- 2 patients with deviations involving urine drug screening
- 1 patient who was allowed to enter the study on transdermal clonidine therapy for hot flashes
- 1 patient who was allowed to remain in the study after it was discovered that she was receiving clonidine therapy for hypertension

Class II Deviations:
- 2 patients who were allowed to initiate clonidine therapy during the study

Class III Deviations:
- 4 patients who were inadvertently provided study drug from the wrong arm at one study visit
- 2 patients who were inadvertently provided the wrong study drug kit (at one study visit), yet who received the correct treatment (that is, the kit provided was from the same treatment arm as the kit the patient was supposed to receive)
- 8 patients who took an incorrect dose during the early weeks of dose escalation because they misunderstood the dosing instructions
- 3 cases of patient errors in dosing during later weeks of the study
- 1 manufacturing error resulting in an empty dose-escalation bottle inadvertently provided to a patient.

Class IV Deviations:
- 74 deviations involving the short-term use of a narcotic/opioid, benzodiazepine, steroid, or muscle relaxant due to development of an intervening medical or surgical condition

33 deviations involving initiation of an alternative FMS therapy immediately before the patient's early termination
- 5 deviations involving the use of alternative rescue therapies (i.e., other than hydrocodone);
- 5 deviations involving the use of alternative sleep medications (i.e., other than zolpidem);
- 7 deviations involving the use of triptans other than rizatriptan
- 9 deviations involving the temporary use of benzodiazepines or muscle relaxants for symptoms related to FMS flaring
- 20 deviations from protocol-specified use of rescue therapy
- 1 patient who used an anticonvulsant owing to migraine
- 2 deviations involving the short-term use of tramadol
- 1 patient who briefly used of an antidepressant (inadvertently prescribed by the patient's local physician).
- 8 excluded procedures including transcutaneous electrical nerve stimulation, trigger point injections, and nerve blocks.

There were approximately 2700 entries onto the Protocol Deviation Log, some of which were duplicate entries, patients who failed screening or entries that were not actual protocol deviations.

Discovery of a patient's violation of an entry criterion led to Investigator assessment of the overall risk versus benefit to the patient if he or she remained in the study. Based on this assessment, the Investigator then decided whether discontinuation was appropriate. For example, 33 patients initiated therapy with excluded medications immediately before early termination

from the study. About 70 deviations involved the short-term use of excluded medications to treat conditions that developed during study participation (e.g., comorbid medical or surgical conditions or adverse events unrelated to study drug).

Although intra-articular injections were not excluded, they were tracked on the deviation log as a means of ensuring sufficient documentation. There were 22 reports of intra- articular injections involving steroids, anesthetics, or hyaluronic acid.

"Other" Deviations

There were approximately 2,400 protocol deviations classified as "Other". Most of them involved dosing of study drug and a variety of miscellaneous deviations, including missed or late assessments, visit window violations, and informed consent issues.

The Applicant is of the opinion that the review of the protocol deviations did not indicate any potential impact on the integrity of the study. I do not concur as the Class IV included patients that received prohibited medication s and interventions which may impact the evaluation of the pain endpoint.

Subject Disposition

There were 888 randomized patients and all were included in the ITT and safety population. Altogether, there were 233 patients in the placebo group, 224 patients in the milnacipran 100 mg/day group, and 441 patients in the milnacipran 200 mg/day arm.

The table below presents the disposition of the patients by treatment group and reason for withdrawal at the 3-month landmark for the ITT population (non-UPA population).

Table 70. Patient Disposition at the 3-Month Primary Endpoint- ITT Population

	Placebo (N=228) n (%)	Milnacipran 100 mg (N=224) n (%)	Milnacipran 200 mg (N=441) n (%)	Total (N=888) n (%)
Completed 3-month Treatment Period	161 (72.2)	140 (62.5)	264 (59.9)	565 (63.6)
Administrative 3-Month Completer	0	0	0	0
All other 3-month completers	161 (72.2)	140 (62.5)	264 (59.9)	565 (63.6)
Discontinued	62 (27.8)	84 (37.5)	177 (40.1)	323 (36.4)
Reason for Premature Discontinuation				
Death	1 (0.4)	0	0	1 (0.1)
Adverse Event	19 (8.5)	39 (17.4)	108 (24.5)	166 (18.7)
Therapeutic Failure	28 (12.6)	23 (10.3)	41 (9.3)	92 (10.4)
Protocol Violation	0	0	1 (0.2)	1 (0.1)
Non-Compliant W/ Protocol Requirements	3 (1.3)	1 (0.4)	5 (1.1)	9 (1.0)
Patient Withdrawal Of Consent	7 (3.1)	10 (4.5)	12 (2.7)	29 (3.3)
Investigator Withdrew The Patient	0	1 (0.4)	0	1 (0.1)
Lost To Follow-Up	2 (0.9)	7 (3.1)	8 (1.8)	17 (1.9)
Other	2 (0.9)	3 (1.3)	2 (0.5)	7 (0.8)

(Source: Applicant's Table 1.2B, Clinical Summary of Efficacy, p. 121)

At the primary endpoint landmark of 3 months, 565 patients or 63.6% were in the study. Most of the withdrawals occurred in the group treated with milnacipran 200 mg daily (40.1% of patients) compared to the placebo and the milnacipran 100 mg/day groups (27.9% and 37.5% of patients, respectively). The most common causes for withdrawal were adverse events (18.7%) and therapeutic failure (10.4%). Discontinuation due to adverse events was more common in the milnacipran treatment arms: 17.4% (39/224) in the milnacipran 100 mg/day arm and higher, 24.5% (108/441) in the milnacipran 200 mg/day arm compared with 8.5% (19/223) in the placebo arm. On the other hand, therapeutic failure was the most common cause for discontinuation in the placebo arm, 12.6% (28/223), compared with 10.3% (23/224) in the milnacipran 100 mg/day arm and 9.3% (41/441) in the milnacipran 200 mg/day treatment arm. Only one patient from the milnacipran 200 mg/day was discontinued by the 3-month landmark due to a protocol violation.

At the 6-month landmark there were 512 patients (57.7%) in the study. Across the entire study population, the most common causes for withdrawal were also adverse events (2.9%) and therapeutic failure (12.3%). Adverse events were more common in the milnacipran treatment arms: 19.6% (44/224) in the milnacipran 100 mg/day arm and higher, 27% (119/441) in the milnacipran 200 mg/ day arm compared to 23 of 223 10.3% (23/223) in the placebo arm. On the other hand, therapeutic failure was the most common cause for discontinuation in the placebo treated arm 10.3% (23/223) compared to 11.6 % (26/224) in the milnacipran 100 mg/day and 11.1% (49/441) in the milnacipran 200 mg/day treatment arms.

Table 71. Number (%) of Patients Discontinued From the Study at 6 Months- ITT Population

	Placebo (N = 223)	*Milnacipran*		*Total (N = 888)*
		100 mg/d (N = 224)	*200 mg/d (N = 441)*	
Completed Study	145 (65.0)	128 (57.1)	239 (54.2)	512 (57.7)
Withdrawn From Study	78 (35.0)	96 (42.9)	202 (45.8)	376 (42.3)
Reason for Withdrawal				
Adverse Event	23 (10.3)	44 (19.6)	119 (27.0)	186 (20.9)
Therapeutic Failure	34 (15.2)	26 (11.6)	49 (11.1)	109 (12.3)
Withdrawal of Consent	9 (4.0)	13 (5.8)	14 (3.2)	36 (4.1)
Lost to Follow-Up	2 (0.9)	7 (3.1)	9 (2.0)	18 (2.0)
Lack of Compliance	4 (1.8)	1 (0.4)	7 (1.6)	12 (1.4)
Investigator Withdrew Patient	0	1 (0.4)	0	1 (0.1)
Protocol Violation	0	0	1 (0.2)	1 (0.1)
Death	1 (0.4)	0	0	1 (0.1)
Other	5 (2.2)	4 (1.8)	3 (0.7)	12 (1.4)

(Source: Applicant's Table 10.1-1, Clinical Study Report FMS-031, Vol. 1, p. 78)

When the UPA criteria were applied (BDI score ≤ 25 and FIQ-PF score ≥ 4 at baseline), there were 715 patients in the UPA population. The disposition of this patient population is presented below.

Table 72. Number of Patients Discontinued from the Study in the 3-Month Treatment Period-UPA Population

	Placebo (N=171)	*Milnacipran*		*Total (N=715)*
		100 mg (N=189)	*200 mg (N=355)*	
Completed study	124 (72.5)	116 (61.4)	223 (62.8)	463 (64.8)
Withdrawn from study	47 (27.5)	73 (38.6)	132 (37.2)	252 (35.2)
Reason for withdrawal				
Adverse event	13 (7.6)	36 (19.0)	78 (22.0)	127 (17.8)
Therapeutic failure	21 (12.3)	17 (9.0)	31 (8.7)	69 (9.7)
Withdrawal of consent	6 (3.5)	9 (4.8)	8 (2.3)	23 (3.2)
Lost to follow-up	2 (1.2)	7 (3.7)	8 (2.3)	17 (2.4)
Noncompliant	3 (1.8)	0	4 (1.1)	7 (1.0)
Investigator withdrew patient	0	1 (0.5)	0	1 (0.1)
Protocol violation	0	0	1 (0.3)	1 (0.1)
Other	2 (1.2)	3 (1.6)	2 (0.6)	7 (1.0)

(Source: Applicant's Table 3-1, Clinical Study Report FMS-031, Vol. 2, p. 22106)

At the 3-month endpoint landmark, 64.8% (463/ 715) of the patients in the UPA population were in the study. Similar to the ITT population, the most common causes for withdrawal were adverse events and treatment failure (17.8% and 9.7% of all patients, respectively). Again, adverse events were more common in the milnacipran treatment arms: 19% (36/189) and 22% (78/355) in the milnacipran 100 mg/day and milnacipran 200mg/day respectively versus 7.6% (13/171) in the placebo arm. Also, as was previously observed, therapeutic failure was the cause for discontinuation in 12.3% (21/171) the placebo treated arm versus 9% (17/189) and 8.7% (31/355) in the milnacipran 100 mg/day and 200mg/day treatment arms respectively.

Overall therefore, the disposition of the ITT and UPA populations was comparable.

Extent of Exposure

As per the disposition data of the ITT population 61.5% of the patients in the active treatment arms, MLN 100 mg/day and 200 mg/day (574/888) were exposed to milnacipran for 3 weeks (Tx3), 55.06% (489/888) for 7 weeks, 45% (404/888) for 3 months, and 41.3% (367/888) for 6 months. The dropout rate was higher in the treatment arms versus the placebo arm. The table below presents the number of patients that completed the study at the 3-month and 6-month landmark by treatment group.

Table 73. Number (%) of Patients Who Reached Different Study Visits

	Placebo (N = 323)	*Milnacipran*		*Total* (N = 888)
		100 mg/d (N = 224)	*200 mg/d* (N = 441)	
Tx3	204 (91.5)	195 (87.1)	379 (85.9)	778 (87.6)
Tx7	130 (80.7)	169 (75.4)	320 (72.6)	669 (75.3)
Tx15 (3-Month Landmark)	161 (72.2)	140 (62.5)	264 (59.9)	565 (63.6)
Tx27 (6-Month Landmark)	145 (65.0)	128 (57.1)	239 (54.2)	512 (57.7)

(Source: Applicant's Table 10.1-2, Clinical Study Report FMS031, Vol. 1, p. 79)

Demographics

The baseline characteristics were similar across all treatment groups and in both the UPA and ITT populations. In the ITT population the age range spanned from 20 to 70 years old (mean 49.4, median 51) across all treatment groups. The majority of patients were female (96.6%), and the proportion of males to females was approximately 1: 20 for all treatment groups. Most of the subjects were Caucasian (93.6%).

The mean weight of the patients was 181lbs. with a range of 89 to 391 lbs. and the maximum weight values, 358 and 391 lbs were in the MLN treatment groups.

Table 74. Demographic and Baseline Characteristics- FMS-031- ITT Population

Demographic Parameter	Placebo (N=223)	Milnacipran 100 mg (N=224)	Milnacipran 200 mg (N=441)	Total (N=888)
Age (years)				
Mean	49.4	49.9	49.2	49.4
SD	10.12	10.62	11.01	10.69
Median	51.0	50.5	51.0	51.0
Min, Max	22.0, 70.0	22.0, 70.0	20.0, 70.0	20.0, 70.0
n	223	224	441	888
P-value		0.799	0.774	
Age (years) Group, n (%)				
< 20	0	0	0	0
20-39	39 (17.5)	38 (17.0)	78 (17.7)	155 (17.5)
40-49	59 (26.5)	66 (29.5)	116 (26.3)	241 (27.1)
50-59	93 (41.7)	67 (29.9)	171 (38.8)	331 (37.3)
>= 60	32 (14.3)	53 (23.7)	76 (17.2)	161 (18.1)
Sex, n (%)				
Male	10 (4.5)	11 (4.9)	18 (4.1)	39 (4.4)
Female	213 (95.5)	213 (95.1)	423 (95.9)	849 (95.6)
P-value		0.856	0.736	
Ethnicity, n (%)				
Hispanic Or Latino	15 (6.7)	10 (4.5)	18 (4.1)	43 (4.8)
Not Hispanic Or Latino	208 (93.3)	214 (95.5)	423 (95.9)	845 (95.2)
P-value		0.256	0.111	

Notes: p-values for comparison to placebo for continuous variables are from a two-way ANOVA model with treatment group and study center as factors.
p-values for comparison to placebo for binary variables are from a Cochran-Mantel-Haenszel test, controlling for study center.
For race, comparison was done for Caucasian vs. Non-Caucasian.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
*The time from diagnosis does not necessarily represent the duration of FMS, as patients may have had symptoms for variable periods prior to diagnosis, and some may not have had a diagnosis made until entry into the study.
Report Generated by Program: /sasprog/mln/mlnmc01/programs/tables/tdemo.sas. FINAL 09/21/2005 08:20

(Source: Applicant's Table 14.2.1, Clinical Study Report, FMS-031, Vol.1, p. 219)

APPEARS THIS WAY
ON ORIGINAL

Table 74. Demographic and Baseline Characteristics- FMS-031- ITT Population (continued)

Demographic Parameter	Placebo (N=223)	Milnacipran 100 mg (N=224)	Milnacipran 200 mg (N=441)	Total (N=888)
Race, n (%)				
Caucasian	211 (94.6)	208 (92.9)	412 (93.4)	831 (93.6)
Non-Caucasian	12 (5.4)	16 (7.1)	29 (6.6)	57 (6.4)
American-Indian Or Alaska Native	1 (0.4)	2 (0.9)	2 (0.5)	5 (0.6)
Asian	1 (0.4)	1 (0.4)	3 (0.7)	5 (0.6)
Black Or African-American	7 (3.1)	12 (5.4)	17 (3.9)	36 (4.1)
Native Hawaiian / Other Pacific Islander	0	0	0	0
Other	3 (1.3)	1 (0.4)	7 (1.6)	11 (1.2)
P-value		0.402	0.583	
Weight (lbs)				
Mean	181.9	180.6	181.3	181.3
SD	40.66	41.42	44.32	42.66
Median	180.0	178.0	175.0	178.0
Min, Max	108.0,303.6	91.0,358.0	89.0,391.8	89.0,391.8
n	223	224	441	888
P-value		0.663	0.919	
Height (ins)				
Mean	64.7	64.7	64.6	64.7
SD	2.55	2.77	2.97	2.82
Median	64.6	64.4	64.0	64.2
Min, Max	59.0, 73.0	57.0, 73.0	55.0, 75.0	55.0, 75.0
n	223	224	441	888
P-value		0.902	0.705	

Notes: p-values for comparison to placebo for continuous variables are from a two-way ANCVA model with treatment group and study center as factors.
p-values for comparison to placebo for binary variables are from a Cochran-Mantel-Haenszel test, controlling for study center.
For race, comparison was done for Caucasian vs. Non-Caucasian.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
*The time from diagnosis does not necessarily represent the duration of FMS, as patients may have had symptoms for variable periods prior to diagnosis, and some may not have had a diagnosis made until entry into the study.
Report Generated by Program: /sasprog/mln/mlnmd01/programs/tables/tdemo.sas. FINAL 09/21/2005 08:20

(Source: Applicant's Table 14.2.1, Clinical Study Report, FMS-031, Vol.1, p. 220)

Table 74. Demographic and Baseline Characteristics- FMS-031- ITT Population (continued)

Demographic Parameter	Placebo (N=223)	Milnacipran 100 mg (N=224)	Milnacipran 200 mg (N=441)	Total (N=888)
FMS Duration (year)*				
Mean	6.0	5.6	5.5	5.6
SD	5.85	6.30	5.14	5.56
Median	4.1	4.2	4.0	4.0
Min, Max	0.0, 37.0	0.0, 24.1	0.0, 25.0	0.0, 37.0
n	223	224	441	888
P-value		0.353	0.259	

Notes: p-values for comparison to placebo for continuous variables are from a two-way ANCVA model with treatment group and study center as factors.
p-values for comparison to placebo for binary variables are from a Cochran-Mantel-Haenszel test, controlling for study center.
For race, comparison was done for Caucasian vs. Non-Caucasian.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
*The time from diagnosis does not necessarily represent the duration of FMS, as patients may have had symptoms for variable periods prior to diagnosis, and some may not have had a diagnosis made until entry into the study.
Report Generated by Program: /sasprog/min/mlnmd01/programs/tables/tdemo.sas. FINAL 09/21/2008 08:20

(Source: Applicant's Table 14.2.1, Clinical Study Report, FMS-031, Vol.1, p. 221)

APPEARS THIS WAY
ON ORIGINAL

Table 74. Demographic and Baseline Characteristics- FMS-031- ITT Population (continued)

Demographic Parameter	Placebo (N=223)	Milnacipran 100 mg (N=224)	Milnacipran 200 mg (N=441)	Total (N=888)
FMS Duration (year)*				
Mean	6.0	6.6	5.5	5.6
SD	5.85	6.30	5.14	5.36
Median	4.1	4.2	4.0	4.0
Min, Max	0.0, 37.0	0.0, 24.1	0.0, 35.0	0.0, 37.0
n	223	224	441	888
P-value		0.363	0.259	

Notes: p-values for comparison to placebo for continuous variables are from a two-way ANCVA model with treatment group and study center as factors.
p-values for comparison to placebo for binary variables are from a Cochran-Mantel-Haenszel test, controlling for study center.
For race, comparison was done for Caucasian vs. Non-Caucasian.
SD = Standard Deviation, Min = Minimum, Max = Maximum.
*The time from diagnosis does not necessarily represent the duration of FMS, as patients may have had symptoms for variable periods prior to diagnosis, and some may not have had a diagnosis made until entry into the study.
Report Generated by Program: /sasprog/mln/mlnmd01/programs/tables/tdemo.sas. FINAL 09/21/2006 08:20

(Source: Applicant's Table 14.2.1, Clinical Study Report, FMS031, Vol.1, p. 222)

Baseline disease characteristics

The mean duration of FMS was 5.6 years and the mean baseline BDI score ranged from 13 to 14. The mean baseline pain score (daily morning VAS pain rating, as recorded in the electronic diary) was 68 and was similar across the treatment arms. Table 75 below summarizes the key efficacy-related characteristics at baseline.

Table 75. Key efficacy-related variables (ITT population)

Table 11.2.3–1. Key Efficacy Variables at Baseline (Mean ± SD)

Parameter	*Placebo (N = 223)*	*Milnacipran*	
		100 mg (N = 224)	*200 mg (N = 441)*
PED Daily Morning Recall Pain	68.3 ± 11.9	68.3 ± 11.5	69.4 ± 11.9
Paper VAS 24-h Recall Pain (Clinic)	74.3 ± 15.1	73.0 ± 16.0	73.9 ± 16.3
FIQ Total Score	64.7 ± 13.4	65.1 ± 13.7	64.3 ± 14.4
FIQ-PF	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7
SF-36-PCS[a]	31.4 ± 7.8	30.8 ± 7.6	31.4 ± 8.0
SF-36-MCS[b]	42.1 ± 12.1	42.4 ± 11.4	41.5 ± 11.7
Beck Depression Score	14.1 ± 9.5	13.2 ± 7.7	14.4 ± 8.6
MFI Total Score	67.0 ± 13.0	67.5 ± 13.1	67.8 ± 13.3
MASQ Total Score	88.5 ± 19.2	88.4 ± 19.7	89.4 ± 18.1

a From Table 14.4.2.5.11.
b From Table 14.4.2.5.12.
FIQ = Fibromyalgia Impact Questionnaire; FIQ-PF = FIQ Physical Function Subscore; MASQ = Multiple Ability Self-Report Questionnaire; MFI = Multidimensional Fatigue Inventory; PED = Patient Experience Diary; SF-36-MCS = Short Form-36 Health Survey–Mental Component Summary; SF-36-PCS = Short Form-36 Health Survey–Physical Component Summary; VAS = visual analog scale.

(Source: Applicant's Table 11.2.3-1, Clinical Study Report for FMS031, p. 86)

Applicant's Efficacy Analysis

Overview

Initially, study FM031 was a 6-month long study to demonstrate the efficacy of two doses of milnacipran-100mg/day and 200mg/day- compared to placebo, for the treatment of fibromyalgia syndrome. The applicant found that initial protocol-specified analysis failed to demonstrate the efficacy of milnacipran for both the treatment of pain of fibromyalgia and the treatment of fibromyalgia syndrome.

However, as per agreement with the Division, the data of this study were re-analyzed to conform to the efficacy endpoints that were utilized in a second efficacy trial (study MLN-MD-02). When the data were re-analyzed utilizing the Uniform Plan Analysis, the applicant found that milnacipran was effective for the treatment of the pain of fibromyalgia and for the treatment of fibromyalgia at the 3-month endpoint landmark.

Primary Efficacy Analysis

The primary efficacy analysis was performed on both the initial ITT population and with the population defined by the UPA criteria.
The primary efficacy analysis comprised a composite responder analysis. The definition of response for the "treatment of fibromyalgia syndrome" indication for the composite responder analysis consisted of the three endpoints below, analyzed at the 3 month time point:

- ≥ 30% improvement of pain from baseline
- score of 1 or 2 on the 7-point Likert PGIC scale
- improvement ≥ 6 points on the SF-36 from baseline

All patients included in the UPA had a FIQ-PF score of ≥ 4 and BDI score of ≤ 25 at baseline.

The imputation method for missing data used initially was the LOCF but the method specified by the UPA was the BOCF. The Applicant analyzed the data using both methods of imputation. The efficacy analysis, using the LOCF method and taking the multiplicity adjustment into account, failed to demonstrate efficacy for both claims at all dosages. For the "treatment of fibromyalgia syndrome" indication, although the proportion of responders in the milnacipran 200 mg group (23.6%) was higher than in the placebo group (20.2%), the difference did not reach statistical significance. The proportion of responders in the milnacipran 100 mg arm (19.6%) was less than that in the placebo group. For the "treatment of the pain of fibromyalgia" indication, 33.5% and 34.9% of patients in the milnacipran 100 mg and 200 mg groups were responders, compared to 27.8% of placebo patients. Neither of these differences was statistically significant.

When the Applicant applied the UPA analysis including BOCF imputation, the data showed that the efficacy of milnacipran for the "treatment of FMS" did achieve statistical significance for the 100mg/day and 200mg/day doses, and it achieved statistical significance for the "treatment of fibromyalgia pain" for the 200mg/day dose only. The percentage of "FMS" responders was 12.1% in the placebo group, compared to 19% in both of the milnacipran arms ($p < 0.05$ for both comparisons). The percentage of "pain of fibromyalgia" responders was approximately 19% in the placebo group, and 27% in the milnacipran groups. Whereas the p-value of the difference between the milnacipran 200 mg day vs. placebo group reached statistical significance ($p = 0.032$), the p-value for the 100-mg day group did not ($p=0.056$).

The Applicant's efficacy results are presented in the table below.

Table 76. Composite Responder Rates for Milnacipran Versus Placebo for Syndrome and Pain at the 3-Month Landmark (ITT Population)

Indication	*Syndrome*			*Pain*		
Method of Analysis	*Placebo (N = 223)*	*Milnacipran*		*Placebo (N = 223)*	*Milnacipran*	
		100 mg/d (N = 224)	200 mg/d (N = 441)		100 mg/d (N = 224)	200 mg/d (N = 441)
Original analysis (LOCF),[a] % responders	20.2	19.6	23.6	27.8	33.5	34.9
OR (95% CI)		0.96 (0.60, 1.54)	1.22 (0.82, 1.82)		1.31 (0.88, 1.97)	1.41 (0.99, 2.00)
p-Value[b]		.865	.328		.187	.058
Uniform Program Analysis (BOCF),[c] % responders	12.1	19.6	19.3	19.3	27.2	26.8
OR (95% CI)		1.84 (1.07, 3.17)	1.80 (1.11, 2.94)		1.55 (0.99, 2.42)	1.54 (1.04, 2.28)
p-Value[b]		.028	.017		.056	.032
Observed cases analysis,[d,e] % responders	17.3	32.8	32.8	27.2	45.2	45.4
OR (95% CI)		2.42 (1.36, 4.28)	2.43 (1.46, 4.04)		2.19 (1.34, 3.58)	2.22 (1.45, 3.40)
p-Value		.003	< .001		.002	< .001

a Original protocol-specified definition of response for pain, patient global (ie, PGIC = 1, 2, or 3), and physical function (using FIQ-PF) for syndrome.

b All p-values are nominal and based on the logistic regression models specified in the final protocol and the statistical analysis plan of FMS031.

c Final (UPA) definition of response with respect to pain, patient global (ie, PGIC = 1 or 2), and physical function (using SF-36 PCS as agreed upon with the FDA for syndrome). For the BOCF (UPA) analysis, the alternative model without baseline–value-score-by-treatment–group interaction (the model for the Study MLN-MD-02 primary efficacy analysis) had nominal p-values of .035 and .020 for composite syndrome and .048 and .032 for composite pain, respectively, for the comparison of 100 mg/d with placebo and 200 mg/d with placebo (see ISE After-Text Tables 3.1B and 6.1B).

d Completers of the 3-month landmark with observed values for responder assessment (no imputation for missing data) using UPA methodology.

e The sample size for the OC analysis was 156, 134, and 259 for placebo and 100-mg and 200 mg/d, respectively, for syndrome and 158, 135, and 260 for placebo and 100-mg and 200 mg/d, respectively, for pain.

BOCF = baseline observation carried forward; CI = confidence interval; FIQ-PF = Fibromyalgia Impact Questionnaire–Physical Function; ITT = Intent-to-Treat; LOCF = last observation carried forward; OC = observed cases; OR = odds ratio; PGIC = Patient Global Impression of Change; UPA = Uniform Program Analysis.

(Source: Applicant's Table 1.4-2, Summary of Clinical Efficacy, p.31)

The analysis utilizing the UPA determined criteria demonstrates that the drug's efficacy reaches statistical significance for both dosages, for both indications at the 3-month endpoint as presented in the table below. In the table below the Applicant shows the results of a *post hoc* analysis of the UPA population which is a subset of the ITT population, utilizing the UPA

analysis. One must bear in mind however that the study was not originally designed for this type of analysis and the p values must be interpreted with caution.

Table 77. Composite Responder Analyses for the Treatment of Pain and Syndrome of Fibromyalgia at the 3-Month (BOCF) and 6-Month Endpoints (BOCF/LOCF) - UPA Population

	Placebo (N=171)	*Milnacipran 100 mg (N=189)*	*Milnacipran 200 mg (N=355)*		
	n (%)	*n (%)*	*n (%)*	*OR (95% CI)*	*p-Value*
Milnacipran 200 mg vs placebo					
Pain at Weeks 14-15	31 (18.1)	---	99 (27.9)	1.75 (1.11, 2.76)	.015
Pain at Weeks 26-27	31 (18.1)	---	95 (26.8)	1.67 (1.06, 2.64)	.028
Syndrome at Weeks 14-15	21 (12.3)	---	73 (20.6)	2.14 (1.20, 3.82)	.010
Syndrome at Weeks 26-27	24 (14.0)	---	69 (19.4)	1.55 (0.91, 2.65)	.107
Milnacipran 100 mg vs placebo					
Pain at Weeks 14-15	31 (18.1)	52 (27.5)	---	1.73 (1.04, 2.87)	.034
Pain at Weeks 26-27	31 (18.1)	50 (26.5)	---	1.63 (0.98, 2.70)	.060
Syndrome at Weeks 14-15	21 (12.3)	39 (20.6)	---	2.05 (1.10, 3.81)	.024
Syndrome at Weeks 26-27	24 (14.0)	35 (18.5)	---	1.31 (0.72, 2.37)	.374

NOTE: The UPA Population consisted of all patients in the ITT Population who had baseline measurements of BDI ≤ 25 and FIQ-PF ≥ 4.

BDI = Back Depression Inventory; BOCF = baseline observation carried forward; FIQ-PF = Fibromyalgia Impact Questionnaire-Physical Function; ITT = Intent-to-Treat; LOCF = last observation carried forward; N = number of patients in each treatment group; n = number of responders within a group; OR = odds ratio; UPA = Uniform Program Analysis.

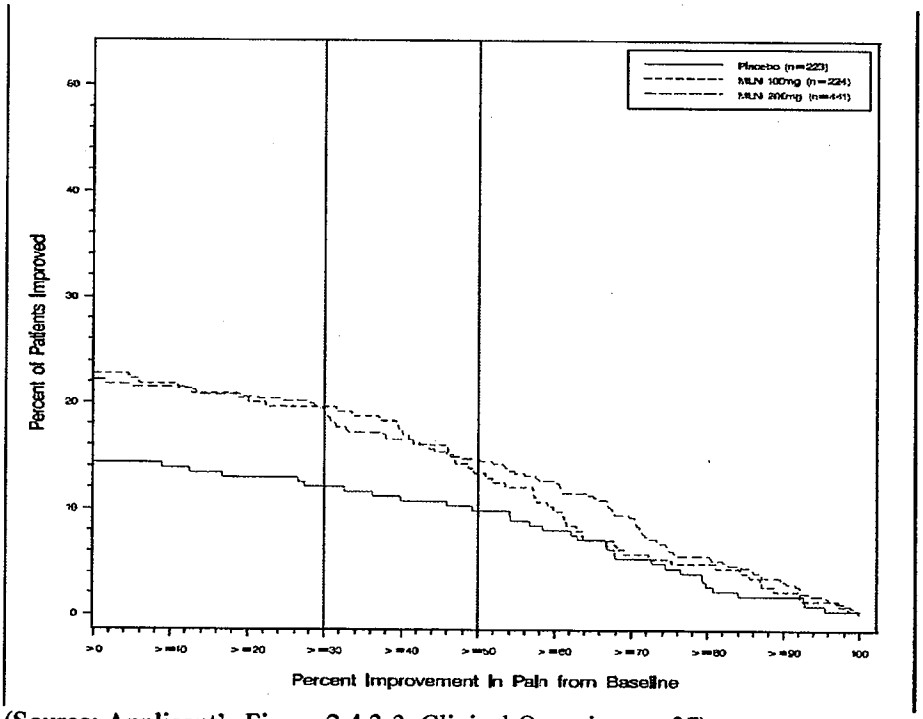
(Source: Applicant's Table 6.1-1, Clinical Study Report, FMS-031, Vol. 2, p. 22110)

Responder Analysis Curves

The Applicant presented a responder analysis curve for both indications as displayed below. In these curves the Applicant provides a visual representation of the composite responder analysis. The plots demonstrate that the placebo and the MLN curves separate indicating that MLN is better than placebo. The plots also demonstrate that there is no separation between the doses which indicates that one is not better than the other. Note however that the plots are not drawn to scale. The y axis just goes up to 50% which gives a misleading impression of the difference between the treatment arms.

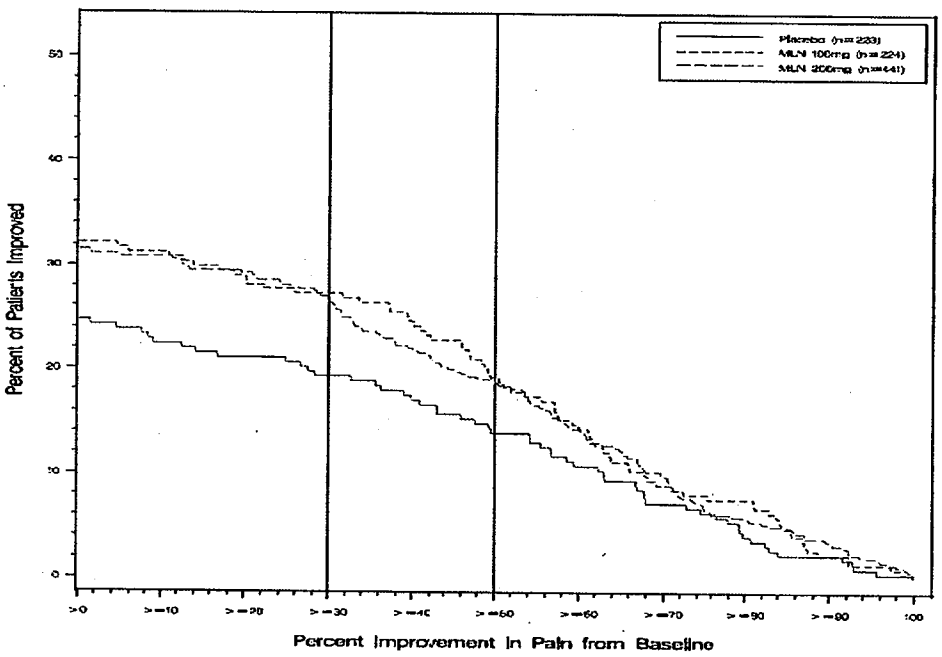
The continuous responder analysis for pain demonstrates that there is a separation of the two curves at different definitions of responder and not only at the 30% improvement endpoint Similarly, this plot is not drawn to scale in the y axis which amplifies the separation between the curves.

Figure 16. Percentage of Responders for the Fibromyalgia Syndrome Endpoints with PGIC ≤ 2, ≥ 6 Points Improvement on the SF-36 PCS and Meeting Different Levels of Reductions From Baseline in Pain (VAS, PED) at 3 Months (BOCF, ITT Population)



(Source: Applicant's Figure 2.4.3-3, Clinical Overview, p. 27)

Table 78. Percentage of Responders for the Fibromyalgia Pain Endpoints with PCIG ≤ 2 and Meeting Different Levels of Reductions From Baseline in Pain (VAS, PED) at 3 Months (BOCF, ITT)



Additional efficacy explorations

1. Responder analyses for the individual components of the composite responder criteria.

Below is the Applicant's responder analysis for the individual domains (components) of the composite responder criteria (i.e. pain, patient global, and physical function), at the 3-month and 6-month time points.

With respect to the pain domain, the Applicant calculated the percentage of patients in each treatment group that had a pain reduction of at least 30% on the 24-hour recall pain score. The Applicant found that both the milnacipran 100 mg and 200 mg groups had a higher percentage of responders (34 and 38%, respectively) compared to the placebo group (28%). Only the result for MLN 200 mg/day versus placebo reached statistical significance. However, because these were post-hoc analyses, the p-values should be interpreted with caution.

For the responder analysis of the patient global component (i.e., a rating of "much improved" or "very much improved" on the PGIC), the Applicant found that there was a statistically significant improvement in pain and global response at 3 months for the 200 mg/day milnacipran dose compared with placebo, but not for the 100 mg/day dose of milnacipran. The 200 mg/day group had 35% responders, whereas the 100 mg/day and placebo groups each had 26% responders. Again, for this post-hoc analysis, the p-values should be interpreted cautiously.

The Applicant's responder analysis for the physical function domain (i.e. improvement of ≥ points on the SF-36 PCS score) showed that the responder rates for the milnacipran 100 mg/day (32.8%) and 200 mg/day groups (32.4%) were slightly greater than the placebo rate (28.1%), but the differences did not reach statistical significance. As described above, given that these were post-hoc analyses, the p-values should be interpreted with caution.

Table 79. Responder Analyses for Pain, Global and Physical Function Domains at the 3-Month Landmark (BOCF) - UPA Population

	Placebo (N=171)	*Milnacipran 100 mg (N=189)*	*Milnacipran 200 mg (N=355)*		
	n (%)	*n (%)*	*n (%)*	*OR (95% CI)*	*p-Value*
Milnacipran 200 mg vs placebo					
Pain	47 (27.5)	---	133 (37.5)	1.60 (1.07, 2.39)	.021
Global (PGIC)	45 (26.3)	---	125 (35.2)	1.52 (1.02, 2.28)	.042
Physical function (SF-36)	48 (28.1)	---	115 (32.4)	1.37 (0.89, 2.11)	.159
Milnacipran 100 mg vs placebo					
Pain	47 (27.5)	64 (33.9)	---	1.36 (0.87, 2.14)	.181
Global (PGIC)	45 (26.3)	64 (33.9)	---	1.43 (0.91, 2.26)	.120
Physical function (SF-36)	48 (28.1)	62 (32.8)	---	1.31 (0.81, 2.11)	.267

NOTE: The UPA Population consisted of all patients in the ITT Population who had baseline measurements of BDI ≤ 25 and FIQ-PF ≥ 4.

BDI = Beck Depression Inventory; BOCF = baseline observation carried forward; FIQ-PF = Fibromyalgia Impact Questionnaire-Physical Function; ITT = Intent-to-Treat; N = number of patients in each treatment group; n = number of responders within a group; OR = odds ratio; PGIC = Patient Global Impression of Change; SF-36 = Short Form-36 Health Survey Physical Component Summary; UPA = Uniform Program Analysis.

(Applicant's Table 6.1-2, Clinical Study Report, FMS-031, Vol. 2, p. 22112)

2. Change in mean (average) pain from baseline to the 3-month landmark.

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.

Secondary Efficacy Analyses

The Applicant collected several secondary efficacy endpoints. The main secondary endpoints that were analyzed at the 3-month landmark were the following:

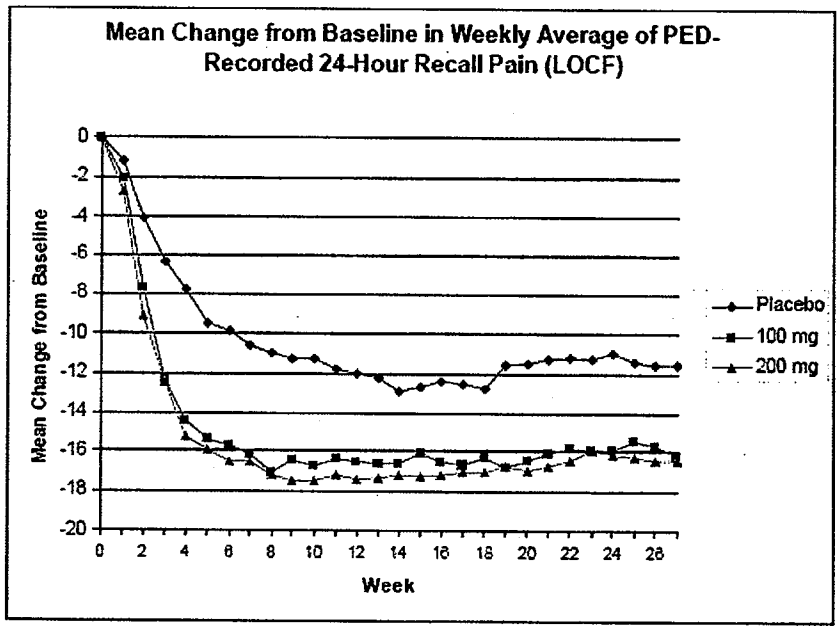
1. Time-weighted average (AUC) of weekly 24-hour recall pain score
2. Time-weighted average of PGIC
3. Time-weighted average of SF-36 PCS
4. Improvement of fatigue per MFI

Only the results of the time- weighted average (AUC) of weekly 24-hour recall pain score and improvement of fatigue (MFI) results are discussed here.

1. Time-weighted average (AUC) of weekly average 24-hour recall pain score

The Applicant found that there was a statistically significant improvement in the pain domain as early as 1-week which was maintained through the study duration and that the patients who received milnacipran 200 mg/day had greater mean pain reduction than those who received milnacipran 100 mg/day. The following figure represents the mean change from baseline in the weekly 24-hour recall pain score:

Figure 17. Mean Change from Baseline in Weekly Average of PED-Recorded 24-Hour Recall Pain (LOCF)



Source: Applicant's Figure 11.4.1-1, Clinical Study Report, FMS-031, Vol. 1, p. 98)

2. Improvement of fatigue using the Multidimensional Fatigue Inventory (MFI)

The Applicant is seeking [ ] b(4)

The MFI consists of 20 items scored to produce five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. According to the Applicant, this tool has been validated in cancer patients, medical students, army recruits, and junior physicians. The change in the MFI dimensions is presented in the table and figure below:

The comparison of the change from baseline in the total score achieved statistical significance for both milnacipran treatment arms at 3 months. With respect to the individual components of the MFI, only analysis of the "reduced motivation" and "mental fatigue" component resulted in a statistically significant result only for the higher dose. It is unclear how the MLN 100mg/day treatment arm achieved a statistically significant result of the total score compared to placebo, when none of the comparisons of the individual components did. The fact that MLN affected "reduced motivation" and "mental fatigue" could be the result of MLN's anti-depressant effect. Such result is not surprising - milnacipran is an anti-depressant and one would expect this particular response to the drug. The data suggest that milnacipran does not impact the other components of the assessment of fatigue which are related to physical activity.

Table 80. Change From Baseline in Multidimensional Fatigue Inventory Dimensions at 3 and 6 Months for Study FMS031 (LOCF)

Parameter	*Placebo (N = 223)*	*Milnacipran*					
		100 mg/d (N = 224)			*200 mg/d (N = 441)*		
	Mean (SE)	**Mean (SE)**	**LSMD[a] (95% CI)**	**p-Value**	**Mean (SE)**	**LSMD[a] (95% CI)**	**p-Value**
Visit Tx15							
Total Score	−3.04 (0.77)	−5.15 (0.81)	−2.20 (−4.31, −0.08)	.042	−5.62 (0.61)	−2.35 (−4.26, −0.45)	.016
General Fatigue	−1.22 (0.20)	−1.39 (0.23)	−0.27 (-0.83, 0.30)	0.353	−1.49 (0.15)	−0.26 (−0.75, 0.22)	.289
Physical Fatigue	−0.88 (0.21)	−1.29 (0.22)	−0.52 (−1.07, 0.03)	0.065	−1.50 (0.16)	−0.60 (−1.09, −0.10)	.019
Mental Fatigue	−0.32 (0.23)	−0.69 (0.19)	−0.41 (−0.97, 0.14)	0.144	−0.99 (0.16)	−0.59 (−1.09, −0.10)	.019
Reduced Motivation	−0.43 (0.21)	−1.03 (0.22)	−0.53 (−1.07, 0.01)	0.056	−0.97 (0.16)	−0.48 (−0.96, −0.01)	.044
Reduced Activity	−0.19 (0.23)	−0.75 (0.25)	−0.43 (−1.04, 0.17)	0.161	−0.66 (0.18)	−0.34 (−0.88, 0.20)	.218
Visit Tx27							
Total Score	−3.35 (0.81)	−5.00 (0.85	−1.88 (−4.10, 0.35)	.098	−5.80 (0.67)	−2.24 (−4.33, −0.16)	.035
General Fatigue	−1.18 (0.21)	−1.28 (0.24)	−0.22 (−0.81, 0.38)	0.469	−1.42 (0.16)	−0.26 (−0.77, 0.25)	.314
Physical Fatigue	−1.01 (0.22)	−1.37 (0.22)	−0.51 (−1.08, 0.06)	0.078	−1.49 (0.16)	−0.45 (−0.97, 0.07)	.087
Mental Fatigue	−0.64 (0.21)	−0.59 (0.19)	−0.03 (−0.57, 0.50)	0.899	−1.07 (0.17)	−0.36 (−0.88, 0.16)	.176
Reduced Motivation	−0.61 (0.22)	−1.15 (0.22)	−0.51 (−1.08, 0.06)	0.077	−1.04 (0.17)	−0.37 (−0.88, 0.14)	.153
Reduced Activity	0.09 (0.24)	−0.61 (0.26)	−0.56 (−1.19, 0.08)	0.086	−0.78 (0.19)	−0.70 (−1.28, −0.12)	.018

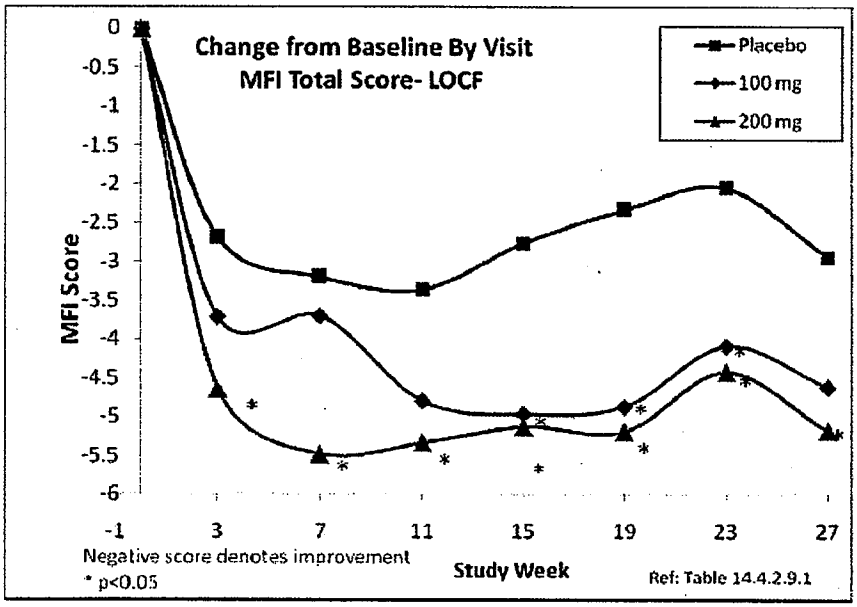
NOTE: Negative change represents improvement.

a Comparisons with placebo are based on the values of change from baseline using an analysis of covariance model with treatment group and study center as factors and baseline value as covariate.

LOCF = last observation carried forward; LSMD = least squares mean difference.

(Source: Applicant's Table 11.4.1.2.7-1, Clinical Study Report, FMS-031, Vol. 1, p. 112)

Figure 18. Multidimensional Fatigue Inventory (MFI) - Change From Baseline



(Source: Applicant's Figure 11.4.1.2.7.1-1, Clinical Study Report, FMS-031, Vol. 1, p. 111)

Discussion of findings and conclusions

The Applicant conducted study FMS-031 to evaluate the efficacy of milnacipran as a treatment for "fibromyalgia syndrome" and "the pain of fibromyalgia." Per the initial protocol-specified analysis, the study failed to demonstrate the efficacy of milnacipran for either these indications.

However, when the data were re-analyzed using a modified population, efficacy endpoints, and imputation method (as agreed upon by the Agency), the composite responder analysis showed efficacy of both the 100 mg/day and 200 mg/day milnacipran doses for the "treatment of fibromyalgia syndrome" indication. The re-analysis also showed evidence of efficacy of the 200 mg/day dose for the "treatment of the pain of fibromyalgia." and 100 mg/day dose did not reach statistical significance by a small margin.

The Applicant's composite responder analysis curves, comparing the proportions of patients with good response with respect to the patient global and/or physical function scores, and who achieved various degrees of pain relief, demonstrate a separation between the active treatment arms and placebo but not between the two active treatment arms for both claims of treatment of fibromyalgia pain and treatment of fibromyalgia syndrome.

The Applicant's responder analyses for each of the components of the composite responder criteria (i.e. pain, patient global, and physical function), showed that:

- There was a numerical difference in the percentage of pain responders between the MLN treatment arms and placebo but this difference was not statistically significant for MLN 100mg/day dose....
- For the responder analysis of the patient global component the Applicant found that there was a statistically significant improvement in global response at 3 months for the 200 mg/day milnacipran dose compared with placebo, but not for the 100 mg/day dose of milnacipran.
- For the responder analysis of the physical function domain there was a numerical difference between placebo and the MLN treatment arms but the difference did not reach statistical significance.

In my opinion, the composite responder analysis and the responder analysis curves for pain and syndrome indicate that milnacipran does have an effect in a proportion of the population. This finding is difficult to explain when the analyses of the each component individually do not support this notion. The responder analyses for pain and patient global achieve statistical significance at the 200 mg/day dose only. One must take into consideration that these p-values are *post-hoc and* must be interpreted with caution.

Regarding the secondary efficacy endpoints, the applicant's analysis of the MFI does not support [ ] b(4)

10.1.2 Study MLN-MD-02

Title: A Phase III Pivotal, Multicenter, Double-Blind, Randomized, Placebo-Controlled Monotherapy Study of Milnacipran for Treatment of Fibromyalgia

Objectives

The objectives of the study were:

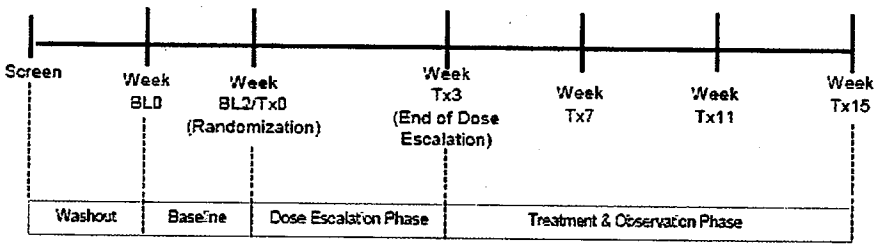
Primary objective: Demonstrate the safety and efficacy of milnacipran in the treatment of the fibromyalgia syndrome (FMS) or the pain associated with fibromyalgia (FM).

Secondary objectives:
1. Compare the statistical and clinical efficacy of 100 mg/day and 200 mg/day of milnacipran in the treatment of FMS based on each component of the composite responder analysis, as well as on a number of additional secondary endpoints including fatigue, sleep and mood.
2. Establish and compare the safety profiles of 100 and 200 mg milnacipran daily in patients with FMS.

Study Design

The original version of this protocol was dated September 3, 2004. This was to be a prospective, double-blind, randomized, placebo-controlled, multi-center study and it was to be conducted in 45 to 50 centers in the United States. The treatment duration was to be at least 12 weeks long after a three-week escalation phase totaling 15 weeks of exposure. The duration of the patient participation in the study was expected to be up to approximately 6 months.

Figure 19. Study Timeline



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

Study Population and Treatment Arms

The study plan was to randomize 600 patients, 200 in each arm as follows:

- placebo (n=200)
- 100 mg milnacipran daily (n=200) divided in two daily doses (50 mg twice daily) or
- 200 mg milnacipran daily (n= 200) divided in two daily doses (100 mg twice daily)

Inclusion Criteria

The following were the main inclusion criteria:

1. Patients must have been diagnosed with primary FM, as defined by the 1990 ACR Criteria for the Classification of Fibromyalgia.
2. Patients of both genders between the ages of 18 and 70 years were to be included.
3. Females must have been either postmenopausal for at least 1 year or status post-hysterectomy or oophorectomy (bilateral) or, if of childbearing potential, must have had a negative urine pregnancy test prior to randomization, and have been using a medically acceptable form of contraception such as hormonal birth control, IUD, double barrier (male condom, female condom, diaphragm) or a barrier method plus a spermicidal agent (contraceptive foam, jelly, or cream).
4. Patients must have had the ability to give informed consent.
5. Patients must have been willing to withdraw from CNS-active therapies commonly used for FMS, including anti-depressants, anti-convulsants, and mood stabilizers.
6. Patients must have been willing to discontinue treatment with transcutaneous electrical nerve stimulation, biofeedback, tender and trigger point injections, acupuncture, and anesthetic or narcotic patches.
7. Patients must have scored ≥ 4 on the physical function component of the FIQ performed at the BL0 visit to be eligible for enrollment.
8. Patients must have been willing and able to use a Patient Experience Diary (PED) device daily for a minimum of 17 weeks.
9. Patients must have had completed at least 70% of the Random Prompts during the relevant days of the baseline period. The relevant days were defined as the 14 days prior to BL2 during the time interval between BL0 and BL2; if the time between BL0 and BL2 was 14 days or less, the relevant days were to be considered all days between BL0 and BL2. The baseline period must have been a minimum of 10 days.
10. Patients must have not missed greater than two morning reports during the relevant days of the baseline period.
11. Patients must have had an average visual analog scale (VAS) intensity pain scale recording of at least 40 or more on a 0-100 scale at the end of the second week of the baseline period based on the electronic diary daily pain recall.

Exclusion Criteria

The following were the exclusion criteria:

1. Severe psychiatric illness as determined by investigator judgment or the screening exam, the Mini-International Neuropsychiatric Interview (MINI)

2. Patients suffering from a current major depressive episode (MDE-current), as defined by the MINI
3. **Patients with a significant risk of suicide, according to the investigator's judgment** or scoring 2 or 3 for question 9 of the Beck Depression Inventory (BDI) regarding suicidal ideation administered at BL2/Tx0 visit
4. Patients abusing alcohol, benzodiazepines or other drugs, as demonstrated by positive drug screening or the MINI
5. Any history or behavior that would, **in the physician's estimation, prohibit** compliance for the duration of the study
6. Patients with a history of myocardial infarction within the past 24 months, active cardiac disease (American Heart Association Functional Class 2, 3 or 4), congestive heart failure, hemodynamically significant valvular heart disease (including patients with a prosthetic heart valve), and/or clinically significant cardiac rhythm or conduction abnormalities
7. Patients with pacemakers
8. Patients with pulmonary dysfunction or severe chronic obstructive pulmonary disease that, in the judgment of the investigator, could interfere with study participation and completion
9. Patients with evidence of active liver disease, i.e., levels of alanine aminotransferase (AST), aspartate aminotransferase (ALT) and/or alkaline phosphatase (AP) > 1.5x the upper limit of the normal range for the laboratory performing the test
10. Patients with renal impairment, i.e. creatinine > 1.3x the upper limit of the normal range for the laboratory performing the test
11. Patients with documented autoimmune disease, however, patients diagnosed with **Hashimoto's or Graves' disease** that had been stable for three months prior to screening were allowed to enroll.
12. Patients with systemic infection
13. Patients with active cancer, except for basal cell carcinoma, or patients undergoing therapy for cancer. Patients taking tamoxifen but who were at least one year post active treatments of breast cancer could have been enrolled. Patients receiving tamoxifen solely due to a strong familial cancer risk were also allowed to enroll.
14. Patients with a life expectancy less than one year
15. Patients with sleep apnea severe enough that, in the opinion of the investigator, it would interfere with interpretation of changes in sleep habits. In addition, patients requiring use of CPAP devices were not eligible for the study
16. Patients with active peptic ulcer, inflammatory bowel disease, or celiac sprue
17. Patients with unstable endocrine disease, including unstable diabetes or thyroid disease, however, disorders that had been stable for the preceding 3 months would have been acceptable
18. Male patients with prostatic enlargement or other genito-urinary disorders, who might have been at significant risk of dysuria and/or urinary retention when taking agents with noradrenaline re-uptake inhibition properties
19. Pregnant or breastfeeding patients
20. Patients who had received treatment with an experimental agent within the previous three months

21. Patients with previous exposure to milnacipran
22. Patients who were receiving concomitant therapy with monoamine oxidase (MAO) -A or -B inhibitors, tricyclics, tetracyclics, serotonin selective re-uptake inhibitors (SSRIs), norepinephrine non-specific re-uptake inhibitor, serotonin norepinephrine re-uptake inhibitor (SNRIs), or muscle relaxants
23. Patients who were receiving concomitant therapy with phenytoin or phenobarbital
24. Patients with concurrent usage of St. John's Wort, S-adenosylmethionine or dehydroepiandrosterone (DHEA)
25. Patients with concurrent usage of digitalis (digoxin) preparations
26. Patients with concurrent usage of centrally acting analgesics, including tramadol, codeine, and other opioids or opiates
27. Patients with concurrent usage of systemic steroids (>10 mg prednisone equivalents)

Study Medication and Other Therapies

Milnacipran was provided as capsules of 12.5 mg, 25 mg, and 50 mg. Patients were recommended to take all study drugs with food.

No dose reductions were to be allowed for patients once they had achieved the stable dose for the maintenance phase of the study.

Rescue Medication

Hydrocodone was allowed in doses up to 60 mg per day.

Patients were to have discontinued the use of all narcotics prior to the start of the Baseline period (Visit BL0). The narcotics should also have been discontinued within 48 hours of each office visit and during the last two weeks of the study (visits Tx14 and Tx15), when the primary endpoint pain data was to be collected.

Allowable Concomitant Medications

The following concomitant medications were allowed:

- For migraine headaches: rizartriptan (Maxalt®), sumatriptan (Imitrex®), combination products consisting of butalbital, aspirin/acetaminophen, caffeine (Fiorinal®, Fioricet®)
- For treatment of insomnia zolpidem (Ambien®), zaleplon (Sonata®), sedating anti-histamines, chloral hydrate a
- acetaminophen
- aspirin
- non-steroidal anti-inflammatory drugs (NSAIDS)

Prohibited Concomitant Medications and Treatments

The following medications and treatments were prohibited:

- benzodiazepines: adequate washout was to be documented by a negative urine test at Visit BL0 and prior to randomization
- centrally-acting analgesics: tramadol, anti-epileptic agents, α-1 agonists, codeine, and other opioids including codeine
  Short-term uses of opioid analgesics for indications other than FM were to have obtained a protocol exception and should have been carefully documented.
- joint and soft tissue injections: these treatments must have been completed at least seven days before the primary endpoint determination (Tx15).
- anti-depressants: patients receiving any anti-depressants including MAO-A or MAO-B inhibitors, tricyclics, tetracyclics, SSRI agents, NARI agents, combination re-uptake inhibitors must have undergone a washout period prior to entry into the study.
- digoxin: prohibited due to reports of the association of hypotension and arrhythmias with concomitant use of milnacipran.
- trigger and tenderpoint injections
- anesthetic patches
- biofeedback
- transcutaneous electrical nerve stimulation

Methods and Procedures

The study was designed to have seven office visits and three phone calls. Below is the table of study procedures.

Figure 20. Procedures for Study MLN-02

VISIT NAME	*Screen*	*Wash-Out*	*BL0*	*BL2/Tx0 (randomization/ start drug)*	*Tx1*	*Tx2*	*Tx3 (and dose escalation)*	*Tx7*	*Tx11*	*Tx13*	*Tx15/ ET*[a]
Allowable visit windows	n/a	n/a	n/a	n/a	n/a	n/a	+/- 4 days	+/- 7 days	+/- 7 days	n/a	+/- 7 days
Office Visits	x		x	x	phone	phone	x	x	x	phone	x
Activities											
Informed Consent	x										
Inclusion / Exclusion	x			x[b]							
FMS Related Signs and Symptoms	x										
Medical History	x										
Physical Exam	x										x
Baseline Signs and Symptoms	x	x	x	x							
ACR 1990 FMS criteria	x										
Vital Signs	x		x	x			x	x	x		x
ECG			x								x
MINI	x										
Electronic Diary for Pain			x	x	x	x	x	x	x	x	x
PGIC							x	x	x		x
FIQ			x				x	x	x		x
SF-36, MDHAQ				x			x	x	x		x
Status Testing: BDI, ASEX				x							x
FMS Status: Pain VAS, MASQ, MFI, MOS-Sleep, Pt. Global Disease Status				x			x	x	x		x
Childhood Traumatic Event Scale	x										
Peripheral Symptom Inventory	x										x
Pt. Global Therapeutic Benefit								x	x		x
Pregnancy Test[c]				x							
Laboratory Assessments	x		x[d]								x
Urine Drug Screen			x								
Drug Administration				x			x	x	x		
IVRS	x		x	x			x	x	x		x
Adverse Events					x	x	x	x	x	x	x
Concomitant Medications	x		x	x	x	x	x	x	x	x[e]	x[f]
Rescue Medication Usage				x	x	x	x	x	x	x	x[f]

[a] All Tx15 assessments are to be performed at early termination visit if patient terminates prior to week 15.
[b] Prior to randomization the Inclusion/Exclusion criteria must be reviewed by the investigator and documented as such in the patient's source document.
[c] In-office urine pregnancy test will be performed at screening. Confirmation of negative urine pregnancy test must be obtained prior to randomization.
[d] Laboratory assessments must be repeated in those patients in whom more than 6 weeks have elapsed between initial screening visit and first baseline visit.
[e] Patients will be reminded that they may not take rescue or non-allowed narcotic medication (s) during the 2 weeks of primary endpoint data collection (Tx14-15).
[f] Number of days during which rescue or non-allowed narcotic medication(s) was used 14 days prior to ex 15 will be collected.

(Source: Applicant's Table 3-1, Clinical Study Report, MLN-02, Vol. 1, p. 2127)

Screening

At the initial screening visit, inclusion and exclusion criteria were to be reviewed and the use of prohibited medications was to be verified. In case the patient had taken one of the prohibited medications, the patient would have to undergo a washout period. The screening assessments were to include the following:

- Comprehensive evaluation: including patient demographics, past medical history, FMS treatment history, review of inclusion and exclusion criteria, assessment of baseline signs and symptoms of fibromyalgia, concomitant medication use;
- Vital sign assessments, including temperature, weight, standing and supine blood pressure and heart rate;
- Physical examination, documenting the diagnosis of fibromyalgia by ACR criteria;
- Assessment to measure frequency and improvement of symptoms traditionally seen with IBS, migraines, chronic fatigue syndrome in patients with primary diagnosis of FM (Peripheral Symptom Inventory)
- Psychological assessment with MINI and Childhood Traumatic Event Scale;
- Laboratory assessments, including serum chemistries, hematology and urinalysis.

Baseline and Randomization

After the screening the patient would proceed with the baseline period. The baseline period was 2 weeks long consisting of two visits (BL0 and BL2) and would occur at least 10 days after the screening visit if no washout was required, or up to 21 days if washout was required. At the beginning of the baseline period the patients were to receive a Patient Experience Diary (PED) device and receive training on its use. The PED is an electronic diary by Invivodata, Inc. The data captured on the PED is uploaded by modem to a central server database, where they are archived and analyzed. The central server runs automatic compliance checks and provides updated diary compliance reports for review by the site staff.

At the initial visit of the baseline period (BL0), patients were to repeat the screening laboratory tests if more than 6 weeks lapsed between the initial screening visit and BL0, including urine drug screen.
The following assessments were to occur at BL0 and the final week of the baseline period/randomization visit (BL2/TX0):

- Vital signs
- Primary Outcome Measure: Fibromyalgia Impact Questionnaire (FIQ) and eligibility based on this score
- Adverse events
- Concomitant medication usage

In addition to the assessments listed above the following assessments were to occur at BL2:

- SF-36
- Health Assessment Questionnaire (MDHAQ)
- Beck Depression Inventory (BDI)
- Arizona Sexual Experiences Scale (ASEX)
- Patient pain by VAS
- Patient Global Disease Status by VAS
- Multiple Ability Self-Report Questionnaire (MASQ- Cognition)
- Multidimensional Fatigue Inventory (MFI)

- Medical Outcomes Study-Sleep Index (MOS)

Dose Titration

Once randomized to one of the treatment arms, patients were to enter the 3-week dose titration phase of the study (visits Tx0- Tx2). To maintain the blind, patients who were randomized to placebo were also dose escalated. During the first week of titration (Tx0), the patients were to escalate the treatment dose from 12.5 mg on day 1, to 25 mg on days 2 and 3, to 50 mg on days 4 through 7, of active drug or matching placebo. During the second week (Tx1), all patients were to escalate to 100 mg of active drug or placebo, and remain at that dose for the next 7 days. During the third week of dose escalation (Tx2), the patients that were randomized to receive 200 mg were to escalate to that dose, while the others would undergo a sham dose escalation to maintain the blind of the study. The patients were followed weekly with phone calls over the next two weeks (Tx1 and Tx2) to check on safety issues and compliance.

No dose reductions were to be allowed for patients that completed the dose escalation portion of the study. Patients that were not able to tolerate study treatment after dose escalation were to be discontinued from the study.

Treatment Phase

The treatment phase duration was to be 24 weeks long, consisting of seven office visits, each four weeks apart (Tx3 (wk 3), Tx7 (wk 4), Tx11 (wk 8), and Tx15 (wk 12)). At each visit the patients were to receive their monthly supply of drug. All treatment visits were to have a window of ± 4 days for Tx3, and ± 7 days for Visits Tx7 through Tx15.

The following assessments were to occur at the treatment phase visits Tx3-Tx15:

- PED entries
- Vital signs
- Adverse events and concomitant medication review
- Primary Outcome Measures:
    - Fibromyalgia Impact Questionnaire (FIQ)
    - Patient Global Impression of Change (PGIC)
- Secondary Measures:
    - Patient pain by VAS
    - Multiple Ability Self-Report Questionnaire (MASQ, Cognition)
    - Multidimensional Fatigue Inventory (MFI)
    - MOS-Sleep Index (MOS)
    - Health Assessment Questionnaire (MDHAQ) at Tx15 and Tx27
    - SF-36
    - Patient Global Therapeutic Benefit beginning at Tx7

The following additional assessments were to be obtained at Tx15 or at early termination:

- Physical examination

- Laboratory assessments
- 12-lead ECG
- Beck Depression Inventory (BDI)
- Arizona Sexual Experiences Scale (ASEX)
- Peripheral Symptom Inventory
- Number of days during which rescue or opioid medication was used

Efficacy Measures and Outcomes

Primary efficacy measures

There were three primary efficacy measures: pain, patient global improvement and physical function.

Pain was measured by data collected into the PED. The PED allowed the collection of patient self-reported pain data by random report prompting multiple times daily, daily recall pain and weekly pain. The daily recall pain collected from the morning report was to be used in the primary analysis. The baseline pain score was to be the average of all daily recall pain scores during the 2-week baseline period.

Patient global improvement was to be assessed using a fibromyalgia-specific patient global impression of change (PGIC) instrument at visits Tx3, Tx7, Tx11 and Tx15 or early termination. The specific question and possible responses are 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

Physical function was to be measured by the Fibromyalgia Impact Questionnaire (FIQ) - Physical Function subscale. This eleven question subset of the overall FIQ was originally developed to directly assess physical limitations affecting patient's activities of daily living, providing a score that is used to assess changes in function over time.

Primary efficacy outcome

The primary efficacy endpoint was to be a composite responder analysis of three domains of interest: pain, patient global impression of change and physical function. Two alternative primary analyses were to be performed, one on the proportion of patients who satisfied the definition of response to meet the requirements for a "treatment of FMS" claim at Treatment Weeks 14-15, another one on the proportion of patients who satisfied

the definition of response for a "treatment of the pain of FM" claim at Treatment Weeks 14-15. The primary analysis was to be the percentage of patients who met the criteria for response using the intention-to-treat population (ITT) and the last observation carried forward (LOCF).

For the "pain associated with FM " indication, a patient was to be considered a responder for if he or she reached Visit Tx7 meaning exposure to the stable dose of the double-blind study medication for at least 4 weeks, and satisfied the following criteria:

- Greater than or equal to 30% improvement in change in patient pain from baseline to endpoint.
- PGIC were to be rated as "improved," (i.e., scored as 1, 2 or 3 on the 1-7 scale at endpoint.)

A patient was to be classified as a responder for the "fibromyalgia syndrome" if he or she reached Visit Tx7 (i.e., exposed to the stable dose of the double-blind study medication for at least 4 weeks) and satisfied the following criteria:

- Greater than or equal to 30% improvement in change in patient pain from baseline to endpoint.
- PGIC were to be rated as "improved," (i.e., scored as 1, 2 or 3 on the 1-7 scale at endpoint.)
- Greater than 30% improvement in FIQ-physical function subscale score from baseline to endpoint

In both analyses, patients who took rescue medication or non-allowed narcotic medication on more than 2 days during the primary endpoint period were to be classified as non-responders.

Secondary efficacy outcomes

The following were the secondary efficacy outcomes:

- Change from baseline in average morning pain scores by week
- Change from baseline in pain scores by week
- Analysis of time-weighted average (area under the curve [AUC]) of weekly average PED morning recall pain scores by treatment for Weeks 4 to 15
- Change from baseline in VAS assessments of pain during the past 24 hours and past 7 days by visit
- Patient Global Impression of Change (PGIC) by visit
- Change from baseline in Patient Global Disease Status VAS by visit
- Changes from baseline in the total FIQ score and FIQ physical function sub-score by visit
- Patient Global Therapeutic Benefit by visit
- Change from baseline in SF-36 score by visit
- Change from baseline in MDHAQ disability subscale score by visit
- Change from baseline in BDI total score by visit

- Change from baseline in ASEX total score by visit
- Change from baseline in MFI assessment by visit
- Change from baseline in MOS-SLEEP assessment by visit
- Change from baseline in MASQ assessment by visit

Statistical Analysis in the Original Protocol

All efficacy analyses were to be based on the ITT population which was defined as all patients in the safety population. The safety population was defined as all patients who were randomized and received at least one dose of study medication. Missing values were to be imputed by last observation carried forward (LOCF), unless stated otherwise.

To control the experiment-wise error rate for comparison of both the 200 mg/day and 100 mg/day milnacipran doses with placebo for treatment of both pain associated with FM and FMS, the following closed testing procedure was to be used. First, the 200 mg/day dose was to be compared to placebo at Weeks 14-15 for the proportion of responders for pain associated with FM. If this test were statistically significant at the 5% level of significance, then the 100 mg/day dose was to be compared to placebo at Weeks 14-15 for the proportion of responders for pain associated with FM and the 200 mg/day dose was to be compared to placebo at Weeks 14-15 for the proportion of responders for FMS using the Hochberg adjustment to the Bonferroni procedure for this family of comparisons. If both comparisons were statistically significant at the 5% level of significance, then the 100 mg/day dose was to be compared to placebo at Weeks 14-15 for the proportion of responders for syndrome of FM using a 5% level of significance.

The proportion of responders was to be analyzed using a logistic regression model with treatment group, baseline pain score, baseline FIQ-PF score, and baseline pain by treatment and baseline FIQ-PF by treatment interactions as explanatory variables.

Sensitivity analyses were to be performed to assess the impact of the missing data on the primary efficacy results. The effects of treating patients with missing primary efficacy data at primary time point as non-responders and of assessing response based on OC (observed cases) was to be analyzed respectively.

Key Protocol Amendments

The following were amendments to the protocol:

- Amendment 1 (October 21, 2004):
  - Extension of study duration from 3 months to 6 months and addition of subsequent visits and assessments
  - Increase in the number of patients to be randomized from 600 to 783 due to extended study duration

- Revision of statistical analysis based on extended study duration: the primary endpoint was to be analyzed at Visits Tx15 (week 12) and Tx29 (week 24) or at early termination.

- Amendment 2 (January 26,2006):
  - Increase in the number of patients to be randomized from 783 to approximately 1200;
  - Increase in the number of study centers from 45-50 up to approximately 75;
  - Inclusion and exclusion criteria modifications:
    - Patients with BDI > 25 were to be excluded.
    - Patients were to withdraw from muscle relaxants and opioids during the study.
    - Patients using CPAP could be included, as long as its use had been stable meaning that it had been used for at least one month prior to the study and its use was to remain stable over the course of the study.
  - Change in definition of efficacy parameters:
    - The measure of function to be included in the composite responder analysis for the primary efficacy assessment was changed to an improvement of 6 points or more on the SF-36 PCS at endpoint from baseline instead of the FIQ-PF. Patients scoring < 4 on the FIQ were not eligible.
    - The secondary efficacy assessment was to be the same as the primary efficacy assessment except all responders were to be defined at Visit Tx15.
  - The following secondary efficacy parameters were to be included:
    - Responder status of each individual domain in the definition of the composite responder status
    - Time-weighted average or area under the curve (AUC) of the weekly PED morning recall pain scores for Weeks 4 to 15 (the first 12 weeks of stable dose period) and Weeks 4 to Week 29 (the first 24 weeks of stable dose period) using LOCF and OC
    - Time-weighted average or AUC of the Patient Global Impression of Change for Visit Tx3 to Tx15 and Visit Tx3 to Visit Tx29 using LOCF and OC
    - Time-weighted average or AUC of SF-36 PCS for Visit Tx3 to Visit Tx15 and Visit Tx3 to Visit Tx29 using LOCF and OC
    - Change from baseline in average morning recall pain (PED) by week using LOCF and OC
    - Change from baseline in real time pain scores (PED) by week using LOCF and OC
    - Change from baseline in weekly recall pain scores (PED) by week using LOCF and OC
    - Change from baseline in paper based VAS assessments of pain during the past 24 hours and past 7 days by visit using LOCF and OC
    - PGIC by visit using LOCF and OC
    - Change from baseline in SF-36 PCS score by visit using LOCF and OC

- Change from baseline in SF-36 individual domain and component score (except for PCS score) by visit
- Change from baseline in Patient Global Disease Status VAS by visit
- Changes from baseline in the total FIQ score and FIQ physical function subscore by visit
- Change from baseline in MDHAQ disability subscale score by visit
- Change from baseline in ASEX total score by visit
- Change from baseline in BDI total score by visit
- Change from baseline in MFI assessment, by visit
- Change from baseline in MOS-SLEEP assessment, by visit
- Change from baseline in MASQ assessment, by visit
-

- Modification of statistical methodology: The proportion of responders for the pain domain in the definition of the composite responder status was to be analyzed using a logistic regression model with treatment group and baseline pain score as explanatory variables. The proportion of responders for physical function domain was to be analyzed using a logistic regression model with treatment group, baseline SF-36 PCS score as explanatory variables, and the proportion of responders for PGIC domain was to be analyzed using a logistic regression model with treatment group as an explanatory variable. Analysis of covariance (ANCOVA) was to be employed in the AUC analyses of the weekly average PED morning recall pain scores and SF-36 PCS with treatment and center as the factors and baseline value as covariate. Analysis of variance (ANOVA) was to be employed in the AUC analysis of PGIC with treatment and center as the factors.
- Imputation of missing data: In the primary efficacy analysis, patients who did not complete Visit Tx15 were to be analyzed as non-responders and LOCF approach were only be used to impute the missing data at Tx29 for patients who completed Visit Tx15. Multiple comparison procedure were to be used to control the overall type I error in the primary efficacy analysis.
- Change in the objectives: The primary efficacy endpoint parameters of the study for the indications of the pain of FM and the FMS were to be a composite responder rate at Visit Tx29. The secondary outcome measure was changed to a composite responder status assessing response rates of two doses (100 mg/day and 200 mg/day) of milnacipran as compared to placebo at Visit Tx15.
- **Change in the rating of the PGIC: The PGIC must have been rated as "much or very much improved" meaning a score of 1 or 2 at endpoint.**
- Screening procedures were amended to include tender point examination per ACR Criteria.
- Rescue medication was not to be allowed during the baseline period.
- Eszopicline (Lunesta) was allowed as a treatment of insomnia
- Other non-allowable medications were:
  - anti-epileptics such as phenytoin (Dilantin®); topiramate (Topamax®), carbamazapine (Tegretol®); levetiracetam (Keppra®); tiagabine (Gabitril®); gabapentin (Neurontin®); pregabalin (Lyrica®),

- dopamine receptor agonists such as ropinirole, pramipexole (however, carbidopa/levodopa , e.g., Sinemet® was allowed as an alternative therapy for FMS patients also suffering from restless leg syndrome,
- stimulant medications such as amphetamine/dextroamphetamine (Adderall®), methylphenidate, dextroamphetamine, modafinil,
- anorectic agents such as diethylpropion, sibutramine (Meridia®), and phentermine (Adipex®)
- muscle relaxants such as carisoprodol (Soma®), methocarbamol (Robaxin®), cyclobenzaprine (Flexeril®) metaxalone (Skelaxin®), tizanidine (Zanaflex®), chlorzoxazone (Parafon®), dantrolene (Dantrium®) and baclofen (Lioresal®)
- Others such as buspirone, sodium **oxybate, ramelteon (Rozarem™), St. John's Wort, , S-adenosylmethionine DHEA**

- Amendment 3 (August 3, 2006):
  - Reduction of study duration from 6 months to 3 months
  - Reduction of the number of patients to be randomized from 1200 to 1100 due to reduced study duration
  - The primary efficacy assessment was to be evaluated at Tx15.
  - The secondary efficacy assessments were to be the time-weighted average or AUC of the weekly average Patient Experience Diary (PED) morning recall pain score for Weeks 4 to 15, PGIC, and SF-36 PCS score from Visits Tx3 to Tx15.
  - Completed patients were defined as patients who had completed Visit Tx29 under Amendment #2 or active patients who had completed at least Visit Tx15 when the study was terminated administratively. Patients who successfully completed the double-blind study were eligible to participate in a follow-up extension study.
  - **For the "fibromyalgia syndrome" indication**, the primary efficacy endpoint was modified such that a responder was to demonstrate improvement on the SF-36 PCS score from baseline by an amount at least equivalent to the minimal clinically important difference (defined as ≥6 points).
  - To control the overall type I error for comparisons of two doses of milnacipran with to placebo for two indications, the following sequential gatekeeping multiple-comparison procedure was to be used:
    - Step 1. Closed testing procedure for 100 mg versus placebo at 3 months for the pain indication and 200 mg versus placebo at 3 months for the fibromyalgia pain indication
    - Step 2. Closed testing procedure for 100 mg versus placebo at 3 months for the FMS indication and 200 mg versus placebo at 3 months for the FMS indication.

    At each step above, a closed testing procedure was to be used to test the individual hypothesis in that family at the family-wise 5% level of significance. Step 2 will be performed only if both hypotheses in Step 1 are rejected based on the closed testing procedure. Specifically, within each step, the average effect of the two active doses was to be compared with placebo

using the logistic regression model. If this global test was significant at the two-sided significance level of 0.05, then each active dose was to be compared with placebo simultaneously at the conventional two-sided significance level of 0.05.

- In the primary efficacy analyses, baseline observation carried forward (BOCF) would be used for any patient with a missing value at Visit Tx15. Sensitivity analyses to assess the robustness of the primary efficacy results would include last observation carried forward (LOCF) and the composite responder analysis based on observed cases (OC) at Visit Tx15
- The secondary efficacy parameters were to revised to reflect the reduction in study duration:
  - Time-weighted average (AUC) of the weekly average PED morning recall pain scores for Weeks 4 through 15 of the stable-dose period
  - Time-weighted average (AUC) of PGIC for Visits Tx3 through Tx15
  - Time-weighted average (AUC) of SF-36 PCS for Visits Tx3 through Tx15

- Amendment 4 (May 7, 2007): Consisted of modifications to the planned statistical analysis
  - Four sensitivity analyses were to be performed to assess the robustness of the primary efficacy results and were:
    1) a composite responder analyses analysis using the last observation carried forward (LOCF) approach approaches for any patient with a missing value at Visit Tx15;
    2) a composite responder analysis using a modified BOCF approach for patients who complete the 3-month study but lack data at Visit Tx15 (i.e., the missing values for these patients will be imputed from the last observed value before Visit Tx15);
    3) a composite responder analysis based on observed cases (OC) at Visit Tx15;
    4) a composite responder analysis at Visit Tx15, using BOCF approach, based on all ITT patients with baseline BDI score ≤ 25.

Amendments to the Statistical Analysis Plan (May 8, 2007):

- Two additional sensitivity analyses of the primary efficacy analysis were added:
  1. Analysis using BOCF approach for patients who did not complete the study, and LOCF approach for patients who completed the study but lacked primary efficacy data at the 3-month landmark (modified BOCF).
  2. Analysis using BOCF approach for patients with baseline BDI ≤ 25.

- Added: a responder analyses for the 4 individual SF-36 domains pertaining to physical health.
- Added: a responder analyses for the 3 individual domains in the definition of composite responder (i.e. pain, patient global impression of change, physical function).

- Added: the analyses of rescue usage excluding PRN use, as well as rescue medication use on a PRN basis.
- Re-definition of completer: for the randomized population, a patient was to be defined as completing the study if
  1) the patient had a Visit Tx15; or
  2) the patient had a Visit Tx11 followed by Visit Tx29/ET with the termination reason as other (administratively terminated); or
  3) the patient had a Visit Tx11 followed by Visit Tx29/ET on or after Day 78 of stable dose (SD) period.

Applicant's Study Results

Enrollment

The study randomized 1207 patients at 86 study sites which were all in the United States.

Protocol Violations

The Applicant classified the protocol deviations according to the ICH Clinical Report Guidelines in the following classes:

I. Those that entered the study even though they did not satisfy the entry criteria. (Protocol waivers (or exceptions) were granted if the Applicant felt that the deviation would not significantly impact patient safety or the efficacy analysis.)
II. Those in whom withdrawal criteria developed during the study but who were not withdrawn
III. Those who received an incorrect dose
IV. Those who received an excluded concomitant treatment

The table below summarizes the protocol deviations according to this classification system.

Table 81. Summary of Protocol Deviations in MLN-MD-02

Class	*Description*	*Number of Deviations*
I.	Those who entered the study even though they did not satisfy the entry criteria	244
II.	Those who developed withdrawal criteria during the study but were not withdrawn	13
III.	Those who received an incorrect dosage	4
IV.	Those who received an excluded concomitant treatment	187
Other	Discrepancies between expected versus actual number of capsules returned (27) Missed protocol assessments or other procedural deviations (809) Visit conducted outside the protocol-specified visit window (345) Rescue medications not withheld prior to visit (187) Issues related to informed consent (41) Permission to use non-allowed medication for rescue (48) Miscellaneous queries (510; not deviations)	~2000
	TOTAL	~2450

(Source: Applicant's Table from Clinical Study Report, MLN-MD-02, Vol. 1, p. 84)

Subject Disposition

There were 1207 patients randomized to treatment but only 1196 were included in the safety and intention-to-treat (ITT) populations.

Among the 11 patients excluded from the safety and ITT populations were 9 from study center 242 which was closed by the Applicant during the study due to failure to comply with Good Clinical Practices. Of the remaining t2 patients, one did not take any study drug, and one had a second patient number. This patient participated at two separate study centers (patient #20914 was randomized at Study Center 209 on November 23, 2005, and patient #24623 was randomized at Study Center 246 on December 15, 2005). This patient completed the study at both centers. The data from this patient as #20914 were included in all efficacy and safety analyses, since this was the earlier randomization. This decision was made prior to database lock.

The table below presents the disposition of the patients by treatment group and reason for withdrawal at the 3-month landmark.

Table 82. Patient Disposition at the 3-Month Primary Endpoint- Safety Population

	Placebo (N = 401)	*Milnacipran*		*Total (N = 1196)*
		100 mg/d (N = 399)	*200 mg/d (N = 396)*	
Completed 3-month study	290 (72.3)	264 (66.2)	257 (64.9)	811 (67.8)
Discontinued from study	111 (27.7)	135 (33.8)	139 (35.1)	385 (32.2)
Reason for Discontinuation				
Adverse event	38 (9.5)	78 (19.5)	94 (23.7)	210 (17.6)
Therapeutic failure	36 (9.0)	28 (7.0)	19 (4.8)	83 (6.9)
Withdrawal of consent	20 (5.0)	14 (3.5)	15 (3.8)	49 (4.1)
Lost to follow-up	10 (2.5)	7 (1.8)	5 (1.3)	22 (1.8)
Noncompliant	5 (1.2)	4 (1.0)	3 (0.8)	12 (1.0)
Investigator withdrew patient	1 (0.2)	2 (0.5)	1 (0.3)	4 (0.3)
Protocol violation	1 (0.2)	1 (0.3)	1 (0.3)	3 (0.3)
Other	0	1 (0.3)	1 (0.3)	2 (0.2)

(Source: Applicant's Table 10.1-1, Clinical Study Report, MLN-MD-02, Vol. 1, p. 82)

At the 3-month primary endpoint, 811 patients or 67.8% of patients were in the study. Most of the withdrawals occurred in the group treated with milnacipran 200 mg daily (35.1%). The most common causes for withdrawal were adverse events (17.6%) and therapeutic failure (6.9%). Adverse events were more common in the milnacipran treatment arms: 19.5% (78/399) in the milnacipran 100 mg/day arm and higher, 23.7% (94/396) in the milnacipran 200 mg/day arm compared with 9.4% (38/401) in the placebo arm. On the other hand, therapeutic failure was the most common cause for discontinuation in the placebo arm, 8.9% (36/401), compared with 7% (28/399) in the milnacipran 100 mg/day arm and 4.7% (19/396) in the milnacipran 200 mg/day treatment arm. One patient from each treatment group was discontinued by the 3-month landmark due to a protocol violation.

Extent of Exposure

As per the disposition data of the ITT population, 88.3% of the patients who were in the active treatment arms, MLN 100 mg/day and 200 mg/day (703/795) were exposed to milnacipran for 3 weeks (visit Tx3), 75.9% (604/795) for 7 weeks (visit Tx7), 67.5% for 11 weeks (visit Tx11), and 65.5% (521/795) for 3 months. The dropout rate was higher in the active treatment arms compared with the placebo arm. The table below presents the number of patients that completed the study at the 3-month landmark by treatment group.

Table 83. Number (%) of Patients Who Reached Different Study Visits

	Placebo (N=401)	*Milnacipran*		*Total (N=1196)*
		100 mg/d (N=399)	*200mg/d (N=396)*	
Tx3	367 (91.5)	357 (89.5)	345 (87.1)	1069 (89.4)
Tx7	328 (81.8)	304 (76.2)	300 (75.8)	932 (77.9)
Tx11	300 (74.8)	270 (67.7)	267 (67.4)	837 (70.0)
Completed 3-month treatment	290 (72.3)	264 (66.2)	257 (64.9)	811 (67.8)

(Source: Applicant's Table 10.1-2, Clinical Study Report MLN-MD-02, Vol. 1, p. 83)

Demographics

The baseline characteristics were similar across all treatment groups. The population age range spanned from 18 to 74 years old (mean 50.2, median 52) across all treatment groups. Approximately 96% of patients were female, with the proportion of males to females being approximately 1: 24 for all treatment groups. Most of the subjects were Caucasian (93.5%).

The mean weight of the patients was 180.8 lbs with a range of 92.2 to 438.6 lbs. and the maximum weight value (438.6 lbs) was in the placebo arm; the maximum weight values in the MLN treatment arms were 339 lbs in the 100 mg/day arm and 328 lbs and in the 200 mg/day group.

Table 84. Demographic and Baseline Characteristics- MLN-MD-02- Safety Population

Demographic Parameter	Placebo (N=401)	Milnacipran 100 mg (N=399)	Milnacipran 200 mg (N=396)	Total (N=1196)
Age (years)				
Mean	50.7	49.5	50.4	50.2
SD	10.42	10.87	10.61	10.64
Median	52.0	51.0	52.0	52.0
Min, Max	18.0, 70.0	19.0, 70.0	22.0, 74.0	18.0, 74.0
n	401	399	396	1196
P-value		0.110	0.678	
Age (years) Group, n (%)				
< 20	1 (0.2)	1 (0.3)	0 (0.0)	2 (0.2)
20 - 39	56 (14.0)	75 (18.8)	65 (16.4)	196 (16.4)
40 - 49	119 (29.7)	100 (25.1)	102 (25.8)	321 (26.8)
50 - 59	150 (37.4)	148 (37.1)	151 (38.1)	449 (37.5)
>= 60	75 (18.7)	75 (18.8)	78 (19.7)	228 (19.1)
Sex, n (%)				
Male	21 (5.2)	12 (3.0)	12 (3.0)	45 (3.8)
Female	380 (94.8)	387 (97.0)	384 (97.0)	1151 (96.2)
P-value		0.116	0.155	
Ethnicity, n (%)				
Hispanic Or Latino	23 (5.7)	13 (3.3)	25 (6.3)	61 (5.1)
Not Hispanic Or Latino	378 (94.3)	386 (96.7)	371 (93.7)	1135 (94.9)
P-value		0.039	0.698	

Notes: p-values for comparison to placebo for continuous variables are from a two-way ANOVA model with treatment group and study center as factors.
p-values for comparison to placebo for binary variables are from a Cochran-Mantel-Haenszel test, controlling for study center.
For race, comparison was done for Caucasian vs. Non-Caucasian.
SD = Standard Deviation, Min = Minimum, and Max = Maximum.
*The time from diagnosis does not necessarily represent the duration of FMS, as patients may have had symptoms for variable periods prior to diagnosis, and some may not have had a diagnosis made until entry into the study.

(Source: Applicant's Table 14.2.1, Clinical Study Report, MLN-MD-02, Vol.1, p. 236)

Table 84 Demographic and Baseline Characteristics- MLN-MD-02- Safety Population (continued)

Demographic Parameter	Placebo (N=401)	Milnacipran 100 mg (N=399)	Milnacipran 200 mg (N=396)	Total (N=1196)
Race, n (%)				
Caucasian	375 (93.5)	375 (94.0)	368 (92.9)	1118 (93.5)
Non-Caucasian	26 (6.5)	24 (6.0)	28 (7.1)	78 (6.5)
American-Indian Or Alaska Native	4 (1.0)	3 (0.8)	1 (0.3)	8 (0.7)
Asian	3 (0.7)	3 (0.8)	6 (1.5)	12 (1.0)
Black Or African-American	11 (2.7)	13 (3.3)	14 (3.5)	38 (3.2)
Native Hawaiian / Other Pacific Islander	0	0	0	0
Other	8 (2.0)	5 (1.3)	7 (1.8)	20 (1.7)
P-value		0.757	0.771	
Weight (lbs)				
Mean	183.9	179.5	179.2	180.8
SD	44.81	42.24	41.86	43.01
Median	178.6	174.0	174.0	176.0
Min, Max	96.5, 438.6	92.2, 339.0	99.0, 328.0	92.2, 438.6
n	401	399	396	1196
P-value		0.234	0.180	
Height (ins)				
Mean	64.4	64.4	64.4	64.4
SD	2.83	2.94	2.88	2.88
Median	64.0	64.0	64.0	64.0
Min, Max	56.0, 76.4	48.0, 74.0	52.0, 73.0	48.0, 76.4
n	401	397	395	1193
P-value		0.832	0.915	

Notes: p-values for comparison to placebo for continuous variables are from a two-way ANOVA model with treatment group and study center as factors.
p-values for comparison to placebo for binary variables are from a Cochran-Mantel-Haenszel test, controlling for study center.
For race, comparison was done for Caucasian vs. Non-Caucasian.
SD = Standard Deviation, Min = Minimum, and Max = Maximum.
*The time from diagnosis does not necessarily represent the duration of FMS, as patients may have had symptoms for variable periods prior to diagnosis, and some may not have had a diagnosis made until entry into the study.

(Source: Applicant's Table 14.2.1, Clinical Study Report, MLN-MD-02, Vol.1, p. 237)

Table 84. Demographic and Baseline Characteristics- MLN-MD-02- Safety Population (continued)

Demographic Parameter	Placebo (N=401)	Milnacipran 100 mg (N=399)	Milnacipran 200 mg (N=396)	Total (N=1196)
FMS Duration (year)*				
Mean	9.8	9.5	9.9	9.7
SD	8.49	8.04	8.21	8.24
Median	7.0	7.3	8.0	8.0
Min, Max	0.0, 48.0	0.0, 50.0	0.2, 55.0	0.0, 55.0
n	401	399	396	1196
P-value		0.540	0.823	
Baseline BDI				
Mean	13.80	13.60	14.30	13.90
SD	8.980	8.670	8.690	8.780
Median	12.00	11.00	13.00	12.00
Min, Max	0.00, 44.00	0.00, 48.00	0.00, 51.00	0.00, 51.00
n	401	399	396	1196
P-value		0.798	0.430	
BDI > 25	47 (11.7)	43 (10.8)	41 (10.4)	131 (11.0)
BDI <= 25	354 (88.3)	356 (89.2)	355 (89.6)	1065 (89.0)

(Source: Applicant's Table 14.2.1, Clinical Study Report, MLN-MD-02, Vol.1, p. 238)

Baseline disease characteristics

The mean duration of fibromyalgia was 9.7 years, years, and 89.0% of the population had baseline BDI scores ≤ 25 (i.e. no depression to low moderate depression). The mean baseline pain score (daily morning pain, as recorded in the electronic diary) was slightly higher in the placebo group than in either of the milnacipran groups: 65.7 vs. 64.6 for the 100 mg/day group and 64.5 for the 200 mg/day group. Table 85 below summarizes the key efficacy-related characteristics at baseline.

Table 85. Key efficacy-related variables (ITT population)

Table 11.2-2. Key Efficacy Variables at Baseline: ITT Population

Parameter	*Placebo (N=401)*	*Milnacipran 100 mg (N=399)*	*Milnacipran 200 mg (N=396)*
	Mean ± SD		
Daily morning recall pain (PED)	65.7 ± 13.3	64.6 ± 13.5	64.5 ± 13.8
Paper VAS 24-hr recall pain (Clinic)	73.4 ± 17.2	70.8 ± 18.6	72.5 ± 17.5
FIQ total score	62.5 ± 14.1	62.3 ± 13.7	61.9 ± 14.1
FIQ Physical Function Score	1.54 ± 0.59	1.51 ± 0.58	1.46 ± 0.58
SF-36 Physical Component Summary	32.1 ± 7.4	31.9 ± 7.5	32.4 ± 7.3
SF-36 Mental Component Summary	41.6 ± 11.7	42.9 ± 11.5	40.7 ± 11.3
BDI score	13.8 ± 9.0	13.6 ± 8.7	14.3 ± 8.7
MFI total score	69.4 ± 12.3	68.4 ± 13.3	69.5 ± 13.2
MASQ total score	92.5 ± 18.9	92.2 ± 19.4	93.4 ± 19.1

BDI = Beck Depression Inventory; FIQ = Fibromyalgia Impact Questionnaire; MASQ = Multiple Ability Self-Report Questionnaire; MFI = Multidimensional Fatigue Inventory; PED = patient experience diary; SF-36 = Short-Form 36; VAS = visual analog scale.

(Source: Applicant's Table 11.2-2, Clinical Study Report, MLN-MD-02, Vol.1, p. 127274)

Applicant's Efficacy Analysis

Overview

The Applicant had initiated a 6-months study to demonstrate the efficacy of two doses of milnacipran- 100mg/day and 200mg/day- compared to placebo. After discussion with the Division in a Type C meeting (June 2, 2006) it was agreed that this ongoing study could be truncated to 3 months for assessment of efficacy. A subset of patients received up to 29 weeks of placebo-controlled treatment.

Primary Efficacy Analysis

The primary efficacy analysis was performed in the ITT population by using a composite responder analysis. The ITT population comprised all randomized patients who received at least one dose of study drug. All patients had to have a BDI score ≤ 25 and FIQ-PF ≥ 4

The definition of response for the "treatment of FMS" composite responder analysis consisted of the three endpoints below:

- 30% improvement of pain from baseline recorded as the average 24-hour recall pain score for the 14 days preceding and including the first treatment visit (Tx0)
- score of 1 or 2 on the 7-point Likert PGIC scale
- improvement ≥ 6 points on the SF-36 from baseline

The definition of response for the "treatment of FM pain" composite responder analysis was based on the first two domains described above:

- 30% improvement of pain from baseline recorded as the average 24-hour recall pain score for the 14 days preceding and including the first treatment visit (Tx0)
- score of 1 or 2 on the 7-point Likert PGIC scale

Both the "treatment of FMS" and "treatment of pain due to FM" were analyzed at the 3-month endpoint landmark.

The imputation method for missing data that was utilized in the primary analysis was the BOCF. Sensitivity analyses were conducted using LOCF, modified BOCF and observed cases (OC) approaches for imputing data. The modified BOCF imputation strategy was as follows: BOCF imputation was applied to the 3-month non-completers while the LOCF approach was applied to those patients who completed the 3-month study but lacked primary efficacy data at the 3-month landmark

The table below presents the composite responder analyses data for the treatment of "FM pain" and FMS using the BOCF approach for missing data.

Table 86. Primary Efficacy Analyses: Composite Responder Rates for MLN Versus Placebo at the 3-Month Landmark (BOCF)

Efficacy Claim	*Placebo (N=401)*	*Milnacipran*			
		100 mg/d (N=399)	*200 mg/d (N=396)*		
	Composite Responder Rates, %			**OR (95% CI)**	**P-value[a]**
Placebo vs 100 mg/d					
Pain	16.46	22.81	---	1.50 (1.05, 2.13)	.025
Syndrome	8.73	14.54	---	1.79 (1.14, 2.80)	.011
Placebo vs 200 mg/d					
Pain	16.46	---	24.75	1.68 (1.18, 2.38)	.004
Syndrome	8.73	---	13.89	1.75 (1.11, 2.75)	.015

a nominal P-values were all significant based on the prespecified multiple-comparison procedure.
BOCF = baseline observation carried forward (all patients who did not have an adequate observation for the evaluation of composite responder status at the 3-month landmark visit were defined as nonresponders); CI = confidence interval; OR = odds ratio.

(Source: Applicant's Table 11.4.1.1-1, Clinical Study Report, MLN-MD-02, Vol. 1, p. 91)

According to the Applicant's analyses at the 3-month visit, 16.5% of placebo patients were defined as composite responders for the "treatment of pain of fibromyalgia" endpoint, compared with 22.8% of milnacipran 100 mg/day patients and 24.8% of milnacipran 200 mg/day patients. The increases in composite response observed with milnacipran were statistically significant compared with placebo (p=0.025 for milnacipran 100 mg/day and p=0.004 for milnacipran 200 mg/day).

Treatment with milnacipran at either dosage resulted in an increase in the number of composite responders to the "treatment of FMS" endpoint as well. The composite response rate increased from 8.7% for placebo patients to 14.5% for milnacipran 100 mg/day patients (p=0.011) and to 13.9% for milnacipran 200 mg/day patients (p=0.015).

Table 87 (below) shows that the sensitivity analyses yielded results that were similar to the responder analysis. A higher percentage of milnacipran treated patients were defined as responders to both the treatment of FM pain and FMS when compared to placebo. All of these differences were statistically significant.

Treatment differences favoring milnacipran treatment were also observed using observed cases (OC). The percentage of responders to the treatment of pain of FM increased from 25.2% in the placebo arm to 38.6% in the milnacipran 100 mg/day) arm and 45.6% in the milnacipran 200 mg/day arm. The percentage of responders to the treatment of FMS increased from 13.4% (placebo) to 24.6% (milnacipran 100 mg/day) and 25.6% (milnacipran 200 mg/day).

Table 87. Sensitivity Analyses for Composite Responder Rates

	Sensitivity Analysis 1[a] (LOCF)			*Sensitivity Analysis 2[b] (Modified BOCF)*			*Sensitivity Analysis 3[c] (OC)*		
	Placebo (N=401)	*MLN*	*P-value*	*Placebo (N=401)*	*MLN*	*P-value*	*Placebo (N=262)*	*MLN*	*P-value*
	Composite Responder Rate, %			**Composite Responder Rate, %**			**Composite Responder Rate, %**		
	100-mg MLN (N=399)			*100-mg MLN (N=399)*			*100-mg MLN (N=236)*		
Pain	18.20	25.81	.010	16.96	24.06	.013	25.19	38.56	.001
Syndrome	9.73	16.29	.006	9.23	15.29	.009	13.36	24.58	.002
	200-mg MLN (N=396)			*200-mg MLN (N=396)*			*200-mg MLN (N=215)*		
Pain	18.20	29.55	<.001	16.96	26.26	.001	25.19	45.58	<.001
Syndrome	9.73	16.41	.003	9.23	15.15	.007	13.36	25.58	<.001

a Sensitivity Analysis 1 imputed data using the LOCF approach for all patients who lacked primary efficacy data at the 3-month landmark.

b Sensitivity Analysis 2 used the BOCF approach for patients who were noncompleters at the 3-month landmark, but used the LOCF approach for patients who completed the 3-month study but who lacked primary efficacy data at the 3-month landmark.

c Sensitivity Analysis 3 used observed cases only (ie, patients who completed the 3-month landmark visit with an adequate observation for the evaluation of composite responder status).

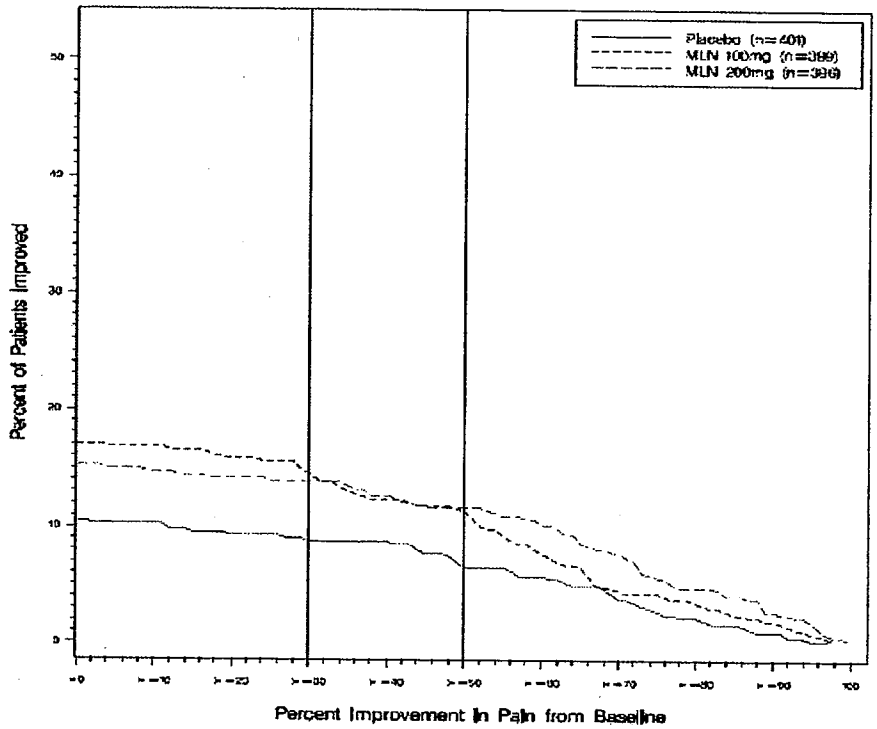
BOCF = baseline observation carried forward; CI = confidence interval; LOCF = last observation carried forward; MLN = milnacipran; OC = observed cases; OR = odds ratio.

(Source: Applicant's Table 11.4.1.1-2, Clinical Study Report, MLN-MD-02, Vol. 1, p. 92)

Continuous Responder Curves

The Applicant also performed a cumulative distribution function for the "treatment of FMS" and "treatment of pain of FM" endpoints. For the former, the Applicant calculated the percentage of patients who achieved various degrees of improvement in pain from baseline to the 3-month landmark and who also rated themselves as very much improved or much improved on the PGIC and achieved improvement in physical function. The graphical presentation of this analysis is displayed in Figure 20. The figure shows that among patients who were much/very much improved on the PGIC and who had reasonable physical function (SF-36 PF score $\geq$ 6), more patients treated with milnacipran had improvement in their pain – across all levels of improvement – compared to placebo-treated patients.

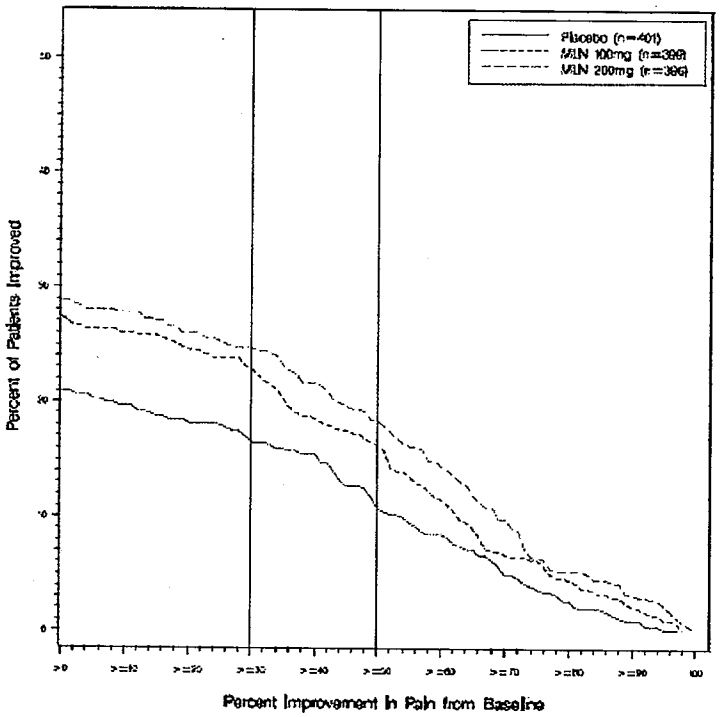
Figure 21. Percentage of Responders for the FMS Endpoints with PGIC ≤ 2, ≥ 6 Points Improvement on the SF-36 PCS and Meeting Different Levels of Reductions from Baseline in Pain (VAS, PED) at 3 Months (BOCF, ITT Population)



(Source: Applicant's Figure 2.4.3-1, Clinical Overview, p. 25)

The Applicant also performed a "treatment of pain of FM" cumulative distribution curve that was based on a calculation of the percentage of patients who achieved various degrees of improvement in pain from baseline to the 3-month landmark and who also rated themselves as markedly or moderately improved on the PGIC. This analysis showed that among these patients, more patients in the milnacipran arms than placebo patients experienced decreased pain, including at the higher degrees of pain improvement (i.e. ≥ 50% improvement).

Figure 22. Percentage of Responders for the Fibromyalgia Pain Endpoints with PCIG ≤ 2 and Meeting Different Levels of Reductions From Baseline in Pain (VAS, PED) at 3 Months (BOCF, ITT)



(Source: Applicant's Figure 2.4.3-2, Clinical Overview, p. 26)

Additional efficacy explorations t

3. Responder analyses for the individual components of the composite responder criteria.

The table below presents the responder analysis for the pain component of the composite responder analysis (i.e., a pain reduction of at least 30% on the 24-hour recall pain score recorded in the PED) at the 3-month landmark visit. The Applicant found that there was a statistically significant (i.e. p-value ≤ 0.05) greater number of responders to milnacipran treatment (in both dosage groups), using LOCF and OC approaches for imputation. However, given that these were post-hoc analyses, the p-values should be interpreted with caution.

Based on the p-values and the confidence intervals, and using the more conservative BOCF imputation, there was no apparent difference in the proportion of patients with ≥ 30% improvement in pain, between either of the milnacipran groups and the placebo group.

Table 88. Responder Analysis for the pain component of the composite responder criteria at the 3-Month Endpoint

Table 11.4.1.3.1-2. Responder Analysis for the Pain Component of the Composite Responder Criteria at the 3-Month Landmark: ITT Population

	Placebo (N=401)	*Milnacipran*			
		100 mg/d (N=399)	*200 mg/d (N=396)*		
	% responders	**% responders**	**% responders**	**OR (95% CI)**	**P-value**
Placebo vs 100 mg/d					
BOCF	25.2	31.1	---	1.33 (0.98, 1.82)	.069
LOCF	28.7	37.3	---	1.49 (1.10, 2.00)	.009
OC[a]	38.4	52.3	---	1.76 (1.23, 2.51)	.002
Placebo vs 200 mg/d					
BOCF	25.2	---	30.1	1.28 (0.93, 1.75)	.125
LOCF	28.7	---	39.9	1.66 (1.23, 2.23)	<.001
OC[a]	38.4	---	54.8	1.95 (1.35, 2.81)	<.001

a For the OC analysis, placebo N=263, milnacipran 100 mg N=237, and milnacipran 200 mg N=217.
BOCF = baseline observation carried forward; LOCF = last observation carried forward; OC = observed cases.

(Source: Applicant's Table 11.4.1.3.5-1, Clinical Study Report, MLN-MD-02, Vol. 1, p. 100)

Table 89 shows the responder analysis for the patient global component of the composite responder analysis (i.e., a rating of "much improved" or "very much improved" on the PGIC) at the 3-month landmark visit. A statistically significant greater number of milnacipran patients (in each dosage group) than placebo patients were classified as responders, regardless of the method of data imputation (i.e. BOCF, LOCF, and OC approaches). As described above, given that these were post-hoc analyses, the p-values should be interpreted with caution.

Table 89.Responder Analysis for the PGIC at the 3-Month Endpoint

Table 11.4.1.3.2-2. Responder Analysis for the Patient Global Component of the Composite Responder Criteria at the 3-Month Landmark: ITT Population

	Placebo (N=401)	*Milnacipran*			
		100 mg/d (N=399)	*200 mg/d (N=396)*		
	% responders	**% responders**	**% responders**	**OR (95% CI)**	**P-value**
		Placebo vs 100 mg/d			
BOCF	22.9	31.3	---	1.53 (1.12, 2.10)	.008
LOCF	24.9	34.6	---	1.59 (1.17, 2.16)	.003
OC[a]	31.8	47.5	---	1.94 (1.37, 2.74)	<.001
		Placebo vs 200 mg/d			
BOCF	22.9	---	32.6	1.62 (1.19, 2.22)	.002
LOCF	24.9	---	38.1	1.86 (1.37, 2.51)	<.001
OC[a]	31.8	---	50.6	2.19 (1.55, 3.11)	<.001

a For the OC analysis, placebo N=289, milnacipran 100 mg N=263, and milnacipran 200 mg N=255.
BOCF = baseline observation carried forward; CI = confidence interval; LOCF = last observation carried forward; OC = observed cases.

(Source: Applicant's Table 11.4.1.3.5-1, Clinical Study Report, MLN-MD-02, Vol. 1, p. 102)

Table 90 presents the responder analysis for the physical function component at the 3-month endpoint. Per the Applicant's analysis, neither of the milnacipran treatment arms had a statistically significant difference in the number of responders compared with the placebo arm by using the BOCF approach. When conducting the analysis using the LOCF and OC approach however, the 100 mg/day milnacipran treatment arm had a statistically significant difference in the number of responders compared to placebo but such result was not observed with the 200 mg/day milnacipran treatment arm. Again, given that these were post-hoc analyses, the p-values should be interpreted with caution.

Table 90. Responder Analysis for the SF 36-PCS at the 3-Month Endpoint

	Placebo (N=401)	*Milnacipran*			
		100 mg/d (N=399)	*200 mg/d (N=396)*		
	% responders	**% responders**	**% responders**	**OR (95% CI)**	**P-value**
Placebo vs 100 mg/d					
BOCF	21.5	27.1	---	1.38 (0.98, 1.92)	.063
LOCF	25.4	32.3	---	1.43 (1.04, 1.98)	.029
OC[a]	29.7	41.1	---	1.69 (1.16, 2.44)	.006
Placebo vs 200 mg/d					
BOCF	21.5	---	22.5	1.10 (0.78, 1.55)	.586
LOCF	25.4	---	27.5	1.17 (0.84, 1.62)	.348
OC[a]	29.7	---	34.9	1.35 (0.93, 1.95)	.118

a For the OC analysis, placebo N=290, milnacipran 100 mg N=263, and milnacipran 200 mg N=255.
BOCF = baseline observation carried forward; CI = confidence interval; LOCF = last observation carried forward; OC = observed cases.

(Source: Applicant's Table 11.4.1.3.5-1, Clinical Study Report, MLN-MD-02, Vol. 1, p. 105)

4. Change in mean (average) pain from baseline to the 3-month landmark.

The changes from baseline in the pain analyses (LOCF) at the 3-month landmark visit are **presented in the table below. The primary pain assessment was the patient's self report of pain,** based on the PED morning report of 24-hour recall pain, as recorded on an electronic VAS scale. **Patients' pain was also recorded using a paper-based VAS scale, at the clinic visits.**

For each method of pain assessment, at the end of the 3-month treatment period, changes from baseline in patient pain assessments following treatment with milnacipran at either dosage were numerically improved relative to placebo treatment. These differences reached statistical significance. However, because this was one of several post-hoc analyses performed without adjustment for multiplicity, the p-values should be cautiously interpreted.

Table 91: Change in Mean Pain from Baseline to the 3-Month Landmark Visit (LOCF)

Table 11.4.1.3.1-1. Pain Assessments: Change from Baseline for the 3-Month Treatment Period at 3-Month Landmark Visit (LOCF)

Parameter	*Placebo (N=401)*	*Milnacipran 100 mg/d (N=399)*			*Milnacipran 200 mg/d (N=396)*		
	Mean (SE)	*Mean (SE)*	*LSMD[a] (95% CI)*	*P-value*	*Mean (SE)*	*LSMD[a] (95% CI)*	*P-value*
Weekly average of PED-recorded morning 24-Hour recall pain scores	−13.00 (1.02)	−15.70 (1.06)	−3.03 (−5.83, −0.23)	.034	−17.41 (1.08)	−4.65 (−7.54, −1.76)	.002
Weekly average of PED-recorded real-time pain scores	−11.46 (1.00)	−14.72 (1.06)	−3.66 (−6.44, −0.87)	.010	−16.30 (1.04)	−5.13 (−7.94, −2.32)	<.001
PED-recorded weekly recall pain scores	−13.21 (1.10)	−16.93 (1.13)	−4.09 (−7.07, −1.12)	.007	−17.79 (1.17)	−4.75 (−7.80, −1.69)	.002
Paper-based VAS assessment of pain over past 24 hours	−16.77 (1.40)	−21.02 (1.46)	−5.91 (−9.63, −2.18)	.002	−22.59 (1.41)	−6.15 (−9.92, −2.37)	.001
Paper-based VAS assessment of pain over past week	−17.09 (1.34)	−21.41 (1.40)	−5.13 (−8.76, −1.51)	.006	−22.79 (1.36)	−5.99 (−9.63, −2.34)	.001

a Comparisons to placebo are based on the values of change from baseline using an ANCOVA model with treatment group and study center as factors and baseline value as covariate.

CI = confidence interval; LOCF = last observation carried forward; LSMD = least square means difference.

(Source: Applicant's Table 11.4.1.3.1-1, Clinical Study Report, MLN-MD-02, Vol.1. p. 97)

Key Secondary Efficacy Analyses

The Applicant collected several secondary efficacy endpoints. The main secondary endpoints that were analyzed at the 3-month landmark were the following:

5. Time-weighted average (AUC) of weekly 24-hour recall pain score
6. Time-weighted average of PGIC
7. Time-weighted average of SF-36 PCS
8. Improvement of fatigue per MFI
9. Patient Global Therapeutic Benefit

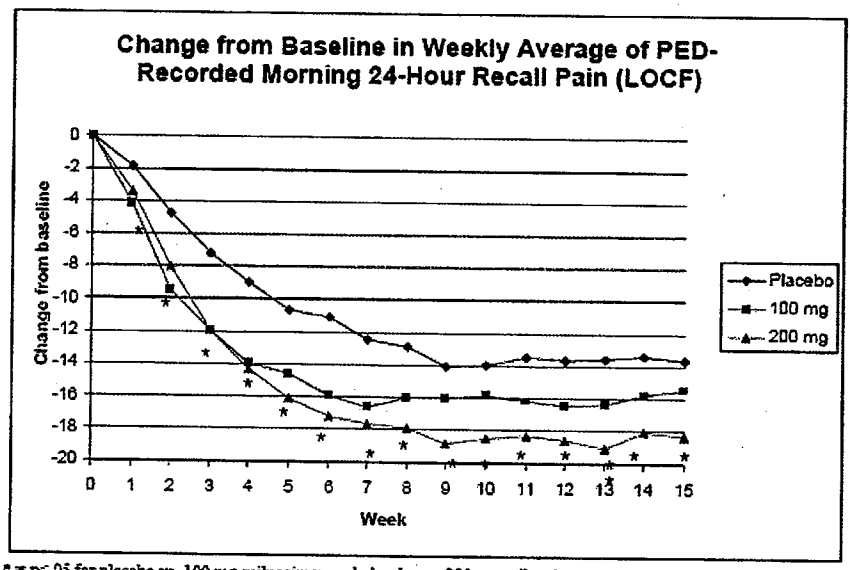
Only the results of the time- weighted average (AUC) of weekly 24-hour recall pain score are discussed here.

1. Time-weighted average (AUC) of the weekly average 24-hour recall pain score

The Applicant found that there was a statistically significant improvement in the pain domain as early as one week which was maintained through the study duration. The Applicant also found

that the patients who received milnacipran 200 mg/day seemed to have had greater mean pain reduction than those who received milnacipran 100 mg/day. The following figure represents the mean change from baseline in the weekly 24-hour recall pain score.

Figure 23. Mean Change from Baseline in Weekly Average of PED-Recorded 24-Hour Recall Pain (LOCF)



* = p<.05 for placebo vs. 100 mg-milnacipran and placebo vs. 200-mg milnacipran.
LOCF = last observation carried forward; PED = patient experience diary.
(Source: Applicant's Figure 11.4.1.3.1-1, Clinical Study Report, MLN-MD-02, Vol.1. p. 98)

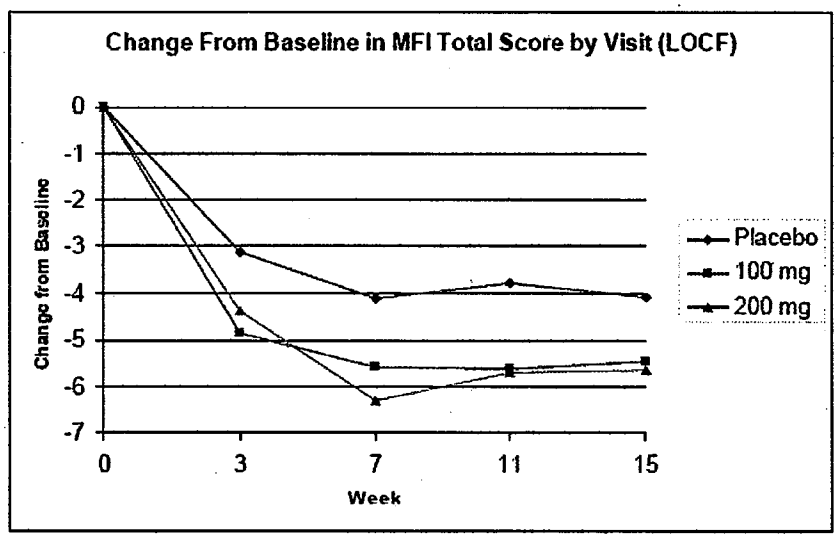
2. Improvement of fatigue using the MFI

The Applicant is seeking [redacted] b(4)

The MFI consists of 20 items scored to produce five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. According to the Applicant, this tool has been validated in cancer patients, medical students, army recruits, and junior physicians. The change in the MFI dimensions is presented in the table and figure below.

The comparison of the change from baseline in the total score achieved statistical significance for only for the milnacipran 100mg/day arm, and not the 200 mg/day arm. With respect to the individual components of the MFI, only analysis of the **"reduced motivation" component** resulted in a statistically significant result for both treatment arms. The data suggest that this component drove the favorable result for the milnacipran 100mg/day arm. Such result is not surprising - milnacipran is an anti-depressant and one would expect this particular response to the drug. The data suggest that milnacipran does not impact the other components of the assessment of fatigue.

Figure 24. Multidimensional Fatigue Inventory (MFI)-Change From Baseline



LOCF = last observation carried forward; MFI = Multidimensional Fatigue Inventory.

(Source: Applicant's Figure 11.4.1.3.8-1, Clinical Study Report, Vol.1, p. 113)

Table 92. Change from Baseline in MFI Components at the 3-Month Endpoint (LOCF)

Dimension	*Placebo (N=401)*	*Milnacipran 100 mg/d (N=399)*			*Milnacipran 200 mg/d (N=396)*		
	Mean (SE)	*Mean (SE)*	*LSMD[a] (95% CI)*	*P-value*	*Mean (SE)*	*LSMD[a] (95% CI)*	*P-value*
Total score	−3.84 (0.60)	−5.39 (0.64)	−1.80 (−3.47, −0.13)	.035	−5.39 (0.61)	−1.55 (−3.17, 0.07)	.061
General fatigue	−1.10 (0.15)	−1.39 (0.16)	−0.28 (−0.71, 0.15)	.196	−1.18 (0.15)	−0.06 (−0.47, 0.35)	.773
Physical fatigue	−1.04 (0.16)	−1.38 (0.17)	−0.40 (−0.82, 0.03)	.068	−1.37 (0.17)	−0.36 (−0.79, 0.07)	.104
Mental fatigue	−0.91 (0.16)	−0.89 (0.15)	−0.08 (−0.48, 0.33)	.712	−1.29 (0.16)	−0.34 (−0.74, 0.07)	.106
Reduced motivation	−0.53 (0.16)	−1.21 (0.17)	−0.79 (−1.21, −0.37)	<.001	−0.92 (0.16)	−0.43 (−0.85, −0.02)	.040
Reduced activity	−0.27 (0.17)	−0.52 (0.19)	−0.31 (−0.78, 0.16)	.190	−0.63 (0.17)	−0.35 (−0.80, 0.10)	.129

Note: Negative change represents improvement.

a Comparisons to placebo are based on the values of change from baseline using an ANCOVA model with treatment group and study center as factors and baseline value as covariate.

CI = confidence interval. LOCF = last observation carried forward; LSMD = least square means difference; MFI = Multidimensional Fatigue Inventory.

(Source: Applicant's Table11.4.1.3.8-1, Clinical Study Report, MLN-MD-02, Vol. 1, p. 114)

Discussion of Findings and Conclusions

The Applicant conducted study MLN-MD-02 to evaluate the efficacy of milnacipran for the "treatment of FMS" and for the "treatment of pain of FM." Per the Applicant's primary analysis, there was a statistically significant effect of both doses of milnacipran compared to placebo for both indications, at the 3-month endpoint.

The applicant's responder analysis curves, comparing the proportions of patients who achieved various degrees of pain relief, demonstrate a considerable separation between the active treatment arms and placebo, but the difference was not as notable between the two active arms.

The Applicant's responder analyses for each of the components of the composite responder criteria (i.e. pain, patient global and physical function) using BOCF imputation showed that:

- There was a numerical difference in the percentage of pain responders between the MLN treatment arms and placebo but this difference was not statistically significant neither MLN treatment arms.
- For the responder analysis of the patient global component the Applicant found that there was a statistically significant improvement response at 3 months for both MLN doses
- For the responder analysis of the physical function domain there was a numerical difference between placebo and the MLN treatment arms but the difference did not reach statistical significance.

In my opinion, the composite responder analysis and the responder analysis curves for pain and syndrome indicate that milnacipran does have an effect in a proportion of the population. In this study, seems that the patient global is driving the favorable result of the composite responder analysis.

Regarding the secondary efficacy endpoints, [redacted] b(4)

10.2 Line-by-Line Labeling Review

A line-by-line labeling review will be conducted with the entire review team.

For a discussion of the broad recommendations for labeling, refer to Section 9.4

10.3 Safety from the Historical Safety Data

10.3.1 Deaths Recorded in the Historical Safety Data

In the Historical Safety Data- Phase 2/3 Clinical studies in the Pierre Fabre MAA for Major Depressive Disorder (MDD) the records revealed that there were 36 deaths which occurred either during the study treatment or within 30 days after the stop date of the study drug. Twenty-two of the death cases occurred in the milnacipran treated patients. The narratives for these cases were submitted by the Applicant but they are for most part, unclear and incomplete. The distribution of the causes of death by cause and treatment arms is presented below.

Table 93. Incidence of Deaths in the Pierre Fabre MAA Phase 2/3 Clinical Studies (Historical Data)

Cause of Death	*Placebo Washout*	*Treatment Group (Patient-Years of Exposure) n [incidence]*[a]			
		Placebo (59.82)	*Milnacipran (975.27)*	*TCAs (177.68)*	*SSRIs (47.90)*
Suicide	3	1 [1.67]	14 [1.43]	3 [1.68]	1 [2.08]
Cardiovascular and cerebral disorders	0	0	4 [0.40]	2 [1.12]	1 [2.08]
Infectious diseases	0	0	2 [0.20]	1 [0.56]	0
Other causes	0	0	1 [0.10]	1 [0.56]	0
Unknown causes	0	0	1 [0.10]	1 [0.56]	0
Total number of deaths	3	1 [1.67]	22 [2.25]	8 [4.50]	2 [4.17]

a [incidence] = number of deaths per 100 patient-years of exposure.
TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor.

(Source: Applicant's Table 6.2.3-1, Summary of Clinical Safety, Vol. 1, p. 96)

According to the Applicant, suicide was the most frequent cause of death (n=14) in the milnacipran group however, the number of suicides per 100 patient-years of exposure among milnacipran-treated patients (1.43) was similar to that of other active treatment groups (1.68 for tricyclic anti-depressants –TCAs, and 2.08 for selective serotonin reuptake inhibitors- SSRIs) and placebo (1.67). The occurrence of suicides is not unexpected given that patients in the study were patients with MDD. The second most frequent cause of death was due to cardiovascular and cerebral disorders. My review of the narratives for the deaths in this group of studies accounts for 25 deaths in the milnacipran group: 14 suicides, 5 cardiovascular and cerebral disorders, 2 due to infectious diseases, 2 due to other causes (1 car accident and 1 presumably by choking), 2 deaths of unknown cause.

10.3.2 Serious Adverse Events from the Historical Safety Data and Clinical Pharmacology Studies

In the historical safety data (Phase II/III Clinical Studies in the Pierre Fabre MAA) there were 391 SAEs reported in 365 of 5732 (6.4%) patients: 277 were reported in the milnacipran treatment groups, 19 in the placebo groups, and 80 in the comparator groups; in addition, 15 SAEs occurred during placebo washout periods. The incidence of SAEs, expressed as the number of SAEs per 100 patient-years of exposure, was comparable between the milnacipran (28.40) and placebo (31.76) treatment groups. Among the most prevalent SAEs were depression/depression aggravated (26% of total milnacipran SAEs, 21% of total placebo SAEs), suicide attempt (18% milnacipran, 26% placebo), suicide, and anxiety (4.3% milnacipran, 5.3% placebo). The number of psychiatric SAEs per 100 patient-years of exposure was similar in the milnacipran (17.22) and placebo (20.06) treatment groups.

Other commonly involved organ systems in which SAEs were reported among milnacipran-treated patients were general disorders (10% of total milnacipran SAEs, 11% of total placebo SAEs), central and peripheral nervous system disorders (5.4% milnacipran, 0% placebo), cardiovascular disorders (5.4% milnacipran, 0% placebo), and gastrointestinal disorders (5.1% milnacipran, 0% placebo). In addition, 5 seizures were reported in milnacipran-treated patients: 2 generalized epilepsy, 2 focal epilepsy, and 1 unspecified (see Section 11.11.3.3 for discussion of seizures).

10.3.3 Discontinuations Due to Serious Adverse Events in the Historical Safety Data

Discontinuation due to SAEs occurred in 261 (4.6%) patients: 172 received milnacipran, 14 received placebo, and 62 received comparator drug; in addition, 13 patients discontinued because of SAEs during placebo washout periods. The number of SAEs leading to discontinuation per 100 patient-years of exposure, the incidence was similar for milnacipran- (17.63) and placebo-treated (23.40) patients. Furthermore, the most prevalent SAEs leading to discontinuation were psychiatric in nature for both the milnacipran (119/172 [69%]) and placebo (11/14 [79%]) treatment groups.

10.3.4 Discontinuations Due to Adverse Events in the Historical Safety Data

Of the 3376 patients who received milnacipran (all doses combined), 343 (10.2%) discontinued because of AEs compared with 24 (6.1%) of 394 patients who received placebo. The most common AEs that occurred in at least 0.5% of patients receiving milnacipran treatment group were nausea, insomnia, vomiting and headache. According to the Applicant, 79% of the patients with drew during the first month of treatment. The profile of the treatment-emergent adverse events that led to discontinuation in this safety database is in concordance with the observations from the other safety populations. Table 94 displays the TEAEs reported in ≥0.5% of the patients

in the milnacipran 100 mg/day treatment group in the historical safety database. Although this data derives from studies in non-FM patients the overall adverse event profile is similar and does not raise other safety concerns in any particular system organ class.

Table 94. Discontinuations Due to Treatment-Emergent Adverse Events in ≥ 0.5% of Patients Treated with Milnacipran 100 mg/Day in the Historical Safety Data

	Placebo (N = 394)		*Milnacipran 50 mg (N = 426)*		*Milnacipran 100 mg (N = 1871)*		*Milnacipran 200 mg (N = 865)*	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
ADOs[a]	**24**	**(6.1)**	**52**	**(12.2)**	**143**	**(7.6)**	**130**	**(15.0)**
Nausea	5	(1.3)	7	(1.6)	43	(2.3)	35	(4.0)
Vomiting	2	(0.5)	6	(1.4)	22	(1.2)	19	(2.2)
Insomnia	10	(2.5)	13	(3.1)	21	(1.1)	37	(4.3)
Abdominal pain	1	(0.3)	7	(1.6)	17	(0.9)	6	(0.7)
Headache	4	(1.0)	6	(1.4)	14	(0.7)	19	(2.2)
Dizziness	2	(0.5)	2	(0.5)	14	(0.7)	2	(0.2)
Dysuria	0	–	1	(0.2)	14	(0.7)	4	(0.5)
Anxiety	2	(0.5)	3	(0.7)	13	(0.7)	11	(1.3)
Palpitations	0	–	1	(0.2)	9	(0.5)	5	(0.6)

(Source: Applicant's Table 6.4.3-1, Summary of Clinical Safety, Vol. 1, p. 125)

10.4 Safety Tables

10.4.1 Serious Adverse Events from Placebo-Controlled Non-Fibromyalgia Studies (Group 2) - Only Milnacipran Treated Groups

Table 4.6.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term, and Preferred Term
Double-Blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	Placebo (N=523) n (%)	MLN 50 mg (N=162) n (%)	MLN 100 mg (N=395) n (%)
Patients with at least one SAE	16 (3.1)	2 (1.3)	20 (5.0)
Blood and lymphatic system disorders	3 (0.6)	0	2 (0.5)
Platelet disorders	1 (0.2)	0	0
Thrombocytopenias	1 (0.2)	0	0
Thrombocytopenic purpura	1 (0.2)	0	0
White blood cell disorders	2 (0.4)	0	2 (0.5)
Neutropenias	2 (0.4)	0	2 (0.5)
Neutropenia	2 (0.4)	0	2 (0.5)
Cardiac disorders	0	0	1 (0.3)
Cardiac arrhythmias	0	0	1 (0.3)
Rate and rhythm disorders NEC	0	0	1 (0.3)
Tachycardia	0	0	1 (0.3)
Gastrointestinal disorders	0	0	2 (0.5)
Anal and rectal conditions NEC	0	0	1 (0.3)
Anal and rectal disorders NEC	0	0	1 (0.3)
Anal fissure	0	0	1 (0.3)
Gastrointestinal ulceration and perforation	0	0	1 (0.3)
Gastric ulcers and perforation	0	0	1 (0.3)
Gastric ulcer	0	0	1 (0.3)

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (placebo-controlled Non-FMS) studies: 0232 F2207 91 WI08, 0288 F2207 91 WI03, 0284 F2207 92 US08, 0972 F2207 97 US02, and F02207-US201.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Total*: Only Milnacipran groups included.

Table 4.6.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term,and Preferred Term
Double-Blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	MLN 150 mg (N=15) n (%)	MLN 200 mg (N=804) n (%)	MLN Total* (N=772) n (%)
Patients with at least one SAE	0	0	22 (2.8)
Blood and lymphatic system disorders	0	0	2 (0.3)
Platelet disorders	0	0	0
Thrombocytopenias	0	0	0
Thrombocytopenic purpura	0	0	0
White blood cell disorders	0	0	2 (0.3)
Neutropenias	0	0	2 (0.3)
Neutropenia	0	0	2 (0.3)
Cardiac disorders	0	0	1 (0.1)
Cardiac arrhythmias	0	0	1 (0.1)
Rate and rhythm disorders NEC	0	0	1 (0.1)
Tachycardia	0	0	1 (0.1)
Gastrointestinal disorders	0	0	2 (0.3)
Anal and rectal conditions NEC	0	0	1 (0.1)
Anal and rectal disorders NEC	0	0	1 (0.1)
Anal fissure	0	0	1 (0.1)
Gastrointestinal ulceration and perforation	0	0	1 (0.1)
Gastric ulcers and perforation	0	0	1 (0.1)
Gastric ulcer	0	0	1 (0.1)

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (placebo-controlled Non-FMS) studies: C232 F2207 91 M1C8, C288 F2207 91 M1D3, C284 F2207 92 C2C8, C972 F2207 97 C2C2, and F02207-C2C01.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Total*: Only milnacipran groups included.

Report Generated by Program: /saspro9/mln/FMS/pt/programs/tables/tseinc04.sas
Final 05/14/2007 11:09

APPEARS THIS WAY
ON ORIGINAL

Table 4.6.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term,and Preferred Term
Double-blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	Placebo (N=520) n (%)	MLN 50 mg (N=152) n (%)	MLN 100 mg (N=995) n (%)
Hepatobiliary disorders	0	0	1 (0.1)
Hepatic and Hepatobiliary disorders	0	0	1 (0.1)
Hepatocellular damage and hepatitis NEC	0	0	1 (0.1)
Hepatocellular damage	0	0	1 (0.1)
Infections and infestations	0	0	2 (0.2)
Infections - pathogen class unspecified	0	0	2 (0.2)
Abdominal and gastrointestinal infections	0	0	2 (0.2)
Diverticulitis	0	0	1 (0.1)
Enterocolitis infectious	0	0	1 (0.1)
Injury, poisoning and procedural complications	1 (0.2)	1 (0.7)	1 (0.1)
Injuries NEC	1 (0.2)	0	1 (0.1)
Non-site specific injuries NEC	1 (0.2)	0	1 (0.1)
Road traffic accident	1 (0.2)	0	1 (0.1)
Medication errors	0	1 (0.7)	0
Overdoses	0	1 (0.7)	0
Intentional overdose	0	1 (0.7)	0
Investigations	1 (0.2)	0	0
Hepatobiliary investigations	1 (0.2)	0	0
Liver function analyses	1 (0.2)	0	0
Alanine aminotransferase increased	1 (0.2)	0	0

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (placebo-controlled Non-FMS) studies: C092 F2207 91 M100, C093 F2207 91 M103, C094 F2207 92 GE300, C972 F2207 97 GE302, and F02207-GE201.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Total*: Only milnacipran groups included.

Table 4.6.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term, and Preferred Term
Double-blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	MLN 150 mg (N=15) n (%)	MLN 200 mg (N=204) n (%)	MLN Total* (N=772) n (%)
Hepatobiliary disorders	0	0	1 (0.1)
Hepatic and hepatobiliary disorders	0	0	1 (0.1)
Hepatocellular damage and hepatitis NEC	0	0	1 (0.1)
Hepatocellular damage	0	0	1 (0.1)
Infections and infestations	0	0	2 (0.3)
Infections - pathogen class unspecified	0	0	2 (0.3)
Abdominal and gastrointestinal infections	0	0	2 (0.3)
Diverticulitis	0	0	1 (0.1)
Enterocolitis infectious	0	0	1 (0.1)
Injury, poisoning and procedural complications	0	0	2 (0.3)
Injuries NEC	0	0	1 (0.1)
Non-site specific injuries NEC	0	0	1 (0.1)
Road traffic accident	0	0	1 (0.1)
Medication errors	0	0	1 (0.1)
Overdoses	0	0	1 (0.1)
Intentional overdose	0	0	1 (0.1)
Investigations	0	0	0
Hepatobiliary investigations	0	0	0
Liver function analyses	0	0	0
Alanine aminotransferase increased	0	0	0

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (placebo-controlled Non-FMS) studies: C232 F2207 91 M1CB, C288 F2207 91 M1D3, C284 F2207 92 C23C8, C972 F2207 97 C2302, and F02207-02581.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Total*: Only milnacipran groups included.

Report Generated by Program: /sasprog/mln/FMS/pf/programs/tables/tssincd4.sas
Final 05/14/2007 11:09

Table 4.5.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term, and Preferred Term
Double-blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	Placebo (N=520) n (%)	MLN 50 mg (N=152) n (%)	MLN 100 mg (N=395) n (%)
Metabolism and nutrition disorders	1 (0.2)	0	0
Glucose metabolism disorders (incl diabetes mellitus)	1 (0.2)	0	0
Diabetes mellitus (incl subtypes)	1 (0.2)	0	0
Diabetes mellitus inadequate control	1 (0.2)	0	0
Nervous system disorders	2 (0.4)	0	1 (0.3)
Mental impairment disorders	1 (0.2)	0	0
Memory loss (excl dementia)	1 (0.2)	0	0
Amnesia	1 (0.2)	0	0
Neurological disorders NEC	1 (0.2)	0	0
Coma states	1 (0.2)	0	0
Coma	1 (0.2)	0	0
Neuromuscular disorders	0	0	1 (0.3)
Muscle tone abnormal	0	0	1 (0.3)
Hypertonia	0	0	1 (0.3)
Pregnancy, puerperium and perinatal conditions	0	1 (0.7)	0
Abortions and stillbirth	0	1 (0.7)	0
Abortions not specified as induced or spontaneous	0	1 (0.7)	0
Abortion	0	1 (0.7)	0
Psychiatric disorders	7 (1.3)	0	9 (2.3)

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (placebo-controlled Non-FMS) studies: 0232 F2207 91 M108, 0233 F2207 91 M103, 0284 F2207 92 02308, 0972 F2207 97 02302, and F02207-02201.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Totals: Only milnacipran groups included.

Table 4.5.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term, and Preferred Term
Double-blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	MLN 150 mg (N=15) n (%)	MLN 200 mg (N=204) n (%)	MLN Total* (N=772) n (%)
Metabolism and nutrition disorders	0	0	0
Glucose metabolism disorders (incl diabetes mellitus)	0	0	0
Diabetes mellitus (incl subtypes)	0	0	0
Diabetes mellitus inadequate control	0	0	0
Nervous system disorders	0	0	1 (0.1)
Mental impairment disorders	0	0	0
Memory loss (excl dementia)	0	0	0
Amnesia	0	0	0
Neurological disorders NEC	0	0	0
Coma states	0	0	0
Coma	0	0	0
Neuromuscular disorders	0	0	1 (0.1)
Muscle tone abnormal	0	0	1 (0.1)
Hypertonia	0	0	1 (0.1)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.1)
Abortions and stillbirth	0	0	1 (0.1)
Abortions not specified as induced or spontaneous	0	0	1 (0.1)
Abortion	0	0	1 (0.1)
Psychiatric disorders	0	0	9 (1.2)

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (placebo-controlled Non-FMS) studies: C232 F2207 91 MICO, C288 F2207 91 MI03, C284 F2207 92 GE3C8, C972 F2207 97 GE3C2, and F02207-GE2C1.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Total*: Only milnacipran groups included.

Report Generated by Program: /sasprog/mln/FMS/pf/programs/tables/tseincd4.sas

Final 05/14/2007 11:09

APPEARS THIS WAY
ON ORIGINAL

Table 4.5.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term, and Preferred Term
Double-blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	Placebo (N=529) n (%)	MLN 50 mg (N=152) n (%)	MLN 100 mg (N=395) n (%)
Anxiety disorders and symptoms	2 (0.4)	0	1 (0.3)
Anxiety symptoms	2 (0.4)	0	1 (0.3)
Anxiety	2 (0.4)	0	1 (0.3)
Depressed mood disorders and disturbances	4 (0.8)	0	5 (1.3)
Depressive disorders	4 (0.8)	0	5 (1.3)
Depression	4 (0.8)	0	5 (1.3)
Disturbances in thinking and perception	0	0	1 (0.3)
Perception disturbances	0	0	1 (0.3)
Derealisation	0	0	1 (0.3)
Suicidal and self-injurious behaviours NEC	1 (0.2)	0	2 (0.5)
Suicidal and self-injurious behaviour	1 (0.2)	0	2 (0.5)
Suicide attempt	1 (0.2)	0	2 (0.5)
Renal and urinary disorders	0	0	1 (0.3)
Urolithiasis	0	0	1 (0.3)
Renal lithiasis	0	0	1 (0.3)
Nephrolithiasis	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	0
Respiratory disorders NEC	1 (0.2)	0	0
Respiratory tract disorders NEC	1 (0.2)	0	0

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (Placebo-controlled Non-FMS) studies: 0232 F2207 91 MICO, 0238 F2207 91 MI93, 0284 F2207 92 GE2C8, 0972 F2207 97 GE3G2, and F02207-G220I.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Total*: Only Milnacipran groups included.

Table 4.6.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term,and Preferred Term
Double-Blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	MLN 150 mg (N=15) n (%)	MLN 200 mg (N=204) n (%)	MLN Total* (N=772) n (%)
Anxiety disorders and symptoms	0	0	1 (0.1)
Anxiety symptoms	0	0	1 (0.1)
Anxiety	0	0	1 (0.1)
Depressed mood disorders and disturbances	0	0	5 (0.6)
Depressive disorders	0	0	5 (0.6)
Depression	0	0	5 (0.6)
Disturbances in thinking and perception	0	0	1 (0.1)
Perception disturbances	0	0	1 (0.1)
Derealisation	0	0	1 (0.1)
Suicidal and self-injurious behaviours NEC	0	0	2 (0.3)
Suicidal and self-injurious behaviour	0	0	2 (0.3)
Suicide attempt	0	0	2 (0.3)
Renal and urinary disorders	0	0	1 (0.1)
Urolithiases	0	0	1 (0.1)
Renal litniasis	0	0	1 (0.1)
Nephrolithiasis	0	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	0	0
Respiratory disorders NEC	0	0	0
Respiratory tract disorders NEC	0	0	0

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (placebo-controlled Non-FMS) studies: 0232 F2207 91 M100, 0288 F2207 91 M193, 0284 F2207 92 02308, 0972 F2207 97 02302, and F02207-02201.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Total*: Only milnacipran groups included.
Report Generated by Program: /sasprog/mln/FMS/pf/programs/tables/tsaincd4.sas
Final 05/14/2007 11:09

Table 4.6.4
Incidence of On-Therapy Serious Adverse Events
by System Organ Class, High Level Group Term, High Level Term, and Preferred Term
Double-blind Placebo-controlled Non-FMS Studies (Group 2)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	Placebo (N=520) n (%)	MLN 50 mg (N=162) n (%)	MLN 100 mg (N=395) n (%)
Lung disorder	1 (0.2)	0	0
Surgical and medical procedures	1 (0.2)	0	0
Nervous system, skull and spine therapeutic procedures	1 (0.2)	0	0
Peripheral nerve therapeutic procedures	1 (0.2)	0	0
Peripheral nerve decompression	1 (0.2)	0	0
Vascular disorders	0	0	1 (0.3)
Vascular hypertensive disorders	0	0	1 (0.3)
Vascular hypertensive disorders NEC	0	0	1 (0.3)
Diastolic hypertension	0	0	1 (0.3)

Notes: MedDRA 9.1 was used to code adverse events.
Based on Group 2 (placebo-controlled Non-FMS) studies: C032 F2207 91 WI08, 3228 F2207 91 WI03, C284 F2207 92 C2308, C572 F2207 97 C2302, and F02207-C2201.
n = Number of patients who had an On-Therapy serious adverse event.
On-Therapy serious adverse events (SAEs) include SAEs during the study or within 30 days of last dose of study medication.
MLN = Milnacipran.
MLN Total = Only milnacipran groups included.
Report Generated by Program: /sasprog/mln/FUS/pf/programs/tables/tesinc04.sas
Final 05/14/2007 11:09

(Source: Applicant's Table 4.6.4, Summary of Clinical Safety, Vol. 5, p. 9039-9049)

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Jane Filie
8/28/2008 01:14:58 PM
MEDICAL OFFICER

Mwango Kashoki
8/28/2008 01:23:45 PM
MEDICAL OFFICER

6/18/08

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	22-256
Brand Name	Not available
Generic Name	Milnacipran HCL
Sponsor	Forest Laboratories, Inc. and Cypress Bioscience, Inc.
Indication	Treatment of fibromyalgia Syndrome
Dosage Form	Tablets: 12.5 mg, 25 mg, 50 mg, and 100 mg
Drug Class	Norepinephrine and serotonin reuptake inhibitor (NSRI) with preferential inhibition of norepinepherine reuptake over serotonin reuptake
Therapeutic Dose	Maintenance Dose: 50 mg BID, up to 100 mg BID
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	[ ] b(4)
Application Submission Date	December 18, 2007
Review Classification	Standard NDA
Date Consult Received	February 4, 2008
Clinical Division	DAARP, HFD-170
PDUFA Date	October 15, 2008

1 SUMMARY

1.1 QT-IRT'S RECOMMENDATION

There are several limitations to the study which decrease our confidence in the study results. The main limitations are:

(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.

We recommend that the sponsor performs a repeat TQT study incorporating the following elements:

- Use exercise or 24-h ambulatory ECG monitoring at baseline as a method to increase the range of heart rates to compute an individual-correction factor.
- Collect additional ECGs during the titration of milnacipran to determine the dose/concentration-response relationship for QT prolongation.
- Moxifloxacin control should be conducted concurrently with the other arms.
- In this study, over-encapsulation of the moxifloxacin tablet may have caused a decrease in moxifloxacin exposure. We recommend that blinding is performed using a double-dummy approach.

1.2 Overall Summary of Findings

The sponsor used an individual correction factor, QTcNi, as the primary endpoint. The sponsor asserts that milnacipran does not cause QTc prolongation because the maximum mean increase in ΔΔQTcNi is -5 (-9.4, -0.08) ms based on their analysis (see Table 3). We do not agree with their analysis because QTcNi does not appropriately correct for heart rate during treatment with milnacipran. QTcNi was computed using drug free, resting ECG recordings at baseline (Day -1). The range of heart rates during baseline is significantly lower than the range observed following milnacipran treatment; the mean increase in heart rate was 22 bpm (see Figure 8). Based on our analysis of the QT/RR data (see section 5.1), QTcF is a better than the sponsor's QTcNi in correcting the QT for heart rate. However, one can argue that either QTcF or QTcNi is not an appropriate heart rate correction method after treatment with milnacipran because neither correction method completely removed the QT/RR relationship in all subjects (see Figure 9).

This study failed to exclude a 10-ms increase in the QTcF interval for the supratherapeutic dose of milnacipran. Following b.i.d. administration of 300 mg milnacipran (3 times higher than highest therapeutic dose of 100 mg bid), the largest upper limit of the two-sided 90% CI for ΔΔQTcF was greater than 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

In this randomized, positive- and placebo-controlled parallel study, 88 healthy subjects received either multiple doses of milnacipran or placebo for 37 days. A single dose of moxifloxacin 400 mg was given on day 1 to establish assay sensitivity. This design is not optimal to demonstrate assay sensitivity. Table 1 presents the overall study findings ***using QTcF as the primary endpoint.***

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Milnacipran (300 mg BID) and the Largest Lower Bound for Moxifloxacin for QTcF (FDA Analysis)

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 (see Table 10)

Moxifloxacin failed to demonstrate assay sensitivity based on the statistical criteria that the lower limit of the two-sided confidence interval is ≥ 5 ms. 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 (see section 5.3.1). Thus, we concluded that the lower moxifloxacin response is expected for the observed exposures.

The supratherapeutic dose is acceptable. For the treatment of Fibromyalgia Syndrome the target dose is 100 mg/day but the dose could be increased to 200 mg/day based on patient response. The mean C_{max} following administration of 100 mg bid milnacipran is 455 ng/ml (CV=18%) in study F2207M146. Following administration of 300 mg bid milnacipran, the mean C_{max} is 1908 ng/ml (CV=20%); thus, the supratherapeutic dose provided a 4-fold increase in exposure compared to the highest clinical dose. The expected high exposure scenario is when 200 mg/day milnacipran is administered to patients with severe renal impairment. The steady state mean increase in C_{max} is ~2.4-fold higher which is covered by the supratherapeutic exposures. Furthermore the sponsor is asking for dose adjustment of 50% in subjects with severe renal impairment.

Exposure-response analysis using ΔΔQTcF gives a shallow but statistically significant slope of 3 ms per μg/ml milnacipran (see section 5.3.1). Based on this relationship, it expected that milnacipran will not significantly increase the QTcF interval over the therapeutic exposure range.

There has been one case of TdP reported based in our MGPS data mining analysis. Although this was confounded by co-morbidities (age, sex, hypomagnesemia) and concomitant medications that prolong the QT interval (see section 5.4.3), it was associated with a QT of 500 ms and occurred after taking milnacipran. We would like to bring this to the attention of the review division.

2 PROPOSED LABEL

The Sponsor has submitted the following information in the proposed label

12.2 Pharmacodynamics

Cardiovascular Electrophysiology. [redacted] b(4)

[ ] b(4)

Reviewer's Comment: In the absence of a repeat TQT study, we recommend the results of QTcF are used for labeling.

Cardiovascular Electrophysiology. [

[ ] b(4)

3 BACKGROUND

Milnacipran is a novel norepinephrine-serotonin reuptake inhibitor (NSRI) being co-developed by Forest Research Institute and Cypress Bioscience, Inc. Milnacipran is proposed for the treatment of fibromyalgia syndrome (FMS), which is defined by achievement of concurrent and clinically meaningful improvement in the domains of pain, patient global assessment, and physical function.

3.1 MARKET APPROVAL STATUS

In 1997, milnacipran was approved in France for use in patients with MDD. Since then, it has received marketing approval in more than 50 countries, with greatest use in [ ] b(4)

3.2 PRECLINICAL INFORMATION

Source: Non-Clinical Summary

> "The effects of milnacipran on hERG channel activity were studied in stably transfected HEK293 cells by patch-clamp technique. Milnacipran showed no effects at concentrations of 3 and 10 µM but significantly inhibited hERG channel activity at 30 µM (21.3% inhibition, vehicle corrected). The IC_{20} value was calculated to be 20.7 µM (see Study MLN-TX-01000 Part 1). This concentration is approximately 100- to 2000-fold higher than the efficacious concentration determined for the inhibition of NE and 5-HT uptake in vitro (10-200 nM). Actual milnacipran concentrations were verified by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) measurements from perifusates and found to be close to the nominal values (see Study MLN-TX-01000 Part 2).
>
> "The effects of milnacipran on action potential parameters (resting potential, amplitude, maximal rate of depolarization, effective refractory periods, and durations of the action potential to 30%, 50%, and 90% repolarization [ie, APD_{30}, APD_{50}, and APD_{90}]) were measured in isolated guinea pig ventricular fibers under standard conditions. Milnacipran prolonged action potential duration to a similar extent as imipramine. At a concentration of 10 µM, milnacipran increased APD_{50} and APD_{90} by 9.9 % (155 ± 4 ms vs 141 ± 4 ms) and 6.7 % (191 ± 3 ms vs 179 ± 3 ms), respectively. At 3 µM (ie, a concentration in the range of therapeutic plasma levels of milnacipran), the compound increased APD_{90} to 187 ± 2 ms vs

179 ± 3 ms in the control (+4.3%). Imipramine (3 μM) increased the APD90 to 197 ± 4 ms vs 190 ± 4 ms in the control experiment (+3.6%). Moreover, milnacipran showed a less marked depression of the maximal rate of depolarization (10 μM: .Vmax = 16 V/sec) than imipramine (10 μM: .Vmax = 57 V/sec) (see Study P068).

"The effect of milnacipran on the duration of action potentials was also studied in isolated frog atrial fiber. Milnacipran significantly prolonged APD30, APD50, and APD90 at 10 μM but not at higher concentrations. In contrast, action potential amplitude (APA) and Vmax were significantly depressed at 100 μM and 500 μM but not at 10 μM. Further analysis of channels that participate in the generation of the cardiac action potential suggested that milnacipran (100 μM) reduced the amplitude of the sodium current and depressed the slow calcium-sodium current (see Study P082).

"In a cardiac electrophysiological evaluation in closed thorax anesthetized dogs, IV milnacipran tended to produce tachycardia at 0.5-1 mg/kg but caused significant bradycardia at higher doses (= 4 mg/kg IV). Milnacipran (= 2 mg/kg IV) slowed the conduction time in the atrioventricular node (A-H). The conduction in the His bundle (H-V) was decreased at all doses (0.5-8 mg/kg IV). The QRS complex was moderately widened at 2 and 4 mg/kg IV, and this effect was further increased at 8 mg/kg. At doses of 4 and 8 mg/kg IV, milnacipran increased the QT interval by 40% and 51% (at 5 minutes), respectively, and increased atrial and ventricular refractory periods in a dose-dependent manner. Milnacipran also significantly increased the sinus cycle after IV injections of 4 mg/kg (14% at 5 minutes) and 8 mg/kg (32% at 5 minutes) (see Study P076). It is important to note that different results were obtained in a clinical study (see Study MLN-PK-10), where no QTc prolongation was observed at a milnacipran dose of 300 mg twice daily (ie, at least 3 times greater than the intended therapeutic dose for the treatment of fibromyalgia (ie, 100 mg twice daily).

"Although the predominant effect of milnacipran on heart rate in animals was bradycardia, the compound consistently increased heart rate in human trials. Therefore, the obtained nonclinical study results may be of limited value in the prediction of cardiovascular effects of milnacipran in humans."

Reviewer's Comment: Prolonged APD in the atria and ventricle with effects on the sodium and calcium currents were noted in the in vitro studies. Effects on HR, QT interval and cardiac conduction were also noted in the in vivo studies.

3.3 Previous Clinical Experience

Source: Summary of Clinical Safety and Appendix 12.37, Special Topics report-Cardiovascular

"In all, 2596 patients have been treated with milnacipran in phase II/III clinical studies; 822 have been treated for at least 6 months, and 354 patients have been treated for 12 months. The maximum duration of treatment was 529 days (17.6 months).

"Postmarketing studies for different non-fibromyalgia indications have been conducted by Pierre Fabre; Pierre Fabre, the worldwide safety database holder, has also received spontaneous reports from the more than[ ] patient-months of global exposure. Spontaneous reports submitted to the Pierre Fabre worldwide safety database as of June 30, 2007, are summarized in this section. b(4)

"Because the primary biochemical mechanism of action of milnacipran is the inhibition of active reuptake of NE and 5-HT, there is an increase in the intrasynaptic concentrations of these monoamines and their availability in the brain, consistent with the agent's putative mechanism of action. The increased concentrations of these monoamines also occur in peripheral tissues, where their cardiovascular effects might be seen. The cardiovascular effects of NE, primarily tachycardia and vasoconstriction, are well known. 5-HT may also produce significant effects on the heart and blood vessels, including tachycardia, arrhythmias, and vasoconstriction. Thus, it is expected, a priori, that milnacipran administration could be associated with changes in both HR and BP, as has been the experience with other agents that inhibit NE reuptake.

"In historical data from Pierre Fabre clinical studies in the MAA for major depression, the incidence of seizures was reported to be 0.51% (n = 5) in milnacipran-treated patients and 0.16 % (n = 1) in placebo-treated patients. In all five cases the causal relationship to milnacipran was called "dubious." The European and Japanese SPCs contain a precaution about using milnacipran in patients with epilepsy and recommend discontinuation of milnacipran in any patient developing a seizure.

"The Pierre Fabre safety surveillance database contains 53 serious spontaneous reports of various types of seizures, most of them from Japan. Nine of these patients had a history of epilepsy and were using anticonvulsants. Two of the seizures occurred in connection with a cerebral hemorrhage, two with a brain tumor, and two with a multiple-drug overdose. The most commonly used concomitant medications were benzodiazepines, anticonvulsants, amoxapine, paroxetine, and sulpiride; no concomitant medications were reported in 10 patients. Four of the cases were fatal: three in connection with suicide attempts with multiple medications and one that occurred in a chronically ill 78-year-old patient who developed septic shock and subsequently died from respiratory failure approximately 8 days after stopping milnacipran and approximately 5 days after experiencing a "convulsion on her face and around pharynx."

The Sponsor draws the following conclusions in the special topics report-cardiovascular analyses (Appendix 12.37)

"•Milnacipran produces sympathomimetic CV effects consistent with its profile as a reuptake inhibitor of NE and 5–HT

•[ ] patient-months of milnacipran use outside of the United States indicated that CV related SAEs and deaths are rare b(4)

•Mean changes of 3.1 / 2.4 mm Hg in SBP / DBP, and mean changes in heart rate of about 7–8 bpm, were observed in patients with FMS participating in phase III

with little difference observed between the 100 mg/d and 200 mg/d doses of milnacipran

•Cardiovascular AEs associated with milnacipran are infrequent, tend to be mild or moderate in intensity, and hemodynamic effects are reversible with drug discontinuation

•The relative risks of a categorical shift in blood pressure, receiving a new diagnosis new or worsening hypertension, or having a change in hypertensive medication during treatment with either 100 mg/d or 200 mg/d of milnacipran are generally between 1.5 and 3 times that of placebo patients

•The CV effects of milnacipran are similar to those seen with other currently agents affecting NE and/or 5–HT reuptake

•The BP and heart rate effects of milnacipran should be monitored to provide optimal treatment of the patient"

Reviewer's Comment: There are no reports of TdP in the clinical data base. There are 38 cases of serious or fatal tachycardia, cardiac failure, myocardial infarction, cardiogenic shock and cardiac arrest reported under the cardiac disorders SOC in the sponsor's post-marketing report. The narratives were reviewed. Most of the serious cases of tachycardia in younger individuals with no pre-existing heart disease were associated with overdose, seizures, serotonin syndrome, hyperthyroidism, anxiety and concomitant medications that could increase HR. Consistent with this drug class, the elderly, patients with pre-existing CAD/CHF, conduction disturbances or renal impairment, who would be more sensitive to the HR increase, and may be more prone for adverse outcomes. Overall the effects appear comparable with other agents affecting NE and/or 5-HT uptake. Please also refer to the DCRP consult on Cardiac Safety by Dr. Gail Moreschi).

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of milnacipran's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

4.2 TQT STUDY

The QT-IRT reviewed the study report for studies MLN-PK-10 including electronic datasets and waveforms submitted to the ECG warehouse. Studies C241 and M146 were reviewed by DCaRP in a separate consult.

4.2.1 Title

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

4.2.2 Protocol Number

MLN-PK-10

4.2.3 Study Dates

July 13, 2005 to November 28, 2005

4.2.4 Objectives

This was a two-part study. The objectives of this study were:

- Part A: to evaluate the safety and tolerability of milnacipran HCl at doses up to 300 mg twice daily (BID)
- Part B: to determine if the highest dose of milnacipran determined 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

4.2.5 Study Description

4.2.5.1 Design

Part A: This was a randomized, double-blind, placebo-controlled, dose-escalation study.

Part B: This was a randomized (stratified by gender), double-blind, active drug and placebo-controlled, parallel-group, multiple-dose study.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was blinded (by using the encapsulated tablet).

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There are two arms included in the study,

- Milnacipran Placebo / 400 mg Moxifloxacin Arm and
- 300 mg Milnacipran Arm / Moxifloxacin Placebo Arm

4.2.6.2 Sponsor's Justification for Doses

"The milnacipran dose of 300 mg BID, which is at least three times greater than the intended recommended dose in patients with FM, was chosen to account for possible increases in plasma milnacipran levels caused by renal impairment, drug interactions, etc. This study was designed to evaluate the effect of milnacipran on cardiac repolarization at doses that were at least three times the expected marketed dose of milnacipran for the treatment of FM. As per US Food and Drug Administration (FDA) Guidance on E14 Clinical Evaluation of QT/QTc Interval

Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, drugs should be tested at concentrations that are substantial multiples of the expected maximum therapeutic exposure (US Food and Drug Administration, 2005)."

Instructions with Regard to Meals

Doses were administered with food. A standardized low-fat (<20 g) meal were consumed and doses taken at the same time on each occasion.

4.2.6.3 ECG and PK Assessments

Table 2: Sampling Schedule (Part B)

Study Day	-1	1	2 – 37	38
Intervention	Placebo	Moxifloxacin Placebo or Moxifloxacin #1	Placebo or Milnacipran Capsule #2	Placebo or Milnacipran #3
12-Lead ECGs	Record ECGs#7	Record ECGs#8	None recorded	Recorded ECGs #8
PK Samples	None collected	Collected#4	Collected on Day37 #5	Collected #6

#1: Moxifloxacin: Encapsulated Moxifloxacin tablet
Moxifloxacin Placebo: Matching formulation for Moxifloxacin.

#2: Titration Phase: Milnacipran was administered by the following dosing scheme:

- Day 2: 12.5 mg milnacipran HCl (one 12.5-mg capsule and two placebo capsules) at 2000 hours
- Days 3 through 4: 12.5 mg milnacipran HCl (one 12.5-mg capsule and two placebo capsules) at 0800 hours and 2000 hours
- Days 5 through 8: 25 mg milnacipran HCl (one 25-mg capsule and two placebo capsules) at 0800 hours and 2000 hours
- Days 9 through 15: 50 mg milnacipran HCl (one 50-mg capsule and two placebo capsules) at 0800 hours and 2000 hours
- Days 16 through 22: 100 mg milnacipran HCl (one 100-mg capsule and two placebo capsules) at 0800 hours and 2000 hours
- Days 23 through 26: 150 mg milnacipran HCl (three 50-mg capsules) at 0800 hours and 2000 hours
- Days 27 through 30: 200 mg milnacipran HCl (two 100-mg capsules and one placebo capsule) at 0800 hours and 2000 hours
- Days 31 through 34: 250 mg milnacipran HCl (two 100-mg capsules and one 50-mg capsule) at 0800 hours and 2000 hours
- Days 35 through 37: 300 mg milnacipran HCl (three 100-mg capsules) at 0800 hours and 2000 hours

#3: 300 mg milnacipran HCl (three 100-mg capsules)

#4: Predose and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hr postdose

#5: Predose
#6: Predose and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hr postdose
#7: Predose and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hr post dose
#8: Predose and 1, 2, 2.5, 3, 4, 6, and 12 hr post dose

4.2.6.4 Baseline

The sponsor used time-matched baseline (Day -1) for the QT assessment.

4.2.7 ECG Collection

Continuous ECGs were recorded in Part B of the study for 12 hours by a 12-lead Holter ECG machine [redacted] at Baseline on Day –1 and during the course of treatment on Days 1 and 38. Subjects were supine for at least 6 minutes prior to each time point. b(4)

The continuous 12-lead Holter recordings were stored in digital (PCMCI) flash cards ECGs were extracted and measured in triplicate by the central ECG vendor approximately 2 minutes apart at the time points specified above.

The ECG intervals PR, QRS, RR, and QT were manually read using on-screen analysis tools at the appropriate time points, and were interpreted by cardiologists. On-screen analysis and interval measurement was done in XML format using mouse-driven caliper to manually measure all intervals in accordance with regulatory guidelines. The cardiologists were blinded to all information regarding the subject, including subject number, demographics, treatment, and time of assessment. ECG analysis was not done sequentially. The same cardiologist read all ECG data for a specific subject. Lead II was used for PR, RR, and QT intervals; lead V2 or V3 was used for QRS measurements.

The ECG vendor provided Forest with raw data of RR, PR, QRS, and QT intervals for each subject. At each time point, there were a maximum of 15 readings per time point representing 3 to 5 ECG complexes per each triplicate measurement (snapshot).

Safety ECG tracings were collected after vital sign assessments and before any corresponding blood sample was collected (section 6.2).

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

One hundred (53 male , 43 female) subjects between 18-59 yrs of age with a normal baseline ECG and mean weight between 47 - 99 kg were enrolled in Part B of the study, and 88 subjects completed the study.

Nine subjects receiving milnacipran discontinued the study, 8 of them because of AEs (increased blood pressure [BP]; hypersensitivity; epididymitis, orchitis and testicular pain; micturition urgency, testicular pain and penile discharge; dysuria, urine abnormality, and testicular pain; diarrhea and abdominal pain; hematochezia (bloody stool); and muscle spasms, transient blindness [loss of vision for a few seconds after standing up, which occurred intermittently], orthostatic hypotension, dizziness, nausea, and tachycardia). Another subject, also from the milnacipran group, withdrew consent following the 12-hour blood sample on Day 38. From the moxifloxacin/placebo group,

one subject discontinued because of AEs (rectal hemorrhage, pain in extremity, and chest pain), and two subjects withdrew consent.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary PD parameter was defined as the largest time-matched mean difference between milnacipran (Treatment B1, Day 38) and placebo (Treatment B2, Day 38) in change from time-matched Baseline (Day –1) in QTcNi interval over the ECG sampling schedule (page 51, mln-pk-10.pdf). The QTcNi interval was defined as the QT interval corrected for the heart rate using the individual correction formula. The comparison of milnacipran with placebo was based on the Day 38 ECG data from Treatments B1 and B2, while the comparison of moxifloxacin and placebo was based on the Day 1 ECG data.

The analysis of the primary PD parameter was firstly based on changes from the time-matched baseline in QTcNi, between milnacipran and placebo, by time point. Then the maximum of those changes was computed.

An ANCOVA model was used by the sponsor for the primary analysis of QTcNi:

For the comparison of the primary PD parameter, a mixed-effect model was used (with treatment group, gender, time, and treatment group–by-time interaction as factors, age and mean Baseline value [the average value of the 12 hourly values on Day –1] as covariates, and unstructured covariance matrix for within-subject observations) to evaluate between-treatment group differences in change from time-matched Baseline with least squares mean estimate and corresponding CI obtained for each post-Baseline time point. The estimate of the primary PD parameter was the largest observed estimated difference over time between milnacipran and placebo in change from time-matched Baseline in QTcNi interval over the ECG sampling schedule. Similarly, the largest observed upper limit of the CIs over time was the estimated upper limit of the CI for the primary PD parameter (page 54, mln-pk-10.pdf).

The sponsor used the following codes for the MIXED procedure in SAS to specify the ANCOVA model based on which the results of the primary analysis was based.

```
model change= treat ehradose treat*ehradose meanbsvl sex age;
repeated/type=un subject=subjno;
lsmeans treat*ehradose / diff=all alpha=0.1 cl;
estimate 'treat 1 at time 1'
    treat 1 -1 treat*ehradose 1 0 0 0 0 0 0 -1/alpha=0.1 cl;
```

(Source: The sponsor's program, t_eglmeand.sas, for its primary analysis table, Table 14.3.6.6)

The sponsor's results are demonstrated in the following tables. Table 3 demonstrates the comparisons between milnacipran and placebo by time point.

Table 3: Sponsor's Table 11.3-1 Comparison of change from time-matched baseline to Day 38 in QTcNi between placebo and milnacipran

	Placebo	Milnacipran	Milnacipran - Placebo	
Time (h)	Adjusted QTcNi Change From Baseline Mean ± SE, ms	Adjusted QTcNi Change From Baseline Mean ± SE, ms	Baseline-Adjusted QTcNi Difference, ms	90% CI*
1	–1.57 ± 1.95	–7.60 ± 2.06	–6.03	–10.81, –1.25
2	**–2.78 ± 1.89**	**–7.52 ± 2.01**	**–4.74**	**–9.40, –0.08**
2.5	–1.23 ± 1.94	–8.24 ± 2.07	–7.01	–11.81, –2.22
3	–1.89 ± 1.89	–8.57 ± 2.00	–6.68	–11.33, –2.03
4	–2.62 ± 1.63	–10.17 ± 1.73	–7.55	–11.59, –3.51
6	–5.80 ± 1.96	–15.29 ± 2.11	–9.49	–14.34, –4.64
12	–3.62 ± 2.11	–17.15 ± 2.23	–13.53	–18.69, –8.37

*Based on a 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 Day –1.

The sponsor concluded, "The largest time-matched mean difference in time-matched Baseline-adjusted QTcNi between milnacipran and placebo was -4.74 ms, with an upper CI limit of -0.08 ms observed at 2 hours postdose (page 70, mln-pk-10.pdf)."

Reviewer's Comment: As detailed in section 5.1, QTcNi might not be appropriate to use as the primary endpoint. We repeated the analyses using QTcF.

ASSAY SENSITIVITY

Table 4 demonstrates the comparisons between moxifloxacin and placebo by time point.

Table 4: Sponsor's Table 11.3-2 Comparison of change from time-matched baseline to Day 1 in QTcNi between placebo and moxifloxacin

	Placebo	Moxifloxacin	Moxifloxacin -Placebo	
Time (h)	Adjusted QTcNi Change From Baseline Mean ± SE, ms	Adjusted QTcNi Change From Baseline Mean ± SE, ms	Baseline-Adjusted QTcNi Difference, ms	90% CI
1	0.77 ± 1.24	1.07 ± 1.26	0.30	–2.65, 3.25
2	–1.88 ± 1.16	2.03 ± 1.14	3.91	1.19, 6.64
2.5	–1.21 ± 1.29	3.37 ± 1.27	4.57	1.56, 7.59
3	0.66 ± 1.13	5.23 ± 1.14	4.57	1.88, 7.26
4	0.10 ± 1.06	5.42 ± 1.08	5.32	2.79, 7.86
6	**–7.00 ± 1.32**	**–1.03 ± 1.30**	**5.97**	**2.88, 9.07**
12	–3.70 ± 1.28	2.15 ± 1.31	5.85	2.81, 8.90

Reviewer's Comment: To establish assay sensitivity, we need to see the effect around 5 ms for moxifloxacin over placebo as evidenced by at least one 90% lower bound being greater than 5 ms.

4.2.8.2.2 Categorical Analysis

The following table shows the sponsor's categorical analysis. Table 5 presents the subjects with QTcNi values greater than 450 ms.

Table 5: Sponsor's Table 11.3–5 Listing of subjects with post-baseline QTcNi values greater than 450 ms

Treatment Group	Subject No.	Day	Time	Maximum QTcNi, ms
Placebo	B012	1	1.0	454.99
Placebo	B012	1	4.0	451.95
Moxifloxacin	B042	1	1.0	454.01
Placebo	B099	38	2.5	451.19
Placebo	B099	38	4.0	451.87
Placebo	B121	1	2.5	450.13
Placebo	B121	1	6.0	451.16
Placebo	B121	1	12.0	460.67
Milnacipran	B121	38	2.5	456.04
Milnacipran	B121	38	4.0	466.07
Milnacipran	B121	38	12.0	453.21

Source: page 73, mln-pk-10.pdf

Reviewer's Comment: The sponsor's numbers appear to be incorrect after an examination of the data. Table 11 shows the maximum QTcNi values based on the sponsor's data ECGANA. None of maximum QTcNi values are greater than 450 ms for the subjects specified.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study. As reported earlier there were 8 discontinuations from the milnacipran group due to AEs.

Discontinuations due to Cardiac AEs: Subject B008 (48-year-old white man) discontinued because of increased BP on Day 16 after receiving the first 100-mg dose. Subject B105 (19-year-old white woman) discontinued because of muscle spasms, transient blindness (loss of vision for a few seconds after standing up; it occurred intermittently), orthostatic hypotension, dizziness, nausea, and tachycardia on Day 33 while receiving 250 mg BID milnacipran.

Overall 4 patients reported palpitations and 2 patients experienced tachycardia. There were no significant changes in the PR and QRS intervals with milnacipran in this study.

Change s in BP and HR are shown in Table 6. Average change from Screening to End of Study in pulse was greater for the milnacipran group than for the moxifloxacin/placebo group (22.5 ± 14.2 bpm for milnacipran and 5.1 ± 9.2 for moxifloxacin/placebo).

Table 6: Sponsor's Table 12.5.1.2-1. Mean Change in Vital Signs

Vital Signs	*Moxifloxacin/Placebo (N=51)*			*Milnacipran (N=49)*			*All Subjects (N=100)*		
	Screening	*End of Study*	*Change From Screening*	*Screening*	*End of Study*	*Change From Screening*	*Screening*	*End of Study*	*Change From Screening*
Systolic BP, mm Hg	113.8 ± 10.3	112.4 ± 11.3	−1.5± 10.7	117.5 ± 10.5	119.4 ± 14.1	2.0± 13.7	115.6 ± 10.5	115.8 ± 13.2	0.2 ± 12.4
Diastolic BP, mm Hg	71.5 ± 6.6	67.1 ± 8.6	−4.5± 7.8	75.4 ± 6.9	76.4 ± 6.2	0.9± 6.1	73.5 ± 7.0	71.6 ± 8.9	−1.8± 7.5
Pulse, bpm	70.3 ± 7.9	75.4 ± 8.9	5.1 ± 9.2	69.4 ± 8.8	92.0 ± 13.4	22.5± 14.2	69.9 ± 8.3	83.5 ± 14.0	13.6 ± 14.8
Temperature, °C	36.7 ± 0.4	36.3 ± 0.4	−0.4 ± 0.5	36.6 ± 0.4	36.2 ± 0.3	−0.4 ± 0.4	36.6 ± 0.4	36.3 ± 0.4	−0.4± 0.5
Respiratory Rate, min^{-1}	14.6 ± 2.4	14.6 ± 2.6	0.0 ± 3.8	14.5 ± 2.5	14.8 ± 3.4	0.3 ± 4.2	14.6 ± 2.5	14.7 ± 3.0	0.2± 4.0
Weight, kg	69.8 ± 10.5	69.3 ± 10.6	−0.5 ± 1.5	76.9 ± 11.1	75.5 ± 11.3	−1.4 ± 1.9	73.3 ± 11.4	72.3 ± 11.3	−0.9± 1.7

BP = blood pressure.

Cross-reference: Section 14.3.B, Table14.3.5.1, and Appendix 16.2.B, Listing 16.2.5.1.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean (± SD) plasma concentrations after administration of 300 mg of milnacipran on Day 38 are shown in Figure 1 on linear scales. Similar concentration of the trough levels on Day 37 and Day 38 were observed, indicating the attainment of steady state by Day 37. Moxifloxacin concentration time profile is shown in Figure 3. The major pharmacokinetic parameters for Milnacipran and Moxifloxacin are presented in Table 7 and Table 8 respectively.

Figure 1: Sponsor's Figure 14.1-1. Mean (± SD) Milnacipran Plasma Concentrations (ng/mL) versus Time Following Dosing of 300 mg Milnacipran on Day 38 of Part B on a Linear Scale.

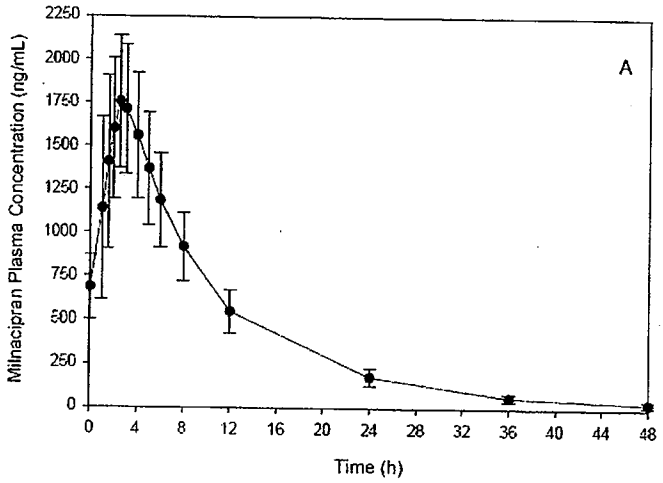


Figure 2: Sponsor's Figure 14.1-2.Mean (± SD) Milnacipran Plasma Concentrations (ng/mL) Prior to Dosing on Days and

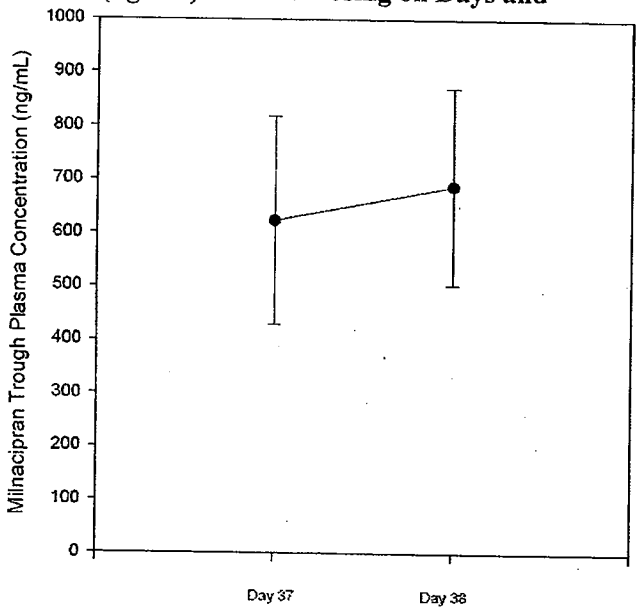


Figure 3: Sponsor's Figure 14.1-5. Mean (± SD) Moxifloxacin Plasma Concentrations (ng/mL) versus Time Following a Single 400-mg Dose on Day 1 of Part B on a Linear Scale

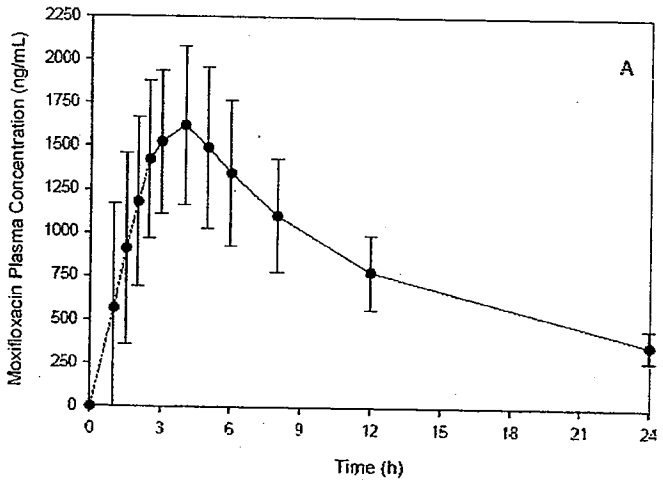


Table 7: Sponsor's Table 11.2.2.1-1. Pharmacokinetic Parameters (Mean ± SD) for Milnacipran After Oral Administration of 300 mg Milnacipran on Day 38 of Part B

PK Parameter	*Milnacipran (Mean ± SD) (N=41)*
C_{max}, ng/mL	1908.31 ± 377.80
T_{max}, h	2.5 ± 0.9 2.5 (1.0-5.0)[a]
$AUC_{0-\tau}$, ng•h/mL	13436 ± 2580
C_{min}, ng/mL	550.50 ± 123.07
C_{av}, ng/mL	1119.65 ± 214.99
$T_{½}$, h	8.8 ± 1.1 8.8 (5.1-11.1)[a]
Fluctuation, %	121.8 ± 20.0
Swing	2.5 ± 0.7

a Median (range).

PK = pharmacokinetic; C_{max} = maximum plasma drug concentration; T_{max} = time of maximum plasma concentration; $AUC_{0-\tau}$ = area under the plasma-concentration versus time curve up to the end of the dosing interval; C_{min} = minimum steady-state plasma concentration; C_{av} = average steady-state plasma concentration; $T_{½}$ = terminal elimination half-life.

Table 8: Sponsor's Table 11.2.2.2-1. Pharmacokinetic Parameters (Mean ± SD) for Moxifloxacin After Oral Administration of 400 mg Moxifloxacin on Day 1 of Part B

PK Parameter	*Moxifloxacin (Mean ± SD) (N=51)*
C_{max}, ng/mL	1731.90 ± 469.11
T_{max}, h	3.4 ± 1.2 4.0 (1.0-6.0)[a]
AUC_{0-t}, ng•h/mL	20174.2 ± 5029.0
$AUC_{0-\infty}$, ng•h/mL	25689.9 ± 5939.9
$T_{½}$, h	10.5 ± 1.8 10.2 (7.1-14.8)[a]

a Median (range).

PK = pharmacokinetic; C_{max} = maximum plasma drug concentration; T_{max} = time of maximum plasma concentration; AUC_{0-t} = area under the plasma-concentration versus time curve up to the last measurable plasma concentration; $AUC_{0-\infty}$ = area under the plasma-concentration versus time curve up to infinity; $T_{½}$ = terminal elimination half-life.

4.2.8.4.2 Exposure-Response Analysis

The sponsor did not perform an exposure-response analysis. Instead, they investigated the relationship between uncorrected QT intervals and plasma milnacipran concentration (Figure 4)[1]. There was no apparent relationship between QT and milnacipran plasma concentration for concentrations in the range of approximately 400 to 2900 ng/mL. Figure 5 presents the relationship between change from time-matched Baseline in QTcNi and milnacipran plasma concentration. The majority of QTcNi changes from Baseline for

[1] This is an odd thing to do, considering milnacipran's effects on heart rate.

milnacipran were negative, indicating a decrease in QTcNi from Baseline. The relationship between change from time-matched Baseline QTcNi and moxifloxacin plasma concentration is presented in Figure 6. Most QTcNi changes from Baseline for moxifloxacin were positive, indicating an increase in QTcNi from Baseline.

Figure 4: Sponsor's Figure 14.4.1.5. Relationship Between Uncorrected QT Intervals and Milnacipran Concentration

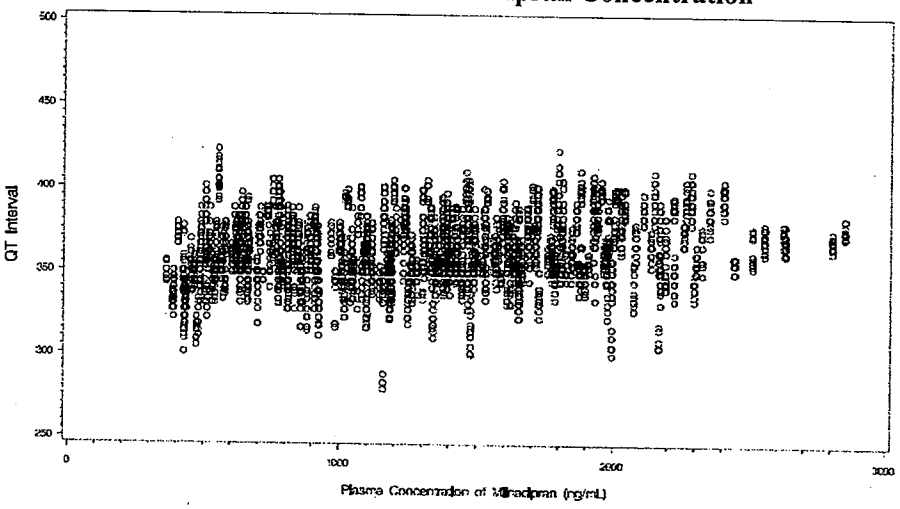


Figure 5: Sponsor's Figure 14.4.1.6A. Change from Time-matched baseline in QTcNi versus Milnacipran Plasma Concentration

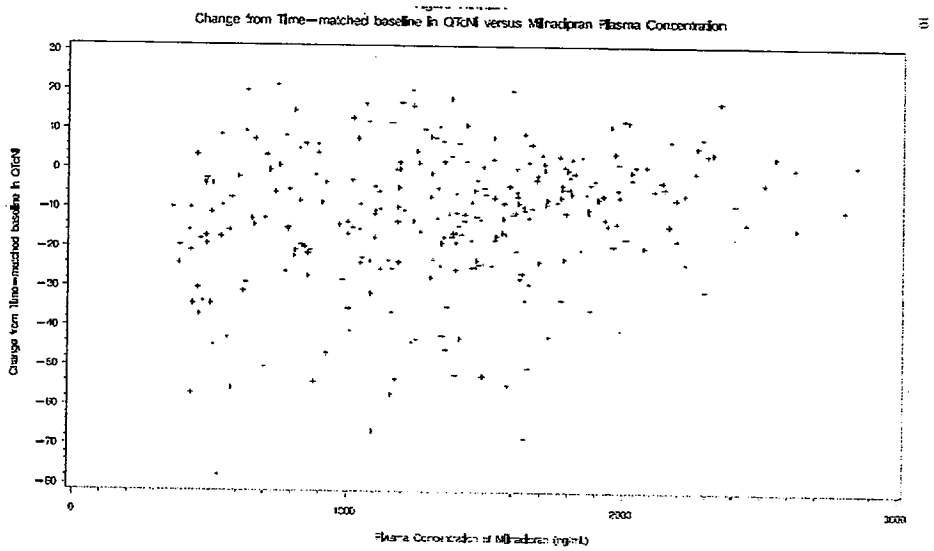
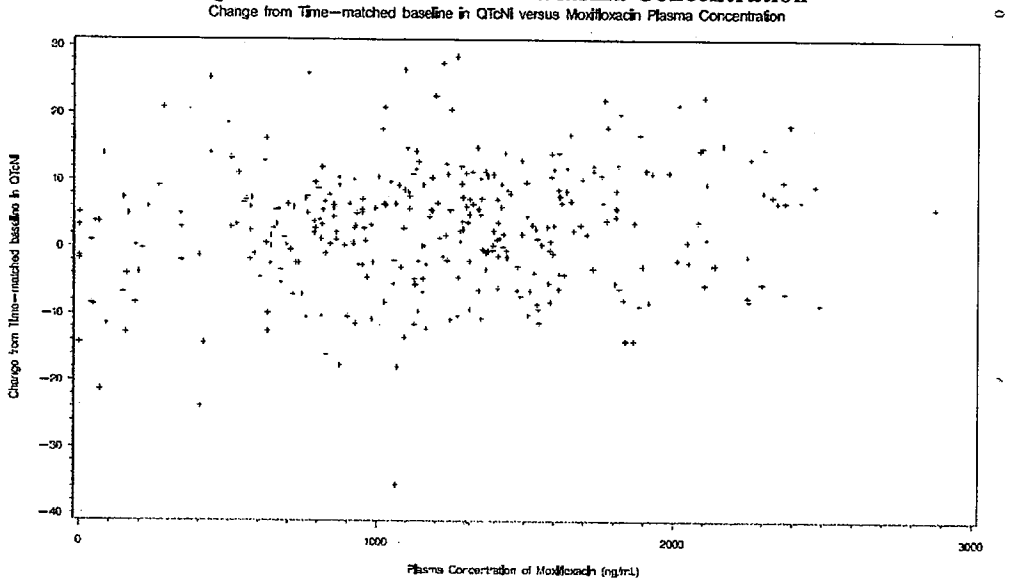


Figure 6: Sponsor's Figure 14.4.1.6B. Change from Time-matched baseline in QTcNi versus Moxifloxacin Plasma Concentration



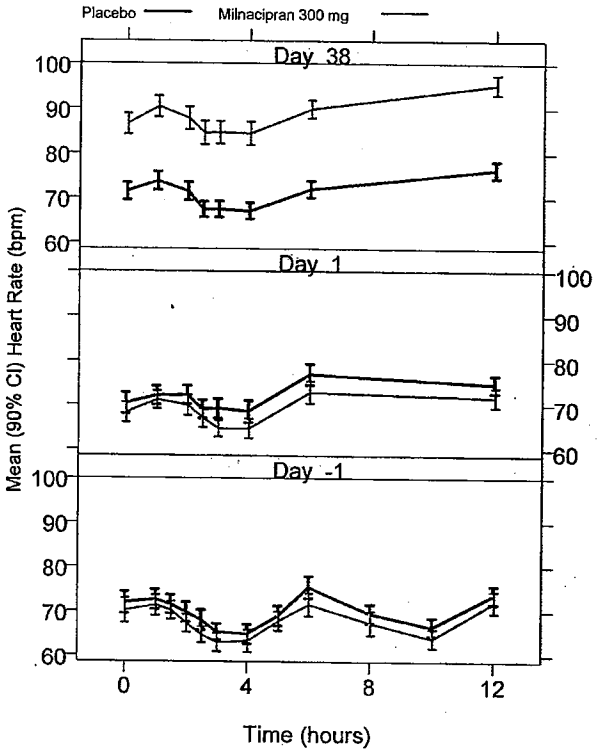
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION

Increased heart rate was observed after long-term use of milnacipran (Figure 7). The increased heart rate does not appear to directly follow the milnacipran concentration-time profile. Under baseline (Day -1) and moxifloxacin / placebo observations (Day 1), mean heart rates were similar between milnacipran and placebo group. In the placebo group, the heart rates were also similar from Day -1 to Day 38. However, mean heart rate was about 22 beats per minute higher in milnacipran treated group compared to placebo group.

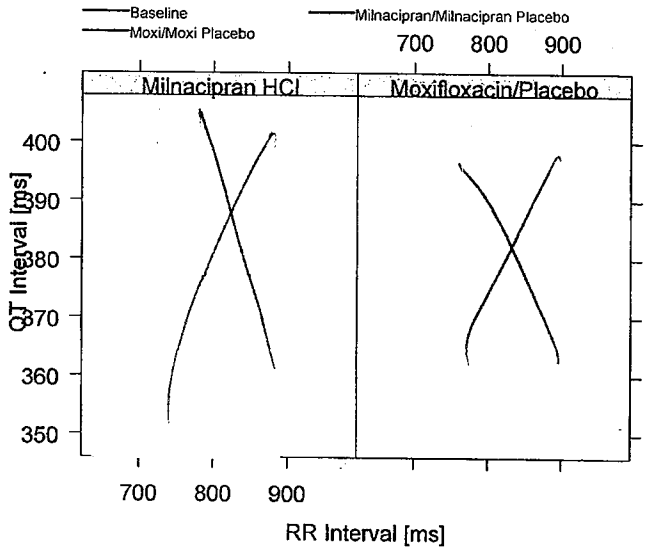
Typically, individual correction is derived from the baseline observation by including each subject's RR interval. As shown in Figure 8, the RR interval range for Milnacipran (Day 38) is much shorter (i.e., heart rate is higher) as compared to the observations on baseline day (Day -1). Thus QTcI for Milnaciparn is calculated at an extrapolated range with no valid evaluation.

Figure 7: Time Course of Mean Heart Rate (90% CI) by Treatment Group and Day



APPEARS THIS WAY
ON ORIGINAL

Figure 8: Relationship between RR and QT at Baseline (Day -1), during Moxifloxacin Treatment (Day 1), and Milnacipran Treatment (Day 38)



b(4)

The primary correction factor posed by the sponsor is QTcNi computed from the linear regression on the log-transformed interval data obtained from resting ECGs at baseline (Day -1). QT intervals for all subjects were also corrected using the Bazett and Fridericia formulae. To evaluate the ability of each correction method to correct QT for heart rate when applied to the ECG data for each subject during milnacipran treatment, we performed the following:

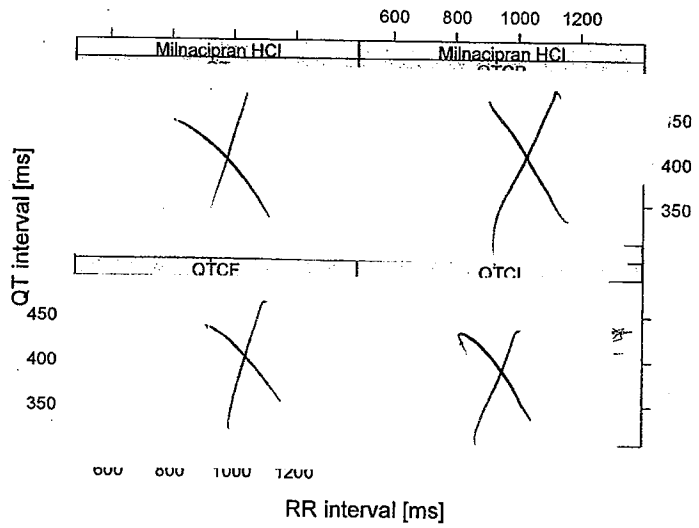
(1) Created a line plot of the QTc vs. RR data for all subjects

(2) Applied a linear regression model to each individual's QTc vs. RR data and a slope of zero represented the better correction method

The observed QT-RR interval relationship is presented together with the Bazett's (QTcB), Fridericia (QTcF), and Individual (QTcNi) correction method in Figure 9.

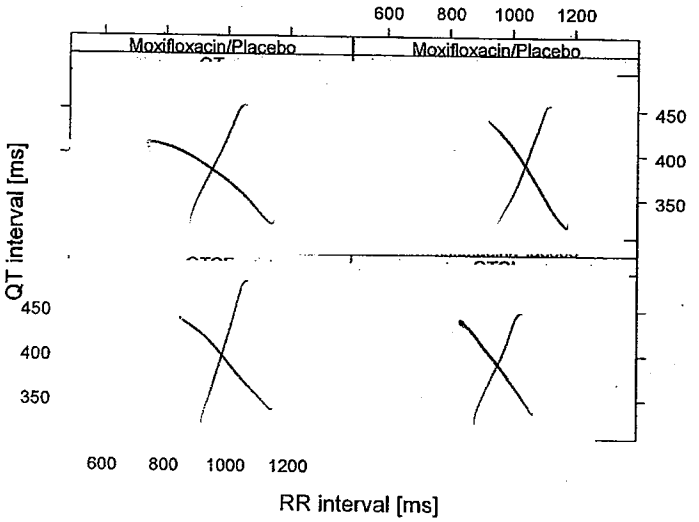
APPEARS THIS WAY
ON ORIGINAL

Figure 9: QT, QTcB, QTcF and QTcI vs. RR by Milnacipran Treatment (A) and Moxifloxacin/Placebo Treatment (B)



(A)

b(4)



(B)

b(4)

We also compare the goodness of correcting QT interval by RR between QTcF and QTcNi. Denote $b_X(i)$ be the slope of liner regression line of QTcX versus RR for individual i. X can be either QTcF or QTcNi.

Define $a_X = \frac{1}{n}\sum_{i=1}^{n}[b_X(i)]^2$. a_X can be used to measure how sufficient the correction method QTcX corrects heart rate. The indication of this index can be summarized as follows:

(1) If $a_X < a_Y$, then in general, QTcX correction method corrects heart rate better than QTcY correction method.

(2) If $a_X = a_Y$, then in general, there is no difference between QTcX and QTcY in terms of correcting heart rate.

(3) If $a_X > a_Y$, then in general, QTcX correction method corrects heart rate not as good as QTcY.

Based on the data, $a_{QTcF} = 0.0039$ and $a_{QTcNi} = 0.0045$. Therefore, QTcF corrects heart rate more sufficiently than QTcNi method. As a result, QTcF, instead of QTcNi, was applied in the reviewer's analysis.

5.2 Statistical Assessments

The statistical reviewer's evaluation is based on the sponsor's data and in accordance with the ICH E14 guideline. The QT data file in XPT format has been converted to a SAS data set, restructured and renamed for the statistical evaluation.

5.2.1 Descriptions of Subjects

In this study, there were 47 (47%) females and 53 (53%) males. Most of them were whites (n=88, 88%). The subjects were 18 to 59 years of age with an average of 37 years.

5.2.2 Analysis of QTcF

Based on the discussion in Section 5.1, QTcF will be used for the statistical analysis. An ANCOVA model was performed including: fixed effects of TREATMENT, SEX; random effect of SUBJECT; and covariate of QTcF_BASELINE. Note that the statistical reviewer's analyses were done using the following SAS program.

```
proc GLM;
by hour;
class treatment sex;
model QTcF_chg = sex treatment QTcF_baseline;
means treatment;
lsmeans treatment/pdiff cl alpha=0.1;
```

The primary analysis results are presented in Table 9 below. The largest upper limit of the 90% confidence intervals for the QTcF mean difference between milnacipran and placebo after baseline adjustment is 11.96 ms (at hour 2).

Table 9: Analysis of QTcF difference between milnacipran and placebo at all time points for Day 38

Scheduled Time in Hours	Treatment Difference (LS-Mean)	Lower Confidence Limit	Upper Confidence Limit
1:00	6.31	2.72	9.90
2:00	**7.74**	**3.51**	**11.96**
2:30	5.16	1.05	9.27
3:00	7.18	2.96	11.41
4:00	5.73	1.83	9.63
6:00	6.55	2.85	10.25
12:00	1.35	-2.20	4.91

Source: Analysis data MILPLA2

5.2.3 Assay Sensitivity Analysis: Moxifloxacin and Placebo Compared

We used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 10.

Table 10: Analysis of QTcF difference between moxifloxacin and placebo at all time points for Day 1*

Scheduled Time in Hours	Treatment Difference (LS-Mean)	Lower Confidence Limit	Upper Confidence Limit
1:00	0.21	-2.84	3.27
2:00	5.26	2.48	8.04
2:30	4.35	1.23	7.47
3:00	**7.09**	**4.61**	**9.56**
4:00	5.92	3.42	8.43
6:00	6.04	3.09	8.98
12:00	6.64	3.67	**9.61**

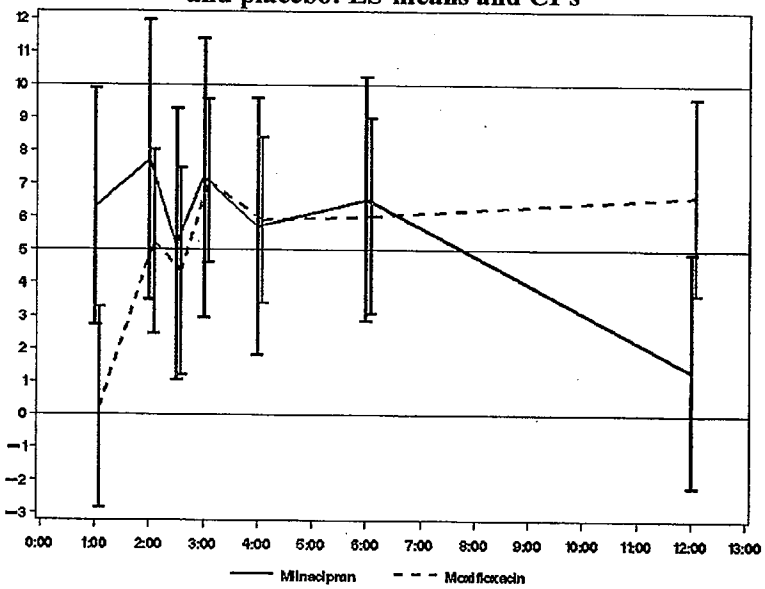
Source: Analysis data MOXPLA2 *The multiple-time-point adjustment is not considered. If a Bonferroni adjustment is applied, the largest lower bound will be 3.12 ms.

Since the largest 90% lower bound is less than 5 ms, we do not think the assay sensitivity has been established.

5.2.4 Mean Difference of Change from Baseline over Time

The mean differences of QTcF between all the treatment arms and placebo after baseline correction as well as 90% CIs over time are displayed in the following picture.

Figure 10: Differences in baseline-corrected QTcF between specified treatments and placebo: LS-means and CI's



Source: Analysis data sets MOXPLA2 and MILPLA2

5.2.5 Categorical Analysis

The categorical analysis based on QTcF observations is shown in Table 11.

Table 11: Categorical analysis of QTcF based on individual observations

Treatment		No Obs	No QTcF>450	No QTcF>480	No QTcF>500
Baseline	Placebo	1745	6	0	0
	Milnacipran	1719	1	0	0
	Moxifloxacin	1745	6	0	0
Postbaseline	Placebo	1131	2	0	0
	Milnacipran	960	0	0	0
	Moxifloxacin	1191	5	0	0

The categorical analysis based on the changes from baseline in QTcF is shown in Table 12.

Table 12: Categorical analysis of QTcF_CHG (QTcF change from baseline) based on individual observations

Treatment	No Obs	No QTcF_CHG>30	No QTcF_CHG>60
Placebo	1068	19	0
Milnacipran	954	46	1
Moxifloxacin	1134	46	0

5.2.6 Summary of Statistical Reviewer's Findings

Table 13 summarizes the statistical findings for this report.

Table 13: Summary of statistical findings based on QTcF

Milnacipran vs. Placebo	Moxifloxacin vs. Placebo
Largest upper CL: 11.96 ms LS mean diff=7.74ms CI=(3.51, 11.96) Hour=2	Largest lower CL: 4.61 ms LS mean diff=7.09 ms CI=(4.61, 9.56) Hour=3

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 Assay Sensitivity

We demonstrated the lower moxifloxacin response is due to the lower moxifloxacin exposures. An exposure-response analysis showed that the slope of 4.5 ms per μg/mL moxifloxacin is similar to what has been observed in 21 other TQT. Applying the current model parameters to the expected mean C_{max} gives a predicted mean ΔΔQTcF of 12 to 14 ms; which is consistent with the observed effect in other studies. Therefore, the moxifloxacin response is interpretable despite not demonstrating assay sensitivity using the primary statistical analysis (see section 5.2.3).

The most likely reasons for the lower exposure are 1) the moxifloxacin tablet was over-encapsulated to maintain study blind and 2) the over-encapsulated product was administered with food. Both of these factors may decrease the release rate; thereby affecting the expected exposure. The observed C_{max} in this study is 1.7 μg/mL which is 40% lower than the expected mean C_{max} of ~ 3.0 μg/mL.

5.3.1.1 Moxifloxacin Associated QTcF Prolongation

We established moxifloxacin concentration and ΔΔQTcF relationship by using the QT observations from moxifloxacin group in the trial. **Table 14** summarizes the results of the moxifloxacin concentration - QTcF analyses. Model 2 was used for further analysis since the model with intercept fixed to 0 was found to fit the data best. The predicted ΔΔQTcF at mean peak moxifloxacin concentration can be found in Table 15.

Table 14: Exposure-Response Analysis of Moxifloxacin associated ΔΔQTcF Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ddQTcF = Intercept + slope * Moxifloxacin Concentration		
Intercept (ms)	2.00 (-0.57; 4.57) 0.197	5.8
Slope (ms per ng/mL)	0.0031 (0.00126; 0.00497) 0.0078	3.4
Residual Variability (ms)	8.0	--
Model 2: ddQTcF = Intercept + slope * Moxifloxacin Concentration (Fixed Intercept)		
Intercept (ms)	0	5.8
Slope (ms per ng/mL)	0.0045 (0.00362; 0.0053) <.0001	3.2
Residual Variability (ms)	8.0	--
Model 3: ddQTcF = slope * Moxifloxacin Concentration (No Intercept)		
Slope (ms per ng/mL)	0.0047 (0.0038; 0.0056) <.0001	2.5
Residual Variability (ms)	8.3	--

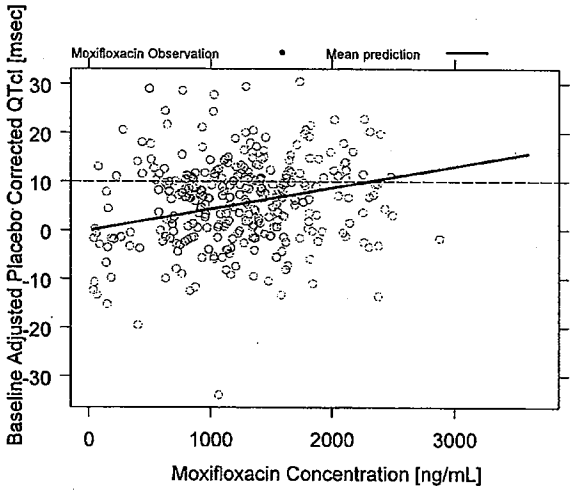
Table 15: Predicted Change of ΔΔQTcF Interval at Mean Peak Moxifloxacin Concentration using Model 1.

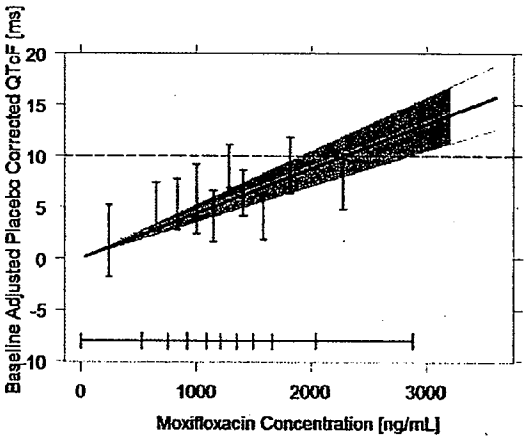
Dose Group	Predicted change in ΔΔ QTcF interval (ms)	
	Mean	90% Confidence Interval
Moxifloxacin		
Mean C_{max} (2800 ng/mL)	12.2	(9.8 ~ 14.7)
Moxifloxacin		
Mean C_{max} (3200 ng/mL)	14.0	(11.2 ~ 16.8)

The relationship between Moxifloxacin concentrations and ΔΔ QTcF is visualized in Figure 14 where the raw data is shown on top together with the population predictions.

The mean (90% CI) predicted ΔΔ QTcF at mean C_{max} is shown in the bottom right graph of Figure 11.

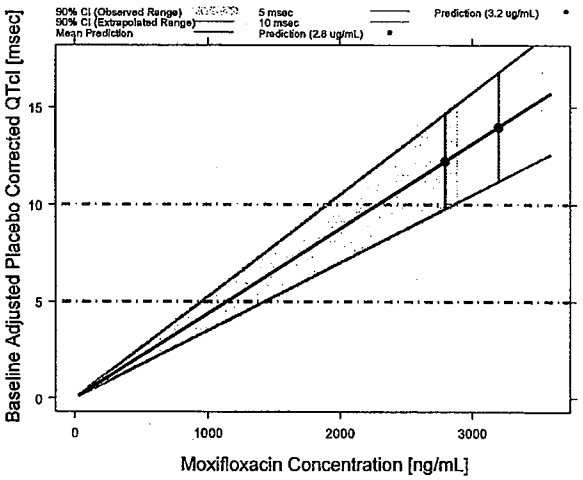
Figure 11: ΔΔ QTcF vs. Moxifloxacin concentration (on the top), and the goodness-of-fit plot (on the bottom).





APPEARS THIS WAY
ON ORIGINAL

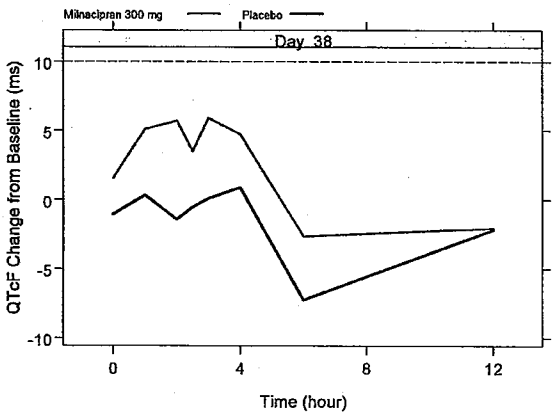
Figure 12: Predicted QTcF under Normal Concentration of Moxifloxacin (2.8 μg/mL or 3.2 μg/mL)

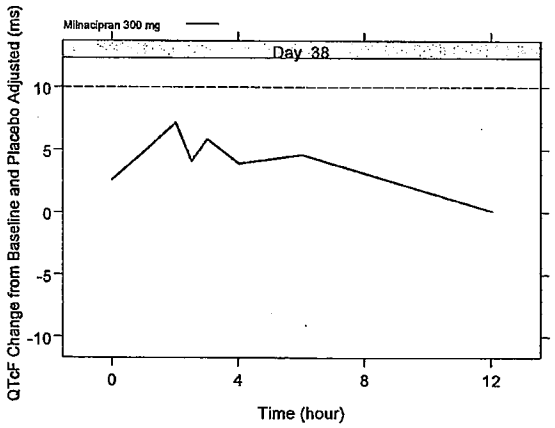


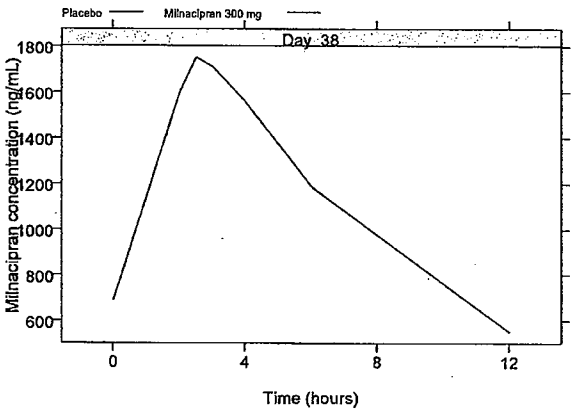
5.3.2 QTcF and Milnacipran Concentration Time Profiles

Milnacipran mean ΔQTcF, ΔΔQTcF, and milnacipran concentration time profiles were presented in Figure 13. ΔΔ QTcF and Δ QTcF time profiles are similar. Milnacipran ΔΔQTcF and concentration time profile both reach peak at about the same time, with no apparent delay can be identified.

Figure 13. Mean Δ QTcF (change from baseline) (top), ΔΔ QTcF (placebo-adjusted change from baseline) (middle), Milnacipran concentration (bottom) time profiles for Milnacipran 300 mg (blue line), NA (red line), moxifloxacin (green line), and placebo (black line).







5.3.1 Milnacipran Concentration-ΔΔQTcF Analysis

The relationship between ΔΔ QTcF and milnacipran concentrations was investigated by linear mixed-effects modeling. Table 16 summarizes the results of the milnacipran concentration - QTcF analyses. Model 2 was used for further analysis since the model with intercept fixed to zero was found to fit the data best. The predicted ΔΔQTcF at mean peak milnacipran concentration can be found in Table 17.

Table 16: Exposure-Response Analysis of Milnacipran associated ΔΔQTcF Prolongation

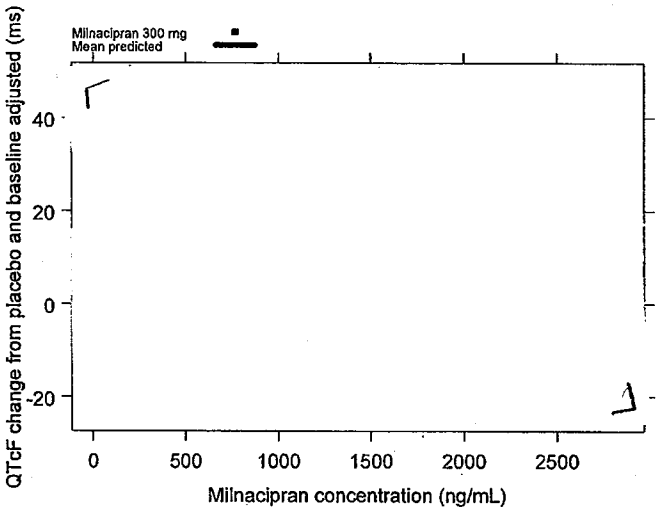
	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ddQTcF = Intercept + slope * Milnacipran Concentration		
Intercept (ms)	0.48 (-2.63; 3.59) 0.7964	7.52
Slope (ms per ng/mL)	0.00288 (0.00102; 0.00475) 0.0136	2.13
Residual Variability (ms)	9.12	--
Model 2: ddQTcF = Intercept + slope * Milnacipran Concentration (Fixed Intercept)		
Intercept (ms)	0	7.52
Slope (ms per ng/mL)	0.00308 (0.00173; 0.00444) 0.0006	2.12
Residual Variability (ms)	9.12	--
Model 3: ddQTcF = slope * Milnacipran Concentration (No Intercept)		
Slope (ms per ng/mL)	0.00333 (0.00166; 0.005) 0.0018	5.71
Residual Variability (ms)	9.48	--

Table 17: Predicted Change of ΔΔQTcF Interval at Mean Peak Milnacipran Concentration using Model 2

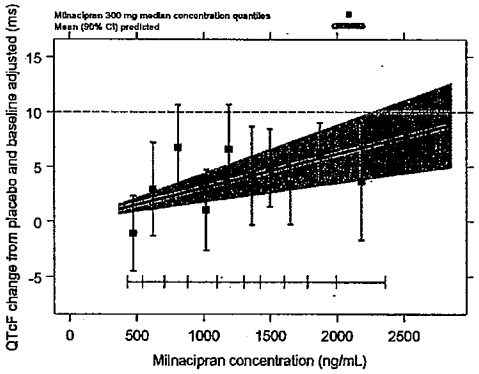
Dose Group	Predicted change in ΔΔ QTcF interval (ms)	
	Mean	90% Confidence Interval
Milnacipran 300 mg		
Mean C_{max} (1890 ng/mL)	5.83	(3.27; 8.4)

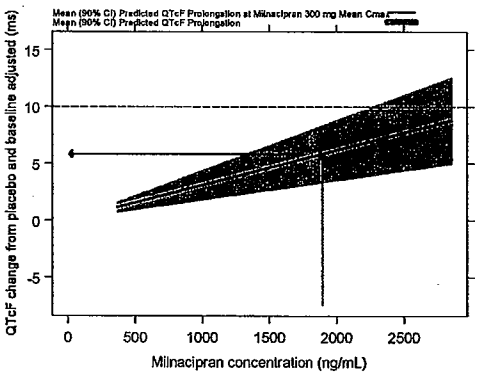
The relationship between Milnacipran concentrations and ΔΔ QTcF is visualized in Figure 14 where the raw data is shown on top together with the population predictions. The goodness-of-fit is illustrated in the bottom left graph of Figure 14 showing the observed median-quantile concentrations and associated mean ΔΔ QTcF (90% CI) together with the mean (90% CI) predicted ΔΔ QTcF (black line with shaded grey area). The mean (90% CI) predicted ΔΔ QTcF at mean C_{max} is shown in the bottom right graph of Figure 14.

Figure 14. ΔΔ QTcF vs. Milnacipran concentration. Observed data (Top), Concentration Quantile plot (Bottom Left), and Predicted ΔΔ QTcF at mean C_{max} (Bottom Right).



b(4)





5.4 CLINICAL ASSESSMENTS

5.4.1 ECG assessments

Waveforms submitted to the ECG warehouse were reviewed. Lead II and V2 were annotated for interval measurements as per protocol. QT bias was < 0.3% according to QT analysis scores computed by the warehouse. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.2 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines i.e. sudden cardiac death, syncope, seizure and serious ventricular arrhythmia occurred in this study.

5.3.2 MGPS Data Mining Analysis

The clinical reviewer performed an MGPS (Multi-item Gamma Poisson Shrinker) data mining analysis of the AERS database for adverse events related to QT prolongation [QT prolongation, TdP, ventricular tachycardia, ventricular fibrillation, sudden cardiac death, fatal (custom term), ventricular asystole, ventricular arrhythmia, syncope and convulsion] reported for Minacipran. The signal scores for another SNRI-venlafaxine, and for the TCAs imipramine and amitryptyline (Table 18) were also reviewed

Overall the EBGM (Empirical Bayes Geometric Mean) values for significant ventricular arrythmias reported for milnacipran were over 1 but under 2 indicating slightly higher than expected reporting of these events. The values were comparable to venlafaxine except for an EBGM value of 3.49 for ventricular asytole of 3.49 with venlafaxine. This appears to be confounded since the CI is wide and there are only 4 cases. Both drugs had signal scores greater than 2 for convulsions (2.1 for venlafaxine and 3.27 for milnacipran) indicating higher than expected reporting of these events

Amitriptyline had signal scores for ventricular tachycardia and fibrillation greater than 2. Both imipramine and amitryptiline had higher signal scores for QT prolongation and TdP compared to milnacipran and venlafaxine.

The narrative for the single case of TdP was reviewed. This was reported in a 70 yr old female who was on multiple medications including diltiazem, zopiclone, domperidone and fenoverine. After taking milnacipran she became near syncopal and then developed syncope leading to hospitalization. On admission she was hypokalemic, possibly hypomagnesemic with QTC of 0.5 s. Potassium and magnesium supplementation along with temporary cardiac stimulation was unsuccessful and she developed TdP. She required a beta-blocker and a definitive pacemaker. While the patients age, electrolyte abnormalities and concomitant medications were contributory there was a causal association with diltiazem and milnacipran which were both discontinued.

Table 18: MGPS data mining Analysis for Milnacipran

name	PT	N	EBGM	EB05	EB95
Venlafaxine	Ventricular tachycardia	52	1.25	0.989	1.56
Venlafaxine	Ventricular fibrillation	29	0.918	0.672	1.23
Venlafaxine	Ventricular asystole	4	3.49	1.43	9.30
Venlafaxine	Ventricular arrhythmia	9	1.29	0.735	2.12
Venlafaxine	Torsade de pointes	18	0.926	0.623	1.34
Venlafaxine	Syncope	197	1.18	1.05	1.33
Venlafaxine	Sudden cardiac death	2	0.693	0.228	1.72
Venlafaxine	Fatal (Custom Term)	1274	0.854	0.815	0.894
Venlafaxine	Electrocardiogram QT prolonged	94	2.25	1.89	2.65
Venlafaxine	Convulsion	653	2.10	1.97	2.24
Trimipramine	Ventricular tachycardia	1	0.715	0.170	2.19
Trimipramine	Ventricular fibrillation	1	0.798	0.190	2.45
Trimipramine	Ventricular arrhythmia	1	1.16	0.277	3.58
Trimipramine	Torsade de pointes	1	1.02	0.243	3.14
Trimipramine	Syncope	5	1.02	0.488	1.95
Trimipramine	Fatal (Custom Term)	62	1.84	1.49	2.25
Trimipramine	Electrocardiogram QT prolonged	7	4.00	2.08	7.40
Trimipramine	Convulsion	15	2.04	1.32	3.04
Milnacipran	Ventricular tachycardia	2	1.70	0.556	4.23
Milnacipran	Ventricular fibrillation	1	1.11	0.263	3.40
Milnacipran	Torsade de pointes	1	1.20	0.286	3.70
Milnacipran	Syncope	2	1.10	0.363	2.74
Milnacipran	Fatal (Custom Term)	24	1.71	1.21	2.35
Milnacipran	Electrocardiogram QT prolonged	2	1.69	0.553	4.21
Milnacipran	Convulsion	11	3.27	1.97	5.18
Imipramine	Ventricular tachycardia	17	1.84	1.22	2.67
Imipramine	Ventricular fibrillation	16	1.89	1.24	2.78
Imipramine	Ventricular arrhythmia	5	1.43	0.682	2.73
Imipramine	Torsade de pointes	7	3.10	1.64	5.46
Imipramine	Syncope	46	1.06	0.828	1.34
Imipramine	Fatal (Custom Term)	427	1.14	1.05	1.23
Imipramine	Electrocardiogram QT prolonged	32	6.43	4.71	8.78
Imipramine	Convulsion	128	1.50	1.30	1.73
Amitriptyline	Ventricular tachycardia	55	3.26	2.60	4.05

name	PT	N	EBGM	EB05	EB95
Amitriptyline	Ventricular fibrillation	28	2.04	1.49	2.75
Amitriptyline	Ventricular arrhythmia	7	1.51	0.805	2.65
Amitriptyline	Torsade de pointes	32	5.32	3.94	7.08
Amitriptyline	Syncope	102	1.49	1.27	1.75
Amitriptyline	Fatal (Custom Term)	1464	1.88	1.80	1.96
Amitriptyline	Electrocardiogram QT prolonged	101	8.57	7.17	10.2
Amitriptyline	Convulsion	244	2.17	1.95	2.41

ID: 586
Type: MGPS
Name: 586 All Ages
Description: fit separate distributions
Project: OND Medical Officers
Configuration: CBAERS BestRep (S)
Configuration Description: CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date: 02/08/2008 00:00:00
Item Variables: Generic name, PT, Outcome
Custom Terms:

(Developed by Dr. Ana Szarfman-DCaRP)

APPEARS THIS WAY
ON ORIGINAL

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Appendix 1 - Highlights of Clinical Pharmacology

Therapeutic dose	Target maintenance dose is 50 mg twice-daily (100 mg/day). Based on individual patient response, dose can be increased to 100 mg twice daily (200 mg/day)	
Maximum tolerated dose	[redacted]	
Principal adverse events	Adverse events most commonly reported by Fibromyalgia patients compared to placebo (≥5% and twice the incidence of that seen in placebo): constipation, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth and hypertension. Most common reactions leading to withdrawal: nausea (5.7%), palpitations (2.6%), headache (1.6%), constipation (1.2%), fatigue (1.2%), heart rate increased (1.2%), hyperhidrosis (1.2%), insomnia (1.1%), anxiety (1.0%) and dizziness (1.0%). No particular adverse event was dose-related to the extent that it would be dose limiting.	
Maximum dose tested	Single Dose	400 mg
	Multiple Dose	300 mg every 12 hours for 37 days
Exposures Achieved at Maximum Tested Dose, Mean (%CV)	Single Dose	Exposure for 300 mg dose (400 mg resulted in vomiting in all subjects and lower plasma levels than 300 mg) Cmax = 893 ng/mL (57.4%) $AUC_{0-\infty}$= 7196 ng/mL (34.9%)
	Multiple Dose	Cmax = 1908 ng/mL (19.8%) $AUC_{0-\tau}$ = 13436 ng·h/mL (19.2%)
Range of linear PK	25 - 300 mg twice-daily	
Accumulation at steady state; Mean (%CV)	1.5-fold (21%) to 2-fold (50%) based on twice-daily dosing	
Metabolites	N-desethyl milnacipran: formed from Phase I metabolic pathway; inactive Carbamoyl O-glucuronide: formed from Phase II metabolic pathway; considered inactive.	
Absorption	Absolute/Relative Bioavailability, Mean (%CV)	Absolute bioavailability: 85% (12%) in one study and 90% (3.3%) in another study
	Tmax, Median (Range)	• Parent: 2.5 h (1 - 5) • Metabolite: Not applicable
Distribution, Mean (%CV)	Vd/F or Vd	Vd = 367 L (27%)
	% bound	12.9 (11.6%)
Elimination	Route	• Primary route - Renal: Parent drug: 55% of dose Carbamoyl O-glucuronide: 19% of dose • Other routes - Hepatic: N-desethyl milnacipran: 8% of dose excreted in urine
	Terminal t½, Mean (%CV)	• Milnacipran: 7.6 h (16%) • Metabolite: Not applicable
	CL/F or CL, Mean (%CV)	CL/F = 35 L/h (15%)
Intrinsic Factors	Age	Steady-state Cmax and AUC increased by 34% and 31% respectively in elderly (> 65 years) compared to young adults

b(4)

	Sex	Steady-state Cmax and AUC increased by 21% and 17%, respectively, in females compared to males
	Race	The effect of race on milnacipran PK was not investigated
	Hepatic & Renal Impairment	**Hepatic Impairment - Change in mean parameters relative to control subjects:** Cmax: mean decrease by about 13% - 17% in patients with hepatic impairment (mild, moderate, and severe) $AUC_{0-\infty}$: mean increase of around 30% (severe group) or less (mild and moderate groups) **Renal Impairment (Study 1) - Change in mean parameters relative to control subjects:** Mild: Cmax, 12%; $AUC_{0-\infty}$ 16% Moderate: Cmax, 26%; $AUC_{0-\infty}$ 52% Severe: Cmax, 59%; $AUC_{0-\infty}$ 199% **Renal Impairment (Study 2) - Change in mean parameters relative to control subjects:** Severe: Cmax, 21%; $AUC_{0-\infty}$ 110%
Extrinsic Factors	Drug interactions	Changes in mean PK parameters for drug in combination versus drug alone **Digoxin - Milnacipran:** Digoxin: Cmax, -3.1%; $AUC_{0-\tau}$, 2.4% Milnacipran: Cmax, -0.7%; $AUC_{0-\tau}$ -0.7% **Warfarin - Milnacipran:** R-Warfarin: Cmax, 15%; $AUC_{0-\infty}$, 0.1% S-Warfarin: Cmax, 15%; $AUC_{0-\infty}$, 0.5% Milnacipran: Cmax, -5.3%; $AUC_{0-\tau}$, -3.3% **Carbamazepine - Milnacipran:** Carbamazepine: Cmax, -4.1%; $AUC_{0-\tau}$, -3.0% Milnacipran: Cmax, -18%; $AUC_{0-\tau}$, -19% **Levomepromazine - Milnacipran** Levomepromazine: Cmax, -17%; $AUC_{0-\tau}$, - 6.4% Milnacipran: Cmax, 20%; $AUC_{0-\tau}$, 10% **Lithium - Milnacipran** Lithium: Cmax, -5.9%; $AUC_{0-\tau}$, -5.5% Milnacipran: Data on administration of milnacipran alone were available after single dosing and for coadministration with lithium, after multiple dosing. Comparison of Cmax data not applicable; AUC, 3.3% **Lorazepam - Milnacipran** Lorazepam: Cmax, -6.3%; AUC, -4.4% d-Milnacipran: Cmax, 1.0%; AUC, -4.1% l-Milnacipran: Cmax, 1.1%; AUC, 0.4% **Alcohol - Milnacipran** Milnacipran: Cmax, -5.3%; AUC, -4.7% **Switch from fluoxetine without washout:** Day 1 Milnacipran: Cmax, 4.2%; AUC, 2.6% Day 4 Milnacipran: Cmax, 9.7 %;

		$AUC_{0-\tau}$, 2.8% **Switch from clomipramine without washout** Day 1 Milnacipran: Cmax, 22%; AUC, 18% Day 4 Milnacipran: Cmax, 12%; $AUC_{0-\tau}$, 10%
	Food Effects	High-fat meal, Fed vs Fasted Change in mean Cmax= -2.7% Change in mean $AUC_{0-\infty}$= -4.9%
Expected High Clinical Exposure Scenario	Renal impairment is the only condition which could lead to significant increase in Cmax and AUC. In the absence of dosage reduction, steady-state Cmax and AUC parameters are expected to be about 2.4-fold and 2 to 3-fold higher in patients with severe renal impairment, respectively. The Sponsor recommends a dose reduction by 50% in these patients, thus the increase in Cmax and AUC is not expected to be higher than 1.5-fold. Therefore, systemic exposure is covered by the supra-therapeutic dose (300 mg twice daily) even in the absence of dosage adjustment for severely renally impaired patients.	

6.2 TABLE OF STUDY ASSESSMENTS

PART B:

DAY	DOSE	DISCHARGE	VITAL SIGNS	BLOOD SAMPLE	HOLTER ECGs	SAFETY ECGs	MEALS	Dose Level
-14 to -2	Screening procedures							
-2	Arrive at the clinic at approximately 1600 hours						S	
-1	All subjects receive placebo at 0800 hours				Pre-dose, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post dose		B, L, D, S	Placebo
1	Study medication dose at 0800		Pre-dose, 1, 2, 4, 8 and 12 hours post 0800 hours dose	Pre-dose, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 12 hours post dose	Pre-dose, 1, 2, 2.5, 3, 4, 6 and 12 hours post dose	Pre-dose and 2 hours post 0800 hr. dose	B, L, D, S	400 mg moxifloxacin
2	Study medication dose at 2000 on an out-patient basis	Subjects are discharged following the completion of all procedures 24 hours following the 0800 hour Day 1 dose and given instructions for out-patient dosing	24 hours post Day 1 0800 hour dose	24 hours post Day 1 0800 hour dose		24 hours post Day 1 0800 hour dose	B	12.5 mg
3-8	Study medication dose at 0800 and 2000 hours on an out-patient basis							Days 3-4: 12.5 mg BID Days 5-8: 25 mg BID
9	Subjects are dosed in the clinic at 0800 hours and out-patient at 2000 hours	Following the 0800 hour dose administration					B	50 mg BID
10-11	Study medication dose at 0800 and 2000 hours on an out-patient basis							50 mg BID
12	Study medication dose at 0800 and 2000 hours on an out-patient basis. Subjects will be called by the site to ensure dose tolerability. The investigator may reduce the dose by half to once a day if necessary for a subject until their return to the clinic on Day 16.							50 mg BID
13-15	Study medication dose at 0800 and 2000 hours on an out-patient basis							50 mg BID
16	Subjects are dosed in the clinic at 0800 hours and out-patient at 2000 hours	Following the 2 hour post dose vital sign assessment	Pre-dose, 1 and 2 hours after the 0800 hours				B	100 mg BID

PART B Continued:

DAY	DOSE	DISCHARGE	VITAL SIGNS	BLOOD SAMPLE	HOLTER ECGs	SAFETY ECGs	MEALS	Dose Level
17	Study medication dose at 0800 and 2000 hours on an out-patient basis. Subjects will be called by the site to ensure dose tolerability. The investigator may reduce the dose by half to once a day if necessary for a subject until their return to the clinic on Day 22.							100 mg BID
18	Subjects are dosed in the clinic at 0800 hours and out patient at 2000 hours	Following the 2 hour post dose vital sign assessment	Pre-dose, 1 and 2 hours after the 0800 hours				B	100 mg BID
19-21	Study medication dose at 0800 and 2000 hours on an out-patient basis							100 mg BID
22	Subjects are dosed out-patient at 0800 hours. Subjects are admitted to the clinic at 1600 hours. Subjects are dosed in the clinic at 2000 hours						D	100 mg BID
23-36	Subjects are dosed in the clinic at 0800 and 2000 hours		Pre-dose, 1, 2, 4, 12, 13 and 14 hours post 0800 hour dose				B, L, D, S	Days 23-26: 150 mg BID Days 27-30: 200 mg BID Days 31-34: 250 mg BID Days 35-36: 300 mg BID
37	Subjects are dosed in the clinic at 0800 and 2000 hours		Pre-dose, 1, 2, 4, 12, 13 and 14 hours post 0800 hour dose	Prior to the 0800 hour dose		Prior to the 0800 hour dose	B, L, D, S	300 mg BID
38	Subjects are dosed in the clinic at 0800 hours		Pre-dose, 1, 2, 4, 8 and 12 hours post 0800 hour dose	Pre-dose, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 12 hours post dose	Pre-dose, 1, 2, 2.5, 3, 4, 6 and 12 hours post dose		B, L, D, S	300 mg
39			24 and 36 hours post Day 38 dose	24 and 36 hours post Day 38 dose		24 hours post Day 38 dose	B, L, D, S	
40		End of study complete physical examination, laboratory evaluations and ECG will be done prior to discharge or within seven days of final blood draw.	48 hours post Day 38 dose	48 hours post Day 38 dose				
47	Subjects will return to the clinic for an additional follow-up visit seven days following the end of study or early termination. Subjects will be questioned to the occurrence of any adverse events.							

B: Breakfast, L: Lunch, D: Dinner, S: Snack

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Christine Garnett
6/17/2008 02:54:40 PM
BIOPHARMACEUTICS

Hao Zhu
6/17/2008 04:04:48 PM
BIOPHARMACEUTICS

Joanne Zhang
6/18/2008 07:10:17 AM
BIOMETRICS

Ted Guo
6/18/2008 08:47:26 AM
BIOMETRICS

Suchitra Balakrishnan
6/18/2008 09:55:29 AM
MEDICAL OFFICER

Norman Stockbridge
6/18/2008 11:10:59 AM
MEDICAL OFFICER

6/22/08

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
MEMORANDUM

DATE: June 10, 2008

FROM: Gail I. Moreschi, M.D., M.P.H., F.A.C.P., Medical Officer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director,
Division of Cardiovascular and Renal Products, HFD-110

TO: Bob Rappaport, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP), HFD-170

SUBJECT: Milnacipran HCL, NDA 22-256

DAARP requested in addition to the QT Interdisciplinary Review evaluating the QT study, that DCaRP also "review studies C241 and M146 to determine their adequacy and what the results show in terms of effects of milnacipran on blood pressure, heart rate and other cardiac parameters."

Milnacipran was approved in France for depression in 1966, has market approval in 44 countries, and has more than [redacted] patient-months of use. It is a reuptake inhibitor of both serotonin and norepinephrine. It is currently being developed in the United States for the treatment of fibromyalgia. b(4)

Studies C241 and M146 were completed together; C241 is the evaluation of the tolerance of milnacipran and M146 is a study of the pharmacokinetics of different doses of milnacipran with single and repeated administration and an evaluation of the pharmacokinetic/pharmacodynamic relationship between concentrations and cardiovascular parameters. These studies were completed in 1994 and 1995 respectively.

Study C241, entitled "Study of cardiovascular tolerance of milnacipran 50, 100, and 200 mg/d versus placebo in healthy volunteers," compares several doses of milnacipran to placebo in 16 healthy volunteers in order to evaluate tolerance. Each dose was divided and given twice a day for 3 days with a wash-out of at least 4 days between doses. The heart rate, blood pressure, ECG, Holter monitor for 24 hours, and an exercise test were evaluated in addition to adverse events and laboratory tests. 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. With the 200 mg dose, the QT interval decreased with the increase in heart rate. With the Holter monitor there were no variations in rhythm or conduction. 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. According to the Sponsor these effects may be attributed to milnacipran's inhibition of noradrenalin uptake.

Study M146, entitled "Pharmacokinetic study of the cardiovascular tolerability of Milnacipran 50 mg/day, 100 mg/day, and 200 mg/day versus placebo in 16 healthy volunteers," was completed simultaneously with the above C241 study. Vital signs (blood pressure, pulse rate) as well as ECG were measured throughout the treatment periods. Plasma samples were collected for a 12 hour interval on days 1 and 3 of each period, directly after vital signs were measured. The M146 trial studied the pharmacokinetics of milnacipran administered at different doses, as single and repeated administration, and the pharmacokinetic/pharmacodynamic relationship between concentrations and cardiovascular parameters.

Milnacipran (F2207) was totally eliminated before the beginning of each treatment period. Concentrations of the two enantiomers, F2695 and F2696, were determined by a double-blind method and F2207 levels were calculated as the sum of each enantiomer. After a single administration, Cmax and $AUC_{(0\text{-}12)}$ increased with the dose. F2695 was approximately 2-fold higher than F2696. After repeated administration for three days, steady state levels were reached for each treatment group, and increased with the dose. F2695 levels were 2.5-fold higher than F2696 levels.

F2696 was eliminated faster than F2695. The F2695/F2696 AUC_τ ratio was approximately 2 at each dose level. Comparison of AUC_τ, values measured on day 3 to $AUC_{(0\text{-}\infty)}$ values usually measured on day 1 indicated equilibrium of the milnacipran pharmacokinetics after repeated administration.

The observed cardiovascular adverse event was palpitations. A limited PK/PD relationship was explored. As the pulse rate seemed the most sensitive cardiovascular parameter, the relationship between pulse rate (1 minute standing) and concentrations of F2695, the most active enantiomer, was assessed. This relationship between pulse rate and F2695 concentrations was characterized in the majority of the cases by a lag-time; the pulse rate increase was delayed from the concentration increase. This is shown graphically by the presence of hysteresis and it explains the delay and the endurance of the PD effect even when plasma concentrations are low or not detected anymore.

According to CDER's Clinical Pharmacologist, Sayed (Sam) Al Habet, R.Ph., Ph.D., there is no direct relationship between Cmax and pulse rate and the effect is higher at the higher dose than the lower dose of 25 mg. He states that the sponsor did not provide individual and mean comparative graphs for these data and other PD parameters.

According to the Sponsor, "In the double blind placebo controlled Phase III clinical trials in patients with fibromyalgia, the blood pressure and heart rate assessments were obtained at protocol specified clinic visits. Steady-state blood levels of milnacipran are achieved within 36 to 48 hours with bid dosing. All post-baseline vital signs including blood pressure and heart rate, were taken at steady state. No prespecified time for determination of vital signs at each clinic visit was required per protocol."

Since the above studies C241 and M146 provided only limited information regarding the effects of milnacipran on blood pressure, heart rate and other cardiac parameters; the adverse events, the post marketing reports, the Investigator's Brochure, and the label of NDA 22,256 were reviewed. As stated in the label under 5.4 Effect on Blood Pressure and Pulse, '

b(4)

The label states that these increases are not dose related. Additionally, the label states that these patients should be followed and treated as necessary and that patients with elevated blood pressures should be treated before starting milnacipran. This review revealed no cardiovascular deaths attributed to milnacipran.

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

Thank you for this interesting consult. If you have any additional questions, please do not hesitate to contact me.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Gail Moreschi
6/22/2008 04:56:12 PM
MEDICAL OFFICER

2/20/08

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-256 **Applicant: Forest** **Stamp Date: 12/18/07**

Drug Name: Milnacipran **NDA Type: Standard**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 FMS031 Indication: Fibromyalgia Pivotal Study #2 MLN-MD-02	X			

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

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

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

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

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

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

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

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jane Filie — February 15, 2008
Reviewing Medical Officer — Date

Mwango Kashoki — February 19, 2008
Clinical Team Leader — Date

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

/s/

Jane Filie
2/19/2008 02:12:37 PM
MEDICAL OFFICER

Mwango Kashoki
2/20/2008 08:06:42 AM
MEDICAL OFFICER