

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

This review will present the data of the deaths and serious adverse events (SAEs) for Group 1 (FM studies) which is the intended population and will, where appropriate, compare those results to the data from Group 2 (non-FM) and Group 3 (Phase 1) studies. Data regarding the incidence of common AEs will be presented for only the Group 1A (controlled FM) studies, comparing the active treatment groups to the placebo group.

7.1.1 Deaths

The following were the two deaths reported during the Group 1 studies (controlled and open label fibromyalgia studies). In my opinion, neither of them can be attributed to the drug:

- Patient # 11214: A 61-year-old woman who was participating in Study FMS031 died of methicillin-resistant staphylococcal pneumonia, sepsis and multi-organ failure 6 days after randomization. She had been on placebo.
- Patient # 13018: A 51-year-old woman died of complications from metastatic renal cell carcinoma approximately 7 months after her discontinuation from Study FMS031. Hematuria and anemia were noted during screening. She had been receiving milnacipran 200 mg/day for 6 days. She was discontinued from the study because of her diagnosis and the need for intensive treatment.

There were no deaths in the Group 2 (placebo-controlled non- fibromyalgia studies), Group 3 (Phase 1 studies), or in the clinical pharmacology studies conducted for the Pierre Fabre Marketing MAA. There were death reports in the foreign post-marketing experience and Historical Safety Data, and these are discussed in sections 7.2.2.2 and 10.3.1 respectively.

7.1.2 Other Serious Adverse Events

7.1.2.1 Serious Adverse Events in the Placebo-Controlled Fibromyalgia Studies (Group 1A)

Forty-six patients experienced SAEs in the fibromyalgia placebo-controlled studies (i.e. studies FMS021, FMS031, and MLN-MD-02). The incidence of SAEs in the placebo treatment group (2.5%) was higher than the observed with the treatment arms MLN 100mg/day (1.8%) and 200 mg/day (2.0%). The Applicant found that the numbers of SAEs per 100 patient-years of treatment were 4.9 and 6.1 for the MLN 100 mg/day and 200 mg/day treatment groups, respectively, compared with 6.5 for the placebo treatment group. The table below summarizes the incidence of SAEs in the pooled FM placebo-controlled studies by treatment group.

Table 18. Incidence of Serious Adverse Events in the Fibromyalgia Placebo-Controlled Studies

Study	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	n/N (%)	n/N (%)	n/N (%)
FMS021	0/28	NA	0/97
FMS031	6/223 (2.7)	3/224 (1.3)	12/441 (2.7)
MLN-MD-02	10/401 (2.5)	8/399 (2.0)	7/396 (1.8)
Total	16/652 (2.5)	11/623 (1.8)	19/934 (2.0)
SAEs/100 patient-years	6.5	4.9	6.1

N = number of patients in the treatment group; n = subset of N with an SAE; NA = not applicable; SAE = serious adverse event.

(Source: Applicant's Table 6.3.1.1-1, Summary of Clinical Safety, Vol. 1, p. 98)

The SAEs that occurred more frequently in the active treatment arms than in the placebo arm in the FM placebo-controlled studies (Group 1A) are presented below by system organ class (SOC) and preferred term (PT).

Table 19. Serious Adverse Events in the FM Placebo-Controlled Studies Higher in the Milnacipran Treatment Arms than Placebo by SOC and PT

System Organ Class Preferred Term	Placebo (N=652)	MLN 100mg/d (N=623)	MLN 200mg/d (N=934)	MLN Total (N=1557)
Cardiac Disorders	0	5 (0.8 %)	3 (0.32 %)	8 (0.51 %)
Angina unstable	0	1 (0.1 %)	0	0
Myocardial Infarction	0	0	1 (0.1%)	1 (0.06%)
Coronary artery disease	0	0	1 (0.1 %)	1 (0.06%)
Atrial fibrillation	0	1 (0.1 %)	0	1 (0.06%)
Atrial flutter	0	1 (0.1 %)	0	1 (0.06%)
Ventricular extrasystoles	0	1 (0.1 %)	0	1 (0.06%)
Palpitations	0	1 (0.1 %)	1 (0.1 %)	2 (0.12%)
Gastrointestinal Disorders	0	1(0.1 %)	3 (0.3 %)	4 (0.25%)
Fecaloma	0	0	1 (0.1 %)	1 (0.06%)
Nausea	0	0	1 (0.1 %)	1 (0.06%)
Gastric ulcer hemorrhage	0	1(0.1 %)	0	1 (0.06%)
Inflammatory bowel disease	0	0	1 (0.1 %)	1 (0.06%)
General disorders& adm. site conditions	2 (0.3%)	3 (0.48%)	3 (0.3 %)	6 (0.38%)
Chest pain	1 (0.15%)	1(0.1 %)	3 (0.3 %)	4 (0.25%)
Non-cardiac chest pain	1 (0.15%)	1(0.1 %)	0	1 (0.06%)
Chest discomfort	0	1(0.1 %)	0	1 (0.06%)
Hepatobiliary disorders	0	1(0.1 %)	0	1 (0.06%)
Sphincter of Oddi dysfunction	0	0	1 (0.1 %)	1 (0.06%)
Infections and infestations	0	1(0.1 %)	2 (0.21%)	3 (0.19%)
Appendicitis	0	0	1 (0.1 %)	1 (0.06%)
Pneumonia	0	0	1 (0.1 %)	1(0.06%)
Staphylococcal infection	0	1(0.1 %)	0	1 (0.06%)
Investigations	0	0	3 (0.3 %)	3 (0.19%)

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Heart rate increased	0	0	1 (0.1 %)	1 (0.06%)
Blood pressure increased	0	0	1 (0.1 %)	1 (0.06%)
Weight decreased	0	0	1 (0.1 %)	1 (0.06%)
Metabolism and nutrition disorders	1(0.15%)	0	1(0.1 %)	1 (0.06%)
Dehydration	1(0.15%)	0	1(0.1 %)	1 (0.06%)
Musculoskeletal & connective tissue dis.	0	1(0.1 %)	0	1 (0.06%)
Intervertebral disc compression	0	1(0.1 %)	0	1 (0.06%)
Neoplasms benign, malignant & unspec.	0	0	2 (0.21%)	2 (0.12%)
Papillary thyroid cancer	0	0	1(0.1 %)	1 (0.06%)
Renal cell metastasis	0	0	1(0.1 %)	1 (0.06%)
Nervous system disorders	0	1(0.1 %)	5 (0.53%)	6 (0.38%)
Ischemic stroke	0	0	1(0.1 %)	1 (0.06%)
Transient ischemic attack	0	0	1(0.1 %)	1 (0.06%)
Headache	0	0	1(0.1 %)	1 (0.06%)
Migraine	0	0	1(0.1 %)	1 (0.06%)
Presyncope	0	0	1(0.1 %)	1 (0.06%)
Cervicobrachial syndrome	0	1(0.1 %)	0	1 (0.06%)
Pregnancy, puerperium & perinatal cond.	0	0	1(0.1 %)	1 (0.06%)
Abortion spontaneous	0	0	1(0.1 %)	1 (0.06%)
Psychiatric disorders	0	0	1(0.1 %)	1 (0.06%)
Suicidal ideation	0	0	1(0.1 %)	1 (0.06%)
Renal and urinary disorders	0	1(0.1 %)	0	1 (0.06%)
Pelvi-ureteric obstruction	0	1(0.1 %)	0	1 (0.06%)
Reproductive syst. and breast disorders	0	1(0.1 %)	1(0.1 %)	2 (0.12%)
Dysmenorrhea	0	0	1(0.1 %)	1 (0.06%)
Uterine enlargement	0	1(0.1 %)	0	1 (0.06%)
Vascular disorders	0	1(0.1 %)	0	1 (0.06%)
Deep vein thrombosis	0	1(0.1 %)	0	1 (0.06%)

(Source: Reviewer's table based on data from the Applicant's table 4.5.1, Summary of Clinical Safety, Vol. 5 p. 8977-8985)

The SAEs that occurred with the greatest frequency were in the SOC "Cardiac Disorders", at an incidence of 0% in the placebo arm versus 0.8% in the MLN 100 mg/day arm and 0.32 % in the MLN 200 mg/day arm and the total incidence in the MLN treatment groups was 0.51 %. Within this SOC each event by PT occurred only once (incidence of 0.1% each) except for palpitations which occurred twice (0.12%) and the SAEs reported were the following: angina unstable, atrial fibrillation, atrial flutter, ventricular extrasystoles and palpitations in the MLN 100 mg/day group and myocardial infarction, coronary artery disease and palpitations in the MLN 200 mg/day group.

Besides the SAEs described under "Cardiac Disorder", other SAEs that occurred at a higher rate in the MLN treatment groups compared with placebo occurred only once except for chest pain [1 patient in the placebo group (0.15%), 1 patient in the MLN 100 mg/day group (0.1%) and 3 patients in the MLN 200 mg/day group (0.3%)].

Following are the narratives of the patients who had SAEs which I considered could be treatment related:

- Study FMS031:
 - Patient #10112 (PT non-cardiac chest pain): 48 year-old white female patient, who had been receiving MLN 100 mg/day for 191 days, presented acute chest discomfort while doing light housework. It was accompanied with nausea, tingling in her hand, and heaviness in her left arm and chest, with no shortness of breath or orthopnea. In the emergency room her ECG revealed “minor inverted T-waves in the anterior leads”. Cardiac catheterization showed no evidence of coronary artery disease. Cardiac enzymes were normal. This patient was not discontinued from the study and she enrolled in the extension study FMS034. The investigator did not consider this SAE to be related to the study drug but this possibility cannot be dismissed.
 - Patient #12423 (chest discomfort): 43 year-old white female patient, who had been on MLN 100 mg/day for 204 days, presented chest pressure and dizziness while at work. She had had similar previous episodes. In the hospital her cardiac enzymes were normal, ECG revealed sinus tachycardia (103 bpm) and inverted T-waves in the inferior leads. EKG: normal left ventricular function and minimal mitral and tricuspid regurgitation. The patient completed Study FMS031 shortly after and enrolled in the extension study FMS034. The investigator considered this SAE to be possibly related to the study drug.
 - Patient #14813 (nausea, dehydration, weight decreased): 54 year-old white female patient who within a few days of starting MLN 200 mg/day developed abdominal pain, post-prandial diarrhea and nausea. Approximately 3 weeks later she was admitted to the hospital due to dehydration. This patient was discontinued from the study. The investigator considered this SAE to be possibly related to study drug.
 - Patient #13908 (chest pain): 61 year-old white female had received MLN 200 mg/day for 89 days when she became hypotensive while exercising, with nausea, dizziness, sweating, chills and chest pain. Her exams in the hospital were normal. She had discontinued the study drug 3 days before the onset of the symptoms. The investigator considered this SAE unlikely to be related to the study drug but because of her abrupt discontinuation of MLN this possibility cannot be dismissed.
 - Patient #11808 (suicidal ideation): 50 year-old male patient was on MLN 200 mg/day for 44 days when the “felt very frightened” because he was contemplating suicide. He was hospitalized and his history revealed that he had contemplated suicide twice the previous month. He had a history of depression and at screening he began washout of sertraline and clonazepam. He was discontinued from the study. The investigator considered this SAE to be not related to the drug which I do not concur. This patient clearly had depression and this is a known AE for this class of drugs.
 - Patient #11219 (chest pain, heart rate increased): 44 year-old female white patient who had been on MLN 200 mg/day for 73 days experienced severe chest pain during vigorous exercise, with rapid heart rate, nausea and dry heaves. She had had a similar episode 5 days earlier. In the hospital, she improved after three doses of nitroglycerine. She had normal ECGs (normal sinus rate 73), EKG, cardiac enzymes,

treadmill stress test. She was discontinued from the study. The investigator considered her SAE to be possibly related to the study drug.

- Patient # 10128 (blood pressure increased, chest pain, headache):: A 58 year-old white female, who after taking MLN 200 mg/day for 5 weeks, presented to the ER with increasing headache and elevated blood pressure. She had been presenting headaches which were exacerbated by exertion for a few months. She noticed that her BP had been higher than her “normal” since she began participating in the study. In the ER her BP was 186/96 mm Hg. Afterwards she presented chest pain which improved after receiving sublingual nitroglycerin and was hospitalized for observation. Her ECGs and cardiac enzymes were normal. She was discharged with atenolol for elevated BP and atrovent for a possible sinusitis. One month after discharge her BP was 140/90 mmHg. The study drug was withheld during hospitalization but resumed after discharge. She continued the study and enrolled in the extension study. Her BP at baseline was 124/82 mmHg, 128/80 mmHg at randomization and 138/94 at Tx3 which occurred 2 weeks before her adverse event. The investigator considered this SAE unlikely to be related to the study drug which I do not concur and an association with the study drug cannot be discarded.
- Study MLN-MD-02:
 - Patient #23534 (unstable angina, chest pain, palpitation, ventricular extrasystoles): 38 year-old white female who after 22 days on MLN 200 mg/day experienced palpitations that were increasing throughout the day. She went to the ER and was admitted due to chest pain and palpitations. The drug was discontinued. Upon admission BP, laboratory tests were normal. The ECG showed frequent premature ventricular contractions. The SAE was considered by the investigator to be possibly related to the study drug. The patient was discontinued from the study.
 - Patient # 21431 (atrial fibrillation, atrial flutter): 60 year-old white female, who had been on MLN 100 mg/day for 36 days when she experienced palpitations, fast heart beat, dizziness, lightheadedness, and nausea. At the hospital her BP was normal but her HR was 136. Her ECG revealed atrial fibrillation and atrial flutter. She completely recovered with medication and was discharged to home. She was discontinued from the study. The investigator considered this SAE to be possibly related to the drug.
 - Patient #21817 (transient ischemic attack, cerebrovascular accident): 58 year-old white female, was receiving MLN 200 mg/day for 29 days when she lost consciousness for 15 minutes. The next day she had another episode and was admitted. Her BP was 157/97 mmHg and HR 72. Neurological exams, laboratory tests, magnetic resonance imaging, computerized tomography ECG were all normal and she was discharged a few days later. One week after discharge she had a mild cerebrovascular accident, which resolved the same day. She was discontinued later from the study. The investigator considered this SAE to be possibly related to the study drug.

- Patient # 24103 (migraine): 39 year-old white female, was receiving MLN 200 mg/day for 204 days when she was admitted to the hospital due to migraine headaches. She had a history of migraines but the frequency and intensity increased in the 6-weeks prior to admission. After inpatient treatment her condition resolved. She was discontinued from the study. The investigator considered this SAE possibly related to the study drug.
- Patient #23525 (fecaloma): 59 year-old white female who was receiving MLN 200 mg/day for 31 days developed a fecaloma. Four days after starting MLN she developed constipation that became progressively worse and did not respond to laxatives and enemas. She was admitted after 31 days for treatment and her condition resolved. She was discontinued from the study. The investigator considered this SAE possibly related to the study drug.
- Patient #24917 (spontaneous abortion): 30 year-old African-American female was on MLN 200mg/day for 54 days when she learned she was pregnant. She had a history of endometriosis and was taking drospirenone and ethinyl estradiol (Yasmin®). The next day she had a miscarriage. She was discontinued from the study because of the pregnancy and miscarriage. The investigator considered this SAE not related to the study drug but I do not concur and the possibility of being related cannot be dismissed.

Eighteen (1.1%) of all patients in the placebo-controlled FM trials discontinued from the study due to an SAE. The incidence of discontinuations due to SAEs was higher in the MLN 200 mg/day group [n=10, (0.64%)] compared to the placebo [n=3 (0.19%)] and MLN 100 mg/day [n=5 (0.32 %)] groups.

The SAEs that lead to discontinuation by PT in the MLN treatment arms were:

- MLN 100 mg/day: atrial fibrillation, atrial flutter, angina unstable, palpitations, ventricular extrasystoles, chest pain, cervicobrachial syndrome, deep vein thrombosis (one case of each, 0.16%)
- MLN 200 mg/day: chest pain, heart rate increased, suicidal ideation, renal cancer metastatic, chest pain, nausea, dehydration, transient ischemic attack, fecaloma, migraine, abortion spontaneous, myocardial infarction, ischemic stroke (one case each, 0.1%)

7.1.2.2 Serious Adverse Events in the Fibromyalgia Extension Studies (Group 1B)

Forty-nine SAEs were reported in the dose-controlled, double-blind FM extension studies. The patients in this group remained under treatment for up to 12 months. The incidence of SAEs reported in the extension studies (Group 1B) was higher than that during the short-term placebo controlled (Group 1A) studies. Altogether, approximately 4% of patients treated with milnacipran 100 mg/day or 200 mg/day experienced an SAE, compared to approximately 2% of milnacipran-treated patients in the short-term controlled trials. The number of SAEs per 100 patient-years of treatment was 8.9 and 9.3 for the milnacipran 100 and 200 mg/d groups,

respectively, which is a higher rate than the observed in the placebo controlled studies. The incidence of SAEs in the double blind-extension studies is presented in Table 20.

Table 20. Incidence of Serious Adverse Events in the FM Extension Studies (Group 1B)

Study	Milnacipran 100 mg/d			Milnacipran 200 mg/d				Total
	Treatment During FMS031 and MLN-MD-02			Treatment During FMS031 and MLN-MD-02				
	Placebo (N = 61)	100 mg/d (N = 41)	Total (N = 102)	Placebo (N = 206)	100 mg/d (N = 202)	200 mg/d (N = 323)	Total (N = 731)	N = 833
	n/N (%)			n/N (%)				n/N (%)
FMS034	1/29 (3.4)	0/19	1/48 (2.1)	0/100	4/92 (4.3)	11/209 (5.3)	15/401 (3.7)	16/449 (3.6)
MLN-MD-04	2/32 (6.3)	1/22 (4.5)	3/54 (5.6)	2/106 (1.9)	5/110 (4.5)	8/114 (7.0)	15/330 (4.5)	18/384 (4.7)
Total	3/61 (4.9)	1/41 (2.4)	4/102 (3.9)	2/206 (1.0)	9/202 (4.5)	19/323 (5.9)	30/731 (4.1)	34/833 (4.1)
SAEs/100 patient-years	11.4	5.4	8.9	2.4	9.7	13.0	9.3	9.3

N = number of patients in the treatment group; n = subset of N with an SAE; SAE = serious adverse event.

(Source: Applicant's Table 6.3.1.2-1, Summary of Clinical Safety, Vol. 1, p. 106)

Of the 49 SAEs reported in the Group 1B trials, 13 events were considered to be possibly treatment related by the Investigators: chest pain (2 patients); hypertension (2 patients), HR increased, HR irregular, migraine, ischemic colitis, gastroenteritis, fall, pelvic fracture, diverticulitis, and abdominal pain (1 patient each).

I concur in part with the adjudication by the Investigators. There was one additional case of ischemic colitis which the investigator did not consider treatment related but I think the possibility relationship to this event to the drug cannot be dismissed.

Eight patients discontinued from the dose-controlled, double-blind FM extension studies because of their SAEs:

- Patient # 15908, Study FMS034, MLN 100 mg: chest pain
- Patient # 10431, Study FMS034, MLN 200 mg: chronic lymphocytic leukemia
- Patient # 10432, Study FMS034, MLN 200 mg: intracranial aneurysm
- Patient # 13015, Study FMS034, MLN 200 mg: amyotrophic lateral sclerosis
- Patient # 11317, Study FMS034, MLN 200mg: gastric bypass
- Patient # 12717, Study FMS034, MLN 200 mg: abdominal pain
- Patient # 21411, Study MLN-MD-04, MLN 200 mg: colitis ischemic
- Patient # 22835, Study MLN-MD-04, MLN 200 mg: abdominal pain, hypertension

7.1.2.3 Serious Adverse Events in the Long-term Safety Fibromyalgia Studies (Group 1C)

In the long-term exposure safety population (Group 1C), which represents the 354 patients who were exposed to milnacipran for at least 1 year, there were 27 (7.6%) patients who presented SAEs. The number of SAEs per 100 patient-years of treatment in this group was 6.7. The most

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commonly reported SAEs were chest pain (3), chest discomfort (2), abdominal pain (2), and colitis ischemic (2).

7.1.2.4 Serious Adverse Events in the Non-Fibromyalgia Studies (Group 2)

In the Group 2 (double-blind, placebo-controlled, Phase 3 non-FM studies), which were conducted in patients with major depressive disorder (MDD) or generalized anxiety disorder (GAD), 38 patients experienced SAEs during the studies (3.1% placebo patients and 2.8% of all MLN-treated patients). The number of SAEs per 100 patient-years of treatment was similar between placebo (23.1) and the milnacipran treatment group (23.5). Appendix 10.4.1 presents the SAEs by SOC and PT for each treatment group in the Group 2 studies.

SAEs experienced by more than 1 patient across all treatment groups were:

- depression 5 (0.64%) in the milnacipran-treated patients versus 4 (0.76%) in the placebo-treated patients
- neutropenia 2 (0.25%) in the milnacipran-treated patients versus 2 (0.38%) in the placebo-treated patients
- suicide attempt 2 (0.25%) in the milnacipran treated patients versus 1 (0.19%) in the placebo-treated patients and
- anxiety 1 (0.12%) in the milnacipran-treated patient, versus 2 (0.38%) in the placebo-treated patients.

The higher incidence of SAEs related to psychiatric disorders is not unexpected given the population that was studied and differentiates the SAE profile of the non-FM studies (Group 2) from the FM-studies. Table 21 below presents the SAEs by preferred term in the double-blind placebo-controlled non-FMS studies in decreasing order of frequency.

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Table 21. Incidence of Serious Adverse Events by Preferred Term in Double Blind, Placebo-Controlled Non-Fibromyalgia Studies

	Placebo	Milnacipran				
	(N = 520)	50 mg (N = 152)	100 mg (N = 398)	150 mg (N = 18)	200 mg (N = 204)	Total (N = 772)
	n (%)	n (%)				
Patients with at least one SAE	16 (3.1)	2 (1.3)	20 (5.0)	0	0	22 (2.8)
Depression	4 (0.8)	0	5 (1.3)	0	0	5 (0.6)
Neutropenia	2 (0.4)	0	2 (0.5)	0	0	2 (0.3)
Suicide attempt	1 (0.2)	0	2 (0.5)	0	0	2 (0.3)
Abortion	0	1 (0.7)	0	0	0	1 (0.1)
Anal fissure	0	0	1 (0.3)	0	0	1 (0.1)
Anxiety	2 (0.4)	0	1 (0.3)	0	0	1 (0.1)
Derealisation	0	0	1 (0.3)	0	0	1 (0.1)
Diastolic hypertension	0	0	1 (0.3)	0	0	1 (0.1)
Diverticulitis	0	0	1 (0.3)	0	0	1 (0.1)
Enterocolitis infectious	0	0	1 (0.3)	0	0	1 (0.1)
Gastric ulcer	0	0	1 (0.3)	0	0	1 (0.1)
Hepatocellular damage	0	0	1 (0.3)	0	0	1 (0.1)
Hypertonia	0	0	1 (0.3)	0	0	1 (0.1)
Intentional overdose	0	1 (0.7)	0	0	0	1 (0.1)
Nephrolithiasis	0	0	1 (0.3)	0	0	1 (0.1)
Road traffic accident	1 (0.2)	0	1 (0.3)	0	0	1 (0.1)
Tachycardia	0	0	1 (0.3)	0	0	1 (0.1)
Alanine aminotransferase increased	1 (0.2)	0	0	0	0	0
Amnesia	1 (0.2)	0	0	0	0	0
Coma	1 (0.2)	0	0	0	0	0
Diabetes mellitus, inadequate control	1 (0.2)	0	0	0	0	0
Lung disorder	1 (0.2)	0	0	0	0	0
Peripheral nerve decompression	1 (0.2)	0	0	0	0	0
Thrombocytopenic purpura	1 (0.2)	0	0	0	0	0

(Source: Applicant's Table 6.3.2-2, Summary of Clinical Safety, Vol. 1, p. 110)

7.1.2.5 Serious Adverse Events in the Phase 1 Studies (Group 3)

During the clinical pharmacology studies that Forest conducted to support for the European marketing application, five healthy subjects experienced SAEs. Three of subjects were receiving milnacipran, one during co-administration of levomepromazine and milnacipran, one during

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administration of milnacipran alone in an elderly subject, and one during co-administration of milnacipran and 1-mg intravenous digoxin dose. The SAEs reported in the three subjects receiving milnacipran, with or without concomitant drug treatment, were urinary retention, hepatic cytolysis and tachycardia, postural hypotension and tachycardia.

During the Forest Phase 1 studies (Group 3) two subjects presented SAEs during Study MLN – PK-01. This study was a double-blind, randomized, placebo controlled multiple-dose escalating study which enrolled 26 healthy subjects. Two subjects presented with increased heart rate upon standing and tachycardia. The two narratives are presented below (extracted from MLN-PK-01 Study Report, p. 53):

- “Subject E001 started dosing on December 1, 2004. Her pulse began to increase on December 7 (pulse of 142 bpm), at which time she was receiving milnacipran 100 mg BID. The last dose of study medication that subject E001 received was 100 mg of milnacipran at 20:01 on December 8, 2004. On December 10, her standing pulse went up to 167 bpm, her supine pulse to 142 bpm, and she complained of not feeling well. The subject was given a saline intravenous infusion and vagal stimulation, which brought her pulse down to 120 bpm. Two hours later, her pulse was down to 110 bpm. ECGs performed on December 10 showed clinically significant sinus tachycardia. The subject’s end-of-study ECG performed on December 11 was abnormal (sinus tachycardia), but not considered clinically significant.
- Subject E010 started dosing on December 1, 2004. On December 9, while receiving milnacipran 100 mg BID, his standing pulse increased to 140 bpm, and his supine pulse to 129 bpm. The last dose of study medication that subject E010 received was 100 mg milnacipran at 20:19 on December 9, 2004. On December 10 his pulse was 139 bpm standing and 125 bpm supine prior to dosing, and he was not dosed. The subject had mild orthostatic hypotension that morning: SBP 146 mm Hg supine and 135 mm Hg standing. An ECG performed on December 10 showed clinically significant sinus tachycardia. The subject was observed and recovered on December 11. The subject’s end-of-study ECG performed on December 12 was normal.”

7.1.2.6 Serious Adverse Events in the Historical Safety Database

The SAEs reported in the historical safety database (i.e. the Phase 2/3 trials conducted in support of the Pierre Fabre MAA (foreign marketing application) are described in Section 10.3.2.

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7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The Applicant conducted a pooled assessment of the patient disposition for the two pivotal studies, FMS031 and MLN-MD-02. Across the two studies, 34% (708/2084) of patients discontinued from the trials. The highest discontinuation rate occurred in the group treated with MLN 200 mg/day (37.8%), followed by the MLN 100 mg/day (35.2%) and placebo (27.7%) patients. The most common cause for discontinuation was adverse event, which was the highest in the MLN 200 mg/day group (24.1%), followed by the MLN 100 mg/day group (18.8%) and the lowest in the placebo group (9.1%). On the other hand, therapeutic failure was the most frequent cause of discontinuation in the placebo group (10.3%), followed by MLN 100 mg/day (8.2%) and MLN 200 mg/day (7.2%). The patients' disposition in the pivotal studies is summarized in Table 22.

Table 22. Pooled Patient Disposition of FMS031 and MLN-MD-02

	Placebo (N=624) n (%)	Milnacipran 100 mg (N=623) n (%)	Milnacipran 200 mg (N=837) n (%)	Total (N=2084) n (%)
Completed 3-month Treatment Period	451 (72.3)	404 (64.8)	521 (62.2)	1376 (66.0)
Administrative 3-Month Completer	48 (7.7)	35 (5.6)	49 (5.9)	132 (6.3)
All other 3-month completers	403 (64.6)	369 (59.2)	472 (56.4)	1244 (59.7)
Discontinued	173 (27.7)	219 (35.2)	316 (37.8)	708 (34.0)
Reason for Premature Discontinuation				
Death	1 (0.2)	0	0	1 (0.0)
Adverse Event	57 (9.1)	117 (18.8)	202 (24.1)	376 (18.0)
Therapeutic Failure	64 (10.3)	51 (8.2)	60 (7.2)	175 (8.4)
Protocol Violation	1 (0.2)	1 (0.2)	2 (0.2)	4 (0.2)
Non-Compliant W/ Protocol Requirements	8 (1.3)	5 (0.8)	8 (1.0)	21 (1.0)
Patient Withdrawal Of Consent	27 (4.3)	24 (3.9)	27 (3.2)	78 (3.7)
Investigator Withdraw The Patient	1 (0.2)	3 (0.5)	1 (0.1)	5 (0.2)
Lost To Follow-Up	12 (1.9)	14 (2.2)	13 (1.6)	39 (1.9)
Other	2 (0.3)	4 (0.6)	3 (0.4)	9 (0.4)

(Source: Applicant's Table 1.1A, Summary of Clinical Efficacy, p. 118)

7.1.3.2 Adverse events associated with dropouts

AEs leading to dropout in the short-term placebo-controlled FM studies (Group 1A)

In the placebo-controlled FM studies (Group 1A studies), there were 445 adverse events leading to drop-out (ADO). The incidence of ADOs was the highest in the MLN 200 mg/day group (26%) followed by the MLN 100 mg/day treatment group (23.0%) and the lowest in the placebo group (12.1%).

The AEs that resulted in discontinuation of $\geq 2\%$ of milnacipran treated patients and at an incidence greater than that of placebo were nausea and palpitations. Other AEs leading to discontinuation from the trials that occurred in at least 1% of milnacipran patients and at a

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greater frequency than that of placebo were heart rate increased, constipation, headache, insomnia, hyperhidrosis, vomiting, dizziness, and fatigue. A dose-response was observed for the following ADOs (i.e. ADOs occurred with increasing frequency with increasing dose): nausea, heart rate increased, constipation, insomnia, hyperhidrosis, and vomiting. Overall, nausea was the most common cause of discontinuation. The incidence of nausea was higher in the MLN treatment arms than the placebo group, and increased with MLN dose (7.1% of patients in the MLN 200 mg/day group and 3.5% in the MLN 100 mg/day group versus 0.6 % in the placebo group).

Depression was the third most frequent ADO. Depression occurred at the highest rate in the placebo group (3.1 % of patients, versus 1.6% and 2.0 % in the MLN 100 mg/day and 200 mg/day respectively). Reports of depression are not unexpected as depression is commonly associated with FM. A greater frequency of dropout due depression in the placebo group than in the MLN groups is also expectant, given that milnacipran has antidepressant effects.

The table below summarizes the AEs that led to discontinuation of at least 1% of patients in the Group 1 studies by treatment and preferred term.

Table 23. Incidence of Adverse Events Leading to Discontinuation of at Least 1% of the Patients in the Placebo-controlled FM Studies

	Placebo	Milnacipran	
	(N = 652)	100 mg/d (N = 623)	200 mg/d (N = 934)
	n (%)	n (%)	n (%)
ADOs	79 (12.1)	143 (23.0)	243 (26.0)
Nausea	4 (0.6)	22 (3.5)	66 (7.1)
Palpitations	4 (0.6)	16 (2.6)	24 (2.6)
Depression	20 (3.1)	10 (1.6)	19 (2.0)
Heart rate increased	1 (0.2)	2 (0.3)	16 (1.7)
Constipation	1 (0.2)	3 (0.5)	15 (1.6)
Headache	1 (0.2)	10 (1.6)	15 (1.6)
Insomnia	5 (0.8)	4 (0.6)	13 (1.4)
Hyperhidrosis	1 (0.2)	5 (0.8)	13 (1.4)
Vomiting	1 (0.2)	3 (0.5)	11 (1.2)
Dizziness	3 (0.5)	7 (1.1)	9 (1.0)
Fatigue	7 (1.1)	10 (1.6)	9 (1.0)
Anxiety	4 (0.6)	8 (1.3)	7 (0.7)
Blood pressure increased	2 (0.3)	6 (1.0)	7 (0.7)
Tachycardia	0	6 (1.0)	6 (0.6)

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

AEs leading to dropout in the dose-controlled extension FM studies (Group 1B)

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In the FM extension studies, 16.7% of patients in the MLN 100 mg/day treatment group and 18.2% of patients in the MLN 200 mg/day treatment group discontinued prematurely from the studies because of one or more AEs. These discontinuation rates were lower than the discontinuation rates in the placebo-controlled studies (23.0% for MLN 100 mg/day and 26.0% for MLN 200 mg/day).

Patients who were treated with placebo in the lead-in studies had higher rates of premature discontinuation than patients who had been treated with milnacipran in the lead-in studies. This likely reflects the fact that a significant number of patients that received MLN in the lead-in studies and continued into the extension studies were a tolerant subset, whereas the placebo treated patients in the lead-in studies were drug naïve when enrolled into the extension studies and included patients who did not tolerate the drug.

The AEs that resulted in discontinuation of at least 1% of all milnacipran-treated patients were nausea (5.2%), headache (1.2%), hyperhidrosis (1.1%), and vomiting (1.0%). The ADO profile was generally similar to the profile for the Group 1A studies.

AEs leading to dropout in the long-term safety FM studies (Group 1C)

In the long-term exposure group (Group 1C), of the 354 patients treated with milnacipran for at least 1 year, seven discontinued due to an AE before completing the extension study. The AEs that resulted in discontinuations were hypertension, colitis ischemic, constipation, abdominal pain, blood pressure increased, hyperhidrosis, and depression.

AEs leading to dropout in the non-FM studies (Group 2)

In the non-FM studies (i.e. Phase 3 studies in MDD and GAD), the discontinuation rate due to adverse events was lower than what was observed in the FM studies. In the non-FMS trials, 8.3% of placebo patients and 17.5% of MLN-treated patients dropped out because of an AE, compared to 12% and 26% of placebo and MLN patients respectively in the controlled FM studies.

The AEs that resulted in discontinuation of $\geq 2\%$ of milnacipran-treated patients and at an incidence greater than that of placebo-treated patients were middle insomnia, nausea, early morning awakening, initial insomnia, dizziness, headache, and vomiting. Insomnia, early morning awakening, and dizziness were more frequent reasons for discontinuation in these patients than in the FM patients. The adverse events listed above occurred at a higher incidence in the MLN 200 mg/day treatment arm with the exception of tachycardia. There was no clear dose relationship and the incidence of these adverse events between the MLN 50 mg and 100 mg/day. The incidence of tachycardia did not seem to have a dose response among the MLN doses tested ranging from 50 mg/day to 200 mg/day.

Table 24 below presents the AEs that led to discontinuation of $\geq 1\%$ of the milnacipran treated patients from the non-FM studies.

Table 24. Discontinuations Due to Treatment-Emergent Adverse Events in $\geq 1\%$ of Patients in the Non-FM Studies

Study	Placebo (N = 520)	Milnacipran				
		50 mg/d (N = 152)	100 mg/d (N = 398)	150 mg/d (N = 18)	200 mg/d (N = 204)	Total (N = 772)
	n (%)	n (%)				
ADOs	43 (8.3)	27 (17.8)	52 (13.1)	4 (22.2)	52 (25.5)	135 (17.5)
Middle insomnia	5 (1.0)	9 (5.9)	11 (2.8)	0	18 (8.8)	38 (4.9)
Nausea	6 (1.2)	5 (3.3)	11 (2.8)	0	22 (10.8)	38 (4.9)
Early morning awakening	5 (1.0)	11 (7.2)	8 (2.0)	0	16 (7.8)	35 (4.5)
Initial insomnia	4 (0.8)	8 (5.3)	8 (2.0)	0	12 (5.9)	28 (3.6)
Dizziness	0	1 (0.7)	8 (2.0)	0	15 (7.4)	24 (3.1)
Headache	4 (0.8)	4 (2.6)	6 (1.5)	0	8 (3.9)	18 (2.3)
Vomiting	2 (0.4)	3 (2.0)	5 (1.3)	0	8 (3.9)	16 (2.1)
Hyperhidrosis	0	1 (0.7)	3 (0.8)	0	11 (5.4)	15 (1.9)
Dry mouth	1 (0.2)	1 (0.7)	3 (0.8)	0	6 (2.9)	10 (1.3)
Tachycardia	1 (0.2)	2 (1.3)	4 (1.0)	1 (5.6)	1 (0.5)	8 (1.0)
Urinary retention	0	2 (1.3)	1 (0.3)	0	5 (2.5)	8 (1.0)

(Source: Applicant's Table 6.4.2-1, Summary of Clinical Safety, Vol.1, p. 124)

AEs leading to dropout in the Phase 1 trials

In the Phase I studies (Group 3), discontinuations were only observed in Study MLN-PK-01 and Study MLN-PK-10, which aimed to determine the maximum tolerated dose (MTD) of MLN and/or evaluate the effect of the MTD on cardiac repolarization. Study MLN-PK-01 was a 10-day dose-escalation study to assess the PK and tolerability in 26 healthy volunteers (6 placebo, 20 MLN). Daily doses of 100 mg and 200 mg were administered. Study MLN-PK-10 was the 37-day thorough QT study in which 115 subjects were dosed with MLN (up to 300 mg QD), moxifloxacin, or placebo.

The most common treatment emergent adverse events (TEAEs) leading to discontinuation in sixteen subjects treated with milnacipran were heart rate increased and tachycardia. The highest milnacipran dosages received by the subjects who discontinued were 50 mg BID (2 subjects), 100 mg BID (8 subjects), and > 100 mg BID (6 subjects). Notably, because of drug intolerance leading to discontinuation, study MLN-PK-01 was amended such that two dose groups (dose escalation to 300 mg BID and dose escalation to 400 mg BID) were not conducted as originally planned. Instead, the protocol was amended to include two additional groups with a slower dose escalation scheme to a maximum MLN dose of 200 mg BID.

In the clinical pharmacology studies in the Pierre Fabre marketing application for MDD, 11 of 654 subjects discontinued because of AEs. Among the healthy subjects who were treated with milnacipran (either alone or in combination with other drugs), discontinuations resulted from

uncontrollable vomiting, urinary retention, ventricular extrasystole, hepatic cytolysis and tachycardia, and postural hypotension and tachycardia.

7.1.3.3 Other significant adverse events

- Cardiovascular Related Adverse Events

The primary biochemical mechanism of action of milnacipran is the inhibition of active reuptake of NE and 5-HT. The increased concentrations of these monoamines occurs in peripheral tissues, which may lead to cardiovascular effects such as tachycardia and vasoconstriction due to NE effect and tachycardia, arrhythmias, and vasoconstriction due to accumulation of 5-HT. These are effects that have been observed with other drugs of this class.

The Applicant submitted an analysis of the cardiovascular adverse events during the Phase 2 and 3 placebo-controlled FM (Group 1A) studies. An independent cardiovascular safety consultant identified MedDRA terms that were associated with AEs that could result from drug-induced changes in BP, pulse rate, or other cardiovascular AEs. Subsequently once the patients with these AEs were identified, they were categorized by whether or not they met criteria for clinically significant hypertension (≥ 140 mmHg SBP or ≥ 90 DBP) and/or demonstrated a clinically significant change in BP from baseline (≥ 15 mmHg SBP or ≥ 10 mmHg DBP). The approach to how cardiovascular AEs were grouped and analyzed seems acceptable to this reviewer.

Overall incidence of Cardiovascular Adverse events

Table 25 (below) summarizes the incidence of cardiac-related adverse events in the placebo-controlled FM studies. Overall, the incidence of these events that were higher in the MLN treatment arms than placebo, by SOC, high-level group term (HLGT) or preferred term (PT) was as follows:

- SOC Cardiac disorders: 4.1% placebo versus 10.6% MLN 100 mg/d and 9.6% MLN 200 mg/d
- SOC Cardiac disorders:
 - PT: Palpitations: 2.3% placebo versus 7.9% MLN 100 mg/day and 6.6% MLN 200 mg/day
- HLGT Cardiac arrhythmias: 1.8% placebo versus 3.4% MLN 100 mg/day and 2.9% MLN 200 mg/day
- HLGT Cardiac arrhythmias:
 - PT: Tachycardia: 0.6% placebo versus 2.7% MLN 100 mg/day and 2.2% MLN 200 mg/day
- HLGT Vascular disorders: 1.8% placebo versus 6.9% MLN 100 mg/day and 4.3% MLN 200 mg/day
- HLGT Vascular disorders
 - PT- Hypertension: 1.8% placebo versus 6.6% MLN 100 mg/day and 4.3% MLN 200 mg/day

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Below is the list of the PT related to cardiovascular events that were coded under the SOC-General disorders and administration site conditions and SOC-Investigations:

SOC-General disorders and administration site conditions

- PT Chest pain: 1.8% placebo, 2.9% MLN 100 mg/day versus MLN 200 mg/day and 2.1% MLN 200 mg/day
- Chest discomfort 0.9% placebo versus 1.6% MLN 100 mg/day and 1.0 mg/day MLN 200 mg/day

SOC-Investigations

- Heart rate increased: 1.1% placebo versus 5.5% MLN 100 mg/day and 5.9% MLN 200 mg/day
- Blood pressure increased: 0.8% placebo versus 3.2% MLN 100 mg/day and 2.6% MLN 200 mg/day

The incidence of cardiovascular related adverse events was higher in the MLN treatment arms but the number of each event was low. The events that occurred in higher numbers were the ones that are probably related to the efficacy of MLN on blood pressure and heart rate and it seems that there is no dose response. The data suggests that there is no increase in cardiac ischemic or thromboembolic risk with use of MLN. There was one case of prolonged QT which occurred in the placebo arm.

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Table 25. Incidence of Cardiac TEAS by SOC and Preferred Terms in Studies FM031 and MLN-MD-02

Table 3.1.1
Incidence of Treatment Emergent Adverse Events
by System Organ Class, High Level Group Term, High Level Term, and Preferred Term
All Double-blind Placebo-controlled Fibromyalgia Studies (Group 1A)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	Placebo (N=652) n (%)	MLN 100 mg (N=623) n (%)	MLN 200 mg (N=934) n (%)	MLN Total* (N=1557) n (%)
Cardiac disorders	27 (4.1)	66 (10.6)	90 (9.6)	155 (10.0)
Cardiac disorder signs and symptoms	15 (2.3)	50 (8.0)	62 (6.6)	112 (7.2)
Cardiac signs and symptoms NEC	15 (2.3)	49 (7.9)	62 (6.6)	111 (7.1)
Palpitations	15 (2.3)	49 (7.9)	62 (6.6)	111 (7.1)
Cardiac disorders NEC	0	1 (0.2)	0	1 (0.1)
Cardiac disorder	0	1 (0.2)	0	1 (0.1)
Cardiac arrhythmias	12 (1.8)	21 (3.4)	27 (2.9)	48 (3.1)
Rate and rhythm disorders NEC	9 (1.4)	18 (2.9)	23 (2.5)	41 (2.6)
Tachycardia	4 (0.6)	17 (2.7)	21 (2.2)	38 (2.4)
Cardiac flutter	3 (0.5)	0	3 (0.3)	3 (0.2)
Postural orthostatic tachycardia syndrome	0	1 (0.2)	0	1 (0.1)
Extrasystoles	2 (0.3)	0	0	0
Supraventricular arrhythmias	3 (0.5)	3 (0.5)	2 (0.2)	5 (0.3)
Atrial fibrillation	0	1 (0.2)	1 (0.1)	2 (0.1)
Sinus tachycardia	0	1 (0.2)	1 (0.1)	2 (0.1)
Atrial flutter	1 (0.2)	1 (0.2)	0	1 (0.1)
Supraventricular extrasystoles	0	1 (0.2)	0	1 (0.1)
Sinus bradycardia	1 (0.2)	0	0	0
Supraventricular tachycardia	2 (0.3)	0	0	0
Cardiac conduction disorders	0	0	2 (0.2)	2 (0.1)
Bundle branch block left	0	0	1 (0.1)	1 (0.1)
Bundle branch block right	0	0	1 (0.1)	1 (0.1)
Ventricular arrhythmias and cardiac arrest	1 (0.2)	1 (0.2)	0	1 (0.1)
Ventricular extrasystoles	1 (0.2)	1 (0.2)	0	1 (0.1)

Notes: MedDRA 9.1 was used to code adverse events.

Based on Group 1A (double-blind placebo-controlled fibromyalgia) Studies: FMS021, FMS031, and MLN-MD-02.

TEAE = Treatment Emergent Adverse Event.

Patients are counted only once within each System Organ Class, High Level Group Term, High Level Term, and Preferred Term.

MLN = Milnacipran.

MLN Total*: Only milnacipran groups included.

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Table 3.1.1
Incidence of Treatment Emergent Adverse Events
by System Organ Class, High Level Group Term, High Level Term, and Preferred Term
All Double-blind Placebo-controlled Fibromyalgia Studies (Group 1A)
Safety Population

System Organ Class High Level Group Term High Level Term Preferred Term	Placebo (N=652) n (%)	MLN 100 mg (N=623) n (%)	MLN 200 mg (N=934) n (%)	MLN Total* (N=1557) n (%)
Coronary artery disorders	1 (0.2)	2 (0.3)	3 (0.3)	5 (0.3)
Ischaemic coronary artery disorders	0	2 (0.3)	2 (0.2)	4 (0.3)
Angina unstable	0	1 (0.2)	1 (0.1)	2 (0.1)
Acute coronary syndrome	0	1 (0.2)	0	1 (0.1)
Myocardial infarction	0	0	1 (0.1)	1 (0.1)
Coronary artery disorders NEC	1 (0.2)	0	1 (0.1)	1 (0.1)
Coronary artery disease	1 (0.2)	0	1 (0.1)	1 (0.1)
Cardiac valve disorders	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.1)
Cardiac valve disorders NEC	0	1 (0.2)	0	1 (0.1)
Cardiac valve disease	0	1 (0.2)	0	1 (0.1)
Mitral valvular disorders	0	0	1 (0.1)	1 (0.1)
Mitral valve prolapse	0	0	1 (0.1)	1 (0.1)
Aortic valvular disorders	1 (0.2)	0	0	0
Aortic valve incompetence	1 (0.2)	0	0	0
Aortic valve sclerosis	1 (0.2)	0	0	0
Myocardial disorders	4 (0.6)	0	1 (0.1)	1 (0.1)
Myocardial disorders NEC	3 (0.5)	0	1 (0.1)	1 (0.1)
Ventricular hypertrophy	2 (0.3)	0	1 (0.1)	1 (0.1)
Cardiomegaly	1 (0.2)	0	0	0
Cardiomyopathies	1 (0.2)	0	0	0
Ischaemic cardiomyopathy	1 (0.2)	0	0	0
Congenital, familial and genetic disorders	1 (0.2)	0	0	0

Notes: MedDRA 9.1 was used to code adverse events.

Based on Group 1A (double-blind placebo-controlled fibromyalgia) Studies: FMS021, FMS031, and MLN-MD-02.

TEAE = Treatment Emergent Adverse Event.

Patients are counted only once within each System Organ Class, High Level Group Term, High Level Term, and Preferred Term.

MLN = Milnacipran.

MLN Total*: Only milnacipran groups included.

Source: Applicant's Table 3.1.1, ISS Vol. 5, p. 213096-213097

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Adverse events in patients with Changes of Clinical Interest (CCI) in Vital Signs

To determine the frequency and type of adverse events in patients with changes of clinical (CCI) interest in vital signs, the Applicant calculated the incidence of adverse events in patients with CCI in blood pressure and in heart rate. The Applicant did not present the incidence of CV AEs by milnacipran dose. Rather, data for the pooled milnacipran 100 mg/day and 200 mg/day doses were shown. The following parameters defined CCI for BP:

- Hypertension = ≥ 140 mm Hg SBP or ≥ 90 mm Hg DBP
- CCI increase = change from baseline in SBP ≥ 15 mm Hg or change from baseline in DBP ≥ 10 mm Hg.
- Sustained increase in BP = absolute BP or change from baseline as above on any 3 consecutive post-baseline visits.

At the end of the placebo-controlled FM (Group 1A) studies, 66/615 (10.73%) placebo patients and 249/1434 (17.36%) milnacipran patients had hypertension (≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic). Also, 49/615 (7.9 %) placebo patients and 271/1434 (18.89%) experienced a change in BP (± 15 mm Hg systolic or ± 10 mm Hg diastolic). In both the placebo and milnacipran groups, patients who experienced CCI BP had a higher frequency of AEs specifically related to BP increases (e.g., hypertension and BP increased) compared to patients who did not have CCI BP. Altogether, 0.5% of placebo patients with no hypertension reported BP increase versus 1.6% of milnacipran patients with no hypertension. Also, BP increase was reported in 3% of the placebo patients with hypertension versus 9.6% of patients with hypertension in the MLN treatment group. Milnacipran patients with CCI BP also experienced higher rates of AEs related to heart rate (tachycardia, heart rate increased, palpitations, and cardiac arrhythmias) compared with placebo patients with CCI BP. In addition, milnacipran patients with CCI BP changes experienced a slightly higher incidence of hyperhidrosis and headache.

Two cerebrovascular events and 4 coronary events were reported during Group 1A studies. All of these events occurred in milnacipran-treated patients without clinically significant changes in BP. The following are a summary of the patients' narratives:

- Cerebrovascular events:
 - Patient #26711, Study MLN-MD-02: 69-year-old woman, with a nine-year history of arteriosclerosis, hypertension, hypercholesterolemia, and mitral and tricuspid valve incompetence, who had been receiving milnacipran 200 mg/d for 77 days when she was brought to the emergency room because of an altered level of consciousness. Her level of consciousness continued to decrease, and she could not follow commands. A neurological examination showed the patient to be flaccid and not moving any of the four extremities. The patient was intubated. Before intubation her SBP rose above 200 mm Hg and after receiving labetalol her SBP fell to 150 mm Hg. A CT scan of the head and laboratory tests were unremarkable. She was hospitalized and repeat CT scan revealed a hyperdense area in the cerebellar region. The patient also underwent cardiac catheterization that showed normal coronary arteries with a large wall motion abnormality in the region of the left anterior descending coronary artery. This was

presumed to represent a myocardial infarction possibly caused by coronary spasm. The patient was started on oral amlodipine and isosorbide dinitrate. A transesophageal EKG showed severe atherosclerotic plaque in the descending aorta. The following day the patient's mental status returned to baseline. A MRI angiogram showed normal cerebral arteries. Study medication was permanently discontinued four days later, and the events were considered resolved. The patient was discharged with a diagnosis of bilateral cerebellar ischemic stroke, likely embolic. The following are her vital signs. At baseline her BP was 152/ 89 mmHg and remained basically the same throughout the study up to visit Tx 27 (BP 146/ 83 mmHg) which was two days before her event.

- Patient #21817, Study MLN-MD-02: A 58 year-old white female, was receiving MLN 200 mg/day for 29 days when she lost consciousness for 15 minutes. The next day she had another episode and was admitted. Her BP was 157/97 mmHg and HR 72. Neurological exams, laboratory tests, ECG and magnetic resonance imaging normal. A CT scan of the head revealed an old left subinsular infarct with no evidence of an acute intracerebral pathologic process. A carotid Doppler scan revealed bilateral plaque formation at the carotid bifurcation with less than 30% stenosis of both internal carotid arteries. She was discharged a few days later. One week after discharge she had a mild cerebrovascular accident, which resolved the same day. Her baseline BP was 135/77 mmHg and at randomization it was 136/82 mmHg. She was discontinued later from the study. The investigator considered this SAE to be possibly related to the study drug.
- Coronary events:
 - Patient #10128, Study FMS031: A 58 year-old white female, who after taking MLN 200 mg/day for 5 weeks, presented to the ER with increasing headache and elevated blood pressure. She had been presenting headaches which were exacerbated by exertion for a few months. She noticed that her BP had been higher than her "normal" since she began participating in the study. In the ER her BP was 186/96 mm Hg. Afterwards she presented chest pain which improved after receiving sublingual nitroglycerin and was hospitalized for observation. Her ECGs and cardiac enzymes were normal. She was discharged with atenolol for elevated BP and atrovant for a possible sinusitis. One month after discharge her BP was 140/90 mmHg. The study drug was withheld during hospitalization but resumed after discharge. She continued the study and enrolled in the extension study. Her BP at baseline was 124/82 mmHg, 128/80 mmHg at randomization and 138/94 at Tx3 which occurred 2 weeks before her adverse event.
 - Patient #11219, Study FMS031: 44 year-old female white patient who had been on MLN 200 mg/day for 73 days experienced severe chest pain during vigorous exercise, with rapid heart rate, nausea and dry heaves. She had had a similar episode 5 days earlier. In the hospital, she improved after three doses of nitroglycerine. She had normal ECGs (normal sinus rate 73), EKG, cardiac enzymes, treadmill stress test. She was discontinued from the study.

- **Patient #12423, Study FMS-031:** A 43-year-old woman receiving milnacipran 100 mg/d who experienced chest pressure and dizziness while at work about 5 months after starting study drug. The pain was described as pressure-like, radiating to her neck, and associated with shortness of breath. The patient, who had experienced similar episodes of chest pain in the past, was taken to the emergency room, treated with nitroglycerin and a “blood thinner”, and admitted for further evaluation and observation. In the hospital her cardiac enzymes were normal, ECG revealed sinus tachycardia (103 bpm) and inverted T-waves in the inferior leads. EKG: normal left ventricular function and minimal mitral and tricuspid regurgitation. The patient was discharged after 1 day with a diagnosis of chest pain of unclear etiology (myocardial infarction ruled out) and fibromyalgia. The patient completed the FMS031 study and subsequently enrolled in the FMS034 extension study.
- **Patient # 13908, Study FMS031:** 61 year-old white female had received MLN 200 mg/day for 89 days when she became hypotensive while exercising, with nausea, dizziness, sweating, chills and chest pain. Her exams in the hospital were normal. She had discontinued the study drug 3 days before the onset of the symptoms. The investigator considered this SAE unlikely to be related to the study drug but because of her abrupt discontinuation of MLN this possibility cannot be dismissed.
- **Patient #14015, Study FMS031:** A 56-year-old woman receiving milnacipran 200 mg/d was admitted to the hospital with a diagnosis of chest pain about 4 months after starting study drug. She had a history of hypertension treated with valsartan/hydrochlorothiazide and entered the study with a BP of 180/86–94. About 5 weeks after starting medication her BP was noted to be elevated, although at a lower level than before randomization, and additional antihypertensive medications were prescribed and then increased one month later. Her hypertension appeared to respond (BP 144/84) but 1 week later she was admitted to the hospital because of chest pain. Her BP at this hospitalization is not in the narrative. After transfer to a second hospital, she underwent cardiac catheterization, which revealed “non-critical coronary artery disease”. She was treated medically for angina and was discharged after 4 days with diagnoses of coronary artery disease and suspected unstable angina. Study medication was resumed after discharge, and the patient completed the FMS031 study and entered the FMS034 extension study. The patient reported no further recurrence of chest pain.
- **Patient #21431, Study FMS031:** A 60 year-old white female, who had been on MLN 100 mg/day for 36 days when she experienced palpitations, fast heart beat, dizziness, lightheadedness, and nausea. She had a past history of “rapid heart beat for 6 years.” At the hospital her BP was 90/72 mmHg and the HR was 136 bpm. Her ECG revealed atrial fibrillation and atrial flutter. A myocardial perfusion scan did not reveal any evidence of myocardial ischemia. She also had a normal adenosine stress test and ECG monitoring that did not show any prolongation of the Q-T interval. She discontinued study medication the following day, and two days later she was completely recovered and discharged to home. Her BP was 110/72 mmHg at baseline,

114/80 mmHg at randomization and 108/78 mmHg at Tx3. Her HR ranged from 66 to 78 bpm between baseline and Tx3.

- **Patient #23534, Study MLN-MD-02:** A 38-year-old woman who had been receiving milnacipran 100 mg/d for 22 days when she experienced palpitations on January 6, 2006. The symptoms increased throughout the day and that night she presented to the emergency room. Study medication was discontinued and on the following day she was admitted to the hospital because of chest pain and palpitations. An ECG revealed frequent PVCs, BP was normal, laboratory tests were unremarkable, and a myocardial infarction was ruled out. The palpitations became stable and she was discharged on the next day, to be followed as an outpatient. All events were considered resolved two days later. The patient discontinued from the study because of the event. A follow-up cardiac stress test was negative for ischemia or angina pectoris, and showed no significant cardiac arrhythmia. That same day an exercise myocardial perfusion scan was normal with no ischemia noted. An echocardiogram revealed mild mitral valve floppiness with trace insufficiency.
- **Patient #23910, Study MLN –MD-02:** a 66-year-old woman with a history of hypertension, hypercholesterolemia, intermittent chest pain (treated with nitroglycerine as needed), asthma, and hypokalemia who had received milnacipran 200 mg/d for 198 days before experiencing a near syncopal episode without losing consciousness. She was advised to go to the emergency room where her assessment was normal. She was admitted for observation with BP of 146/84 mm Hg and heart rate 80 bpm. An ECG showed normal sinus rhythm with occasional PVCs and a Q-Tc of 420ms. A bilateral carotid Doppler examination revealed mild stenosis of the right internal carotid artery. An echocardiogram was normal. The patient had no significant arrhythmias or further syncopal episodes and the event was considered resolved. The patient continued on medication, completed Study MLN-MD- 02, and entered the extension study MLN-MD-04 on the same dose of milnacipran. She discontinued participation in that study after about 6 months because of constipation

Table 26 that follows shows the incidence of CV AEs in the placebo-controlled Phase 3 fibromyalgia efficacy trials, in patients with or without changes of clinical interest (CCI changes) in BP.

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Table 26. Cardiovascular Adverse Events in Patients with Hypertension of Clinically Significant Changes to Blood Pressure at the End of the Study for Group 1A

Adverse Event Term [n, (%)]	Placebo (N = 624)		Milnacipran (N = 1460)		Placebo (N = 624)		Milnacipran (N = 1460)	
	No HTN M = 549	HTN M = 66	No HTN M = 1185	HTN M = 249	No DBP M = 566	DBP M = 49	No DBP M = 1163	DBP M = 271
Cerebrovascular Events:	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)	0 (0)	2 (0.2)	0 (0)
Ischemic Coronary Events:	0 (0)	0 (0)	4 (0.3)	0 (0)	0 (0)	0 (0)	4 (0.3)	0 (0)
General cardiovascular:								
Chest discomfort	5 (0.9)	0 (0)	14 (1.2)	4 (1.6)	5 (0.9)	0 (0)	15 (1.3)	3 (1.1)
Chest pain	10 (1.8)	0 (0)	27 (2.3)	8 (3.2)	10 (1.8)	0 (0)	29 (2.5)	6 (2.2)
Hyperhidrosis	12 (2.2)	1 (1.5)	102 (8.6)	27 (10.8)	12 (2.1)	1 (2.0)	94 (8.1)	35 (12.9)
Syncope	0 (0)	0 (0)	2 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0.4)
Heart rate/rhythm disturbances:								
Cardiac Arrhythmias (HLGT)	11 (2.0)	0 (0)	39 (3.3)	9 (3.6)	11 (1.9)	0 (0)	36 (3.1)	12 (4.4)
Palpitations	14 (2.6)	0 (0)	84 (7.1)	21 (8.4)	14 (2.5)	0 (0)	83 (7.1)	22 (8.1)
Tachycardia	4 (0.7)	0 (0)	29 (2.4)	9 (3.6)	4 (0.7)	0 (0)	26 (2.2)	12 (4.4)
Heart rate increased	7 (1.3)	0 (0)	70 (5.9)	17 (6.8)	7 (1.2)	0 (0)	67 (5.8)	20 (7.4)
Hypertension Events – General:								
BP increased	3 (0.5)	2 (3.0)	19 (1.6)	24 (9.6)	3 (0.5)	2 (4.1)	23 (2.0)	20 (7.4)
Dizziness	35 (6.4)	2 (3.0)	134 (11.3)	22 (8.8)	35 (6.2)	2 (4.1)	124 (10.7)	32 (11.8)
Epistaxis	1 (0.2)	1 (1.5)	6 (0.5)	1 (0.4)	2 (0.4)	0 (0)	5 (0.4)	2 (0.7)
Headache	81 (14.8)	5 (7.6)	213 (18.0)	54 (21.7)	82 (14.5)	4 (8.2)	203 (17.5)	64 (23.6)
Hypertension	10 (1.8)	2 (3.0)	46 (3.9)	32 (12.9)	10 (1.8)	2 (4.1)	52 (4.5)	26 (9.6)
Hypertension Events – Visual:								
Blurred vision	3 (1.5)	0 (0)	18 (1.5)	5 (2.0)	3 (1.4)	0 (0)	18 (1.5)	5 (1.8)
Hypotension:								
Hypotension	1 (0.2)	0 (0)	3 (0.3)	0 (0)	1 (0.2)	0 (0)	3 (0.3)	0 (0)
Orthostatic hypotension	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)
QT prolonged	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)

DB = change in BP (± 15 mm Hg systolic or ± 10 mm Hg diastolic); BP = blood pressure; HTN = hypertension (≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic); M = number of patients with available baseline and end of study values; n = number of patients (subgroup of M) in the category.

(Source: Applicant's Table 8.1.2-1, Summary of Clinical Safety, Vol. 4, p.494)

Adverse events in patients with Potentially Clinically Significant (PCS) changes in Vital Signs

Table 27 presents the list of patients with AEs that were associated with PCS vital sign parameters. There were a total of 37 MLN-treated patients who had potentially clinically significant vital signs associated with adverse events which were related to increases in SBP and DBP or increases in heart rate. The cases associated with increases on BP accounted for approximately 38% of the cases and 62% were due to increases in heart rate.

Among the cases with increases in BP (blood pressure increased, hypertension, accelerated hypertension) the cases were distributed equally between the MLN doses 100 and 200 mg/day, with seven cases each dose which is an indication that there is not a dose response between the two MLN doses. The SBP value associated with AEs in both MLN treatment groups was 180 mmHg and the range of DBP associated with AEs was 110 to 114 mmHg in the MLN 100mg/day treatment arm and it was slightly higher in the MLN 200 mg/day treatment arm which was 110 to 120 mmHg.

There were 23 AEs associated with increases in heart rate (postural orthostatic tachycardia syndrome), 9 of them with MLN 100 mg/day and 12 with MLN 200 mg/day. The range of values observed in the MLN 100 mg/day was 120-140 bpm and was higher for the MLN 200mg/day treatment arm, 120-166 bpm. This finding indicates that there may be a dose response for increases in heart rate between different doses of MLN.

Table 27. Milnacipran Treated Patients with Potentially Clinically Significant Vital Signs Associated with Adverse Events

Study #	PCS Parameter	Patient No.	Treatment Group	Value ^a	Adverse Event	Outcome (End of Lead-in Study)	Patient Disposition (Lead-in/Extension)
MLN-MD-02	Standing DBP	21124	100 mg	110	Blood pressure increased	Ongoing	ET-AE/NA
		23924	100 mg	110	Hypertension	Resolved	ET-AE/NA
		25226	100 mg	114	Hypertension	Ongoing	Other ^b /NA
		25912	200 mg	110	Hypertension	Ongoing	Completed/Completed extension
	Supine DBP	29603	200 mg	114	Hypertension	Ongoing	Other/Did not enter extension
	Standing SBP	28109	200 mg	180	Hypertension	Resolved	Other ^b /Did not enter extension
	Standing PR	20716	100 mg	128	Postural orthostatic tachycardia syndrome	Ongoing	Therapeutic failure/NA
		22211	100 mg	120	Heart rate increased	Resolved	Completed/Lost to follow-up
		24345	100 mg	121	Tachycardia	Ongoing	Withdraw consent/NA
		25231	100 mg	120	Heart rate increased	Resolved	Other ^b /Completed extension
		25448	100 mg	122	Heart rate increased	Ongoing	Other ^b /Did not enter extension
		25903 ^c	100 mg	136	Heart rate increased	Resolved	ET-AE/NA
		27023	100 mg	133	Heart rate increased	Ongoing	Lost to follow-up/NA
		28309	100 mg	121	Palpitations	Resolved	Other ^b /Did not enter extension ^d
		20747	200 mg	123	Tachycardia	Ongoing	Other ^b /Did not enter extension
		24614	200 mg	124	Heart rate increased	Ongoing	Completed/ET-AE
		25429	200 mg	133	Heart rate increased	Ongoing	Completed/Completed extension
		25901	200 mg	132	Tachycardia; palpitations	Ongoing; resolved	Completed/Did not enter extension
		27613	200 mg	130	Tachycardia	Ongoing	Other ^b /Did not enter extension ^d
	Supine PR	25120	100 mg	120	Heart rate increased; palpitations	Resolved	ET-AE/NA

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FMS031	Standing SBP	10428	100 mg	180	Accelerated hypertension ^a	Ongoing	ET-AE/NA
		10428 ^a	100 mg	120			
		13202	100 mg	112	Hypertension	Ongoing	Completed/Did not enter extension
		15621	100 mg	110	Blood pressure increased ^f	Ongoing	ET-AE/NA
		11103	200 mg	110	Hypertension	Resolved	Completed/Completed extension
		12805	200 mg	114	Blood pressure increased	Ongoing	ET-AE/NA
		13017	200 mg	120	Hypertension	Resolved	Completed/Did not enter extension
	Standing PR	14324	200 mg	112	Blood pressure increased	Resolved	Completed/Did not enter extension
		10625 ^b	100 mg	140	Tachycardia	Resolved	ET-AE/NA
		11235	100 mg	129	Tachycardia; heart rate increased ^d	Unknown	ET-AE/NA
		10779	200 mg	126	Tachycardia	Ongoing	Completed/Completed extension
		10824	200 mg	120	Heart rate increased	Ongoing	Completed/Completed extension
		12930	200 mg	166	Sinus tachycardia	Ongoing	Completed/Completed extension
		12968	200 mg	126	Heart rate increased ^d	Resolved	ET-AE/NA
		14902	200 mg	121	Palpitations	Resolved	Completed/Did not enter extension
		15209	200 mg	126	Palpitations ^e	Resolved	ET-AE/NA
		15917	200 mg	134	Palpitations	Ongoing	Completed/Completed extension

a The highest value recorded.

b Termination for reasons other than AE (e.g., therapeutic failure, noncompliance with protocol procedures, patient withdrawal of consent, investigator withdrew the patient); reasons do include administrative termination by Sponsor.

c Patient also had PCS supine PR value.

d Sites were not initiated in the MLN-MD-C4 extension trial.

e Supine DBP was 120.

f Patient discontinued owing to AE.

g Supine PR was 136.

PCS = potentially clinically significant; ET = early termination; AE = adverse event; NA = not applicable owing to early termination (patients were not eligible to enroll in extension studies); DBP = diastolic blood pressure; SBP = systolic blood pressure; PR = pulse rate.

(Source: Applicant's Table 8.1.1.1.2-2, Summary of Clinical Safety, Vol. 1, p. 156)

Five of the patients listed above discontinued from the study as a result of the following AEs which were not considered serious:

- patient #15209- MLN 200 mg/day: palpitations, standing HR 126 bpm
- patient #11235- MLN 100 mg/day: tachycardia and HR increased: standing HR 129 bpm
- patient #10428- MLN 100 mg/day: accelerated hypertension: supine SBP 180 mmHg
- patient #15621- MLN 100 mg/day: BP increased: standing DBP 110 mmHg
- patient #12968- MLN 200 mg/day: heart rate increased: standing HR

The association of increased cardiovascular AEs with hypertension indicates the need for careful monitoring during the use of milnacipran in patients with hypertension.

For "for a more detailed discussion of effects of MLN on BP and HR, refer to Section 7.1.8. (Vital Signs).

- Adverse events related to suicidality

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early Phases of treatment. Pooled analyses

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of short-term placebo-controlled trials of antidepressant drugs (NSRIs, SSRIs and others) showed that these drug increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

Due to its antidepressant action, as well as the prevalence of depression in the fibromyalgia population, the data were analyzed to assess for any signals of suicidality. Also, because the concomitant use of anti-depressants was not allowed in the studies it is plausible that some patients developed worsened depression and/or mood when their anti-depressants were discontinued. Data from the controlled fibromyalgia studies were analyzed to evaluate for events of suicidality.

Depression and Suicidality:– Placebo controlled FM (Group 1A) studies

The Applicant calculated the overall incidence of depression and suicidal ideation in the FM patients and found that the incidence was not higher in the MLN 100 mg/day and 200 mg/day treatment arms compared to placebo. Also, across the overall population, patients in the milnacipran group were less likely than patients in the placebo group to dropout because of depression. See Table 28, below.

Table 28. Overall Incidence of Depression and Suicidal Ideation in the Fibromyalgia Placebo-Controlled Studies (Group 1A)

	Placebo (N = 652)	Milnacipran 100 mg (N = 623)	Milnacipran 200 mg (N = 934)
Depression	7.1%	3.5%	4.2 %
Suicidal ideation	0.5%	0	0.4%
ADO for depression	3.1%	1.6%	2.0%

(Source: Applicant's Table 11.12.1-1, Clinical Summary of Safety, Vol. 1, p. 345)

At baseline, 35% (729/2084) patients in the placebo-controlled fibromyalgia studies (Group 1A) studies had depression (mild to moderate). Although depression is common among patients with fibromyalgia, because the concomitant use of anti-depressants was not allowed in the studies it is plausible that some patients developed depression when their anti-depressants were discontinued.

The Applicant compared the incidence of psychiatric disorders in patients with depression at baseline to that in the sub-group of patients without depression. Altogether, 28-29% of milnacipran-treated patients with depression had a psychiatric adverse event, compared to 25% of placebo patients with depression at baseline. Among patients without depression at baseline, 22% of placebo patients had a psychiatric adverse event during the studies, compared to 19-22% of milnacipran patients. Thus, the risk of a psychiatric AE in the MLN treatment arms appeared greater for patients with depression at baseline.

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With respect to the incidence of depression specifically, the analyses showed that among the patients with depression at baseline, 26% of placebo-treated patients experienced depression during the study, compared to 5% and 8% of MLN 100 mg/day and MLN 200 mg/day patients, respectively. This suggests that milnacipran exerted an antidepressant effect. Among patients without depression at baseline, the effect was less: 5% of placebo patients reported an episode of depression, compared to 3% of MLN 100 mg/day patients and 2% of MLN 200 mg/day patients.

Among patients with depression at baseline, the incidence of suicidal ideation was highest in the MLN 200mg/day group (1.3%) compared to the placebo (0.5%) and MLN 100 mg/day groups. In the patients without depression at baseline, suicidal ideation occurred slightly more frequently in placebo-treated patients (0.5%) than in MLN-treated patients (0%). The data suggest that among patients with depression, treatment with milnacipran – particularly at the higher dose - could increase the risk of suicidal ideation.

There was no evidence of a drug effect with respect to suicide attempt.

In the patients with depression at baseline, the following psychiatric events were more frequent in the milnacipran-treated patients than in the placebo-treated patients: anxiety (6-7% vs. 4%) and insomnia (14% of MLN 200 mg/day patients vs. 11% of placebo patients).

In patients without depression at baseline, insomnia occurred with greater frequency in the milnacipran groups (12% of patients) compared to the placebo group (10% of patients).

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Table 29: Incidence of Psychiatric Disorders in Patients With or Without Depression (Placebo-controlled FM -Group 1A studies)

Table 3.5.1.1
Incidence of Treatment Emergent Adverse Event
by System Organ Class and Preferred Term
By Medical Condition in Patients with or without Depression
All Double-blind Placebo-controlled Fibromyalgia Studies (Group 1A)
Safety Population

System Organ Class Preferred Term	Patients with Depression (N=729)			Patients without Depression (N=1355)		
	Placebo (N=211)	MLN 100 mg (N=211)	MLN 200 mg (N=307)	Placebo (N=413)	MLN 100 mg (N=412)	MLN 200 mg (N=530)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Psychiatric disorders	52 (24.6)	59 (28.0)	90 (29.3)	92 (22.3)	89 (21.6)	101 (19.1)
Abnormal dreams	2 (0.9)	0	0	3 (0.7)	1 (0.2)	2 (0.4)
Affect lability	1 (0.5)	0	0	2 (0.5)	0	1 (0.2)
Agitation	0	3 (1.4)	2 (0.7)	1 (0.2)	2 (0.5)	0
Anger	1 (0.5)	0	1 (0.3)	2 (0.5)	0	0
Anorgasmia	0	0	0	0	0	1 (0.2)
Anticipatory anxiety	0	0	1 (0.3)	0	0	0
Anxiety	9 (4.3)	14 (6.6)	18 (5.9)	20 (4.8)	18 (4.4)	13 (2.5)
Attention deficit/hyperactivity disorder	1 (0.5)	1 (0.5)	0	0	0	0
Blunted affect	1 (0.5)	0	0	0	1 (0.2)	0
Bruxism	0	0	0	1 (0.2)	0	0
Burnout syndrome	0	0	0	1 (0.2)	1 (0.2)	0
Confusional state	0	2 (0.9)	1 (0.3)	1 (0.2)	4 (1.0)	5 (0.9)
Crying	0	1 (0.5)	0	0	0	1 (0.2)
Depressed mood	0	1 (0.5)	1 (0.3)	0	1 (0.2)	2 (0.4)
Depression	26 (12.3)	11 (5.2)	24 (7.8)	19 (4.6)	11 (2.7)	11 (2.1)
Depression suicidal	0	0	1 (0.3)	1 (0.2)	0	0
Disorientation	0	0	0	0	1 (0.2)	0
Dissociation	0	0	1 (0.3)	0	0	1 (0.2)
Early morning awakening	0	0	1 (0.3)	0	0	3 (0.6)
Frustration	0	0	0	1 (0.2)	0	0
Hallucination	0	0	1 (0.3)	2 (0.5)	0	0
Hallucination, visual	0	1 (0.5)	0	0	0	0
Initial insomnia	0	0	0	2 (0.5)	1 (0.2)	0

Notes: MedDRA 9.1 was used to code adverse events.

Based on Group 1A (double-blind placebo-controlled fibromyalgia) Studies: FMS031 and MLN-MD-02.

TEAE = Treatment Emergent Adverse Event.

The diagnosis of Depression is based on patient's self-reported medical history at baseline.

Patients are counted only once within each System Organ Class and Preferred Term.

MLN = Milnacipran.

(Source: Applicant's Table 3.5.1.1, Clinical Summary of Safety, Vol. 5, p. 4736)

Table 3.5.1.1
Incidence of Treatment Emergent Adverse Event
by System Organ Class and Preferred Term
By Medical Condition in Patients with or without Depression
All Double-blind Placebo-controlled Fibromyalgia Studies (Group 1A)
Safety Population

System Organ Class Preferred Term	Patients with Depression (N=729)			Patients without Depression (N=1355)		
	Placebo (N=211)	MLN 100 mg (N=211)	MLN 200 mg (N=307)	Placebo (N=413)	MLN 100 mg (N=412)	MLN 200 mg (N=530)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Insomnia	23 (10.9)	22 (10.4)	44 (14.3)	40 (9.7)	50 (12.1)	63 (11.9)
Libido decreased	1 (0.5)	0	3 (1.0)	3 (0.7)	2 (0.5)	2 (0.4)
Loss of libido	0	0	0	0	0	1 (0.2)
Middle insomnia	0	0	1 (0.3)	0	0	0
Mood altered	1 (0.5)	1 (0.5)	0	4 (1.0)	0	1 (0.2)
Mood swings	0	0	0	1 (0.2)	0	2 (0.4)
Nervousness	1 (0.5)	2 (0.9)	3 (1.0)	1 (0.2)	1 (0.2)	0
Nightmare	1 (0.5)	1 (0.5)	0	1 (0.2)	0	0
Panic attack	1 (0.5)	1 (0.5)	0	1 (0.2)	3 (0.7)	0
Panic disorder	0	0	1 (0.3)	0	0	1 (0.2)
Restlessness	3 (1.4)	2 (0.9)	1 (0.3)	3 (0.7)	3 (0.7)	2 (0.4)
Sleep disorder	0	0	2 (0.7)	1 (0.2)	2 (0.5)	3 (0.6)
Sleep walking	1 (0.5)	0	0	0	0	0
Stress	0	2 (0.9)	3 (1.0)	0	2 (0.5)	4 (0.8)
Suicidal ideation	1 (0.5)	0	4 (1.3)	2 (0.5)	0	0
Suicide attempt	1 (0.5)	0	0	0	0	0
Renal and urinary disorders	7 (3.3)	9 (4.3)	14 (4.6)	7 (1.7)	11 (2.7)	15 (2.8)
Bladder pain	0	1 (0.5)	1 (0.3)	0	0	0
Chromaturia	1 (0.5)	0	1 (0.3)	0	0	0
Cystitis interstitial	0	0	0	0	0	1 (0.2)
Dysuria	0	2 (0.9)	2 (0.7)	3 (0.7)	4 (1.0)	6 (1.1)
Haematuria	1 (0.5)	1 (0.5)	1 (0.3)	1 (0.2)	0	1 (0.2)
Micturition frequency decreased	0	0	1 (0.3)	0	0	0

Notes: MedDRA 9.1 was used to code adverse events.

Based on Group 1A (double-blind placebo-controlled fibromyalgia) Studies: FMS031 and MLN-MD-02.

TEAE = Treatment Emergent Adverse Event.

The diagnosis of Depression is based on patient's self-reported medical history at baseline.

Patients are counted only once within each System Organ Class and Preferred Term.

MLN = Milnacipran.

(Source: Applicant's Table 3.5.1.1, Clinical Summary of Safety, Vol. 5, p. 4737)

Depression and suicidality— Postmarketing experience with milnacipran

There have been reports of suicidality in the post-marketing experience (115 suicide attempts, 31 completed suicides). However, as discussed above, in the controlled FM studies, the incidence of depression was not higher in the MLN treatment arms compared to placebo but the incidence of suicidal ideation was higher in the MLN treatment arm (see Table 29 above).

Depression and concomitant use of antidepressants

The Applicant is of the opinion that since treatment with milnacipran produces near-maximal inhibition of serotonin reuptake, adding an SSRI to milnacipran would be expected to produce no greater effect on serotonin reuptake or, at most, would mimic an increased dose of milnacipran. However, until this has been demonstrated clinically the Applicant recommends that such drug combinations should be avoided.

- Adverse Events Related to Hepatotoxicity

Placebo controlled FM studies (Group 1A)

The assessment of reported hepatic adverse effects did not suggest that that milnacipran is associated with hepatotoxicity. Overall, in the placebo-controlled FM studies, 0.9% of placebo patients had a hepatobiliary-related adverse event, compared to 0.3% of patients in the MLN 100 mg/day and 0.9% of MLN 200 mg/day patients. The most frequently reported types of hepatobiliary AEs that were that occurred more frequently in the MLN treatment arms were as follows by PT are displayed in Table 30 below:

Table 30. Most Frequently Reported Hepatobiliary AEs in the Group 1A Studies

PT	Placebo (%)	MLN 100mg/day (%)	MLN 200 mg/day (%)
Hepatic function abnormal	0	0.2	0.1
Hepatic steatosis	0	0	0.1
Hepatitis	0	0	0.1
ALT increased	0	0.5	0.6
AST increased	0.2	0.5	0.2
Hepatic enzyme increased	0	0.2	0.2
Liver function test abnormal	0	0.2	0

(Source: Table compiled by the reviewer based on Applicant's Table 3.3.1, Summary of Clinical Safety, Vol. 5, p. 3200)

Transaminase elevations: ALT

MLN treatment was more frequently associated with mild ALT elevations compared to placebo. As demonstrated below in the shift table from baseline values to maximum post-baseline value, elevations in ALT above the upper limit of normal (ULN) from normal values at baseline were seen in:

- 3.3% of patients receiving placebo
- 5.7% of patients on MLN 100 mg/day and
- 7.3% of patients receiving MLN 200 mg/day

Among the patients who had a shift upwards in the ALT:

- mild shifts (1 – 3 x ULN) were observed in 3.3 % of patients in the placebo arm, 5.5% in the MLN 100 mg/day arm and 7.0% in the MLN 200 mg/day arm
- a moderate shift (3-5 x ULN) was observed only in the MLN 200 mg/day dose (n=1 patient) and
- a large shift (>5 x ULN) occurred in the MLN 100 mg/day arm but was less than 10 x ULN (n=1 patient)

Among the patients who had baseline ALT values between 1 -3 x ULN, 0 patients in the placebo a and the MLN 200 mg/day arms shifted upward, and only one patient taking MLN 100 mg/day

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where had an increase to 3-5 x ULN. This suggests that MLN does not worsen ALT in patients with slightly elevated values at baseline.

Table 31. Summary of Shift from Baseline to Maximum Post-Baseline Value in ALT Values- Studies FMS031 and MLN-MD-02

Lab Parameters	Treatment Group	End of Study	Baseline					
			<=1xULN	>1xULN	<=5xULN	>5xULN	>=10xULN	>=20xULN
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine Aminotransferase (AST)	Placebo		N=553	V= 13				
		<=1 xULN	550 (96.7)	5 (45.2)				
		> 1 xULN- < 3xULN	13 (2.3)	7 (53.8)				
		>=3 xULN- < 5xULN	0 (0.0)	0 (0.0)				
		>=5 xULN	0 (0.0)	0 (0.0)				
		>=10xULN	0 (0.0)	0 (0.0)				
		>=20xULN	0 (0.0)	0 (0.0)				
	Milnacipran 100		N=560	V= 13				
		<=1 xULN	558 (94.9)	5 (38.5)				
		> 1 xULN- < 3xULN	9 (1.6)	7 (53.8)				
		>=3 xULN- < 5xULN	0 (0.0)	1 (7.7)				
		>=5 xULN	1 (0.2)	0 (0.0)				
		>=10xULN	0 (0.0)	0 (0.0)				
		>=20xULN	0 (0.0)	0 (0.0)				
	Milnacipran 200		N=753	V= 24				
		<=1 xULN	704 (92.8)	10 (41.7)				
		> 1 xULN- < 3xULN	53 (7.0)	14 (58.3)				
		>=3 xULN- < 5xULN	2 (0.3)	0 (0.0)				
		>=5 xULN	0 (0.0)	0 (0.0)				
		>=10xULN	0 (0.0)	0 (0.0)				
		>=20xULN	0 (0.0)	0 (0.0)				

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Notes: Based on Group 1AA (double-blind placebo-controlled fibromyalgia) studies: FMS031, and MLN-MD-02.
Only patients with both baseline and at least one post-baseline assessment are included.
Baseline is defined as the last assessment before the first dose of double-blind study medication.
* N= n/M where N is the number of patients who had both baseline and at least one post baseline value with baseline value in the specified category.

(Source: Applicant's Table 1, eCTD 33, p. 2)

Only one patient in the MLN 100 mg/day arm (0.2%) had an elevation from normal at baseline to ≥ 5 x ULN but <10 x ULN as described below:

- Patient #21818 (Study MLN- MD-02): This 53 year-old white female was receiving MLN 200 mg/day for 116. She experienced hepatitis and her highest ALT value was 216 U/L and AST of 70. Her condition resolved after discontinuation of the drug. Other AEs reported by her during the study were: nausea, insomnia, pruritus, hot flush, cardiac flutter, nasopharyngitis, and weight increased. Concomitant medications were atorvastatin, desloratadine, ibuprofen and zopiclone.

In my opinion is possible that although this event is confounded by multiple medications including atorvastatin which can cause an increase in liver enzymes, this AE may be related to the study drug.

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Transaminase elevations: AST

Similar to ALT, MLN treatment is associated with an increase in AST. A shift table from baseline values to maximum post-baseline value elevations in AST above the upper limit of normal (ULN) was analyzed and showed that elevations in AST above the upper limit of normal (ULN) from normal values at baseline were seen in:

- 1.9% of patients receiving placebo
- 3.2% of patients on MLN 100 mg/day
- 5.3% of patients receiving MLN 200 mg/day

Among the patients who had a shift upwards in the AST, all had mild shifts (1 – 3 x ULN). No moderate shifts (3-5 x ULN) or large shifts (>5 x ULN) were observed in any of the treatment arms. Only one patient who had a baseline AST between 1-3 x ULN had a shift to a value between 3-5 x ULN. There were no patients with an elevation of AST ≥ 5 x ULN (refer to the table below).

Table 32. Summary of Shifts from Baseline to Maximum Post- Baseline Value in AST- Studies FMS031 and MLN-MD-02

Lab Parameters	Treatment Group	End of Study	Baseline					
			<=1xULN		>1xULN <3xULN		>=3xULN <5xULN	
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Aspartate Aminotransferase (ASOT)	Placebo		N=572		N= 10			
		<=1 xULN	561 (98.1)		7 (70.0)			
		> 1 xULN <= 3xULN	11 (1.9)		3 (30.0)			
		>=3 xULN <= 5xULN	0 (0.0)		0 (0.0)			
		>=5 xULN	0 (0.0)		0 (0.0)			
		>=10xULN	0 (0.0)		0 (0.0)			
		>=20xULN	0 (0.0)		0 (0.0)			
	Milnacipran 100		N=566		N= 7			
		<=1 xULN	548 (96.8)		3 (42.9)			
		> 1 xULN <= 3xULN	18 (3.2)		3 (42.9)			
		>=3 xULN <= 5xULN	0 (0.0)		1 (14.3)			
		>=5 xULN	0 (0.0)		0 (0.0)			
		>=10xULN	0 (0.0)		0 (0.0)			
		>=20xULN	0 (0.0)		0 (0.0)			
	Milnacipran 200		N=771		N= 12			
		<=1 xULN	730 (94.7)		10 (83.3)			
		> 1 xULN <= 3xULN	41 (5.3)		2 (16.7)			
		>=3 xULN <= 5xULN	0 (0.0)		0 (0.0)			
		>=5 xULN	0 (0.0)		0 (0.0)			
		>=10xULN	0 (0.0)		0 (0.0)			
		>=20xULN	0 (0.0)		0 (0.0)			

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Notes: Based on Group 1AA (double-blind placebo-controlled fibromyalgia) studies: FMS031, and MLN-MD-02.
Only patients with both baseline and at least one post-baseline assessment are included.
Baseline is defined as the last assessment before the first dose of double-blind study medication.
* % = n/N where N is the number of patients who had both baseline and at least one post baseline value with baseline value in the specified category.

(Source: Applicant's Table 1, eCTD 33, p. 3)

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Alkaline phosphatase (AP) elevations

The table below shows the shifts from baseline to maximum post-baseline value in AP. There was no significant difference between the MLN treatment arms and placebo in the percent of patients who shifted AP categories. The shifts from normal to abnormal occurred in only 4 patients total: 0.2% of the patients on placebo and MLN 100 mg/day and 0.3% of patients on MLN 200 mg/day.

Table 33. Summary of Shifts from Baseline to Maximum Post-Baseline Value in AP- Studies FMS031 and MLN-MD-02

Lab Parameters	Treatment Group	End of Study	Baseline	
			≤1.5xULN (%)	>1.5xULN n (%)
Alkaline Phosphatase	Placebo		N=502	
		≤1.5xULN	501 (99.8)	
		> 1.5xULN	1 (0.2)	
	Milnacipran 100		N=573	
		≤1.5xULN	572 (99.8)	
		> 1.5xULN	1 (0.2)	
	Milnacipran 200		N=763	
		≤1.5xULN	761 (99.7)	
		> 1.5xULN	2 (0.3)	

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Notes: Based on Group 1AA (double-blind placebo-controlled fibromyalgia) studies: FMS031, and MLN-MD-02.
Only patients with both baseline and at least one post-baseline assessment are included.
Baseline is defined as the last assessment before the first dose of double-blind study medication.
* % = n/N where N is the number of patients who had both baseline and at least one post baseline value with baseline value in the specified category.

(Source: Applicant's Table 1, eCTD 33, p. 5)

Bilirubin Elevations

There were no cases of bilirubin $\geq 1.5 \times \text{ULN}$. The table below with shifts from baseline to maximum post-baseline value indicates that the incidence of shifts from normal to abnormal was not higher in the MLN treatment than in the placebo group. There were 2 patients in the placebo arm (0.3%) versus 0.1% in the MLN 200 mg/day who had increases in bilirubin $> 1 \times \text{ULN}$, and none in the MLN 100 mg/day treatment arms. The shift that occurred in the MLN treated patient

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did not exceed 1.5 x ULN. No cases in the MLN placebo-controlled studies satisfied the criteria for Hy's Law.

Table 34. Summary of Shifts from Baseline to Maximum Post-Baseline Value in Bilirubin Levels- Studies FMS031 and MLN-MD-02

Lab Parameters	Treatment Group	End of Study	Baseline			
			<=1xULN n (%)	>1xULN n (%)	>1.5xULN n (%)	>2xULN n (%)
Bilirubin, Total Placebo			N=580	N= 2		
		<=1 xULN	578 (99.7)	2 (100.0)		
		> 1 xULN	2 (0.3)	0 (0.0)		
		>=1.5xULN	0 (0.0)	0 (0.0)		
		>=2 xULN	0 (0.0)	0 (0.0)		
Milnacipran 100			N=573			
		<=1 xULN	573 (100.0)			
		> 1 xULN	0 (0.0)			
		>=1.5xULN	0 (0.0)			
		>=2 xULN	0 (0.0)			
Milnacipran 200			N=780	N= 3		
		<=1 xULN	779 (99.9)	3 (100.0)		
		> 1 xULN	1 (0.1)	0 (0.0)		
		>=1.5xULN	0 (0.0)	0 (0.0)		
		>=2 xULN	0 (0.0)	0 (0.0)		

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Notes: Based on Group 1AA (double-blind placebo-controlled fibromyalgia) studies: FMS031, and MLN-MD-02.
Only patients with both baseline and at least one post-baseline assessment are included.
Baseline is defined as the last assessment before the first dose of double-blind study medication.
* % = n/M where M is the number of patients who had both baseline and at least one post baseline value with baseline value in the specified category.

(Source: Applicant's Table 1, eCTD 33, p. 4)

For additional discussion of hepatic laboratory values in the placebo-controlled FM studies, refer to Section 7.1.7 (Laboratory Findings).

Dose-controlled FM extension studies (Group 1B)

In the long-term FM extension studies, there were three patients with ALT ≥ 3x ULN, one of whom had an elevation ≥ 5 x ULN. No patient had an elevation of ALT ≥ 10 x ULN.

No patients had AST or AP ≥ 3 x ULN, and no patient had elevated bilirubin.

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One patient, who had completed Study FMS031 uneventfully and was participating in the extension study FMS034, developed an ALT elevation of 9.3 x ULN at her final visit of FMS034. This was 3 days after the patient had undergone a breast biopsy, and she also was exposed to azithromycin and promethazine. The enzymes rapidly returned toward normal, but they had not completely normalized at the last follow-up.

No cases of transaminase elevation satisfied the criteria for Hy's rule.

Placebo controlled non-FM studies (Group 2)

The liver profile in the non-FM studies (MDD and GAD studies) was similar to that observed in the FM studies

One patient had an elevation of ALT ≥ 3 x ULN but < 5 x ULN. There were no cases of AST or AP ≥ 3 x ULN and only one case of bilirubin ≥ 2 x ULN but < 3 x ULN. No cases satisfied the criteria for Hy's rule.

Postmarketing experience:

There are reports of three cases of fulminant hepatitis in the post-marketing experience. These three cases occurred in female patients age 81-82 with underlying significant clinical conditions such as liver cirrhosis, angina pectoris, impaired kidney function, breast cancer, diabetes, hypertension, myocardial infarction, chronic cardiac failure, cholelithiasis, among others. These cases were also confounded by the use of several concomitant medications which precludes this reviewer to make any hepatotoxicity attributions to MLN.

7.1.4 Other Search Strategies

No other special search strategies were utilized in the course of this review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the FM studies all AEs reported spontaneously by the patient or patient representative were documented. Study personnel asked open-ended questions to obtain information about AEs at every visit and during any contact with a patient or patient representative occurring outside of a defined study visit, including any contact up to 30 days after study completion. The AEs included:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the principal investigator or study personnel

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- All concurrent diseases that occurred after the start of the study, including any change in severity or frequency of preexisting diseases
- All clinically relevant laboratory abnormalities or physical findings that occurred during the study

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events (AEs) were defined as treatment-emergent adverse events (TEAEs) if their onset date was not prior to the date of the first dose of study medication, or their onset date is prior to the date of the first dose of study medication but their severity increased during the treatment period.

AEs were re-coded using Version 9.0, or newer, of MedDRA, across all individual studies in Groups 1, 2, and 3 of the safety database. Since different dictionaries might have been used for coding in the individual studies, impact tables were provided for each study with a list of preferred terms or hierarchy mapping changed during recoding for the integrated summary of safety (ISS). An AE that occurred more than 30 days after the last dose of the study medication was not be counted as an AE. The 6-month studies (Group 1A) did not include any AE with a start date in the extension studies.

For the extension studies (Group 1B) with lead-in studies, an AE was considered a TEAE if it occurred after the date of the first dose of study medication in the extension study, or its onset date was prior to the date of the first dose of double-blind study medication in the lead-in study in Group 1A, but its severity increased during the treatment period of the extended-treatment or extension study. An AE with a start date in the lead-in study and continued through the extension study was only considered an AE in the lead-in study.

In the long-term safety studies (Group 1C), AEs were classified by preferred term and counted only once with the greatest severity reported if more than one AE with the same preferred occurred across the two study periods.

In summary, the categorization of the AEs and the coding system were appropriately utilized by the Applicant for the organization and presentation of the safety database.

7.1.5.3 Incidence of common adverse events

7.1.5.4 Common adverse event tables

- Common adverse events in the fibromyalgia studies

Placebo-controlled FM (Group 1A) studies

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Overall, the percentage of patients with at least one TEAE was higher in the MLN treatment arms: 89% (831/934) in the MLN 200 mg/day group, 89.1% (555/623) in the MLN 100 mg/day group and 82.8 % (540/652) in the placebo arm. The most commonly reported TEAEs among all patients were nausea (37%), headache, (18%), constipation (16%), hot flush (12%), insomnia (12%), and dizziness (11%).

Table 35 below presents the TEAEs (by system organ class (SOC) and preferred term) that occurred in ≥ 2 % of patients in either MLN treatment groups and at a higher incidence than placebo in the Group 1A studies.

The SOC that presented the most number of TEAEs was gastrointestinal (GI) disorders. The most common GI TEAEs that occurred in the MLN treatment arms were nausea (39% MLN 200 mg/ day, 35% MLN 100 mg/ day, 20 % placebo), constipation (16% MLN 200 mg/ day, 15% MLN 100 mg/ day, 4 % placebo), and vomiting (7% MLN 200 mg/ day, 6% MLN 100 mg/ day, 2 % placebo).

Nervous system disorders were the second most frequent SOC. Headache was experienced by 17% of the MLN 200 mg/day group, compared 19% of the MLN 100 mg/day and 14 % of the placebo groups. Dizziness as also more frequent in the milnacipran groups compared to the placebo group: 17% of patients treated with MLN 200 mg/day, 19% of patients in the MLN 100 mg/day arm, and 6% of the placebo patients.

The profile of the TEAEs indicates that there is no dose-response between the incidence of TEAEs and dose levels of MLN.

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

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

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

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There were 19.3% TEAE reports that were considered severe among the MLN-treated patients compared with 14.9% of the placebo-treated patients. Nausea was the most frequent severe TEAE but overall, these TEAEs were not concentrated in a particular system organ class and do not raise any safety signals. Table 36 presents the severe TEAEs that were considered to be severe in at least 1% of the MLN treated patients.

Table 36. Severe Treatment-Emergent Adverse Events that Occurred in $\geq 1\%$ of Milnacipran-Treated Patients in the Placebo-Controlled Fibromyalgia Studies (Group 1)

	Placebo	Milnacipran		
	(N = 652)	100 mg/d (N = 623)	200 mg/d (N = 934)	Total (N = 1557)
	n (%)	n (%)	n (%)	n (%)
Patients with at least one severe TEAE	97 (14.9)	132 (21.2)	168 (18.0)	300 (19.3)
Nausea	8 (1.2)	21 (3.4)	33 (3.5)	54 (3.5)
Headache	8 (1.2)	14 (2.2)	18 (1.9)	32 (2.1)
Migraine	7 (1.1)	17 (2.7)	14 (1.5)	31 (2.0)
Insomnia	6 (0.9)	6 (1.0)	13 (1.4)	19 (1.2)
Vomiting	2 (0.3)	8 (1.3)	11 (1.2)	19 (1.2)
Back pain	3 (0.5)	11 (1.8)	8 (0.9)	19 (1.2)
Constipation	1 (0.2)	5 (0.8)	9 (1.0)	14 (0.9)
Hot flush	0	6 (1.0)	6 (0.6)	12 (0.8)
Anxiety	3 (0.5)	6 (1.0)	5 (0.5)	11 (0.7)
Chest pain	3 (0.5)	6 (1.0)	3 (0.3)	9 (0.6)

(Source: Applicant's Table 6.1.1.1-3, Summary of Clinical Safety, Vol. 1, p. 81)

Dose-controlled FM extension studies (Group 1B)

In the FM extension studies (Group 1B), the overall incidence of TEAEs was approximately 82.2%. The profile of the events resembles the observations in the FM placebo-controlled studies. The most common TEAEs were nausea (25.5%), headache (13.1%), and constipation (9.1%). The AEs were more frequent among the patients that were treated with MLN for the first time (patients who were in the placebo group in the lead-in study). The severe TEAEs that occurred in the extension studies were nausea (2.6%), headache (1.9%), and migraine (1.3%).

Long-term open label safety studies (Group 1C)

In the long-term studies (Group 1C) where 354 patients were treated at least for 1 year, the TEAE profile did not differ from what was observed in the Group 1A and 1B studies. Nausea, headache, constipation, sinusitis and insomnia were the most common TEAEs. The TEAEs that did demonstrate a dose effect were nausea, headache, sinusitis, insomnia, hot flush, nasopharyngitis, fatigue, depression, arthralgia, UTI, back pain, pain in extremity, muscle spasms, dry mouth, anxiety, chest pain. All the TEAEs mentioned occurred at a higher rate in the

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MLN 200mg/day arm than in the MLN 100 mg/day arm. Certain TEAEs of interest, such as dizziness, hypertension, heart rate increased, palpitations, and blood pressure increased all occurred more frequently in the 100 mg/day arm compared with the 200mg/day arm.

- Common adverse events in the non-fibromyalgia studies

In the placebo-controlled non-fibromyalgia studies (Group 2), the incidence of TEAEs was higher among the MLN-treated patients (74%) than in the placebo-treated patients (56%).

The overall profile is similar despite the difference in the populations in Groups 1 and 2. The population in the non-FM studies consisted of patients with MDD and GAD, included a larger number of males and the age range differed as well. The most common TEAEs were nausea, headache, dizziness and dry mouth. In the GAD and MDD populations, there were more reports related to sleep disturbances such as middle insomnia, early morning awakening, initial insomnia, somnolence, insomnia. Gender-specific TEAEs to the male non-FM population were urinary hesitation, ejaculatory disorder, and erectile dysfunction.

7.1.5.5 Identifying common and drug-related adverse events

Refer to Section 7.1.5.4.1

7.1.5.6 Additional analyses and explorations

Common adverse events in male patients

Because FM is a disease with significantly higher prevalence in females, adverse events that occur in males may not be evident in the overall assessment of AEs and were therefore explored. The placebo-controlled FM (Group 1A) studies were used for this assessment.

A total of 87 (3.9%) of the patients in the Group 1A studies were male: 23 treated with 100 mg/day, 32 treated with MLN 100 mg/day, and 32 treated with PBO. The most commonly reported TEAE among male patients treated with MLN in the FM-studies was dysuria (23.6% patients) compared to only 0.1% female patients treated with milnacipran who reported this event.

Other genitourinary AEs that were observed at a higher incidence in male patients taking milnacipran compared with male placebo-treated patients included ejaculation problems (7.3% in the MLN group versus 0% in the placebo group) and erectile dysfunction (5.5% in the MLN group versus 0% in the placebo group). These findings are not unexpected because of the noradrenergic component of the mechanism of action of milnacipran.

Among the male patients treated with milnacipran, 38.2% discontinued because of one or more AEs compared with 24.3% female patients treated with MLN. Dysuria was the AE most

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frequently associated with discontinuation in male patients (7.3%); none of the female patients discontinued because of dysuria.

Because of the observation of genitourinary AEs in the male population, the label should indicate that milnacipran should be used with caution in male patients with a history of dysuria, prostatic hypertrophy, prostatitis, or other lower urinary tract obstructive disorders.

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

7.1.6 Less Common Adverse Events

Mydriasis is a known effect of drugs that affect norepinephrine reuptake. The approved NSRIs address this effect in the Warnings and Precautions section of their labels. From the venlafaxine extended release (Effexor XR) label:

Mydriasis has been reported in association with venlafaxine; therefore patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored

Mydriasis was one of the less common adverse events observed: 0.3% in the MLN 200 mg/day group versus none in the placebo group. Although this AE occurred infrequently it may need attention in terms of labeling. This AE is a known effect of drugs that affect nor-epinephrine reuptake and other NSRIs address this effect in the precautions section of their labels.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

According to the protocols of the placebo-controlled fibromyalgia studies FMS031 and MLN-MD-02, patients were to have laboratory evaluations at screening, baseline and Week 15, in addition to an assessment at week 27 for Study FMS031. In the Phase 2 placebo controlled fibromyalgia study, Study FMS021, the laboratory assessments occurred at screening, baseline and week 8. The clinical laboratory evaluations were as follows:

- Hematology: red blood cell count (RBC); hemoglobin (Hgb); hematocrit (Hct); mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular

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- hemoglobin concentration (MCHC); white blood cell count (WBC), including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils); and platelet count
- Chemistry: sodium; potassium; chloride; carbon dioxide (CO₂); calcium; phosphorus; glucose; blood urea nitrogen (BUN); creatinine; alkaline phosphatase (AP); total bilirubin; direct bilirubin; aspartate aminotransferase (AST); alanine aminotransferase (ALT); lactate dehydrogenase (LDH); total protein; albumin; triglycerides; cholesterol; and uric acid
 - Urinalysis: blood; protein; glucose; and microscopy (casts and WBC per high-power field)

Fasting was not required for the blood or urine sample collection. Patients with stable diabetes were accepted into the trial. In addition to the tests listed above, the female patients of childbearing potential were to have a pregnancy test at baseline for all studies and in addition, at week 27 for FM-031.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The main safety database selected for the laboratory analysis consists of the combined data from the three fibromyalgia placebo-controlled studies (Group 1A). This data was analyzed for safety signals associated with dose-related abnormal laboratory tests. This reviewer also examined the safety data for the fibromyalgia extension studies (Group 1B and 1C) seeking for potential safety signals associated with long term treatment with MLN.

7.1.7.3 Standard analyses and explorations of laboratory data

- Analyses focused on measures of central tendency

Placebo-Controlled Fibromyalgia Studies (Group 1A)

Hematological parameters

Among the Group 1A FM studies, the only hematological parameters that presented a change of at least 1 unit in value were hemoglobin and platelets.

At the end of the placebo-controlled treatment, the placebo group experienced a mean hemoglobin decrease of 0.04 g/L, compared to a mean increase of 1.19 g/L in the MLN 100 mg/day group and 0.31 g/L in the MLN 200 mg/day group. The mean change in hemoglobin is not considered clinically significant.

The mean change in platelets values at the end of the study was -2.4 ± 47.5 (10^9 /L) in the placebo group, compared with an increase of 12.4 ± 52.3 (10^9 /L) in the MLN 100 mg/day group and 16.1 ± 50.8 (10^9 /L) in the MLN 200 mg/day group (normal range $140-370 \times 10^9$ /L). This suggests that there is an effect of milnacipran on platelet production and the mean increase is higher in the highest MLN dose. None of these values are of clinical significance as they were not above values that were considered potentially clinically significant (i.e. $> 666 \times 10^9$ /L).

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Chemistry parameters

The only chemistry laboratory tests that presented a mean change of at least 1 unit in value were ALT, alkaline phosphatase and AST:

- AST: -1.40 U/L in the placebo group versus 1.47 U/L in the MLN 100 mg/day group and 1.90 U/L in the MLN 200mg/day
- alkaline phosphatase: -2.5 U/L in the placebo group versus 1.7 U/L in the MLN 100 mg/day group and 3.0 mg U/L in the MLN 200 mg/day group
- ALT: -1.7 U/L in the placebo group versus 0.9 U/L in the MLN 100 mg/day group and 1.1 U/L in the MLN 200 mg/day group.

For more detailed information on effects of milnacipran treatment on tests of liver function, see Section 7.1.3.3. (Other Significant Adverse Events- *Adverse events related to hepatotoxicity*)

There was no apparent effect of milnacipran on other chemistry parameters, including creatinine and glucose.

Table 37 below shows the change in mean values for selected laboratory measurements, by treatment group.

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Table 37. Change from Baseline in Selected Clinical Laboratory Parameters at the End-of-Study Visit: Placebo-controlled Fibromyalgia Syndrome Studies.

Table 7.1.1.1-1. Change From Baseline in Selected Clinical Laboratory Parameters at the End-of-Study Visit: Placebo-Controlled Fibromyalgia Syndrome Studies

Parameter (units)	Placebo N = 652		Milnacipran			
			100 mg/d N = 623		200 mg/d N = 934	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
CHEMISTRY						
<i>Alanine aminotransferase, U/L</i>						
Baseline	608	22.52 ± 10.34	573	22.50 ± 10.87	871	22.84 ± 10.44
End of Study	608	21.12 ± 11.30	573	23.97 ± 14.58	871	24.74 ± 13.25
Change	608	-1.40 ± 9.52	573	1.47 ± 11.65	871	1.90 ± 10.76
<i>Aspartate aminotransferase, U/L</i>						
Baseline	608	22.3 ± 7.4	573	21.7 ± 6.8	871	22.3 ± 7.2
End of Study	608	20.5 ± 6.8	573	22.6 ± 8.8	871	23.4 ± 9.0
Change	608	-1.7 ± 7.0	573	0.9 ± 7.6	871	1.1 ± 8.4
<i>Blood urea nitrogen, mmol/L</i>						
Baseline	608	5.35 ± 1.60	573	5.29 ± 1.56	872	5.34 ± 1.65
End of Study	608	5.40 ± 1.61	573	5.26 ± 1.58	872	5.28 ± 1.62
Change	608	0.05 ± 1.34	573	-0.03 ± 1.41	872	-0.05 ± 1.32
<i>Creatinine, µmol/L</i>						
Baseline	608	78.4 ± 16.7	573	78.9 ± 17.4	872	75.2 ± 15.9
End of Study	608	76.1 ± 15.8	573	76.2 ± 15.5	872	73.8 ± 15.1
Change	608	-2.4 ± 12.1	573	-2.7 ± 12.5	872	-1.4 ± 11.4
<i>Glucose (nonfasting), mmol/L</i>						
Baseline	607	5.28 ± 1.28	573	5.27 ± 1.20	869	5.28 ± 1.34
End of Study	607	5.42 ± 1.63	573	5.48 ± 1.62	869	5.53 ± 1.80
Change	607	0.14 ± 1.20	573	0.21 ± 1.21	869	0.25 ± 1.42
<i>Uric acid, µmol/L</i>						
Baseline	608	285.8 ± 73.0	573	285.9 ± 79.4	871	287.4 ± 76.5
End of Study	608	288.9 ± 72.8	573	286.1 ± 83.2	871	286.8 ± 78.9
Change	608	3.1 ± 48.1	573	0.2 ± 47.2	871	-0.6 ± 46.7

(Source: Applicant's Table 7.1.1.1-1, Summary of Clinical Safety, Vol. 1, p. 133)

Table 37. Change from Baseline in Selected Clinical Laboratory Parameters at the End-of-Study Visit: Placebo-controlled Fibromyalgia Syndrome Studies (continued).

Table 7.1.1.1-1. Change From Baseline in Selected Clinical Laboratory Parameters at the End-of-Study Visit: Placebo-Controlled Fibromyalgia Syndrome Studies

Parameter (units)	Placebo N = 652		Milnacipran			
			100 mg/d N = 623		200 mg/d N = 934	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
HEMATOLOGY						
<i>Hematocrit, %</i>						
Baseline	601	41.8 ± 3.5	571	41.6 ± 3.5	874	42.1 ± 3.4
End of Study	601	41.0 ± 3.5	571	41.3 ± 3.8	874	41.8 ± 3.7
Change	601	-0.8 ± 2.8	571	-0.3 ± 3.0	874	-0.3 ± 3.0
<i>White blood cell count, 10⁹/L</i>						
Baseline	601	7.1 ± 2.1	571	7.4 ± 2.1	873	7.3 ± 1.9
End of Study	601	7.1 ± 2.0	571	7.5 ± 2.1	873	7.5 ± 2.1
Change	601	-0.0 ± 1.6	571	0.1 ± 1.7	873	0.1 ± 1.6
<i>Platelet count, 10⁹/L</i>						
Baseline	597	276.8 ± 63.7	570	285.6 ± 63.9	869	283.9 ± 65.8
End of Study	597	274.4 ± 64.3	570	298.1 ± 68.5	869	300.0 ± 71.4
Change	597	-2.4 ± 47.5	570	12.4 ± 52.3	869	16.1 ± 50.8

Based on three double-blind, placebo-controlled fibromyalgia studies: FMS021, FMS031, and MLN-MD-02.

N = number of patients in the treatment group; n = subset of N for the category.

(Source: Applicant's Table 7.1.1.1-1, Clinical Summary of Safety, Vol. 1, p. 134)

Dose-Controlled Fibromyalgia Extension Studies (Group 1B)

Chemistry parameters

In the FM extension studies (Group 1B) the changes from baseline in laboratory values were comparable between the MLN treatment groups, with no significant differences for most of the laboratory tests. The changes were small and not clinically relevant.

Hematological parameters

In the Group 1B studies, the change in platelets from baseline was less than the observed in the Group 1A studies: the mean difference from baseline was $4.68 \times 10^9 / L$ (range -3.70 to $8 \times 10^9 / L$) and occurred in all treatment arms. The highest changes in mean platelet values occurred in

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the treatment arms in which the patients received doses of MLN 200 mg/day, and there seems to be a dose relationship: patients who received (lead-in study/ open label study) MLN 100/100 mg the mean change was $5.23 \times 10^9/L$, for patients who received MLN it was 100/200 mg $7.61 \times 10^9/L$ and for patients who received MLN 200/200 mg it was $8.07 \times 10^9/L$. None of the increases in platelet values were considered potentially clinically significant (PCS).

In the Group 1B studies there were increases in hemoglobin, with mean change from baseline 1.17 g/L (range 0.44 to 3.0 g/L) and mean corpuscular hemoglobin concentration, with mean change 6.34g/L (range 3.07 to 9 g/L). These changes occurred across all treatment arms and were not dose related. The importance of such changes is of unknown significance.

- Analyses focused on outliers or shifts from normal to abnormal

Placebo-Controlled Fibromyalgia Studies (Group 1A)

Hematological parameters

There was a small proportion of patients who presented shifts from normal at baseline to abnormal at the end of the study in regard to the hematological parameters:

- high white blood cell counts ($WBC > 10.8 \times 10^9/L$): placebo 2.4%, MLN 100 mg/day 5.2% and MLN 200 mg/day 4.6%, which does not seem to be related to any particular cell line
- high platelet counts ($> 400 \times 10^9/L$) placebo 2.5%, MLN 100 mg/day 6.5%, MLN 200 mg/day 6.3%

The shifts occurred more frequently in the MLN treatment arms but did not seem to have a dose relationship. None of the patients reached a potentially clinically significantly high value.

Chemistry parameters

There was a small proportion of patients who presented shifts from normal at baseline to abnormal at the end of the study in regard to chemistry parameters. The shifts that occurred at a rate higher than 1% are listed below:

- electrolytes:
 - low sodium ($< 135 \text{ mmol/L}$): placebo 0.3%, MLN 100 mg/day 1.2%, MLN 200 mg/day 1.8%. This information is relevant because although these numbers are small, cases of hyponatremia as the result of syndrome of anti-diuretic hormone secretion (SIADH) have been described with other NSRIs. None of these patients reached what was considered a potentially clinically significant low value ($< 0.9 \text{ LLN} = 121 \text{ mmol/L}$)
 - low chloride ($< 98 \text{ mmol/L}$): placebo 0.9%, MLN 100 mg/day 2.7, MLN 200 mg/day 3.7
 - high potassium ($> 5.3 \text{ mmol/L}$): placebo 1.2%, MLN 100 mg/day 2.2%, MLN 200 mg/day 1.0%
 - high bicarbonate ($> 30 \text{ mmol/L}$): placebo 6.3%, MLN 100 mg/day 8.7%, MLN 200 mg/day 6.5%
 - high calcium ($> 2.6 \text{ mmol/L}$): placebo 1.0%, MLN 100 mg/day 1.2, MLN 200 mg/day 2.1%

- liver function tests:
 - high ALT (> 55 U/L): placebo 1.8%, MLN 100 mg/day 4.1%, MLN 200 mg/day 4.5%
 - high alkaline phosphatase (> 147 U/L): placebo 1.3%, MLN 100 mg/day 2.2%, MLN 200 mg/day 2.0%
 - high AST (> 45 U/L): placebo 1.4%, MLN 100 mg/day 1.2%, MLN 200 mg/day 3.1%
 - high lactate dehydrogenase (> 223 U/L): placebo 3.8%, MLN 100mg/day 6.7%, MLN 200 mg/day 6.4%. The clinical significance of this finding is unclear.

For more detailed information on effects of milnacipran treatment on tests of liver function, see Section 7.1.3.3.3 (Other significant adverse events – *Adverse events related to hepatotoxicity*)

- lipids:
 - high triglycerides (>2.3 mmol/L): placebo 9.2%, MLN 100 mg/day 15.6%, MLN 200 mg/day 12.7% but this laboratory tests was not conducted under fasting conditions.
 - high total cholesterol (> 5.1 mmol/L): placebo 8.6%, MLN 100 mg/day 16.5%, MLN 200 mg/day 10.2 %, but this laboratory tests was not conducted under fasting conditions. One patient (0.3%) in the MLN 100 mg/day treatment arm reached a potentially clinically significant value (> 1.6 ULN= 8.1 mmol/L)

There were shifts in glucose levels in all treatment arms but these changes cannot be taken into consideration as the laboratory tests were not done under fasting conditions.

Urinalysis parameters

There were shifts in the proportion of patients who had negative urine glucose at baseline and shifted to positive urine glucose: placebo 1.1%, MLN 100 mg/day 1.8% and MLN 200 mg/day 2.2%. A higher proportion of patients in the MLN treatment arms had glucose levels > 2+, placebo 0.7%, MLN 100 mg/day 1.1% and MLN 200 mg/day 1.8% but the urine tests were not conducted in fasting conditions which needs to be taken into consideration for interpretation of this information.

In respect to the presence of protein in the urine 0.6% of placebo patients who were negative at baseline had protein in the urine versus 2.7% of the MLN 100mg/day and 1.9% of the MLN 200 mg/day patients. The clinical relevance of this finding is unclear.

- Marked outliers and dropouts for laboratory abnormalities

Placebo-Controlled Fibromyalgia Studies (Group 1A)

One patient discontinued the study due to a laboratory abnormality and I believe that this AE is possibly related to the study drug:

- Patient #21818 (Study MLN- MD-02): This 53 year-old white female was receiving MLN 200 mg/day for 116. She experienced hepatitis and her highest ALT value was 216 U/L. Her

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condition resolved after discontinuation of the drug. Other AEs reported by her during the study were: nausea, insomnia, pruritus, hot flush, cardiac flutter, nasopharyngitis, and weight increased. Concomitant medications were atorvastatin, desloratadine, ibuprofen and zopiclone. In my opinion is possible that this AE is related to the study drug.

Dose-Controlled Fibromyalgia Extension Studies (Group 1B)

Two patients discontinued the extension studies due to adverse events associated with laboratory abnormalities and I believe only one of them (patient #24012) discontinued because of the study drug:

- **Patient #24012 (Study MLN –MD-04):** This 28 year-old white female was receiving MLN 200 mg/day for 114 days after participating in MLN-MD-02 during which she received MLN 100 mg/day. The patient discontinued the study drug due to leucopenia. Her white blood cell count was 2.9×10^9 /L. The patient reported severe musculoskeletal stiffness and psoriasis prior to starting the extension study. After starting MLN 200 mg/day dose in the extension study the patient reported multiple allergies, nausea, upper abdominal pain, increased blood cholesterol, fatigue, chills, and gastroesophageal reflux disease. Her condition resolved. Concomitant medications were: vitamins, clobetasol propionate, ethinyl estradiol with norgestrel, pantoprazole sodium, and spironolactone. In my opinion this AE could be related to the study drug.
- **Patient #10431 (Study FMS034):** This 51 year-old white female was receiving MLN 200 mg/day for 57 days in the extension study. She had received MLN 200 mg/day in study FMS031. At screening for FMS031 she was noted to have elevated lymphocyte count (55%-normal range 17-47) and never normalized as noticed during the follow-up visits. She was diagnosed with chronic lymphocytic leukemia and discontinued from the study. I do not believe this AE is related to the study drug.

7.1.7.4 Additional analyses and explorations

In its evaluation of effects of milnacipran on laboratory parameters, the Applicant established limits for potentially clinically significant (PCS) laboratory tests (see Table 38). The percentages of patients who met these criteria were calculated. The percentages were calculated relative to the number of patients who had available non-PCS baseline values and at least one post-baseline assessment. The numerator was the total number of patients who had at least one PCS post-baseline value. The analysis of the data of the Group 1A allowed this reviewer to assess for PCS safety signals that were dose related. The Group 1B and 1C analyses explored whether there were any PCS safety signals associated to prolonged exposure to the drug.

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Table 38. Criteria for Potentially Clinically Significant Laboratory Tests

Parameter	Unit	Low Limit	High Limit
Chemistry			
Albumin	g/dL	$< 0.8 \times \text{LLN}$	—
Alanine aminotransferase	U/L	—	$> 3 \times \text{ULN}$
Alkaline phosphatase	U/L	—	$> 3 \times \text{ULN}$
Aspartate aminotransferase	U/L	—	$> 3 \times \text{ULN}$
Bicarbonate	mmol/L	$< 0.8 \times \text{LLN}$	$1.2 \times \text{ULN}$
Bilirubin (total)	mg/dL	—	$> 1.5 \times \text{ULN}$
Bilirubin (conjugated)	mg/dL	—	$> 1.5 \times \text{ULN}$
Bilirubin (unconjugated)	mg/dL	—	$> 1.5 \times \text{ULN}$
Calcium	mg/dL	$< 0.9 \times \text{LLN}$	$> 1.1 \times \text{ULN}$
Cholesterol	mg/dL	—	$> 1.6 \times \text{ULN}$
Creatinine	mg/dL	—	$> 1.8 \times \text{ULN}$
γ -Glutamyl transferase	U/L	—	$> 3 \times \text{ULN}$
Glucose (fasting)	mg/dL	$< 0.8 \times \text{LLN}$	$> 1.2 \times \text{ULN}$
Glucose (nonfasting)	mmol/L	$< 0.8 \times \text{LLN}$	$> 1.4 \times \text{ULN}$
Phosphate	mg/dL	$< 0.8 \times \text{LLN}$	$> 1.2 \times \text{ULN}$
Potassium	mmol/L	$< 0.9 \times \text{LLN}$	$> 1.1 \times \text{ULN}$
Sodium	mmol/L	$< 0.9 \times \text{LLN}$	$> 1.1 \times \text{ULN}$
Thyroid-stimulating hormone	mIU/L	$< 0.3 \times \text{LLN}$	$> 1.5 \times \text{ULN}$
Total protein	g/dL	—	$> 1.1 \times \text{ULN}$
Urate	mg/dL	—	$> 1.2 \times \text{ULN}$
Blood urea nitrogen	mg/dL	—	$> 1.3 \times \text{ULN}$
Hematology			
Basophils	%	—	$> 2 \times \text{ULN}$
Eosinophils	%	—	$> 2 \times \text{ULN}$
Lymphocytes	%	$< 0.6 \times \text{LLN}$	$> 1.6 \times \text{ULN}$
Neutrophils	%	$< 0.5 \times \text{LLN}$	$> 1.6 \times \text{ULN}$
Hematocrit	%	$< 0.8 \times \text{LLN}$	$\geq 1.1 \times \text{ULN}$
Hemoglobin	g/L	$< 0.8 \times \text{LLN}$	$\geq 1.1 \times \text{ULN}$
Monocytes	%	—	$> 2 \times \text{ULN}$
Platelet count	$10^9/\text{L}$	$< 0.5 \times \text{LLN}$	$> 1.8 \times \text{ULN}$
Red blood cell count	$10^{12}/\text{L}$	$< 0.8 \times \text{LLN}$	$> 1.2 \times \text{ULN}$
White blood cell count	$10^9/\text{L}$	$< 0.7 \times \text{LLN}$	$> 1.8 \times \text{ULN}$
Urinalysis			
Glucose	mmol/L	—	> 15
Protein	g/L	—	> 1.0
Glucose (alternate units)	Units	—	$> 2+$
Protein (alternate units)	Units	—	$> 2+$

LLN = lower limit of the normal value (provided by the laboratory); ULN = upper limit of the normal value (provided by the laboratory).

(Source: Applicant's Table 7.1.1.1-1, Summary of Clinical Safety, Vol. 1, p. 133-134)

Incidence of PCS laboratory changes – Placebo controlled FM studies (Group 1A)

Overall, the incidence of PCS laboratory changes was low and there were no major differences between placebo and the MLN treated groups. The only PCS laboratory values that occurred in

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at least 1% of milnacipran-treated patients were those for elevated blood glucose (placebo, 1.0% versus MLN 1.3%) and urine glucose (placebo, 0.7% versus MLN 1.5%).

Other PCS laboratory changes such as increases in ALT, AST, cholesterol, and uric acid values had slightly higher incidences in the milnacipran-treated patients compared with the placebo-treated patients. For a more detailed discussion regarding increases in ALT and AST, refer to Section 7.1.3.3 (Other significant adverse events- *Adverse events related to hepatotoxicity.*)

The PCS laboratory changes in the Group 1A studies are listed in Table 39.

Table 39. Incidence of Potentially Clinically Significant Laboratory Changes in the Placebo Controlled FM Studies (Group 1A)

Laboratory Parameter (units)	PCS Category	Placebo (N = 652)	Milnacipran		
			100 mg/d (N = 623)	200 mg/d (N = 934)	Total (N = 1557)
		n/N ₁ (%)	n/N ₁ (%)		
HEMATOLOGY					
Basophils	High	0/601	0/571	1/873 (0.1)	1/1444 (0.1)
Eosinophils	High	0/598	1/571 (0.2)	0/872	1/1443 (0.1)
Hematocrit	High	0/600	1/569 (0.2)	2/873 (0.2)	3/1442 (0.2)
	Low	3/600 (0.5)	2/569 (0.4)	2/873 (0.2)	4/1442 (0.3)
Hemoglobin	High	0/601	0/570	1/874 (0.1)	1/1444 (0.1)
	Low	2/601 (0.3)	1/570 (0.2)	2/874 (0.2)	3/1444 (0.2)
Lymphocytes	High	0/599	1/569 (0.2)	1/873 (0.1)	2/1442 (0.1)
	Low	5/599 (0.8)	3/569 (0.5)	4/873 (0.5)	7/1442 (0.5)
Monocytes	High	0/601	0/571	2/873 (0.2)	2/1444 (0.1)
Neutrophils	Low	0/601	1/571 (0.2)	2/873 (0.2)	3/1444 (0.2)
Platelet count (thrombocytes)	High	0/598	0/570	2/869 (0.2)	2/1439 (0.1)
	Low	1/598 (0.2)	0/570	0/869	0/1439
Red blood cell count	Low	0/601	0/571	2/873 (0.2)	2/1444 (0.1)
White blood cell count	High	1/600 (0.2)	0/571	0/872	0/1443
	Low	4/600 (0.7)	1/571 (0.2)	2/872 (0.2)	3/1443 (0.2)
CHEMISTRY					
Alanine aminotransferase	High	0/608	2/573 (0.3)	2/871 (0.2)	4/1444 (0.3)
Aspartate aminotransferase	High	0/608	1/573 (0.2)	0/871	1/1444 (0.1)
Bicarbonate	High	0/606	1/573 (0.2)	2/870 (0.2)	3/1443 (0.2)
	Low	1/606 (0.2)	4/573 (0.7)	1/870 (0.1)	5/1443 (0.3)
Bilirubin, direct (conjugated)	High	1/605 (0.2)	2/569 (0.4)	3/870 (0.3)	5/1439 (0.3)
Blood urea nitrogen	High	4/604 (0.7)	4/569 (0.7)	4/867 (0.5)	8/1436 (0.6)
Cholesterol, total	High	1/605 (0.2)	5/568 (0.9)	5/866 (0.6)	10/1434 (0.7)
Creatinine	High	0/608	0/573	1/872 (0.1)	1/1445 (0.1)

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Glucose, nonfasting	High	6/602 (1.0)	8/570 (1.4)	11/859 (1.3)	19/1429 (1.3)
	Low	3/602 (0.5)	3/570 (0.5)	3/859 (0.3)	6/1429 (0.4)
Phosphorus	High	0/605	1/571 (0.2)	4/870 (0.5)	5/1441 (0.3)
	Low	3/605 (0.5)	7/571 (1.2)	3/870 (0.3)	10/1441 (0.7)
Potassium, mmol/L	High	1/607 (0.2)	1/570 (0.2)	0/868	1/1438 (0.1)
	Low	2/607 (0.3)	4/570 (0.7)	3/868 (0.3)	7/1438 (0.5)
Uric acid, mmol/L	High	1/606 (0.2)	4/565 (0.7)	4/869 (0.5)	8/1434 (0.6)
URINALYSIS					
Glucose	≥ 2	4/598 (0.7)	6/564 (1.1)	15/855 (1.8)	21/1419 (1.5)
Protein	≥ 2	1/607 (0.2)	1/567 (0.2)	1/867 (0.1)	2/1434 (0.1)

(Source: Applicant's Table 7.1.1.2-1, Summary of Clinical Safety, Vol.1, p. 135)

One patient in the Group 1A studies discontinued from the study due to an adverse event related to abnormal laboratory parameters:

- Patient #21818 (Study MLN- MD-02): This 53 year-old white female was receiving MLN 200 mg/day for 116. She experienced hepatitis and her highest ALT value was 216 U/L. Her condition resolved after discontinuation of the drug. Other AEs reported by her during the study were: nausea, insomnia, pruritus, hot flush, cardiac flutter, nasopharyngitis, and weight increased. Concomitant medications were atorvastatin, desloratadine, ibuprofen and zopiclone. In my opinion is possible that this AE is related to the study drug.

PCS laboratory changes – Dose- controlled FM extension studies (Group 1B)

There were few PCS abnormalities noted in the Group 1B studies:

- high glucose values (> 6.9 mmol/L) were observed in 1.6% of patients in the milnacipran 200-mg/day group compared with 0 % in the 100-mg/d group. However, these tests were non-fasting therefore one cannot necessarily attribute this effect to the drug, although elevated glucose did occur at a higher rate in the MLN 200 mg/day treatment group.
- low phosphorus (< 0.68 or < 0.87) values occurred at an incidence of 2% of patients in the 100-mg/day group and 1.2% of patients in the 200-mg/d group. The incidence of this abnormality was 0.3% in the placebo group and 0.5% in the MLN treatment groups in the Group 1A studies.
- high BUN values (> 7.8 mmol/L) were observed in 1.4% of patients in the 200-mg/d group. The incidence of this abnormal laboratory value was comparable between placebo (0.7%) and MLN treatment arms (0.6%) in the Group 1A studies.

Two patients in the Group 1B studies discontinued from the study due to an adverse event related to abnormal laboratory parameters:

- Patient # 24012 who had received 100 mg/day in the lead-in study and 200 mg/day in the extension study MLN-MD-04, presented with moderate leucopenia. She had been on the study drug for 114 days.

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- Patient #10431 who had received MLN 200 mg/day in the lead in study and continued the same dose in the extension study was diagnosed with chronic lymphocytic lymphoma.

7.1.7.5 Special assessments

No special laboratory assessments were conducted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

According to the Phase 2 and 3 protocols, vital signs were obtained from the patients at baseline and at each post-baseline visit (i.e. every 2–4 weeks). The Applicant provided descriptive statistics for the vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate [PR], weight) at baseline, each post-baseline visit and change from baseline to each post-baseline visit.

Baseline values were defined as the average of the two or three available measurements before the first dose of study drug. End-of-treatment values were defined as the average of the last three visits after the first dose of study drug or the average of all visits for patients with less than three visits.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The safety data from the three placebo-controlled FM-studies (Group 1A) were analyzed for abnormal vital signs associated with dose-related toxicity. The Applicant submitted a special analysis of the cardiovascular events but some of the analyses excluded study FM-021 because the MLN doses were flexible and could possibly confound the analysis. This reviewer will indicate whether the data utilized in this review includes all studies from the FM placebo-controlled studies (Group 1A) or whether the data exclude Study FMS-021 from the assessment. The safety data from the extension studies and long term studies were analyzed for abnormal vital signs possibly associated with prolonged exposure to MLN.

7.1.8.3 Standard analyses and explorations of vital signs data

- Analyses focused on measures of central tendencies – Blood Pressure

Placebo-Controlled FM trials (FMS-031 and MLN-MD-02)

Overall, the mean increase in supine SBP at the end of the study was 3.1 mmHg for the MLN 100 mg/day and 3 mmHg for the 200 mg/day groups, compared with a decrease of -0.1 mmHg in

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the placebo group. The increase in SBP did not appear to be dose related. There were also increases in the supine DBP in the MLN treatment arms: mean increase of 3.1 mmHg in the MLN 100 mg/day and 2.6 mm Hg in the MLN 200/day groups compared to 0.4 mm HG in the placebo group.

Table 40 below presents the mean changes in supine vital signs at the end of the study from baseline.

Table 40. Changes from Baseline in Supine Vital Signs at the End-of-Study Visit in the Placebo-Controlled FM-Studies

Parameter	Placebo N = 652		Milnacipran			
			100 mg/d N = 623		200 mg/d N = 934	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Systolic blood pressure, mm Hg						
Baseline ^a	641	122.1 ± 14.5	614	122.8 ± 14.5	912	121.7 ± 14.1
End of Study	641	122.0 ± 14.5	614	126.0 ± 14.5	912	124.7 ± 14.3
Change	641	-0.1 ± 13.7	614	3.1 ± 14.0	912	3.0 ± 12.9
Diastolic blood pressure, mm Hg						
Baseline ^a	641	75.9 ± 9.1	614	77.2 ± 8.9	912	76.3 ± 8.5
End of Study	641	76.3 ± 9.2	614	80.3 ± 9.2	912	78.9 ± 9.2
Change	641	0.4 ± 9.5	614	3.1 ± 9.4	912	2.6 ± 9.0
Pulse rate, bpm						
Baseline ^a	641	72.4 ± 9.5	614	72.7 ± 9.0	912	72.1 ± 9.0
End of Study	641	72.1 ± 9.5	614	79.3 ± 12.5	912	79.2 ± 11.2
Change	641	-0.3 ± 9.9	614	6.6 ± 12.1	912	7.1 ± 11.2

End-of-Study values are LOCF.

^a Baseline is defined as the last assessment before the first dose of study drug.

N = number of patients in the treatment group; n = subset of N for the category; LOCF = last observation carried forward.

(Source: Applicant's Table 8.1.1.1.1-1, Summary of Clinical Safety, Vol. 1, p. 151)

Dose-Controlled FM extension trials (FMS-034 and MLN-MD-04)

In the extension studies, more patients were assigned to the MLN 200 mg/day arm (n=323). Because of the lack of a placebo arm to allow an adequate safety comparison, I will focus on analyzing whether longer exposure to the MLN doses will affect the mean changes in blood pressure compared to the values obtained in each MLN treatment arm in the lead-in studies.

In the group of patients treated with MLN 200 mg/day in the lead-in study there was an increase in the mean change in supine SBP across all the treatment arms of the extension study. The mean

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change in supine SBP in the placebo controlled study was 3 mmHg and in the extension studies the changes are as follows:

- Placebo (lead-in)/ MLN 200 mg/day (extension study): 4.4 mmHg
- MLN 100 mg / MLN 200 mg/day: 4.2 mmHg
- MLN 200 mg / MLN 200 mg/day: 3.9 mm Hg

The data indicates that there is a small increase in the mean SBP with longer exposure. Among patients who continued on MLN treatment after 3-6 months in the Phase 3 efficacy trials, blood pressure increased by an additional 1-2 mmHg, on average. Among the 209 patients that received MLN 200 mg/day beyond 1 year, the mean change in supine SBP was 2.6 mm Hg, and for the 120 patients who were in the MLN 100 mg/200 mg/day arm the mean change in supine BP was 5.1 mmHg. The data indicates that there is no clear dose relationship but the mean change in SBP did slightly increase with time.

In terms of DBP, there was a difference in the mean changes in DBP in the extension studies. The mean change in supine DBP in the placebo controlled study was 2.6 mmHg and in the extension studies the changes are as follows:

- Placebo/ MLN 200 mg/day: 3.9 mmHg
- MLN 100 mg / MLN 200 mg/day: 3.1 mmHg
- MLN 200 mg / MLN 200 mg/day: 2.5 mm Hg

The data indicates that there is an increase in the DBP but there is no clear dose relationship. Among the 209 patients that received MLN 200 mg/day beyond 1 year, the mean change in supine DBP was 2.6 mm Hg and for the 120 patients who were in the MLN 100 mg/200 mg/day arm the mean change in supine BP was 3.3 mmHg. The data indicates that there is no clear dose relationship but the mean change in SBP did increase slightly with time.

For the patients who received MLN 100 mg/day in the lead-in study and remained at this dose during the extension study there was a decrease in the mean change in SBP and DBP. The mean changes in SBP and DBP at the end of the placebo-controlled study were 3.1 mmHg for both. At the end of the extension study the mean change in supine SBP was 0.2 mmHg and 1.1 for the DBP. Among the 25 patient that continued at this dose beyond 1 year the mean changes in SBP were 1.5 mmHg and 2.7 mmHg for the DBP.

- Analyses focused on outliers or shifts from normal to abnormal – Blood Pressure

Placebo-Controlled FM trials (FMS-031 and MLN-MD-02)

The Applicant provided a Response to FDA information request (letter date August 12, 2008) containing a shift table which presents the maximum changes from baseline in blood pressure.

Table 41 below indicates that more patients in the MLN treated arms had a shift upward in SBP from normal (<120 mmHg) to abnormal (>120 mmHg, including pre-hypertensive and hypertensive values):

- 52.28% of patients in the placebo arm versus

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- 64.75 % in the MLN 100 mg/day and
- 62.08 % in the MLN 200 mg/day treatment arms.

The table also shows the percent of patients who shifted in SBP from normal at baseline to pre-hypertension levels (SBP 120- 139mm Hg) and hypertension levels (SBP >140 mmHg):

- Percent of patients who shifted from normal to pre-hypertension levels: 46.67% for placebo versus 55.4% for MLN 100 mg/day and 56.59% for MLN 200 mg/day
- Percent of patients who shifted from normal to hypertension levels: 5.61% for placebo versus 9.35% MLN 100 mg/day and 5.49% MLN 200 mg/day

A higher proportion of patients that presented SBP at hypertension levels occurred in the MLN 100mg/day arm. The incidence of changes to SBP > 160 mmHg did not differ among the three treatment arms: 0.35% for placebo versus 0.36 in the MLN 100mg/day arm and 0% in the MLN 200 mg/day arm

Among all patients who were pre-hypertensive at baseline more patients in the MLN treatment arms had increases in BP to hypertensive levels compared to placebo: 33.46% in the placebo arm versus 41.17% in the MLN 100 mg/day arm and 36.58% in the MLN 200 mg/day arm.

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Table 41. Summary of Shifts from Baseline to Maximum Post-Baseline Value in Systolic Blood Pressure in Group 1AA

Maximum Post Baseline Value		Placebo(N=624)					Milnacipran 100 mg(N=623)					Milnacipran 200 mg(N=837)				
		Baseline					Baseline					Baseline				
		<=120	>120-<=140	>140-<=160	>160	<=120	>120-<=140	>140-<=160	>160	<=120	>120-<=140	>140-<=160	>160			
	M	285	275	51	4	278	272	61	3	364	391	61	4			
<=120	n	136	25	0	0	90	15	0	0	130	17	2	0			
	%=n/M	47.72	9.09			35.25	5.51			37.91	4.35	3.28				
>120-<=140	n	133	158	5	0	154	145	10	2	206	231	11	0			
	%=n/M	46.67	57.45	9.8		55.4	53.31	16.39	66.67	56.59	59.00	18.03				
>140-<=160	n	15	82	30	2	25	100	31	1	20	133	40	0			
	%=n/M	5.26	29.82	58.82	50	8.99	36.76	50.82	33.33	5.49	34.02	65.57				
>160	n	1	10	16	2	1	12	20	0	0	10	8	4			
	%=n/M	0.35	3.64	31.37	50	0.36	4.41	32.79			2.58	13.11	100			

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Note: Group 1AA: Double-blind, placebo-controlled, fibromyalgia studies consisting of all safety data collected in studies FUS031 and MLN-WD-02.

Only patients with available baseline and post baseline values are included in the analysis.

M: for each treatment M is number of patients who had both baseline and at least one post baseline values with baseline value in the specified interval.

Baseline is defined as the average value of assessments prior to first dose of double-blind study medication.

(Source: Applicant's Table 2, eCTD sequence 33, p.6)

In regard to the changes in the DBP, Table 42 below indicates that more patients in the MLN treated arms had a shift in DBP from normal values (≤ 80 mmHg) to abnormal values (> 80 mmHg, including pre-hypertensive and hypertensive values):

- 43.68 % of patients in the placebo arm versus
- 58.86 % in the MLN 100 mg/day and
- 56.02 % in the MLN 200 mg/day treatment arms.

The table also shows the percent of patients who had an increase in DBP from normal at baseline to pre-hypertension levels (DBP > 80 -90 mmHg) and hypertension (DBP > 90 mmHg):

- Percent of patients who shifted from normal to pre-hypertension values: 38.62% for placebo versus 36.95% for MLN 100 mg/day and 43.8% for MLN 200 mg/day
- Percent of patients who shifted from normal to hypertension values: 5.06% for placebo versus 15.74% MLN 100 mg/day and 9.49% MLN 200 mg/day

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Among all patients who had pre-hypertensive DBP at baseline, more patients in the MLN treatment arms presented DBP at hypertensive levels compared to placebo: 27.68% in the placebo arm versus 53.70% in the MLN 100 mg/day arm and 48.35% in the MLN 200 mg/day arm. The highest DBP values (> 100 mmHg) were observed in the MLN treatment arms: 0% in the placebo arm, versus 2.09% in the MLN 100 mg/day and 0.55% in the MLN 200 mg/day treatment arms. The data indicates that the incidence of hypertension was increased in patients with pre-hypertension.

Table 42. Summary of Shift from Baseline to Maximum Post-Baseline Value in Diastolic Blood Pressure

Maximum Post-Baseline Value	Placebo (N=624)						Milnacipran 100 mg (N=623)						Milnacipran 200 mg (N=637)					
	Baseline						Baseline						Baseline					
	<=80	>80-<=90	>90-<=100	>100-<=110	>110		<=80	>80-<=90	>90-<=100	>100-<=110	>110		<=80	>80-<=90	>90-<=100	>100-<=110	>110	
	M	435	159	21	0	0	394	203	16	1	0	548	242	29	1	0		
<=80	n	245	20	1	0	0	162	19	1	0	0	241	19	2	0	0		
	%n/M	56.32	12.58	4.76			41.12	9.36	6.25			43.98	7.85	6.9				
>80-<=90	n	168	95	6	0	0	170	75	0	0	0	255	106	6	0	0		
	%n/M	38.62	59.75	28.57			43.15	36.95				46.53	43.8	20.69				
>90-<=100	n	22	40	9	0	0	54	94	9	1	0	49	99	11	0	0		
	%n/M	5.06	25.16	42.86			13.71	46.31	56.25	100		8.94	40.91	37.93				
>100-<=110	n	0	3	3	0	0	7	13	5	0	0	3	14	7	0	0		
	%n/M		1.89	14.29			1.78	6.4	31.25			0.55	5.79	24.14				
>110	n	0	1	2	0	0	1	2	1	0	0	0	4	3	1	0		
	%n/M		0.63	9.52			0.25	0.99	6.25				1.65	10.34	100			

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Note: Group 1AA: Double-blind, placebo-controlled, fibromyalgia studies consisting of all safety data collected in studies FMS031 and MLN-WD-02.
Only patients with available baseline and post baseline values are included in the analysis.
M: for each treatment M is number of patients who had both baseline and at least one post baseline values with baseline value in the specified interval.
Baseline is defined as the average value of assessments prior to first dose of double-blind study medication.

(Source: Applicant's Table 3, eCTD sequence 33, p. 7)

Incidence of hypertension – Placebo-controlled FM studies

The following table presents another analysis of the percentage of patients who presented a change in hypertension status, using clinical and objective criteria. Normotensive patients at baseline treated with MLN had approximately a two-fold increase in clinical outcomes related to hypertension (TEAE or medication adjustment) as compared with placebo and the objective outcome of meeting the 140/90 mm Hg criterion for hypertension (HTN by BP) was increased 2.5-fold as compared to placebo.

Table 43. Change in Hypertension Status by Clinical and Objective Criteria for Normotensive Patients at Baseline

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

(Source: Table created by the reviewer based on data from the Applicant's Table 6.3.6.2.2-1, Vol. 4, p. 466)

The relative risk of having HTN by BP measurement in patients normotensive at baseline is 2.7 for the MLN 100 mg/day and 2.3 for the MLN 200 mg/day treatment arms.

- Marked outliers and dropouts for vital sign abnormalities – Blood Pressure

Placebo-Controlled FM trials (FMS-031 and MLN-MD-02)

The Applicant used data from only the studies FM-031 and MLN-MD-02 to calculate the percentage of patients with various magnitudes of change in supine blood pressure from baseline. Data from study FM-021 were excluded because the dose of MLN was flexible in this trial.

Overall, changes in supine systolic and diastolic blood pressure occurred more frequently in the MLN treatment groups than in the placebo group. Changes of ≥ 20 mm Hg systolic BP were observed in 4.4% of the MLN 100 mg/day treatment group and 3.3% of the MLN 200 mg/day treatment group compared with 1.5% in the placebo group. Although changes of ≥ 30 mm Hg SBP were observed in $< 1\%$ of the patients in the three treatment arms, this effect still occurred at a higher frequency in the MLN treatment arms.

Changes in the DBP for cut-offs of ≥ 5 mm Hg to ≥ 20 mm Hg also were observed at a higher frequency in the MLN treatment arms compared to placebo. Altogether, 1% of placebo patients had an increase in DBP of ≥ 15 mm, compared to 4-5% of MLN-treated patients. Less than 1% of patients across all groups had a DBP increase of ≥ 20 mm. A dose relationship for the changes in both SBP and DBP was not observed.

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Table 44. Increase in Supine Blood pressure by Magnitude of Change at End of the Study in Studies FM-031 and MLN-MD-02

Group	Placebo (N= 624)			Milnacipran 100 mg/d (N= 623)			Milnacipran 200 mg (N= 837)		
Total	M	n	%	M	n	%	M	n	%
Systolic blood pressure (mm Hg)									
Total	615			614			820		
Δ = ≥ 10		74	12.0		141	23.0		167	20.4
Δ = ≥ 20		9	1.5		27	4.4		27	3.3
Δ = ≥ 30		1	0.2		3	0.5		5	0.6
Δ = ≥ 40		0	0		0	0		0	0
Diastolic blood pressure (mm Hg)									
Total	615			614			820		
Δ = ≥ 5		109	17.7		223	36.3		281	34.3
Δ = ≥ 10		31	5.0		91	14.8		107	13.0
Δ = ≥ 15		6	1.0		31	5.0		33	4.0
Δ = ≥ 20		2	0.3		4	0.7		4	0.5
Δ = ≥ 25		0	0		2	0.3		0	0
Δ = ≥ 30		0	0		0	0		0	0

Δ = change from baseline; mm Hg = millimeters of mercury; M = number of patients with available baseline and end of study values; n = Number of patients (subset of M) in the category

Based on Studies FM031 and MLN-MD-02

(Source: Applicant's Table 6.3.4-1, Summary of Clinical Safety, Vol.4, p. 455)

In the Group 1A studies the proportion of patients who discontinued due to the adverse event PT "blood pressure increased" was 0.3 in the placebo arm versus 1% of the patients in the MLN 100 mg/day arm and 0.7% patients in the MLN 200 mg/day arm. (For further details, refer to Section 7.1.3.2 - Table 23 Incidence of AEs leading to DC of at least 1% of patients in the Placebo-controlled studies.)

- Additional analyses and explorations – Blood Pressure

Potentially clinically significant (PCS) vital signs – Placebo -Controlled FM studies

The Applicant also calculated potentially clinically significant (PCS) for vital sign values for the Group 1A studies. A vital sign value was considered potentially clinically significant (PCS) if the value met both the observed value criteria and the change from baseline criteria listed in Table 45. The percentages were calculated relative to the number of patients who had baseline and at least one post-baseline assessment. The numerator is the total number of patients who had at least one PCS post-baseline value.

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Table 45. Criteria for Potentially Clinically Significant Vital Signs

<i>Vital Sign Parameter</i>	<i>Flag</i>	<i>Criteria</i>	
		<i>Observed Value</i>	<i>Change From Baseline</i>
Systolic blood pressure (mm Hg)	High	≥ 180	Increase of ≥ 20
	Low	≤ 80	Decrease of ≥ 20
Diastolic blood pressure (mm Hg)	High	≥ 110	Increase of ≥ 10
	Low	≤ 50	Decrease of ≥ 15
Pulse rate (bpm)	High	≥ 120	Increase of ≥ 20
	Low	≤ 50	Decrease of ≥ 15
Weight	High	—	Increase of $\geq 7\%$
	Low	—	Decrease of $\geq 7\%$

a A postbaseline value was considered to be a PCS value if it meets both the observed value and change from baseline criteria.

bpm = beats per minute.

(Source: Applicant's Table 4.3.6.1-1, Summary of Clinical Safety, Vol. 1, p. 37)

The Applicant found that the only PCS vital sign values that occurred more frequently in the MLN treatment groups compared to placebo were:

- increases in supine DBP and pulse rate,
- increases and decreases in standing DBP and pulse rate
- decreases in body weight.

Overall the PCS vital sign abnormalities were not dose related. The incidence of all the abnormalities was $< 1\%$ except for:

- increase in supine pulse rate (1.1% in the MLN 100 mg/day versus 0% in the placebo group),
- increase in standing DBP (2% in the MLN 100 mg/day and 1.9% in the MLN 200 mg/day, versus 1.1% in the placebo group),
- increase in standing pulse rate (5.7% and 4.6% in the MLN 100 and 200 mg/day groups versus 0% in the placebo group)
- decrease in body weight (9.9% and 7.2% in the MLN 100 mg/day and 200 mg/day groups compared with 5.3% in the placebo group)

All the PCS vital sign abnormalities are presented below in Table 46.

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Table 46. Incidence of Potentially Clinically Significant Vital Sign Abnormalities in the FM Placebo Controlled Studies.

Vital Sign	Criteria		Placebo	Milnacipran	
			(N = 632)	100 mg (N = 623)	200 mg (N = 934)
			n/N ₁ (%)	n/N ₁ (%)	n/N ₁ (%)
SBP (supine)	≤ 80 mm Hg and decrease ≥ 20	Low	0	1/614 (0.2)	0
	≥ 180 mm Hg and increase ≥ 20	High	1/641 (0.2)	1/614 (0.2)	2/912 (0.2)
DBP (supine)	≤ 50 mm Hg and decrease ≥ 15	Low	7/641 (1.1)	3/614 (0.5)	1/912 (0.1)
	≥ 110 mm Hg and increase ≥ 15	High	2/641 (0.3)	5/614 (0.8)	8/912 (0.9)
PR (supine)	≤ 50 bpm and decrease ≥ 15	Low	2/641 (0.3)	0	0
	≥ 120 bpm and increase ≥ 20	High	0	7/614 (1.1)	3/912 (0.3)
SBP (standing)	≤ 80 mm Hg and decrease ≥ 20	Low	2/641 (0.3)	1/614 (0.2)	2/914 (0.2)
	≥ 180 mm Hg and increase ≥ 20	High	3/641 (0.5)	3/614 (0.5)	4/914 (0.4)
DBP (standing)	≤ 50 mm Hg and decrease ≥ 15	Low	1/641 (0.2)	1/614 (0.2)	6/914 (0.7)
	≥ 110 mm Hg and increase ≥ 15	High	7/641 (1.1)	12/614 (2.0)	17/914 (1.9)
PR (standing)	≤ 50 bpm and decrease ≥ 15	Low	1/641 (0.2)	2/614 (0.3)	1/913 (0.1)
	≥ 120 bpm and increase ≥ 20	High	0	35/614 (5.7)	42/913 (4.6)
Weight	Decrease ≥ 7%	Low	34/643 (5.3)	61/614 (9.9)	66/914 (7.2)
	Increase ≥ 7%	High	21/643 (3.3)	16/614 (2.6)	27/914 (3.0)

N = number of patients in treatment group; N₁ = number of patients with nonmissing baseline assessment and at least one postbaseline assessment; n = number of patients (subset of N₁) who had at least one PCS postbaseline assessment; SBP = systolic blood pressure; DBP = diastolic blood pressure; bpm = beats per minute; PR = pulse rate.

(Source: Applicant's Table 8.1.1.1.2-1, Summary of Clinical Safety, Vol. 1, p. 153)

Changes of Clinical Interest in Vital Signs – Placebo-Controlled FM studies

A more stringent analysis of the changes in BP than the PCS analysis was the evaluation of patients with changes of clinical interest in BP. The Applicant calculated the percentages of patients in each group that that were changes of clinical interest (CCI) for blood pressure, as defined in the table below:

Table 47. Criteria of Interest for Blood Pressure

Parameter	Criteria	
	Observed Value	Change from Baseline
SBP (mmHg)	≥ 140	≥ 20
DBP (mmHg)	≥ 90	≥ 10
SBP and DBP	SBP ≥ 140 and DBP ≥ 90	SBP ≥ 20 and DBP ≥ 10

(Source: Applicant's Table 10.1-2, Summary of Clinical Safety, Vol. 2, p. 26)

As shown in Table 48, more patients in the MLN treatment arms became hypertensive by CCI criteria than in the placebo group: 11-12% of patients in the MLN arms had a SBP > 140 mmHg

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compared to 8% of placebo patients. Similarly, 7-10% of MLN patients had a DBP > 90 mmHg versus 3% of placebo patients.

Table 48. Patients with Changes of Clinical Interest in Blood Pressure in FMS-031 and MLN-MD-02

	Placebo	Milnacipran 100 mg	Milnacipran 200 mg
End of Study ^a Value	(M = 615)	(M = 614)	(M = 820)
SBP > 140 mm Hg [n, (%)]	51 (8)	74 (12)	89 (11)
Δ SBP \geq 15 mm Hg [n, (%)]	27 (4)	58 (9)	70 (9)
DBP > 90 mm Hg [n, (%)]	17 (3)	60 (10)	61 (7)
Δ DBP \geq 10 mm Hg [n, (%)]	31 (5)	91 (15)	107 (13)
Sustained Increases	(N ₁ = 501)	(N ₁ = 459)	(N ₁ = 611)
SBP ^b [n, (%)]	12 (2)	39 (9)	35 (6)
DBP ^c [n, (%)]	19 (4)	59 (13)	61 (10)

a End of study = last visits (up to 3)

b Sustained increase SBP = Δ SBP \geq 15 mm Hg on 3 consecutive visits

c Sustained increase DBP = Δ DBP \geq 10 mm Hg on 3 consecutive visits.

Δ = change from baseline; DBP = diastolic blood pressure; M = patients with a baseline and an end-of-study assessment.

mm Hg = millimeters of mercury; N₁ = patients with non-missing baseline value and at least 3 consecutive postbaseline assessments; SBP = systolic blood pressure.

(Source: Applicant's Table 6.3.5-1, Clinical Summary of Safety, Vol. 4, p. 456)

Sustained hypertension – Placebo-controlled FM studies

The Applicant also analyzed the BP data for the incidence of sustained hypertension, which was defined as BP that met the criteria delineated in Table 49 on at least three consecutive post-baseline visits. Blood pressure recordings involved single measurements in patients in both the supine and standing positions.

Table 49. Criteria for Determining Sustained Hypertension

Vital Sign Parameter	Flag	Criteria	
		Observed Value	Change From Baseline
Systolic blood pressure (mm Hg)	High	≥ 140	≥ 20
Diastolic blood pressure (mm Hg)	High	≥ 90	≥ 10

a A postbaseline value had to meet both the observed value and change from baseline criteria to be considered a value of interest.

(Source: Applicant's Table 4.3.6.1-2, Clinical Summary of Safety, Volume 1, p. 38)

Table 50 below presents the distribution of patients that meet the requirements above. The table demonstrates that sustained increases in blood pressure did occur more frequently in the MLN treatment arms and it does not seem to be dose related. The proportion of patients who met the

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criteria above was 0.3% in the placebo arm versus 0.7% in the MLN 100 mg/day and 0.5% in the MLN 200 mg/day treatment arms.

Table 50. Number of Patients with Sustained Hypertension- FM Placebo Controlled Studies

	Placebo (N= 652) n/N _i (%)	Milnacipran ^a		
		100 mg/d (N= 623) n/N _i (%)	200 mg/d (N= 934) n/N _i (%)	Total MLN (N= 1557) n/N _i (%)
Sustained Supine Blood Pressure (mm Hg)				
1. SBP ≥ 140 and increase of ≥ 20 from Baseline	0	6/614 (1.0)	9/912 (1.0)	15/1526 (1.0)
2. DBP ≥ 90 and increase of ≥ 10 from Baseline	1/641 (0.2)	22/614 (3.6)	13/912 (1.4)	35/1526 (2.3)
3. Patients satisfying both criteria 1 and 2, above	0	2/614 (0.3)	6/912 (0.7)	8/1526 (0.5)

a The data came from the pooled placebo-controlled fibromyalgia syndrome studies FMS021, FMS031 and MLN-MD-02.

DBP = diastolic blood pressure; MLN = milnacipran; mm Hg = millimeters of mercury; N_i = number of patients with non-missing baseline assessment and at least one post-baseline assessment; n = Number of patients who met the criteria on at least 3 consecutive measurements at all scheduled postbaseline visits; SBP = systolic blood pressure.

(Source: Table 6.3.5-2, Summary of Clinical Safety, Vol. 4, p.457)

- Analyses focused on measures of central tendencies – Heart Rate

As presented in Table 51 below the mean increase in pulse rate was higher in the MLN treatment arms and the values indicate a relationship between increased pulse rate (PR) and MLN dose. There was a mean increase of 6.6 bpm for the MLN 100 mg/day and 7.1 bpm for the MLN 200 mg/day groups compared with a decrease of -0.3 bpm in the placebo group.

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Table 51. Changes from Baseline in Supine Vital Signs at the End-of-Study Visit in the Placebo-Controlled FM-Studies

Parameter	Placebo N = 652		Milnacipran			
			100 mg/d N = 623		200 mg/d N = 934	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Systolic blood pressure, mm Hg						
Baseline ^a	641	122.1 ± 14.5	614	122.8 ± 14.5	912	121.7 ± 14.1
End of Study	641	122.0 ± 14.5	614	126.0 ± 14.5	912	124.7 ± 14.3
Change	641	-0.1 ± 13.7	614	3.1 ± 14.0	912	3.0 ± 12.9
Diastolic blood pressure, mm Hg						
Baseline ^a	641	75.9 ± 9.1	614	77.2 ± 8.9	912	76.3 ± 8.5
End of Study	641	76.3 ± 9.2	614	80.3 ± 9.2	912	78.9 ± 9.2
Change	641	0.4 ± 9.5	614	3.1 ± 9.4	912	2.6 ± 9.0
Pulse rate, bpm						
Baseline ^a	641	72.4 ± 9.5	614	72.7 ± 9.0	912	72.1 ± 9.0
End of Study	641	72.1 ± 9.5	614	79.3 ± 12.5	912	79.2 ± 11.2
Change	641	-0.3 ± 9.9	614	6.6 ± 12.1	912	7.1 ± 11.2

End-of-Study values are LOCF.

^a Baseline is defined as the last assessment before the first dose of study drug.

N = number of patients in the treatment group; n = subset of N for the category; LOCF = last observation carried forward.

(Source: Applicant's Table 8.1.1.1.1-1, Summary of Clinical Safety, Vol. 1, p. 151)

- Analyses focused on outliers or shifts from normal to abnormal – Heart Rate

Placebo-Controlled FM trials (FMS-031 and MLN-MD-02)

The Applicant provided a Response to FDA information request (letter date August 12, 2008) containing a shift table which presents the maximum changes in pulse rate from baseline.

Table 52 below shows the percent of patients who had an increase in PR from normal values (<100 bpm):

- Percent of patients who had an increase in PR from normal to > 100 bpm:
 - 0.81% for placebo versus
 - 14.50% for MLN 100 mg/day and
 - 11.84% for MLN 200 mg/day
- Percent of patients who had PR values > 120 bpm:
 - 0% for placebo versus
 - 0.49% MLN 100 mg/day and
 - 0.37% MLN200 mg/day

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The table also indicates that more patients in the MLN treated arms had a shift in PR from normal (< 100 bpm) to abnormal (> 100 bpm) and the greatest increases also occurred in the MLN treatment arms. There does not seem to be a dose relationship in the increased of PR.

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

Maximum Post Baseline Value	Placebo (N=624)					Milnacipran 100 mg(N=623)					Milnacipran 200 mg(N=637)				
	Baseline					Baseline					Baseline				
	<=100	>100-<=110	>110-<=120	>120	<=100	>100-<=110	>110-<=120	>120	<=100	>100-<=110	>110-<=120	>120			
	M	614	1	0	0	614	0	0	0	820	0	0	0		
<=100	n	809	1	0	0	525	0	0	0	723	0	0	0		
	%=n/M	99.19	100			85.5				88.17					
>100-<=110	n	4	0	0	0	63	0	0	0	75	0	0	0		
	%=n/M	0.65				10.26				9.15					
>110-<=120	n	1	0	0	0	23	0	0	0	19	0	0	0		
	%=n/M	0.16				3.75				2.32					
>120	n	0	0	0	0	3	0	0	0	3	0	0	0		
	%=n/M					0.49				0.37					

Note: Group 1AA: Double-blind, placebo-controlled, fibromyalgia studies consisting of all safety data collected in studies FMS031 and MLN-MD-02.
Only patients with available baseline and post baseline values are included in the analysis.
M: for each treatment M is number of patients who had both baseline and at least one post baseline values with baseline value in the specified interval.
Baseline is defined as the average value of assessments prior to first dose of double-blind study medication.

(Source: Applicant's Table 4, eCTD sequence 33, p. 8)

Overall, changes in PR occurred more frequently in the MLN treatment groups than in the placebo group. Table 53 below provides the different magnitudes of shifts in PR which confirms the data from the shift table that more changes occur in the MLN treatment arms compared with placebo. Increases of PR >30 bpm were noted only in the MLN treated arms and again there seems that there is no significant difference in the increases of heart rate with the highest MLN dose.

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Table 53. Changes in Supine Pulse Rate at the End-of-Study in FMS-031 and MLN-MD-02

Group	Placebo			Milnacipran 100 mg/d			Milnacipran 200 mg/d		
	M	n	% (n/M)	M	n	% (n/M)	M	n	% (n/M)
Group 1AA	615			614			820		
Δ ≥ 0 bpm		317	52		498	81		676	82
Δ ≥ 10 bpm		42	7		208	34		330	40
Δ ≥ 20 bpm		2	0.3		47	8		68	8
Δ ≥ 30 bpm		0	0		7	1		9	1

M = number of patients with available baseline and End-of-Study values. Δ = change from baseline.

End-of-Study Values are based on at least 1 postbaseline assessment or the average of up to 3 postbaseline assessments if available.

(Source: Applicant's Table 6.5.1.2-1, Summary of Clinical Safety, Vol. 4, p.478)

- Marked outliers and dropouts for vital sign abnormalities – Heart Rate

The distribution of the pulse rate at the end of the study is presented in Table 54 below. The data indicates that at the end of the study more patients in the MLN treatment arms had PR > 100 bpm compared with placebo: 0% placebo versus 3% MLN 100 mg/day and 2% MLN 200 mg/day. None has PR > 120 bpm at the end of the study.

Table 54. Distribution of pulse Rate at End of Study- FMS031 and MLN-MD-02

Group	Placebo (N = 624)			Milnacipran 100 mg/d (N = 623)			Milnacipran 200 mg/d (N = 837)		
	M	n	% (n/M)	M	n	% (n/M)	M	n	% (n/M)
GROUP 1AA	615			614			820		
≤ 60 bpm		40	7		12	2		11	1
> 60 – ≤ 80 bpm		493	80		325	53		431	53
> 80 – ≤ 100 bpm		82	13		261	42		359	44
> 100 – ≤ 120 bpm		0	0		16	3		19	2
> 120 bpm		0	0		0	0		0	0

bpm = beats per minute; M = number of patients with available baseline and end of study values; n = Number of patients in the category.

(Source: Applicant's Table 6.5.1.1-1, Summary of Clinical Safety, Vol. 4, p. 478)

In the Group 1A studies the proportion of patients who discontinued due to the increases in heart rate was as follows:

- For the PT “heart rate increased”: 0.2% in the placebo arm versus 0.3% of the patients in the MLN 100 mg/day arm and 1.7% of patients in the MLN 200 mg/day arm
- For the PT “tachycardia”: 0% placebo in the placebo arm versus 1.0% in the MLN 100mg/day arm and 0.6% in the MLN 200 mg/day treatment arm.

For further detail refer to Section 7.1.3.2 - Table 23. Incidence of AEs Leading to DC of at Least 1% of Patients in the Placebo-controlled Studies

- Additional analyses and explorations – Heart Rate

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Changes of Clinical Interest in Heart Rate – Placebo -Controlled FM studies

The incidence of changes of clinical interest in pulse rate (HR > 100 bpm or change $\geq 20\%$) was higher in the MLN treatment arms (9-10%) compared to the placebo arm (0.5%), as presented below in the Table 55.

Table 55. Patients with Changes of Clinical Interest in Pulse Rate in Studies FMS-031 and MLN-MD-02

	Placebo (N = 624)	Milnacipran 100 mg/d (N = 623)	Milnacipran 200 mg/d (N = 837)
Heart rate > 100 bpm or $\Delta \geq 20$ bpm at end of study [n, (%)]	(M = 615) 3 (0.5)	(M = 614) 56 (9)	(M = 820) 78 (10)
Sustained increase in heart rate during study [n, (%)]	(M = 501) 1 (0.2)	(M = 459) 35 (8)	(M = 611) 63 (10)

Δ = change from baseline. M = number of patients with available baseline and end of treatment values; n = number of patients in the category.

Sustained increases refer to at least 32 consecutive postbaseline measurements

(Source: Applicant's Table 6.5.1.3-1, Clinical Summary of Safety, Vol. 4, p. 479)

Orthostatic Hypotension

The mean changes in standing vital signs in the Phase 3 placebo-controlled FM trials were similar to the ones observed in the supine VS parameters:

- mean SBP increase of 2.4 and 1.8 mm Hg in the MLN 100mg/day and 200 mg/day treatment arms respectively compared to a decrease of -0.2 mmHg in the placebo arm
- mean DBP increase of 2.3 mmHg in both MLN treatment arms compared to 0.4 in the placebo arm
- mean PR increase of 6.4 bpm and 6.8 bpm in the MLN 100mg/day and 200 mg/day treatment arms respectively compared to 0.1 bpm in the placebo arm

Body Weight

In terms of differences in weight at the end of the study from baseline, the use of MLN was associated with a reduction in body weight. The mean change in body weight was -0.2 kg in the placebo group compared with -0.8 kg in both MLN treatment groups.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG data in the FM studies were collected only in studies MLN-MD-02 and the extension study MLN-MD-04. ECG data were not collected in Study FMS031 and in the non-FM placebo-

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controlled studies. In Study MLN-MD-02, 12-lead ECGs were collected at baseline and at Tx 15 (or Tx 29) or early termination visit. The ECGs were transmitted for analysis according to instructions of the central interpretation laboratory

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7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The Applicant provided descriptive statistics for ECG parameters (e.g., PR interval, QRS interval, QT interval, and QTc interval) at baseline and change from baseline to end of study. The QTc interval was calculated using Bazett's and Fridericia methods.

7.1.9.3 Standard analyses and explorations of ECG data

- Analyses focused on measures of central tendency

The following table presents the mean changes from baseline in electrocardiographic parameters at end-of- study for MLN-MD-02. The only notable difference between MLN and placebo observed was the increase in heart rate that occurred in the MLN treatment arms (7.2 ± 11.2 bpm for MLN 100 mg/day and 7.3 ± 10.6 bpm for MLN 200 mg/day compared to -2.4 ± 8.2 bpm in the placebo group).

There was a increase in the mean QTc interval among the MLN groups when the Bazzett method was used (-1.8 ± 20.7 msec in the placebo group versus 6.3 ± 22 msec in the MLN 100 mg/day and 6.8 ± 21.9 msec in the MLN 200 mg/day treatment groups) with no dose relationship between the MLN treatment groups. When the QTc interval was corrected using the Fridericia formula there was no change in the mean QTc interval from baseline for the MLN treatment groups.

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Table 56. Changes from Baseline in ECG Parameters at the End of Study for MLN-MD-02

Parameter	Placebo N = 401		Milnacipran			
			100 mg/d N = 399		200 mg/d N = 396	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Heart rate, bpm						
Baseline	360	70.1 ± 10.5	355	71.4 ± 10.5	359	71.0 ± 10.8
End of Study	360	67.7 ± 10.6	355	78.6 ± 12.1	359	78.4 ± 11.9
Change	360	-2.4 ± 8.2	355	7.2 ± 11.2	359	7.3 ± 10.6
QRS interval, msec						
Baseline	360	88.0 ± 11.6	355	87.7 ± 11.3	359	88.7 ± 11.3
End of Study	360	86.8 ± 11.6	355	85.5 ± 10.8	359	87.3 ± 12.4
Change	360	-1.2 ± 11.5	355	-2.2 ± 10.5	359	-1.4 ± 11.1
PR interval, msec						
Baseline	360	153.4 ± 23.9	355	154.6 ± 21.2	359	153.0 ± 22.3
End of Study	360	155.2 ± 24.3	355	148.1 ± 18.6	359	146.1 ± 20.3
Change	360	1.8 ± 14.0	355	-6.5 ± 15.3	359	-6.8 ± 14.6
QT interval, msec						
Baseline	360	382.6 ± 27.1	355	383.7 ± 28.1	359	383.3 ± 27.5
End of Study	360	388.0 ± 27.0	355	371.6 ± 27.9	359	371.1 ± 28.2
Change	360	5.4 ± 23.0	355	-12.1 ± 25.1	359	-12.2 ± 24.3
RR interval, msec						
Baseline	360	874.1 ± 127.8	355	858.8 ± 125.4	359	864.1 ± 131.5
End of Study	360	907.7 ± 139.4	355	782.2 ± 123.1	359	784.3 ± 125.2
Change	360	33.6 ± 106.6	355	-76.5 ± 121.4	359	-79.8 ± 124.0
QTcB interval, msec						
Baseline	360	411.0 ± 21.8	355	415.7 ± 22.6	359	414.2 ± 22.0
End of Study	360	409.2 ± 22.4	355	422.1 ± 22.5	359	421.0 ± 22.0
Change	360	-1.8 ± 20.7	355	6.3 ± 22.0	359	6.8 ± 21.9
QTcF interval						
Baseline	360	401.1 ± 19.5	355	404.5 ± 20.5	359	403.4 ± 19.5
End of Study	360	401.8 ± 19.3	355	404.2 ± 19.9	359	403.4 ± 19.8
Change	360	0.7 ± 18.4	355	-0.3 ± 18.4	359	0.0 ± 18.3

N = number of patients in treatment group; n = subset of N for the category; bpm = beats per minute;
QTcB = corrected QT interval based on Bazett's correction formula; QTcF = corrected QT interval based on
Fridericia's correction formula.

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(Source: Applicant's Table 12.5.1-1, MLN-MD-02 Clinical Study Report, Vol. 1, p. 157)

The ECG parameters were considered to be Potentially Clinically significant if they met or exceeded the ULN values listed in Table 57 below.

Table 57. Criteria for Potentially Clinically Significant ECG Parameters

<i>ECG Parameter</i>	<i>Unit</i>	<i>Low Limit</i>	<i>High Limit</i>
QRS interval	msec	—	≥ 150
PR interval	msec	—	≥ 250
QTc interval	msec	—	≥ 500

(Source: Applicant's Table 4.3.6.2-1, Summary of Clinical safety, Vol. 1, p. 39)

- Analyses focused on outliers or shifts from normal to abnormal

The Applicant provided upon request tables of shift from baseline to the end of study for ECG parameters including QT intervals.

The Fridericia correction method was selected for use for the construction of the tables. There were basically no changes from normal baseline to abnormal, in the ECGs that were more frequent in the MLN treatment arms than placebo. There were no shifts in the QT intervals for male or females or QTcF for males. Only one female shifted from normal baseline QTcF to QTcF 470- < 500 (0.29%).

Below are the shift tables with changes in PR intervals and QRS intervals from baseline to end of Study MLN-MD-02.

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Table 58. Summary of Shift from Baseline to End of Study in QRS- Study MLN-MD-02

End of Study		Placebo (N=624)			Milnacipran 100 mg (N=628)			Milnacipran 200 mg (N=637)		
		Baseline			Baseline			Baseline		
		<=120	>120-<150	>=150	<=120	>120-<150	>=150	<=120	>120-<150	>=150
	N	357	3	0	353	2	0	356	2	1
<= 120	n	355	0	0	352	0	0	354	0	0
	%=n/M	99.44			99.72			99.44		
>120 - <150	n	2	3	0	1	2	0	2	1	0
	%=n/M	0.55	100		0.29	100		0.55	50	
>= 150	n	0	0	0	0	0	0	0	1	1
	%=n/M								50	100

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Note: Group 1AA: Double-blind, placebo-controlled, fibromyalgia studies consisting of all safety data collected in Studies FMS031 and MLN-MD-02.

Only patients with available baseline and End of Treatment values are included in the analysis.

N: for each treatment N is number of patients who had both baseline and End of Treatment values with baseline value in the specified interval.

Baseline is defined as assessments prior to first dose of double-blind study medication.

End of Treatment is the scheduled assessment at the end of the double-blind treatment period of the study.

(Source: Applicant's Table 4, Response to Information Request, eCTD 28, p. 38)

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Table 59. Summary of Shift from Baseline to End of Study in PR- Study MLN-MD-02

End of Study		Placebo (N=624)			Milnacipran 100 mg (N=623)			Milnacipran 200 mg (N=637)		
		Baseline ≤200	Baseline >200-≤250	Baseline >250	Baseline ≤200	Baseline >200-≤250	Baseline >250	Baseline ≤200	Baseline >200-≤250	Baseline >250
	N	345	14	0	348	7	0	349	10	0
≤ 200	n	339	4	0	347	2	0	348	5	0
	%n/N	97.98	28.57		99.71	28.57		99.71	50	
>200 - ≤250	n	7	9	0	1	5	0	1	5	0
	%n/N	2.02	64.29		0.29	71.43		0.29	50	
> 250	n	0	1	0	0	0	0	0	0	0
	%n/N		7.14							

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Note: Group 1AA: Double-blind, placebo-controlled, fibromyalgia studies consisting of all safety data collected in Studies FMS031 and MLN-MD-02.

Only patients with available baseline and End of Treatment values are included in the analysis.

N: for each treatment N is number of patients who had both baseline and End of Treatment values with baseline value in the specified interval.

Baseline is defined as assessments prior to first dose of double-blind study medication.

End of Treatment is the scheduled assessment at the end of the double-blind treatment period of the study.

(Source: Applicant's Table 5, Response to Information Request, eCTD 28, p. 39)

- Marked outliers and dropouts for ECG abnormalities

Two patients in Study MLN-MD-02 had met criteria for PCS abnormalities:

- Patient # 25914, placebo arm: had a PR interval of 276 msec at the end of the study, up from 238 at baseline
- Patient # 28121, MLN 200 mg/day arm: had a QRS interval of 157 msec at the end of the study from 137
- Patient # 23601, MLN 200 mg/day arm: had a QRS interval of 156 msec at end of study from 167 at baseline

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There were eight patients with clinically significant ECG abnormalities: 3 in the placebo arm, 2 in the MLN 100 mg/day arm and 3 in the MLN 200 mg/day arm. The table below summarizes the list of patients with clinically significant abnormalities.

Table 60. List of Patients with Post-Baseline Clinically Significant Abnormalities

Treatment Group	Patient ID	Study Center	Age/Sex/Race	Date of First/Last Dose of Study Drug	Baseline Date	Baseline Result	Final/Last Result	Final/Last Assessment Date	Comments
Placebo	21420	214	64/Female/White	21MAR05/27JUL05	2005-03-10	Abnormal, NCS	Abnormal, CS	2005-07-28	EKG CHANGES T WAVE INVERSION NEEDS CARDIOLOGY EVALUATION
	21831	218	39/Female/White	28AUG06/10DEC06	2006-08-10	Normal	Abnormal, CS	2006-12-11	ABNORMAL EKG FOLLOWED UP BY A 24-HOUR HOLTER MONITOR-TO BE FOLLOWED BY TREADMILL
	29010	290	47/Female/Other	18AUG06/11DEC06	2006-08-08	Abnormal, NCS	Abnormal, CS	2006-12-11	PROLONGED QT INTERVAL
Milnacipran 100 mg	25911	259	53/Female/White	17AUG05/08MAR06	2005-08-03	Abnormal, NCS	Abnormal, CS	2006-03-08	PROLONGED QTC INTERVAL FROM BASELINE REPEAT EKG AT VISIT LATER THIS WEEK TO SEE IF STABLE
	27009	276	44/Female/White	22JUN06/10AUG06	2006-06-12	Normal	Abnormal, CS	2006-08-11	NEG T WAVES PER CHEST PAIN -AE
Milnacipran 200 mg	24339	243	66/Female/White	21JUL05/10AUG05	2005-08-30	Abnormal, NCS	Abnormal, CS	2005-08-11	LEFT BUNDLE BRANCH BLOCK
	25901	259	47/Female/White	03MAY05/18NOV05	2005-04-12	Normal	Abnormal, CS	2005-11-18	SINUS TACHYCARDIA
	29004	290	61/Male /White	13JUL06/09AUG06	2006-06-26	Abnormal, NCS	Abnormal, CS	2006-08-18	WORSENING OF PATTERN OF ANTEROLATERAL ISCHEMIA SENDING COPY OF ASSESSMENT TO HIS CARDIOLOGIST

Note: Baseline is defined as the last non-missing assessment prior to first dose of double-blind medication.

CS = Clinically significant, NCS = Abnormal, not clinically significant.

Center 243 utilized all available patient numbers and was assigned another Center number, 296, to accommodate the large number of patients screened.

(Source: Applicant's Table 14, Clinical Study Report, Study MLN-MD-02, Vol. 1, p. 2100)

7.1.9.4 Additional analyses and explorations

No additional analyses were performed.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

The preclinical studies indicate that milnacipran is not carcinogenic.

7.1.12 Special Safety Studies

The Applicant conducted a through QT study (Study MLN-PK-10) in 100 healthy volunteers using MLN 300 mg BID with a double-blind, placebo and active-controlled, parallel-group, multiple-dose study.

The Applicant concluded that milnacipran is unlikely to cause QT prolongation because the maximum increase in $\Delta\Delta Q_{TcNi}$ was -5 (-9.4, -0.08). The IRT-QT review team did not concur with these results and based on another correction method (Fridericia) QT_{cF} , the mean increase $\Delta\Delta QT_{cF}$ is 7.7 (3.5, 12.0). In addition, the IRT-QT team also considered that the study design was suboptimal to demonstrate the QT effect of milnacipran because it did not have a concurrent moxifloxacin control arm. Because moxifloxacin was double encapsulated, the exposure to moxifloxacin might have also been lower than expected. The IRT-QT team recommends that the Applicant repeat the TQT study incorporating the additional elements listed below:

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

Please also refer to Section 5.2 (Pharmacodynamics.)

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The pre-clinical program for MLN included abuse liability potential studies in monkey models. According to the Applicant, MLN did not cause psychological dependence liability in drug-naïve monkeys through self-administration of drug (lever-press conditioning test) or drug-seeking behavior after injections. Piloerection (mild withdrawal sign) was noticed in one of four animals upon discontinuation of the drug after four weeks of dosing and after another 4-week dosing period two of four animals had piloerection and apprehension (mild withdrawal signs). Other non-classified signs were noted in all animals such as agitation, cage biting, vocalization, grooming and scratching. Another test in which a benzodiazepine-receptor antagonist was injected after 24 days of treatment with MLN caused one MLN-treated monkey to present mild withdrawal signs such as ptosis, piloerection, mydriasis, dozing. This test was repeated after

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another 24-day treatment period and three of four animals presented piloerection and the fourth animal had no signs of withdrawal.

The abuse potential in humans was evaluated by the Applicant by assessing AEs from clinical trials and spontaneous reports. There were no reports of drug abuse neither in the FM clinical trials nor in the database. The European label provided does not have specific information regarding physical dependence but it recommends gradual discontinuation of the drug. In respect to abuse potential it mentions that a few cases of overdosage have been observed with MLN. There is no information in the Japanese label regarding these issues.

The Controlled Substance Staff (CSS) concluded that MLN can induce physical dependence based on the presence of a withdrawal syndrome in non-fibromyalgia patients following MLN discontinuation. In their opinion, the Applicant provided insufficient information to adequately assess the abuse potential of MLN. CSS recommends the Applicant conduct the following studies:

- A receptor binding study with F-2800, the N-desethyl metabolite of milnacipran. If the receptor binding study demonstrates significant binding at sites associated with abuse potential, then animal abuse studies will need to be conducted with the metabolite.
- An appropriately-designed self-administration study with MLN should be conducted in rats or monkeys including a drug with known abuse potential as a positive control.
- A human abuse potential study may be required depending on the results of the self-administration study and the metabolite study.
- A prospective human physical dependence study in FM patients to characterize the withdrawal syndrome that occurs following discontinuation of MLN.

7.1.14 Human Reproduction and Pregnancy Data

The Applicant provided the outcomes of 50 pregnancies reported. Twelve of the cases occurred among patients enrolled in non-FM trials and the remaining are spontaneous reports from France and Japan and post-marketing cases from Japan.

- 7 reports of spontaneous abortions
- 2 reports of therapeutic abortions
- 2 reports of complications during pregnancy
- 8 reports of elective abortions
- 3 reports of transient neonatal complications after delivery
- 13 reports of normal pregnancies and healthy infants
- 15 cases in which the final outcome remains unknown

There are no published cases of AEs associated with MLN exposure during pregnancy or breastfeeding. The language foreign label states that there are no data showing teratogenic or fetotoxic effects of MLN when administered in pregnancy and "in the absence of demonstrated teratogenic effects in animals, malformations in humans are not expected."

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The Applicant submitted a spontaneous report received by the French Health Authorities describing a case of fetal exposure to MLN during pregnancy. The mother (age not specified) had anorexia and depression, and was treated with MLN during her entire pregnancy, clobazepam at therapeutic doses (unknown length of treatment) and bromazepam (unknown dose and length of treatment). At one-day post birth this child was described as born with microcephaly, clinodactily and dysmorphic facial features (oblique palpebral cleft and elongated philtrum). The report does not mention the child's gestational age. The birth weight was 1335 grams and length 42.5cm. The case reported that at age 29-months, the child had "intellectual tardiness"

7.1.15 Assessment of Effect on Growth

This submission does not contain any assessments of the effect of this drug on growth as the Applicant was granted a deferral to conduct pediatric studies until after approval of this new molecular entity in adults.

7.1.16 Overdose Experience

There were no reports of milnacipran overdose in US fibromyalgia studies.

There were three cases of milnacipran overdose reported in the post-marketing experience (major depression) database and they were coded as intentional overdose, non-accidental overdose and multiple-drug overdose. There were also 9 reports that were coded as suicide attempt, totaling 12 cases of overdose. The patients' ages ranged from 19 to 49 years, 7 females and 4 males (1 patient had incomplete information). According to the information available the doses ranged from 250 mg to 1g. Eleven patients recovered and there was no outcome information for one patient. Five of the cases involved milnacipran alone and in 7 of the cases the patients took multiple-drug overdoses involving mainly benzodiazepines.

The symptoms noted on the patients that took milnacipran alone were: unresponsiveness (1), increased BP (1), tachycardia (2), apneic spells (1), shallow respirations (1), vomiting (2), increased bilirubin (1), and fever (1).

7.1.17 Postmarketing Experience

Please refer to Section 7.2.2.2 for this reviewer's evaluation of the post-marketing experience in foreign countries.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Refer to Section 7.1 for a description of the clinical data sources used to evaluate safety.

The primary safety data sources were the Phase 2 (FMS-021) and Phase 3 (FMS-031, FMS-034, MLN-MD-02, and MLN-MD-04) trials in fibromyalgia patients.

7.2.1.1 Study type and design/patient enumeration

Refer to the tables in Section 1.3.1 (Brief Overview) for a tabular listing of the clinical trials in this NDA.

7.2.1.2 Demographics

The table below summarizes the demographic characteristics of the patients in the pooled Phase 3 efficacy studies. The vast majority of enrolled patients were female, with a mean age of 50 years. They had moderate pain at baseline (approximately 66 mm on a 100 mm VAS).

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Table 61. Key Demographic Characteristics – Studies FMS-031 and MLN-MD-02

Table 3.2-2. Pooled Pivotal Studies—Demographic and Baseline Characteristics (ITT Population)

Parameter	Placebo (N = 624)	Milnacipran		Total (N = 2084)
		100 mg/d (N = 623)	200 mg/d (N = 837)	
Age, y				
Mean (SD)	50.2 (10.3)	49.7 (10.8)	49.8 (10.8)	49.9 (10.7)
Age group, n (%)				
< 60	517 (82.9)	495 (79.5)	683 (81.6)	1695 (81.3)
≥ 60	107 (17.1)	128 (20.5)	154 (18.4)	389 (18.7)
Sex, n (%)				
Male	31 (5.0)	23 (3.7)	30 (3.6)	84 (4.0)
Female	593 (95.0)	600 (96.3)	807 (96.4)	2000 (96.0)
Race, n (%)				
Caucasian (white)	586 (93.9)	583 (93.6)	780 (93.2)	1949 (93.5)
Non-Caucasian	38 (6.1)	40 (6.4)	57 (6.8)	135 (6.5)
Weight (lb)				
Mean (SD)	183.2 (43.4)	179 (41.9)	180.3 (43.2)	181.0 (42.9)
Baseline BDI				
Mean (SD)	13.9 (9.2)	13.5 (8.3)	14.4 (8.6)	14.0 (8.7)
Baseline pain				
Mean (SD)	66.7 (13.0)	65.9 (12.9)	67.1 (13.0)	66.6 (13.0)
Baseline SF-36 PCS				
Mean (SD)	31.8 (7.6)	31.5 (7.5)	31.9 (7.7)	31.8 (7.6)

BDI = Beck Depression Inventory; ITT = Intent-to-Treat; N = population size; n = number of responders within a group; SF-36 PCS = Short Form-36 Physical Component Summary; SD = Standard deviation

Cross-reference: ISE After-Text Table 2.1A.

(Source: Applicant's ISE, Table 3.2-2, p. 1223)

7.2.1.3 Extent of exposure (dose/duration)

The Applicant fulfilled the ICH requirements regarding the number of patients to be exposed to a drug for chronic use. In the Phase II and III studies in FM patients (Group 1) and the studies in patients with non-FM disorders (Group 2) a total of 2596 patients were treated with milnacipran, 354 of them for at least 1 year, of whom 209 were treated at the highest dosage (200 mg/d). Table 62 presents the number of patients exposed to MLN in the Group 1 and 2 studies by dose and Table 63 present the length of exposure in the Group1 studies.

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Table 62. Number of Patients Exposed to Milnacipran in the Group 1 and 2 Studies

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

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

^b Included in the MAA.

^c 150 mg/d.

^d 150 to 200 mg/d.

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

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

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Table 63. Extent of Exposure of All FM Patients (Group 1)

	Milnacipran			
	Placebo (N = 652)	100 mg/d (N = 634)	200 mg/d (N = 1342)	Total (N = 1824)
Treatment duration, d				
Mean	137.9	143.6	172.5	180.6
SD	69.3	95.0	133.4	144.7
Median	168	164	141	141
Range	1, 260	1, 505	0, 510	0, 529
Treatment duration, n (%)				
≥ 3 weeks	616 (94.5)	624 (91.2)	1217 (90.7)	1650 (90.5)
≥ 7 weeks	550 (84.4)	538 (78.7)	1068 (79.6)	1426 (78.2)
≥ 15 weeks	432 (66.3)	433 (63.3)	788 (51.7)	1074 (58.9)
≥ 27 weeks	296 (45.4)	315 (46.1)	607 (45.2)	822 (45.1)
≥ 12 months	0	25 (3.7)	209 (15.6)	354 (19.4)
Patient-Years Exposure				
	246.1	269.0	633.2	902.1

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

(Source: Applicant's Table 5.2.1-1, Summary of Clinical Safety, Vol. 1, p.64)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

In addition to the Phase 2 and 3 clinical trial data, safety information was obtained from the Applicant's summary of the safety experience of patients in the clinical trials used to support the European marketing application for MDD, and from the Applicant's summary of the postmarketing experience with milnacipran.

I also conducted a brief search of PubMed to identify any published literature on milnacipran.

7.2.2.1 Other studies

None.

7.2.2.2 Postmarketing experience

The post-marketing experience with milnacipran is derived mainly from patients with depression and consists of two data sources: post-marketing studies and spontaneous reports. The post-marketing studies include three MDD and one smoking cessation studies conducted by Pierre Fabre and five post-marketing clinical pharmacology studies.

The Applicant estimates that there have been over 1 patient-months of postmarketing exposure to milnacipran in global use. In Europe, the vast majority of patients received an

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estimated average daily dose of 75 mg; in Japan, the product was typically used at a 75 mg average daily dose of 75 mg.

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The worldwide spontaneous reporting database for milnacipran includes a total of 1496 spontaneous case reports and covering the period from the first marketing authorization by the French Regulatory Authority on December 6, 1996, until the safety cutoff for the NDA submission of June 30, 2007.

- Deaths from the post-marketing experience

Most of the patients in the postmarketing safety database received milnacipran for the indication of MDD, the currently approved indication.

There were 69 fatal cases (5%) among the 1496 reported postmarketing AE cases. Below is a table with the number of fatal cases reported by the Applicant, as obtained through spontaneous post-marketing reporting.

Table 64. Tabulation of Serious Adverse Events and Fatal Cases by SOC

<i>System organ class</i>	<i>Total Number of Serious Cases</i>	<i>Total Number of Fatal Cases</i>
Blood and lymphatic system disorders	29	3
Cardiac disorders	38	6
Congenital, familial, and genetic disorders	0	0
Ear and labyrinth disorders	1	0
Endocrine disorders	2	0
Eye disorders	8	0
Gastrointestinal disorders	28	1
General disorders and administration site conditions	16	8
Hepatobiliary disorders	35	3
Immune system disorders	5	0
Infections and infestations	3	0
Injury, poisoning, and procedural complications	32	3
Investigations	33	0
Metabolism and nutrition disorders	14	1
Musculoskeletal and connective tissue disorders	7	0
Neoplasms, benign, malignant, and unspecified (including cysts and polyps)	2	0
Nervous system disorders	138	3
Pregnancy, puerperium, and perinatal conditions	2	0
Psychiatric disorders	126	37
Renal and urinary disorders	24	2
Reproductive system and breast disorders	9	0
Respiratory, thoracic, and mediastinal disorders	12	1
Skin and subcutaneous tissue disorders	64	0
Social circumstances	1	0
Surgical and medical procedures	0	0
Vascular disorders	23	1
Total	652	69

(Source: Applicant's Table 10.5-1, Summary of Clinical Safety, Vol. 1, p. 209)

The highest number of fatal cases occurred in the SOC "Psychiatric disorders". The listing of events (by SOC) that were associated with the fatal cases is presented below and was compiled based on the line listing and narratives of the fatal SAE cases. The discrepancy in the total numbers is explained by the fact that one fatal case may be associated to more than one SOC term:

- Blood and lymphatic system disorders: There were 2 fatal cases with agranulocytosis and one case with thrombocytopenia.
- Cardiac disorders: The fatal cases were as follows: tachycardia (2), arrhythmia (1), cardiac arrest (1), cardiac failure (2), cardiac failure acute (1), cardiogenic shock (1), cardio-respiratory arrest (1), chest discomfort (1), cyanosis (1).
- Endocrine disorders: There was one fatal case in which diabetes insipidus was mentioned along with cardiac disorder and suicide.
- Gastrointestinal disorders: There was one fatal case of hemorrhagic pancreatitis, one case of aspiration of vomit in the context of drug overdose, and one case of upper gastrointestinal hemorrhage.
- General disorders and administration site conditions: There were three cases listed as "death". The narratives indicate that two of these cases were due to cardiac arrest, another was due to septic shock and arrhythmia. Three cases were listed under this SOC as "sudden death". There were three fatal cases with pyrexia.
- Hepatobiliary disorders: There were two fatal cases of fulminant hepatitis and one described as liver disorder.
- Injury, poisoning and procedural complications: There was one case of road traffic accident which was confounded by alcohol ingestion before the accident. Under the term "Other events" the "road traffic accident" was also listed, as well a case that was listed under "General disorders and administration site conditions- Pyrexia".
- Metabolism and nutritional disorders: there was one fatal case involving anorexia, which was also described under Cardiac disorders.
- Musculoskeletal and connective tissue disorders: There was one fatal case with "rhabdomyolysis."
- Nervous system disorders: The following were events associated with the fatal cases under this SOC: dyskinesia (1), neuroleptic malignant syndrome (3), convulsions (6).
- Psychiatric disorders: There were reports of 42 completed suicides.
- Renal and urinary disorders: There were six fatal cases that were associated with urinary retention (1), polyuria (1), poriomania (1), renal failure (3).
- Respiratory, thoracic and mediastinal disorders: pneumonia (2), respiratory insufficiency (1), bilateral alveolar pneumopathy (1).
- Vascular disorders: there was one fatal suicide case that was associated with hypertension.

7.2.2.3 Literature

A literature search through PubMed conducted by myself encountered one death report describing one motor vehicle accident associated and alcohol ingestion associated with milnacipran. There were no other death reports in the literature provided by the Applicant.

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7.2.3 Adequacy of Overall Clinical Experience

The Applicant fulfilled the ICH requirements regarding the number of patients to be exposed to a drug for chronic use, as well as the duration of exposure (see Section 7.2.1.3).

Although there were very few males in the clinical trials (~ 5%), this is reflective of the demographics of the fibromyalgia population in general.

The lowest dose that the Applicant evaluated for efficacy and safety was 100 mg/day. Although the Agency previously requested that a lower dose be explored, the Applicant did not do so, theorizing that based on previous experience with antidepressants in fibromyalgia, a lower dose (such as 50 mg) would not be efficacious. Of note, doses of 50 mg/day are used abroad for the treatment of MDD.

The Phase 3 trials excluded patients with moderately severe to severe depression. Therefore the psychiatric effects of MLN in this population are unknown.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

In the Phase 3 trials, laboratory testing was performed at every clinic visit (i.e. approximately every 4 weeks). This was adequate.

The only clinical trial in which ECGs were assessed was MLN-MD-02. ECGs were collected at each study visit. Notably, this study was truncated from 6 to 3 months' duration; therefore for the majority of subjects there is only 3 months' worth of ECG data. This amount of data does not seem to be adequate to assess the effects of MLN on the ECG, especially with the nature of the cardiac adverse events that were observed.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The evaluation of the metabolic pathway and potential for drug-drug interactions is discussed in Section 5, and also in the Clinical Pharmacology review.

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7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The potential cardiovascular, psychiatric, and urinary effects of SNRIs are known. The Applicant performed appropriate tests (including blood pressure, heart rate, ECGs, spontaneous adverse event reporting) to assess for these effects.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the data submitted for the NDA were of good quality and were reasonably complete.

7.2.9 Additional Submissions, Including Safety Update

The Applicant submitted a 120 -day safety update, with a clinical cut-off date of December 31, 2007.

The following are the ongoing studies as of December 2007 and the approximate number of patients exposed to MLN. The studies are being conducted in healthy volunteers, FM, and MDD patients. Two new studies were not included in the original integrated summary of safety:

- Study MLN-MD-12: A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of Milnacipran 100 and 200 mg Daily in Patients With Fibromyalgia: Effects on 24-Hour Ambulatory Blood Pressure Monitoring (conducted under US IND)
- Study MLN-PK-17: Comparative Bioavailability and Food Effect Study of Milnacipran Capsule [] Formulation) and Immediate-Release Tablet in Healthy Subjects (conducted under US IND)

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Table 65. Ongoing Studies with Milnacipran and Patient Exposure as of December 2007.

	Number of Subjects			
	Placebo	Milnacipran		
		≤ 56 mg/d	100 mg/d	200 mg/d
Fibromyalgia studies				
MLN-MD-03 (phase III pivotal trial) ^{a,b}	512	0	513	0
MLN-MD-06 (extension of six US FMS studies) ^a	0	0	1000 ^c	0
F02207 GE 204 (functional MRI)	46	0	0	46
F02207 GE 302 (EU phase III in FMS)	446	0	0	430
F02207 GE 304 (extension of F2207 GE 302)	0	0	0	450 ^d
F02207 GE 205 (nociceptive flexion reflex) ^b	40	0	0	40 ^d
MLN-MD-12 (ABPM) ^{a,b}	90	0	0	180 ^a
Studies in patients with MDD				
F02207 GE 303 (milnacipran vs venlafaxine) ^{b,f}	0	0	0	90
F02207 GE 402 (milnacipran vs imipramine) ^g	0	0	60	0
Studies in healthy volunteers				
MLN-PK-17 ^a	0	30	0	0
Total no. of subjects (estimated)	1134	30	1573	1236

a US Investigational New Drug study.

b Study still blinded to drug treatment.

c Flexible dosing to a maximum of 200 mg/d.

d Estimated number for all milnacipran dosages (100 mg/d, 150 mg/d, and 200 mg/d).

e All patients randomized to milnacipran will receive 100 mg/d, which if tolerated will be escalated to 200 mg/d.

f 90 patients to be treated with venlafaxine.

g 60 patients to be treated with imipramine.

ABPM = ambulatory blood pressure monitoring; EU = European Union; FMS = fibromyalgia syndrome;

MDD = major depressive disorder; MRI = magnetic resonance imaging; US = United States.

(Source: 120-Safety Update, eCTD amendment 12, dated April 17, 2008, p.12)

There were no new deaths, SAEs or discontinuations due to AEs in the newly completed studies MLN-PK-14 and MLN-PK-15.

There was one death in an ongoing study F02207 GE 302 which is a Phase 3 study in FM patients being conducted in Europe. A 46 year-old female on MLN who completed suicide. Data regarding the patient's past medical history and dose of MLN were not provided in the Safety Update. There was another death in a Study F02207 GE 303, which is a blinded study comparing MLN and venlafaxine in which a 46 year-old female had a ruptured aneurysm. The treatment arms are still blinded, therefore a relationship to MLN cannot be determined at this time.

In the ongoing MLN studies mentioned above, there have been 35 new serious adverse event reports: 17 are still blinded and the other 16 cases were on MLN. Among the cases of patients on MLN there were no hepatotoxicity related cases, and among the cardiotoxicity related cases there

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were 2 cases one aortic dissection and one of arterial occlusive disease. Among the blinded cases there was one case of increased hepatic enzymes which resolved and one case of chest pain.

There were an additional 688 SAEs reported in the post-marketing experience: 72 deaths, 688 serious cases, and 41 non-serious cases. There were 3 fatal cases which are not documented. In addition there were also three cases of abnormal liver enzymes:

- a case of "hepatitis" with enzyme elevations ($2 \times \text{ULN}$) with no report of bilirubin elevation,
- a case from Japan of markedly increased AST levels ($9 \times \text{ULN}$) without mention of levels of ALT or bilirubin, and
- a case of elevated liver enzymes (unspecified, but said to be up to $10 \times \text{ULN}$).

Below is the table of the new SAE reports in the post-marketing reporting system:

Table 66. New SAE Reports from the Postmarketing Database

<i>System Organ Class</i>	<i>Total Serious Cases</i>	<i>New Serious Cases</i>	<i>Total Fatal Cases</i>	<i>New Fatal Cases</i>
Blood and lymphatic system disorders	30	1	3	0
Cardiac disorders	39	1	6	0
Congenital, familial and genetic disorders	1	1	0	0
Ear and labyrinth disorders	1	0	0	0
Endocrine disorders	3	1	0	0
Eye disorders	8	0	0	0
Gastrointestinal disorders	30	2	1	0
General disorders and administration site conditions	13	2	3	0
Hepatobiliary disorders	36	2	3	0
Immune system disorders	5	0	0	0
Infections and infestations	3	0	0	0
Injury, poisoning and procedural complications	34	2	4	1
Investigations	33	1	0	0
Metabolism and nutrition disorders	14	0	1	0
Musculoskeletal and connective tissue disorders	9	2	0	0
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	2	0	0	0
Nervous system disorders	147	9	3	0
Pregnancy, puerperium and perinatal conditions	3	1	0	0
Psychiatric disorders	125	9	39	2
Renal and urinary disorders	26	2	2	0
Reproductive system and breast disorders	9	0	0	0
Respiratory, thoracic and mediastinal disorders	11	0	1	0
Skin and subcutaneous tissue disorders	66	4	0	0
Social circumstances	1	0	0	0
Surgical and medical procedures	0	0	0	0
Vascular disorders	24	1	1	0
Total	688	41	72	3

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following are important adverse events associated with milnacipran treatment:

- Increased risk of suicidal ideation in patients with depression (Section 7.1.3.3)
- Elevated blood pressure (Section 7.1.8)
- Elevated heart rate (Section 7.1.8)
- Mild increases in transaminases (Section 7.1.3.3)
- Dysuria (males) (Section 7.1.5.6)
- Mydriasis (Section 7.1.6)

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

See Section 7.1

7.4.1.2 Combining data

See Section 7.1

7.4.2 Explorations for Predictive Factors

Refer to Sections 7.1.1 through 7.1.9 for a discussion of my explorations for predictive factors for observed safety signals, including:

- Explorations for dose dependency for adverse findings
- Explorations for time dependency for adverse findings
- Explorations for drug-demographic interactions

7.4.3 Causality Determination

Refer to Sections 7.1.1 through 7.1.9

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

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

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

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

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

Based on the clinical pharmacology data, MLN may be given with or without food and the latter may make the drug more tolerable in respect to nausea. A 50% reduction in the dose will be necessary in patients with severe renal impairment. Caution should be exercised when treating patients with mild to moderate renal impairment and severe hepatic impairment.

The Applicant may wish to consider studying the efficacy of 50 mg/day, as discussed in the IND development phase.

8.2 Drug-Drug Interactions

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

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Because MLN is not metabolized by CYP450 system the risk of pharmacokinetic drug-drug interactions is low. The risk of pharmacodynamic interactions with other drugs that increase heart rate and blood pressure was not studied.

8.3 Special Populations

The special populations were reasonably adequately assessed in the studies. No special dosing recommendations will be made based on race, gender or age. Studies with milnacipran have not been conducted in the pediatric population.

8.4 Pediatrics

In a letter dated September 11, 2007, the Division agreed to the Applicant's plan of deferral of pediatric studies in all pediatric patients for MLN, until adequate safety and efficacy are demonstrated in the adult fibromyalgia population.

8.5 Advisory Committee Meeting

An Advisory Committee Meeting was deemed not necessary for this new molecular entity as this is not the first in this class of drugs and there is considerable safety data available to support the safety of this product.

8.6 Literature Review

Refer to Section 7.2.2.3.

8.7 Postmarketing Risk Management Plan

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

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

The Applicant found that milnacipran is more efficacious than placebo for the treatment of “fibromyalgia pain” and “fibromyalgia syndrome”. The Applicant chose to demonstrate the efficacy by using a composite responder analyses for the “treatment of pain of FM” and “treatment of FM syndrome”. Patients were considered responders for pain if they achieved a 30% improvement in pain from baseline and provided a good patient global score (“very much improved” and “much improved”) concomitantly at the 3-month endpoint. Patients were considered responders for the treatment of FM syndrome if they had improvement in function (measured by an improvement of at least 6 points on the SF-36 PCS), pain and global endpoints concomitantly. This is the first time the Agency has accepted a composite responder analysis as an efficacy endpoint for a drug seeking this indication.

My efficacy review focused on the efficacy results of the composite pain responder analysis as pain is the main component of this disorder and this more closely reflects the sort of analysis that would be accepted by the Division’s current standards. I found that the difference in the number of responders between the placebo and milnacipran treatment arms achieved statistical significance for 200mg/day in both controlled studies and only in one study for milnacipran 100 mg/day. The difference between milnacipran 100mg/day and placebo did not meet statistical significance in one of the studies by a small margin, but the proportion of patients who were responders for the pain endpoint was numerically higher in the MLN 100 mg/day treatment arm which indicates that MLN 100 mg/day does have an effect in a number of patients. Although the analysis of the responder rate for “pain only” does not indicate that MLN has a significant effect on pain, the composite pain responder analysis indicates that milnacipran does have an overall positive effect on fibromyalgia.

Safety

My safety review for MLN found that the adverse event profile is consistent with the safety profile of other NSRIs. The most common AEs reported in the MLN treated patients were nausea, headache, constipation, hot flush, insomnia and dizziness. The incidence of serious adverse events was low (<0.5 % for any give PT) and the ones that occurred more frequently were related to cardiac effects of MLN such as chest pain, chest discomfort, palpitations, heart rate increased. The most common AEs that lead to discontinuation in at least 1% of MLN-treated patients were nausea and palpitations, heart rate increased, constipation, headache, insomnia, hyperhidrosis, vomiting, dizziness and fatigue.

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

The safety data indicated that patients treated with MLN who were depressed at initiation of therapy had a higher incidence of suicidal ideation compared with patients on placebo who were depressed at baseline. Patients with moderately severe depression were excluded from these controlled studies, so the effects of MLN in this group are not known, and the label may need to reflect that this safety finding was limited to a restricted population with non-severe depression.

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

The effects of MLN on vital signs were also noted. The controlled studies demonstrated that milnacipran increases heart rate, mean increase in heart rate 6.6 bpm and 7.1 bpm for MLN 100 and 200 mg/day respectively. Changes > 10 bpm were noted in 34 to 40 % of the patients on milnacipran and approximately 12-15% of the milnacipran treated patients had heart rates above 100 bpm but less than 1% were above 120 bpm. A dose response was not observed. Monitoring of heart rate should be recommended in the label.

Milnacipran also caused increases in blood pressure. The mean increases in systolic blood pressure, were 3.1 mmHg and 3.0 mmHg and for diastolic blood pressure the mean increases were 3.1 mmHg and 2.6 mmHg for MLN 100mg/day and MLN 200 mg/day respectively. Again a dose response was not observed. Patients who are normal or pre-hypertensive upon treatment initiation are more at risk of developing hypertension (relative risk of approximately 2) but patients who are hypertensive at drug initiation do not seem to worsen with therapy. The increases in blood pressure seem to stabilize with time which indicates that tolerance may develop with prolonged treatment. Monitoring of blood pressure should be recommended in the label.

9.2 Recommendation on Regulatory Action

I recommend that milnacipran be approved for the treatment of fibromyalgia.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

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

9.3.2 Required Phase 4 Commitments

The Applicant will need to conduct the following studies as required Phase 4 commitments:

- studies in the pediatric population 12 years of age and older.

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- another thorough QT (TQT) study as the one submitted in the NDA does not adequately elucidate the effect of MLN on the QT interval.
- an Ames assay using the clinical batch.
- studies for assessment of abuse potential as recommended by CSS.

9.3.3 Other Phase 4 Requests

The Applicant may wish to explore the efficacy of MLN at a dose of 50 mg/day as a dose lower than 100 mg/day was not explored during the development program. The proportion of responders was low in both treatment arms but similar between the two dose levels. The incidence of adverse events was higher with the highest dose of MLN. The Applicant may wish to explore a lower dose (50 mg/day) especially if it may lead to fewer discontinuations of medications due to adverse effects.

9.4 Labeling Review

The proposed label will require changes for approval. Because the clinical studies excluded patients with moderate and severe depression healthcare providers will need to be aware that FM patients with co-morbid depression may be at risk of suicidal ideation. When describing the effects on blood pressure the label should inform about the increased risk for the development of hypertension in patients with normal and especially with pre-hypertension.

The section 12.2 Pharmacodynamics will need to be amended to present the values obtained in the study that was conducted and should not state that [REDACTED] b(4)

The plots for the composite responder analyses will need to be replaced. The graphs currently on the label are misleading because [REDACTED] and visually they misrepresent the efficacy findings. b(4)

The consult to DMEP regarding the adequacy of the trade name and packaging was pending at the time of this review.

9.5 Comments to Applicant

The Applicant should be advised that upon approval of MLN, the following Phase 4 studies should be conducted:

- Studies in the pediatric population 12 years of age and older evaluating the safety and efficacy of milnacipran as a treatment for fibromyalgia.

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

The Applicant should also consider evaluating the efficacy of MLN at doses lower than 100 mg/day (e.g. 50 mg/day), as this was not explored during the development program.

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10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study FMS031

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

Objectives

The protocol specified objectives of the study were:

Primary objective: Demonstrate safety and efficacy, both clinical and statistical, of milnacipran in the treatment of the fibromyalgia syndrome (FMS).

Secondary objectives:

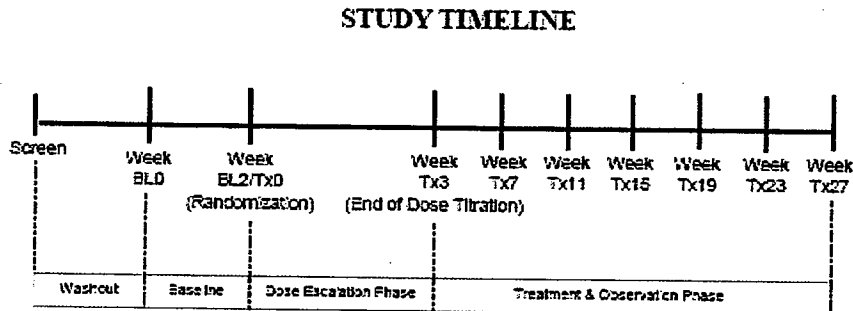
1. Compare statistical and clinical efficacy of 100 mg/day and 200 mg/day milnacipran in the treatment of the fibromyalgia syndrome based on each component of the composite responder analysis, as well as on a number of additional secondary endpoints including fatigue, sleep and mood.
2. Establish and 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 August 7, 2003. This was to be a prospective, double-blind, randomized, placebo-controlled, multi-center study. It was to be conducted in 25 to 30 centers in the United States. The treatment duration was to be 24 weeks long, after a three-week escalation phase, totaling 27 weeks of exposure.

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Figure 13. Study Timeline- Study FMS031



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

Study Population and Treatment Arms

The study plan was to enroll 500 patients which were to be randomized to one of the following treatment arms in a ratio of 1: 1: 2, as follows:

- placebo (n=125)
- 100 mg milnacipran daily (n=125) divided in two daily doses (50 mg twice daily) or
- 200 mg milnacipran daily (n= 250) divided in two daily doses (100 mg twice daily)

Inclusion Criteria

The following were the inclusion criteria:

1. Patients must have been diagnosed with primary fibromyalgia, as defined by the 1990 American College of Rheumatology (ACR) Criteria for the Classification of Fibromyalgia.
2. Patients of both genders between the ages of 18 and 70 years.
3. Females must have been either postmenopausal (no menses for at least 1 year) or status post-oophorectomy (bilateral) or, if of childbearing potential, must have had a negative urine pregnancy test prior to entry into the study, and have been using a medically acceptable form of contraception [i.e., 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 an average visual analog intensity pain scale (VAS) recording of at least 50 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.
5. Patients must have had the ability to give informed consent.
6. Patients must have been able to read and understand English.
7. Patients must have been willing and able to use a patient experience diary (PED) daily for a minimum of 29 weeks.
8. Patients must have been willing to withdraw from CNS-active therapies commonly used for FMS, including anti-depressants, anti-convulsants, and mood stabilizers.

The following were the exclusion criteria:

1. Severe psychiatric illness as determined by patient self-report or the screening exam, the Mini-International Neuropsychiatric Interview (MINI);
2. Current major depressive event (MDE), as defined by the MINI;
3. **Patients with a significant risk of suicide according to the investigator's judgment;**
4. Patients abusing alcohol, benzodiazepines or other drugs as demonstrated by positive drug screening;
5. Any history or behavior that would, in the physician's estimation, prohibit compliance for the duration of the study;
6. **Patients with any actively pending disability claim, workman's compensation claim, or litigation;**
7. Patients with myocardial infarction within the past 24 months, active cardiac disease (American Heart Association Functional Class 2, 3 or 4), congestive heart failure, prosthetic heart valve, hemodynamically significant valvular heart disease, or known cardiac rhythm or conduction abnormalities;
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 (creatinine > 1.3 the upper limit of the normal range for the laboratory performing the test, adjusted for patient gender, age and lean body weight);
11. Patients with documented autoimmune disease;
12. Patients with current systemic infection;
13. Patients with active cancer, except basal cell carcinoma, or patients currently undergoing therapy for cancer;
14. Patients with a current 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 and patients requiring use of CPAP devices were not eligible for the trial;
16. Patients with active peptic ulcer or inflammatory bowel disease;
17. Patients with unstable endocrine disease, including unstable diabetes or thyroid disease;
18. Disorders that had been stable for the preceding 3 months were acceptable;
19. Male patients with prostatic enlargement or other genito-urinary disorders, who might have been at significant risk of dysuria when taking agents with noradrenaline re-uptake inhibition properties;
20. Pregnant or breastfeeding patients;
21. Patients who had received treatment with an experimental agent within the last 3 months;
22. **Refractory patients, defined as those who have failed for efficacy reasons, at least two courses of tricyclics, tetracyclics or serotonin norepinephrine re-uptake inhibitor (SNRI) agents for FMS treatment and intolerance of tricyclics, tetracyclics or SNRI's was not reason for exclusion;**

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23. Patients who were receiving concomitant therapy with MAO-A or -B inhibitors, tricyclics, tetracyclics, selective serotonin re-uptake inhibitor (SSRI) agents, norepinephrine non-specific re-uptake inhibitor (NARI) agents, SNRI agents or alpha-agonists;
24. Patients who were receiving concomitant therapy with metabolic enzyme inhibitors (i.e., cimetidine) and enzyme inducers (including phenytoin and phenobarbital), oral anticoagulants (warfarin), anticonvulsants (phenytoin), type 1C antiarrhythmics (propafenone, flecainide, encainide);
25. Patients with concurrent usage of known or suspected psychoactive agents, including St. John's Wort and S-adenosylmethionine;
26. Patients with concurrent usage of digitalis (digoxin) preparations;
27. Patients with concurrent usage of centrally acting analgesics, including tramadol (Ultram®), codeine, or other opioids/opiates.

Study Medication and Other Therapies

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

Patients were to take one capsule in the morning and in the evening.

Rescue Medication

Hydrocodone use up to 10 days was to be allowed as a rescue therapy for the management of pain, at the dose of 2.5 mg- 10 mg, every 4 to 6 hours as needed for acute pain. The rescue medication was to be discontinued or withheld 48 hours prior to a scheduled clinic visit.

Allowable Concomitant Medications

The following concomitant drugs were allowed:

- rizatriptan (Maxalt®) for the treatment of migraine headaches
- zolpidem (Ambien®) for adjunctive treatment of insomnia
- acetaminophen
- aspirin
- non-steroidal anti-inflammatory drugs (NSAIDS)

Prohibited Concomitant Medications

The following were prohibited concomitant medications:

- 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 were to be avoided.
- joint and soft tissue injections: these treatments must have been completed at least seven days before the primary endpoint determination (Tx15).

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- 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: was prohibited due to reports of the association of hypotension and arrhythmias and concomitant use with milnacipran.

Methods and Procedures

The study was to consist of 10 visits and 4 phone calls over 27 weeks. Table 65 on the following page shows the study procedures.

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VISIT NAME	Screen	Washout	BL0	BL/Tx0	Tx1	Tx2	Tx3	Tx7	Tx11	Tx13	Tx15	Tx19	Tx23	Tx27 ET
				Randomization/ Start Drug	Phone	Phone	End Date Escalation							
Office Visits	X		X	X	Phone	Phone	X	X	X	Phone	X	X	Phone	X
Activities														
Informed Consent	X													
Inclusion/Exclusion	X													
FMS History	X													
Medical History	X													
Physical Examination	X													
Baseline Signs and Symptoms	X		X											
ACR 1990 FMS criteria	X													
Vital Signs	X		X	X			X	X	X		X	X		X
MMT	X													
Electronic Diary for Pain			X	X	X	X	X	X	X	X	X	X	X	X
PGIC							X	X	X	X	X	X	X	X
FIQ-SF-36, MDHAQ				X			X	X	X		X	X		X
Status Testing: BDI, ASEX				X										
FMS Status: Pain VAS, MASQ, MFI, MOS-Sleep, Pt. Global Disease Status				X			X	X	X		X	X		X
Pregnancy Test ^a				X										
Laboratory Assessments	X		X								X			X
Urine Drug Screen			X											
Drug Administration and IVRS	X ^c		X ^c	X	X	X	X	X	X		X	X		X ^d
Adverse Events				X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications			X	X	X	X	X	X	X	X ^e	X	X	X ^e	X

a Tx27 assessments were to be performed at early Termination Visit if patient remitted before Week 27.
b In-office urine pregnancy test. Negative pregnancy test had to be confirmed before randomization.
c Laboratory assessments had to be repeated in patients in whom more than 6 weeks elapsed between the initial Screening Visit and first Baseline Visit.
d No drug administration at screening, BL0 and Tx17/ET.
e Patients were reimbursed not to take rescue therapy during the 2 weeks of primary end point data collection (Tx 14-15 and Tx 26-27).
ACR = American College of Rheumatology; ASEX = Arizona Sexual Experiences Scale; BDI = Beck Depression Inventory; BL0 = Baseline Period Visit; BL2/Tx0 = Randomization Visit; ET = early termination; IVRS = interactive voice response system; FIQ = Fibromyalgia Impact Questionnaire; FMS = Fibromyalgia Syndrome; MASQ = Multiple Ability Self-Report Questionnaire; MDHAQ = Multidimensional Health Assessment Questionnaire; MFI = Multidimensional Fatigue Inventory; MOS = Medical Outcomes Survey; PGIC = Patient Global Impression of Change; SF-36 = Short Form-36 Health Survey; Tx1, Tx2 = Dose-Escalation Phase; Tx3-Tx7 = treatment and observation phase; Tx3 = end of dose-escalation (Treatment Week 3); Tx7, Tx11, Tx15, Tx19, Tx23, Tx27 = at the end of the 4th, 8th, 12th, 16th, 20th, and 24th week of the Treatment and Observation Phase; VAS = visual analog scale.

(Source: Applicant's Table 9.5.1-1, Clinical Study Report, FMS-031, Vol. 1, p. 45)

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:

1. Comprehensive evaluation: including patient demographics, past medical history, fibromyalgia treatment history, review of inclusion and exclusion criteria, assessment of baseline signs and symptoms of fibromyalgia
2. Physical examination, documenting the diagnosis of fibromyalgia by ACR criteria;
3. Psychological assessment (MINI);
4. Laboratory assessments, including serum chemistries, hematology and urinalysis.
5. Vital sign assessments, including temperature, weight, standing and supine blood pressure and heart rate.

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. During this baseline period the patients were to become comfortable with the device, establish their baseline pain and disease activity, as well as their daily variability with respect to pain and sleep.

The following assessments were to occur at the first (BL0) and second (BL2) baseline visits:

1. Vital signs
2. Primary Outcome Measures:
 - a. Fibromyalgia Impact Questionnaire (FIQ)
 - b. Short Form-36 Health Survey (SF-36)
 - c. Multidimensional Health Assessment Questionnaire (MDHAQ)
3. Assessment of adverse events
4. Assessment of concomitant medication usage

At the BL0 visit, 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.

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

- a. Beck Depression Inventory (BDI)
- b. Arizona Sexual Experiences Scale (ASEX)
- c. Patient pain VAS
- d. Multiple Ability Self-Report Questionnaire (MASQ, Cognition)
- e. Multidimensional Fatigue Inventory (MFI)
- f. Medical Outcomes Study-Sleep Index (MOS)

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Patients would be randomized if they were successful in entering their responses to at least 5 of the 7 daily report prompts during the second week of the baseline period. Confirmation of a negative pregnancy test was necessary at randomization.

Dose Titration

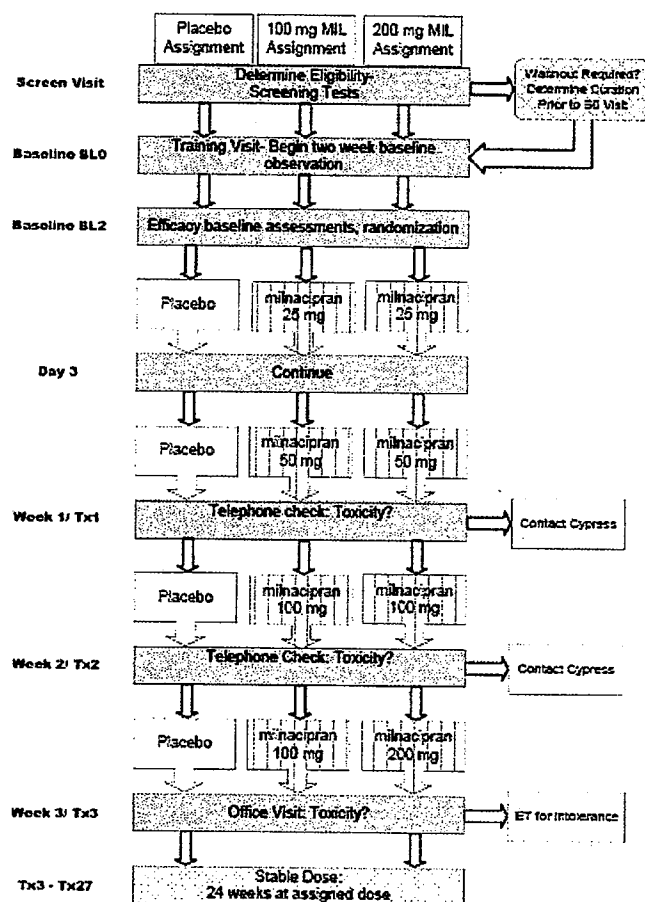
Once randomized to one of the treatment arms, patients were to enter the 3-week dose titration phase of the study (visits Tx1- Tx3). To maintain the blind, patients who were randomized to placebo were also dose escalated. During the first week of titration (Tx1), the patients were to escalate the treatment 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-Tx2), 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-Tx3), 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 blinding of the study. The patients were followed weekly by phone call 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.

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Figure 14. Schematic of the Dose Titration for Study FMS031



(Source: Applicant's Figure, Clinical Study Report, FMS-031, Vol.1, p. 2166)

Treatment Phase

The treatment phase duration was to be 24 weeks long, consisting of seven office visits, each four weeks apart (Tx3 (week 4), Tx7 (week 7), Tx11 (week 11), Tx15 (week 15), Tx19 (week 19), Tx23 (week 23), and Tx27 (week 27)). All treatment visits were to have a window of ± 7 days, except for the last visit which had a window of ± 10 days.

Patients were to collect data into the PED device throughout the treatment phase. This device would prompt the patient several times a day in a semi-random fashion for information regarding their current level of pain; an evening prompt (around bedtime) also would request information about their current level of pain. There was an additional weekly report on Friday evenings that captured information about the patient's degree of fatigue and quality of life, and a weekly recall question asking about the patient's overall pain during the preceding week.

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At each of the visits during the treatment phase, the patients were to obtain their month supply of drug. Also, at these visits information concerning adverse events, sleep and pain, as well as psychological and functional status, were to be collected.

The specific assessments that were to occur during the visits throughout the treatment phase (Tx3-Tx27) were as follows:

1. Daily and Weekly PED entries
2. Vital signs
3. Adverse Event and Concomitant Medication Review
4. Patient Global Impression of Change (PGIC)
5. Primary Outcome Measures:
 - a. Fibromyalgia Impact Questionnaire (FIQ)
 - b. SF-36
6. Secondary Measures:
 - a. Patient pain VAS
 - b. Multiple Ability Self-Report Questionnaire (MASQ, Cognition)
 - c. Multidimensional Fatigue Inventory (MFI)
 - d. MOS-Sleep Index (MOS)
 - e. Health Assessment Questionnaire (MDHAQ) at Tx15 and Tx27

The following additional assessments were to be obtained at visits Tx15 and Tx27 or at early termination:

1. Laboratory Assessment
2. Beck Depression Inventory (BDI)
3. Arizona Sexual Experiences Scale (ASEX)
4. Multidimensional Health Assessment Questionnaire (MDHAQ).

At visit Tx27 or at early termination a urine pregnancy test was to be performed.

Patients who successfully completed the 24-week treatment phase would be eligible to participate in an open-label trial.

Efficacy Measures and Outcomes

Primary efficacy measures

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

- Pain was to be measured using a VAS scale, and the data collected into the PED.

Patient global improvement was to be assessed using a fibromyalgia-specific patient global impression of change (PGIC) instrument at each of the visits during the treatment phase. The specific question and possible responses were as follows:

“Since the start of the study, overall my fibromyalgia is:”

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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 using two different instruments:

- 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 can be used to assess changes in functioning over time. The entire FIQ was to be administered.
- Short Form-36- Physical Component Summary (PCS): This is a section of the SF-36 that was to be used to assess changes in function over time. The entire SF-36 was to be administered.

The FIQ and SF-36 were to be administered to patients at each of the baseline and treatment phase visits.

Secondary efficacy measures

The following were the secondary efficacy assessment tools and/or endpoints:

- Pain data obtained at all visits through the PED
- VAS pain measurements based on patients' recall of pain over the previous 24 hours and previous 7 days on paper and weekly pain recall at visits,
- Pain component of the FIQ which has a VAS for pain over the previous 24 hours.
- Beck Depression Inventory (BDI) at visits BL2, Tx15 and Tx27
- Arizona Sexual Experiences Scale (ASEX) at visits BL2, Tx15 and Tx27
- Mini International Neuropsychiatric Interview (MINI) at screening
- Multidimensional Fatigue Inventory (MFI) at visits BL2, Tx3, Tx7, Tx11, Tx15, Tx19, Tx23 and Tx27
- MOS-Sleep Index scale at visits BL2, Tx3, Tx7, Tx11, Tx15, Tx19, Tx23 and Tx27
- Multiple Ability Self-Report Questionnaire (MASQ) at visits BL2, Tx3, Tx7, Tx11, Tx15, Tx19, Tx23 and Tx27
- Stanford Multidimensional Health Assessment Questionnaire (MDHAQ) at visits BL2, Tx3, Tx7, Tx11, Tx15, Tx19, Tx23 and Tx27

Primary efficacy outcome

The primary efficacy outcome to support efficacy of milnacipran as a "treatment of FMS" was to be the percentage of patients of the ITT population (all patients who had been randomized to treatment) who successfully met the criteria for response based on a responder analysis that incorporated the following three domains:

1. Pain

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2. Patient global improvement.

3. Physical function

A patient was to be classified as a responder if they s/he the following criteria:

- $\geq 30\%$ improvement in pain from baseline to endpoint
 - PGIC rating of "improved" (i.e. a score of 1, 2 or 3 on the 1-7 scale) at endpoint
- AND

- Improvement in at least one of the following measures of function:
 - $\geq 20\%$ improvement in FIQ-PF score from baseline to endpoint
 - ≥ 5 units of improvement in the SF-36 PCS score from baseline to endpoint

The baseline pain score was to be the average of all recorded daily pain scores during the 2-week period between BL0 and BL2. If more than 14 days of baseline pain data were collected on the PED, they were all to be averaged to obtain the pain baseline. The physical function baseline score was to be the value recorded at BL2 or if both were available, the average of the two.

The endpoint pain score was to be the average of all recorded daily pain values for weeks Tx14 and Tx15, or the last two weeks on study for early termination patients. For the PGIC and physical function scales, it was to be the values recorded at Tx15, or at the early termination visit.

Figure 15. Definition of Responders for the Treatment of FM Pain and FMS as Specified in the Original Protocol

	Domain Improvement Definition			Handling of Missing Data
	Pain	Global	Physical Function	
Treatment of Pain @ 3-Month Landmark (Tx15)	$\geq 30\%$ improvement from baseline to landmark on PED pain	Improved, much improved, or very much improved at landmark (score of 1, 2, or 3 on PGIC)	None	BOCF for weeks 0-7; LOCF from Tx7 to landmark
Treatment of Pain @ 6-Month Landmark (Tx27)				
Treatment of Syndrome @ 3-Month Landmark (Tx15)			$\geq 30\%$ improvement from baseline to landmark on FIQ-PFS score	
Treatment of Syndrome @ 6-Month Landmark (Tx27)				

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

(Source: Applicant's Table 9.7.1.5.1.3-1, Clinical Study Report, FMS-031, Vol. 1, p. 65)

Statistical Analysis in the Original Protocol

The primary efficacy analysis was to utilize the last observation carried forward (LOCF). If a patient withdrew from the study prior to visit Tx27, two approaches were to be used:

- Using the LOCF, data from the patient's last week in the study (two weeks for the pain data) was to be used for the endpoint analyses.

- A second set of analyses was to be performed without the LOCF, and patients who had not reached the endpoint were to be excluded from this observed case analysis (OC).

The primary efficacy analysis was to use a closed testing procedure (Hochberg) to control for experiment-wise error rate. Under this procedure, testing was to continue at an alpha of 0.05 until non-significance was reached. The testing was to begin with a responder analysis of pain and global for 200 mg versus placebo. If that analysis were significant, then a responder analysis of pain, global and functional status for 200 mg versus placebo was to be done. If both of the analysis proved to be significant, they were to be repeated in the same order for 100 mg versus placebo comparisons. Superiority was to be claimed for endpoints for both doses if both were significant versus placebo at the 0.05 alpha level.

Key Protocol Amendments

The following were the key amendments to the conduct of the study:

- Amendment 1 (October 2, 2003):
 - Addition of two sensitivity analyses to assess the impact of missing data on the primary efficacy results:
 - Patients prematurely discontinuing from the study prior to the 3-month landmark (Visit Tx15) were to be treated as nonresponders at the 3-month time point, while the LOCF approach would be applied to the data from patients who completed the 3-month landmark visit. A similar sensitivity analysis would be performed for the 6-month landmark time point.
 - The other sensitivity analysis was similar to the second one, except that the LOCF approach would be applied to patients who completed the 3-month landmark visit (Visit Tx15), but prematurely discontinued from the study prior to completing the 6-month landmark visit (Visit Tx27)
 - Removal of SF-36 as a primary efficacy variable and including it as a secondary efficacy variable
 - Patient global assessment of disease status was added as a secondary measure of fibromyalgia
 - For the composite responder endpoint, the change from baseline in FIQ-PF score was to be $\geq 30\%$ in order for a patient to be considered a responder
 - Prohibition of the use of the following concomitant treatments: trigger and tender point injections, anesthetic patches, biofeedback, transcutaneous electrical nerve stimulation.
 - Primary endpoint data were to be collected at Visits Tx26 and Tx27. The data collected at Visits Tx14 and Tx15 were to be analyzed as secondary endpoints.
- Amendment 2 (February 3, 2004):
 - Increase in the sample size to approximately 800 patients, based on the revised definition of composite responder specified in protocol Amendment 1.
 - **At the FDA's request: patients that completed the study were to enroll in a blinded extension study, in which all patients were to be blinded to the dose of milnacipran that they received.**

- At the FDA's request: The Patient Global Therapeutic Benefit Assessment was added as a secondary efficacy measure.
 - Dosing during the escalation phase was modified allowing for more flexibility with regard to patient symptom management during the first week: the patients were advised to take the medication with food, skip a dose, or after week 1, they could remain at the same dose level for up to four additional days.
 - At the FDA's request, the use of corticosteroids was clarified: Patients could take less than 10mg of prednisone or its equivalent as long as they were on a stable dose.
- Amendment 3 (March, 2005): *The Statistical Analysis Plan (SAP)*: The following are the amendments to the SAP:
 - Changes to the proposed indication: efficacy of milnacipran for two indications would now be sought:
 - treatment of the syndrome of fibromyalgia, and
 - treatment of the pain of fibromyalgia.
 - Changes to the primary objective: The revised primary objective was to demonstrate the efficacy of milnacipran 100 mg/day and 200 mg/day as compared to placebo in the treatment of the syndrome of fibromyalgia during Treatment Weeks 14-15 (3-month) or Treatment Weeks 26-27 (6-month), or in the treatment of the pain of fibromyalgia during Treatment Weeks 14-15 (3-month) or Treatment Weeks 26-27 (6-month).

The primary efficacy parameter for the "treatment of pain of fibromyalgia" indication was to be the composite responder status based on the morning 24-hour recall pain score and Patient Global Impression of Change (PGIC) rating at Visit Tx15 and Visit Tx27/ET.

A patient was to be classified as a responder for the "treatment of pain of fibromyalgia" indication if s/he reached Visit Tx7 and satisfied the following criteria at Visit Tx15 and Visit Tx27:

- $\geq 30\%$ pain reduction in the 24-hour recall pain score
- PGIC must have been rated as "improved," (i.e., scored as 1, 2 or 3 on the 1-7 scale).

The primary efficacy parameter for the "treatment of fibromyalgia syndrome" indication was to be the composite responder status based on the two domains described above, plus the additional domain of physical function as recorded on the Fibromyalgia Impact Questionnaire Physical Function Subscale (FIQ-PF) at Visit Tx15 and Visit Tx27/ET.

A patient was to be classified as a responder for the treatment of the "syndrome of fibromyalgia" if s/he satisfied the responder criteria for the treatment of pain of fibromyalgia and also presented greater than 30% improvement in FIQ physical function subscale score from baseline at Visit Tx15 and Visit Tx27.

- Baseline Determination: The baseline pain score was to be the average of the last 14 valid daily PED morning report daily 24-hour recall pain scores recorded during the 2-week

baseline interval. For other baseline values, it was defined as the value obtained at Visit BL2/Tx0 for CRF based efficacy data.

- Endpoint Determination: The endpoint for pain was to be the average of all valid daily 24-hour recall pain values collected on the PED during Weeks Tx14 and Tx15 (for the Visit Tx15 endpoint), and during Weeks Tx26 and Tx27 (for the Visit Tx27 endpoint), or the last two weeks on study for those patients terminating prior to Visit Tx27. For the PGIC and the FIQ-physical function scale, the endpoint determinations were to be the values recorded at Visits Tx15 and Tx27, or at the early termination visit for those patients terminating prior to Visit Tx27.
- A multiple comparisons procedure was to be used to control the overall type I error for comparisons of two doses of milnacipran to placebo at two primary time points and for two indications. The eight (8) primary comparisons described above were to be performed using the following sequential gatekeeping multiple testing procedure:
 - 1) 200 mg vs. placebo on pain at Weeks 14-15,
 - 2) 200 mg vs. placebo on syndrome at Weeks 14-15 and 200 mg vs. placebo on pain at Weeks 26-27,
 - 3) 200 mg vs. placebo on syndrome at Weeks 26-27,
 - 4) 100 mg vs. placebo on pain at Weeks 14-15,
 - 5) 100 mg vs. placebo on syndrome at Weeks 14-15 and 100 mg vs. placebo on pain at Weeks 26-27,
 - 6) 100 mg vs. placebo on syndrome at Weeks 26-27.

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

- Sensitivity analyses were to be performed to assess the impact of the missing data on the primary efficacy results by treating patients with missing primary efficacy data at primary time point as non-responders in the primary analyses. For the pain domain, patients with less than 7 valid observations during the primary time point period were to be treated as non-responders in the sensitivity analyses.
 - In the first sensitivity analysis, patients lacking primary efficacy data at the primary time point were to be treated as non-responders at the corresponding time point. For the pain domain, patients with less than 7 valid observations during the primary time point period were to be treated as non-responders in the sensitivity analyses.
 - In the second sensitivity analysis, patients prematurely discontinuing from the study prior to the 3-month landmark (Visit Tx15) were to be treated as non-responders at the 3-month time point, while the LOCF approach for the primary efficacy analyses was to be applied to the data from patients who completed the 3-month landmark visit. A similar sensitivity analysis was to be performed for the 6-month landmark time point.

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- The third sensitivity analysis is similar to the second one, except that the LOCF approach was to be applied to patients who complete the 3-month landmark visit (Visit Tx15), but prematurely discontinue from the study prior to completing the 6-month landmark visit (Visit Tx27).
- Changes to the secondary objectives: The secondary objectives were:
 - Compare the efficacy of 100 mg/day and 200 mg/day of milnacipran to placebo on the time course and durability of response, as well as on a number of additional secondary endpoints including fatigue, sleep, and mood.
 - Establish and compare the safety profiles of 100 and 200 mg milnacipran daily.
- Key secondary efficacy parameters to be added were as follows:
 - Responder status of each individual domain in the definition of the composite responder status at Visit Tx15 and Visit Tx27
 - Change from baseline in average morning 24-hour recall pain score (PED) by week
 - Change from baseline in average real time pain scores (PED, defined as morning current pain score, evening current pain score, and random prompt pain score) by week
 - Change from baseline in weekly pain scores (PED) by week
 - Analysis of time-weighted average (area under the curve [AUC]) of weekly average PED morning 24- hour recall pain scores for Weeks 4 to 15 and Weeks 4 to 27
 - Change from baseline in VAS assessments of pain during the past 24 hours and past 7 days by visit
- No multiple comparisons procedures were to be used for secondary parameters.

The Uniform Program Analysis

At time of the pre-NDA meeting (March, 2007), the Division required that studies evaluating the efficacy of treatments for fibromyalgia be only 3-months long. Also, the Division stated that it preferred conservative methods for imputing missing data, such as the baseline observation carried forward (BOCF) method. At that time, study FMS-031 was already concluded and the other Phase 3 pivotal study (MLN-02) was ongoing. The following were the differences in the two efficacy studies:

- Patients who had a BDI (Beck Depression Inventory) score higher than 25 were excluded from Study MLN-MD-02.
- Patients with a FIQ-PF (Fibromyalgia Impact Questionnaire-Physical Function) score of less than 4 at baseline were excluded from Study MLN-MD-02.
- Overall improvement as measured by the PGIC (Patient Global Impression of Change) was defined in Study FMS031 as a score of 1, 2, or 3, whereas it was defined as a score of 1 or 2 in Study MLN-MD-02.
- The LOCF was used in the primary analysis to impute missing data in Study FMS031, whereas BOCF was used in the primary analysis to impute missing data in Study MLN-MD-02.

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At the pre-NDA meeting it was agreed that the data from study FMS-031 could be re-analyzed similar to study MLN-MD-02. The Uniform Program Analysis (UPA) was developed to allow comparison of the efficacy results between the studies using the same methods. The UPA population (i.e. the population for which data were to be analyzed) was defined as all patients with:

- FIQ-PF score of ≥ 4 baseline
- BDI scores of ≤ 25 at baseline

The UPA was defined as:

- Primary efficacy endpoint: at 3 months
- Responder definition for the “treatment of fibromyalgia syndrome” indication:
 - Pain: 30% improvement in pain from baseline
 - Global: Score of 1 or 2 on the 7-point Likert PGIC scale
 - Physical function: improvement from baseline ≥ 6 on the SF-36
- Responder definition for the “treatment of fibromyalgia pain” indication:
 - Pain: 30% improvement in pain from baseline
 - Global: Score of 1 or 2 on the 7-point Likert PGIC scale
- Imputation method: BOCF

The table below summarizes the definition of treatment responders according to the UPA:

Table 68. Definition of Responder According to the UPA

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

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

(Source: Applicant's Table 9.7.1.5.1.3-2, Clinical Study Report, FMS-031, Vol. 1, p. 65)

Applicant's Study Results

Enrollment

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The study enrolled 888 patients in 46 study sites (3 sites did screen but did not enroll any patients to the study). All study sites were 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
- 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.

Table 69. Summary of Protocol Deviations in FMS031

<i>Class</i>	<i>Description</i>	<i>No. of Deviations</i>
I	Those who entered the study even though they did not satisfy the entry criteria	69
II	Those in whom withdrawal criteria developed during the study but who were not withdrawn	2
III	Those who received an incorrect dose	18
IV	Those who received an excluded concomitant treatment	165
Other	<ul style="list-style-type: none"> • Deviations in drug dosing (~1,500) • Missed protocol assessments or other procedural deviations (536) • Visit conducted outside the protocol-specified visit window (231) • Informed consent-related issues (119) 	~2400
	Total	~2700

(Source: Applicant' Table from Clinical Study Report, Vol. 1, p. 80)

The following is a listing of the protocol deviations by class:

Class I Deviations:

- 16 patients who were permitted to remain in the study after the Principal Investigator's and Medical Monitor's assessment of patients with medical conditions generally considered exclusionary (e.g., sleep apnea requiring CPAP, but generally well controlled; treated Hashimoto's thyroiditis)
- 14 patients in whom an alternative form of birth control was allowed
- 13 patients with positive criteria on the screening Mini-International Neuropsychiatric Interview (mostly involving patients with history of a suicide attempt but deemed to be at minimal overall risk for suicide)
- 7 patients with average baseline PED morning report pain scores < 50 (0-100 scale)
- 4 patients in whom tender point examination was not performed before randomization
- 4 patients with insufficient washout of excluded medications
- 2 patients in whom compliance with random prompt completion was < 70%
- 3 patients in whom screening laboratory assessments were not completed before randomization
- 2 patients with disability claims at time of randomization