CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-256

MEDICAL REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 2, 2008

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
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To: Diana Walker, PhD
Regulatory Project Manager
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Subject: QT-IRT Consult to NDA 22-256

This memo responds to your consult to us dated 21 August 2008 regarding the sponsor's responses to FDA comments on Study MLN-PK-10, entitled: An Evaluation of the Safety and Tolerability of Sequential Multiple-Dose Regimens of Milnacipran HCl and the Effect of the Maximum Tolerated Dose on Cardiac Repolarization in Healthy Subjects.

The QT-IRT received and reviewed the following materials:

- Your consult
- Responses to the FDA Discipline Review Letter dated 23 July 2008
- QT-IRT Review of Study MLN-PK-10 dated 18 June 2008

1. Background

A part of the NDA application for milnacipran, Forest Laboratories, Inc. submitted a 'thorough QT' study. The QT-IRT reviewed the study and provided comments to DAARP in a consult dated 18 June 2008. In our opinion, there were several limitations to the study which decreased our confidence in the study results. The main limitations were:

(1) At a dose of 300 mg bid, milnacipran increased the heart rate by a mean of 22 bpm. The sponsor derived an individual-specific heart rate correction factor (QTcNi) using interval data collected at rest on day -1. This is not 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. According to the sponsor's analysis, the mean increase in ΔΔQTcNi is -5 (-9.4, -0.08) ms. If, however, the same

analysis is performed using QTcF, the mean increase in ΔΔQTcF is 7.7 (3.5, 12.0) ms. We used QTcF in our analysis of the data.

(2) The study is 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 of around 5 ms.

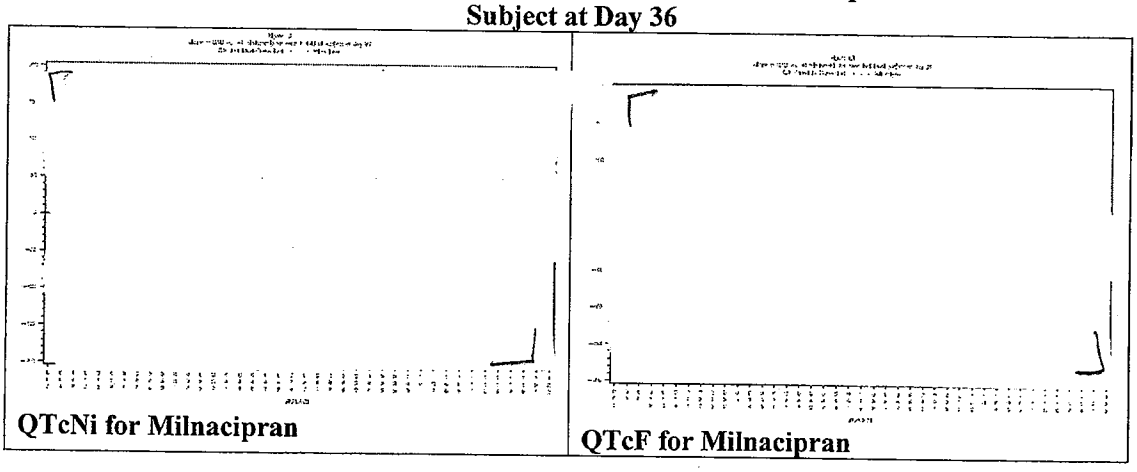
2. Sponsor's Submission

The sponsor performed additional analysis to address each of the FDA comments. Below we have presented highlights of the sponsor's response to each comment and whether we agree or disagree.

2.1 Sponsor's Responses to FDA Comment 1

"To assess the adequacy of the various correction methods, the slopes of QTc vs. RR interval were plotted for each individual subject at Day 38 by treatment group based on both individual-specific correction method and the Fridericia method (Figures 1.1 to 1.4). These plots indicate that the individual-specific correction method tends to under-correct the QT intervals for milnacipran subjects as evidenced by the positive slopes after the correction, while the Fridericia method tends to over-correct the QT intervals for both the milnacipran and placebo subjects. Therefore, these graphs indicate that the QTc Fridericia does not yield a more correct measurement than the QTc individual and, therefore, the QTcF results do not invalidate the conclusion that a 10 ms increase in QTc has been ruled out."

Sponsor's Figure 1.1 to Figure 1.4: Slope of QTc vs. RR Relationship for Each Individual Subject at Day 36



QTcNi for Milnacipran | **QTcF for Milnacipran**

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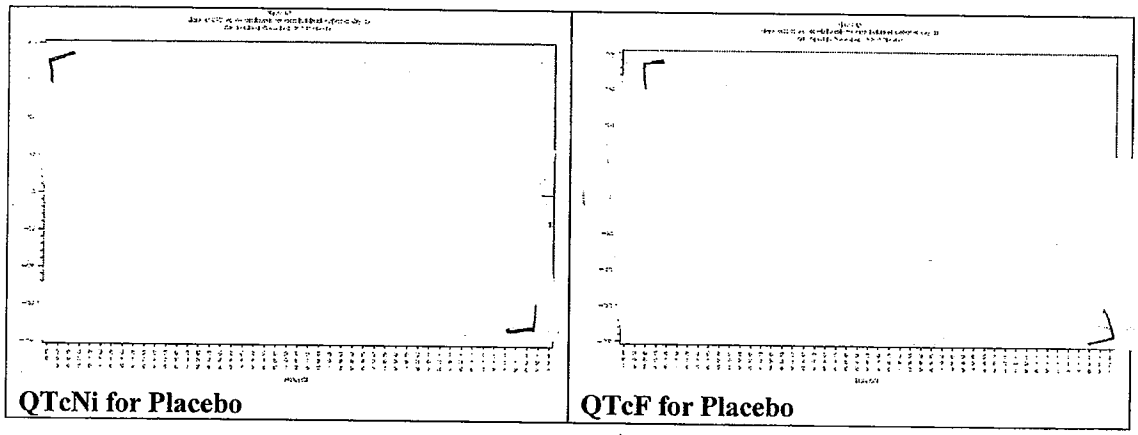


QTcNi for Placebo **QTcF for Placebo**

b(4)

Reviewer's Comments: We agree that neither QTcNi nor QTcF is an appropriate heart rate correction method because neither correction method completely removes the QT/RR relationship in all subjects. As stated in the original review, QTcF corrects for the heart rate more sufficiently than QTcNi when pooling all treatment from all subjects (see section 5.1 of QT-IRT Review, dated 18 June 2008). However, when the data are stratified by treatment group, QTcF corrects the heart rate effect more efficiently for milnacipran as summarized in FDA Table 1. The sponsor's QTcNi is better for placebo data as shown in FDA Table 2.

FDA Table 1. Sum of Squares of Slopes for Milnacipran (Selected QTc vs. RR)

Dependent QT/QTc Variable	N	Average of Sum of Squared Slopes
QT	40	0.0238
QTcB	40	0.0238
QTcF	40	0.0039
QTcNi	40	0.0045

FDA Table 2. Sum of Squares of Slopes for Placebo (Selected QTc vs. RR)

Dependent QT/QTc Variable	N	Average of Sum of Squared Slopes
QT	48	0.0135
QTcB	48	0.0179
QTcF	48	0.0035
QTcNi	48	0.0017

"To address the issue of drug-induced heart rate increase, and the non-linearity of the QT/RR relationship at higher heart rates, piecewise individual-specific corrections were calculated based on a dichotomous cut of the RR interval data at 800 ms (corresponding to a heart rate of 75 bpm). Specifically, for each subject, linear regression models QT =ai + bi*RR were fit using baseline (Day -1) data separately for RR $\leq$ 800 ms and for RR > 800 ms. Following that, the post-baseline (Day 38) QT interval was corrected using the formula QTcNi=QT+bi*(1000-RR) which included the appropriate QTcNi based on whether the post-baseline RR interval was $\leq$ 800 ms or > 800 ms.

"The results of the analysis based on the piecewise individual correction method are summarized in Table 4."

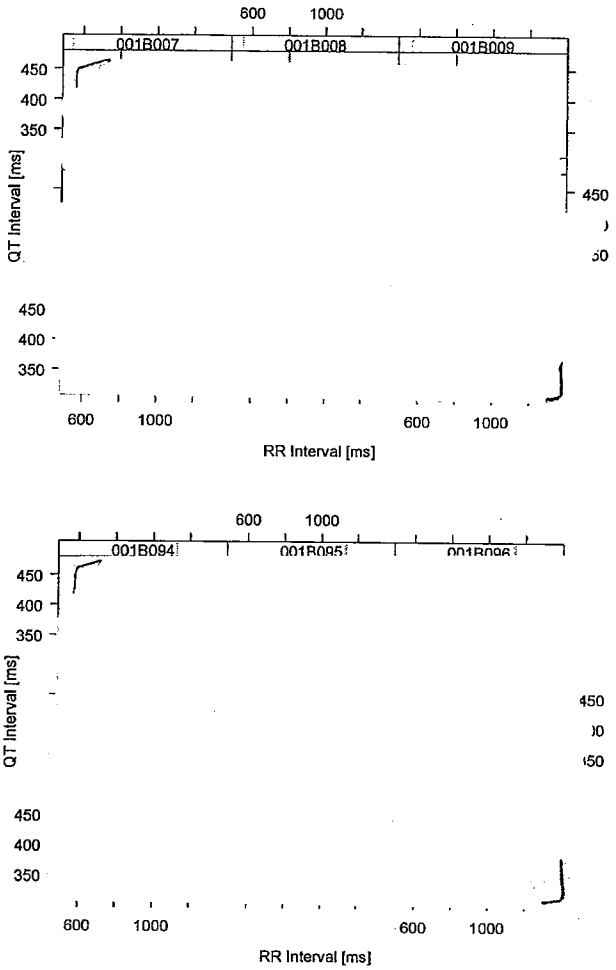
Table 4. **Change From Time-Matched Baseline to Day 38 in QTcNi Based on Piecewise Individual Correction**

	Placebo	*Milnacipran*	*Milnacipran - Placebo*	
Time (h)	*Adjusted QTcNi Change from Baseline Mean±SEM (ms)[a]*	*Adjusted QTcNi Change from Baseline Mean±SEM (ms)[a]*	*Baseline-adjusted QTcNi Difference (ms)[a]*	*90% CI[a]*
1	-1.83 ±3.57	-4.52 ± 3.81	-2.69	-11.48, 6.09
2	-3.21 ±3.02	-2.35 ± 3.21	0.86	-6.58, 8.31
2.5	-1.94 ± 2.88	-3.05 ± 3.07	-1.12	-8.24, 6.01
3	-1.45 ± 2.91	-3.88 ± 3.08	-2.43	-9.6, 4.75
4	-2.32 ± 2.51	-6.33 ± 2.66	-4.02	-10.25, 2.21
6	-5.82 ± 3.37	-13.89 ± 3.66	-8.07	-16.45, 0.32
12	-1.22 ± 4.15	-15.84 ± 4.45	-14.62	-24.83, -4.41

a Based on mixed effect model with treatment group, gender, time and treatment group-by-time interaction as factors, age and mean baseline value as covariates, and unstructured covariance matrix for within subject observations; Baseline is Treatment B2, Day -1 for placebo and Treatment B1, Day -1 for milnacipran.

Reviewer's Comments: Using a piecewise correction approach is still inadequate. For some subjects (e.g. 001B004, 001B002), the baseline RR observations (Green = Day -1) are all greater than 800 ms, whereas RR intervals from the treatment group (Red = Day 38) are all less than 800 ms. Therefore, it is impossible to calculate the QTcNi based on the sponsor's proposed piecewise linear regression method with a cutoff RR of 800 ms. Other subjects have baseline RR intervals ≤800 ms; however, the range of baseline RR intervals is too narrow to cover the entire RR range observed in treatment group. Furthermore, the QT and RR linear relationship derived from the baseline data appears to have a different slope from the treatment group (see subjects 001B090 and 001B089). Therefore, it is not appropriate to extrapolate the QTcNi and RR relationship obtained from baseline group using the piecewise approach.

FDA Figure 1 Individual QT vs RR Plots for a Random Subset of 18 Subjects (All Treatments)
Green = Day -1; Blue = Day 1; Red = Day 38



b(4)

b(4)

"Post hoc concentration-QTc analyses were performed for the ΔΔQTcNi (derived by original analysis) and ΔΔQTcF versus milnacipran concentration relationships (Milnacipran Concentration Plots). These analyses indicated that at the highest therapeutic dose, 100 mg BID (mean C_{max} of 0.54 μg/mL), the predicted QTcF change for milnacipran relative to placebo is 2.7 ms with a 90% CI of -0.09, 5.5 ms. The results of these analyses are presented in Table 5. Furthermore, at the mean C_{max} of 1.908 μg/mL the upper CI for ΔΔQTcF was determined to be less than 10 ms (7.83 ms), again indicating that MLNPK-10 is a negative thorough QT/QTc study."

Table 5. ΔΔQTc vs Milnacipran Concentration Relationship and Predicted ΔΔQTc at C_{max}

	Individual Correction Method	*Fridericia Correction*
Regression Equation	*-15.19+4.05 x Concentration*	*1.61 – 2.05 x Concentration*
Mean (90% CI) ΔΔQTc at C_{max} =0.54 µg/mL	-13.01 (-17.52, -8.50)	2.72 (-0.09, 5.53)
Mean (90% CI) ΔΔQTc at C_{max} =1.908 µg/mL	-7.47 (-10.94, -3.99)	5.53 (3.23, 7.83)

Reviewer's Comments: Concentration-QT analysis results based on the original QTcNi are difficult to interpret. If milnacipran shortens the QTc interval as the sponsor claims then one would expect a negative slope. As shown in the Sponsor's Table 5, the slope is positive which means the QTc interval increases with higher milnacirpran concentrations. This analysis further supports that the QT-RR correction factor is not adequate.

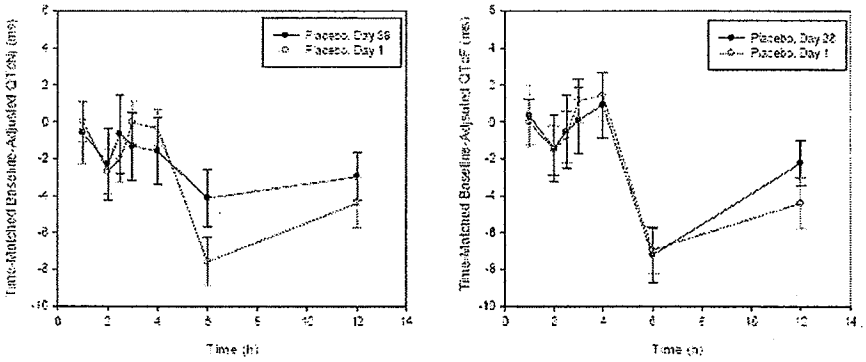
2.2 Sponsor's Response to FDA Comment 2

2.2.1. Timing of the Moxifloxacin Treatment Relative to Milnacipran

"Although moxifloxacin treatment was not administered concurrently with milnacipran, the sponsor does not believe that there would be a difference in effect of a single dose of moxifloxacin on the QTc on Day 1 as opposed to Day 38. Experimental conditions were similar between Days 1 and 38. For example, meals were administered at the same time and subjects were required to be supine for at least 6 minutes prior to each ECG timepoint evaluation.

"Since QTc data are available from the groups receiving placebo at the beginning (Day 1; Treatment B1) and the end (Day 38; Treatment B2) of the study, the effects of time (as extrapolated from these two timepoints in the study) on the QTc interval in these placebo treated groups were further examined. A comparison of the two placebo groups showed similar changes in mean QTc change from time-matched baseline during the course of the day examined (Figure 1). Thus, there is consistency of the QTc behavior over the duration of the study. Extrapolating from these data, one would not expect a difference in QTc response to an active control treatment between the study start and end (Days 1 and 38).

Figure 1. Time-Matched, Baseline-Adjusted QTc Intervals (Mean ± SE) Following Administration of Placebo on Days 1 and 38 of the Study



"To further support the lack of effect of study day on the moxifloxacin effect on QTc, an additional analysis of the baseline adjusted moxifloxacin effect on QTc was performed. The prespecified assessment performed in study MLN-PK-10 evaluated the change in time-matched baseline-adjusted QTc intervals of moxifloxacin from placebo using Treatment B1, Day 1 placebo data. A post hoc, additional analysis using Treatment B2, Day 38 as placebo indicates similar changes in time-matched baseline-adjusted QTc intervals of moxifloxacin from placebo. This further supports the similarity of the Day 1 and Day 38 placebo groups (Table 2) and the lack of effect of study day on the QTc.

Table 2. Mean Change (90% CI) in Time-Matched Baseline-Adjusted QTc of Moxifloxacin from Placebo

	QTcNi		*QTcF*	
Time (h)	*Day 1 Placebo*[a]	*Day 38 Placebo*[b]	*Day 1 Placebo*[a]	*Day 38 Placebo*[b]
1	0.30 (-2.65, 3.25)	1.71 (-1.32, 4.74)	1.16 (-2.06, 4.39)	0.68 (-2.51, 3.86)
2	3.91 (1.19, 6.64)	4.30 (1.08, 7.53)	5.47 (2.47, 8.47)	5.23 (2.31, 8.15)
2.5	4.57 (1.56, 7.59)	3.70 (0.53, 6.86)	4.61 (1.34, 7.87)	4.48 (1.58, 7.38)
3	4.57 (1.88, 7.26)	6.72 (3.45, 9.98)	7.13 (4.63, 9.62)	8.94 (5.72, 12.16)
4	5.32 (2.79, 7.86)	7.85 (4.90, 10.81)	6.44 (3.76, 9.13)	8.39 (5.64, 11.14)
6	5.97 (2.88, 9.07)	4.08 (1.35, 6.82)	7.11 (4.04, 10.17)	7.72 (5.16, 10.29)
12	5.85 (2.81, 8.90)	5.23 (2.86, 7.61)	7.32 (4.22, 10.41)	4.64 (2.29, 7.00)

a Placebo from Treatment B1; across group comparison

b Placebo from Treatment B2; within-subject group comparison

Reviewer's Comments: In general, it is more optimal to evaluate both moxifloxacin and milancipran around the same time in order to avoid the potential long-term shifting on ECG observations. For this particular study, we agree with you that your data do not demonstrate that there is much difference of moxifloxacin QTc (both QTcNi and QTcF) change from both Day 1 placebo and Day 38 placebo.

In terms of placebo time profile, it appears that QTcF demonstrates more consistent results over time (there is about 4 ms difference at 6 hr post dose between Day 1 placebo and Day 38 placebo if using QTcNi).

2.2.2. QT-Moxifloxacin Relationship

"The slope of the C-QT relationship in Study MLN-PK-10, 3.6 ms per µg/mL for QTcNi and 5.5 ms per µg/mL for QTcF is in agreement with reported values and predicts a mean change at the targeted C_{max} of moxifloxacin (3.1 µg/mL) in line with many reports (Garnett et al, 2008; Darpo et al., 2006). Thus, QTc prolongation observed for moxifloxacin in Study MLN-PK-10 is consistent with the reduced plasma exposure of moxifloxacin that was obtained in this study, possibly due to over-encapsulation. This provides additional evidence that assay sensitivity was achieved in study MLN-PK-10."

Table 3. ΔΔQTc vs Moxifloxacin Concentration Relationship and Predicted ΔΔQTc at C_{max}

	Individual Correction	*Fridericia Correction*
Regression Equation	*0.58+3.65 x Concentration*	*-1.02 + 5.49 x Concentration*
Mean (90% CI) ΔΔQTc at C_{max} =1.7319 µg/mL	6.70 (4.07, 9.32)	8.49 (6.08, 10.90)
Mean (90% CI) ΔΔQTc at C_{max} =3.1 µg/mL	11.69 (6.98, 16.39)	16.01 (11.58, 20.44)

Reviewer's Comments: Based on the statistical criteria that the lower limit of the two-sided confidence interval is ≥ 5 ms, moxifloxacin failed to demonstrate assay sensitivity. This is caused by the decrease in exposure; the mean C_{max} is 1.7 µg/ml which is lower than the expected mean of ~3 µg/ml. Furthermore, the time-course of mean plasma moxifloxacin concentrations is indicative of a slower release / absorption rate as evidenced by a prolonged median T_{max} of 4 hours (range: 1 to 6 hours). A slower release / absorption rate and apparent decrease in exposure could have been caused by over-encapsulating the moxifloxacin tablet to maintain blinding and /or administering moxifloxacin with food. The exposure-response relationship was, however, consistent with other studies that we have reviewed. Thus, we concluded that the lower moxifloxacin response is expected for the observed exposures.

QT-IRT Comments for DAARP

1. The study was not designed adequately to correct the QT interval for heart rate. The range of heart rates collected during baseline is significantly lower than the range observed following milnacipran treatment; the mean increase in heart rate was 22 bpm with the supratherapeutic dose (300 mg bid x 38 days). Based on our analysis of the QT/RR data across all treatment arms, QTcF is a better than the sponsor's QTcNi in correcting the QT for heart rate.
2. We do agree with the sponsor that QTcF has a tendency to over-correct the QT interval for heart rate, i.e., QTc will be larger at higher heart rates, and QTcNi has a tendency to under-correct, i.e., QTc will be smaller at higher heart rates. Therefore, one can view QTcF as a 'conservative' estimate of the heart-rate corrected QT interval.
3. Based on QTcF, the maximum mean increase in QTc is 8 ms (90% CI: 3.5, 12.0) ms for milnacipran 300 mg bid. The dose level provides exposures that are 3- to 4-fold greater than the highest clinical dose of 100 mg bid. Exposure-response analysis using ΔΔQTcF gives a shallow but statistically significant slope of 3 ms per µg/ml milnacipran (see section 5.3.1 of the original review). Based on this relationship, it expected that milnacipran will not significantly increase the QTcF interval over the therapeutic exposure range. For example, the expected mean C_{max} in a severe renal impaired patient

taking milnacipran 100 mg bid is 1092 ng/ml [based on a 2.4-fold increase in C_{max} in subjects with severe renal impairment (source: Sponsor's Highlights of Clinical Pharmacology) and a mean C_{max} of 455 ng/ml for 100 mg bid (source: study F2207M146)]. Based on the exposure-response relationship, the expected increase in QTcF is 3.5 ms.

4. We recommend the results of QTcF are used for labeling. We defer all labeling decisions to the clinical review division.

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Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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CLINICAL REVIEW

Application Type	NDA
Submission Number	22-256
Submission Code	N
Letter Date	December 18, 2007
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PDUFA Goal Date	October 18, 2008
Reviewer Name	Jane Filie, M.D.
Review Completion Date	July 17, 2008
Established Name	Milnacipran
(Proposed) Trade Name	Savella®
Therapeutic Class	NSRI
Applicant	Forest Laboratories, Inc.
Priority Designation	S
Formulation	Tablets
Dosing Regimen	50 mg BID and 100 mg BID
Indication	Fibromyalgia
Intended Population	Fibromyalgia

Clinical Review
Jane Filie, M.D.
NDA 22-256
Savella® (milnacipran)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of milnacipran 100mg/day and 200 mg/day for the treatment of fibromyalgia.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No specific risk management steps beyond the product labeling are recommended at this time.

1.2.2 Required Phase 4 Commitments

The following are the required Phase 4 commitments:

- The Applicant will need to conduct studies in the pediatric population 12 years of age and older.
- The Applicant will need to conduct another thorough QT (TQT) study as the one submitted in the NDA does not adequately elucidate the effect of MLN on the QT interval.
- The Applicant will need to conduct an Ames assay using the clinical batch.
- CSS recommends the following studies:
  - A receptor binding study with F-2800, the N-desethyl metabolite of milnacipran. If the receptor binding study demonstrates significant binding at sites associated with abuse potential, then animal abuse studies will need to be conducted with the metabolite.
  - An appropriately-designed self-administration study with MLN should be conducted in rats or monkeys including a drug with known abuse potential as a positive control.
  - A human abuse potential study may be required depending on the results of the self-administration study and the metabolite study.
  - A prospective human physical dependence study in FM patients to characterize the withdrawal syndrome that occurs following discontinuation of MLN.

1.2.3 Other Phase 4 Requests

The Applicant may wish to explore the efficacy of MLN at a dose of 50 mg/day as a dose lower than 100 mg/day was not explored during the development program.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Milnacipran (MLN) is a norepinephrine and serotonin reuptake inhibitor (NSRI) and has an anti-depressant effect. It has been approved in other countries since 1997 for the treatment of major depression disorder (MDD) and generalized anxiety disorder (GAD). The Applicant intended to obtain a new indication, treatment of fibromyalgia syndrome (FMS), based on achieving simultaneous and clinically significant improvement of three domains of fibromyalgia syndrome: pain, patient global impression of improvement and physical function. The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) has determined that these elements are inter-related in such a manner in this disease, that it does not allow for distinction between claims of treatment of fibromyalgia (FM), treatment of FM pain or treatment of FM syndrome. **The Division's position is that the indication** to be granted for this population should be **"treatment of FM".**

The Applicant submitted two Phase 3 trials to support the efficacy of MLN for the treatment of FM, Studies FMS 031 and MLN-MD-02. These studies were randomized, double blind, placebo-controlled which enrolled 2084 patients with FM. These studies evaluated the efficacy and safety of 100 mg MLN in two divided doses and 200 mg MLN in two divided doses, up to 12 weeks of treatment.

Additional supporting safety data consisted of the Phase 2 placebo controlled study in 125 patients with FM, Study FMS-021, and long-term safety data from the extension Study FMS034 which included 449 patients treated with MLN 100 mg/day and 200 mg/day up to 28 weeks and Study MLN-MD-04 which included 384 patients treated for up to 39 weeks. Studies FMS 031 and MLN-MD-02 were conducted in the United States (see Table 1 below). The Applicant also submitted post-marketing data of MLN which includes post-marketing studies and spontaneous reports since its approval in other countries.

Table 1. Summary of Clinical Trials

Study Number	*Study Design/Objective*	*Treatment Groups*	*No. of Patients Randomized*	*Treatment Duration*
Pivotal Studies				
MLN-MD-02	Randomized, double-blind, placebo-controlled, parallel-group, fixed-dose Pivotal safety and efficacy	Placebo	401	up to 29 weeks[a]
		Milnacipran 100 mg/d (BID)	399	
		Milnacipran 200 mg/d (BID)	396	
FMS031	Randomized, double-blind, placebo-controlled, parallel-group, fixed-dose Pivotal safety and efficacy	Placebo	223	27 weeks[a]
		Milnacipran 100 mg/d (BID)	224	
		Milnacipran 200 mg/d (BID)	441	
Extension Studies				
MLN-MD-04	Randomized, double-blind, parallel-group, fixed-dose Long-term safety and persistence of efficacy	Milnacipran 100 mg/d (BID)	54	up to 39 weeks
		Milnacipran 200 mg/d (BID)	330	
FMS034	Randomized, double-blind, parallel-group Long-term safety and persistence of efficacy	Milnacipran 100 mg/d (BID)	48	28 weeks
		Milnacipran 200 mg/d (BID)	401	
Phase II				
FMS021	Randomized, double-blind, placebo-controlled, parallel-group, flexible-dose Initial safety, efficacy, and tolerability	Placebo	28	12 weeks
		Milnacipran 25-200 mg/d (QD)	46	
		Milnacipran 25-200 mg/d (BID)	51	

a Pivotal efficacy evaluation performed at 15-week landmark.
BID = twice a day; QD = once a day

(Source: Applicant's Table 2.1.4-1, Clinical Overview, p. 12 -13)

In summary, 1824 patients with FM were treated with MLN, 1460 of them in the placebo-controlled efficacy trials and the number is patients in the safety database is 2596 patients with FM and non-FM disorders exposed to MLN.

1.3.2 Efficacy

The support of efficacy of this new molecular entity (NME) was obtained from two Phase 3 efficacy studies, FMS-031 and MLN-MD 02. The two studies were randomized, double-blind, placebo-controlled, multicenter studies but were designed with slightly different study populations and different durations.

In Study FMS031, patients were treated for 6-months, with follow-up visits at 4-week intervals during the maintenance phase. The study included patients with pain of at least 50 mm on the 100 mm VAS pain intensity scale and patients with depression were excluded by the MINI questionnaire. In the other study, MLN-MD-02, patients were initially treated up to 29 weeks, with follow-up visits at 4-week intervals during the maintenance phase. Study MLN-MD-02 included patients with pain scores of at least 40 mm on the VAS, and a Fibromyalgia Impairment Questionnaire – Physical Function (FIQ-PF) score of at least 4 at baseline, and excluded patients with a BDI of 25 or more.

After discussion with the Division during the development program the Applicant was informed that 6-month data was no longer required for evidence of efficacy. Instead, two 3-month studies would be required to support efficacy of the product and that Study MLN-MD-02 which was ongoing as a 6-month study, could be truncated to 3 months for analysis.

When Study FMS031 was completed, analysis of the data was not favorable for milnacipran. The company believed this was due to the population characteristics and inability to show a treatment effect in the population. Agreement was reached that the data from this study could be re-analyzed *post-hoc*, using a modified population that was the same as that of Study MLN-MD-02, with efficacy analyzed at the 3-month landmark. For the re-analysis of the data of FMS031 the company would use what was designated a "uniform program analysis (UPA)" meaning that the population considered for this *post- hoc* analysis would consist of patients who had a Beck Depression Inventory score under 25 and would use a more stringent definition of response for the PGIC: a score of 1 (very much improved) or 2 (much improved). By doing this population adjustment, the two studies would be analyzing populations with homogeneous characteristics and allow for more accurate replication of results. The baseline observation carried forward (BOCF) would be the imputation method for missing data.

The Applicant chose a pain composite responder analysis as the primary endpoint for the indication of "treatment of fibromyalgia pain". In this pain composite responder analysis patients were considered responders if they met the following criteria for improvement concomitantly:

- 30% improvement in pain from baseline
- A Patient Global Impression of Change (PGIC) of 1 (very much improved) or 2 (much improved) at the 3-month landmark

For the indication of "treatment of fibromyalgia syndrome" the Applicant presented a composite responder analysis for FM syndrome. In this composite responder analysis, patients were considered responders if in addition to the two criteria above they also had an improvement of at least 6 points on the SF-36 PCS score.

As the indication of treatment of FM syndrome is not being considered, my recommendation is based on the results of the pain composite responder analysis as this more closely reflects the sort of analysis that would be accepted by the Division's current standards. The FDA analyses of the composite "FM pain" responder analysis of the two studies indicate that there is replicated evidence of efficacy for the MLN 200 mg/day dose. For the MLN 100 mg/day dose, only Study MLN-MD-02 demonstrated that there was a statistically significant effect. Nevertheless, in Study FMS031, a numerical difference between the proportion of responders in the MLN100 mg/day

and placebo groups was demonstrated, which indicates that some patients may respond to the lower dose of MLN. Nevertheless, despite the difference in the efficacy between placebo and MLN in both studies, the overall proportion of patients that responded to MLN was relatively low (approximately 25%).

1.3.3 Safety

The safety database consisted of 2596 patients exposed to MLN:

- 1824 patients with FM from one Phase 2 and four Phase 3 studies
- 772 patients with non-FM disorders, namely major depression disorder (MDD) and generalized anxiety disorder (GAD) from five Phase 3 studies

A subset of 354 patients was treated with MLN for at least one year and 209 of them were treated at 200 mg/day.

The Applicant provided additional supportive safety data derived from:

- historical safety data derived from studies in MDD conducted prior to 1996 for the Marketing Authorization Application
- nine post-marketing studies
- spontaneous reports

The incidence of serious adverse events was low (<0.5%) and the ones that occurred more than once were chest pain, palpitations. The most common adverse events were .nausea, headache, constipation, dizziness, and vomiting.

In respect to suicidality, the data showed that MLN increases the incidence of suicidal ideation in patients with depression at treatment initiation. Patients with moderate and severe depression were excluded from these studies, so the effects of MLN in this group are not known, and the label may need to reflect that finding was limited to a restricted population with non-severe depression.

The controlled studies did not indicate that MLN increases the risk of hepatotoxicity.

The safety data in the controlled studies indicate that MLN increases systolic blood pressure (mean increase SBP 3.1 mmHg and 3 mmHg for MLN 100 and 200 mg/day respectively) and diastolic blood pressure (mean increase DBP 3.1 mmHg and 2.6 mmHg for MLN 100 and 200 mg/day respectively) these effects do not seem to be dose related. In addition, patients who have normal blood pressure or are pre-hypertensive at baseline have an increased risk of developing hypertension while on milnacipran. Monitoring of blood pressure should be recommended in the label.

The controlled studies also demonstrated that milnacipran increases heart rate (mean increase in heart rate 6.6 bpm and 7.1 bpm for MLN 100 and 200 mg/day respectively). Changes > 10 bpm

were noted in 34 to 40 % of the patients on milnacipran and approximately 12-15% of the milnacipran treated patients had heart rates above 100 bpm but less than 1% were above 120 bpm. Monitoring of heart rate should be recommended in the label.

1.3.4 Dosing Regimen and Administration

The dosing regimen proposed by the Applicant is 50 mg twice a day after a week-long titration period as follows:

- Day 1: 12.5 mg
- Days 2-3: 12.5 mg twice daily (25 mg/day)
- Days 4-7: 25 mg twice daily (50 mg/day)
- After Day 7: 50 mg twice daily (100 mg/day)

The Applicant also proposes a higher dose, 200 mg/day, based on individual patient response.

This titration scheme and dosing regimen were used in the Phase 3 trials. The patients that received 200 mg/day, received 100 mg/day during the second week of treatment and the dose was increased to 200 mg/day at the third week of treatment.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were conducted with the following drugs: alcohol, carbamazepine, clomipramine, digoxin, fluoxetine, lithium, lorazepam, and warfarin. The interaction studies with digoxin, warfarin, lithium, lorazepam and alcohol demonstrated that there were no PK interactions between these drugs and MLN. The drug-drug interaction studies with levopromazine and carbamazepine revealed PK changes that were considered not clinically significant by the Applicant.

Two studies investigated the effect of switching from fluoxetine and clomipramine to milnacipran without a washout. Switching from fluoxetine to MLN did no change the PK of MLN. On the other hand, switching from clomipramine to MLN without washout increased the C_{max} of MLN by 18% and 10% after 4 days of dosing with the observation of adverse effects such as euphoria, postural hypotension, headache, insomnia and nausea.

1.3.6 Special Populations

The safety and effectiveness of MLN were not studied in the pediatric population, or in pregnant women and nursing mothers. The effect of MLN on labor and delivery is unknown.

Special dosing recommendations will be made for patients with renal impairment: the drug should be used with caution in patients with moderate renal impairment, and the dose should be reduced by 50% in patients with severe renal impairment. MLN should also be used with caution in patients with severe hepatic impairment.

No dose adjustments are necessary in the geriatric population.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Milnacipran (Z-2-aminomethyl-1-phenyl-N, N-diethylcyclopropane-carboxamide, hydrochloride [HCl]) is a new molecular entity (NME) being jointly developed in the United States by Cypress Bioscience, Inc., and Forest Laboratories, Inc., for the treatment of fibromyalgia. Milnacipran is a *cis*-(*d*, *l*) racemate (Z form) composed of two (*d*- and *l*-) enantiomers. Figure XX presents the chemical structure of milnacipran.

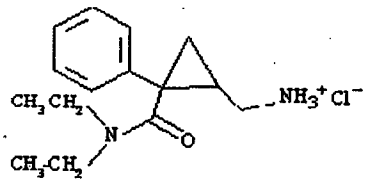


Figure 1.Chemical Structure of Milnacipran

Milnacipran is a norepinephrine (NE) and serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitor (NSRI) drug with antidepressant activity, with preferential inhibition of NE reuptake over 5-HT reuptake. Milnacipran is a small molecule that is structurally unrelated to other antidepressants, such as tricyclic antidepressants (TCAs) and more recently developed compounds.

The Applicant proposes to market this drug as immediate-release (IR) tablets of different strengths- 12.5 mg, 25 mg, 50 mg and 100 mg- to allow gradual titration up to 100 mg/day, up to the maximum proposed dose which is 200 mg/day.

The proposed dosing regimen for adults is 50 mg twice a day after a week-long titration period as follows:

- Day 1: 12.5 mg
- Days 2-3: 12.5 mg twice daily (25 mg/day)
- Days 4-7: 25 mg twice daily (50 mg/day)
- After Day 7: 50 mg twice daily (100 mg/day)

The Applicant also proposes a higher dose, 200 mg/day (100 mg BID), based on individual patient response. The Applicant does not propose a tapering for discontinuation of the drug.

This drug is marketed in Europe under the trade name Ixel® available as 25 mg and 50 mg capsules for the treatment of major depressive episodes in adults, and in Japan under the trade

name Toledomin® available as 15 mg and 25 mg tablets for the treatment of depression. The maximum recommended doses in Europe and Japan is 100 mg daily in two divided doses.

2.2 Currently Available Treatment for Indications

Two drugs are approved in the United States for the treatment of fibromyalgia: pregabalin (Lyrica®) and duloxetine (Cymbalta®). Other drug treatments are used off-label including anti-depressants, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), sedatives, muscle relaxants, anti-epileptic drugs, and local injection of trigger points. These drugs target symptoms associated with fibromyalgia. Non-pharmaceutical treatments include exercise, physical therapy, massage, acupuncture and cognitive behavioral therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Milnacipran is a new molecular entity and it is not currently marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

The approved norepinephrine and serotonin reuptake inhibitors (NSRIs) are associated with adverse events including suicide ideation and suicidal behavior in children, adolescents, and young adults. This led to the incorporation of a boxed warning in all of the product labels for this drug class. Other adverse events associated with this class of drugs are serotonin syndrome, potential interaction with monoamine oxidase inhibitors, changes in blood pressure and heart rate, discontinuation syndrome, neuroleptic malignant syndrome, visual problems (midriasis), hyponatremia, bleeding, urinary retention, dysuria, seizures, withdrawal symptoms, and anxiety.

2.5 Presubmission Regulatory Activity

There is no guidance for the development of drugs for the treatment of fibromyalgia. In June 2003, the Arthritis Advisory Committee met to discuss the development program of drugs for this condition. The consensus was that not only the improvement of pain was important but also improvement of other aspects of the disease needed to be taken into consideration. Therefore, the evaluation of drugs for the treatment of FM should evaluate improvement in pain as well as measures of health-related quality of life domains of function and patient global well being. Because this is a chronic condition, the studies would be required to have duration of at least 3 months to establish durability of response in FM patients. At that time, the position of the Agency was that two indications would be possible:

- Pain of FM: This would require efficacy only of the pain endpoint.

- Fibromyalgia syndrome: This would require evidence of efficacy on three co-primary endpoints: pain, function and global well-being.

In 2007, the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) reassessed the position regarding the appropriateness of having two different indications for fibromyalgia and came to the conclusion that the pain, function, patient global and other elements are inter-related in such a manner in this disease, that they do not allow for distinction between claims of "treatment of FM", "treatment of FM pain" or "treatment of FM syndrome." The Division has determined that the indication that should be granted for this class of drugs is "treatment of FM".

The following is a chronological summary of the interactions with the applicant during the product development:

- November 2001- Filing of IND 63,736 to study the use of MLN in FMS.

- April 2003- End-of Phase 2 and Special Protocol Assessment (SPA): The previous Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (DAAOP) agreed that the program would have two pivotal studies and there were two potential claims for FM. One of the studies would demonstrate efficacy at 6 months with a positive trend at 3 months. Superiority of MLN over placebo would be demonstrated based on a responder analysis of pain and global for the indication of pain of FM or pain, global and function for the indication of FMS. The second study would be a 3-month study using the same endpoints at the 3-month landmark. Clinically significant endpoints were specified as:

    - 30% improvement in pain from baseline,
    - score of 1, 2 or 3 on the seven point Likert Patient Global Impression of Change (PGIC), and
    - 30% improvement from baseline on the Fibromyalgia Impairment Questionnaire (FIQ).

- July 2003- Type C- General Guidance Meeting: The use of the electronic diary was deemed acceptable by DSI and DAAOP after a meeting on July 25, 2003.

- October 2003- Type A- Post SPA Review: Meeting for clarifications on the review of the SPA for FMS031 and extension study MLN-MD-02.

- May 2005- General Guidance Meeting: DAAOP agreed that the power calculation for MLN-MD-02 could be updated based on the final results of FMS031 as long as the data of the former study were still unblinded and not analyzed. The responders for the 6-month endpoint were defined by at least 27 weeks of therapy and for the 3-month endpoint by at least 15 weeks of therapy.

- June 2006- Type C- Clinical and Statistical Issues: The newly established DAARP informed the Applicant that 6-month data were no longer required for evidence of efficacy and that

two 3-month studies were acceptable for registration. At that time, FMS031 which was originally 6-months long had been completed and MLN-MD-02 was ongoing. The Division agreed that the ongoing study could be truncated to 3 months for analyses. The Division also agreed that they could exclude severely affected patients but ultimately the database for the application should included patients with co-morbid depression. The Applicant proposed a more stringent definition of global response by the PGIC (much improved and very much improved) and stated that they preferred to utilize a composite responder analysis for the analysis of the data for studies addressing the treatment of FMS and the Division was agreeable to the proposal. Study MLN-MD-02 would be truncated at the 3-month landmark once the last recruited patients had been treated for three months and the imputation method for missing data would be the baseline observation carried forward (BOCF). The analysis of two doses for the two potential indications was considered acceptable.

- March 2007- Type B- Pre-NDA Meeting: The following key agreements were reached:
  - Two indications were possible for MLN: treatment of pain or treatment of fibromyalgia syndrome.
  - The trials could have duration of 3 months.
  - SF-36 PCS could be used as a measure of physical function.
  - Continuous responder analyses were recommended but not required.
  - The Applicant would re-analyze study FMS031 using the analysis methods of MLN-MD-02. In FMS031 physical function was measured using the FIQ-PF scale. Patients with depression as measured by the Mini International Neuropsychiatric Interview (MINI) would be excluded from the analysis. In MLN-MD-02 SF-36 PCS was used to measure physical function and excluded patients that had a score ≥ 25 as assessed by the Beck Depression Inventory (BDI). In study FMS031, SF-36 PCS and BDI scores were collected as secondary endpoints and re-analyzing the data using the same parameters would make the two efficacy studies symmetrical.
  - The safety data would be grouped in four subgroups consisting of: core safety data generated from good clinical practice (GCP) studies in normal volunteers and patients with FM, from supporting safety data generated from GCP and placebo-controlled studies in non-fibromyalgia patients, from historical safety data and from post-marketing experience.
  - Pediatric studies would be deferred until approval in adults.

- February 2008- Teleconference: The Applicant was notified that the current position of **DAARP was to grant the indication of "treatment of fibromyalgia" for all the drugs of this** class and would no longer consider the indications **"treatment of fibromyalgia pain" and treatment of fibromyalgia syndrome". The Applicant** was also notified that this drug did not meet the requirements for priority review.

Although milnacipran is an NME, an Advisory Committee was not deemed necessary because milnacipran is not the first drug in its class and there is a considerable body of knowledge regarding the NSRIs.

2.6 Other Relevant Background Information

Pierre Fabre is the discoverer and manufacturer of the active pharmaceutical ingredient, milnacipran HCl. Pierre Fabre conducted the initial preclinical and clinical development program and was responsible for the registration of MLN as an antidepressant in France. Cypress Bioscience, Inc., in California and Forest Laboratories, Inc., in New York co-developed MLN for the treatment of fibromyalgia in the United States. The US Investigational New Drug Application (IND) for the clinical study of milnacipran was filed by Cypress in 2001. In 2004, Forest became the agent for the milnacipran IND.

Since the European marketing authorization of MLN in 1997, Pierre Fabre received the following requests for labeling changes:

- [redacted]

b(4)

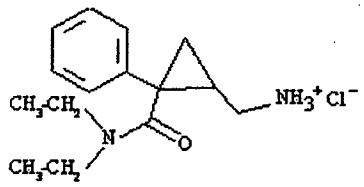
[redacted] It is not clear in the submission how this issue was addressed.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

The reviews for Chemistry, Manufacturing and Control (CMC) and Animal Pharmacology and Toxicology were not finalized at the time of this review. The information presented here is based on data from the Applicant's submission and preliminary discussions with the review teams of these disciplines.

3.1 CMC (and Product Microbiology, if Applicable)

Milnacipran is a novel small molecule that is structurally unrelated to other antidepressants, such as tricyclic antidepressants (TCAs) and more recently developed compounds. Milnacipran is a cis-(d, l) racemate (Z form) composed of two (d- and l-) enantiomers.



Molecular Formula: $C_{15}H_{23}C_lN_{2O}$
Molecular Weight: 282.8

Figure 2. Chemical Structure of Milnacipran

Milnacipran HCl is a white to off white powder and is freely soluble in water, methanol, ethanol, chloroform and methylene chloride, and is very slightly soluble in diethyl ether.

The to-be-marketed formulation of milnacipran is an IR tablet containing 12.5 mg, 25 mg, 50 mg and 100 mg of MLN. The inactive ingredients used in the manufacture of the finished dosage form are [ ] dibasic calcium phosphate [ ] [ ] povidone [ ] carboxymethylcellulose calcium, colloidal silicon dioxide, talc, magnesium stearate and [ ] coatings. b(4)

Notably, the clinical studies were conducted utilizing an IR capsule formulation. Although the [ ]. A biowaiver request for the bioequivalence of the capsule and tablet formulations was submitted to the IND (August 14, 2006) and was granted by the Agency (December 14. 2006).

At the time of writing of this review, no chemistry and manufacturing control issues have been identified. For further details regarding the CMC assessment of the NDA, please refer to the reviews of the drug substance and drug product by Dr. Elsbeth Chikhale and Dr. Craig Bertha.

3.2 Animal Pharmacology/Toxicology

Dr. Elizabeth Bolan reviewed the acute toxicology and the carcinogenicity data. Dr. Asoke Mukherjee reviewed the toxicology data. No approvability issues have been encountered.

Key findings from Dr. Bolan's review are as follows:

- The acute toxicology studies in mice demonstrated that the oral administration of high doses of MLN (racemic mixture, and each of the isomers) led to hypoactivity, cyanosis, prostration, and convulsions. The intravenous (IV) administration of the racemic mixture caused hypoactivity, piloerection, prostration and convulsions were observed. LD_{50} values were similar in males and females with PO and IV administration.
- The acute toxicology studies in the rat, similar clinical signs of hypoactivity, prostration, convulsions and congested lungs were observed at the higher doses with oral administration for the three compounds tested. Milnacipran with IV administration caused tremors, apathy, gasping and decreased respiration at higher doses. LD_{50} values were similar in males and females with both oral and IV administration.
- The 26-week carcinogenicity study with MLN was conducted in a transgenic rasH2 mouse model utilized MLN daily oral doses up to 125 mg/kg. There was no increase in the incidence of neoplastic lesions. The most frequent neoplasms noted included pulmonary tumors, hemangiomas and hemangiosarcomas. A trend test for multiple organ hemangiosarcomas in females was significant but no significant pairwise comparisons were seen. The incidence of hemangiosarcomas observed for females was similar to the historical control values provided by the Applicant. Various neoplasms or pre-neoplastic lesions were observed but all were similar to levels observed in vehicle controls and/or similar to levels observed in the historical controls. The Executive Carcinogenicity Assessment Committee agreed that the study was negative for any statistically significant drug-related neoplasms.

The carcinogenicity data indicates that MLN does not cause an increased risk for the incidence of cancer. Key findings from Dr. Mukherjee's review of the genotoxicity studies are as follows:

- Milnacipran was negative in Ames assay of reverse mutation in the absence and presence of S-9 liver mixtures, however, the Applicant did not provide purity data for the test substance According to Dr. Mukherjee, the Applicant will need to conduct another Ames assay as a Phase 4 commitment, using the clinical batch of milnacipran.
- Milnacipran did not induce chromosomal aberration in vitro in the absence and presence of S-9 mixtures in human peripheral blood lymphocytes.
- F2207, the active enantiomer of MLN, is not mutagenic in the absence and presence of S-9 liver mixtures.
- F2207 is negative in mouse micronucleus assay in vivo.

The following were the key findings from the reproductive and developmental toxicology studies:

- The mating performance was delayed at milnacipran doses of 20 and 80 mg/kg. The fertility of rats was reduced at 80 mg/kg. The no effect dose was 5 mg/kg in Wistar rats.

- In the F2207 oral gavage fertility study in the rat, MLN had no effect on mating performance in rats up to 60 mg/kg (360 mg/m^2). However, reduced fertility and embryocidal effect was observed in female rats at 5 mg/kg (30 mg/m^2) and higher doses in Sprague Dawley rats. Based on this data, Dr. Mukherjee recommends that MLN be designated Pregnancy Category C.
- In the F2207 oral gavage teratology study in rabbits, no maternal toxicity was observed up to 60 mg/kg. Nevertheless, a single extra rib was noted in rabbits at 15 and 60 mg/kg as a variation. No teratogenicity was observed in the study.
- In the F2207 oral teratology study in the mouse, treatment at 5, 25 and 125 mg/kg did not show any skeletal and visceral malformation in pregnant mice. However, fetal weight was reduced at 25 and 125 mg/kg. No maternal toxicity was noted at any dose. Based on the maternal toxicity data, the maximum tolerated dose (MTD) was not clearly defined.
- In the study that evaluated the effects of F2207 on peri- and post-natal development of the rat by gavage during late gestation and lactation, data suggest that the treatment with MLN at 60 mg/kg had an adverse effect on survival and weight of F_1 pups. Surviving pups did not show abnormality in the physical development and behavioral assays.
- The peri and postnatal study in rats treated orally with TN-912 showed a reduction of survival of F1 pups at 5 mg/kg and higher doses. The treatment had no effect on gestation and delivery.
- From the oral gavage carcinogenicity study Dr. Mukherjee concluded that the dietary administration of MLN up to 50 mg/kg for 104 weeks did not increase the incidence of tumors.

In summary, Dr. Mukherjee concluded that the label should indicate that milnacipran is not mutagenic as based on the Ames, chromosomal aberration in human lymphocytes, mouse lymphoma in TK +/- cell line and mouse micronucleus tests. Because of the inadequacies of the original Ames test, Dr. Mukherjee also recommends that the Applicant conducts another Ames assay a Phase 4 commitment, using the clinical batch.

The labeling recommendations based on the pre-clinical reviews areas follows:

- The label should indicate that milnacipran is not mutagenic as based on the Ames, chromosomal aberration in human lymphocytes, mouse lymphoma in TK +/- cell line and mouse micronucleus tests.
- Milnacipran should be designated Pregnancy Category C, based on the findings of reduced fertility and embryocidal effect observed in female rats at 5 mg/kg (30 mg/m^2) and higher doses in Sprague Dawley rats.
- The label should also include the result of the carcinogenicity study: A carcinogenicity study was conducted in Tg rasH2 mice for 6 months at oral gavage doses of up to 125 mg/kg/day. Milnacipran did not show carcinogenic potential in Tg rasH2 mice at any dose tested.

For further details please refer to the pre-clinical reviews by Dr. Elizabeth Bolan and Dr. Asoke Mukherjee.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data reviewed in support of this NDA submission were generated from the following studies:

1) The final study report for Study FMS021, a clinical trial conducted in the United States by the Applicant entitled: A Phase II, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of Milnacipran for the Treatment of Fibromyalgia.
2) The final study report for Study FMS031, a clinical trial conducted in the United States by the Applicant entitled: A Phase III Pivotal, Multicenter, Double-Blind, Randomized, Placebo-Controlled Monotherapy Study of Milnacipran for t Treatment of Fibromyalgia
3) The final study report for Study MLN-MD-02, a clinical trial conducted in the United States by the Applicant entitled: A Phase III Pivotal, Multicenter, Double-Blind, Randomized, Placebo-Controlled Monotherapy Study of Milnacipran for Treatment of Fibromyalgia.
4) The final study report for Study FMS034, a clinical trial conducted in the United States by the Applicant entitled: A Phase III, Multicenter, Double-Blind, Randomized, Monotherapy Extension Study of Milnacipran for Treatment of Fibromyalgia.
5) The final study report for Study MLN-MD-04, a clinical trial conducted in the United States by the Applicant entitled: An Extension Study of MLN-MD-02 for the Treatment of Fibromyalgia

Other sources of data were the safety database consisting of placebo-controlled studies in non-fibromyalgia (non-FM) patients, historical safety data from studies in the 1997 European Marketing Authorisation Application (MAA) for Major Depression Disorder (MDD), post-marketing experience consisting of post-marketing studies in non-FM patients and spontaneous adverse event (AE) reports.

4.2 Tables of Clinical Studies

The following is a tabular listing of all the clinical studies conducted:

Table 2. Tabular Listing of Clinical Studies

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
BA	**M038:** Study of the Absolute Bioavailability of F2207 in the Healthy Subject by Comparison of the Capsule Form With an Intravenous Infusion at the Dose of 50 mg	5.3.1.1.1	To assess the absolute bioavailability of F2207 (milnacipran). To establish the pharmacokinetic characteristics of milnacipran and evaluate its urinary elimination.	Randomized, open-label, 2-way crossover study with 15-day washout	25-mg solution; 50 mg single dose; intravenous infusion over 1 hour 25-mg capsule; 50 mg single dose; oral	12	Healthy	Single dose	Complete; Full
BA	**MLN-PK-04:** A Single-Center, Randomized, Open-Label, Single-Dose, Two-Way Crossover Study Comparing the Effect of Food on the Oral Bioavailability of Milnacipran HCl Capsules	5.3.1.1.2	To evaluate the effect of food on the bioavailability of 100 mg milnacipran HCl.	Open-label, single-dose study	100-mg capsule; 100 mg single dose fasted and fed; oral	31	Healthy	Single dose	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
BA	**M039/M124:** Influence of Food on the Pharmacokinetics of F2207	5.3.1.1.3	M039: To evaluate the possibility of administering the drug with food without decreasing its bioavailability M124 (Addendum to M039): To evaluate the influence of food on the pharmacokinetics of milnacipran based on the calculation of confidence intervals of pharmacokinetic parameters according to the present recommendations.	Randomized, open-label, 3-way crossover study	50-mg capsule; 50 mg single dose, fasted, with a low fat breakfast, and with a high-fat breakfast; oral	12	Healthy	Single dose	Complete; Full
BA/BE	**M048:** Study on Relative Bioavailability of Two F2207 Oral Formulations After Single Administration in Twelve Healthy Volunteers	5.3.1.2.1	To compare the bioavailability of two F2207 formulations, after single administration at a dose of 50 mg.	Randomized, open-label, 2-way crossover with 1-week washout between treatments	50-mg capsule; 50 mg single dose; oral 50-mg tablet; 50 mg single dose; oral	12	Healthy	Single dose	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
BA/BE	**M112/M113:** Comparative bioavailability study of three F2207 formulations (milnacipran) after single 50 mg oral administration in 24 healthy volunteers	5.3.1.2.2	M112: To evaluate the relative bioavailability of three different oral F2207 formulations by measuring F2207 plasma and urine levels, and to study the tolerance of the two new F2207 formulations versus the reference formulation after single 50 mg oral administration. M113 (Addendum to M112): To evaluate the behavior of each enantiomer of F2207 after administration of different formulations of milnacipran and to determine whether equivalence is also observed for the enantiomers (F2695 and F2696).	Randomized, open-label, 3-way crossover study with a 7-day washout between treatments	50-mg dibasic calcium phosphate-based tablet; 50 mg single dose; oral 50-mg dibasic calcium phosphate-based capsule; 50 mg single dose; oral 50-mg lactose-based capsule; 50 mg single dose; oral	24	Healthy	Single dose	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
BE	**M140:** Bioequivalence Study of a New Milnacipran Oral Formulation: 100 mg Score Tablet After Single Administration -½ score Tablet (50 mg) Versus 50 mg Milnacipran Tablet in Twelve Normal Healthy Volunteers-100 mg Scored Tablet Versus 100 mg Milnacipran Tablet in Twelve Normal Healthy Volunteers	5.3.1.2.3	To test the bioequivalence of a new F2207 oral formulation (100 mg score tablet) versus reference formulations (50 mg and 100 mg tablets)	Open-label, randomized, 2-way crossover study in 3 groups of subjects:	*Group A:* 100-mg score tablet; 50 mg single dose with a standard breakfast; oral 50-mg tablet; 50 mg single dose with a standard breakfast; oral *Group B:* 100-mg scored tablet; 100 mg single dose with a standard breakfast; oral 100-mg tablet; 100-mg single dose with a standard breakfast; oral *Group C:* 100-mg scored tablet; 100 mg single dose with a modified breakfast; oral 100-mg tablet; 100 mg single dose with modified breakfast; oral	37	Healthy	Single dose	Complete; Full
BA/BE	**M141:** Comparative Bioavailability Study of Two F2207 Formulations (Milnacipran) After Single 50-mg Oral Administration in Healthy Volunteers	5.3.1.2.4	To compare the bioavailability of two different oral F2207 formulations after single 50 mg oral administration by measuring F2207 plasma and urine levels.	Randomized, open-label, single dose study	100-mg scored dibasic calcium phosphate-based tablet; 50 mg single dose with a standard breakfast; oral 50-mg lactose-based capsule; 50 mg single dose with a standard breakfast; oral	24	Healthy	Single dose	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
PK	**M036:** Profile of the Plasma Kinetics of F2207 in Relation to the Dose Administered During Clinical Safety/Acceptability Evaluation After Single and Repeated Dosing	5.3.3.1.1	To determine an initial pharmacokinetic profile of milnacipran in relation to the dose administered.	*Part I:* Randomized, placebo-controlled, 3-sequence study with increasing single doses and 3-day washout between treatments *Part II:* Repeated dosing for 14 days	Part I: 25-mg capsule; 25 and 50 mg single doses; oral 100-mg capsule; 100, 200, 300, and 400 mg single doses; oral Placebo; single dose; oral Part II: 25-mg capsule; 25 mg multiple dose every 12 hours; oral 50-mg capsule; 50 mg multiple dose every 12 hours; oral 75-mg capsule; 75 mg multiple dose every 12 hours 100-mg capsule;100 mg multiple dose every 12 hours; oral 200-mg capsule; 200 mg multiple dose every 12 hours; oral	22 (Part I: 12; Part II: 10)	Healthy	Single dose or 14 days	Complete; Full
PK	**M037:** Pharmacokinetics Study of F2207 by Repeated Dosing in the Healthy Volunteer	5.3.3.1.2	To define the pharmacokinetic parameters of milnacipran following a single and multiple dose administration of milnacipran	Randomized, double-blind, placebo-controlled, parallel-group study	50-mg capsule; 50 mg single dose and 50 mg multiple dose every 12 hours; oral placebo capsule; single or multiple dose every 12 hours; oral	13 (10 active, 3 placebo)	Healthy	16 days	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
PK	**M040:** Study of the Linearity of the Pharmacokinetics of F2207 in Relation to the Dose Administered	5.3.3.1.3	To investigate the relation between pharmacokinetic response and dose	Open-label, 4 single increasing doses with 7-day washout between each treatment	25-mg capsule; 25 mg single dose; oral 50-mg capsule; 50 mg single dose; oral 100-mg capsule; 100 mg single dose; oral 100-mg capsule; 200 mg single dose; oral	6	Healthy	Single dose	Complete; Full
PK	**M115:** Pharmacokinetics of Milnacipran and Its Enantiomers After Single Oral Doses in Healthy Subjects	5.3.3.1.4	To investigate the pharmacokinetics of the two milnacipran enantiomers when given separately and in combination in order to evaluate their kinetic properties and possible interactions when administered together.	Randomized, double-blind, 3-way crossover study	25-mg *d,l*-milnacipran capsule; 50 mg single dose; oral 25-mg *d*-milnacipran capsule; 25 mg single dose; oral 25-mg *l*-milnacipran capsule; 25 mg single dose; oral Placebo capsule; single dose; oral	12	Healthy	Single dose	Complete; Full

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PK	**M146** Study of the Cardiovascular Tolerance of Milnacipran 50, 100, and 200 mg/d Versus Placebo in Healthy Volunteers	5.3.3.1.5	To evaluate the cardiovascular safety/acceptability of several doses of milnacipran, administered twice daily (50, 100, and 200 mg/d) compared with placebo in healthy volunteers, determine milnacipran pharmacokinetics and investigate the relationship between cardiovascular parameters and milnacipran concentrations (Cardiovascular tolerability data presented in study report C241)	Randomized, double-blind, 4 × 4 latin-square; 4–7-day washout between treatments	25-mg capsule; 25, 50 and 100 mg multiple doses every 12 hours; oral Placebo capsule; multiple doses every 12 hours; oral	19	Healthy	9 days (3 days at each milnacipran dose)	Complete; Full
PK	**MLN-PK-01:** Double Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Tolerability of Milnacipran HCl Following Escalating Multiple Dose Administration to Healthy Subjects	5.3.3.1.6	To evaluate the safety and tolerability of milnacipran HCl and to characterize milnacipran pharmacokinetics over a range of multiple ascending dose levels in healthy adult subjects	Randomized, double-blind, placebo-controlled, dose-escalation study	12.5-mg, 25-mg, 50-mg, and 100-mg capsules; dose escalation to 100 mg dose or 200 mg dose every 12 hours; oral	26 (6 placebo, 20 active)	Healthy	9 days for Group A; up to 10 days for Groups B and E	Complete; Full

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PK	**MLN-PK-05:** A Study of the Mass Balance and Metabolism of [^{14}C]-Milnacipran Hydrochloride in Healthy Subjects	5.3.3.1.7	To determine the tolerability of a 100 mg milnacipran hydrochloride dose given as an oral solution.	Open-label, single-dose study	20 mg/mL solution; 100 mg single dose; oral 20 mg/mL solution containing [^{14}C] milnacipran; 100 mg single dose; oral	20	Healthy	Single dose	Complete; Full
PK	**M002/M034:** The Pharmacokinetics of ^{14}C-F2207 in Man	5.3.3.1.8	M002: To evaluate the extent of absorption, plasma concentrations and excretion routes of radioactivity after oral administration of [^{14}C] milnacipran M034 (Addendum to M002): To determine the plasma concentrations of milnacipran and its conjugate.	Open-label, single dose study	50-mg [^{14}C] milnacipran capsule; 50 mg single dose; oral	2	Healthy	Single dose	Complete; Full

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PK	**M120:** A double-blind, multicenter, comparative, dose-finding study of the clinical efficacy, tolerability and safety of 50, 100, and 200 mg daily doses of milnacipran and placebo in the treatment of major depressive episodes: A pharmacokinetic substudy in a satellite group of patients.	5.3.3.2.1	To define the dose-response relationship of 50 mg, 100 mg and 200 mg of milnacipran compared to placebo in patients with a major depressive episode.	Multicenter, randomized, double-blind, placebo-controlled trial with 4 parallel treatment groups. This study is part of a large efficacy/ safety trial (C232)	12.5-mg, 25-mg, and 50-mg capsules; dose escalation to 50 mg dose every 12 hours; oral Placebo capsule; multiple dose every 12 hours; oral	74 (55 active, 19 placebo)	Depressed patients	56 days	Complete; Full
PK	**M042:** Pharmacokinetic Study of F2207 by Single Dosing in the Elderly Subject	5.3.3.3.1	To study the pharmacokinetics of F2207 in the elderly subject.	Open-label, single-dose study	50-mg capsule; 50 mg single dose; oral	20	Healthy elderly	Single dose	Complete; Full
PK	**M043:** Study of the Pharmacokinetics of F2207 by Repeated Dosing in the Elderly Patient	5.3.3.3.2	To study the pharmacokinetics of milnacipran in elderly depressed patients in the context of a trial aiming to evaluate the antidepressant effect and safety/acceptability of the drug.	Randomized, double-blind, placebo-controlled, in 2 parallel groups	25-mg capsule; 25 mg single dose and 25 mg multiple dose every 12 hours; oral	14	Depressed patients, elderly	29 days	Complete; Full

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PK	**M116:** Pharmacokinetics and Tolerability of Milnacipran at Steady State in Healthy, Elderly and Young Subjects	5.3.3.3.3	To investigate the effect of old age on the pharmacokinetics of oral milnacipran in comparison to young subjects; to evaluate the tolerability of milnacipran in healthy young and healthy elderly subjects.	Open-label, parallel study	50-mg capsule; 50 mg multiple dose every 12 hours; oral	23 (8 young, 15 elderly)	Healthy elderly and young	5 days	Complete; Full
PK	**M041:** Study of the Pharmacokinetics of F2207 Administered Orally in Children (25 mg Capsule)	5.3.3.3.4	To study the pharmacokinetics of F2207 in the child.	Open-label, single-dose study	25-mg capsule; 25 mg single dose; oral	12	Healthy Children	Single dose	Complete; Full
PK	**MLN-PK-02:** A Single Dose Pharmacokinetic Study of Milnacipran in Healthy Subjects and Subjects With Mild to Severe Impaired Renal Function	5.3.3.3.5	To evaluate the pharmacokinetic characteristics of milnacipran following a single 50-mg dose in subjects with various degrees of renal function.	Open-label, single-dose study	50-mg capsule; 50 mg single dose; oral	28 (8 healthy subjects; 8 with mild, 8 with moderate, 4 with severe, renal impair-ment)	Healthy and mild to severe renal impairment	Single dose	Complete; Full

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PK	**M045/M117:** Study of the Pharmacokinetics of F2207 in Subjects with Chronic Renal Failure	5.3.3.3.6	M045: To evaluate the pharmacokinetics of milnacipran in patients with various degrees of renal impairment compared to healthy subjects. M117 (Addendum to M045): To evaluate the pharmacokinetics of *d*- and *l*-milnacipran in patients with various degrees of renal impairment compared to healthy subjects.	Open-label, single-dose, parallel-group study	50-mg capsule; 25 mg single dose; oral	14 (7 subjects with creatinine clearance > 80 mL/min and, 7 with renal impairment, ie, creatinine clearance < 80 mL/min)	Healthy subjects and subjects with chronic renal impairment	Single dose	Complete; Full
PK	**MLN-PK-11:** A Single Dose Pharmacokinetic Study of Milnacipran in Healthy Subjects and Subjects with Impaired Hepatic Function	5.3.3.3.7	To evaluate the effect of hepatic function on the pharmacokinetic (PK) characteristics of a 50-mg single oral dose of milnacipran hydrochloride HCl.	Open-label, single-dose study	50-mg capsule; 50 mg single dose; oral	29 (8 healthy subjects; 8 with mild, 8 with moderate, 5 with severe hepatic impairment)	Healthy subjects and subjects with impaired hepatic function	Single dose	Complete; Full

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PK	**M046:** Pharmacokinetic Study of F2207 in Subjects with Hepatic Failure	5.3.3.3.8	To define the pharmacokinetic parameters of milnacipran, as a single dose, orally and intravenously, in patients with hepatocellular failure and to compare with those of a control group showing no evidence of any impaired function of excretory organs.	Open-label, parallel-group; 2 treatments per subject	50-mg capsule; 50 mg single dose; oral 50-mL solution; 50 mg single dose; intravenous infusion over 1 hour	17 (6 control subjects, 11 hepatic subjects)	Control subjects (normal hepatic and renal function) and subjects with hepatic failure	Single dose	Complete; Full
PK	**M244:** Study of the Influence of Milnacipran on the Activity of Cytochrome P450 Iso-Enzymes	5.3.3.3.9	To assess the influence of repeated administrations of milnacipran on various probes for the activity of cytochrome P450 (CYP) iso-enzymes, namely sparteine (CYP2D6), mephenytoin (CYP2C19), caffeine (CYP1A2) and endogenous 6β-hydroxy-cortisol excretion (CYP3A4). To compare the pharmacokinetics of milnacipran in extensive metabolizers (EM) versus pro metabolizers (PM) of sparteine and mephenytoin.	Open-label, one-period, parallel-group study with a fixed treatment sequence in extensive and poor metabolizers of sparteine and mephenytoin	50-mg capsule; 50 mg single dose and 50 mg multiple dose, every 12 hours; oral	25	Extensive and poor metabolizers of sparteine and mephenytoin	8 days	Complete. full

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PK	**MLN-PK-08:** A Single-Center, Randomized, Open-Label, Crossover Pharmacokinetic Interaction Study between Milnacipran and Digoxin in Normal Healthy Volunteers	5.3.3.4.1	To investigate whether there is an effect on the pharmacokinetics of digoxin following multiple-dose administration of milnacipran	Open-label, multiple-dose, 3-way crossover, drug-interaction study	0.2 mg Lanoxicaps; multiple dose of 0.2 mg every 12 hours on Day 1 and every 24 hours thereafter alone or with milnacipran; oral 12.5 mg, 25-mg, 50-mg and 100-mg milnacipran capsule; uptitration to 100 mg every 12 hours alone or together with Lanoxicaps; oral	30	Healthy	18 days of milnacipran (9 days alone and 9 days together with digoxin)	Complete; Full
PK	**M135:** Pharmacokinetic Interaction Study Between Milnacipran and Digoxin in Normal Healthy Volunteers	5.3.3.4.2	To investigate the possible pharmacokinetic interaction between milnacipran and digoxin. To evaluate whether repeated co-administration of milnacipran and digoxin was well tolerated.	Two-parallel-group study; each group of an open-label, randomized, 2-way crossover design; 4-7 days washout between treatments	50-mg milnacipran capsule; 50 mg multiple dose every 12 hours alone or with single dose digoxin; oral 0.5 mg/2 mL injectable solution of digoxin; 1 mg single dose alone or with multiple dose milnacipran; intravenous infusion over 1 hour	13	Healthy	6 days milnacipran	Complete; Full
PK	**MLN-PK-07:** A Single-Center, Randomized, Open-Label, Two-Way Crossover Pharmacokinetic Interaction Study between Steady-State Milnacipran and Single-Dose Warfarin in Healthy Volunteers	5.3.3.4.3	To assess the effects of milnacipran at steady state on the pharmacokinetics and pharmacodynamics of a single dose of warfarin. To assess the effects of a single dose of warfarin on the pharmacokinetics of milnacipran at steady-state.	Open-label, multiple-dose, 2-way crossover drug interaction study	25-mg, 50-mg, and 100-mg milnacipran capsule; uptitration to 100 mg multiple dose every 12 hours alone or with warfarin; oral 25-mg Coumadin tablet; 25 mg single dose; oral	28	Healthy	11 days milnacipran	Complete; Full

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PK	**M126:** Study of the Pharmacodynamic and Pharmacokinetic Interactions Between Milnacipran and Levomepromazine in Healthy Volunteers	5.3.3.4.4	To investigate the possible pharmacodynamic and pharmacokinetic interaction between milnacipran and levomepromazine (Pharmacodynamic data are presented in study report C221)	Non-randomized, open-label, crossover study with a 5 day washout between Period 1 (milnacipran alone) and Period 2 (levomepromazine alone for 11 days, then together with milnacipran)	50-mg milnacipran capsule; 50 mg multiple dose every 12 hours alone (Period 1) or together with levomepromazine (end of Period 2); oral Nozinan (levomepromazine) 4% oral solution; 15 mg multiple dose every 12 hours alone (Period 2) or together with milnacipran (end of Period 2); oral	14	Healthy	6 days milnacipran	Complete; Full

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PK	**M130:** Pharmacokinetic Interaction Study Between Milnacipran and Carbamazepine in 12 Healthy Male Volunteers	5.3.3.4.5	To evaluate a possible pharmacokinetic interaction between carbamazepine and milnacipran. To evaluate whether repeated coadministration of milnacipran and carbamazepine was well tolerated.	Open-label, multiple dose, 3-period study with fixed treatment sequence and 7-day washout between Periods 1 (milnacipran alone) and 2 (carbamazepine alone); no washout between Period 2 and Period 3 3 (carbamazepine + milnacipran)	50-mg milnacipran capsule; 50 mg multiple dose every 12 hours alone (Period 1) or with carbamazepine (Period 3); oral 100-mg and 200-mg carbamazepine tablets; carbamazepine uptitrated to 200 mg multiple dose every 12 hours alone (Period 2) or together with milnacipran (Period 3); oral	12	Healthy	11 days milnacipran	Complete; Full
PK	**M125:** Pharmacokinetic Interactions Between F2207 and Lithium After Repeated Oral Administrations in Normal Healthy Volunteers	5.3.3.4.6	To evaluate the pharmacokinetic interaction between F2207 and lithium after repeated oral administration.	Randomized, open-label, 2-way crossover; 1-week washout between treatments	50-mg milnacipran capsule; 50 mg single dose and 50 mg multiple dose every 12 hours with lithium; oral 250-mg lithium tablet; 375 mg multiple dose every 12 hours alone or together with milnacipran; oral	12	Healthy	4 days milnacipran	Complete; Full

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PK	**M138:** Pharmacokinetic and Pharmacodynamic Interaction Study of Milnacipran and Lorazepam	5.3.3.4.7	To evaluate the potential pharmacokinetic and/or pharmacodynamic interaction between milnacipran and lorazepam. (PD data not provided in report)	Randomized, double-blind, 4-way crossover study with 1-week washout between treatments	50-mg milnacipran capsule; 50 mg single dose alone or with lorazepam; oral 0.5-mg and 1.0-mg Ativan (lorazepam) tablets placed into a gelatine capsule; 1.5 mg single dose alone or with milnacipran; oral	9	Healthy	Single dose	Complete; Full
PK	**F2207 GE M212:** Study of the Risk of Pharmacokinetic Interaction Between Milnacipran and Fluoxetine in Healthy Volunteers when Switching from Flouxetine to Milnacipran	5.3.3.4.8	To evaluate the influence of decreasing concentrations of fluoxetine from steady-state levels on the pharmacokinetics of milnacipran To define the conditions of switch from fluoxetine treatment to milnacipran treatment based on pharacokinetics and tolerability data	Open-label, multiple dose, three period with fixed treatment sequence, 5-10 days washout between Periods 1 (milnacipran alone) and 2 (fluoxetine alone), and no washout between Periods 2 and 3 (switch to milnacipran)	50-mg milnacipran capsule; 50 mg multiple dose every 12 hours alone or after switch from fluoxetine; oral 20-mg Prozac (fluoxetine) capsule; 20 mg multiple dose every 24 hours; oral	12	Healthy	8 days milnacipran	Complete; Full

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PK	**F2207 GE M213:** Study of the Risk of Pharmacokinetic Interaction Between Milnacipran and Clomipramine in Healthy Volunteers When Switching from Clomipramine to Milnacipran	5.3.3.4.9	To evaluate the influence of decreasing concentrations of clomipramine from steady-state levels on the pharmacokinetics of milnacipran and to define the conditions of switch from clomipramine treatment to milnacipran treatment based on pharacokinetic and tolerability data.	Open-label, multiple dose, three period with a fixed treatment sequence, 5-10 days washout between Periods 1 and 2, and no washout between Periods 2 and 3	50-mg milnacipran capsule; 50 mg multiple dose every 12 hours alone or after switch from clomipramine; oral 25-mg clomipramine tablet; uptitration to 75 mg multiple dose every 23 hours; oral	12	Healthy	8 days milnacipran	Complete; Full

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PK/PD	**MLN-PK-10:** An Evaluation of the Safety and Tolerability of Sequential Multiple-Dose Regimens of Milnacipran HCl and the Effect of the Maximum Tolerated Dose on Cardiac Repolarization in Healthy Subjects	5.3.4.1.1	Two part study: Part A: To evaluate the safety and tolerability of milnacipran HCl at doses up to 300 mg BID Part B: To determine if the highest dose of milnacipran found to be safe and tolerable from Part A had any effect on cardiac repolarization, as measured by manual interpretation of the heart rate-corrected QT interval on repeated digitally recorded 12-lead electrocardiogram (ECG) tracings.	*Part A:* Randomized, double-blind, placebo-controlled study *Part B:* Randomized, double-blind, (stratified by gender), parallel-group, multiple-dose, active-drug and placebo-controlled study	12.5-mg, 25-mg, 50-mg, and 100-mg capsules; uptitration to 300 mg multiple dose every 12 hours; oral 400-mg Avelox (moxifloxacin) encapsulated tablet; 400 mg single dose; oral Placebo capsules, multiple dose every 12 hours; oral	*Part A:* 15 (3 placebo, 12 milnacipran) *Part B:* 100 (49 milnacipran, 51 moxifloxacin/ placebo)	Healthy	37 days	Complete; Full

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PD	**C241** Study of the Cardiovascular Tolerance of Milnacipran 50, 100, and 200 mg/d Versus Placebo in Healthy Volunteers	5.3.4.1.2	To evaluate the cardiovascular safety/acceptability of several doses of milnacipran, administered twice daily (50, 100, and 200 mg/d) compared with placebo in healthy volunteers, determine milnacipran pharmacokinetics and investigate the relationship between cardiovascular parameters and milnacipran concentrations (PK data are presented in study report M146)	Randomized, double-blind, 4 × 4 latin-square; 4–7-day washout between treatments	25-mg capsule; 25, 50 and 100 mg multiple doses every 12 hours; oral Placebo capsule; multiple doses every 12 hours; oral	19	Healthy	9 days (3 days at each milnacipran dose)	Complete; Full
PD	**C001:** Single Rising Dose Tolerance Study of the Antidepressant Milnacipran in Healthy Male Volunteers	5.3.4.1.3	To investigate the tolerance and pharmacodynamic effects of single oral doses of milnacipran in healthy male volunteers.	Randomized, double-blind, placebo-controlled study with 72-hour washout between treatments (2 milnacipran and 1 placebo treatment per subject)	25-mg and 100-mg capsules; 25, 50, 100, 200, 300, 400 mg single doses; oral Placebo capsule; single dose; oral	12	Healthy	Single dose	Complete; Full

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PD	**C002:** The Tolerance of Normal Human Subjects to Repeated Oral Doses of the Antidepressant Agent Milnacipran	5.3.4.1.4	To investigate the tolerance and pharmacodynamic effects of milnacipran administered orally twice daily for 14 days.	Single-blind, placebo-controlled study with two parallel groups	25-mg capsule; 25 mg multiple dose every 12 hours; oral 50-mg capsule; 50 mg multiple dose every 12 hours; oral Placebo capsule; Multiple dose every 12 hours	5 (4 active, 1 placebo)	Healthy	14 days	Complete; Full
PK	**C003:** Tolerance and Pharmacokinetic Study of the Antidepressant Agent Milnacipran Administered in Multiple Oral Doses (Ranging From 75-200 mg Twice Daily) for 14 Days to Healthy Male Volunteers	5.3.4.1.5	To investigate the tolerance and pharmacodynamic effects of milnacipran administered orally for 14 days in twice daily doses ranging from 75-200 mg to healthy male volunteers.	Single-blind, placebo-controlled study	75-mg, 100-mg, and 200-mg capsules; 75, 100, and 200 mg multiple doses every 12 hours; oral Placebo capsule; multiple dose every 12 hours; oral	5 (4 active, 1 placebo)	Healthy	14 days	Complete; Full
PD	**C242:** Single Rising Intravenous Dose Tolerance Study of Milnacipran in Healthy Male Volunteers	5.3.4.1.6	To assess tolerance to single rising doses of milnacipran administered by intravenous infusion, in 2 groups of 10 healthy volunteers	Double-blind, placebo-controlled study in 2 groups	10-mg, 25-mg, and 50-mg solution; 10, 25, 50, and 75 mg single dose; intravenous infusion over 2 hours Placebo solution, single dose; intravenous infusion over 2 hours	20 (12 active, 8 placebo)	Healthy	Single dose	Complete; Full

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PD	**C015:** Investigation of a Range of Doses of Milnacipran on CNS Activity, Cognitive and Psychomotor Function and Subjective Appraisals of the Drug Effects	5.3.4.1.7	To evaluate the effects of a range of doses of milnacipran on objective measures of performance, CNS activity and the subjective measures of alertness and side effects.	Randomized, double-blind, placebo-controlled, 4 way crossover study	12.5-mg, 25-mg, 50-mg and 100-mg capsules; 12.5, 25, 50, and 100 mg single doses: oral Placebo capsule; single dose; oral	10	Healthy	Single dose	Complete; Full
PD	**C029:** A Double-Blind Placebo Controlled Investigation of the Cognitive Effects of Milnacipran and Amitriptyline in Healthy Elderly Subjects	5.3.4.1.8	To evaluate the psychometric effects of milnacipran compared to amitriphtyline in elderly subjects	Randomized, double-blind, placebo-controlled, 3-way crossover study with 7-day washout between treatments	25-mg milnacipran capsule; 75-mg multiple dose for 3 days; oral 25-mg amitriptyline capsule; 25-mg multiple dose every 12 hours; oral Placebo capsule; multiple dose: oral	12	Healthy elderly	3 days	Complete; Full
PD	**C197:** A Comparative Study of the Effects of Milnacipran and Placebo on Cognitive Functions in Healthy Volunteers	5.3.4.1.9	To investigate any possible effect of milnacipran on memory, attention and psychomotor performance of healthy volunteers.	Randomized, double-blind, placebo-controlled, crossover study with 1-week washout between treatments	50-mg tablet; 50 mg multiple dose every 12 hours; oral Placebo tablet; multiple dose every 12 hours; oral	12	Healthy	7 days	Complete; Full

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PD	**C205:** Study of the Effects of Milnacipran Combined With Alcohol Towards Neuro-Sensorial Alertness on Car Driving	5.3.4.1.10	To investigate possible effects of administration of alcohol together with milnacipran, at the usual therapeutic dose, on driver's neuro-sensorial alertness.	Randomized, double-blind, placebo-controlled, crossover study in 4 sequences; 10-day washout between treatments	50-mg tablet; 50 mg multiple dose every 12 hours alone or with alcohol; oral Placebo tablet; multiple dose alone or with alcohol; oral	12	Healthy	7 days	Complete; Full
PD	**F2207 95 GE 103:** Double-Blind Pharmacokinetic and Pharmacodynamic Study of Alcohol Interaction with Milnacipran Versus Amitriptyline and Placebo in Normal Healthy Volunteers	5.3.4.1.11	To evaluate the effect of alcohol on the pharmacodynamics, pharmacokinetics and tolerability of milnacipran, amitriptyline, and placebo in healthy male subjects.	Double-blind, placebo-controlled, crossover study with a 1-week washout between treatments	50-mg milnacipran capsules encapsulated in a gelatine capsule; 50 mg multiple dose every 12 hours alone or with alcohol; oral 25-mg amitiptyline capsule encapsulated in a gelatine capsule; 25 mg multiple dose every 12 hours alone or with alcohol; oral Placebo gelatine capsule; multiple dose every 12 hours alone or with alcohol; oral	17	Healthy	8 days	Complete; Full

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PD	**C221:** Study of the Pharmacodynamic and Pharmacokinetic Interactions Between Milnacipran and Levomepromazine in Healthy Volunteers	5.3.4.1 .12	To investigate the possible pharmacodynamic and pharmacokinetic interaction between milnacipran and levomepromazine. (Pharmacokinetic data are presented in study report M126)	Non-randomized, open-label, crossover study with a 5 day washout between Period 1 (milnacipran alone) and Period 2 (levome-promazine alone for 11 days, then together with milnacipran)	50-mg milnacipran capsule; 50 mg multiple dose every 12 hours alone (Period 1) or together with levomepromazine (end of Period 2); oral Nozinan (levomepromazine) 4% oral solution; 15 mg multiple dose every 12 hours alone (Period 2) or together with milnacipran (end of Period 2); oral	14	Healthy	6 days	Com-plete; Full
PD	**C012:** A Comparison of the Anticholinergic Actions of Milnacipran, Amitriptyline and Placebo in Normal Subjects	5.3.4.1 .13	To compare the anticholinergic effects of milnacipran with amitriptyline and placebo using spontaneous salivation as an index of peripheral cholinergic activity.	Randomized, double-blind, placebo-controlled, 3 sequence crossover study with 1-week washout between treatments	25-mg milnacipran capsule; 50 mg single dose; oral 25-mg amitriptyline capsule; 75 mg single dose; oral Placebo capsule; single dose; oral	8	Healthy	Single dose	Com-plete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
PK	**C016:** Repeated Administration Study of Hormonal Tolerance and Pharmacokinetics of Milnacipran in Healthy Volunteers	5.3.4.1 .14	To evaluate hormonal modifications induced in normal volunteers by a repeated administration of milnacipran	Randomized, double-blind, placebo-controlled study with 2 parallel groups	50-mg capsule; 50 mg single dose and 50 mg multiple dose every 12 hours; oral Placebo capsule; single and multiple dose every 12 hours; oral	13 (10 active, 3 placebo)	Healthy	15 days	Com-plete; Full
PD	**C220:** Tolerance Study of Two F2207 Formulations (Milnacipran) After Single 50 mg Oral Administration in Healthy Volunteers	5.3.4.1 .15	To evaluate the tolerance of a new milnacipran formulation (100 mg scored tablet) versus a reference milnacipran formulation (50 mg capsule) after a single oral 50 mg administration. To evaluate the bioavailability of two different oral milnacipran formulations by measuring milnacipran urinary levels.	Randomized, open-label, crossover study, with a 1 week washout period between treatments	50-mg capsule; 50 mg single dose; oral 100-mg tablet; 50 mg single dose; oral	100	Healthy	Single dose	Com-plete; Full
PD	**C223:** Tolerance Study of Three F2207 Formulations (Milnacipran) After Single 50 mg Oral Administration in 120 Healthy Volunteers	5.3.4.1 .16	To determine the tolerance of three milnacipran oral formulations administered at a single dose of 50 mg.	Randomized, open-label, parallel-group study	50-mg dibasic calcium phosphate tablet; 50 mg single dose; oral 50-mg dibasic calcium phosphate-based capsule; 50 mg single dose; oral 50-mg lactose-based capsule; 50 mg single dose; oral	120	Healthy	Single dose	Com-plete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
PD	**F02207 GE 1 01:** Effect of Subchronic (11 days) Treatment with Milnacipran or Placebo on the Subjective and Vegetative Effects of the Pentagastrin Challenge in Healthy Subjects	5.3.4.1 .17	To evaluate a putative broad band anxiolytic effect of F2207 on symptoms induced by pentagastrin.	Randomized, double-blind, placebo-controlled, single-center, 2-way crossover study with a 7 to 17 day washout period	25-mg milnacipran capsule; 50 mg multiple dose every 12 hours; oral 0.5 mg Peptavlon (pentagastrin); 0.6 µg/kg, single dose 2 hours after milnacipran or placebo on Day 11; intravenous Placebo capsules; multiple dose every 12 hours; oral	27	Healthy	11 days	Complete, full
Efficacy	**FMS-021:** A Phase II, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of Milnacipran for Treatment of Fibromyalgia	5.3.5.1.1	Primary: To characterize the efficacy of milnacipran in the treatment of fibromyalgia syndrome (FMS).	Randomized, double-blind, placebo-controlled, parallel, flexible-dose study	Placebo Milnacipran 25-200 mg QD Milnacipran 12.5-100 mg BID capsules oral	125 (28/46 /51)	Fibromyalgia	12 weeks	Complete; Full
Efficacy	**FMS-031 (MLN-MD-01):** A Phase III Pivotal, Multicenter, Double-Blind, Randomized, Placebo-Controlled Monotherapy Study of Milnacipran for Treatment of Fibromyalgia	5.3.5.1.2	To demonstrate the efficacy of milnacipran 100mg/day as compared to placebo in the treatment of the syndrome of fibromyalgia during treatment weeks 14-15 (3-month) or treatment weeks 26-27 (6-month).	Randomized, double-blind, placebo-controlled, parallel, fixed-dose study	Placebo Milnacipran 50 mg BID Milnacipran 100 mg BID capsule or tablet oral	888 (223/ 224/ 441)	Fibromyalgia	27 weeks	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
Efficacy	**MLN-MD-02:** A Phase III Pivotal, Multicenter, Double-Blind, Randomized, Placebo-Controlled Monotherapy Study of Milnacipran for Treatment of Fibromyalgia	5.3.5.1.3	To demonstrate the safety and efficacy of milnacipran in the treatment of the fibromyalgia syndrome (FMS) or the pain associated with fibromyalgia.	Randomized, double-blind, placebo-controlled, parallel, fixed-dose study	Placebo Milnacipran 50 mg BID Milnacipran 100 mg BID capsules oral	1196 (401/ 399 /396)	Fibromyalgia	29 weeks	Complete; Full
Efficacy	**FMS-034 (MLN-MD-05):** A Phase III, Multicenter, Double-Blind, Randomized, Monotherapy Extension Study of Milnacipran for the Treatment of Fibromyalgia	5.3.5.2.1	To demonstrate the long-term safety of milnacipran for the treatment of fibromyalgia syndrome (FMS).	Randomized, double-blind, parallel, fixed-dose study	Milnacipran 50 mg BID Milnacipran 100 mg BID capsules oral	449 (48/401)	Fibromyalgia	28 weeks	Complete; Full
Efficacy	**MLN-MD-04:** An Extension Study of MLN-MD-02 for the Treatment of Fibromyalgia	5.3.5.2.2	To evaluate the long-term safety and efficacy of milnacipran used for the treatment of fibromyalgia.	Randomized, double-blind, parallel, fixed-dose study	Milnacipran 50 mg BID Milnacipran 100 mg BID capsules oral	384 (54/330)	Fibromyalgia	39 weeks	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
Efficacy	**C232 F2207 91 MI 08:** A Double-Blind, Multicenter, Comparative, Dose-Finding Study of the Clinical Efficacy, Tolerability, and Safety of 50, 100, and 200 mg Daily Doses of Milnacipran and Placebo in the Treatment of Major Depressive Episodes (Part of Pierre-Fabre MAA)	5.3.5.4.1	To define the dose-response relationship of 50 mg, 100 mg and 200 mg of milnacipran compared to placebo in patients with a major depressive episode.	Randomized, double-blind, placebo-controlled, multicenter study with 4 parallel treatment groups	Placebo Milnacipran 50 mg/d Milnacipran 100 mg/d Milnacipran 200 mg/d capsules oral	527 (133/131/130/133)	Major Depressive Disorder	6 months	Complete; Full
Efficacy	**C233 F2207 91 MI 03:** A Double-Blind Comparative Study of the Efficacy, Tolerability and Safety of Milnacipran 200 mg Compared to Placebo and Amitriptyline 150 mg in the Treatment of Major Depressive Disorder (Part of Pierre-Fabre MAA)	5.3.5.4.2	To study the antidepressant efficacy and tolerability of milnacipran 100 mg BID in comparison with placebo in patients with major depressive disorder. Amitriptyline was used as positive control.	Randomized, double-blind, placebo-controlled, parallel-group, comparative study	Placebo Amitriptyline 150 mg/d Milnacipran 200 mg/d capsules oral	169 (58/55/56)	Major Depressive Disorder	6 weeks	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
Efficacy	**C234 F2207 92 GE 303:** Study of the Efficacy and Safety of Milnacipran Capsules Given at 100 mg/d for 6 Weeks in Major Depressive Episodes (Double-Blind vs. Placebo) (Part of Pierre-Fabre MAA)	5.3.5.4.3	To assess the efficacy and tolerability of milnacipran 100 mg/day versus placebo, in the treatment of patients with a major depressive episode, as defined by the DSM III-R criteria.	Randomized, double-blind, multicenter, placebo-controlled, parallel-group study	Placebo Milnacipran 100 mg/d capsules oral	117 (49/68)	Major Depressive Disorder	6 weeks	Complete; Full
Efficacy	**C972 F2207 97 GE 302:** A Placebo-Controlled Comparative Study of the Clinical Efficacy and Safety of Milnacipran 50 mg BID, and Sertraline 50 mg QD in Patients with Major Depression (Part of Pierre-Fabre Post-Marketing Study)	5.3.5.4.4	The main objective was to evaluate the efficacy and safety of milnacipran 50 mg BID compared to placebo for 42 days in patients with moderate or severe major depression.	Randomized, multinational, multicenter, double-blind active- and placebo-controlled; 3 parallel groups	Placebo Milnacipran 50 mg BID Sertraline 50 mg QD capsules oral	410 137/139/134	Major Depressive Disorder	6 weeks	Complete; Full
Efficacy	**F02207 GE 201:** Study of milnacipran efficacy in outpatients with Generalized Anxiety Disorder	5.3.5.4.5	The main study objective was to study the clinical efficacy of milnacipran (50-150 mg/d) compared to placebo in outpatients with Generalized Anxiety Disorder.	A 12 week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Milnacipran 25 mg capsules, 1, 2, or 3 taken bid, oral Placebo	198 (107/91) 193 subjects were included in analysis	Generalized Anxiety Disorder	12 Weeks	Complete; Full

Type of Study	*Study Identifier*	*Location of Study Report*	*Objectives of the study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status: Type of Report*
Efficacy	**FMS-OL1:** Milnacipran Pilot Protocol for Fibromyalgia: An Open-Label, Single-Center, Fixed-Dosing Study of Milnacipran on Evoked Pain in Fibromyalgia	5.3.5.4.6	The primary objective of this single-center, open-label study was the assessment of evoked pain threshold testing as an objective measure of therpeutic response to pharmacological intervention in patients with fibromyalgia syndrome (FMS).	Open-label, single-center, fixed-dosing study	Milnacipran 50-mg capsule; BID; oral	9	Fibromyalgia	10 Weeks	Complete: Abreviated

(Source: Applicant's tabular listing from Synopsis of Individual Studies, p. 5-33)

4.3 Review Strategy

The main focus of the efficacy review consisted of the pivotal studies FMS031 and MLN-MD-02.

The review of safety was focused on data from all three placebo-controlled studies in FM patients including the Phase 2 study FMS021, as well as data from the long-term FM safety studies. Safety in the fibromyalgia populations was compared to the safety experience in placebo-controlled trials in non-FM patients, and the Phase 1 studies conducted by Forest. Safety data from the historical database, post-marketing experience, adverse event reporting and a PubMed search conducted by myself were also reviewed to support the safety of this drug.

4.4 Data Quality and Integrity

Following a preliminary review of safety and efficacy, four study sites of each efficacy trial were selected for inspection by the Division of Scientific Investigations (DSI). A total of eight sites were selected because both of the pivotal efficacy studies were large, with multiple participating centers: Study FMS031 was conducted in 59 study centers and Study MLN-MD-02 was conducted in 86 study centers. Therefore the inspection of only two sites per study might not yield sufficient information to guide the regulatory action.

Based on the site reports received by DSI no approvability issues have been encountered.

4.5 Compliance with Good Clinical Practices

According to the Applicant, the clinical studies were conducted in full compliance with the guidelines for Good Clinical Practice (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR, 312.120.

4.6 Financial Disclosures

None of the investigators that participated in the FM clinical studies had financial agreements with the Applicant; nevertheless, a financial disclosure was not obtained for 19 of the investigators. Six of these investigators were participants of Study FMS031 and there was no explanation why the disclosure form was not obtained. Other two investigators were participants of Study MLN-MD-02 only for approximately two weeks. Because of the large number of study centers and participating investigators, I do not believe this would impact the integrity of the data.

5 CLINICAL PHARMACOLOGY

At the time of this review the clinical pharmacology review by Dr. Sayed Al Habet had not been finalized. The data presented is based on the Applicant's study reports and the proposed label.

5.1 Pharmacokinetics

Milnacipran is a *cis-(d, l)* racemate composed of the *d*- and *l*- enantiomers. Milnacipran is rapidly absorbed after oral administration and is extensively distributed in the body within 1 to 2 hours. The mean volume of distribution of MLN following single intravenous (IV) dosing to healthy subjects is approximately 400 L. Plasma protein binding is 13%. Absolute bioavailability of MLN is high (85%-90%). Peak plasma concentrations occur at approximately 2 to 4 hours following administration.

Terminal elimination half-life ($T_{½}$) is 6 to 8 hours. The active enantiomer, *d*-milnacipran, has a longer elimination half-life (8-10 hours) than the *l*-enantiomer (4-6 hours) and there is no inter-conversion between the enantiomers. After twice-daily administration steady state levels are reached within 36 to 48 hours and twice-daily dosing leads to higher plasma levels of MLN at steady state by approximately 70%.

Drug elimination occurs by biotransformation and renal excretion. Approximately 55% of the drug is excreted by the kidneys as unchanged parent drug, and the remainder of the drug undergoes limited hepatic metabolism. The *l*-milnacipran carbamoyl-O-glucuronide is the major metabolite excreted in urine and accounts for approximately 17% of the dose; approximately 2% of the dose is excreted in urine as *d*-milnacipran carbamoyl-O-glucuronide. Altogether, 8% of the dose is excreted in urine as the N-desethyl milnacipran metabolite.

Dose proportionality was observed following single doses of milnacipran HCl between 25 and 300 mg and following multiple doses between 25 and 300 mg twice daily.

The Applicant proposes dose reduction in subjects with severe renal impairment. In Study MLN-PK-02, a decrease in MLN plasma clearance and an increase in C_{max} and AUC parameters were observed in subjects with impaired renal function; the relationship of these parameters to renal function (creatinine clearance) was linear. In subjects with severe renal impairment (creatinine clearance 5-29 mL/min), C_{max}, $AUC_{0-\infty}$, and $T_{½}$ increased by 59%, 199%, and 122%, respectively. In subjects with moderate renal impairment C_{max}, $AUC_{0-\infty}$, and $T_{½}$ increased by 26%, 52%, and 41%, respectively. These data suggest a dose reduction is necessary for patients with severe renal impairment but not for patients with mild or moderate renal impairment.

The proposed labeling for patients with renal insufficiency is as follows:

"2.2 Patients with Renal Insufficiency

b(4)

The PK of MLN was evaluated following single oral administration of 50 mg of MLN to subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment and matched healthy subjects by age , gender and weight. $AUC_{0-\infty}$ and $T_{½}$ were similar in healthy subjects and subjects with mild and moderate hepatic impairment. Subjects with severe hepatic impairment had a 31% higher $AUC_{0-\infty}$ and 55% higher $T_{½}$. The Applicant does not propose dosing adjustments for patients with hepatic impairment.

The PK of MLN was evaluated in healthy subjects > 65 years old and compared with healthy young adults 18 to 45 years old in studies M042 and M116. Based on historical data (Study M037) the Applicant found that C_{max} and AUC values were approximately 35% to 60% greater in elderly subjects compared with young adults after single dosing and by about 30% after multiple dosing, likely as a consequence of the reduced renal function in the elderly subjects. No dose adjustment for the elderly population is being proposed by the Applicant, unless renal function is reduced to values for which dose adjustment is recommended.

Following single dosing, female subjects had a 22% increase in C_{max} compared with male subjects, but similar $AUC_{0-\infty}$. With multiple dosing, there were no differences in the PK of *d*-milnacipran, which is the active enantiomer, in young female and male subjects, but higher plasma exposure was observed in elderly female subjects (22% for C_{max} and 16% for $AUC_{0-\tau}$) compared with elderly male subjects. The Applicant does not propose dosing adjustments based on gender as well.

In vitro studies in pooled hepatic microsomes suggested that MLN does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems, indicating a low potential of interactions with drugs metabolized by these enzymes.

Drug-interaction studies were conducted and MLN did not affect the PK of the following drugs: alcohol, digoxin, warfarin, carbamazepine, levopromazine, lithium, lorazepam, In addition, two studies evaluated the switch from steady state fluoxetine or clomipramine to MLN treatment without a washout period. The switch from fluoxetine to MLN without a washout period did not appear to affect the PK of MLN. The switch from clomipramine to MLN without a washout period did not appear to cause significant changes in the PK of MLN but there was an apparent increase in adverse events such as euphoria and postural hypotension. This last finding suggests the need for monitoring of patients if a treatment switch from clomipramine to MLN needs to occur.

5.2 Pharmacodynamics

Data from Study MLN-PK-01 indicates that there is a direct relationship between dose of MLN and cardiac effects. This study was originally designed to evaluate four treatment arms 100 mg twice daily, 200 mg twice daily, 300 mg twice daily and 400 mg twice daily. Due to significant increases in blood pressure, pulse rate and tachycardia the Applicant discontinued the treatment arms with 200 mg twice daily and higher.

Two studies conducted by the Applicant evaluated the cardiovascular effects of MLN- Studies C241 and M146. The Division of Cardiovascular and Renal Products (DCRP) was consulted to determine the adequacy of the studies and provide their input regarding the results. Study C241 compared several doses of MLN (50 mg, 100 mg and 200 mg) versus placebo in healthy volunteers in order to evaluate cardiovascular tolerability. The following were the findings reported by Dr. Gail Moreschi for Study C241:

- The heart rate increased with milnacipran over placebo, but did not differ between doses, and was greater during exercise than rest.
- The blood pressure increases were small and did not differ between dose strength.
- There were no modifications of PR and QRS on the ECG.
- The QT interval decreased with the increase in heart rate with the 200 mg dose,
- There were no variations in rhythm or conduction with the Holter monitor.
- Exercise testing done 12 hours after the last dose showed cardiovascular tolerability.
- The adverse events reported most frequently at the highest dose of 200 mg/d were nausea, palpitations and headache.

Study M146 studied the PK of MLN at different doses, 50 mg daily, 100 mg daily and 200 mg daily, with single and repeated administration, and the PK/PD relationship between concentrations and cardiovascular parameters. In this study, according to Dr. Moreschi, a limited PK/PD relationship was explored. The adverse event observed was palpitation. Pulse rate was the most sensitive parameter. A relationship between the concentration of the most active

enantiomer revealed a lag-time, meaning that the increase of pulse rate was delayed from the concentration increase and endurance of the PD effect, even when plasma concentration of MLN are low or not detected anymore. Despite the fact that the effects in the cardiac parameters were not fully explored, the increases in the cardiac parameters reported in the clinical trials were modest in the opinion of the DCRP reviewer: 3.1 mm Hg in systolic blood pressure, 2.4 mm Hg in diastolic blood pressure and 7 to 8 beats per minute in pulse rate. DCRP states that, based on their previous experience with epidemiological data on essential hypertension and controlled studies with anti-hypertensive drugs, the clinical implications of these changes is that if the effects persist throughout the dosing interval and with chronic treatment, for every 6 mm Hg change in blood pressure there is doubling of cardiovascular risk (death, myocardial infarction, and stroke). In the case of MLN this increased risk would be of an estimated 50%, but in a population with a small baseline cardiovascular risk this risk may be smaller. Because of these findings, I recommend monitoring of blood pressure as is done for other drugs from the NSRI class.

Study MLN-PK-10 was reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT). The study evaluated the safety and tolerability of MLN at doses up to 300 mg twice daily and was to determine if the highest dose of MLN safely tolerated had any effect on cardiac repolarization. This was a randomized, positive- and placebo-controlled parallel study. Eighty-eight subjects received a single dose of moxifloxacin 400 mg on day 1 to establish assay sensitivity, followed by either multiple doses of MLN up to 600 mg/day or placebo for 37 days. The IRT-QT team remarked that this design is not optimal to demonstrate assay sensitivity - a moxifloxacin control should have been conducted concurrently with the other arms. In this study, moxifloxacin failed to demonstrate assay sensitivity based on the statistical criteria that the lower limit of the two-sided confidence interval is ≥5 ms. The exposure to moxifloxacin was lower than expected and it likely occurred because of the over-capsulation of moxifloxacin to maintain the blind and because of administration with food. Table XX below is from the IRT-QT consult which presents the overall study findings using QTcF as the primary endpoint.

Table 3. The Point Estimates and the 90% Confidence Intervals Corresponding to the largest Upper Bounds for Milnacipran (300 mg twice daily) and the Largest Lower Bound for Moxifloxacin for QTcF

Treatment	Time (h)	ΔΔQTcF (ms)	90% CI (ms)
Milnacipran 300 mg BID	2	7.7	3.5, 12.0
Moxifloxacin 400 mg*	3	7.1	4.6, 9.6

* If Bonferroni adjustment is applied for 7 time points, the lower bound is 3.12 ms
(Source: Table 1 from the IRT-QT consult, p. 3)

Based on the Applicant's analysis MLN does not cause QTc prolongation because the maximum increase in ΔΔQTcNi was -5 (-9.4, -0.08). The IRT-QT team did not agree with the Applicant's calculation for the QT interval using QTcNi as the primary endpoint. The IRT-QT team re-calculated the QT interval using QTcF because it corrects for the increase in heart rate caused by MLN. The average change of heart rate from screening to the end-of-study was 22.5 ± 14.2 bpm for MLN and 5.1 ± bpm for placebo. Using the QTcF, the mean increase in the ΔΔQTcF is 7.7

(3.5, 12.0). An exposure-response analysis using ΔΔQTcF resulted in a shallow but statistically significant slope of 3 ms per µg/ml MLN. Based on this relationship, it is expected that MLN will not significantly increase the QTcF interval over the therapeutic exposure range.

After reviewing the cardiovascular cases in the clinical database the QT-IRT review team concluded that the effects were comparable with other drugs that affect nor-epinephrine and /or serotonin uptake. There were no reports of *torsades de points* in the clinical database and a data mining analysis found one report that was confounded by co-morbidities and concomitant medications that prolong the QT interval.

The IRT-QT team recommended that the Applicant conduct a repeat TQT study incorporating the following elements:

- Use exercise or 24 hour ambulatory ECG monitoring at baseline as a method to increase the range of heart rates to compute an individual-correction factor.
- Collect additional ECGs during the titration of MLN to determine the dose/concentration-response relationship for QT prolongation.
- Moxifloxacin control should be conducted concurrently with other arms.
- The blinding for the moxifloxacin should use a double-dummy approach instead of overcapsulation.

In my opinion the effect of MLN on the QT interval has not been fully elucidated and the data does not provide the needed safety information for this NME. Sudden death cases have been reported with atomoxetine, which is a drug that affects norepinephrine uptake. Therefore, I recommend that the Applicant repeat the TQT study for this NME.

5.3 Exposure-Response Relationships

During the End-of-Phase 2 meeting the Applicant was advised to consider a dose-ranging study and a trial using a 50 mg/day fixed dose during the efficacy assessment period especially because other anti-depressants are used at lower doses when for treating fibromyalgia. A dose ranging study to assess the efficacy of 50 mg/ day was not conducted. Instead, the Applicant estimated that, based on extrapolations from the use of MLN as an anti-depressant, the 50 mg/day would not be efficacious.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Applicant's desired indications were "treatment of fibromyalgia pain" and "treatment of fibromyalgia syndrome". However, the current position of DAARP is that these elements are inter-related in such a manner in this disease, that it does not allow for distinction between claims of "treatment of FM", "treatment of FM pain" or "treatment of FM syndrome". It is the current position of the Division that the indication that will be considered for this class of drugs is "treatment of FM".

6.1.1 Methods

The efficacy data reviewed were derived from two placebo-controlled studies, FMS-031 and MLN-MD-02 which were randomized, double-blind, placebo-controlled trials.

6.1.2 General Discussion of Endpoints

Fibromyalgia is a chronic condition in which chronic widespread pain is the main feature, but patients may also exhibit a range of other symptoms such as sleep disturbance, fatigue, irritable bowel syndrome, headache, mood disorders, stiffness, skin tenderness, post-exertional pain, cognitive disturbance, irritable bladder syndrome or interstitial cystitis, fluid retention, paresthesias, restless legs and Raynaud's phenomenon. Among all the associated symptoms, three key features are present in most patients with FM: pain, fatigue and sleep disturbance.

Prior to the reorganization of the Office of New Drugs (OND), the Division of Anti-Inflammatory, Analgesic and Ophthalmology Drug Products (DAAODP) was responsible for the review of fibromyalgia applications. DAAODP considered that efficacy of therapies for fibromyalgia were to be based on three domains: patient's pain, patient's function, and patient's report of global (overall) improvement. DAAODP allowed for two possible indications: "treatment of fibromyalgia syndrome" (based on achieving simultaneous and clinically significant improvement in all three domains), and "treatment of the pain of fibromyalgia" (based on achieving simultaneous and clinically significant improvement of the pain and patient global impression of improvement domains).

During the IND phase, several changes in endpoints occurred and are detailed in the description of each individual study design. After discussions with the Division, agreement was reached that efficacy could be evaluated based on a composite responder analysis based on two domains for the "treatment of pain of FM" indication:

- Pain by morning 24-hour recall using a VAS
- Patient global status by the PGIC

Patients were considered responders for the "treatment of pain of FM" if they met the following criteria concurrently:

- A decrease in pain of 30% or more from baseline

- A score of 1 (very much improved) or 2 (much improved) on the PGIC

Later, when DAARP became the review division for fibromyalgia applications, the Applicant was told that a composite responder analysis was optional, not required, for the "FM pain" indication. Efficacy could be based on an analysis of the effects on pain only and the patient global could be evaluated as a secondary outcome.

For the indication "treatment of fibromyalgia syndrome", the composite analysis would include a physical endpoint, an improvement from baseline of ≥ 6 points on the SF-36 Physical Component Summary (PCS). That is, patients were considered responders for the "treatment of FM syndrome" if they met the following criteria concurrently:

- A decrease in pain of 30% or more from baseline
- A score of 1 (very much improved) or 2 (much improved on the PGIC
- An improvement from baseline of at least 6 points on the SF-36 PCS

Pain was to be recorded in a Patient Electronic Diary, using a 0-100 visual analog scale (VAS).

For the patient global status, a fibromyalgia-specific patient global impression of change (PGIC) question with seven possible answers collected on a standard Likert scale was used as follows: "Since the start of the study, overall my fibromyalgia is:

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse"

The measures of physical function utilized in the clinical trials were the Fibromyalgia Impact Questionnaire-Physical Function (FIQ-PF) and the SF-36 physical component summary (PCS). The FIQ-PF is a subset of eleven questions of the overall FIQ and it was originally developed to assess physical limitations that affect patients' activities. This questionnaire provides a score that can be used to assess changes in function over time.

The SF-36-PCS is a subset of the Short Form-36 (SF-36) which is a health survey. Similar to the FIQ-PF, the SF-36 also is intended to provide a score that allows assessing change over time in physical function.

The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) has subsequently determined that three main efficacy elements (patient pain, function, and overall impression of improvement in their condition) are inter-related in such a manner in this disease, that it does not allow for distinction between claims of treatment of FM, treatment of FM pain or treatment of FM syndrome. The current position of DAARP is that "treatment (management) of FM" is the preferred indication for drugs intended to treat this condition. Efficacy is based on effects on pain

as the primary endpoint, and the effects on patient function and the patient global as secondary endpoints. DAARP allows for inclusion of these other components of fibromyalgia in the product labeling if the efficacy studies provide compelling evidence that the effect is essentially independent of the treatment effect on the pain component.

DAARP informed the Applicant of the revised wording for the indication as well as the approach to assessment of efficacy of drugs for fibromyalgia; however these changes occurred after the Applicant had completed its pivotal studies.

6.1.3 Study Design

The two efficacy studies seemed to be adequately blinded and randomized.

Both efficacy studies included adults 18 to 70 years of age. All patients included had to meet the diagnostic criteria for FM established by the American College of Rheumatology (ACR): presence of chronic widespread pain involving all 4 quadrants of the body and the axial skeleton for at least 3 months, and the presence of at least 11 of 18 tender points on palpation examination with an approximate force of 4 kg/cm^2. The patients were required to withdraw from CNS-active therapies for FM and discontinue non-pharmacologic treatments for FM. The studies excluded patients that had an ongoing major depressive disorder by the Mini International Neuropsychiatric Interview (MINI).

Some differences in the study populations were as follows:

- Study FMS031 required patients to have a baseline average VAS pain score of at least 50 mm on a 100 mm Visual Analog Scale (VAS)
- Study MLN-MD-02 required patients to have a baseline average VAS pain score of at least 40 mm on the VAS, a Fibromyalgia Impact Questionnaire-Physical Function (FIQ-PF) score ≥ 4, and excluded patients with moderate to severe depression who also had a Beck Depression Inventory (BDI) score >25.

Both studies prohibited the use of benzodiazepines, centrally-acting analgesics, anti-depressants. Joint and soft tissue injections had to be completed at least seven days before the primary endpoint determination. Study MLMN-MD-02 also prohibited trigger and tender point injections, anesthetic patches, biofeedback and transcutaneous electrical nerve stimulation. Short-term uses of opioid analgesics for indications other than FM were to have an exemption and should have been carefully documented.

The allowed concomitant medications were: acetaminophen, aspirin, NSAIDs, medications for the treatment of migraine (rizatriptan, sumatriptan, combination products of butalbital, aspirin/ acetaminophen and caffeine) and insomnia (zolpidem, zaleplon, sedating anti-histamines, chloral hydrate). Rescue medication was to be discontinued or withheld 48 hours prior to a scheduled clinic visit.

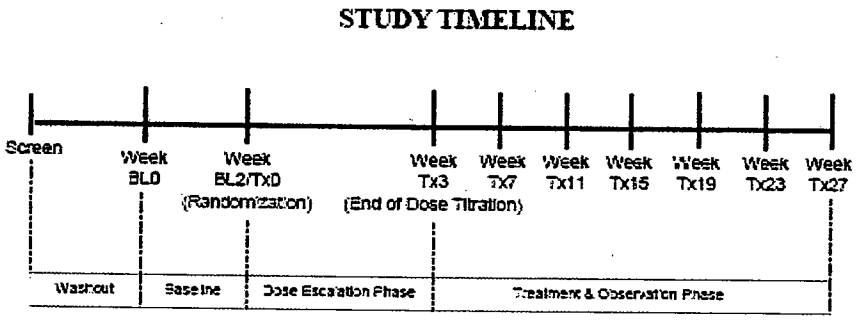
6.1.3.1 Study Design of Study FMS031

Study FMS031 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, three-arm parallel-group study to investigate the safety and efficacy of MLN 100 mg/day and 200 mg/day in patients with FM. The study was conducted at 59 sites in the United States. After a washout period from disallowed medications, patients entered a 2-week baseline period during which baseline pain scores were captured in a Patient Electronic Diary (PED).

The study excluded patients with current major depressive disorder using the MINI. To meet eligibility requirements patients had to have a minimum baseline average VAS pain score of 50 mm on a VAS. Eligible patients were randomized to treatment with placebo or with 100 mg/day or 200 mg/day of milnacipran (1:1:2), orally, in two divided doses.

Patients received up to 24 weeks of treatment after the 3-week dose-escalation phase, for a total of up to 27 weeks of drug exposure. Efficacy and safety assessments during office visits were conducted at the screening visit, randomization, at the end of dose escalation (Week 3), and at 4-week intervals thereafter. Patients recorded their pain in the PED daily and also using paper-based assessments at the office visits. The following is a study diagram for Study FMS031.

Figure 3. Study Timeline-Study FMS031 from the Original Protocol



(Source: Applicant's Figure 1, FMS-031 Protocol, Vol. 1, p. 2165)

In October 2003, the Applicant submitted a Special Protocol Assessment (SPA) for the design of this study. In the initial study protocol patients had to meet the following three primary efficacy endpoints at 6 months to be considered responders for the treatment of fibromyalgia syndrome:

- 30% reduction in pain from baseline in the 24-hour recall pain score recorded daily in the PED
- PGIC score of 1, 2, or 3
- 30% reduction from baseline in the FIQ-PF

To be considered responders for "the treatment of FM pain" patients had to meet only the pain and PGIC endpoints described above.

The imputation method for missing data was the last observation carried forward (LOCF) approach. Multiple comparisons with respect to time points (3 and 6 months), primary efficacy parameters (pain and syndrome), and dosage (MLN 100 mg/day and 200 mg/day versus placebo) were controlled using a sequential gatekeeping multiple comparison procedure.

Agreement was not reached on this protocol under a SPA because we did not agree to the protocol proposed in respect to exclusion criteria, study endpoints and statistical analysis proposed by the Applicant.

There were several changes in the study design during the IND phase of this product. At a Type C meeting held in June 2006, the Applicant was notified that the studies were no longer required to have 6-months duration, but that two studies of 3-months duration would suffice to meet registration requirements. There was also agreement that SF-36 PCS would replace the FIQ-PF as a measure of function and the endpoint of PGIC was made more stringent, as patients were adjudicated as responders if they had a PGIC of 1 or 2. Study FMS031 was already completed at the time of the Type C meeting.

Finally at the pre-NDA meeting held in April 2007, the Applicant proposed to conduct a re-analysis of FMS031 prior to database lock in Study MLN-MD-02, using the same criteria that were used in Study MLN-MD-02 and the Division concurred with this approach. The re-analysis would evaluate the efficacy at the 3-months endpoint, using a more stringent PGIC endpoint (scores of 1 or 2 at study end), as well as physical function improvement based on the SF-36 PCS (change of at least 6 points). The baseline observation carried forward (BOCF) was the imputation method applied for missing data. This *post hoc* analysis was designated as the Uniform Program Analysis (UPA) for FMS031.

This UPA was conducted in the ITT population and further applied in a population subset designated UPA Population. The UPA Population parallels the population analyzed in Study MLN-MD-02. The UPA Population is defined as the subset of the ITT population with baseline FIQ-PF score ≥ 4 and baseline BDI score ≤ 25. The BDI was collected in Study FMS031 as a secondary measure and was not an exclusionary criterion as in Study MLN-MD-02. The figure below summarizes the changes in the efficacy analyses for study FMS031.

Figure 4. Protocol Pre-specified and Uniform Program Analysis Definitions

Table 9.7.1.5.1.3–1. Protocol Prespecified Definitions

	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	Improved, much improved, or very much improved at landmark (score of 1, 2, or 3 on PGIC)	None	BOCF for weeks 0-7; LOCF from Tx7 to landmark
Treatment of Pain @ 6-Month Landmark (Tx27)				
Treatment of Syndrome @ 3-Month Landmark (Tx15)			≥ 30% improvement from baseline to landmark on FIQ-PFS score	
Treatment of Syndrome @ 6-Month Landmark (Tx27)				

BOCF = baseline observation carried forward; FIQ-PFS = Fibromyalgia Impact Questionnaire–Physical Function Subscale; LOCF = last observation carried forward; PED = Patient Experience Diary; PGIC = Patient Global Impression of Change.

Table 9.7.1.5.1.3–2. Uniform Program Analysis Definitions

	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: Applicant's Tables 9.7.1.5.1.3-1 and 9.7.1.5.1.3-2, FMS031 Study Report, Volume 1, p. 65)

6.1.3.2 Study Design of Study MLN-MD-02

Study MLN-MD-02 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, three-arm parallel-group study to investigate the safety and efficacy of MLN 100 mg/day and 200 mg/day orally, in patients with FM. This study was conducted at 86 sites in the United States. After a washout period from disallowed medications, patients entered a 2-week baseline period during which baseline pain scores were captured in a Patient Electronic Diary (PED). The

study excluded patients with current major depressive disorder using the MINI. To meet eligibility patients were required to have a minimum average VAS pain score of at least 40 mm and FIQ-PF ≥4 at baseline. Eligible patients were randomized to treatment with placebo or with 100 mg/day or 200 mg/day of milnacipran (1:1:1), with twice daily dosing.

According to the initially proposed protocol patients received up to 26 weeks of treatment after the 3-week dose-escalation phase, for a total of up to 29 weeks of drug exposure. Efficacy and safety assessments during office visits were conducted at the screening visit, randomization, at the end of dose escalation (Week 3), and at 4-week intervals thereafter. Patients completed the PED daily and paper-based assessments at the office visits.

In the initial statistical analysis plan, patients had to meet the following three primary efficacy endpoints at 29 weeks to be considered responders for the treatment of FMS:

- 30% reduction in pain from baseline in the 24-hour recall pain score recorded daily in the PED
- PGIC score of 1, 2, or 3
- 30% reduction from baseline in the FIQ-PF

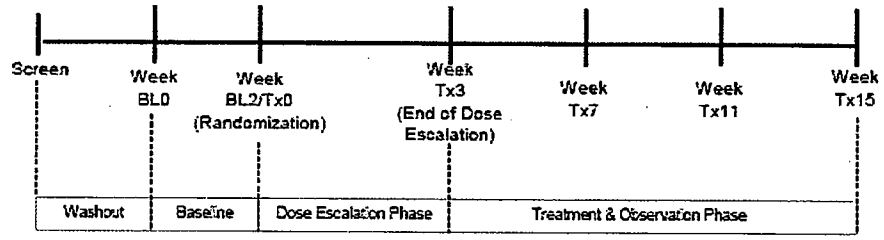
To be considered responders for the treatment of FM pain patients had to meet only the pain and PGIC endpoints described above. The imputation method for missing data was the LOCF approach.

There were changes to the protocol during the IND stage. In January 2006 the Applicant amended the protocol to exclude patients with BDI score > 25 because it was found in Study FMS031 that the MINI did not fully exclude a number of patients with significant clinical depression.

At the Type C meeting held in June 2006, the Applicant was notified that studies of 6 months were no longer required, but instead, two studies of 3-months duration were required for registration. This study was ongoing and there was agreement that this study could be truncated at 3 months, despite the fact that some patients had already received up to 29 weeks of drug exposure. Other changes that occurred after this meeting were as follows:

- Physical function would be measured by the SF-36 PCS and responders would have to demonstrate improvement of ≥ 6 points
- The definition of global response was changed to PGIC 1 or 2 instead of 1, 2 and 3
- The imputation method for missing data became the BOCF approach.

Figure 5. Study Timeline- Study MLN-MD-02



(Source: Applicant's Appendix C, Clinical Study Report, MLN-02, Vol.1, p. 2186)

Methods to handle multiplicity

In Study FMS031, a multiple comparisons procedure was to be used to control the overall type I error for comparisons of two doses of milnacipran to placebo at two primary time points and for two indications. The eight (8) primary comparisons described below were to be performed using the following sequential gatekeeping multiple testing procedure:

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

For the UPA analysis of study FMS-031, the Applicant adopted the same strategy as described **above to handle multiplicity for both "treatment of fibromyalgia syndrome" and "treatment of FM pain" analyses.**

In Study MLN-MD-02, the following sequential gatekeeping multiple comparison procedure was used:

1. 100 mg versus placebo at 3 months for the pain indication and 200 mg versus placebo at 3-months for the pain indication
2. 100 mg versus placebo at 3-months for the syndrome indication and 200 mg versus placebo at 3-months for the syndrome indication

6.1.4 Efficacy Findings

Dr. Joan Buenconsejo performed the statistical review of the efficacy data, with input from the clinical team. Refer to her review for details regarding these efficacy analyses.

Disposition:

Among the ITT population of the FMS-031 and MLN-MD-02, a total of 34.0% (708/2084) patients (27.7% placebo, 35.2% milnacipran 100 mg/d, and 37.8% milnacipran 200 mg/d) prematurely discontinued from the studies (before 3 months). The most common reason for discontinuation among the milnacipran-treated patients was an adverse event (AE) (18.8% and 24.1% for the 100 mg/d and 200 mg/d milnacipran treatment groups, respectively), whereas therapeutic failure (10.3%) was the most common reason for premature discontinuation among the placebo-treated patients.

Table 4. Patient Disposition- Pooled Data from Study FMS031 and MLN-MD-02

Table 3.2–1. Pooled Pivotal Studies—Patient Disposition (ITT Population)

Parameter	*Placebo, N (%)*	*Milnacipran, N (%)*	
		100 mg/d	*200 mg/d*
	N = 624	**N = 623**	**N = 837**
Completed 3-month treatment period	451 (72.3)	404 (64.8)	521 (62.2)
Administrative 3-month completers	48 (7.7)	35 (5.6)	49 (5.9)
All other 3-month completers	403 (64.6)	369 (59.2)	472 (56.4)
Discontinued	173 (27.7)	219 (35.2)	316 (37.8)
Reason for discontinuation			
Death	1 (0.2)	0	0
Adverse event	57 (9.1)	117 (18.8)	202 (24.1)
Therapeutic failure	64 (10.3)	51 (8.2)	60 (7.2)
Protocol violation	1 (0.2)	1 (0.2)	2 (0.2)
Noncompliant with protocol	8 (1.3)	5 (0.8)	8 (1.0)
Withdrawal of consent	27 (4.3)	24 (3.9)	27 (3.2)
Investigator withdrew the patient	1 (0.2)	3 (0.5)	1 (0.1)
Lost to follow-up	12 (1.9)	14 (2.2)	13 (1.6)
Other	2 (0.3)	4 (0.6)	3 (0.4)

ITT = Intent-to-Treat; N = population size.

(Source: Applicant's Table 3.2.1, ISE, p. 62)

6.1.4.1 Efficacy Findings of Study FMS031

Applicant's Efficacy Analysis

The Applicant submitted several analyses of the efficacy of milnacipran utilizing the initially proposed protocol parameters at 3 months and 6 months and the latest proposed Uniform Program Analysis (UPA) utilizing both the intention-to-treat (ITT) and UPA defined population. This efficacy review will focus mainly on the efficacy data that was derived from the UPA, utilizing the ITT population as this was ultimately agreed upon at the pre-NDA meeting and most closely resembles the efficacy parameters of Study MLN-MD-02. Also, the results of the same analyses performed on the UPA population are very similar to those of the ITT population **(refer to Dr. Buenconsejo's review for these analyses).**

Composite responder analysis for the "treatment of FM pain" composite endpoint

The data for the composite responder analysis for the "treatment of FM pain" using the UPA of the ITT population and of the UPA population are presented below. Note that the number of patients (N) in each population differs because the ITT group includes all randomized patients who took at least one dose of study medication, whereas the UPA population excludes patients with a baseline FIQ-PF score of 4 or more and a baseline BDI score of 25 or less.

Table 5. Study FMS031- Composite Responder Analyses for the Treatment of Pain of FM at the 3-month Endpoint- Uniform Program Analysis[1] with ITT and UPA Populations

Time point: 3 months	ITT Population			UPA Population[2]		
	Placebo (N=223)	MLN		Placebo (N=171)	MLN	
		100 mg (N=224)	200 mg (N=441)		100 mg (N=189)	200 mg (N=355)
Composite responder rates (n, %)	43 (19.3)	61 (27.2)	118 (26.8)	31 (18.1)	52 (27.5)	99 (27.9)
Odds ratio (95% CI)	-	1.52 (0.96, 2.39)	1.54 (1.04,2.28)	-	1.73 (1.04,2.87)	1.75 (1.11,2.76)
p- value	-	0.056	0.032	-	0.034	0.015

[1] BOCF as imputation method, improvement in pain > 30% of baseline and PGIC 1 or 2
[2] Excluded patients with BDI≤ 25 and FIQ-PF ≥4
(Source: Table compiled by the reviewer based on the Applicant's Tables 11.4.1.1.3-1 from FMS031 Study Report, Vol.1, p. 94 and Table 6.1-1 from the FMS031 Uniform Program Analysis, Efficacy Results, Vol.2, p. 22110)

The Applicant's data demonstrates that in the ITT population, 19.3% of placebo-treated patients met criteria for the "fibromyalgia pain" composite responder analysis, compared to 27.2% of patients on MLN 100 mg/day and 26.8% of patients on MLN 200 mg/day. The efficacy of MLN 200 mg/day compared with placebo achieved statistical significance (p=0.032), but did not for MLN 100 mg/day by a small margin (p=0.056). In addition, because of the pre-specified 8-step sequential gatekeeping multiple testing procedures, only the efficacy of the MLN 200 mg/day dose is supported for the treatment of FM pain. Because this dose did not "win" on the step number three of the testing procedure, none of the other endpoints can be considered or tested for significance.

In the UPA of the UPA population analysis (i.e. the ITT population excluding the patients with moderate to severe depression and decreased function), the proportion of "FM pain" treatment responders was also higher in the MLN treatment arms compared to the placebo arm 18.1% of placebo patients were responders, compared to 27.5% of patient on MLN 100 mg/day and 27.9% of patients on MLN 200 mg/day. According to the Applicant, this analysis demonstrated that the difference between placebo and the MLN treatment arms did achieve statistical significance: for

the treatment group on MLN 200 mg/day (p= 0.015) and for the treatment group on MLN 100 mg/day (p=0.034). One must bear in mind that this latter analysis was *post-hoc*. The study was not initially powered for these sub-analyses, the p-values obtained are unadjusted, and should be interpreted with caution.

The Applicant's data indicates that only MLN 200 mg/day is efficacious for the treatment of FM when considering the ITT population but when utilizing the UPA population which most closely resembles the population from the other efficacy study, MLN-MD-02, both MLN treatment arms demonstrate efficacy. The statistical data provided by the Applicant was confirmed by our statistical reviewer.

Composite responder analysis for the "treatment of FM syndrome" composite endpoint

The Applicant also submitted data for the composite **responder analysis for the "treatment of FM syndrome" using the UPA of the ITT population** and the UPA population which is presented below. Note that the number of patients (N) in each population differs because the ITT group includes all randomized patients who took at least one dose of study medication, whereas the UPA population excludes patients with a baseline FIQ-PF score of 4 or more and a baseline BDI score of 25 or less.

Table 6. . Study FMS031- Composite Responder Analyses for the Treatment of FM Syndrome at the 3-month Endpoint- Uniform Program Analysis[1] with ITT and UPA Populations

Time point: 3 months	ITT Population			UPA Population[2]		
	Placebo (N=223)	MLN		Placebo (N=171)	MLN	
		100 mg (N=224)	200 mg (N=441)		100 mg (N=189)	200 mg (N=355)
Composite responder rates (n, %)	27 (12.1)	44 (19.64)	85 (19.27)	21(12.28)	39 (20.69)	73(20.56)
Odds ratio (95% CI)	-	1.84 (1.07, 3.17)	1.80 (1.11, 2.94)	-	2.05 (1.10, 3.81)	2.14 (1.20, 8.82)
p- value	-	0.028	0.017	-	0.024	0.010

[1] BOCF as imputation method, improvement in pain > 30% of baseline and PGIC 1 or 2
[2] Excluded patients with BDI≤ 25 and FIQ-PF ≥4
(Source: Table compiled by the reviewer based on **the Applicant's UPA Tables 4.8A and 4.8B** from FMS031 Uniform Program Analysis, Efficacy Results, Vol.2, p. 22219 and 22220)

The Applicant's data demonstrate that in the ITT population, 12.2% of placebo-treated patients **met criteria for the "fibromyalgia syndrome" responder definition, compared to 19.64% of** patients on MLN 100 mg/day and 19.27% of patients on MLN 200 mg/day patients. According **to the Applicant's data, the efficacy of both doses of MLN achieved statistical significance when** compared to placebo: MLN 100 mg/day p= 0.028 and MLN 200 mg/day p=0.017. However, only the efficacy of the MLN 200 mg/day dose is supported for the treatment of FM syndrome -

because this dose did not "win" on the step number three of the multiple testing procedure, none of the other endpoints can be considered or tested for significance.

The composite responder analysis for the treatment of FM syndrome was also analyzed in the UPA population. In this analysis the proportion of treatment responders was also higher in the MLN treatment arms compared to the placebo arm: 12.28% of placebo-treated patients were responders, compared to 20.69% of patients on MLN 100 mg/day and 20.56% of patients on MLN 200 mg/day. According to the Applicant, this analysis demonstrated that the difference between placebo and the MLN treatment arms did achieve statistical significance: for the treatment group on MLN 100 mg/day (p= 0.024) and for the treatment group on MLN 200 mg/day (p=0.010). As previously mentioned, this latter analysis was *post-hoc*. The study was not initially powered for these sub-analyses, the p-values obtained are unadjusted, and therefore, should be interpreted with caution.

The efficacy data presented above was confirmed by the statistical reviewer, Dr. Joan Buenconsejo.

FDA's Efficacy Analysis

The Applicant proposed efficacy endpoints that the Division does not typically use to support efficacy of a treatment for fibromyalgia. As discussed in Section 6.1.2 (General Discussion of Endpoints), for this indication, efficacy is based on effects on pain as the primary endpoint and the effects of treatment on patient function and the patient global are considered secondary endpoints. To further characterize the efficacy of milnacipran in fibromyalgia, FDA conducted other analyses to:

- compare the change in mean pain scores for each treatment group
- provide an understanding of the impact of each component on the efficacy result generated by the composite responder analysis, and to verify that the observed dose effect is consistent in each of the domains,
- compare the continuous (cumulative) responder analyses for the patients' pain and global components of the "FM pain" composite endpoint.

Mean pain score analysis

The average pain score mean changes from baseline indicate that there is a numerically higher difference in MLN treatment arms compared with placebo and the magnitude seems to be dose related. The change in mean pain scores at 3 months for placebo was 12.7, 14.5 for MLN 100 mg/day and 15.2 for MLN 200 mg/day (on a 100 mm VAS). The difference between MLN 100 mg/day and placebo change in mean pain scores was 1.8, and the difference between the MLN 200 mg/day and placebo was 2.5. These differences are rather small and the clinical significance of this finding is unclear. Based on this analysis MLN does not seem to be better than placebo.

Responder analysis for the patient pain and global components of the "FM pain" composite endpoint

The purpose of conducting a continuous responder analysis for the pain and the PGIC domains separately is to gain understanding of how each component of the composite endpoint affects the result of the composite responder analysis. It is also important to understand how milnacipran affects pain as this is one of the main aspects of fibromyalgia.

Below are the responder analyses for two of the components of the composite responder endpoints: pain and PGIC independently, based on Dr. Buenconsejo's review utilizing the UPA analysis for the ITT population and BOCF as the imputation method at the 3-month endpoint. For the analysis of pain responders, the proportion of patients who had ≥ 30% improvement in pain from baseline was calculated. In terms of the responder analysis for the PGIC, the proportion of patients who had a PGIC score of 1 or 2 at study end were calculated.

Table 7. Study FMS031-Responder Analyses on Pain and PGIC for the ITT Population at 3 Months (BOCF)

Endpoints at 3-months		Placebo N=	Milnacipran 100 mg N=	Milnacipran 200 mg N=
Pain	Responders n (%)	62 (28%)	76 (34%)	155 (35%)
	OR	-	1.34 (0.9, 2.0)	1.42 (<1.0, 2.0)
PGIC	Responders n (%)	60 (27%)	74 (33%)	145 (33%)
	OR	-	1.34 (0.9,2.0)	1.33 (0.9, 1.9)

(Source: Table compiled by the reviewer based on Tables 31 and 32 from the statistical review by Dr. Joan Buenconsejo)

The data indicate that a higher proportion of patients were considered responders for pain from the MLN treatment groups compared to placebo: placebo 28%, versus MLN 100 mg/day 34%, and MLN 200 mg/day 35%. Despite the numerical difference between placebo and the MLN treatment groups, a statistically significant difference is not supported by the confidence intervals. The confidence intervals include 1, which indicates that a significant difference between the treatment arms is less likely.

The data indicate that also a higher proportion of patients were considered "patient global" responders in the MLN treatment groups than in the placebo group: placebo 27%, versus MLN 100 mg/day and MLN 200 mg/day, both 33%. As above, despite the numerical difference between placebo and the MLN treatment groups, this difference also is not supported by the confidence intervals. The confidence intervals include 1, which decreases the likelihood that there is a significant difference between the treatment arms. The proportion of patients who improved in each domain is very similar suggesting that both pain and PGIC contributed equally to the efficacy result obtained in the composite responder analysis for pain.

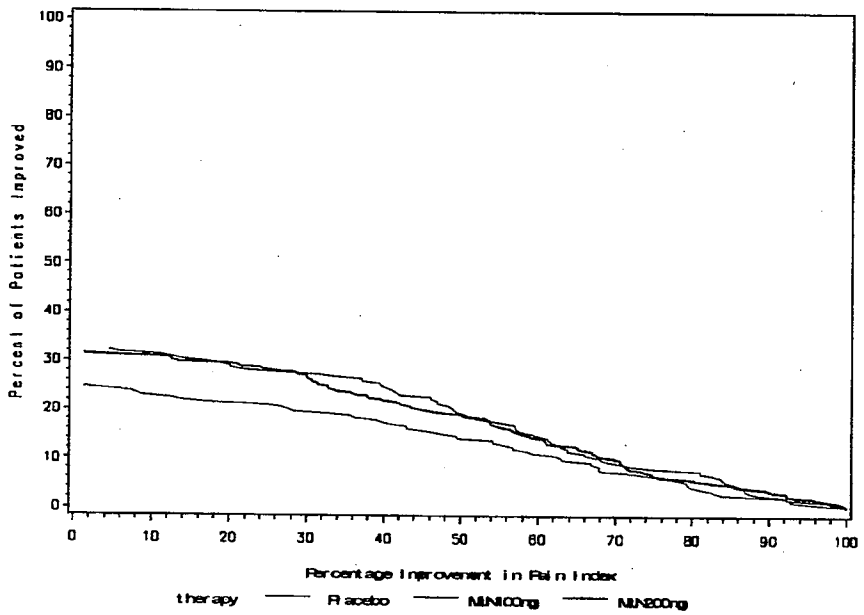
Continuous (cumulative) responder analysis for the "FM pain" composite endpoint

An additional analyses conducted by the FDA statistical reviewer was the continuous responder plot of the composite pain endpoint utilizing the UPA analysis of the ITT population at the 3 month landmark. The plot provides a visual display of the proportion of composite responders

across a continuum of definitions of improvement in pain, rather than at only one level of definition of improvement (e.g. ≥ 30% improvement). This data serves to confirm whether the difference in the proportion of composite treatment responders between the MLN and placebo groups is maintained if the definition of pain response is changed. Note that the composite pain endpoint is a more stringent analysis which selects only patients that were responders for both pain and a PGIC score of 1 or 2. Thus, this analysis includes a subset of the ITT population.

The plot for the composite pain response profile below demonstrates that although small, there is a difference between the MLN treatment arms and placebo, at each level of pain improvement. However, there is no considerable difference in effect between the two MLN doses.

Figure 6. Study FM031- Composite Pain Response Profile (UPA Analysis- ITT population)

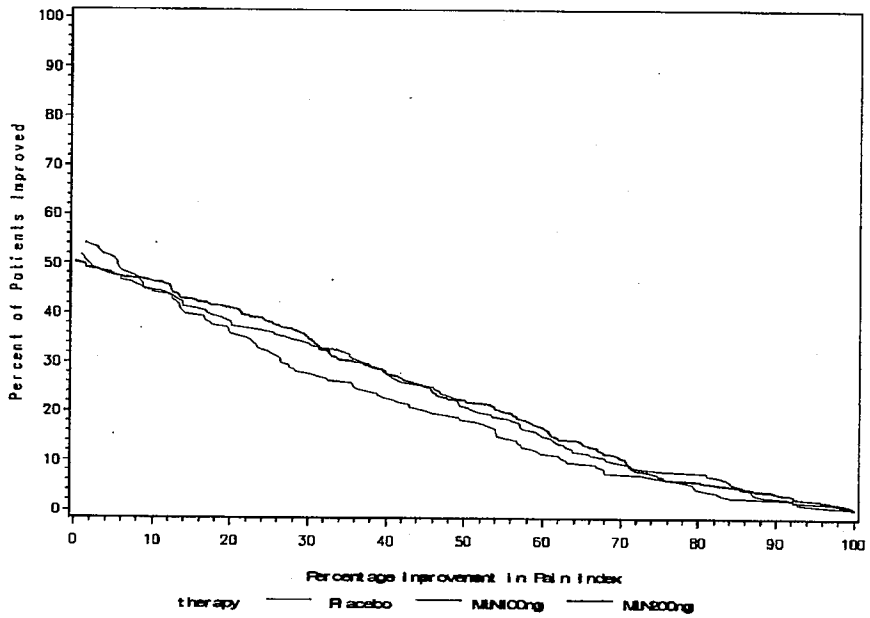


(Source: Figure 12 from the statistical review by Dr. Joan Buenconsejo)

Continuous (cumulative) responder analysis for "pain only" component of the composite endpoint

The continuous responder curves for the "pain only" responders demonstrate that overall, there is no clear separation between the MLN and placebo curves across different definitions of pain improvement, as demonstrated in the figure below. The separation between the curves is small and is more evident between 20 and 60% improvement of pain. The overall findings suggest that perhaps, an improvement in pain was not the primary contributor to the results of composite endpoint for "FM pain.

Figure 7. Study FM031-Pain Response Profile



(Source: Figure 12 from the statistical review by Dr. Joan Buenconsejo)

Percent "pain only" and "PGIC only" responders

The analysis of the percent of responders with respect to the pain and patient global tests is another mean of exploring the contribution of the pain and global response to the composite pain responder findings. The following is a table by Dr. Buenconsejo which summarizes the proportion of patients who were responders for pain and PGIC (composite pain responders), pain only and PGIC only. Patients were defined as pain responders if they had ≥ 30% improvement in pain and as patient global responders if they had a score of 1 or 2 on the PGIC.

Table 8. Study FMS031- Analysis of Pain and Global Tests (UPA Analysis, BOCF)

	N	Pain/PGIC (Yes/Yes)	Pain/PGIC (Yes/No)	Pain/PGIC (No/Yes)	Pain/PGIC (No/No)
Placebo	223	43 (19%)	19 (9%)	17 (8%)	144 (65%)
MLN100	224	61 (27%)	15 (7%)	13 (6%)	135 (60%)
MLN200	441	118 (27%)	37 (8%)	27 (6%)	259 (59%)

(Source: Table 34 from the statistical review by Dr. Joan Buenconsejo)

There are a higher proportion of MLN patients who were responders for the composite pain responder endpoint than placebo (Column Pain/PGIC Yes/Yes: placebo 19 % versus MLN 100 mg/day 27% and MLN 200 mg/day 27%). The overall proportion of all patients who had an improvement of pain is similar to the proportion of patients who were responders for the PGIC,

which demonstrates that the results of the composite pain analysis (Pain + PGIC responders) are not driven by the PGIC component. As shown below, when we look at the proportion of patients who improved in "pain alone" compared to the proportion of patients who had a good global score, we note that the proportion of patients on placebo who improved with respect to their pain only -Pain Yes/ PGIC No- and who achieved a good global score only- Pain No/ PGIC Yes- was similar (9% and 8% respectively). In the MLN 100 mg and 200 mg treatment arms, the proportion of patients who had a good global score only –Pain No/ PGIC Yes- (6% and 6% respectively) was similar to the proportion of patients who improved on pain only (MLN 100 mg 7% and MLN 200 mg 8%). These findings suggest that both endpoints contributed equally to the efficacy result of the pain composite responder endpoint:

- Overall proportion of patients who were responders for pain:
  Placebo: 25% (Pain Yes/ PGIC Yes 19% + Pain Yes/ PGIC No 9%)
  MLN 100 mg/day: 34% (Pain Yes/ PGIC Yes 27% + Pain Yes/ PGIC No 7%)
  MLN 200 mg/day: 35% (Pain Yes/ PGIC Yes 27% + Pain Yes/ PGIC No 8%)

- Overall proportion of patients who were responders for the PGIC:
  Placebo: 27% (Pain Yes/ PGIC Yes 19% + Pain No/ PGIC Yes 8%)
  MLN 100 mg/day: 33% (Pain Yes/ PGIC Yes 27% + Pain No/ PGIC Yes 6%)
  MLN 200 mg/day: 33% (Pain Yes/ PGIC Yes 27% + Pain No/ PGIC Yes 6%)

The data also show that more people met the definition for "pain only" response than that for the composite "FM pain" response (i.e. pain + PGIC responders).

To explore how, if at all, the patients who met criteria for the "pain only," PGIC only," and composite "FM pain" responder were different, Dr. Buenconsejo explored several characteristics and whether any of these would have contributed to the efficacy differences between the treatment arms. The baseline characteristics explored were demographics (age, race, gender), baseline BDI, baseline pain scores, and change in mean pain score (Table 9, below).

Dr. Buenconsejo found that there were no significant differences in the baseline characteristics among the treatment groups. The table also shows that, overall, the change in mean pain scores at 3 months among the composite pain responders (Pain/PGIC, yes/yes) – average of 43 - was greater compared to change in mean pain scores in among the "pain only" responders (Pain/PGIC, yes/no) - average of 30- and greater than the change in mean pain score compared to the "PGIC only" responders (Pain/PGIC, no/yes) - average of 7. This finding indicates that there is a greater effect on the improvement of pain among patients that met the composite responder criteria compared to the other groups of responders. However, when we look across the treatment arms of each responder group, the change in mean pain scores is similar across all the treatment arms in all responder groups:

- among the composite responders – mean change of 43 for all treatment arms (placebo= MLN 100= MLN 200)
- among the "pain only" responders- the mean change was similar between the treatment arms but slightly lower on the MLN 100 treatment arm: 31 for placebo, 28 for MLN 100 and 33 for MLN 200 (MLN 100 < placebo < MLN 200)

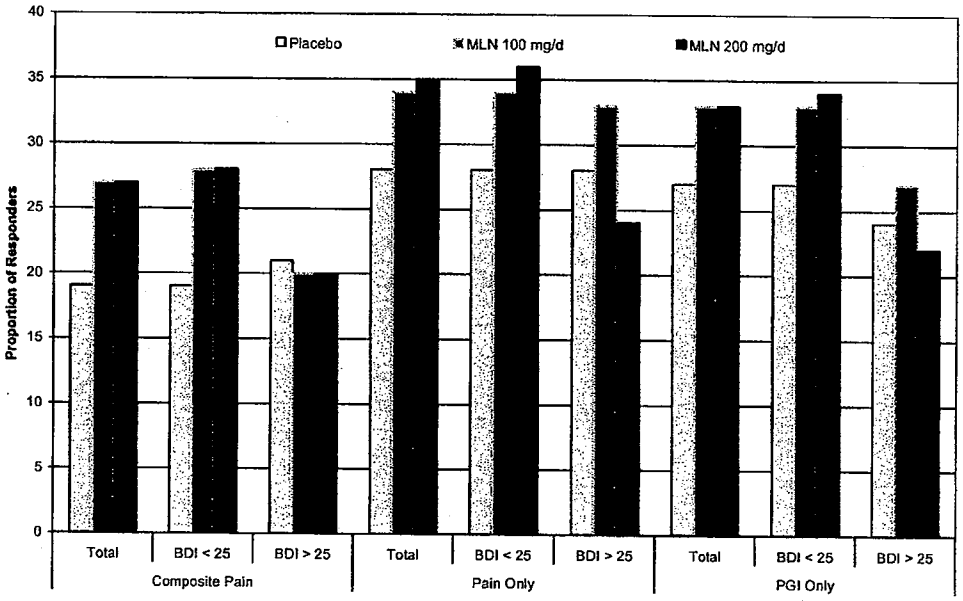
- **among the "global only" responders- the mean change** was similar across the treatment arms but slightly lower in the placebo arm and higher in the MLN 200 arm : 6 for placebo, 8 for MLN 100 and 9 for MLN 200 (placebo< MLN 100< MLN 200)

Table 9. Study FMS031- Comparison of Change in Mean Pain Scores and Baseline Characteristics (Source: Statistical review by Dr. Joan Buenconsejo)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Total		N=223	N=224	N=441
Pain/PGIC (Yes/Yes)		43 (19%)	61 (27%)	118 (27%)
	Sex (F)	43 (98%)	60 (98%)	117 (99%)
	Race (W)	38 (88%)	56 (92%)	112 (95%)
	Age, in yrs (mean)	48.7 (8.9)	50.0 (10.3)	49.3 (10.7)
	Baseline BDI	14.2 (10.2)	12.2 (7.1)	14.5 (7.5)
	Duration of FMS	6.2 (5.6)	4.7 (4.9)	5.1 (4.5)
	Mean Pain Score (Range) - BOCF	68 (52 – 96)	69 (52 – 89)	69 (47 – 99)
	Baseline	24 (0 – 62)	25 (0 – 52)	26 (0 – 60)
	3-month landmark*	43 (24 – 88)	43 (19 – 71)	43 (17 – 86)
	Change from Baseline†			
Pain/PGIC (Yes/No)		19 (9%)	15 (7%)	37 (8%)
	Sex (F)	19 (100%)	15 (100%)	37 (100%)
	Race (W)	18 (95%)	15 (100%)	33 (89%)
	Age, in yrs (mean)	53.6 (9.4)	54.1 (9.9)	51.4 (10.4)
	Baseline BDI	13.2 (12.0)	16.5 (6.9)	14.4 (7.9)
	Duration of FMS	7.4 (5.8)	5.1 (5.1)	6.4 (6.1)
	Mean Pain Score (Range)-BOCF			
	Baseline	67 (53 – 85)	62 (49 – 83)	66 (49 – 87)
	3-month landmark*	36 (25 – 56)	35 (23 – 46)	33 (15 – 54)
	Change from Baseline†	31 (17 – 49)	28 (16 – 59)	33 (15 – 51)
Pain/PGIC (No/Yes)		17 (8%)	13 (6%)	27 (6%)
	Sex (F)	16 (94%)	13 (100%)	26 (96%)
	Race (W)	17 (100%)	11 (85%)	26 (96%)
	Age, in yrs (mean)	42.9 (11.2)	45.9 (9.2)	46.5 (9.7)
	Baseline BDI	12.2 (7.2)	12.6 (7.8)	12.3 (7.1)
	Duration of FMS	5.6 (4.7)	6.0 (4.3)	5.0 (4.7)
	Mean Pain Score (Range) - BOCF	66 (52 – 92)	64 (50 – 82)	66 (53 – 89)
	Baseline	57 (33 – 90)	54 (24 – 66)	55 (30 – 83)
	3-month landmark*	6 (-11 – 21)	8 (-7 – 20)	9 (-7 – 22)
	Change from Baseline†			

One characteristic of great interest is the BDI at baseline, as MLN's anti-depressant effect could directly affect efficacy. Dr. Buenconsejo's analysis of the efficacy data and the BDI baseline scores confirmed the Applicant's claim that the effect observed on the efficacy results was not due to an anti-depressant effect. These findings are shown in the bar graph below (taken from Dr. Buenconsejo's review), representing the composite pain responder, pain responder and PGIC responder by baseline BDI (≤ 25 or > 25). For further detail please refer to the statistical review.

Figure 8. Study FMS031- Composite Pain Responder, Pain Responder and PGIC Responder by Baseline BDI ($\leq$25 or >25) – BOCF, UPA Analysis



(Source: Figure 35 from the statistical review by Dr. Joan Buenconsejo)

Percent "pain only" and "PGIC only" responders – UPA population

The results of the responder analysis for the individual "pain only" and "PGIC only" domains were similar to those of the UPA Analysis utilizing the ITT population. The proportion pain and PCIG responders is similar in the treatment groups. The proportion of pain responders was 27% in the placebo group, 34% in the MLN 100 mg/day group, and 37% in the in the MLN 200 mg/day group. The proportion of global improvement (PGIC) responders was 26% in the placebo group, 34% in the MLN 100 mg/day group, and 35% in the in the MLN 200 mg/day group. This data confirms that the result is not being driven by any of the components of the composite endpoint.

Also according to this data, MLN 200 mg/day seems to have a greater effect on patient's pain and their sense of overall improvement (PGIC score) than the 100 mg/day treatment arm and the

placebo arm. A summary of the responder analysis on pain and PGIC for the UPA population is presented below.

Table 10. Study FMS031-Responder Analyses on Pain and PGIC for the UPA Population

Endpoints at 3-months		Placebo N=171	Milnacipran 100 mg N=189	Milnacipran 200 mg N=355
Pain	Responders n (%)	47 (27%)	64 (34%)	133 (37%)
	OR	-	1.36 (0.9, 2.1)	1.60 (1.1, 2.4)
PGIC	Responders n (%)	45 (26%)	64 (34%)	125 (35%)
	OR	-	1.43 (0.9,2.3)	1.52 (1.0,2.3)

(Source: Table compiled by the reviewer based on Table 38 from the statistical review by Dr. Joan Buenconsejo)

Composite responder analysis for the "treatment of FM syndrome" composite endpoint

Although "treatment of FM syndrome" will no longer be considered as an indication, we evaluated the syndrome composite responder analysis which includes patients that were responders for the function endpoint (improvement of at least 6 points on the SF-36 PCS score) in addition to the pain and PGIC endpoints concomitantly. This analysis would provide information whether by improving function, MLN proves effective for the treatment of FM. Below is a table summarizing the syndrome composite responder analysis and the results of the responder analysis for the individual "function only" endpoint.

Table 11. Study FMS031- Composite Syndrome Responder Analysis and Function (SF-36 PCS) - ITT, BOCF

Time point : 3 months	Placebo (N=223)	MLN 100 mg (N=224)	MLN 200 mg (N=441)
Composite responder rate (%)	27(12%)	44 (20%)	85 (19%)
Odds ratio(95%CI)		1.84 (1.1, 3.2)	1.80 (1.1, 2.9)
p-value		p=0.0277	p= 0.0175
SF-36 PCS (%)	61 (27%)	71 (32%)	131 (30%)
Odds ratio(95%CI)		1.28 (0.8, 2.0)	1.18 (0.8, 1.7)
p-value		p= 0.254	p= 0.403

(Source: Table compiled by the reviewer based on Table 36 of the statistical review by Dr. Joan Buenconsejo)

There is a higher proportion of patients who were considered responders for the composite syndrome responder analysis (placebo 12%, MLN 100 mg/day 20%, and MLN 200 mg/day 19%). Once again, only the efficacy of the MLN 200 mg/day dose (p=0.0175) is supported for the treatment of FMS because it did not win on the step number three of the multiple testing procedure, therefore none of the other endpoints can be considered or tested for significance. In

addition, despite the fact that a higher proportion of patients on MLN were considered responders for the composite syndrome responder analysis, the difference between the function endpoint of the MLN treatment arms and placebo was not significant making it difficult to explain how this information correlates with the result of the composite syndrome responder analysis.

Summary

The results of the composite pain responder analysis indicate that MLN is efficacious for the treatment of FM. The data provides statistically significant evidence of efficacy for the MLN 200 mg/day dose compared to placebo and there is some indication of efficacy for the MLN 100mg/day dose based on the numerical difference between the proportion of responders in the MLN 100 mg/day treatment arm and placebo. The difference between the MLN treatment arms was also demonstrated in the plot for the composite pain response profile where there is a small difference between both MLN treatment arms and placebo, at each level of pain improvement. Although there is a statistically significant difference between MLN 200 mg/day and placebo, clinically, only a relatively low proportion of treated patients (27%) responded to MLN 200 mg/day.

6.1.4.2 Efficacy Findings of Study MLN-MD-02

Applicant's Efficacy Analysis

Study MLN-MD-02 was designed as a 6-month trial. The study was ongoing when the Applicant was notified that the efficacy studies no longer were required to have 6-months duration. The study was then truncated to 3 months. The Applicant submitted the analysis of the efficacy of MLN at the 3-month endpoint as agreed upon during the IND phase, and the results are presented below.

Composite responder analysis for the "treatment of FM pain" composite endpoint

The data for the composite responder analysis for the "treatment of FM pain" using the ITT population is presented below. The Applicant's data show that there is a higher proportion of "FM pain" responders in the MLN treatment arms compared to placebo and that these differences achieved statistical significance. In the placebo arm 16.4% of the patients were responders for the pain composite whereas 22.8% (p= 0.024) in the MLN 100 mg/day arm and 24.75% (p= 0.004) in the MLN 200 mg/day arm were responders.

Table 12. Study MLN-MD-02- Composite Responder Analysis for the Treatment of Pain of FM at the 3-Month Endpoint- ITT Population

Time point: 3 months	ITT Population		
	Placebo (N=401)	MLN	
		100 mg (N=399)	200 mg (N=396)
Composite responder rates (%)	66 (16.46)	91 (22.81)	98 (24.75)
Odds ratio (95% CI)	-	1.50 (1.05, 2.14)	1.67 (1.18,2.37)
p- value	-	0.024	0.004

(Source: Table compiled by the reviewer based on the Applicant's Table 3.1C, Summary of Clinical Efficacy, p. 157)

Composite responder analysis for the "treatment of FM syndrome" composite endpoint

The Applicant also submitted data for the composite responder analysis for the "treatment of FM syndrome" which is summarized below.

Table 13. Study MLN-MD-02- Composite Responder Analyses for the Treatment of FM Syndrome at the 3-month Endpoint- ITT, BOCF

	Placebo (N=401)	MLN	
		100 mg (N=399)	200 mg (N=396)
Composite responder rates (n, %)	35(8.73)	58 (14.54)	55(13.89)
Odds ratio (95% CI)	-	1.79 (1.14,2.80)	1.75 (1.11, 2.75)
p- value	-	0.011	0.015

(Source: Table compiled by the reviewer based on Table 14.4.1.2A, MLN-MD-02 Clinical Study Report, Vol.1, p. 412)

The Applicant's data demonstrates that 8.73% of placebo-treated patients met the responder criteria for the "fibromyalgia syndrome" responder definition, compared to 14.54% of patients on MLN 100 mg/day and 13.89% patients on MLN 200 mg/day. According to the Applicant's data, the efficacy of both doses of MLN achieved statistical significance when compared to placebo: MLN 100 mg/day p=0.011 and MLN 200 mg/day p=0.015. The data indicates that there is a statistically significant difference in the composite syndrome responder rate between placebo and the MLN treatment arms when the pre-specified two-step multiplicity adjustment is applied.

The efficacy data presented above was confirmed by the statistical reviewer. Although one clinical site was terminated due to non compliance with Good Clinical Practices and the Applicant excluded this site from its analyses, Dr. Buenconsejo found that the results were not affected by the inclusion of the 10 patients from this one center, nor from exclusion of class 4 violators and the removal of restrictions in the definition of a treatment responder. For further detail, please refer to the statistical review.

FDA's Efficacy Analysis

As previously mentioned, the Division conducted additional efficacy analyses to further characterize the efficacy of milnacipran in fibromyalgia. The other analyses were conducted to provide an understanding of the impact of each component on the efficacy result generated by the composite responder analysis, and to verify whether the effect seen on the primary analysis is consistent in each of the domains of the composite endpoint. Following is the analysis of the change in mean pain scores and the responder analyses for the patients' pain and global components of the "FM pain" composite endpoint.

Mean pain score analysis

There was a numerically higher difference the in the average change in mean pain score from baseline in the MLN treatment arms compared with placebo, and seemed to be dose related. The change in mean pain score for placebo was 10.0 (on a 100 mm VAS), 12.4 for MLN 100 mg/day and 12.9 for MLN 200 mg/day. The difference between MLN 100 mg/day and placebo was 2.4, and the difference between MLN 200 mg/day and placebo was 2.9. These differences are rather small, and they seem to increase with higher dose. The clinical significance of these differences in the mean changes from baseline is unclear.

Responder analysis for the patient pain and global components of the "FM pain" composite endpoint

Once again, the purpose of conducting a responder analysis for pain and the PGIC separately is to gain understanding of how each component of the composite affects the composite endpoint result as well as the effect of each dose. In the case of this drug product it is important to understand how it affects pain, as this is one of the main aspects of fibromyalgia.

Below are the responder analyses for two of the components of the composite "FMS pain" responder endpoint: pain and PGIC independently, based on Dr. Buenconsejo's preliminary review for the ITT population and utilizing BOCF as the imputation method at the 3-month endpoint. For the "pain only" responder analysis, the proportion of patients who had $\geq$ 30% improvement in pain from baseline was calculated. In terms of the patient global responder analysis, the proportion of patients who had a PGIC score of 1 or 2 at study end was calculated.

Table 14. Study MLN-MD-02-Responder Analyses on Pain and PGIC for the ITT Population at 3 Months (BOCF)

Endpoints at 3-months		Placebo N=401	Milnacipran 100 mg N=399	Milnacipran 200 mg N=396
Pain	Responders n (%)	101 (25%)	124 (31%)	119 (30%)
	OR	-	1.34 (<1.0, 1.8)	1.28 (0.9, 1.8)
PGIC	Responders n (%)	92 (23%)	125 (31%)	145 (33%)
	OR	-	1.53 (1.1, 2.1)	1.62 (1.2, 2.2)

(Source; Table compiled by the reviewer based on Table 20 of the statistical review by Dr. Joan Buenconsejo)

The data indicates that a higher proportion of patients were considered responders for "pain only" from the MLN treatment groups compared to placebo: placebo 25.2%, versus MLN 100 mg/day 31.08% and MLN 200 mg/day 30.05%. Despite the numerical difference between placebo and the MLN treatment groups, a statistical difference is not supported by the confidence intervals. The confidence intervals include 1, which indicates that a significant difference between the treatment arms is less likely.

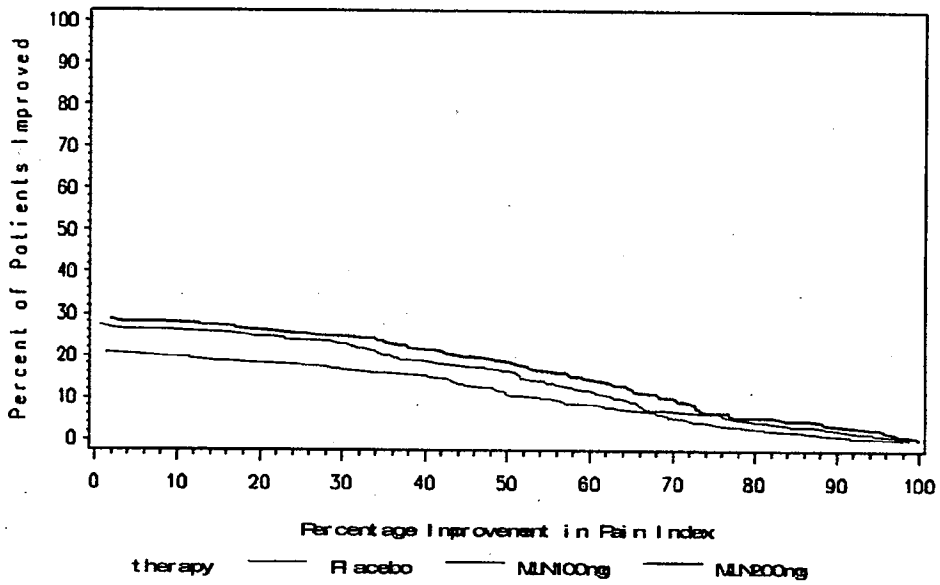
The data also indicate that a higher proportion of patients were considered "patient global" responders in the MLN treatment groups than in the placebo group: placebo 22.94%, versus MLN 100 mg/day 31.33% and MLN 200 mg/day 32.58%. In this analysis, a statistical difference is supported by the confidence intervals. The data suggest that the PGIC may have driven the efficacy result obtained in the composite responder analysis for pain.

Continuous (cumulative) responder analysis for the "FM pain" composite endpoint

As in the analysis of Study FMS031, a continuous responder plot of the composite "FM pain" endpoint at the 3 month landmark was conducted by the statistical reviewer, utilizing the ITT population. The plot provides a visual display of the proportion of responders across a continuum of definitions of improvement in pain and not at only one level (e.g. $\geq$ 30% improvement). This data serves to confirm whether the difference across groups that was observed for the composite primary endpoint is maintained if the definition of pain response is changed.

The continuous responder plot for the composite "FM pain" endpoint below demonstrates that although small, there is a difference in the proportion of responders between the MLN treatment arms and placebo, which is more evident when a less stringent definition of pain response is used. The graph also indicates that there is a very small difference of effect between the two MLN doses.

Figure 9. Study MLN-MD-02- Composite Pain Response Profile (ITT population)

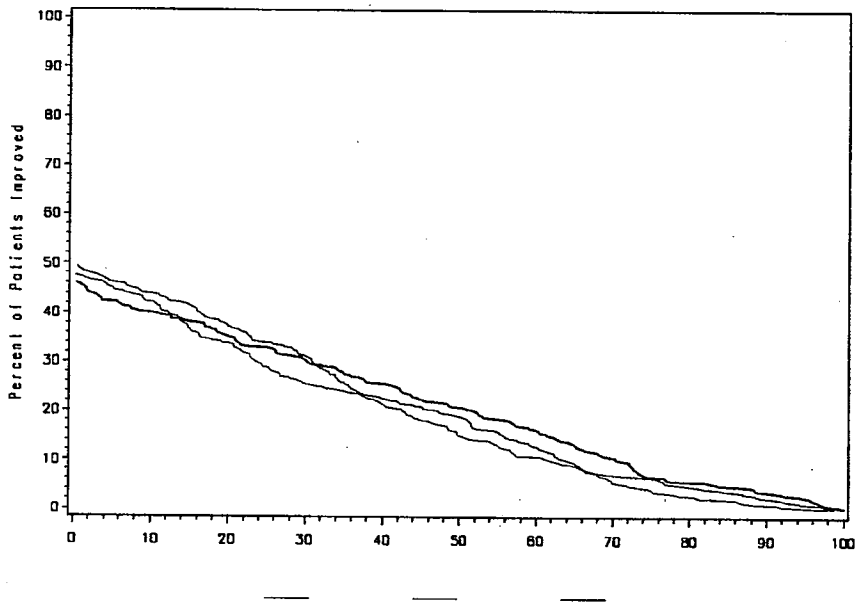


(Source: Figure 2 from the statistical review by Dr. Joan Buenconsejo)

Continuous (cumulative) responder analysis for the "pain" component of the composite endpoint

The continuous responder curves for the "pain only" responders demonstrate that there is no clear separation between the MLN and placebo curves across different definitions of pain improvement. This suggests that perhaps improvement in pain alone did not drive the positive result of the composite "FM pain" responder analysis. This analysis suggests that the difference in the composite responder rate may be attributed to the number of patients with good scores in the PCIG (i.e. the other component of the composite endpoint).

Figure 10.Study MLN-MD-02-Pain Response Profile



(Source: Figure 2 from the statistical review by Dr. Joan Buenconsejo)

Percent "pain only" and "PGIC only" responders

The analysis of the percent of responders with respect to the pain and patient global tests is another mean of exploring the contribution of the pain and global response to the composite pain responder findings. The following is a table by Dr. Buenconsejo which summarizes the number of patients who were responders for both improvement in pain and PGIC score (composite pain responders), improvement in "pain only" and improvement on the PGIC only.

Table 15. Study MLN-MD-02- Analysis of Pain and Global Tests (BOCF)

	N	Pain/PGIC (Yes/Yes)	Pain/PGIC (Yes/No)	Pain/PGIC (No/Yes)	Pain/PGIC (No/No)
Placebo	401	66(16%)	35(9%)	26 (6%)	274 (68%)
MLN100	399	91(23%)	33 (8%)	34 (12%)	241 (60%)
MLN200	396	98 (25%)	21(5%)	31 (8%)	246 (62%)

(Source: Table 22 from the statistical review by Dr. Joan Buenconsejo)

There was a higher proportion of patients who were responders for the composite responder analysis (placebo 16 % versus MLN 100 mg/day 23%, and MLN 200 mg/day 25%). Based on this analysis, the data demonstrates that the **results of the composite "FM pain" endpoint are** driven by the PGIC component. As shown below, when we look at the proportion of patients who improved in pain compared to the proportion of patients who had a good global score, we

note that there were more patients on placebo who improved with respect to their pain only -Pain Yes/ PGIC No- than patients on placebo who achieved a good global score only- Pain No/ PGIC Yes- (9% vs. 6%), whereas in the MLN treatment arms, there were more patients who had a good global score only (MLN 100, 8% and MLN 200 mg 12%) than patients who improved on pain only (MLN 100, 5% and MLN 200, 8%):

- Overall proportion of patients who were responders for pain:
  Placebo: 25% (Pain Yes/ PGIC Yes % 16 + Pain Yes/ PGIC No 9 %)
  MLN 100 mg/day: 31% (Pain Yes/ PGIC Yes % 23 + Pain Yes/ PGIC No 8%)
  MLN 200 mg/day: 30% (Pain Yes/ PGIC Yes % 25 + Pain Yes/ PGIC No 5%)

- Overall proportion of patients who were responders for the PGIC:
  Placebo: 22% (Pain Yes/ PGIC Yes 16% + Pain No/ PGIC Yes 6%)
  MLN 100 mg/day: 35% (Pain Yes/ PGIC Yes 23% + Pain No/ PGIC Yes 12%)
  MLN 200 mg/day: 33% (Pain Yes/ PGIC Yes 25% + Pain No/ PGIC Yes 8%)

In summary:

- 25% of placebo patients improved on pain and only 22% had good PGIC scores
- 31% of the patients on MLN 100mg/day improved on pain but 35% had good PGIC scores
- 30% of the patients on MLN 200mg/day improved on pain but 33% had good PGIC scores

To explore how, if at all, the patients who met criteria for the "pain only," PGIC only," and composite "FM pain" responder were different, Dr. Buenconsejo explored several characteristics of the composite pain responders to understand whether any of these would have contributed to the efficacy differences between the treatment arms (as was performed for Study FMS031). The baseline characteristics explored were demographics (age, race, gender), baseline BDI, baseline pain scores, and change in mean pain score (Table 16 below).

Dr. Buenconsejo found that there were no significant differences in the baseline characteristics among the treatment groups also in this study. The data indicates that the results were not influenced by any of the characteristics analyzed as the groups seem to have a similar profile in terms of gender, age race, baseline BDI, and duration of FMS. The table also shows that, overall, the change in mean pain score at 3-months among the composite pain responders (Pain/PGIC, yes/yes) – average of 40 - was greater compared to change in mean pain scores in among the "pain only" responders (Pain/PGIC, yes/no) - average 30- and greater than the change in mean pain score compared to the "PGIC only" responders (Pain/PGIC, no/yes) - average of 6. This finding indicates that there is a greater effect on the improvement of pain among the patients who were "composite" responders compared to the other groups of responders. However, when we look across the treatment arms of each responder group the change in mean pain scores is similar across all the treatment arms in all responder groups:

- among the composite responders – mean change was similar for all treatment groups with a slightly smaller change for MLN 100: 40 for placebo, 39 for MLN 100 and 40 for MLN 200 (MLN 100 < placebo=MLN 200)
- among the "pain only" responders- the mean change was similar between the treatment arms but slightly lower on the MLN 100 treatment arm: 31 for placebo, 27 for MLN 100 and 33 for MLN 200 (MLN 100 < placebo < MLN 200)

- **among the "global only" responders- the mean change** was similar across the treatment arms but slightly higher in the placebo arm: 8 for placebo, 5 for MLN 100 and 5 for MLN 200 (placebo< MLN 100< MLN 200)

Because the mean change in pain scores was not significantly higher in the MLN treatment arms when compared to placebo, the data suggests that the difference in the proportion on responders in the pain composite responder endpoint may have been driven by the PGIC.

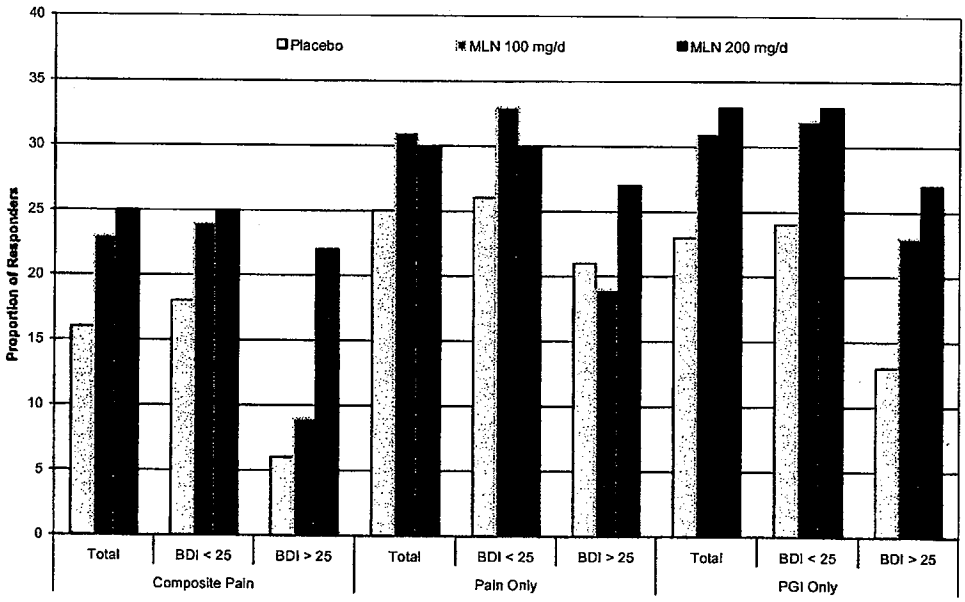
Table 16. Study MLN-MD-02- Comparison of Change in Mean Pain Scores and Baseline Characteristics (Source: Statistical review by Dr. Joan Buenconsejo)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Total		N=401	N=399	N=396
Pain/PGIC (Yes/Yes)		66 (16%)	91 (23%)	98 (25%)
	Sex (F)	62 (94%)	88 (97%)	97 (99%)
	Race (W)	64 (97%)	87 (96%)	92 (94%)
	Age, in yrs (mean)	51.3 (9.8)	49.5 (9.5)	50.7 (10.2)
	Baseline BDI	12.4 (6.6)	12.2 (7.5)	13.6 (9.1)
	Duration of FMS	10.8 (9.3)	9.6 (8.1)	10.0 (7.9)
	Mean Pain Score (Range)			
	Baseline	65 (42 – 94)	65 (39 – 99)	63 (39 – 90)
	3-month landmark*	25 (1 – 52)	25 (1 – 54)	23 (0 – 57)
	Change from Baseline†	40 (18 – 75)	39 (16 – 80)	40 (13 – 81)
Pain/PGIC (Yes/No)		35 (9%)	33 (8%)	21 (5%)
	Sex (F)	35 (100%)	32 (97%)	20 (95%)
	Race (W)	34 (97%)	31 (94%)	21 (100%)
	Age, in yrs (mean)	51.6 (9.9)	53.5 (9.5)	49.6 (11.6)
	Baseline BDI	14.7 (9.4)	15.0 (9.2)	13.5 (7.6)
	Duration of FMS	9.6 (9.3)	11.2 (8.6)	8.4 (7.2)
	Mean Pain Score (Range)			
	Baseline	63 (43 – 91)	63 (42 – 91)	67 (45 - 91)
	3-month landmark*	31 (12 – 52)	35 (7 – 55)	34 (4 – 54)
	Change from Baseline†	31 (15 – 60)	27 (14 – 51)	33 (17 – 65)
Pain/PGIC (No/Yes)		26 (6%)	34 (12%)	31 (8%)
	Sex (F)	26 (100%)	34 (100%)	31 (100%)
	Race (W)	24 (92%)	34 (100%)	29 (94%)
	Age, in yrs (mean)	51.1 (6.0)	51.3 (9.6)	48.6 (10.6)
	Baseline BDI	13.2 (8.1)	15.5 (8.9)	15.0 (9.5)
	Duration of FMS	7.8 (8.1)	8.4 (6.2)	7.8 (6.2)
	Mean Pain Score (Range)			

	Baseline	69 (41 – 89)	63 (42 – 99)	66 (43 – 95)
	3-month landmark*	58 (17 – 88)	56 (24 – 99)	60 (20 – 95)
	Change from Baseline†	8 (-4 – 24)	5 (-5 – 23)	5 (-7 – 23)

One characteristic of interest is the BDI at baseline as MLN's anti-depressant effect could directly affect efficacy. Once again, Dr. Buenconsejo's analysis of the efficacy data and the BDI baseline scores does not indicate that the baseline BDI score affected the results. Below is a bar graph from Dr. Buenconsejo's review representing the composite pain responder, pain responder and PGIC responder values by baseline BDI (≤ 25 or > 25). For further detail please refer to the statistical review.

Figure 11. Study MLN-MD-02- Composite Pain Responder, Pain Responder and PGIC Responder by Baseline BDI (≤25 or >25) – BOCF



(Source: Figure 33 from the statistical preliminary review by Dr. Joan Buenconsejo)

Composite responder analysis for the "treatment of FM syndrome" composite endpoint

As performed with Study FMS031, we performed a "FM syndrome" composite responder analysis, which calculates the percent of patients that were responders for the function endpoint (improvement of at least 6 points on the SF-36 PCS score), in addition to the pain and PGIC endpoints concomitantly. This analysis would provide information whether MLN is effective for the treatment of these three key characteristics of FM. Below is a table summarizing the FM syndrome composite responder analysis and the results of the responder analysis for the individual "function only" endpoint.

Table 17. Study MLN-MD-02- Composite Syndrome Responder Analysis and Function (SF-36 PCS) - ITT, BOCF

Time point : 3 months	Placebo (N=401)	MLN	
		100 mg (N=399)	200 mg (N=396)
"FM Syndrome" Composite responder rate (%)	35 (9%)	58 (15%)	55(14%)
Odds ratio(95%CI) p-value		1.79 (1.1, 2.8) p=0.011	1.75(1.1, 2.8) p= 0.015
"Function only" (SF-36 PCS) responder rate (%)	86 (21%)	108 (27%)	89 (22%)
Odds ratio(95%CI) p-value		1.37 (<1.0, 1.9) p= 0.0628	1.10 (0.8, 1.6) p= 0.4611

(Source: Table compiled by the reviewer based on Table 24 of the statistical review by Dr. Joan Buenconsejo)

There is a higher proportion of patients who were considered responders for the composite syndrome responder analysis (placebo 9%, MLN 100 mg/day 15%, and MLN 200 mg/day 14%). The differences between placebo and the MLN treatment arms are statistically significant: placebo versus MLN 100mg/day p= 0.011 and placebo versus MLN 200mg/day p=0.015 and this finding is confirmed by the confidence intervals that do not include 1.

The proportion of patients who met responder criteria for "function only" was greatest in the MLN 100 mg/day group (27%), compared to the MLN 200 mg/day group (22%) and placebo group (21%). The difference between the "function" endpoint of the MLN treatment arms and placebo was not statistically significant. These results are not consistent with the results if the composite syndrome response analysis, making it difficult to explain how these findings correlate.

Summary

The results of the composite "FM pain" responder analysis indicate that MLN is efficacious for the treatment of FM. The data provides statistically significant evidence of efficacy for MLN at both doses compared to placebo and this result seems to be driven by the PGIC. The difference between the MLN treatment arms was also demonstrated in the continuous responder plot for the composite "FM pain" endpoint, where there is a small difference between both MLN treatment arms and placebo, at each level of pain improvement. Although there is a statistically significant difference between the MLN treatment arms and placebo, the absolute proportion of patients that responded to MLN is relatively low (23% for MLN 100mg/day and 25% for MLN 200mg/day), and this is in concordance with the results achieved in Study FMS031.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

After several discussions held with DAARP the Applicant modified the study design and endpoints of studies FMS031 and MLN-MD-02. Both trials were intended to be 6-months long. The former study was already concluded and the latter was ongoing but was truncated to 3-months duration. These changes in design and endpoints recommended by the Agency reflected the current approach on the evaluation of drugs for FM. The Applicant chose to show efficacy using two composite responder endpoints at 3- months. According to the Applicant, the efficacy data demonstrates that MLN was effective for the treatment of "pain of FM" and "FM syndrome" in Study FMS031 and in Study MLN-MD-02, at the doses of 100 mg/day and 200 mg/day.

Our analysis of the data is not in concordance with the Applicant's conclusion of efficacy. With respect to our analysis of the "FM pain" composite endpoint in Study FMS031, the treatment effect of MLN was statistically significant only for the 200 mg/day dose. The p value for the MLN dose of 100 mg/day cannot be accepted as support of efficacy because MLN did not "win" on the step number three of the sequential testing procedure that was pre-determined by the Applicant; therefore none of the other endpoints can be considered or tested for significance. In this study, the positive efficacy result for the composite "FM pain" endpoint both the pain and patient global components seem to have an equal impact on the efficacy result. Despite the statistically significant difference between placebo and the MLN 200 mg/day treatment arm the data indicates that a relatively small proportion of patients (27%) will respond to MLN 200mg/day. Although the MLN 100mg/day dose did not achieve statistical significance there is a proportion of patients that seem to respond to this dose.

In our analysis of Study MLN-MD-02, the treatment effect of MLN did achieve statistical significance for both doses for the "FM pain" composite endpoint. Despite the statistically significant result of the pain composite response analysis, the analysis of "pain only" response did not seem to correlate with the composite endpoint results (i.e. there was no difference in the proportion of "pain only" responders between the MLN group and placebo). The PGIC component seems to have driven the results of the composite endpoint favorably. Again, despite the statistically significant difference of efficacy between the MLN treatment arms and placebo, the numbers indicate that a small proportion of patients is expected to respond to MLN, 23% with MLN 100mg/day and 25% with MLN 200mg/day.

I conclude that even though the analysis of the "pain only" responder rates does not indicate that there is a significant effect MLN on pain, MLN seems to improve FM, as indicated by the composite "FM pain" responder analysis (i.e. the proportion of patients who had good pain and PGIC responses). The means by which MLN has an overall positive effect on FM is unclear.

Several variables were explored such as demographics (age, race gender), baseline BDI, and baseline pain scores, none of which revealed an impact on the efficacy results. The BDI was of particular interest as MLN through its anti-depressant effect could affect the results. This hypothesis was not confirmed by several sub-group analyses conducted by the statistical reviewer.

The efficacy data for the composite "FM pain" endpoint was statistically significant for MLN 200 mg/day in both studies. The efficacy data was statistically significant for MLN 100mg/day, only in Study MLN-MD-02. Nevertheless, there is indication that there is some efficacy of the MLN 100 mg/day dose based on the numerically higher proportion of composite "FM pain" responders in the MLN 100 mg/day treatment group compared to placebo. Also the continuous responder rate plots for the "FM pain" composite responder analysis using different definitions of pain response indicate that a proportion of patients do respond to the lower MLN dose.

Lastly, although the indication "treatment of FM syndrome" is no longer being considered, we analyzed the data for the "FM syndrome" endpoint as additional evidence of the efficacy of this product. There was evidence of efficacy for the composite syndrome responder analysis for the two doses in Study MLN-MD-02 and only for the higher dose in Study FMS031 because MLN did not "win" on the step three of the multiple comparisons gatekeeping procedure as previously mentioned. The difference in the "function only" endpoint did not achieve statistical significance which does not correlate to the findings from the composite syndrome responder analysis. The higher proportion of responders in the MLN treatment arms, however, suggests that there may be an effect in improvement of function in FM patients.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Integrated Summary of Safety (ISS) submitted by the Applicant summarizes data from five study groups as follows:

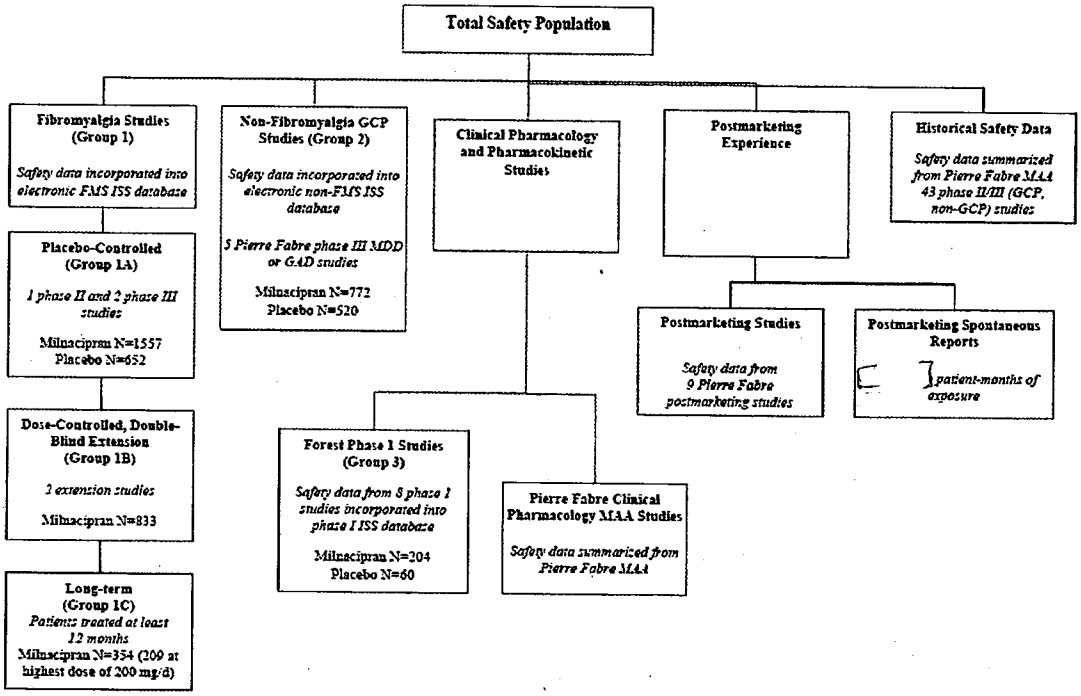
1. Fibromyalgia (FM) Safety Data (Group 1)
   - One Phase II and two Phase III double-blind, placebo-controlled studies in FM conducted by Forest/Cypress (Group 1A)
   - Two double-blind extension studies in FM conducted by Forest/Cypress (Group 1B which consists of a subset of 1A patients)
   - Long-term safety data from FM patients treated with milnacipran (MLN) for at least 12 months (Group 1C which consists of a subset of 1B patients)
2. Non-Fibromyalgia Safety Data (Group 2)
   - Five double-blind, placebo-controlled Phase III studies in major depressive disorder (MDD) or generalized anxiety disorder (GAD) conducted by Pierre Fabre
3. Historical Safety Data

- Forty-three Phase II and III studies in the Pierre Fabre MAA (both GCP, and non-GCP)

4. Clinical Pharmacology/PK Safety Data
   - Eight Phase I PK studies conducted by Forest (Group 3)
   - PK studies from the Pierre Fabre MAA
5. Post-marketing Experience
   - Nine post-marketing studies (Pierre Fabre studies conducted after the approval of MLN in Europe)
   - Spontaneous event reporting

This grouping of safety data was agreed to by the Division at the pre-NDA meeting. The sub-groups of the total safety population are illustrated in the figure below.

Figure 12. Clinical Studies in the Development Program for Milnacipran



b(4)

(Source: Applicant's Figure 5.1.1-1, Summary of Clinical Safety, Vol.1, p.42)

The safety population was for Groups 1, 2, and 3 all patients who took at least one dose of the study drug. Adverse events were re-coded using version 9.1 of the *Medical Dictionary for Regulatory Activities* (MedDRA) across all individual studies. An AE that occurred more than 30 days after the last dose of study drug was administered was not counted as an AE. AEs were defined as treatment-emergent adverse events (TEAEs) if their onset dates were after the date of the first dose of study drug, or if their onset dates were before the date of the first dose of study drug but their severity increased during the treatment period.