – Study MLN-MD-02

Treatment Group	Pain Score (Using BOCF)		
	Baseline	LSMean Change*	p-value†
Placebo	68.4	12.7	
Milnacipran 100 mg/d	68.3	14.5	0.3652
Milnacipran 200 mg/d	69.4	15.2	0.1559

*ANCOVA with treatment and baseline score as explanatory variables; positive implies improvement

** ANOVA with treatment; PGI score 1 (very much improved) to 7 (very much worse)

† unadjusted p-value

Again, in this study, the results of the comparison of means are not consistent with the findings of the primary efficacy (composite responder) analyses and cumulative responder curves. Whereas the primary analyses showed that more MLN 200 mg/day patients than placebo patients had good responses with respect to improvement in pain, function and global status, the comparison of means found that there was equivalent improvement of pain across the treatment groups.

Responder Analysis: Pain responders (at 3 months)

- a. Proportion of patients with $\geq 30\%$ improvement in pain from baseline

The proportions of “pain only” responders in each of the treatment groups were compared. For the composite “FM pain” and “FM syndrome” endpoints, the Applicant defined pain response as $\geq 30\%$ decrease in pain from baseline.

Dr. Buenconsejo found that there were numerically more “pain only” responders in the MLN 100 mg/day and 200 mg/day groups (34% and 35%, respectively) than in the placebo group (28%). There was no evidence of a dose response. The point estimates for the odds ratios

were favorable for MLN, but based on the 95% confidence intervals, there is insufficient evidence to show that the difference in “pain only” responders is statistically relevant.

(Adapted) Statistical Reviewer’s Table 32: Pain Only Responder Rate for Milnacipran Versus Placebo at the 3-Month (UPA Analysis) - Study FMS-031

Versus Placebo at the 3-Month (G-A Analysis) - Study FMS-051				
		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Three-month landmark				
“Pain Only” Responders				
	BOCF†	62 (28%)	76 (34%) 1.34 (0.9, 2.0)	155 (35%) 1.42 (<1.0, 2.0)
	BOCF‡	62 (28%)	76 (34%) 1.34 (0.9, 2.0)	155 (35%) 1.43 (1.0, 2.0)

†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

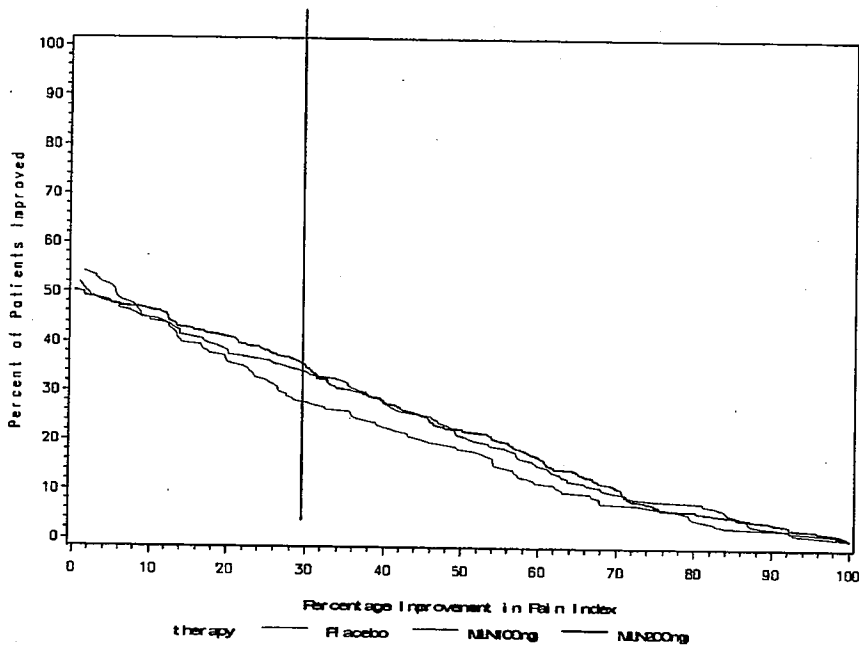
Like the results of the comparison of mean pain scores at study end, the finding of no considerable difference in the “pain only” responder rates between the MLN and placebo groups suggests that the results of the composite responder analysis were more due to treatment differences in function or patient global response, than to differences in pain.

b. Cumulative (continuous) responder profile - Pain responders

The previous “pain only” responder analysis calculated the frequency of response based on a single criterion ($\geq 30\%$ decrease in pain from baseline). To determine whether a difference between the MLN and placebo treatment arms was observed when multiple levels of pain improvement were used to define treatment response, a continuous responder curve was plotted. The UPA population was used for this analysis (i.e. the ITT population minus patients with FIQ-PF score < 4 and BDI score > 25).

This analysis found that the response curves for the MLN and placebo groups overlapped at the two extremes of the graph (that is at pain response definitions of $\leq 20\%$ decreased pain and $\geq 70\%$ decreased pain). Overall therefore, across multiple levels of pain response, MLN did not show a difference from placebo. Again, this finding suggests that MLN did not have a clear analgesic effect for the fibromyalgia patients and indicated the need for exploration of treatment differences with respect to the function and patient global outcomes.

Statistical Reviewer's Figure 15: Pain Response Profile – Study FMS-031



Responder Analysis: Patient Global

The rates of “patient global only” responders in each of the groups were compared, using the definition of response that was employed for the composite “FM pain” and “FM syndrome” endpoints, namely a PGIC score of 1 or 2 at study end.

There were only slightly more “patient global only” responders in the MLN 100 mg/day and 200 mg groups (33%) than in the placebo group (27%). The confidence intervals for the odds ratios did not support a statistically significant difference. Thus, the data show that the placebo- and MLN-treated patients reported equivalent rates of overall improvement with treatment.

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(Adapted) Statistical Reviewer's Table 33: Patient Global Improvement Only Responder Rate for Milnacipran Versus Placebo at the 3-Month Landmark (UPA Analysis) - Study FMS-031

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Three-month landmark				
"Patient Global" Only Responder				
	BOCF*	60(27%)	74 (33%) 1.34 (0.9, 2.0)	145 (33%) 1.33 (0.9, 1.9)
	BOCF§	60 (27%)	75 (33%) 1.37 (0.9, 2.1)	146 (33%) 1.34 (0.9, 1.9)

*implies subjects who dropped out are considered nonresponders

For PGIC domain: logistic regression model with treatment group as explanatory variable.

The preceding analyses suggest that the positive results of the primary composite "FM pain" responder analysis were not contributed to by MLN's effects on pain or patient's global impression of change.

Even though, per the pre-specified multiplicity adjustment method, there was no difference in composite "FM syndrome" response rates between the MLN and placebo groups, there were numerically more MLN-treated patients than placebo that met this definition of response. Therefore the data were explored to determine whether the observed differences in "FM syndrome" responders were primarily contributed to by effects of treatment on patient function.

Responder Analysis: Function

For the composite "FM pain" and "FM syndrome" endpoints, function response was defined as a decrease in SF-36 PCS score of at least 6 points from baseline. This definition was used to compare the rates of "function only" responders in each of the groups.

There were slightly more "function only" responders in the MLN 100 mg/day and 200 mg/day groups (32% and 31%, respectively) compared to the placebo group (27%). The 95% CIs and the unadjusted p-values show that the inter-group differences did not reach statistical significance. Thus a treatment difference in "function only" responder rates does not – in and of itself - explain the observed differences between placebo and MLN in composite "FM syndrome" responders.

As was discussed previously, the Division prefers the SF-36 PF as a measure of function. Dr. Buenconsejo calculated the change in mean SF-36 PF values for each of the treatment groups. Her analysis showed that, compared to the placebo group, the MLN groups had comparable changes in mean SF-36 PF values as well as ranges in changes of SF-36 PF values.

(Adapted) Statistical Reviewer's Table 37: SF-36 Physical Component Score for Milnacipran Versus Placebo at the 3-Month Landmark – Study FMS-031

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
SF-36 PCS Score		N=223	N=224	N=441
	BOCF†	61 (27%)	71 (32%) 1.28 (0.8, 2.0) p=0.254	131 (30%) 1.18 (0.8, 1.7) p=0.403

†For Composite Syndrome and Syndrome only domain – Sponsor-pre-specified logistic regression model with treatment group, baseline pain, baseline SF36 PCS, baseline pain by treatment interaction, and baseline SF36 PCS by treatment interaction as explanatory variables. The superiority of milnacipran over placebo was tested at the overall median value of baseline pain score and baseline SF36 PCS score for patients included in the model. p-values are unadjusted

Responder Analyses: “Function only” Responder Rates at the 3-Month Landmark (ITT population), based on the SF-36 PF – Study FMS-031

	Placebo	Milnacipran	
	N=223	N=224	N=441
	58 (26%)	51 (23%)	118 (27%)
Mean Pain Score (Range) - BOCF	33 (15 – 55)	32 (15 – 55)	33 (15 – 55)
Baseline	35 (15 – 55)	35 (15 – 57)	36 (15 – 57)
3-month landmark*	-2.1 (-32 – 19)	-2.8 (-27 – 15)	-3.0 (-32 – 11)
Change from Baseline†			

The finding of a difference between the MLN 200 mg/day and placebo composite “FM pain” responder rates, but no difference between the groups with respect to the “pain only” responder rates was further explored. Also explored was the observation that not that many patients met the single criterion for pain responder (i.e. $\geq 30\%$ improvement in pain) than patients who met the composite “FM pain” criteria (i.e. $\geq 30\%$ improvement in pain and PGIC score of 1 or 2). The data were examined for any differences with respect to the magnitude of change in pain intensity for the composite “FM pain” responders versus the “pain only” responders. Perhaps a difference in the distribution of pain scores would provide further insight.

Across all treatment groups, the mean change in pain score (from baseline to study end) for the composite “FM pain” responders was approximately 43 mm, compared to mean pain change of approximately 40 mm for the “pain only” responders. Thus, the “pain only” responders showed slightly less of an improvement in pain than did the composite “FM pain” responders. The composite “FM pain” and “pain only” responders also had a similar range of pain intensity scores at study end, as well as median pain scores at study end.

Thus it appears that the composite “FM pain” responders did have not a greater change in absolute pain intensity than the “pain only” responders, which is consistent with the findings of the change in mean pain and “pain only” continuous responder analyses. This suggests that

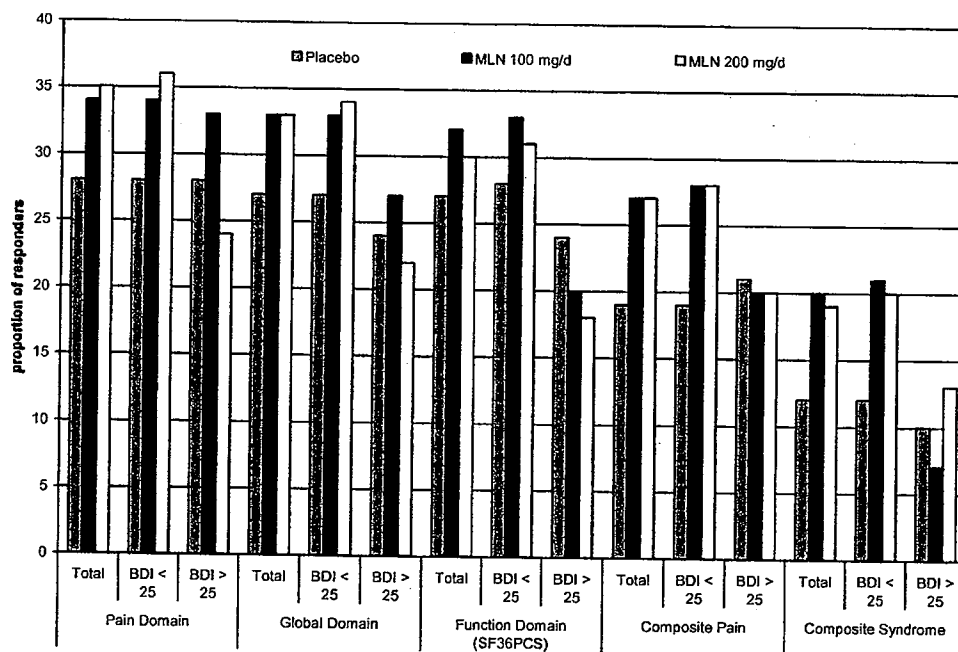
the composite responders' report of an overall feeling of improvement in fibromyalgia (i.e. good PGIC score) may be due to effects of MLN on other aspects of the disease, such as depression.

Responder Analysis: Patients with depression vs. Patients without depression

The UPA population comprised patients without current major depressive episode (based on the MINI) or a BDI score > 25 (moderately severe to severe depression). The BDI score was used to determine whether the proportions of treatment responders varied by depression status using the following BDI categories: (i) BDI > 25; (ii) BDI ≤ 25; (iii) BDI score 0 to 9; (iv) BDI score 10-16; (v) BDI score 17-29; and (vi) BDI score 30-63.

The analysis of response rates for "FM pain," "FM syndrome," as well as "pain only," "function only," and "global only" definitions showed that there was no difference in the proportions of responders for patients with BDI scores > 25 and patients with BDI scores ≤ 25. In general, there were more MLN treatment responders for each definition of response than placebo responders. There was no evidence of a dose response.

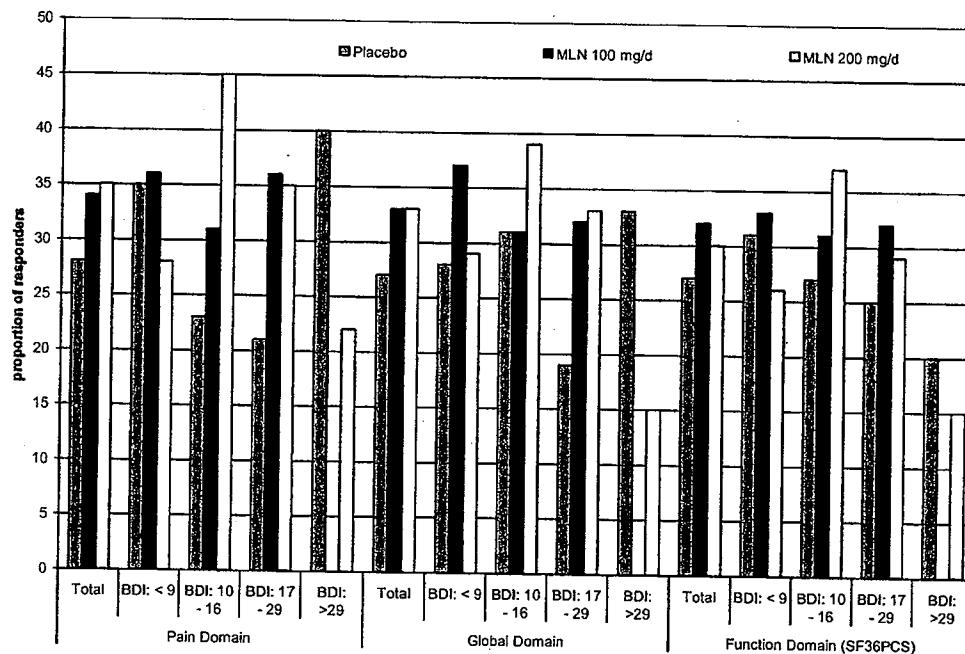
Statistical Reviewer's Figure 36: Responder Analysis at Weeks 14-15 (BOCF), by Baseline BDI score (> 25 vs. ≤ 25) – Study FMS-031



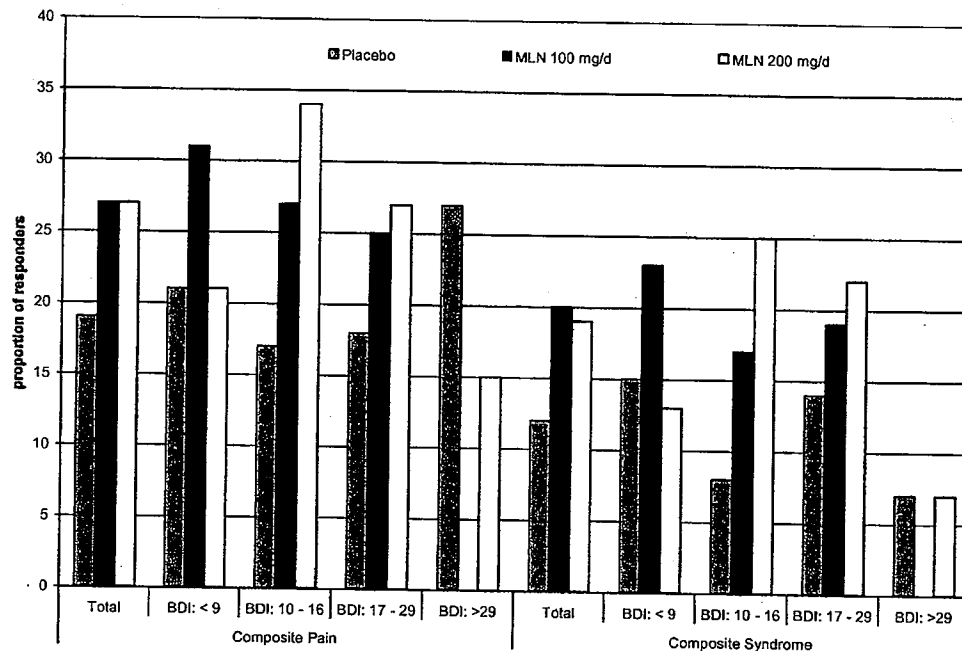
The analysis of response based on the 4 sub-categories of BDI score showed that overall, more MLN patients met criteria for treatment response than did placebo patients. Also, there was no clear difference in response rates between the MLN 100 and 200 mg/day groups. There were relatively similar proportions of responders across the various levels of depression.

The results of the analysis of response rates by baseline depression severity do not support the theory that milnacipran's antidepressant effect contributed to the positive composite responder efficacy findings.

Statistical Reviewer's Figure 39: Responder Analysis at Weeks 14-15 (BOCF), by multiple categories of Baseline BDI score – Study FMS-031



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Efficacy Summary – FMS-031:

Based on the applicant's primary efficacy analysis, only 200 mg/day demonstrated superior efficacy to placebo with respect to the composite "FM pain" endpoint. *Post hoc* analyses of effects of treatment on each of the individual domains of the composite endpoints found that there were no treatment differences in pain and function, and patient global responder rates. Exploration of the data found that differences in baseline pain, duration of FM symptoms, distribution of pain scores at study end, mean pain scores at study end, or baseline depression level do not explain the statistical difference in MLN 200 mg/day composite "FM pain" responder rates but not "pain only" responder rates. This implies that other effects than an effect of MLN on pain are responsible for the observed efficacy of MLN.

Other Analyses – To address efficacy claims

Onset of effect

The Applicant seeks to claim that some patients experienced a decrease in pain within one week of treatment with milnacipran. Notably, in the clinical trials, the dose of MLN was up-titrated over 3 weeks.

Dr. Buenconsejo's analysis found that a separation among the groups in terms of composite responder rates was most apparent starting around Week 3.

Durability of effect

The Applicant seeks to rely on data from study FMS-031, and the two double-blind, dose-controlled extension studies, MLN-MD-04 and FMS-034 to support _____

b(4)

Discussion - Efficacy

Study MLN-MD-02 showed that there were statistically more "FM pain" and "FM syndrome" composite responders in the MLN 100- and 200 mg/day groups than in the placebo group. Study FMS-031 showed that only the 200 mg/day group was statistically superior to placebo with respect to the rates of "FM pain" composite responders. There were numerically more MLN 100 mg/day treatment responders than placebo responders. Across both studies, there were no clear differences between the MLN and placebo groups in terms of effects on pain, function, or patient global impression of improvement. Exploration of the data did not find an explanation for the difference in composite responder rates but absence of a difference in rates of pain, function or global response rates.

Overall, the data show that among patients who consider themselves "improved" or "very much improved," more MLN-treated patients have a decrease in pain compared to placebo patients. Treatment with MLN 100 mg/day and 200 mg/day provides similar results.

Differences in responder rates between the MLN and placebo groups were observed starting at week 3.

8. Safety

Exposure

The Applicant provided an adequate database to support the safety of MLN. The database exceeded the ICH requirements for a new molecular entity intended to treat a chronic indication. The integrated safety database (ISS) for milnacipran is derived from the fibromyalgia trials, as well as depression and generalized anxiety disorder trials that were conducted to support the European marketing application. Altogether, the ISS comprised 2596 patients. There were 1824 patients exposed to MLN in the fibromyalgia trials: 1557 patients in the placebo-controlled efficacy trials and an additional 267 patients in dose-controlled safety

extension trials. Of these, 1109 were treated with 200 mg/day, and 354 were treated for at least 1 year.

The tables below, taken from Dr. Filie's review, summarize the number of patients exposed to MLN and the duration of exposure.

	Number of Subjects			
	Placebo	Milnacipran ^a		
		≤ 50 mg/d	100 mg/d	200 mg/d
Placebo-controlled FMS studies				
FMS021 (12 weeks)	28	24	7	66
FMS031 (27 weeks)	223	0	224	441
MLN-MD-02 (15-29 weeks)	401	0	399	396
Subtotal	652	24	630	903
Dose-controlled FMS extension studies				
FMS034 (6 months)—new exposures	0	0	29	100
MLN-MD-04 (3-9 months)—new exposures	0	0	32	106
Subtotal	0	0	61	206
Total number of FMS patients	652	24	691	1109
Studies in MDD				
C232 F2207-91-MI 08 ^b	131	128	125	130
C233 F2207-91-MI 03 ^b	75	0	0	74
C234 F2207-92-GE 303 ^b	49	0	68	0
C972 F2207-97-GE 302	158	0	156	0
Studies in GAD				
F2207 GE 201	107	24	49	18 ^c
Total number of non-FMS patients	520	152	398	222^d
All patients	1172	176	1089	1331

a Based on the randomized dose group, except for Study FMS021, which is based on the maximal dose attained.

b Included in the MAA.

c 150 mg/d.

d 150 to 200 mg/d.

MDD = major depressive disorder; FMS = fibromyalgia syndrome; GAD = generalized anxiety disorder;
MAA = Marketing Authorisation Application.

(Source: Applicant's Table 5.2-1, Summary of Clinical Safety, Vol. 1, p. 63)

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	Milnacipran			
	Placebo (N = 652)	100 mg/d (N = 684)	200 mg/d (N = 1342)	Total (N = 1824)
Treatment duration, d				
Mean	137.9	143.6	172.5	180.6
SD	69.3	95.0	133.4	144.7
Median	168	164	141	141
Range	1, 260	1, 505	0, 510	0, 529
Treatment duration, n (%)				
≥ 3 weeks	616 (94.5)	624 (91.2)	1217 (90.7)	1650 (90.5)
≥ 7 weeks	550 (84.4)	538 (78.7)	1068 (79.6)	1426 (78.2)
≥ 15 weeks	432 (66.3)	433 (63.3)	788 (51.7)	1074 (58.9)
≥ 27 weeks	296 (45.4)	315 (46.1)	607 (45.2)	822 (45.1)
≥ 12 months	0	25 (3.7)	209 (15.6)	354 (19.4)
Patient-Years Exposure				
	246.1	269.0	633.2	902.1

Based on fibromyalgia studies FMS021, FMS031, MLN-MD-02, FMS034, and MLN-MD-04.

(Source: Applicant's Table 5.2-1, Summary of Clinical Safety, Vol. 1, p. 63)

Deaths and other Serious Adverse Events (SAEs)

Initial NDA submission

There were 2 deaths in the FM trials, neither of which was likely due to MLN treatment: one patient died from pneumonia, and the other from renal cell carcinoma.

In the placebo-controlled FM trials, the incidence of serious adverse events (SAEs) in the placebo treatment group (2.5%) was higher than in the MLN 100mg/day (1.8%) and 200 mg/day (2.0%) treatment arms. The SAEs that occurred with the greatest frequency were in the system organ class (SOC) "Cardiac Disorders:" 0% of the placebo group, 0.8% of the MLN 100 mg/day group, and 0.32 % of the MLN 200 mg/day group. Within this SOC, each preferred term (PT) event occurred only once (incidence of 0.1% each) except for palpitations which occurred twice (0.12%).

The types of SAEs that were considered likely related to MLN treatment were, for the most part, cardiac in nature:

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

There was no clear pattern with respect to the type of SAE and the MLN dose.

Discontinuations due to adverse events (AEs)

Of the 2084 patients enrolled in studies FMS-031 and MLN0MD-02, 34% (708/2084) of patients discontinued from the trials. The highest discontinuation rate occurred in the MLN 200 mg/day group (37.8%), followed by the MLN 100 mg/day (35.2%) and placebo (27.7%) groups. The most common cause for discontinuation was adverse event, and was the highest in the MLN 200 mg/day group (24.1%), followed by the MLN 100 mg/day group (18.8%) and the lowest in the placebo group (9.1%). On the other hand, therapeutic failure was the most frequent cause of discontinuation in the placebo group (10.3%), followed by MLN 100 mg/day (8.2%) and MLN 200 mg/day (7.2%).

The AEs that most commonly resulted in discontinuation (at a rate greater in the MLN arms than in the placebo arm) were nausea, palpitations, depression, heart rate increased, constipation, headache, insomnia, hyperhidrosis, vomiting, dizziness, and fatigue. For the majority of AEs, the rate of discontinuation increased with increasing MLN dose. Table 23 from Dr. Filie's review shows the most frequent adverse events that led to dropout.

Reviewer's Table 23. Incidence of Adverse Events Leading to Discontinuation of at Least 1% of the Patients in the FM Studies

	Placebo	Milnacipran	
	(N = 652)	100 mg/d (N = 623)	200 mg/d (N = 934)
	n (%)	n (%)	n (%)
ADOs	79 (12.1)	143 (23.0)	243 (26.0)
Nausea	4 (0.6)	22 (3.5)	66 (7.1)
Palpitations	4 (0.6)	16 (2.6)	24 (2.6)
Depression	20 (3.1)	10 (1.6)	19 (2.0)
Heart rate increased	1 (0.2)	2 (0.3)	16 (1.7)
Constipation	1 (0.2)	3 (0.5)	15 (1.6)
Headache	1 (0.2)	10 (1.6)	15 (1.6)
Insomnia	5 (0.8)	4 (0.6)	13 (1.4)
Hyperhidrosis	1 (0.2)	5 (0.8)	13 (1.4)
Vomiting	1 (0.2)	3 (0.5)	11 (1.2)

Reviewer's Table 23. Incidence of Adverse Events Leading to Discontinuation of at Least 1% of the Patients in the FM Studies (continued)

Dizziness	3 (0.5)	7 (1.1)	9 (1.0)
Fatigue	7 (1.1)	10 (1.6)	9 (1.0)
Anxiety	4 (0.6)	8 (1.3)	7 (0.7)
Blood pressure increased	2 (0.3)	6 (1.0)	7 (0.7)
Tachycardia	0	6 (1.0)	6 (0.6)

(Source: Applicant's Table 6.4.1.1, Clinical Summary of Safety, Volume 1, p. 121)

120-day Safety Update

Two new Phase 1 studies were included in the 120-day Safety Update. There were no new deaths, SAEs, or discontinuations due to AE in these newly completed studies.

There was one death in an ongoing non-IND study (F02207 GE 302). This is a Phase 3 study in FM patients that being conducted in Europe. This patient was a 46 year-old female on MLN who completed suicide.

Common Adverse Events

In the placebo –controlled FM studies, more patients in the MLN treatment groups reported AEs than did patients in the placebo group: 89% (831/934) in the MLN 200 mg/day group, 89.1% (555/623) in the MLN 100 mg/day group and 82.8 % (540/652) in the placebo arm. Across all treatment arms, the most commonly reported AEs were nausea (37%), headache, (18%), constipation (16%), hot flush (12%), insomnia (12%), and dizziness (11%). There was no clear evidence of a dose-response for the adverse events.

The system organ class (SOC) that presented the most number of AEs was gastrointestinal (GI) disorders, followed by nervous system disorders and psychiatric disorders.

Adverse events related to increased heart rate were reported as palpitations (7% of MLN patients vs. 2% of placebo patients), tachycardia (2% of MLN patients vs. 1% of placebo patients), and heart rate increased (6% of MLN patients vs. 1% of placebo patients). "Blood pressure increased" was reported by 3% of MLN-treated patients compared to 1% of placebo patients.

The table below, taken from Dr. Filie's review, shows the AEs that occurred in at least 2% of patients in the placebo-controlled FM studies.

Table 35. Treatment-Emergent Adverse Events Reported in $\geq 2\%$ of Patients in the Milnacipran Treatment Groups and at a Higher Incidence than Placebo in the FM Placebo-Controlled Studies (Group 1A)

System Organ Class Preferred Term	Milnacipran			
	100 mg/day n = 623 %	200 mg/day n = 934 %	All MLN* n = 1557 %	Placebo n = 652 %
Cardiac Disorders				
Palpitations	8	7	7	2
Tachycardia	3	2	2	1
Eye Disorders				
Vision blurred	1	2	2	1
Gastrointestinal Disorders				
Nausea	35	39	37	20
Constipation	16	15	16	4
Vomiting	6	7	7	2
Dry mouth	5	5	5	2
Abdominal pain	3	3	3	2
General Disorders and Administration Site Conditions				
Chest pain	3	2	2	2
Chills	1	2	2	0
Chest discomfort	2	1	1	1
Infections and Infestations				
Upper respiratory tract infection	7	6	6	6
Investigations				
Heart rate increased	5	6	6	1
Blood pressure increased	3	3	3	1
Metabolism and Nutrition Disorders				
Decreased appetite	1	2	2	0
Nervous System Disorders				
Headache	19	17	18	14
Dizziness	11	10	10	6
Migraine	6	4	5	3
Paraesthesia	2	3	2	2
Tremor	2	2	2	1
Hypoesthesia	1	2	1	1
Tension headache	2	1	1	1
Psychiatric Disorders				
Insomnia	12	12	12	10
Anxiety	5	3	4	4
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	2	2	2	1
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	8	9	9	2
Rash	3	4	3	2
Pruritus	3	2	2	2
Vascular Disorders				
Hot flush	11	12	12	2
Hypertension	7	4	5	2
Flushing	2	3	3	1

(Source: Applicant's Table 6.1.1.1-2, Summary of Clinical Safety, Vol. 1, p. 80)

Data from the blinded, dose-controlled FM extension studies showed that the type and incidence of the commonly reported AEs did not increase with continued dosing (refer to Dr. Filie's review for details).

Notably, the Phase 1 trials that were conducted for the FM development program showed higher rates of nausea, vomiting, and increased heart rate and blood pressure than the Phase 3 trials. In the Phase 1 trials, healthy volunteers were administered MLN doses ranging from 25 to 300 mg in single-dose trials, and up to 375 mg in multiple-dose trials (3 –37 days duration). The studies showed that when MLN is administered without titration, and/or in high doses, there is a considerable incidence of nausea and vomiting. For example, in studies C241 and M146 (studies to evaluate the cardiovascular tolerability of MLN), when patients were given MLN 100 mg BID for 3 days, the incidence of nausea was 65% and the incidence of vomiting was 24%. In contrast, in study MLN-PK-08 (a 9-day study of the effects of digoxin on the PK of MLN), after patients were started on MLN 12.5 mg BID and increased to 100 mg BID, the incidences of nausea and vomiting were 14% and 0% respectively.

Refer to the Clinical Pharmacology review by Dr. Al Habet for details of the adverse event experience in the Phase 1 trials.

Laboratory testing

Laboratory testing was performed in each of the clinical studies, and comprised chemistry, hematology, and urinalysis testing.

The data showed that treatment with MLN did not result in significant changes on any laboratory parameters other than platelets and transaminases.

Platelets

As indicated in the table below, the placebo group had an average decrease in platelets of $2.4 \times 10^9/L$, compared to an increase of 12 and $16 \times 10^9/L$ in the MLN 100- and 200-mg/day groups. Analysis also showed that more MLN patients (approximately 6%) than placebo patients (2.5%) shifted from normal platelet values at baseline to high ($> 400 \times 10^9/L$).

Daily dose (mg)	Platelet values Mean Δ from BL ($10^9/L$)	% patients shift from nl platelet values to to high values (i.e. $> 400 \times 10^9/L$)
PBO	-2.4 ± 47.5	2.5%
MLN 100	12.4 ± 52.3	6.5%
MLN 200	16.1 ± 50.8	6.3%

The observed effects on platelets are not considered to be of major clinical significance. Adverse event data from the FM trials did not show evidence of platelet-related events in

MLN-treated patients, specifically thrombotic events. The foreign labels for MLN describe risks of abnormal bleeding.

Transaminases

Refer to the *Special Safety Concerns – Hepatic effects* section, below.

ECG testing

In the Phase 3 studies, ECG testing was performed only in the MLN-MD-02 study. ECG testing was also conducted in select Phase 1 trials, including a thorough QT (TQT) study.

For a new molecular entity, this extent of ECG testing is relatively limited. However, because of MLN belongs to a class of drugs (NSRIs) that is not typically associated with changes in ECG parameters, and because the considerable foreign experience with MLN does not suggest adverse ECG effects, the available ECG data appear to be sufficient to characterize the effects on cardiac conduction/repolarization

There was no clinically relevant effect of MLN on ECG parameters.

Refer to Section 5 for details of the TQT results.

Special Safety Concerns

i. Cardiovascular effects

Because milnacipran inhibits the reuptake of norepinephrine (NE) and serotonin (5-HT), this may lead to cardiovascular effects such as tachycardia and vasoconstriction (NE effect), and tachycardia, arrhythmias, and vasoconstriction (5-HT effect).

Cardiovascular-related AEs

Refer to Dr. Filie's review for details regarding the frequency and types of CV-related adverse events.

In MedDRA, cardiac-related AEs are coded under the system organ classes: Cardiac Disorders; Investigations; and General Disorders and Administrative Site Conditions. Overall, in the placebo-controlled FM studies, fewer placebo patients (4.1%) than MLN 100 mg/d and MLN 200 mg/d patients (10.6% and 9.6%, respectively) experienced an AE that was coded under the "cardiac disorders" system organ class (SOC). Similarly cardiac-related AEs occurred in the MLN groups than in the placebo group. The types of events that occurred more frequently in the MLN groups than in the PBO groups related to elevations in heart rate and blood pressure. There was no evidence of a dose response.

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

a) Effects on Blood Pressure

Mean change in blood pressure

In the Phase 2 and 3 FM trials, the MLN groups showed a mean increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of the study, whereas the placebo group showed a negligible change in blood pressure.

The mean increase in SBP was 3.1 mmHg among the MLN 100 mg/day patients and 3 mmHg for the 200 mg/day group, compared with a mean SBP decrease of -0.1 mmHg in the placebo group. Similar magnitudes of change were observed for DBP: the MLN 100- and 200- mg/day arms showed a mean DBP increase of 3.1 mmHg in and 2.6 mm Hg, respectively, versus a 0.4 mmHg increase in the placebo group.

Shifts in blood pressure status

The Applicant provided shift analyses, comparing the proportions of patients in the treatment arms that shifted from normal (or abnormal) blood pressure at baseline to abnormal (or even more abnormal) values. Data on shifts at study end and to maximum value were submitted. Because the maximum value data represent the “worst case scenario,” these data are presented here.

The data show that among patients that had a SBP \leq 120 mmHg at baseline, more MLN 100 mg/day and MLN 200 mg/day patients (55% and 57%) than placebo patients (47%) developed a maximal SBP of >120-140 mmHg (i.e. prehypertension). The incidence of shifts to even higher SBP values (>140-160 mmHg and > 160 mmHg) was low, and a considerable difference was not observed across treatment groups.

Among patients that were prehypertensive at baseline by SBP criteria (SBP of >120-140 mmHg), MLN treatment again appeared to confer greater risk of worsened blood pressure. In the placebo group, 30% of placebo patients experienced a SBP value of >140-160 mmHg, compared to 27% and 34% of MLN 100- and 200-mg/day patients.

With regard to DBP, more patients in the MLN 100 and 200 mg/day arms than in the placebo arm who had a normal DBP at baseline (≤ 80 mmHg) experienced a maximal value of >80-90 mmHg: 43% and 46%, respectively versus 39%. Also, among patients with normal DBP at baseline, 5% of placebo patients had a reading of >90-100 mmHg, compared to 14% of MLN 100 mg/day patients and 9% of MLN 200 mg/day patients.

The same type of effect was observed for patients who were prehypertensive at baseline by DBP criteria (>80-90 mmHg). Of the placebo patients, 25% recorded a DBP of >90-100 mmHg, compared to 46% and 41% of MLN 100 and 200 mg/day patients.

The applicant also evaluated the AE data to assess the incidence of hypertension in patients who were normotensive at baseline. Hypertension was defined as:

- An AE report of hypertension
- A change in hypertension medications
- Finding of hypertension by blood pressure (> 140/90 mmHg)

The data show that milnacipran appears to increase the likelihood of developing prehypertension in patients who were previously normotensive. At baseline, the treatment groups were fairly similar in terms of the proportions of patients that had a normal blood pressure. However, at study end, more than twice as many MLN-treated patients than placebo patients met the Applicant's criteria for hypertension. For example, the incidence of hypertension by BP was 7% in placebo patients compared to 20% and 17% of MLN 100 mg/day and 200 mg/day patients.

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

The Applicant also analyzed the BP data for the incidence of sustained hypertension, which was defined as elevated BP on at least three consecutive post-baseline visits. In the placebo-controlled FM studies, 0.3% patients in the placebo arm versus 0.7% in the MLN 100 mg/day

and 0.5% in the MLN 200 mg/day met criteria for sustained hypertension. That is, MLN treatment does not appear to increase the risk of sustained hypertension. analysis of the data from the Phase 3 safety extension trials showed that long-term treatment with MLN is not associated with progressive increases in blood pressure.

Blood pressure in males versus females

Dr. Filie found that altogether, 87 (3.9%) male patients were enrolled in the placebo-controlled fibromyalgia studies. Of these, 23 were treated with 100 mg/day, 32 treated with MLN 100 mg/day, and 32 treated with placebo.

Per Dr. Filie's review:

Notably, [AE reports of] increased blood pressure was more frequent among male patients taking milnacipran versus placebo: whereas 0% of male placebo patients experienced increased blood pressure, 8.7% and 12.5% of the MNL 100 mg/day and 200 mg/day patients, respectively, experienced this AE. Also, increased blood pressure was more frequent in male milnacipran-treated patients than female milnacipran-treated patients. Among females taking MLN 100 mg/day and 200 mg/day, the incidence of increased blood pressure was 3% and 2.2%, respectively.

The Applicant calculated the change in mean BP for both male and female patients, employing a placebo-corrected change from baseline. Forrest found that male patients did not have greater changes in BP than female patients. For SBP, the mean placebo-corrected change from baseline in female patients treated with milnacipran was 2.8 mm Hg; in males it was 1.9 mm Hg. For DBP the mean placebo-corrected change from baseline in females was 3.2 mm Hg and for males it was 3.1 mm Hg. The range of SBP changes in female patients treated with milnacipran (-35, 37) was at least as great as that seen in male patients (-16, 23) treated with milnacipran, and the range of DBP changes in female patients (-30, 28) was at least as great as that seen in male patients (-13, 18).

The Applicant was asked to conduct a comparative analysis of shifts in blood pressure status between males and females. The analyses showed that among females, 13 % in the 100 mg/day group versus 10% in 200 mg/day group shifted from non-hypertension to hypertension (BP > 140/90) status. In the male group, 21% (4 out of 19 patients) in 100 mg/day group versus 30% (7 out of 23 patients) in 200 mg/day group shifted from non-hypertension to hypertension status. Because this gender difference was also seen in placebo treated patients (6% in female patients versus 12% [3 out of 26] male patients), the Applicant argued that factors other than milnacipran might play a role in the shift in hypertensive status.

The Applicant also calculated the proportions of patients that shifted from one BP category to another (Appendices 1 and 2). No clinically significant differences in categorical changes in SBP pressure by gender were observed. In female patients, 25% of the 100 mg/day group, 21% of the 200 mg/day group, and 14% of placebo had a shift upward in SBP category. In comparison, male patients had a shift upward in SBP category in 5/21 (24%) of the 100 mg/day group, 5/31 (16%) of the 200 mg/day group and 6/31 (19%) of placebo group.

Shifts in DBP by gender were also calculated. In female patients, 28% of the 100 mg/day group, 22% of the 200 mg/day group, and 12% of placebo had a shift upward in DBP category. In comparison, male patients had a shift upward in SBP category in 9/21 (43%) of the 100 mg/day group, 13/31 (42%) of the 200 mg/day group and 2/31 (6%) of placebo group.

Due to the small number of male patients in the studies, any gender differences in blood pressure should be cautiously interpreted. Nevertheless, the data suggest that while, on average, MLN treatment does not worsen BP more in males than females, males on MLN therapy appear more likely than females to shift from a lower BP to a higher BP.

b) Effects on Heart Rate

Mean change in heart rate (HR)

In the placebo-controlled FM trials, there was a mean increase in HR of 6.6 bpm for the MLN 100 mg/day and 7.1 bpm for the MLN 200 mg/day groups, compared with a decrease of -0.3 bpm in the placebo group.

Shifts in heart rate status

The analysis of shift from baseline to maximal HR value showed that more patients in the MLN groups had a shift in from normal (< 100 bpm) to abnormal (> 100 bpm) and the greatest increases also occurred in the MLN treatment arms.

Altogether, 0.81% of placebo patients had an increase in HR from normal to > 100 bpm, versus 14.50% of the MLN 100 mg/day and 11.84% of the MLN 200 mg/day groups. Similar low proportions of placebo and MLN patients had HR values > 120 bpm

The data did not show a dose relationship to elevated HR.

Clinical Reviewer's Table 52. Summary of Shift from Baseline to Maximum Post-Baseline Value in Heart Rate- Group 1AA

		Placebo(N=624)				Milnacipran 100 mg(N=623)				Milnacipran 200 mg(N=637)			
Maximum Post Baseline Value		Baseline				Baseline				Baseline			
		<=100	>100-<=110	>110-<=120	>120	<=100	>100-<=110	>110-<=120	>120	<=100	>100-<=110	>110-<=120	>120
	M	614	1	0	0	614	0	0	0	620	0	0	0
<=100	n	609	1	0	0	525	0	0	0	723	0	0	0
	%=n/M	99.19	100			85.5				88.17			
>100-<=110	n	4	0	0	0	63	0	0	0	75	0	0	0
	%=n/M	0.65				10.26				9.15			
>110-<=120	n	1	0	0	0	23	0	0	0	19	0	0	0
	%=n/M	0.16				3.75				2.92			
>120	n	0	0	0	0	3	0	0	0	3	0	0	0
	%=n/M					0.49				0.37			

Using data from approved labels, the Applicant compared the mean effects of MLN on blood pressure and heart rate to that of other NSRIs. The data showed that MLN has a similar magnitude of effect to other approved drugs in its class.

Table 10-1. Comparison of the Effects of Norepinephrine Reuptake Inhibitors on Blood Pressure and Heart Rate

Change in BP or Heart Rate	Venlafaxine (Effexor)		Sibutramine (Meridia)	Atomoxetine (Strattera)		Duloxetine (Cymbalta) Non-FMS		Duloxetine (Cymbalta) FMS ^{a,b}	Milnacipran ^b FMS
	IR 75-375 mg/d	XR 75-225 mg/d	5-20 mg/d	Peds 1.2-1.4 mg/kg/d	Adults 80-100 mg/d	40-120 mg/d	200 mg BID	60-120 mg/d	100-200 mg/d
SBP, mm Hg	NA	NA	1-3	1.5	3	2.1	4.7-6.8	NA	3.1
DBP, mm Hg	1.6-6.3	1.2-2.6	1-3	1.5	1	2.3	4.5-7	3.1	2.4
HR, bpm	NA	NA	4-5	6	5	NA	5-6.8	2.7	7-8

a Source: 2007 ACR Published abstracts (Chappell et al., 2007).

b Not approved for marketing in the United States.

Change in vital signs: Phase I studies

With respect to increased heart rate and blood pressure, two studies designed to evaluate the effects of MLN on cardiac parameters (C241 and M146) showed that in healthy volunteers dosed with MLN 50 mg QD, 100 mg QD, or 200 mg QD, heart rate increased by 10-20 bpm, on average. In the same studies, MLN treatment increased systolic and diastolic blood pressure by approximately 10 mmHg. The studies also showed that the effect of MLN on blood pressure and heart rate progressively increased over the 3-day dosing period. There was no evidence of a dose-response for increased heart rate or for increased blood pressure.

Note that these were short-term studies in which MLN was administered either as a single dose or without titration. Thus it is not surprising that these studies showed greater effects on heart rate and blood pressure than were observed in the Phase 3 trials.

In summary, as was expected, MLN has an effect on CV parameters (blood pressure and heart rate). These effects should be described in the product label for MLN, in the same way that they are for other approved NSRIs.

c) Effects on the QT interval

Refer to Section 5, above.

ii. Effects on mood

As discussed above, depressed mood can occur in patients with fibromyalgia. Suicide is a known risk of depression and certain other psychiatric disorders, and antidepressants – such as MLN - may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. The data from the placebo-controlled efficacy trials were therefore analyzed to determine whether MLN is associated with worsening mood or suicidality in FM patients. Notably, these trials excluded patients with current major depressive episode, moderately severe depression, or who were anticipated to acutely require antidepressant therapy during the trial period.

At baseline, 35% (729/2084) patients in the placebo-controlled fibromyalgia studies had depression. As stated in Dr. Filie's review:

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 group (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 suicidal 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.

The findings of an increased risk of suicidal ideation and psychiatric AE (anxiety, insomnia) – particularly at the higher MLN dose – should be described in the product label.

iii. Hepatic effects

Based on the AE data, MLN did not appear to have an adverse hepatobiliary effect: in the placebo-controlled FM studies, 0.9% of placebo patients had a hepatobiliary-related AE compared to 0.3% of patients in the MLN 100 mg/day and 0.9% of MLN 200 mg/day patients. There were no serious hepatic AEs.

Dr. Filie found that with respect to transaminase levels, MLN was more likely than placebo to result in mildly elevated levels. Per her review, elevations in ALT above the upper limit of normal (ULN) from normal values at baseline were seen in 3.3% of patients receiving placebo, compared to 5.7% of patients on MLN 100 mg/day and 7.3% of patients receiving MLN 200 mg/day.

In terms of AST changes, elevations in AST above the upper limit of normal (ULN) from normal values at baseline were seen in 1.9% of placebo patients versus 3.2% of patients on MLN 100 mg/day and 5.3% of patients receiving MLN 200 mg/day. Among the patients who had a shift upwards in the AST, all had mild shifts (1 – 3 x ULN). No moderate shifts (3-5 x ULN) or large shifts (>5 x ULN) were observed in any of the treatment arms.

There were no cases of bilirubin $\geq 1.5 \times$ ULN. There were 2 patients in the placebo arm (0.3%) versus 0.1% in the MLN 200 mg/day who had increases in bilirubin $> 1 \times$ ULN, and none in the MLN 100 mg/day treatment arms.

There were no patients that met Hy's Law criteria.

In the postmarketing safety database, there were two reports of fulminant hepatitis. However, these cases were confounded by comorbidities to which the hepatitis could be attributed.

The European product labels for MLN describes “rare” occurrence of moderate transaminase elevations. The Japanese label states that hepatic function disorder and jaundice can occur (<0.1%), as well as increased AST, ALT, and γ -GTP. The Japanese label recommends that patients be monitored for these effects.

Because of the finding in the FM database of transaminase elevations with MLN treatment, the US label for MLN should recommend periodic monitoring of transaminases.

iv. Withdrawal/Discontinuation-Emergent Symptoms

The European MDD database includes 2 spontaneous reports of withdrawal symptoms in patients whose MLN dose was either tapered or abruptly discontinued.

Case 1: This patient experienced emotional lability when her MLN dose was decreased from 200 mg/day to 150 mg/day.

Case 2: This patient experienced anguish, insomnia, flush, hot sensation upon sudden discontinuation of her daily MLN 100 mg dose.

The European marketing labels recommend tapering of the MLN dose (“[M]ilnacipran treatment should be discontinued gradually.”) This is usual clinical practice when treating depression.

The Applicant cited a published study in which patients with MDD were treated with either MLN or paroxetine for 6-24 weeks. In this study, both drugs produced withdrawal symptoms upon discontinuation of treatment. Discontinuation of MLN produced anxiety and insomnia,

The FM studies did not incorporate a drug taper, and the AE profile did not suggest emergence of withdrawal symptoms in patients. However, a formal assessment of withdrawal symptoms was not pre-specified in the clinical protocols. Because depression commonly occurs in FM patients, tapering of MLN in this population is also recommended.

v. Drug abuse and dependence

Refer to Section 11 (Other Discipline Consults – Controlled Substance Staff).

Post-marketing experience

The post-marketing experience with milnacipran was derived mainly from patients with depression and consisted of two data sources: post-marketing studies and spontaneous reports. The Applicant estimates that there have been over patient-months of postmarketing exposure to milnacipran in global use.

b(4)

The postmarketing data show that the safety profile in FM patients is similar to that in MDD patients, with the exception of a higher risk of psychiatric AEs in the latter population.

Refer to Dr. Filie’s review for details regarding the postmarketing safety experience.

9. Advisory Committee Meeting

Although milnacipran is a new molecular entity, an advisory committee meeting was not held for this product because it is not the first drug in the class of norepinephrine-serotonin reuptake inhibitors (NSRIs).

10. Pediatrics

On June 19, 2007 the Applicant submitted a Proposed Pediatric Study Request (PPSR). A letter denying the Written Request but granting deferral of pediatric studies in fibromyalgia (until adequate safety and efficacy are demonstrated in the adult population) was faxed to the Applicant on September 11, 2007. However, after the letter was faxed it was determined that it should not have included the decision regarding the deferral of pediatric studies. The letter was not officially mailed to the Applicant, but was maintained in the DFS archive according to CDER policy. The attributes of this letter were changed to Advice. The division was to issue the Applicant a corrected Inadequate Proposed Pediatric Study Request letter.

Since implementation of FDA Amendments Act (FDAAA), a pediatric plan is necessary for this application and during the NDA review cycle, the Applicant was asked to submit a pediatric plan.

The Applicant requested a waiver of studies in FM patients less than 13 years of age because the prevalence of juvenile primary fibromyalgia syndrome (JPFS) in this population is low and the diagnosis is controversial. The Applicant also requested deferral of studies in patients 13-17 years of age until safety and efficacy of milnacipran has been established in adults. The Applicant's proposed pediatric development plan is outlined below.

b(4)

At the time of writing of this memo, the pediatric plan had not yet been reviewed by the Pediatric Review Committee (PeRC).

11. Other Relevant Regulatory Issues

Exclusivity or patent issues of concern

Because a 505(b)(1) application was submitted, there are no patent certification issues for this application. If approved, MLN would be eligible for 5 years of market exclusivity.

Financial disclosures,

There were no financial conflicts.

DSI audits

The final DSI review was not complete at the time of writing of this memo. However, reports from the individual site inspections found no issues.

Other discipline consults

Cardio-Renal Consult

In addition to reviewing the TQT data, the Division of Cardio-Renal Products (DCRP) was asked to review the results of the Phase 1 cardiovascular tolerability studies, C241 and M146. Because of the limited scope of the studies, DCRP also reviewed the adverse events, the post marketing reports, the Investigator's Brochure to characterize the effect of MLN on cardiovascular outcomes.

DCRP's division director, Norman L. Stockbridge, M. D., Ph.D. concluded:

"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."

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.

Refer to Section 8 (Safety-Special Safety Concerns – Cardiovascular Effects) for a discussion of the review by the QT Interdisciplinary Review Team in DCRP.

Controlled Substances Staff (CSS)

CSS concluded that the Applicant supplied insufficient information to adequately assess the abuse potential of milnacipran.

Nevertheless, CSS found that milnacipran is not a controlled substance. Also, based on the presence of a withdrawal syndrome in non-fibromyalgia patients following milnacipran discontinuation (as cited in the proposed drug label), CSS concluded that milnacipran can induce physical dependence.

In its initial review, CSS recommended that the Applicant conduct the following studies as post-marketing requirements, in order to better characterize the abuse potential of milnacipran:

- 1) A receptor binding study should be conducted with F-2800, the N-desethyl metabolite of milnacipran.
- 2) An appropriately-designed self-administration study of milnacipran in rats or monkeys.
- 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 in fibromyalgia patients to characterize the withdrawal syndrome that occurs following milnacipran discontinuation.

Following further discussion with the Division, CSS is currently considering whether the available for this NME are sufficient to allow for more complete assessment of abuse potential data milnacipran following drug approval. Also, CSS is considering whether more detailed epidemiological data regarding foreign abuse patterns would be sufficient to determine the abuse potential of milnacipran. CSS' final decision had not been made at the time of this review.

Division of Medication Error Prevention and Analysis (DMEPA) (labeling)

DMEPA has no objections to the use of the proprietary name, Savella, for this product at this time.


DMEPA noted that the Applicant proposed various starter package configurations, which include a starter pack (to be dispensed by the pharmacist) and a patient starter kit (to be provided by a prescriber) in 2 week ☐ and 4 week titration regimens. The only apparent difference between these regimens (besides their distribution path) is the length of the maintenance phase.

DMEPA also noted that, based on the the product package insert labeling that the patients would need monitoring and/or feedback with the prescriber due to the adverse effect profile for this drug, and to find the most appropriate maintenance dose. Given this, DMEPA questioned the need to have the longer maintenance phase that is provided with the ☐ 4 week starter kit.

b(4)

Finally, DMEPA questioned the utility of the 10 count sample, in view of the need for titration of this drug and the chronic nature of treating fibromyalgia. Ten tablets of a single strength cannot meet the titration recommendations and is not enough to provide chronic pain management.

DMEPA requested that the Applicant:

- Provide a rationale for having multiple packaging configurations (i.e., the pack versus the kit, and the 2 week  versus 4 week offerings).
- Provide the patient criteria that a prescriber would use in choosing the 2- or 4 week starter kit.
- Provide a rationale for the longer maintenance phase.
- State the role for of the 10 count sample.

b(4)

At the time of this review, resolution of these issues was still in progress.

Division of Drug Marketing, Advertising, and Communication (DDMAC)

DDMAC had no objects to the proprietary name, Savella.

General comments about the content of the originally proposed label were provided to the Applicant.

12. Labeling

The proposed label is appropriately in Physician Labeling Rule (PLR) format.

The Applicant's proposed proprietary name, Savella, is considered acceptable.

Refer to section 11, above, regarding the outstanding carton/container labels identified in the DMEPA review.

At the time of this review, the adequacy of the Applicant's abuse liability studies was still being evaluated by the CSS. The current proposed label does not include a Drug Abuse and Dependence section. This section of the label cannot be finalized until the final review by CSS.

Milnacipran is and NSRI and has antidepressant properties. In the US, all antidepressants have boxed warnings and a Medication Guide that inform both prescribers and patients of the risk of worsened mood and suicide in treated patients. The MLN label for the FM indication should also have a boxed warning and a Medication Guide (see Section 13, below).

Because the Applicant demonstrated efficacy based on a composite responder endpoint that incorporated effects on patients' pain, function, and overall (global) status, the clinical studies section of the label should describe the effects on all of these domains.

The treatment indication should be "treatment of fibromyalgia."

The Dosing and Administration section should recommend gradual discontinuation (tapering) of MLN. Because a specific drug taper schedule was not studied in the clinical trials, one cannot be recommended in the label.

The approved FM label should include all important/relevant safety information from the foreign labels, including pharmacodynamic drug interactions.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of this application for MLN as a treatment for fibromyalgia in adults, pending satisfactory resolution of the outstanding abuse liability and labeling issues.

- Risk Benefit Assessment

MLN treatment results in a greater proportion of patients who report improvement as based on assessments of pain, function, and global "overall" status compared to placebo patients. Among patients who report feeling "improved" or "very much improved," more MLN-treated patients decreased pain compared to placebo-treated patients. Treatment with MLN 100 mg/day and 200 mg/day produces similar efficacy results.

Patients treated with MLN are likely to experience gastrointestinal AEs (nausea) as well as cardiovascular effects (increased heart rate and blood pressure). Development of prehypertension or hypertension is more likely in MLN-treated patients compared to placebo patients. Prolonged MLN treatment does not result in even greater increases in blood pressure. Elevations in heart rate can result in clinical adverse events (e.g. palpitations). The average magnitudes of effect of MLN on heart rate and blood pressure are similar to other approved NSRIs.

MLN treatment increases the risk of psychiatric adverse event in patients with depression at baseline: anxiety, insomnia, depression, and suicidal ideation.

MLN treatment also is associated with mild elevations in transaminases (AST and ALT).

The effects of MLN on heart rate and blood pressure did not appear to increase with increased dose (i.e. there was no dose response). However, a dose response was suggested for elevated transaminases and risk of psychiatric AEs.

Effects on mood, heart rate, blood pressure, and transaminases can be monitored, and tend to resolve with discontinuation of study drug.

Overall, in certain patients with FM, the benefits of MLN outweigh its risks. The recommended MLN dose is 100 mg/day. Treatment with 200 mg/day may be necessary for some patients.

- Recommendation for Postmarketing Risk Management Activities

Milnacipran belongs to the class of norepinephrine-serotonin reuptake inhibitors (NSRI) antidepressants. In the US, all approved antidepressants have language in the package insert describing the increased risk of suicide and depressed mood in pediatric patients – regardless of whether the patients are prescribed these products for depression. The approved product labeling for all antidepressants also includes a Medication Guide for patients.

Patients with FM commonly also have depression. Therefore MLN treatment may have an antidepressant effect in these patients, putting them at risk for suicide and depressed mood. The AE experience in FM patients shows that these events did occur more frequently in MLN-treated patients than in placebo-treated patients.

Under the Food and Drug Administration Amendments Act (FDAAA), a new Medication Guide qualifies as Risk Evaluation and Mitigation Strategies (REMS). As such, the Applicant was notified that a REMS is required for this application, in the form of a Medication Guide.

- Recommendation for other Postmarketing Study Requirements and Commitments

The following Phase IV requirements must be met upon approval of milnacipran for marketing

Pediatric studies

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients are required to contain an assessment of the safety and effectiveness of the product in pediatric patients, unless this requirement is waived or deferred.

The Division generally waives the pediatric study requirement for FM studies in patients aged 0-12 years, and is deferring pediatric studies of milnacipran for the treatment of fibromyalgia in pediatric patients aged 13-17 years.

Pregnancy registry and Lactation study

Fibromyalgia is predominantly a diagnosis of women. The clinical trial and foreign post-marketing data on pregnancy outcomes in pregnant women are insufficient to assess the signal of a serious risk of adverse reactions in a fetus exposed to milnacipran, or to identify an unexpected serious risk to the nursing infants of women who are treated with milnacipran.

Therefore the Applicant should develop and maintain a prospective, observational pregnancy registry study, conducted in the United States, that compares the pregnancy and fetal outcomes of women exposed to milnacipran during pregnancy to an unexposed population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will also be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA acknowledges that sufficient data has been collected.

The Applicant should also conduct an open-label, single dose, pharmacokinetic clinical study in healthy lactating women. Concentrations of milnacipran should be assessed in maternal plasma and breast milk, so as to estimate potential infant exposure.

Ames assay

Because the Applicant did not provide certificate of analysis for the drug used in the Ames assay, the results of this study cannot be considered definitively negative. The Ames assay should be repeated, using a clinical batch for milnacipran and the certificate of analysis for this batch should be provided.

- Recommended Comments to Applicant

Pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are deferred for this application. They are considered postmarketing study requirements, as follows:

Deferred pediatric study under PREA for the management of fibromyalgia in pediatric patients ages 13 to 17.

A lactation study to assess levels of milnacipran in breast milk and to estimate infant exposure is required postmarketing. The study shall be designed as follows:

A single dose, pharmacokinetic, open-label, clinical study in healthy lactating women.

Concentrations of pregabalin will be assessed in maternal plasma and breast milk so as to estimate potential infant exposure.

Effects of MLN on pregnancy outcomes have not been fully investigated. The Applicant should evaluate the safety of MLN in pregnant patients with fibromyalgia, through such mechanisms as a pregnancy registry study that compares pregnancy outcomes in MLN-exposed patients versus a non-exposed population.

The Ames assay submitted in the NDA could not be considered definitively negative. The Ames assay should be repeated, using a clinical batch for milnacipran, and the certificate of analysis for this batch should be provided.

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Appendix 1: Systolic Blood Pressure (SBP) shift from baseline to study end, by Sex – Placebo controlled FM studies

Table 4
Summary of Shift from Baseline to End of Study in Systolic Blood Pressure
All Double-blind Placebo-controlled Fibromyalgia Studies (Group 1A)
By SEX
Safety Population

Female

End of Treatment	Placebo (N=620)				Milnacipran 100 mg (N=600)				Milnacipran 200 mg (N=902)			
	Baseline				Baseline				Baseline			
	<=120	>120-<=140	>140-<=160	>160	<=120	>120-<=140	>140-<=160	>160	<=120	>120-<=140	>140-<=160	>160
M	288	270	48	4	269	261	60	3	420	397	61	3
n	226	65	0	0	162	41	1	0	294	72	4	0
%=n/M	78.47	24.07			60.22	15.71	1.67		70	18.14	6.56	
>120-<=140												
n	61	180	30	1	104	185	27	2	123	271	30	0
%=n/M	21.18	66.67	62.5	25	38.66	70.88	45	66.67	29.29	68.26	49.18	
>140-<=160												
n	1	25	17	1	3	35	28	1	3	51	25	1
%=n/M	0.35	9.26	35.42	25	1.12	13.41	46.57	33.33	0.71	12.85	42.62	33.33
>160												
n	0	0	1	2	0	0	4	0	0	3	1	2
%=n/M			2.08	50			6.67			0.76	1.64	66.67

(Source: Applicant's Table 4; Aug 11 2008 response to FDA information request (8/6/08))

Appendix 1: Systolic Blood Pressure (SBP) shift from baseline to study end, by Sex – Placebo controlled FM studies

Table 5
Summary of Shift from Baseline to End of Study in Diastolic Blood Pressure
All Double-blind Placebo-controlled Fibromyalgia Studies (Group 1A)
By SEX
Safety Population

Female

End of Treatment	Placebo (N=620)						Milnacipran 100 mg (N=600)						Milnacipran 200 mg (N=902)					
	Baseline						Baseline						Baseline					
	<=80	>80.<=90	>90.<=100	<=110	>110	>100.<=110	<=80	>80.<=90	>90.<=100	<=110	>110	>100.<=110	<=80	>80.<=90	>90.<=100	<=110	>110	>100.<=110
M	437	152	21	0	0	384	192	16	1	0	613	242	26	0	0			
n	375	61	2	0	0	252	49	1	0	0	456	66	4	0	0			
%n/M	85.81	40.13	9.52			65.63	25.52	6.25			74.39	27.27	15.38					
>80.<=90	58	84	14	0	0	118	111	5	0	0	147	144	9	0	0			
%n/M	13.27	55.26	66.67			30.73	57.81	31.25			23.98	59.5	34.62					
>90.<=100	4	7	3	0	0	14	32	8	1	0	10	28	11	0	0			
%n/M	0.92	4.61	14.29			3.65	16.67	50	100		1.63	11.57	42.31					
>100.<=110	0	0	2	0	0	0	0	2	0	0	0	3	1	0	0			
%n/M			9.52					12.5				1.24	3.85					
>110	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0			
%n/M												0.41	3.85					

(Source: Applicant's Table 5; Aug 11 2008 response to FDA information request (8/6/08))

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/s/

Mwango Kashoki
9/14/2008 09:31:54 PM
MEDICAL OFFICER