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RESEARCH**

APPLICATION NUMBER:

22-256

STATISTICAL REVIEW(S)

4/8/09



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIostatISTICS

Report of Field Inspection

CLINICAL STUDIES

NDA: 22-256

Name of drug: milnacipran

Indication: fibromyalgia

Applicant: Forest/Cypress

Dates: Received 12/18/07; user fee (10 months) 10/18/08

Review priority: S

Biometrics division: Division of Biometrics II

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Clinical reviewer: Jane Filie, M.D.

Project manager: Diana Walker

At the request of the Division of Anesthesia, Analgesia and Rheumatology Products and of the Division of Scientific Investigations, I participated in an inspection at Forest Research Institute, Jersey City, New Jersey 1–2 December 2008. My participation in this inspection was occasioned by a letter to Thomas Laughren, M.D. 6 October 2008 from Mark Cohen, Executive Director of the Government Accountability Project. Mr. Cohen passed on the complaint of an anonymous informant concerning the handling of missing data. The informant called attention to 57 patients for whom the pain data that would partly determine the primary outcome measure were missing. He or she provided internal communications discussing possible efforts to retrieve data on these patients. Mr. Cohen particularly noted that “only the PED data of the 23 patients who were known to be positive responders to milnacipran were recovered.”

During the inspection I interviewed John V. Castellana, Ph.D., Senior Vice President, Biometrics & Medical Writing, Forest Research Institute. I asked about efforts to retrieve missing data and consideration of changes to the statistical analysis plan, hoping to receive information about the internal communications without revealing the existence and substance of the complaint. Dr. Castellana appeared to be unaware of the nature of our concern, but said there were no changes to the statistical analysis plan concerning the handling of missing data.

Dr. Castellana and I discussed the protocol and statistical analysis plan in detail. The primary measure of outcome was a “responder analysis” in which patients could be classified as responders only if they *both* reported a good global outcome (PGIC 1 or 2) and recorded a good pain score in their electronic diary. The 23 patients in question were those who had PGIC 1 or 2 and therefore might be classified as responders if they had good pain scores. The other 34 of the 57 patients would be nonresponders regardless of their pain scores. Thus, it was entirely appropriate to try to retrieve pain data for the 23 patients in case some truly were responders; it was less important to retrieve pain data for the 34 who would be classified as nonresponders regardless of the pain data. Note that these 34 were not left out of the analysis, but correctly classified as nonresponders.

It also appears from electronic data submitted in the application and reviewed by Joan Buenconsejo, Ph.D. that 22 of the 23 patients were ultimately classified as nonresponders anyway, either because pain data could not be retrieved or because it did not meet the responder criterion. Furthermore, the one patient classified as a responder was in the placebo group.

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

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

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/s/

Thomas Permutt
1/8/2009 09:17:27 AM
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9/8/08



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCE
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Statistical Review and Evaluation CLINICAL STUDIES

NDA: 22-256/N000

Name of drug: Milnacipran

Indication: Treatment of fibromyalgia syndrome

Applicant: Forest Research Institute and Cypress Bioscience, Inc.

Dates: Received 12/18/07, PDUFA 10/18/08

Review priority: S

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Keywords: NDA review, clinical studies

Table of Contents

1 Executive Summary	6
1.1 Conclusions and recommendations	6
1.2 Brief overview of clinical studies	6
1.3 Statistical issues and findings	7
2 Introduction	10
2.1 Overview	10
2.2 Data sources	12
3 Statistical Evaluation	13
3.1 Evaluation of efficacy	13
3.1.1 <i>study design and analysis plan</i>	13
3.1.2 <i>patient characteristics and dispositions</i>	20
3.1.2.1 <i>Study MLN-MD-02</i>	20
3.1.2.2 <i>Study FMS-031</i>	25
3.1.3 <i>Summary of results</i>	29
3.1.3.1 <i>Evaluation of Pain, Patient Global Improvement, Function Score in Controlled Studies</i>	29
3.2 Evaluation of safety	76
4 Findings in Subgroups and Special Populations	77
4.1 Sex, race and age	77
4.2 Other subgroups and special populations	82
5 Summary and Conclusions	88
5.1 Statistical issues and collective evidence	88
5.2 Conclusions and recommendations	89
6 Labeling	90
7 Appendix	102

List of Tables

Table 1: (Primary) Endpoint Analyses at 3 months landmark	9
Table 2: Overview of Clinical Efficacy Studies in Fibromyalgia.....	13
Table 3: Protocol Prespecified Definitions	18
Table 4: Uniform Program Analysis Definitions	18
Table 5: Patient Population – Study MLN-MD-02	20
Table 6: Summary of Patient Disposition – Study MLN-MD-02	21
Table 7: Number (%) of Patients who completed 3-month study – Study MLN-MD-02.....	21
Table 8: Number (%) of Patients who reached different study visits* – Study MLN-MD-02.....	23
Table 9: Number (%) of Patients with protocol violations – Study MLN-MD-02.....	24
Table 10: Number (%) of Patients – Study MLN-MD-02.....	24
Table 11: Patient Population – Study FMS-031	25
Table 12: Summary of Patient Disposition at 3 months – Study FMS-031.....	25
Table 13: Summary of Patient Disposition at 6 months – Study FMS-031.....	26
Table 14: Number (%) of Patients who reached different study visits* – Study FMS-031.....	27
Table 15: Number (%) of Patients with protocol violations – Study FMS-031	27
Table 16: Number (%) of Patients – Study FMS-031	28
Table 17: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark.....	29
Table 18: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark (Sensitivity Analyses)	30
Table 19: Average Pain Score Mean Change from Baseline to Endpoint and PGI at Endpoint	30
Table 20: Pain Only Responder Rate for Milnacipran Versus Placebo at the 3-Month Landmark.....	31
Table 21: Patient Global Improvement Only Responder Rate for Milnacipran Versus Placebo at the 3-Month Landmark.....	32
Table 22: Composite Pain Responder Rate for Milnacipran Versus Placebo by Week (ITT Population) – Study MLN-MD-02.....	39
Table 23: Analysis of Pain and Global Response Criteria (BOCF).....	42
Table 24: Analysis of Pain and Global Tests (BOCF) by Baseline Characteristics – Study MLN-MD-02.....	43
Table 25: SF-36 Physical Component Score and Composite Responder Rate for Syndrome for Milnacipran Versus Placebo at the 3-Month Landmark	44
Table 26: Composite Syndrome Responder Rate for Milnacipran Versus Placebo by Week (ITT Population)	45
Table 27: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark – Original Protocol-Specified Analysis (Study FMS-031)	48
Table 28: Primary Efficacy Analyses: Composite Syndrome Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark – Original Protocol-Specified Analysis (Study FMS-031)	49
Table 29: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran versus Placebo at the 3-Month Landmark – UPA Analysis (Study FMS-031)	51
Table 30: Primary Efficacy Analyses: Composite Syndrome Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark – UPA Analysis (Study FMS-031).....	52
Table 31: Average Pain Score Mean Change from Baseline to Endpoint and PGI at the 3-month landmark – UPA Analysis (Study FMS-031).....	53
Table 32: Pain Only Responder Rate for Milnacipran Versus Placebo at the 3-Month and 6-month Landmark (UPA Analysis) (Study FMS-031).....	54
Table 33: Patient Global Improvement Only Responder Rate for Milnacipran Versus Placebo at the 3-Month Landmark (UPA Analysis) - Study FMS-031	54
Table 34: Composite Pain Responder Rate for Milnacipran Versus Placebo by Week (UPA Analysis) – Study FMS-031	63
Table 35: Analysis of Pain and Global Tests (UPA Analysis, BOCF) – Study FMS-031.....	68

Table 36: Analysis of Pain and Global Tests (BOCF) at the 3-month landmark by Baseline Characteristics – Study FMS-031	69
Table 37: SF-36 Physical Component Score and Composite Responder Rate for Syndrome for Milnacipran Versus Placebo at the 3-Month Landmark – Study FMS-031	70
Table 38: Composite Syndrome Responder Rate for Milnacipran Versus Placebo by Week (ITT Population), BOCF – Study FMS-031	72
Table 39: Primary Endpoint at 3 months landmark – UPA Population	73
Table 40: Primary Endpoint at 6 months landmark – UPA Population	73
Table 41: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran versus Placebo at the 6-Month Landmark – UPA Analysis (Study FMS-031)	75

List of Figures

Figure 1: Timeline for Studies MLN-MD-02 and FMS031	14
Figure 2: Pain Response Profile for Patients with PGI =1 or PGI=2 (i.e. Composite Pain) – Study MLN-MD-02.....	33
Figure 3: Pain Response Profile for Patients with PGI > 2 – Study MLN-MD-02.....	34
Figure 4: Pain Response Profile – Study MLN-MD-02.....	34
Figure 5: Continuous Responder Analysis (Pain only) by Visit – Study MLN-MD-02.....	35
Figure 6: Pain Only Responder Rate (> 30% improvement) for Milnacipran Versus Placebo by Week – BOCF (Study MLN-MD-02)	38
Figure 7: Patient Global Impression of Change Responder Rate (very much improved or improved) for Milnacipran Versus Placebo by Week (ITT Population) – Study MLN-MD-02	39
Figure 8: Composite Pain Responder Rate for Milnacipran Versus Placebo by Week (ITT Population) – Study MLN-MD-02.....	40
Figure 9: Proportion of Responders by Week (>30% Improvement in Pain and < 2 in Global) – Study MLN-MD-02	41
Figure 10: Proportion of Responders by Week (>30% Improvement in Pain) – Study MLN-MD-02	41
Figure 11: Change from Baseline SF-36 Physical Component Score Responder Rate (> 6) for Milnacipran Versus Placebo by Week (ITT Population) - BOCF.....	45
Figure 12: Composite Syndrome Responder Rate for Milnacipran Versus Placebo by Week (ITT Population)	46
Figure 13: Pain Response Profile for Patients with PGI =1 or PGI=2 (i.e. Composite Pain) – Study FMS-031 (UPA Analysis).....	56
Figure 14: Pain Response Profile for Patients with PGI >2 – Study FMS-031 (UPA Analysis)	56
Figure 15: Pain Response Profile – Study FMS-031 (UPA Analysis)	57
Figure 16: Continuous Responder Analysis (Pain only) by Visit – FMS-031	58
Figure 17: Pain Only Responder Rate (> 30% improvement) for Milnacipran Versus Placebo by Week (UPA) – Study FMS-031	62
Figure 18: Patient Global Impression of Change Responder Rate (very much improved or improved) for Milnacipran Versus Placebo by Week (UPA) using BOCF – Study FMS-031	63
Figure 19: Composite Pain Responder Rate for Milnacipran Versus Placebo by Week (UPA analysis) – Study FMS-031	64
Figure 20: Proportion of Responders by Week (>30% Improvement in Pain and < 2 in Global) at the 3-month landmark – Study FMS-031	65
Figure 21: Proportion of Responders by Week (>30% Improvement in Pain and < 2 in Global) at the 6-month landmark – Study FMS-031	65
Figure 22: Proportion of Responders by Week up to week 15 (>30% Improvement in Pain) – Study FMS-031.....	66

Figure 23: Proportion of Responders by Week up to week 27 (>30% Improvement in Pain) – Study FMS-031.....	67
Figure 24: Change from Baseline SF-36 Physical Component Score Responder Rate (> 6) for Milnacipran Versus Placebo by Week (ITT Population) BOCF – Study FMS-031	71
Figure 25: Composite Syndrome Responder Rate for Milnacipran Versus Placebo by Week (ITT Population)	72
Figure 26: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Pooled Data	78
Figure 27: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Pooled Data	78
Figure 28: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Pooled Data.....	79
Figure 29: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Study FMS-031	79
Figure 30: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Study FMS-031	80
Figure 31: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Study FMS-031	80
Figure 32: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Study MLN-MD-02.....	81
Figure 33: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Study MLN-MD-02.....	81
Figure 34: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Study MLN-MD-02	82
Figure 35: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Pooled Studies	83
Figure 36: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study FMS-031	83
Figure 37: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study MLN-MD-02	84
Figure 38: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Pooled Studies	85
Figure 39: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study FMS-031	86
Figure 40: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study MLN-MD-02	87

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The Applicants, Forest Research Institute and Cypress Bioscience, Inc, seek to market Milnacipran HCl for the treatment of fibromyalgia syndrome (FMS). The Applicant defined treatment of FMS by achievement of concurrent and clinically meaningful improvement in the domains of pain, patient global assessment, and physical function.

The evidence taken collectively from studies reviewed indicated statistical support in favor of milnacipran 200 mg/day in the treatment of pain using the composite pain responder definition and treatment of fibromyalgia syndrome using the composite syndrome responder definition at the 3-month landmark. There is also evidence supporting the 100 mg/d dose.

Based on the weekly responder analyses of the improvement in pain scores, as well as the response profile among responders at Week 12, some patients experience a decrease in pain as early as Week 3 after the dose titration period ends, which persists throughout the study.

When the domains (i.e. pain, global and function by SF36-PCS) are analyzed separately, there is no evidence that the milnacipran groups are different from placebo in each domain (i.e. pain, global or SF36 PCS) in Study FMS-031 and in pain and SF36-PCS in Study MLN-MD-02. In Study FMS-031, it appears that the composite response is influenced by combination of these domains. Meanwhile, in Study MLN-MD-02, it appears that treatment difference in the composite response may be influenced by patients achieving a good global score.

There is insufficient evidence to show that milnacipran-treated patients are associated with significant improvement in pain based on the composite pain response criteria or improvement in syndrome based on composite syndrome response criteria at six months. Furthermore, there is no evidence that patients treated with milnacipran continue to respond for up to 68 weeks.

Presence of depressive disorder based on baseline Beck Depression Index (BDI) score was also examined to determine whether it had an impact on patient response. Like the other subgroups studied (age, gender, and race), there were no remarkable effects of baseline BDI status according to the composite pain endpoint and composite syndrome analyses. Because nearly all subjects in each study had BDI score of ≤ 25 at enrollment, it is difficult to distinguish the possible treatment effects for the subgroups of depression status.

I defer discussion on the clinical relevance of the treatment differences as well as the dosing regimen to Dr. Filie in terms of pain reduction, positive global and improve functioning scores.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Milnacipran hydrochloride (HCl) is being codeveloped by Forest Research Institute and Cypress Bioscience, Inc.

The proposed dosage recommendation is to initiate treatment at 12.5 mg on the first day and increase to 50 mg twice a day (100 mg/day) within the first week based on efficacy and tolerability. Patients who do not experience sufficient benefit at 50 mg BID may be further increased to 100 mg BID based on individual patient response. Furthermore, they propose that the dose should be adjusted in patients with severe renal impairment

The development plan for the treatment of fibromyalgia syndrome was introduced to the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products under IND 63,736. Following the reorganization of the therapeutic areas in the Center for Drug Evaluation and Research, the drug fell under the purview of the Division of Anesthesia, Analgesia, and Rheumatology Products. Key elements of the advice received from the Division were: 1) two adequate and well-controlled trials of three-month duration, 2) two possible indications for milnacipran: treatment of the pain of fibromyalgia, or treatment of fibromyalgia syndrome with statistical closed-test procedure for the two hypotheses given the possible change of indication, 3) BOCF as the imputation method for missing data, 4) the SF36 PCS as a measure of physical function, and 5) the use of rescue and non-allowed medication incorporated in the primary endpoint.

Five clinical efficacy studies were conducted in the FMS population (i.e. one phase 2 study, two phase 3 studies, and two long-term extension studies). Data from two of the five efficacy studies, Study MLN-MD-02 and Study FMS031, provide the support for the proposed indication. Key characteristics of these two studies are summarized as follow:

- Study MLN-MD-02 was a multicenter, randomized, double-blind, placebo-controlled, three-arm parallel-group study to investigate the safety and efficacy of milnacipran 200 mg/d and 100 mg/d by mouth (PO) in patients with FMS conducted at 86 study centers in the United States. Eligible patients were then randomized to treatment with placebo or with 100 mg/d or 200 mg/d of milnacipran (1:1:1), BID dosing. Patients received 12 weeks of treatment after the 3-week dose-escalation phase. Primary efficacy was evaluated at the 15-week landmark. A subset of patients received up to 29 weeks of placebo-controlled treatment.
- Study FMS031 was a multicenter, randomized, double-blind, placebo-controlled, three-arm parallel-group study to investigate the safety and efficacy of milnacipran 200 mg/d and 100 mg/d PO in patients with FMS conducted at 59 sites in the United States. Eligible patients were then randomized to treatment with placebo or with 100 mg/d or 200 mg/d of milnacipran (1:1:2), BID dosing. Patients received up to 24 weeks of treatment after the 3-week dose-escalation phase, for a total of up to 27 weeks of drug exposure

1.3 STATISTICAL ISSUES AND FINDINGS

During my review of the submission, I identified some issues that warranted further consideration, and I identified some issues that could be resolved by recoding and re-analyzing the data. One statistical issue is the choice of imputation strategy for the 6-month endpoint in Study FMS-031. I also identified various discrepancies between the raw and derived datasets. Reasons for most of these discrepancies were found not to affect the overall conclusion.

Table 1 presents the results of the primary endpoint analyses.

Based on the evidence taken collectively from the two Phase 3 studies, milnacipran 200 mg/day is different from placebo in the treatment of pain using the composite pain responder definition and treatment of fibromyalgia syndrome using the composite syndrome responder definition at the 3-month landmark. There is evidence in one study that milnacipran 100 mg/day is different from placebo in the treatment of pain using the composite pain responder definition and treatment of fibromyalgia syndrome using the composite syndrome responder definition at the 3-month landmark. Numerically, there appears to be no difference in the proportion of responders (i.e. composite pain or composite syndrome) between the two milnacipran groups. The response profile between these two milnacipran arms appears to be similar across different range of response.

There is no evidence in both Phase 3 studies that milnacipran is associated with improvements in pain (i.e. pain domain only) or improvements in function (i.e. function domain only) at three months of therapy. There is some evidence in one study that the treatment difference seems to occur or being driven by the patient global test score; however this finding is not observed in the other Phase 3 study. Descriptive

statistics of each of these domains suggest that pain, patient global, and function (based on SF-36 PCS) are trending in the direction similar to the primary endpoint.

In summary, 30% to 35% of patients in the milnacipran group will achieve at least a 30% improvement in pain score from baseline at the end of the 3-month landmark compared to 25% to 28% in the placebo group. When patient global is included in the responder definition (i.e. Composite Pain), the proportion of responders becomes 23% to 27% in the milnacipran group and 16% to 19% in the placebo group. When function is included in the responder definition (i.e. Composite Syndrome), the proportion of responder in the milnacipran group is around 14% to 20% and around 9 to 12% in the placebo group. As the responder criteria become more stringent, the proportion of responders also decreases. An important clinical question is whether a quarter of patients who received milnacipran treatment and who responded (based on "composite pain" response criteria) adequate to conclude the efficacy of milnacipran in the treatment of pain.

The 6-month landmark is evaluated in only one study. Although numerically, a higher proportion of patients in the milnacipran groups achieve the composite pain responder criteria as well as the composite syndrome responder criteria compared to the placebo at the 6-month landmark, this evidence was not supported statistically.

In both studies, although there are some patients who experienced a decrease in pain as early as week 1, treatment difference did not occur until after the dose titration period ends (i.e. week 3). Furthermore, from the result of Study FMS-031, it appears that no additional benefit can be seen after Week 15.

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Table 1: (Primary) Endpoint Analyses at 3 months landmark

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
STUDY MLN-MD-02			
	N=401	N=399	N=396
Pain Domain Only	101 (25%)	124 (31%) 1.34 (<1.0, 1.8)	119 (30%) 1.28 (0.9, 1.8)
Global Domain Only	92 (23%)	125 (31%) 1.53 (1.1, 2.1)	129 (33%) 1.62 (1.2, 2.2)
Function Domain Only	86 (21%)	108 (27%) 1.37 (<1.0, 1.9)	89 (22%) 1.10 (0.8, 1.6)
Composite Pain	66 (16%)	91 (23%) 1.50 (1.1, 2.1) p=0.0252	98 (25%) 1.68 (1.2, 2.4) p=0.0037
Composite Syndrome	35 (9%)	58 (15%) 1.79 (1.1, 2.8) p=0.011	55 (14%) 1.75 (1.1, 2.8) p=0.015
STUDY FMS-031 (UPA Analysis Population)			
	N=223	N=224	N=441
Pain Domain Only	62 (28%)	76 (34%) 1.34 (0.9, 2.0)	155 (35%) 1.42 (<1.0, 2.0)
Global Domain Only	60(27%)	74 (33%) 1.34 (0.9, 2.0)	145 (33%) 1.33 (0.9, 1.9)
Function Domain Only	61 (27%)	71 (32%) 1.28 (0.8, 2.0)	131 (30%) 1.18 (0.8, 1.7)
Composite Pain	43 (19%)	61 (27%) 1.55 (<1.0, 2.4) p=0.0554	118 (27%) 1.54 (1.0, 2.3) p=0.0323
Composite Syndrome	27 (12%)	44 (20%) 1.84 (1.1, 3.2) p=0.0277	85 (19%) 1.80 (1.1, 2.9) p=0.0175

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2 INTRODUCTION

2.1 OVERVIEW

Milnacipran hydrochloride (HCl) is a norepinephrine-serotonin reuptake inhibitor (NSRI) being codeveloped by Forest Research Institute and Cypress Bioscience, Inc. and is proposed for the treatment of fibromyalgia syndrome (FMS). The Applicant defined treatment of FMS by achievement of concurrent and clinically meaningful improvement in the domains of pain, patient global assessment, and physical function. The proposed dosage recommendation is to initiate treatment at 12.5 mg on the first day and increase to 50 mg twice a day (100 mg/day) within the first week based on efficacy and tolerability. Patients who do not experience sufficient benefit at 50 mg BID may be further increased to 100 mg BID based on individual patient response. Furthermore, they proposed that the dose should be adjusted in patients with severe renal impairment.

The development plan for the treatment of fibromyalgia syndrome was introduced to the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products under IND 63,736. Following the reorganization of the therapeutic areas in the Center for Drug Evaluation and Research, the drug fell under the purview of the Division of Anesthesia, Analgesia, and Rheumatology Products. The key milestones in the clinical development program are highlighted in Dr. Filie's review. Statistical issues were discussed during several meetings and key issues are summarized below:

1. Special Protocol Assessment SN009 and SN010 (letter September 12, 2003): The Sponsor and the Division did not reach an agreement. The following are some of the comments summarized by the Applicant:
 - a. One 6-month study that demonstrates efficacy at 6 months, with a positive trend at 3 months. Statistical superiority of milnacipran should be demonstrated over placebo based on a responder analysis of pain plus global (two-component analysis) or pain plus global plus function (three-component analysis).
 - b. The second study would be a 3-month study using the same endpoints at the 3-month landmark.
 - c. Success on the two-component composite responder analysis would be consistent with a claim for the treatment of the pain of fibromyalgia, whereas success on the three-component composite responder analysis would be consistent with a claim for the treatment of fibromyalgia syndrome.
 - d. In calculating the composite responder analysis, the pain outcome need to achieve a 30% improvement over baseline values, using a two-week average at baseline and a two-week average at landmark. For the patient global domain, the improvement was defined as a score of 1, 2 or 3 on the 7-point Likert Patient Global Impression of Change (PGIC) scale. For the physical function domain, the Division requested that improvement be defined as a 30% improvement from baseline on the Fibromyalgia Impact questionnaire (FIQ-PF) as the primary outcome variable, and the SF-36 Physical Component Score (SF-36 PCS) as a secondary outcome variable.
2. Type A - Post SPA Review Meeting (October 14, 2003)
 - a. The Division reminded the Sponsor to submit a revised protocol and should contain a detailed Statistical Analysis Plan (SAP). The SAP should include information on how the indication (treatment for fibromyalgia syndrome and treatment for pain related with fibromyalgia syndrome) will be approached.
 - b. The Division stated that the pain and functional outcomes need to demonstrate efficacy on both a landmark (end-of-study) time point as well as a time-weighted average (evaluated at 6-week intervals) during the entire trial. The requirement for a minimum of 30% improvement compared with baseline values applies to both outcomes and both time points. The PGIC should be a dichotomous yes- or no-type outcome.
 - c. Analyses planned for the 3-month study should also be performed for the 6-month study, at the 3-month time point in addition to any planned analyses for the 6-month study.
 - d. Use of rescue medications and how this use will factor in to whether or not a patient is censored from any efficacy analysis should be clearly delineated in the SAP.

3. August 13, 2004 and September 21, 2004 Advice/Response letters
 - a. The Division suggested that the Sponsor considers a statistical closed-test procedure for the two hypotheses given the possible change of indication between the treatments of fibromyalgia versus the pain of fibromyalgia. The Division also cautioned that the proposed method of imputation by the Sponsor (NOT SPECIFIED in the review or letter) for missing pain outcome data is a variation of the LOCF approach and can be problematic for a meaningful interpretation of the results of any data analysis. Therefore, the Division recommended that the Sponsor conduct additional analyses in assessing the impact of missing data. The Division agreed that the use of logistic regression for a responder approach is acceptable.
 - b. The Division reiterated that an indication for the treatment of fibromyalgia syndrome must include assessments of pain, patient global and function that all demonstrate success at the landmark time-point for both the 3- and 6-month trials. In addition, there should be a favorable trend at the 3 month time-point in the 6-month trial for all outcomes. The outcomes, particularly pain, should be characterized throughout the trials with a time-weighted average approach to help understand treatment responses.
 - c. The Sponsor was encouraged to alter the definition of a responder with a smaller number of days of use of rescue within the final assessment period, and to reconsider inclusion of non-allowed narcotics in this definition unless you can provide a justification for why so much use of rescue and non-allowed narcotics could be consistent with a finding of efficacy.

4. Type C – General Guidance Meeting (May 9, 2005)
 - a. The Division stated that a true responder analysis does not need to include imputed data. Patients that are unable to complete the study are designated to be nonresponders. Responders for the 6-month endpoint of Study FMS031 must be defined by at least 27 weeks of therapy (24 weeks after titration). Similarly, for the 3-month endpoint, the definition of responders as patients reaching the 4-week visit is not acceptable. For the 3-month endpoint, 15 weeks (12 weeks after titration) is the appropriate duration to be considered a responder. For a responder analysis, patients who dropout before 3 or 6 months due to lack of efficacy or adverse events can only be considered nonresponders. Patients who dropout for other reasons should be very few in number and should also be considered nonresponders.
 - b. The use of Last Observation Carried Forward (LOCF) as the sole method for imputing missing data is discouraged. The division will evaluate alternate methods of imputing missing data, such as Baseline Observation Carried Forward (BOCF), to assess the effects of the method of imputation and encouraged Forest to do the same. Forest stated that they are using imputation as a secondary analysis as well as Area Under the Curve (AUC). Forest will also perform a responder analysis without imputation at the 15-week (12 weeks after titration) timepoint. If there are numerous dropouts because patients are doing well following the 3- month timepoint, the Division will weigh the totality of evidence when evaluating efficacy at 6 months.

5. Type C – Clinical and Statistical Issues (June 2, 2006)
 - a. The Division stated that two adequate and well-controlled trials would be acceptable for NDA submission and that studies of three-month duration would be adequate. Studies of six-month duration were not deemed necessary, provided the duration of treatment and number of patients still allowed for an adequate safety database. At that point, the original 6-month study, FMS031 has been completed and a second 6-month study, MLN-MD-02 was ongoing, thus will be truncated at the three-month mark once the last patients recruited reached the three-month mark for receiving treatment.
 - b. The Sponsor was informed that the Division was reconsidering the requirements for a pain-related claim and that, as an alternative to the responder approach, a more traditional study design documenting statistical difference in mean change in Visual Analog Scale (VAS) pain from baseline might be an acceptable approach.
 - c. For the fibromyalgia syndrome claim, it would still require a multi-domain responder-based approach.

6. Type B – Pre-NDA meeting (March 16, 2007)
 - a. The Division reminded the Sponsor that the main purpose of the integrated summary of efficacy is to explain how the results of the individual studies support the claims being made. Although required analyses by age, sex, and race are often best conducted on the pooled data, a pooled analysis of individual studies is not usually very helpful in achieving the goal

of the ISE. However, in the case of conflicting results, a statistical meta-analysis of the studies may be appropriate.

- b. The Sponsor described plans to re-analyze Study FMS031 using the analysis methods of MLN-MD-02. The Sponsor confirmed that both the SF36-PCS and the Beck Depression Inventory (BDI) were used during the trial as a secondary efficacy measures.
- c. In Summary, two indications are possible for milnacipran: treatment of the pain of fibromyalgia, or treatment of fibromyalgia syndrome. A trial length of 3 months is adequate, BOCF is an acceptable imputation method and the SF36 PCF can be used as a measure of physical function. The Sponsor also informed that Continuous Responder Analyses are recommended but not required.

Five clinical efficacy studies were conducted in the FMS population. Data from two of the five efficacy studies, Study MLN-MD-02 and Study FMS031, provide the support for the proposed indication. Key characteristics of these two studies are summarized as follows:

- Study MLN-MD-02 was a multicenter, randomized, double-blind, placebo-controlled, three-arm parallel-group study to investigate the safety and efficacy of milnacipran 200 mg/d and 100 mg/d by mouth (PO) in patients with FMS conducted at 86 study centers in the United States. Eligible patients were then randomized to treatment with placebo or with 100 mg/d or 200 mg/d of milnacipran (1:1:1), BID dosing. Patients received 12 weeks of treatment after the 3-week dose-escalation phase. Primary efficacy was evaluated at the 15-week landmark. A subset of patients received up to 29 weeks of placebo-controlled treatment.
- Study FMS031 was a multicenter, randomized, double-blind, placebo-controlled, three-arm parallel-group study to investigate the safety and efficacy of milnacipran 200 mg/d and 100 mg/d PO in patients with FMS conducted at 59 sites in the United States. Eligible patients were then randomized to treatment with placebo or with 100 mg/d or 200 mg/d of milnacipran (1:1:2), BID dosing. Patients received up to 24 weeks of treatment after the 3-week dose-escalation phase, for a total of up to 27 weeks of drug exposure

Three other studies described in the submission consist of two randomized, double-blind extension studies MLN-MD-04 (the extension of Study MLN-MD-02) and FMS-034 (the extension to Study FMS-031) and one randomized, double-blind, phase 2 study FMS-021.

2.2 DATA SOURCES

This statistical review is based on data submitted in studies FMS-031 and MLN-MD-02.

The electronic submission of this NDA can be found at:
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3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The clinical program comprised three double-blind, placebo-controlled studies (conducted from September 1999 to July 2006) and two long-term extension studies. Of the three controlled studies, one was flexible-dose Phase 2 study, and two were Phase 3, randomized, double-blind, fixed-dose studies (Studies FMS031 and MLN-MD-02). Table 2 summarizes the two Phase 3 studies including objectives, treatment duration, and number of patients randomized.

Table 2: Overview of Clinical Efficacy Studies in Fibromyalgia

<i>Study Number</i>	<i>Study Design/Objective</i>	<i>Treatment Groups</i>	<i>No. of Patients Randomized</i>	<i>Treatment Duration</i>
<i>Pivotal Studies</i>				
MLN-MD-02	Randomized, double-blind, placebo-controlled, parallel-group, fixed-dose Pivotal safety and efficacy	Placebo	401	up to 29 weeks ^a
		Milnacipran 100 mg/d (BID)	399	
		Milnacipran 200 mg/d (BID)	396	
FMS031	Randomized, double-blind, placebo-controlled, parallel-group, fixed-dose Pivotal safety and efficacy	Placebo	223	27 weeks ^a
		Milnacipran 100 mg/d (BID)	224	
		Milnacipran 200 mg/d (BID)	441	

^a Reflects final duration after amendments and agency agreement.

BID = twice daily; PO = by mouth; QD = every day.

Source: Summary of Clinical Efficacy page 15

3.1.1 STUDY DESIGN AND ANALYSIS PLAN

The primary focus of my review is on the two randomized, double-blind, fixed-dose studies (Studies FMS031 and MLN-MD-02). Results from these studies were included in the proposed Clinical Section of the product label.

The primary objective of these two phase 3 studies was to evaluate the safety and efficacy of milnacipran relative to placebo for 3 months in the treatment of fibromyalgia syndrome and the treatment of fibromyalgia pain.

Except for study duration and eligibility criteria, the study design of the two studies was nearly identical. Male and female patients aged 18 to 70 who met the 1990 American College of Rheumatology (ACR) criteria for fibromyalgia, had no current major depressive disorder using the Mini International Neuropsychiatric Interview (MINI), had a baseline average visual analog scale (VAS) pain score of 50 (note that in Study MLN-MD-02, the requirement is 40), and met all inclusion/exclusion criteria were eligible for enrollment in Study FMS031. Additional criteria needed to be eligible for enrollment in Study MLN-MD-02 included a willingness to withdraw from CNS-active therapies for FMS and discontinue nonpharmacologic treatments for FMS, a **Fibromyalgia Impact Questionnaire-Physical Function (FIQ-PF) score of ≥ 4** , and a Beck Depression Inventory (BDI) score of ≤ 25 .

In both studies, patients entered a 2-week baseline period after a washout period from disallowed medications.

During this 2-week baseline period, values for baseline safety and efficacy variables using anchored visual analog scales (VAS) were recorded in an electronic Patient Experience Diary (PED). For both studies (MLN-MD-02 and FMS031), study drug was packaged in capsules containing 12.5 mg, 25 mg, and 50 mg of milnacipran or identical placebo. An interactive voice response system (IVRS) was used by study sites for randomization, dose escalation, and resupply.

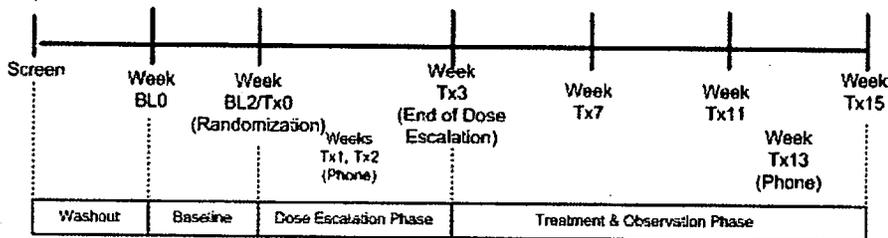
Eligible patients, having a minimum average baseline VAS pain score of 40 (in Study MLN-MD-02) or 50 (in Study FMS-031), were then randomly assigned to one of three treatment groups: placebo, 100 mg/d of milnacipran, or 200 mg/d of milnacipran, all taken twice daily (BID). Patients were assigned to treatment group in a 1:1:2 and 1:1:1 ratio in Studies FMS031 and MLN-MD-02, respectively. Both studies had a 3-week dose escalation period before the assigned dose level was reached. During the first week of dose titration, the doses of patients randomized to active treatment were titrated from 12.5 mg/d (Day 1) to 25 mg/d (Days 2 and 3) to 50 mg/d (Days 4 through 7). In the second week, the doses of all patients were up-titrated to 100 mg/d active drug. During the third week, the doses of patients randomized to 200 mg/d were escalated to that level, while patients randomized to 100 mg/d or placebo underwent a sham dose escalation to maintain blinding integrity.

During the Dose Escalation Phase, the physician may have consulted with the patient to confirm tolerability; telephone contact was made after the first and second weeks. The physician could allow the patient to skip a dose or, after Week 1, to remain at a particular dose level for up to 4 additional days. No dose reduction was allowed for patients after completing the dose escalation portion of the study.

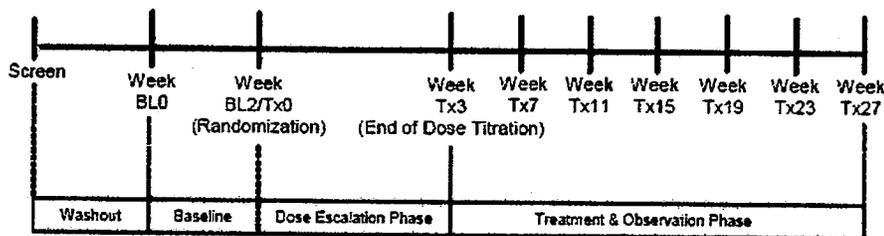
Patients in Study MLN-MD-02 received 12 weeks of treatment after the 3 weeks of the dose-escalation phase, for a total of 15 weeks of drug exposure, while patients in Study FMS031 received 24 weeks of treatment after the 3-week dose escalation phase, for a total of 27 weeks of drug exposure. Figure 1 depicts the study timeline.

Figure 1: Timeline for Studies MLN-MD-02 and FMS031

Study MLN-MD-02



Study FMS031



Patients in both studies completed the electronic diary daily, as well as additional paper-based assessments during office visits.

Efficacy and safety assessments during office visits were conducted at the Screening Visit, the Randomization Visit, the end of dose escalation (Week 3), and at 4-week intervals thereafter. Patients who successfully completed these double-blind studies were eligible to enter an extension study (Study MLN-MD-04 for Study MLN-MD-02 and Study FMS034 for Study FMS031) for additional treatment.

Efficacy Endpoints

Primary efficacy assessment for the treatment of fibromyalgia syndrome was a composite responder analysis at the 3-month landmark based on three domains: pain (VAS, morning 24-hour recall); patient global, as recorded by the PGIC; and physical function, as measured by the SF-36 PCS.

In Study FMS031, the FIQ-PF was used in the original primary efficacy analyses as the measure of physical function in the composite response for fibromyalgia syndrome; SF-36 PCS replaced the FIQ-PF as the prospective physical function component in Study MLN-MD-02, as well as in the reanalysis of Study FMS031.

The primary efficacy endpoint for the treatment of FMS was defined as the proportion of patients who met the following three response criteria concurrently:

- Pain: a 30% reduction from baseline in 24-hour recall pain score recorded in the daily morning report in the PED

AND

- Patient Global: a rating of “very much improved” or “much improved” (i.e., a rating of 1 or 2 on the PGIC)

AND

- Physical Function: improvement from baseline of at least 6 points in the SF-36 PCS

For assessing the treatment of fibromyalgia pain, the primary efficacy assessment was a composite responder analysis at the 3-month landmark based on two domains: pain (morning 24-hour recall) and the PGIC.

The following are the descriptions of the components:

- For the pain domain, the primary pain assessment was the patient’s morning self-report of daily pain (for the past 24-hour period) using anchors of “no pain” and “worst possible pain” on a 0-to-100 VAS, as collected via entries made by patients on an electronic PED. In addition to the daily morning report, instantaneous pain was recorded at a variety of times throughout the day (evening report and randomly prompted pain reports); there was also a weekly pain report (for the past week). Daily pain data collected from the morning report were used in the primary analysis.

The baseline for pain was defined as the last 14 days with valid data immediately before and including the day of Visit BL2/Tx0. In calculating the average pain score, observations within 2 days after any rescue medication or nonallowed narcotic medication use were considered invalid and excluded from the calculation. If there were fewer than 14 days with valid 24-hour recall pain data between Visits BL0 and BL2/Tx0, the average of the available days with valid data was used.

The primary endpoint period for pain was defined as the 14 days immediately before and including the day of Visit Tx15 or Visit Tx27, also referred to as Treatment Weeks 14-15 or Weeks 26-27, respectively.

- For the patient global domain, the fibromyalgia-specific PGIC was recorded as a periodic efficacy assessment. This scale ranged from 1 (very much improved) to 7 (very much worse) relative to the start of treatment with double-blind study drug and was assessed during office visits at Weeks 3, 7, 11, and 15/early termination (ET).

The PGIC at Visit Tx15 or Visit Tx27 had to be rated as “much improved or very much improved,” i.e., 1 or 2 on the 1-7 scale. If no observed PGIC was available, the patient was defined as a nonresponder.

- The physical function domain relative to treatment of fibromyalgia syndrome was measured using the PCS of the SF-36 in the composite response of Study MLN-MD-02 and in the reanalysis of Study FMS031. The SF-36 is a brief, self-administered patient questionnaire for the assessment of health status, functional status, and quality of life. The SF-36 measures eight domains of health status: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and mental health. There are two component summary scores: the Physical Component Summary (SF-36 PCS), and the Mental Component Summary (SF-36 MCS), which are calculated by combining and weighting the various individual domains. The SF-36 PCS and SF-36 MCS have been standardized to have a mean of 50 (SD = 10) in the general healthy US population. The entire SF-36 was administered during office visits at baseline, and Treatment Weeks 3, 7, 11, and 15/ET.

The physical functioning of patients was measured using the physical function (PF) subscale of the FIQ. This measure was replaced with the SF-36 PCS for reanalysis. The FIQ-PF is an 11-question subset of the 20-item FIQ scale that specifically assesses physical limitations affecting a patient's activities of daily living, providing a score that can be used to assess changes in functioning over time. The entire FIQ was administered during office visits at baseline, and Treatment Weeks 3, 7, 11, and 15/ET.

In each component, if a patient took a rescue medication or a nonallowed narcotic medication on more than 2 days (in pain domain) or within 2 days (in patient global domain and function domain) during the primary end point period before the day of the visit, he or she was defined as a nonresponder. In calculating the average pain score, observations within 2 days (excluding starting day of rescue medication or nonallowed narcotic medication use) after any rescue medication or nonallowed narcotic medication use were considered invalid and excluded from the calculation.

The secondary efficacy parameters for both pivotal studies comprised the time-weighted averages (i.e., area under the curve [AUC]) of the weekly average PED morning recall pain scores for Weeks 4 through 15 of the treatment and observation phase, PGIC for visits corresponding to Weeks 3 through 15, and the SF-36 PCS for visits corresponding to Weeks 3 through 15. Additional secondary endpoints assessed various aspects of fibromyalgia including Beck Depression Index score, multidimensional health assessment disability subscale, sleep (MOS-Sleep Scale), fatigue (Multidimensional Fatigue Assessment [MFI]), and Arizona sexual experience scale.

Efficacy Analyses

Efficacy analyses in both studies are based on the ITT population, defined as all randomized patients who received at least one dose of double-blind study drug.

The following is a summary of the analysis plan in Study MLN-MD-02:

The proportion of responders to the treatment of the syndrome of fibromyalgia was analyzed using a logistic regression model, with treatment group, baseline pain score, and baseline SF-36 PCS as explanatory variables. The proportion of responders to the treatment of fibromyalgia pain was analyzed using a logistic regression model, with treatment group and baseline pain score as explanatory variables.

For the composite responder analysis, the baseline observation carried forward (BOCF) technique was applied to patients with missing values at the 3-month landmark for the primary efficacy parameters. Specifically, patients who lacked primary efficacy data at the 3-month landmark were defined as nonresponders.

The Applicant conducted four sensitivity analyses to assess the effect of missing data on results of the primary efficacy analyses:

- In the first sensitivity analysis, the last observation carried forward (LOCF) approach was applied to all patients who lacked primary efficacy data at the 3-month landmark.
- In the second sensitivity analysis, patients prematurely discontinuing the study before the 3-month Landmark Visit (Visit Tx15) were treated as nonresponders at 3 months (BOCF), while the LOCF approach described for the primary efficacy analyses was applied to missing data from patients who completed the 3-month Landmark Visit. This is the modified BOCF approach.
- A third sensitivity analysis was the composite responder analysis based on observed cases (OC) at the 3-month landmark for patients completing the 3-month study.
- A fourth sensitivity analysis was performed to analyze the subpopulation of patients who had a baseline BDI score ≤ 25 using the BOCF approach.

In order to control the overall type I error for comparisons of two dosages of milnacipran to placebo for two indications, the following sequential gatekeeping multiple comparison procedure was used:

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

At each step above, a closed testing procedure was used to test the individual hypothesis in that family at the family-wise 5% level of significance. Step 2 was performed only if both hypotheses in Step 1 were rejected based on the closed testing procedure. Specifically, within each step, the average effects of the two active dosages were compared with placebo using the logistic regression model. If this global test was significant at the two-sided significance level of 0.05, then each individual dosage was compared with placebo simultaneously at the conventional two-sided significance level of 0.05. This is a closed testing procedure that controls the overall type I error strongly within the family.

In order to mimic the analysis plan used in Study MLN-MD-02, the Applicant proposed to analyze the data in Study FMS031 in two ways: protocol pre-specified definitions (Table 3), and Uniform Program Analysis (UPA) definitions (Table 4). The purpose of the UPA is to compare the efficacy results among studies using the same time point, responder definition, missing data imputation method and population. Of note, this UPA methodology uses a definition resembling that used in Study MLN-MD-02 in terms of global response (i.e. using much improved or very much improved only); substitutes the originally proposed measure of physical function (the SF-36-PCS) for the FIQ-PF; and uses baseline observation carried forward (BOCF) for the 3-month landmark in handling missing data. Note that for the 6-month landmark, the Applicant proposed to use BOCF to 3-month landmark and LOCF from 3-month to 6-month landmark, and this was discussed in the protocol under Serial No. 147. The Applicant stated in the protocol that

For the composite responder analysis, the baseline observation carried forward (BOCF) technique will be applied to patients not completing at least 3 months of treatment, after which a last observation carried forward (LOCF) approach will be applied to patients completing at least 3 months of treatment, but lacking primary efficacy data at Visit Tx29. That is, patients who did not reach Visit Tx15 will be analyzed as a nonresponder, while patients who completed at least 3 months of treatment (reaching Visit Tx15) will be analyzed by the LOCF approach. Sensitivity analysis will be performed to assess the robustness of the primary efficacy results. These will include composite responder analysis using BOCF and LOCF approaches for any patient with a missing value at the primary efficacy timepoint, and the composite responder analysis based on observed cases (OC) at the primary efficacy timepoint.

In our letter to the Applicant, our comments were

We understand your concern that patients may stop taking the medication and drop out because they start to feel better after the first three months of treatment. If it can be clearly documented that patients dropped out because of improvement in their condition, it is acceptable to assign them good scores. Practically, it is usually impossible to provide such documentation for patients who literally drop out. It is not necessarily so for patients who discontinue treatment, but continue to be assessed. Such patients need not be considered dropouts and can be included in the primary analysis. Sensitivity analysis based on observed cases (OC) may not be adequate to assess

the effects of missing data. We recommend that you perform responder analysis that designates patients unable to complete the study as nonresponders.

In this review, I assess the reason for dropout between the 3-month landmark and the 6-month landmark.

Table 3: Protocol Prespecified Definitions

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

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

Source: Clinical Study Report FMS-031, page 65

Table 4: Uniform Program Analysis Definitions

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

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

Source: Clinical Study Report FMS-031, page 65

The following is a summary of the analysis plan in Study FMS031:

The proportion of responders to the treatment of the syndrome of fibromyalgia was analyzed using a logistic regression model, with treatment group, baseline pain score, baseline FIQ-PF (SF-36 PCS under UPA) score, and baseline pain-by-treatment group and baseline FIQ-PF (SF-36 PCS under UPA)-by-treatment interactions as explanatory variables. The proportion of responders to the treatment of fibromyalgia pain was analyzed using a logistic regression model, with treatment group, baseline pain score and baseline pain-by-treatment group interaction as explanatory variables.

The original protocol-specified method for handling missing efficacy values in the primary efficacy analyses is the last observation (including baseline value) carried forward (LOCF) procedure. Subsequently, the UPA adopted BOCF procedure for missing efficacy assessments related to the primary efficacy responder analyses.

The Applicant conducted three sensitivity analyses to assess the effect of missing data on results of the primary efficacy analyses:

- In the first sensitivity analysis, patients lacking primary efficacy data at the primary time point were treated as nonresponders at the corresponding time point. For the pain domain, patients with fewer than seven valid observations during the primary time point period were treated as nonresponders in the sensitivity analyses. This is termed the BOCF analysis.
- In the second sensitivity analysis, patients prematurely discontinuing the study before the 3-month Landmark Visit (Visit Tx15) were treated as nonresponders at 3 months, while the LOCF approach described for the primary efficacy analyses was applied to missing data from patients who completed the 3-month Landmark Visit. A similar sensitivity analysis was performed for the 6-month Landmark Visit.
- A third sensitivity analysis was similar to the second except that the LOCF approach described for the primary efficacy analyses was applied to patients who completed the 3-month Landmark Visit (Visit Tx15), but prematurely discontinued the study before completing the 6-month Landmark Visit.

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

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

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

We asked the Applicant for clarification on the approach used to control the overall experiment-wise error rate under the Unified Program Analysis (dated June 2, 2008), and their response was:

In the NDA, the FMS031 UPA analyses for the composite pain responders and composite syndrome responders were performed for both 3-month landmark and 6-month landmark. Since these analyses were performed post-hoc, no multiple comparison procedure was pre-specified or applied.

Based on the agreement with the FDA that the 6-month landmark would not need to be evaluated as part of the primary efficacy evaluation for the MLN clinical program, only the 3-month landmark needs to be considered. If one wishes to adjust for the evaluation of two doses simultaneously, the two-step approach from Study MLN-MD-02 can be applied to the 3-month landmark for Study FMS031.

In the NDA, which evaluated both the 3-month landmark and the 6-month landmark for the UPA analyses, the two-step approach from Study MLN-MD-02 does not apply since it was only intended for a single landmark. Therefore the multiple comparison procedure used for FMS031 in the original statistical analyses (Vol. 1, page 60 of the FMS-031 study report) applies to the UPA analyses.

Sample Size

The sample size for Study MLN-MD-02 was calculated as follows:

A binary response rate for placebo (based on the composite endpoint for pain associated with fibromyalgia) in this study was expected to be about 19%, with a milnacipran response rate expected to be about 28%-29% (ITT

Population). Based on these response rate assumptions and the proposed multiple comparison procedure, 367 patients per treatment group would provide at least 80% power to show statistical significance between each milnacipran dosage group and placebo at an overall two-sided significance level of 0.05.

The sample size for Study FMS031 was calculated as follows:

Sample size was calculated based on assumed triple composite responder rates for the group receiving milnacipran 200 mg/d and the placebo group of 24% and 14%, respectively. It was estimated that 400 patients receiving milnacipran 200 mg/d and 200 receiving placebo would provide 84% power to detect a statistically significant difference between these treatment groups. The smaller sample size of the 100-mg/d group meant that there was a lower power to detect a difference from placebo with this arm.

3.1.2 PATIENT CHARACTERISTICS AND DISPOSITIONS

3.1.2.1 Study MLN-MD-02

Patient Disposition

In Study MLN-MD-02, a total of 2270 patients entered the screening phase. Of these, 1207 patients were randomized to treatment and 1196 patients were included in both the Safety and ITT populations (Table 5). Among the 11 patients excluded, nine were from the terminated study center 242, one did not take any study drug (ID# 24382), and one had a second patient number.

According to the Applicant,

Study Center 242 was closed by the Sponsor during the study due to failure to comply with Good Clinical Practices including improper AE evaluations, lack of physician oversight, and not following study procedures. All patients were discontinued. Thus, data on these patients were not included in efficacy or safety analyses (these patients were excluded from the Safety and Intent-to-Treat (ITT) data sets). The data of patients from this study center are included in the Appendix listings for full disclosure, and the AEs, as reported by the Investigator, for these patients are presented in the Study Report. The decision to exclude Study Center 242 from the analyses was made prior to database lock.

In addition, patients with the PIDs #20914 and #24623 are actually the same individual; this patient participated at two separate study centers (patient #20914 was randomized to placebo at Study Center 209 on November 23, 2005, and patient #24623 was randomized to Milnacipran 200 mg at Study Center 246 on December 15, 2005). This patient completed the study at both centers. The data from this patient as #20914 were included in all efficacy and safety analyses, since this was the earlier randomization. This decision was made prior to database lock. The data from this patient as #24623 are included in the Appendix listings for full disclosure. The AEs for this patient at both sites are presented in the Study Report.

Table 5: Patient Population – Study MLN-MD-02

	Placebo	Milnacipran		Total
		100 mg/d	200 mg/d	
Patients Screened				2270
Patients Randomized	405	401	401	1207
Safety Population	401	399	396	1196
ITT Population	401	399	396	1196

Source: Clinical Study Report, page 85

Except for the patient who did not take any study drug, additional analyses will be conducted including these 10 excluded patients.

Table 6 and Table 7 summarize the 3-month disposition data of these 1196 randomized patients. In total, 32% of randomized patients (28% placebo, 34% milnacipran 100 mg, and 35% milnacipran 200 mg) discontinued prematurely from the study. The main reason for discontinuation among the milnacipran-treated patients was an AE (20% and 24%, for the 100 mg and 200 mg patients, respectively). AEs (10%) and therapeutic failure (9%) contributed to premature discontinuations among the placebo-treated patients. Of the 811 patients who completed the study at Month 3, 79% reached the Tx15 visit. Sixteen percent administratively completed at Month 3 while 5% are Day 78 completers.

Table 6: Summary of Patient Disposition – Study MLN-MD-02

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

Cross-reference: Table 14.1.3.

Source: Clinical Study Report, MLN-MD-02, page 82

Table 7: Number (%) of Patients who completed 3-month study – Study MLN-MD-02

	Placebo	Milnacipran		Total
		100 mg/d	200 mg/d	
Total Completers	290	264	257	811
Reached Tx15 visit	232 (80%)	217 (82%)	193 (75%)	641 (79%)
Administratively Completed at 3-months	48 (17%)	35 (13%)	49 (19%)	132 (16%)
Day 78 completers	10 (3%)	12 (5%)	15 (6%)	37 (5%)

Source: Clinical Study Report, MLN-MD-02, page 127392

We asked the Applicant for further details explaining “Administratively Completed at 3-months” and “completers at Day 78”, and their reply was

In consultation with the Division of Anesthesia, Analgesia, and Rheumatology Products, MLN-MD-02 was modified from a 6-month study to a 3-month study as outlined in Amendment #3. This Amendment occurred after the study had been enrolling for some time, and as a result, there were patients active in the study at all timepoints when the Amendment became effective. Effective with this Amendment, study sites began administrative terminations of patients who had completed at least 3-months of double-blinded treatment. Due to the complexity this change created, a definition of study completion was provided in the MLN-MD-02 SAP Amendment 1 (dated May 8, 2007, Appendix 16.1.9.1 of MLN-MD-02 Clinical Study Report). A patient was defined as a 3-month completer as follows:

For the Randomized Population, a patient is defined as a 3-month completer if:

- the patient has a Visit Tx15; or
- the patient has a Visit Tx11 followed by Visit Tx29/ET with the termination reason as other (administratively terminated); or
- the patient has a Visit Tx11 followed by Visit Tx29/ET on or after Day 78 of stable dose (SD) period.

Patients who completed 6-month of treatment or who have had a Tx15 visit and then subsequently exited the study would fall under criteria 1. These patients were classified as “Reached Visit Tx15”.

Patients who were eligible for administrative termination from the study (completed Tx11, achieved 3 months of treatment) would fall under criteria 2 as the Tx29/ET visit was performed instead of Tx15 in this case. These patients were classified as “Administrative Completed at 3-month”.

Patients who had Tx11 visit, subsequently early terminated the study due to reasons other than as a result of Amendment #3, who also had received at least 12 weeks of assigned treatment dose (\geq 78 days of stable dose) are classified under criteria 3. These patients were classified as “Day 78 Completers”.

This explanation is acceptable. However, the primary analysis will be explored in various patient populations. The number of patients who reached Visits 3, 7, 11, 15, 19, 23, 27 and 29 are summarized in Table 8.

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Table 8: Number (%) of Patients who reached different study visits* – Study MLN-MD-02

		Milnacipran			Total N=1196
		Placebo N=401	100 mg/d N=399	200 mg/d N=396	
Tx3	Completed	367 (92%)	357 (90%)	345 (87%)	1069 (89%)
	Discontinued	34 (9%)	42 (11%)	51 (13%)	127 (11%)
	AE	15 (4%)	33 (8%)	33 (8%)	81 (7%)
	Lack of Efficacy	10 (3%)	3 (1%)	7 (2%)	20 (2%)
	Others	9 (2%)	6 (2%)	11 (3%)	26 (2%)
Tx7	Completed	328 (82%)	304 (76%)	300 (76%)	932 (78%)
	Discontinued	73 (18%)	95 (24%)	96 (24%)	264 (22%)
	AE	24 (6%)	65 (16%)	65 (16%)	154 (13%)
	Lack of Efficacy	26 (7%)	14 (4%)	15 (4%)	55 (5%)
	Others	23 (6%)	16 (5%)	16 (4%)	55 (5%)
Tx11	Completed	300 (75%)	270 (68%)	267 (67%)	837 (70%)
	Discontinued	101 (25%)	129 (32%)	129 (33%)	359 (30%)
	AE	32 (8%)	76 (19%)	89 (23%)	197 (17%)
	Lack of Efficacy	35 (9%)	26 (7%)	18 (5%)	79 (7%)
	Others	34 (8%)	27 (7%)	22 (6%)	83 (7%)
Tx15†	Completed	290 (72%)	264 (66%)	257 (65%)	811 (68%)
	Discontinued	111 (28%)	135 (34%)	139 (35%)	385 (32%)
	AE	38 (10%)	78 (20%)	94 (24%)	210 (18%)
	Lack of Efficacy	36 (9%)	28 (7%)	19 (5%)	83 (7%)
	Others	37 (9%)	29 (7%)	26 (7%)	92 (8%)
Tx19	Completed	262 (65%)	239 (60%)	236 (60%)	737 (62%)
	Discontinued	139 (35%)	160 (40%)	160 (40%)	459 (38%)
	AE	50 (13%)	90 (23%)	104 (26%)	244 (20%)
	Lack of Efficacy	44 (11%)	30 (8%)	24 (6%)	98 (8%)
	Others	45 (11%)	40 (10%)	32 (8%)	117 (10%)
Tx23	Completed	254 (63%)	228 (57%)	227 (57%)	709 (59%)
	Discontinued	147 (37%)	171 (43%)	169 (43%)	487 (41%)
	AE	54 (13%)	95 (24%)	110 (28%)	259 (22%)
	Lack of Efficacy	46 (12%)	32 (8%)	24 (6%)	102 (9%)
	Others	47 (12%)	44 (11%)	35 (9%)	126 (11%)
Tx27	Completed	252 (63%)	222 (56%)	221 (56%)	695 (58%)
	Discontinued	149 (37%)	177 (44%)	175 (44%)	501 (42%)
	AE	54 (13%)	97 (24%)	111 (28%)	262 (22%)
	Lack of Efficacy	46 (12%)	33 (8%)	25 (6%)	104 (9%)
	Others	49 (12%)	47 (12%)	39 (10%)	135 (11%)
Tx29	Completed	251 (63%)	221 (55%)	220 (56%)	692 (58%)
	Discontinued	150 (37%)	178 (45%)	176 (44%)	504 (42%)
	AE	54 (13%)	98 (25%)	112 (28%)	264 (22%)
	Lack of Efficacy	46 (12%)	33 (8%)	25 (6%)	104 (9%)
	Others	50 (12%)	47 (12%)	39 (10%)	136 (11%)

*excludes 11 patients: 9 patients from terminated center 242, 1 patient who received no assigned study drug, and 1 duplicated patient

†includes administratively completed at 3-month and day 78 completer

Source: Clinical Study Report MLN-MD-02, Vol.2 pages 3 – 9

Table 9 summarizes the protocol violations documented by the Applicant. The violations are grouped into classes. Ten patients identified as 'Class 1' did not satisfy the entry criteria; One patient identified as 'Class 2' developed withdrawal criteria, but did not withdraw; Five patients identified as 'Class 3' received wrong treatment or dosage; 179 patients identified as 'Class 4' received excluded concomitant medications. In addition, 52 patients identified as 'Class 4 – Narcotics' received narcotic medications and were classified as nonresponders in the primary efficacy analysis. Note that only two patients were identified as both 'Class 4'

and 'Class 4 – Narcotics'. These two were patients who had an additional protocol violation in one of the Class 1 – 3 categories.

Table 9: Number (%) of Patients with protocol violations – Study MLN-MD-02

	Placebo N=401	Milnacipran		Total N=1196
		100 mg/d N=399	200 mg/d N=396	
Class 1	2	4	4	10
Class 2	0	1	0	1
Class 3	2	2	1	5
Class 4	68	60	51	179
Class 4 - Narcotics	19	14	19	52

Demographic and Baseline Characteristics

Demographic and baseline characteristics for the Safety Population are presented in Appendix 1. The mean age of all patients was 50 years. Approximately 96% of patients were female, and 94% were Caucasian. The mean duration of FMS was 10 years, and 89% of the population had baseline BDI scores ≤ 25. The demographic and baseline characteristics of the key efficacy variables were generally similar among the three treatment groups.

Rescue Medication

The use of rescue medication or non-allowed narcotic medications and the number of valid pain assessments are essential components in the identification of pain responders as well as composite pain responders. In addition, the use of rescue medication or non-allowed narcotic medications is also essential in the identification of global responder or function responder. The following summarizes the proportion of patients who met the two criteria (Table 10). Of note, according to the Applicant, most patients who used rescue medications did so on an as-needed basis, so the precise number of days that rescue medications were used could not be determined with certainty; therefore, a conservative approach was taken in which all days between the start and stop dates of use were counted.

Table 10: Number (%) of Patients – Study MLN-MD-02

	Placebo N=401	Milnacipran	
		100 mg/d N=399	200 mg/d N=396
Number of patients with valid assessments (> 6) for the calculation of 3-month PED pain values	270 (67%)	239 (60%)	223 (56%)
Number of patients with days on rescue medication use during the 13 days prior to the 3-month endpoint cutoff date (<3 days)	354 (87%)	358 (89%)	360 (90%)

Exposure to Study Medication

The mean duration of treatment for patients in each treatment group during the 3-month was 89 days for placebo patients versus 84 days and 83 days for milnacipran 100 mg daily and 200 mg daily patients, respectively.

3.1.2.2 Study FMS-031

Patient Disposition

In Study FMS-031, a total of 1639 patients entered the screening phase. Of these, 888 patients were randomized to treatment and were included in both the Safety and ITT populations (Table 11).

Table 11: Patient Population – Study FMS-031

	Placebo	Milnacipran		Total
		100 mg/d	200 mg/d	
Patient Screened				1639
Patients Randomized	223	224	441	888
Safety Population	223	224	441	888
Intent-to-Treat Population	223	224	441	888

Source: Clinical Study Report, page 83

Table 12 and Table 13 summarize the 3-month and 6-month disposition data of these 888 randomized patients. Sixty four percent of randomized patients (72% placebo, 63% milnacipran 100 mg, and 60% milnacipran 200 mg) reached visit Tx 15 or three months. Of those who prematurely discontinued, the main reason for discontinuation among the milnacipran-treated patients was an AE (17% and 25%, for the 100 mg and 200 mg patients, respectively). AEs (9%) and therapeutic failure (13%) contributed to premature discontinuations among the placebo-treated patients. There was also one recorded death in the placebo arm. Of the 565 patients who completed the study at Month 3, 512 reached the Tx27 visit (six months).

Table 12: Summary of Patient Disposition at 3 months – Study FMS-031

	Placebo (N=223) n (%)	Milnacipran 100 mg (N=224) n (%)	Milnacipran 200 mg (N=441) n (%)	Total (N=888) n (%)
Reached Visit Tx15	161 (72.2)	140 (62.5)	264 (59.9)	565 (63.6)
Prematurely Discontinued before Visit Tx15	62 (27.8)	84 (37.5)	177 (40.1)	323 (36.4)
Reason for Discontinuation				
Death	1 (0.4)	0	0	1 (0.1)
Adverse Event	19 (8.5)	39 (17.4)	108 (24.5)	166 (18.7)
Therapeutic Failure	29 (12.6)	23 (10.3)	41 (9.3)	92 (10.4)
Protocol Violation	0	0	1 (0.2)	1 (0.1)
Non-Compliant w/ Protocol Requirements	3 (1.3)	1 (0.4)	5 (1.1)	9 (1.0)
Patient Withdrawal Of Consent	7 (3.1)	10 (4.5)	12 (2.7)	29 (3.3)
Investigator Withdrew The Patient	0	1 (0.4)	0	1 (0.1)
Lost To Follow-up	2 (0.9)	7 (3.1)	8 (1.8)	17 (1.9)
Other	2 (0.9)	3 (1.3)	2 (0.5)	7 (0.8)

Source: Clinical Study Report, FMS-031, page 189

Table 13: Summary of Patient Disposition at 6 months – Study FMS-031

	Placebo (N = 123)	Mirtazapine		Total (N = 388)
		100 mg/d (N = 224)	200 mg/d (N = 441)	
Completed Study	145 (65.0)	128 (57.1)	239 (54.2)	512 (57.7)
Withdrawn From Study	78 (35.0)	96 (42.9)	202 (45.8)	376 (42.3)
Reason for Withdrawal				
Adverse Event	23 (10.3)	44 (19.6)	119 (27.0)	186 (20.9)
Therapeutic Failure	34 (15.2)	26 (11.6)	49 (11.1)	109 (12.3)
Withdrawal of Consent	9 (4.0)	13 (5.8)	14 (3.2)	36 (4.1)
Lost to Follow-Up	2 (0.9)	7 (3.1)	9 (2.0)	18 (2.0)
Lack of Compliance	4 (1.8)	1 (0.4)	7 (1.6)	12 (1.4)
Investigator Withdrew Patient	0	1 (0.4)	0	1 (0.1)
Protocol Violation	0	0	1 (0.2)	1 (0.1)
Death	1 (0.4)	0	0	1 (0.1)
Other	5 (2.2)	4 (1.8)	3 (0.7)	12 (1.4)

Source: Clinical Study Report, FMS-031, page 78

Unlike Study MLN-MD-02, there were no patients who were categorized as “administratively completed at 3 months”. The number of patients who reached Visits 3, 7, 15, and 27 are summarized in Table 14. Note that between week 15 and week 27, there were 53 more patients who dropped out of the study. Of the 53 who dropped out, 20 patients dropped out due to AE, 17 patients dropped out due to lack of efficacy, 3 patients dropped out due to non-compliant with protocol requirements, 7 patients dropped out due to patient withdrawal of consent, 1 due to lost to follow-up and 5 dropped out and the reason was categorized as “Other”. The Applicant did not explain what ‘Other’ means.

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Table 14: Number (%) of Patients who reached different study visits* – Study FMS-031

		Milnacipran			Total N=888
		Placebo N=223	100 mg/d N=224	200 mg/d N=441	
Tx3	Completed	204 (92%)	195 (87%)	379 (86%)	778 (88%)
	Discontinued	19 (9%)	29 (13%)	62 (14%)	110 (12%)
	Death	1 (0.4%)	0	0	1 (0.1%)
	AE	8 (4%)	15 (7%)	44 (10%)	67 (8%)
	Lack of Efficacy	6 (3%)	5 (2%)	6 (1%)	17 (2%)
	Others	4 (2%)	9 (4%)	12 (3%)	25 (3%)
Tx7	Completed	180 (81%)	169 (75%)	320 (73%)	669 (75%)
	Discontinued	43 (19%)	55 (25%)	121 (27%)	219 (25%)
	Death	1 (0.4%)	0	0	1 (0.1%)
	AE	15 (7%)	25 (11%)	83 (19%)	123 (14%)
	Lack of Efficacy	19 (9%)	14 (6%)	19 (4%)	52 (6%)
	Others	8 (4%)	16 (7%)	19 (4%)	43 (5%)
Tx15†	Completed	161 (72%)	140 (63%)	264 (60%)	565 (64%)
	Discontinued	62 (28%)	84 (37%)	177 (40%)	323 (37%)
	Death	1 (0.4%)	0	0	1 (0.1%)
	AE	19 (9%)	39 (17%)	108 (25%)	166 (19%)
	Lack of Efficacy	28 (13%)	23 (10%)	41 (9%)	92 (10%)
	Others	14 (6%)	22 (10%)	28 (6%)	64 (7%)
Tx27	Completed	145 (65%)	128 (57%)	239 (54%)	512 (58%)
	Discontinued	78 (35%)	96 (43%)	202 (46%)	376 (42%)
	Death	1 (0.4%)	0	0	1 (0.1%)
	AE	23 (10%)	44 (20%)	119 (27%)	186 (21%)
	Lack of Efficacy	34 (15%)	26 (12%)	49 (11%)	109 (12%)
	Others	20 (9%)	26 (12%)	34 (8%)	80 (9%)

Source: Clinical Study Report FMS-031, Vol.1 pages 186 – 9

Table 15 summarizes the protocol violations documented by the Applicant. The violations are grouped into classes. Ten patients identified as ‘Class 1’ did not satisfy the entry criteria; One patient identified as ‘Class 2’ developed withdrawal criteria, but did not withdraw; Five patients identified as ‘Class 3’ received wrong treatment or dosage; 179 patients identified as ‘Class 4’ received excluded concomitant medications. In addition, 52 patients identified as ‘Class 4 – Narcotics’ received narcotic medications and were classified as nonresponders in the primary efficacy analysis. Note that only two patients were identified as both ‘Class 4’ and ‘Class 4 – Narcotics’. These two were patients who had an additional protocol violation in one of the Class 1 – 3 categories.

Table 15: Number (%) of Patients with protocol violations – Study FMS-031

	Milnacipran			Total N=888
	Placebo N=223	100 mg/d N=224	200 mg/d N=441	
Class 1	0	0	0	0
Class 2	0	0	0	0
Class 3	1	1	4	6
Class 4	10	9	12	31
Class 4 - Narcotics	8	16	21	45

Demographic and Baseline Characteristics

Demographic and baseline characteristics for the Safety Population are presented in Appendix 2. The mean age of all patients was 49 years. Approximately 96% of patients were female, and 94% were Caucasian. The mean duration of FMS was 6 years, and 90% of the population had baseline BDI scores ≤ 25. The demographic and baseline characteristics of the key efficacy variables were generally similar among the three treatment groups.

Rescue Medication

Like in Study MLN-MD-02, the use of rescue medication or non-allowed narcotic medications and the number of valid pain assessments are essential components in the identification of pain responders as well as composite pain responders. In addition, the use of rescue medication or non-allowed narcotic medications is also essential in the identification of global responder or function responder. The following summarizes the proportion of patients who met the two criteria (Table 16). Of note, according to the Applicant, most patients who used rescue medications did so, on an as-needed basis, so the precise number of days that rescue medications were used could not be determined with certainty; therefore, a conservative approach was taken in which all days between the start and stop dates of use were counted.

Table 16: Number (%) of Patients – Study FMS-031

	Placebo N=223	Milnacipran		Total N=888
		100 mg/d N=224	200 mg/d N=441	
Number of patients with valid assessments (> 6)				
3-month PED pain values	158 (71%)	135 (60%)	260 (59%)	553 (62%)
6-month PED pain values	140 (63%)	121 (54%)	230 (52%)	491 (55%)
Number of patients with days on rescue medication use during the 13 days				
3-month endpoint cutoff date	216 (97%)	213 (95%)	429 (97%)	858 (97%)
6-month endpoint cutoff date	216 (97%)	216 (96%)	426 (97%)	858 (97%)

Exposure to Study Medication

In Study FMS-031, the mean duration of treatment for patients in each treatment group was 148 days for placebo and 137 days and 133 days for milnacipran 100 and 200 mg/d.

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3.1.3 SUMMARY OF RESULTS

3.1.3.1 Evaluation of Pain, Patient Global Improvement, Function Score in Controlled Studies

3.1.3.1.1 MLN-MD-02

The primary efficacy parameters for Study MLN-MD-02 were the proportion of patients who satisfied the composite response definition for a treatment of the fibromyalgia syndrome (Syndrome) claim and the proportion of patients who satisfied the composite response definition for a treatment of the pain of fibromyalgia (Pain) claim at the 3-month landmark visit.

The result for the primary efficacy parameter for the composite pain response using different imputation strategies is summarized in Table 17. At the 3-month landmark visit under BOCF, 16% of placebo patients were defined as composite responders compared with 23% of milnacipran 100 mg patients and 25% of milnacipran 200 mg patients. Applying the two-step multiplicity adjustment, there is evidence that all pairwise comparisons of single milnacipran dosages to placebo are significant.

Table 17: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Composite Pain		N=401	N=399	N=396
	LOCF	73 (18%)	103 (26%) 1.56 (1.1, 2.2) p=0.0102	117 (30%) 1.90 (1.4, 2.6) p=0.0002
	BOCF	66 (16%)	91 (23%) 1.50 (1.1, 2.1) p=0.0252	98 (25%) 1.68 (1.2, 2.4) p=0.0037
	LOCF/BOCF	65 (16%)	92 (23%) 1.56 (1.1, 2.2) p=0.0146	102 (26%) 1.81 (1.3, 2.6) p=0.0008

Three additional sensitivity analyses were conducted by me. As noted, 11 patients were excluded in the ITT population, nine were from the terminated study center 242, one did not take any study drug (ID# 24382), and one had a second patient number (replicated). The first sensitivity analysis was conducted by including the subjects from center 242 and removing the replicated patient in the ITT population (called MITT population). Also noted, the use of rescue medication or non-allowed narcotic medications and the number of valid pain assessments are essential components in the identification of pain responders as well as composite pain responders. Any patients who took more than 2 days of rescue medications during the primary endpoint period before the day of the visit was defined as a nonresponder. Furthermore, any patients who had no more than 6 valid pain assessments were also defined as nonresponders. In the second analysis, these restrictions were removed such that the definition of responders was less stringent. Finally, there were several patients who had Class 4 violations (i.e. patients who received excluded concomitant medications. In the third analysis, these patients were excluded in the ITT population. The results from these three sensitivity analyses using BOCF were consistent with primary analysis (Table 18). Therefore, inclusion/exclusion of 10 patients, class 4 violators, or removal of restrictions in the definition of responder did not affect the conclusion from the primary analysis.

Table 18: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark (Sensitivity Analyses)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
MITT*		N=404	N=401	N=399
	LOCF	72 (18%)	103 (26%) 1.59 (1.1, 2.2)	119 (30%) 1.97 (1.4, 2.8)
	BOCF	65 (16%)	91 (23%) 1.53 (1.1, 2.4)	98 (25%) 1.71 (1.2, 2.4)
	LOCF/BOCF	64 (16%)	92 (23%) 1.59 (1.1, 1.9)	104 (26%) 1.89 (1.3, 2.3)
remove restriction (ITT)†		N=401	N=399	N=396
	LOCF	77 (19%)	105 (26%) 1.50 (1.1, 2.1)	120 (30%) 1.85 (1.3, 2.6)
	BOCF	72 (18%)	97 (24%) 1.47 (1.0, 2.1)	106 (27%) 1.69 (1.2, 2.4)
	LOCF/BOCF	69 (17%)	93 (23%) 1.47 (1.0, 2.1)	104 (26%) 1.74 (1.2, 2.5)
remove Class 4 (ITT)‡		N=333	N=339	N=348
	LOCF	65 (20%)	98 (29%) 1.67 (1.2, 2.4)	109 (31%) 1.88 (1.3, 2.7)
	BOCF	58 (17%)	86 (25%) 1.61 (1.1, 2.3)	91 (26%) 1.68 (1.2, 2.4)
	LOCF/BOCF	59 (18%)	88 (26%) 1.63 (1.1, 2.4)	95 (27%) 1.75 (1.2, 2.5)

*Includes center 242, remove 20914

†remove rescue medication restriction and number of observations restriction

‡remove class 4 violators

Because there is evidence of an increase in the composite response in the milnacipran group compared to placebo, additional post-hoc analyses were conducted to determine whether there is consistency in results in each domain of the composite pain endpoint (i.e. pain and global test).

Table 19 presents the mean change from baseline to endpoint for the 24-hour recall pain scores and patient global improvement score at endpoint. There is evidence of slight improvement in PGI score among the milnacipran groups compared to the placebo group. In terms of mean pain score, there is some evidence of a treatment difference in the improvement in pain score between milnacipran 200 mg/d group and placebo. An important clinical question is whether a 2.9 treatment difference in average change in pain score (based on 100 point scale) is meaningful.

Table 19: Average Pain Score Mean Change from Baseline to Endpoint and PGI at Endpoint

Treatment Group	Pain Score (Using BOCF)			PGI Score (Using LOCF)	
	Baseline	LSMean Change*	p-value†	LSMean Change**	p-value†
Placebo	65.8	10.0		3.5	
Milnacipran 100 mg/d	64.5	12.4	0.0833	3.1	<0.0001
Milnacipran 200 mg/d	64.3	12.9	0.0354	3.0	<0.0001

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

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

† unadjusted p-value

The following two tables (Table 20 and Table 21) summarize the results for the analyses of the pain responder and global responder using various sensitivity analyses. Because the results are based on post-hoc analyses, no p-values are presented. Instead only the proportion, the odds ratio, and the 95% confidence interval of the odds ratio are presented in the Table.

Using BOCF, there is insufficient evidence to conclude that the proportion of pain responders in the milnacipran group is greater compared to placebo. In contrast, there is some evidence that the proportion of PGI responders is greater in the milnacipran group compared to the placebo group. The result is consistent with the result from the analysis of mean change from baseline in pain score and mean PGI score at endpoint.

Table 20: Pain Only Responder Rate for Milnacipran Versus Placebo at the 3-Month Landmark

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
ITT		N=401	N=399	N=396
	LOCF	115 (29%)	149 (37%) 1.48 (1.1, 2.0)	158 (40%) 1.66 (1.2, 2.2)
	BOCF	101 (25%)	124 (31%) 1.34 (<1.0, 1.8)	119 (30%) 1.28 (0.9, 1.8)
	LOCF/BOCF	109 (27%)	138 (35%) 1.42 (1.0, 1.9)	136 (34%) 1.4 (1.0, 1.9)
MITT*		N=404	N=401	N=399
	LOCF	115 (28%)	149 (37%) 1.48 (1.1, 2.0)	160 (40%) 1.70 (1.3, 2.3)
	BOCF	101 (25%)	124 (31%) 1.34 (<1.0, 1.8)	121 (30%) 1.31 (<1.0, 1.8)
	LOCF/BOCF	109 (27%)	138 (34%) 1.42 (1.0, 1.9)	138 (35%) 1.44 (1.1, 1.9)
remove restriction (ITT)†		N=401	N=399	N=396
	LOCF	122 (30%)	156 (39%) 1.47 (1.1, 2.0)	168 (42%) 1.71 (1.3, 2.3)
	BOCF	108 (27%)	133 (33%) 1.36 (1.0, 1.8)	135 (34%) 1.42 (1.0, 1.9)
	LOCF/BOCF	116 (29%)	144 (36%) 1.39 (1.0, 1.9)	144 (36%) 1.42 (1.1, 1.9)
remove Class 4 (ITT)‡		N=333	N=339	N=348
	LOCF	103 (31%)	140 (41%) 1.56 (1.1, 2.1)	147 (42%) 1.63 (1.2, 2.1)
	BOCF	89 (27%)	117 (35%) 1.44 (1.0, 2.0)	110 (32%) 1.26 (0.9, 1.8)
	LOCF/BOCF	97 (29%)	130 (38%) 1.51 (1.1, 2.1)	126 (36%) 1.38 (<1.0, 1.9)

*Includes center 242; remove 20914

†remove rescue medication restriction and number of observations restriction

‡remove class 4 violators

Table 21: Patient Global Improvement Only Responder Rate for Milnacipran Versus Placebo at the 3-Month Landmark

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
ITT		N=401	N=399	N=396
	LOCF	100 (25%)	138 (35%) 1.59 (1.2, 2.2)	151 (38%) 1.86 (1.4, 2.5)
	BOCF	92 (23%)	125 (31%) 1.53 (1.1, 2.1)	129 (33%) 1.62 (1.2, 2.2)
	LOCF/BOCF	90 (22%)	122 (31%) 1.52 (1.1, 2.1)	131 (33%) 1.7 (1.2, 2.3)
MITT*		N=404	N=401	N=399
	LOCF	99 (25%)	138 (34%) 1.62 (1.2, 2.2)	153 (38%) 1.92 (1.4, 2.6)
	BOCF	91 (23%)	125 (31%) 1.34 (0.99, 1.8)	129 (33%) 1.31 (0.96, 1.8)
	LOCF/BOCF	89 (22%)	122 (30%) 1.55 (1.1, 2.1)	133 (33%) 1.77 (1.3, 2.4)
remove restriction (ITT)†		N=401	N=399	N=396
	LOCF	103 (26%)	144 (36%) 1.63 (1.2, 2.2)	154 (39%) 1.84 (1.4, 2.5)
	BOCF	95 (24%)	127 (32%) 1.50 (1.1, 2.1)	132 (33%) 1.61 (1.2, 2.2)
	LOCF/BOCF	93 (23%)	124 (31%) 1.49 (1.1, 2.0)	132 (33%) 1.66 (1.2, 2.3)
remove Class 4 (ITT)‡		N=333	N=339	N=348
	LOCF	91 (27%)	130 (38%) 1.65 (1.2, 2.3)	139 (40%) 1.77 (1.3, 2.4)
	BOCF	83 (25%)	117 (35%) 1.59 (1.1, 2.2)	119 (34%) 1.57 (1.1, 2.2)
	LOCF/BOCF	83 (25%)	115 (34%) 1.55 (1.1, 2.2)	122 (35%) 1.63 (1.2, 2.3)

*Includes center 242; remove 20914

†remove rescue medication restriction and number of observations restriction

‡ remove class 4 violators

Continuous responder curves for each treatment arm were plotted. The first plot (Figure 2) describes the pain profile for patients who have PGI score equal to 1 (very much improved) or 2 (much improved) at three months (i.e. composite pain definition). The second plot (Figure 3) describes the pain profile for patients who have PGI score greater than 2 at three months. Lastly, the third plot (Figure 4) describes the pain profile regardless of PGI score at three months (i.e. pain only response profile). In these plots, all patients who drop out of the study are considered nonresponders. These figures were created to provide a visual display of the relative benefit of various doses across the entire range of responses. The x-axis shows the percent reduction in pain from baseline (or improvement) to the end of the study, and the y-axis shows the corresponding percentage of patients achieving that level of pain reduction or greater.

When pain response profile is plotted among patients with good global rating at the 3-month landmark (i.e. less than 3), there is a slight separation of curves between milnacipran 200 mg/d group and placebo, and between milnacipran 100 mg/d and placebo. The separation in the milnacipran 100 mg/d group is more

evident when a less stringent definition of response is used. In contrast, the separation between milnacipran 200 mg/d and placebo appears to be consistent across different definitions of response.

When pain response profile is plotted among patients with global score greater than 2, there appears to be a higher proportion of patients responding to placebo compared to milnacipran across different definitions of response, particularly when the definition of response is less stringent (i.e. less than 30% improvement).

When all ITT patients are included in the response profile (i.e. pain only responder), there is no clear separation between the milnacipran groups and placebo. There is some separation in the milnacipran 200 mg/d group against the placebo, particularly in the more stringent definition of response; however, it is difficult to conclude whether this is a meaningful separation or not. Like the mean change from baseline analysis, or the proportion of responder analysis, there is insufficient evidence that shows milnacipran is associated with improvement in pain over placebo.

The following are observed based on these three graphs:

1. There is some suggestion that treatment difference (i.e. milnacipran versus placebo) in the composite responder rate may only be attributed to patients with good global test score.
2. The response curves between the two milnacipran groups do not appear to be different.

Additional exploratory analyses were conducted to understand this phenomenon.

Figure 2: Pain Response Profile for Patients with PGI =1 or PGI=2 (i.e. Composite Pain) – Study MLN-MD-02

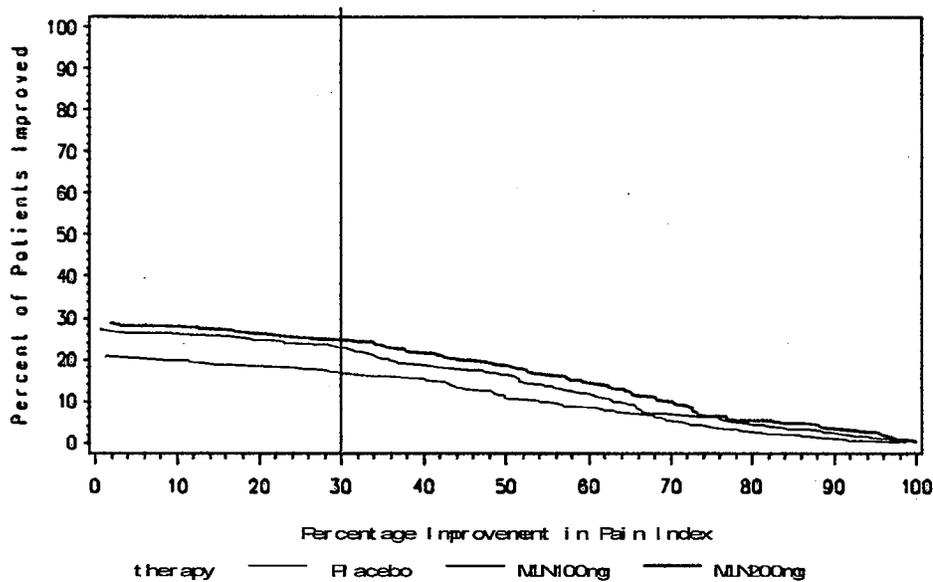


Figure 3: Pain Response Profile for Patients with PGI > 2 – Study MLN-MD-02

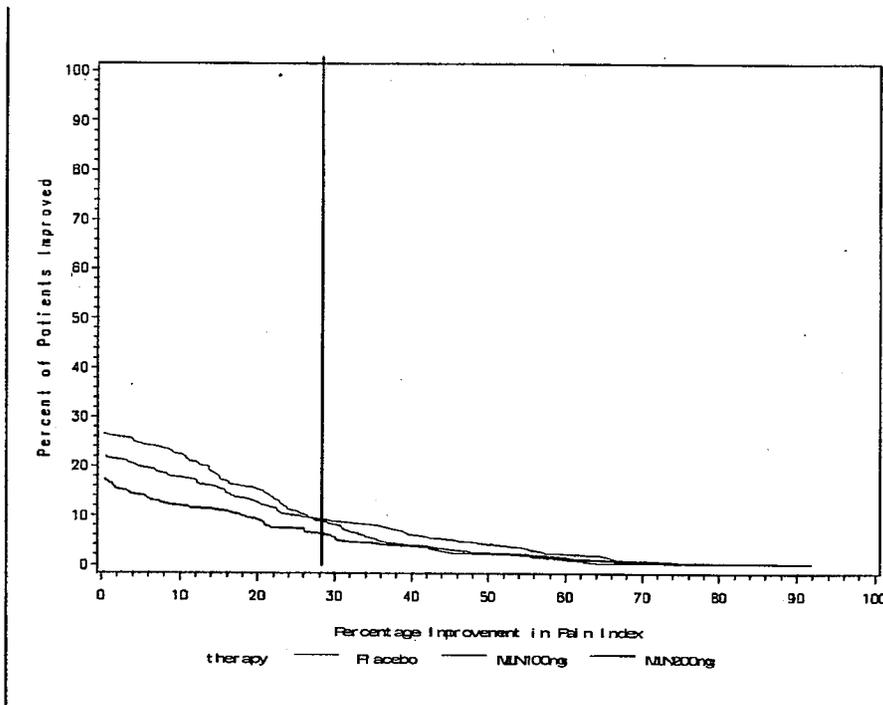
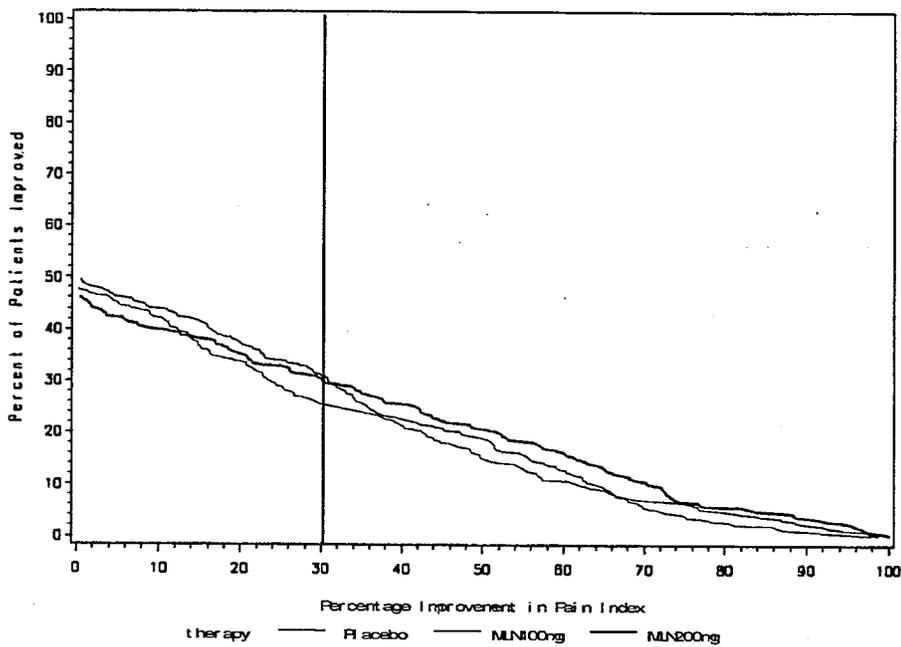


Figure 4: Pain Response Profile – Study MLN-MD-02



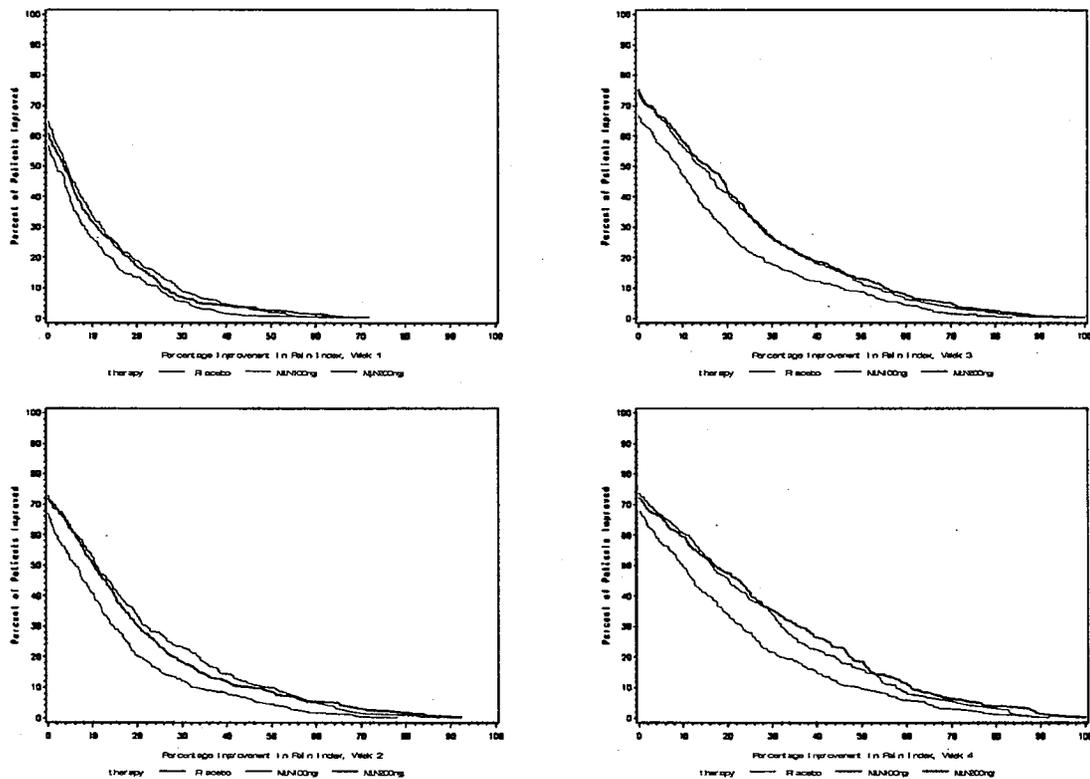
Continuous responder analyses by week are explored in the ITT population (Figure 5). In these plots, all patients who drop out of the study are considered nonresponders. In contrast to the primary endpoint, there were no restrictions in terms of the use of rescue medication or non-allowed narcotic medications and the number of valid pain assessments. Note that these figures were created to provide a visual display of the relative benefit of various doses across the entire range of response, as well over the period of double-blind treatment. The x-axis shows the percent reduction in pain from baseline (or improvement) to endpoint, and the y-axis shows the corresponding percentage of patients achieving that level of pain reduction or greater.

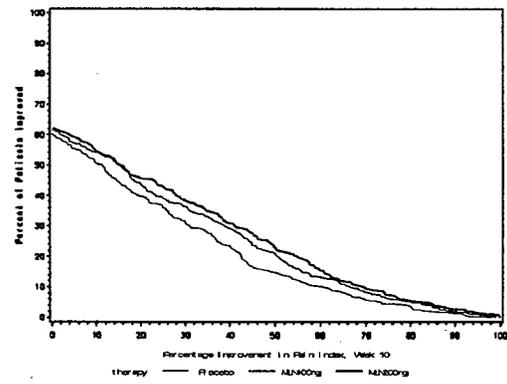
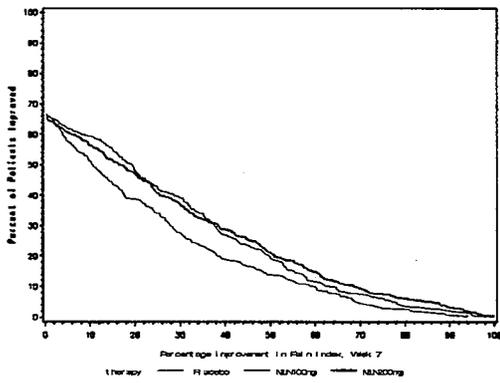
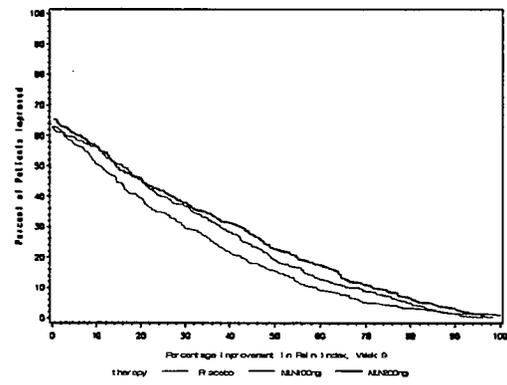
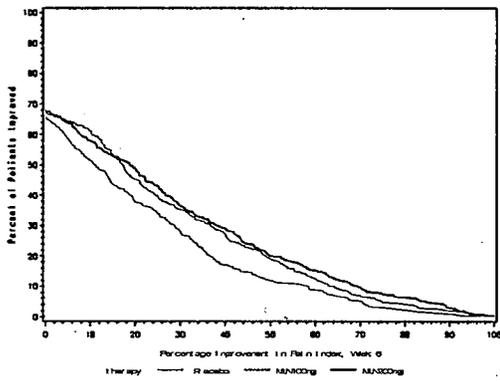
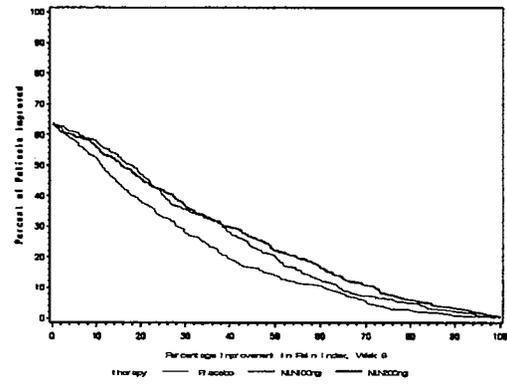
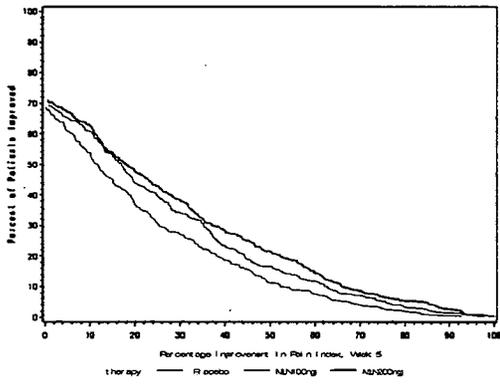
From the plots, there is clear evidence that a slightly higher proportion of patients treated with milnacipran 100 mg/d responded better compared to the placebo as early as Week 2, while patients treated with milnacipran 200 mg/d responded better as early as Week 3.

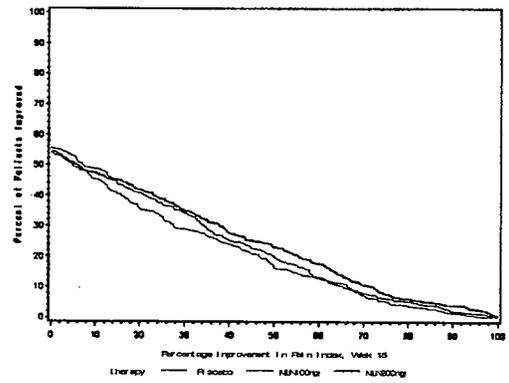
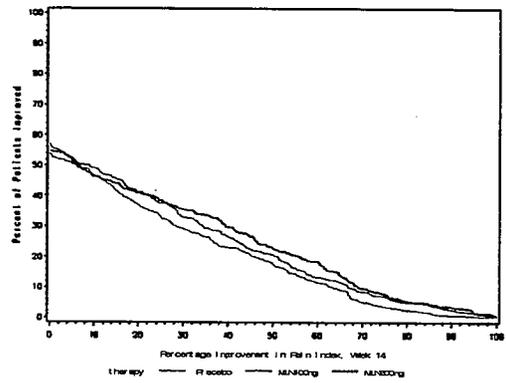
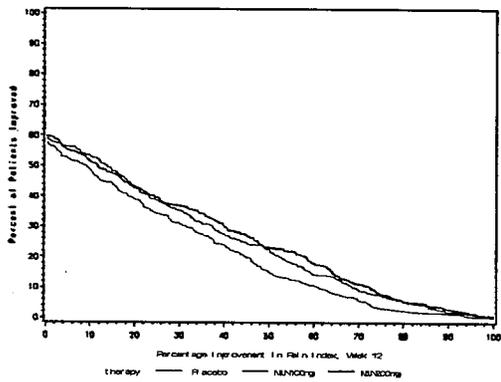
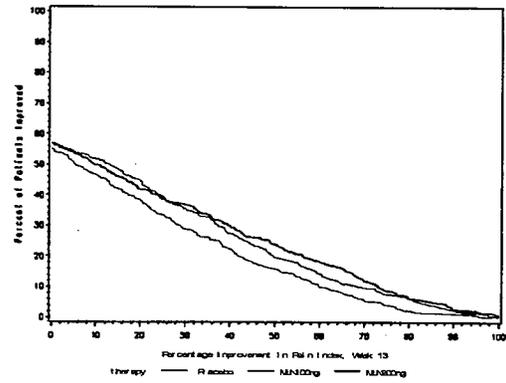
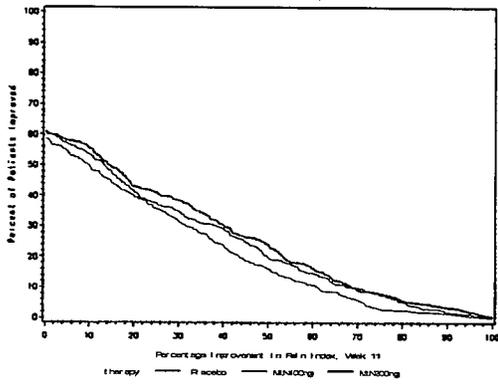
Note that at Week 1 and 2, patients in milnacipran 100 mg/d and milnacipran 200 mg/d are taking the same dosage (i.e. 100 mg/d). Only during week 3 did the milnacipran 200 mg/d group receive their full dose. Therefore, it is rather unusual that there is slight separation of curves between the two milnacipran groups at Weeks 1 and 2, and then these curves converge at week 3.

Nonetheless, the separation seen in both milnacipran groups appears to be consistent up until around week 10, in particular for the milnacipran 200 mg/d group. After week 10, this separation becomes less evident.

Figure 5: Continuous Responder Analysis (Pain only) by Visit – Study MLN-MD-02



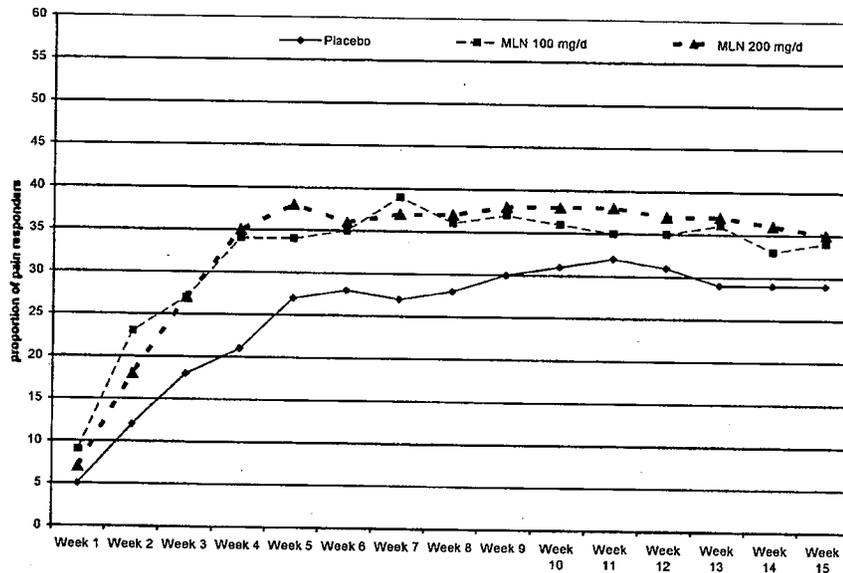




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Figure 6 presents the proportion of patients achieving at least 30% improvement in pain by week (see Appendix 3 for the Table). The results are consistent with the graphs. A higher proportion of responders appear to occur at Week 3 (milnacipran 200 mg/d versus placebo group), and continue to be higher compared to placebo until week 10.

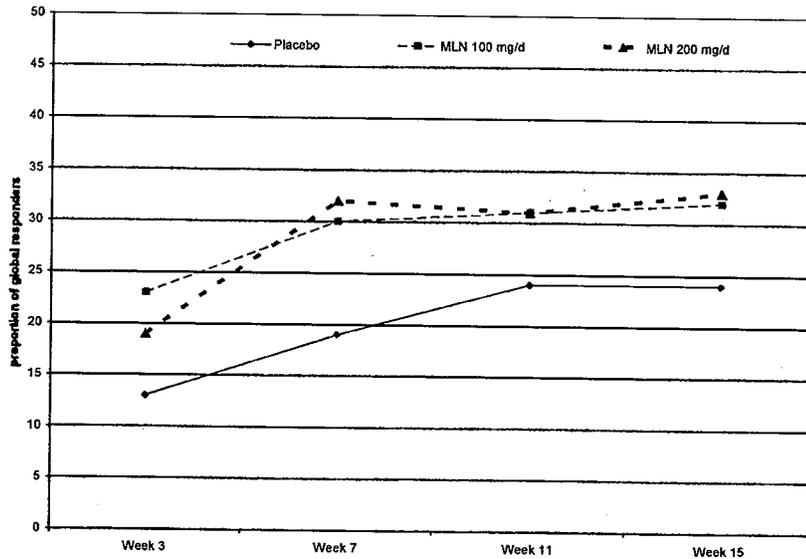
Figure 6: Pain Only Responder Rate ($\geq 30\%$ improvement) for Milnacipran Versus Placebo by Week – BOCF (Study MLN-MD-02)



Patient Global Impression of Change scores were collected on weeks 3, 7, 11, and 15. The results from each week are presented in Figure 7 (see Appendix 4 for the table). Note that unlike the primary endpoint (i.e. composite pain responder), the definition of responder was not restricted to the use of rescue medication or non-allowed narcotic medications.

As a result of the analysis by week, the proportion of patients achieving at least a “very much improved” or “improved” in global test appears to be consistently higher in the milnacipran groups compared to the placebo group across all weeks.

Figure 7: Patient Global Impression of Change Responder Rate (very much improved or improved) for Milnacipran Versus Placebo by Week (ITT Population) – Study MLN-MD-02

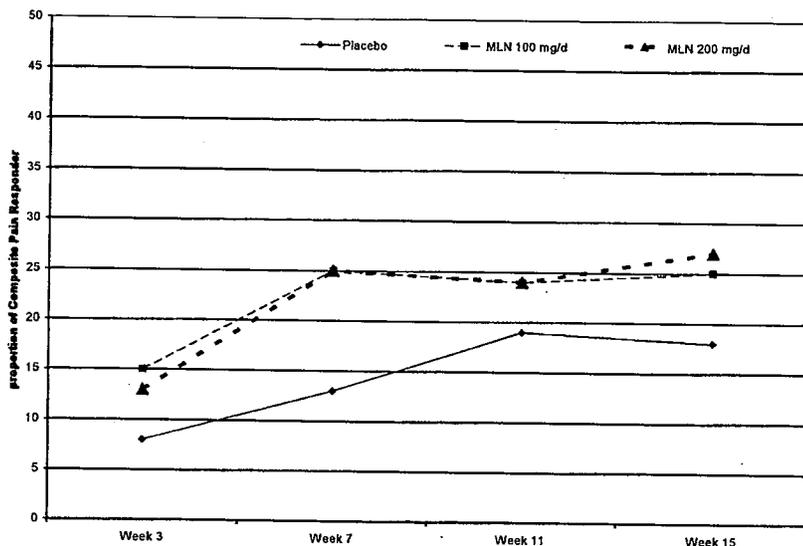


The composite pain responder rate was calculated based on the information from the pain only responder and patient global responder at weeks 3, 7, 11, and 15. The results from each week are summarized in Table 22 and presented graphically in Figure 8. Like the pain responder and global responder, the responder definition is slightly different from the primary endpoint definition, thus the result at Week 15 will be slightly different from the primary endpoint result at three months. A higher proportion of patients in the milnacipran groups achieved at least 30% improvement in pain and achieved at least a “very much improved” or “improved” in global test compared to placebo starting at Week 7. The difference appears to continue until week 15.

Table 22: Composite Pain Responder Rate for Milnacipran Versus Placebo by Week (ITT Population) – Study MLN-MD-02

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=401	N=399	N=396
Week 3	33 (8%)	61 (15%)	53 (13%)
Week 7	54 (13%)	98 (25%)	100 (25%)
Week 11	78 (19%)	94 (24%)	97 (24%)
Week 15	73 (18%)	100 (25%)	108 (27%)

Figure 8: Composite Pain Responder Rate for Milnacipran Versus Placebo by Week (ITT Population) – Study MLN-MD-02

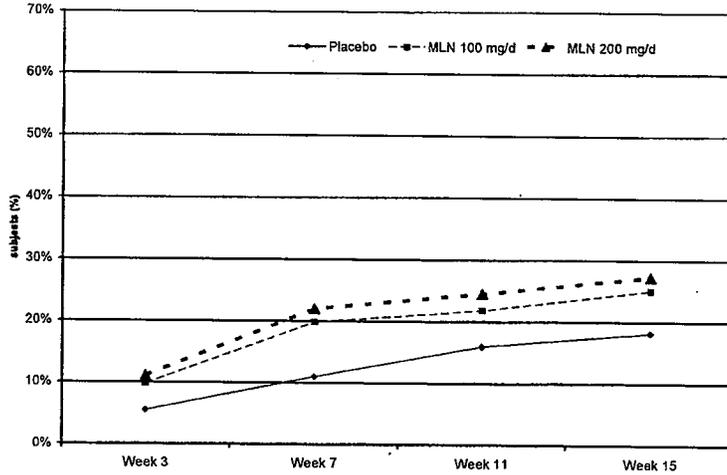


An alternate way to view the treatment effect over time is to explore those patients who completed the study and who responded to treatment, using the 30% responder criteria. For simplicity, the definition of responder will not be restricted on the use of rescue or non-allowed narcotics, or the number of available pain assessments.

In these plots, we examined when these patients started to respond to treatment. In some cases, patients may respond early and then respond late again while some respond all throughout the study. In this plot, we assume that a subject who responded will respond up to the end of the study. Therefore, the x-axis shows the week the subject responded, and the y-axis shows the corresponding percentage of patients who had at least 30% improvement in pain from baseline over time. A total of 811 (68%) patients completed the study. Of these, 281 patients had at least 30% improvement in pain from baseline at the end of the study and achieved a “very much improved” or “improved” in the global test.

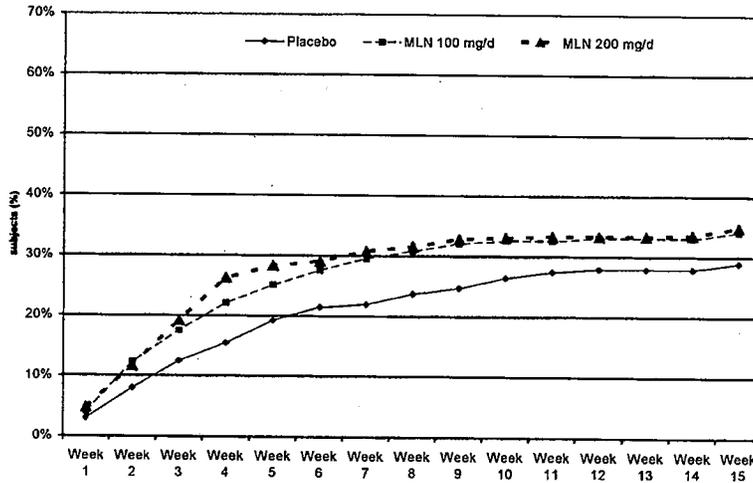
Figure 9 provides a graphical display of patients who responded to treatment. It appears that most patients receiving milnacipran (100 mg or 200 mg) continued to benefit until Week 15. Among patients who responded at Week 15, there is a difference in the proportion of responders as early as Week 3 between the active treatment arms and the placebo.

Figure 9: Proportion of Responders by Week ($\geq 30\%$ Improvement in Pain and ≤ 2 in Global) – Study MLN-MD-02



In terms of the pain only responder, of the 811 patients who completed the study, 390 patients (48%) had at least 30% improvement in pain score from baseline at the end of the study. *Figure 10* provide a graphical display of patients who responded to treatment. It appears that among patients who responded at Week 15, there is a difference in the proportion of responders as early as Week 3 between the active treatment arms and the placebo. It also appears that patients in the milnacipran group, as well as placebo group continued to achieve the level of response up to week 10 before it starts to plateau.

Figure 10: Proportion of Responders by Week ($\geq 30\%$ Improvement in Pain) – Study MLN-MD-02



In collaboration with Dr. Filie and Dr. Kashoki, we explored the contribution of pain response and global response to the composite responder. This is done by analyzing patients who met the pain response criteria only, the global response criteria only or both criteria (Table 23). In this analysis, responder is defined with restrictions on the use of rescue medication or non-allowed medication and on the number of days with valid pain assessments. The column "Pain/PGIC (Yes/Yes)" is the result of the primary endpoint (composite pain responder). Adding the column "Pain/PGIC (Yes/Yes)" with the column "Pain/PGIC (Yes/No)" will result in pain only responder at endpoint. Lastly, adding the column "Pain/PGIC (Yes/Yes)" with the column "Pain/PGIC (No/Yes)" will result in global only responder at endpoint.

Based on the result, it does appear that a higher proportion of placebo patients achieved 30% improvement in pain but did not meet the global response criteria compared to the milnacipran 200 mg/d group. In contrast, a lower proportion of placebo patients achieved a "very much improved" or "improved" global score but did not meet the criteria on pain response compared to milnacipran 100 mg/d group or milnacipran 200 mg/d group. Without any direct statistical analysis, there is some evidence that treatment difference in the composite response rate may be attributed to patients achieving a good global score. This is suggested by larger placebo response on pain (25%) compared to 22% placebo response on global criteria and a larger milnacipran response on global criteria about 35% compared to 30% milnacipran response on pain.

Table 23: Analysis of Pain and Global Response Criteria (BOCF)

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

We explored whether there are differences in baseline characteristics among the treatment groups based on their responses to pain and global rating at the 3-month landmark. There appears to be no substantial difference in baseline characteristics among the treatment groups across different responses to pain and global tests. Although there are no notable differences in endpoint mean pain score and change from baseline score at the 3-month landmark across treatment groups, there appears to be some variation across different responses. It appears that patients have a higher endpoint mean pain score among the discordant pairs (i.e. Pain/PGIC (Yes/No) and Pain/PGIC (No/Yes)) compared to concordant pairs (i.e. Pain/PGIC (Yes/Yes)). Furthermore, the endpoint mean pain score in the milnacipran 200 mg/d group appears slightly higher compared to placebo in the discordant pairs. In contrast, the endpoint mean pain score in the milnacipran 200 mg/d group appears slightly lower compared to placebo in the concordant pair.

Table 24: Analysis of Pain and Global Tests (BOCF) by Baseline Characteristics – Study MLN-MD-02

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Total		N=401	N=399	N=396
Pain/PGIC (Yes/Yes)		66 (16%)	91 (23%)	98 (25%)
	Sex (F)	62 (94%)	88 (97%)	97 (99%)
	Race (W)	64 (97%)	87 (96%)	92 (94%)
	Age, in yrs (mean)	51.3 (9.8)	49.5 (9.5)	50.7 (10.2)
	Baseline BDI	12.4 (6.6)	12.2 (7.5)	13.6 (9.1)
	Duration of FMS	10.8 (9.3)	9.6 (8.1)	10.0 (7.9)
	Mean Pain Score (Range) - BOCF			
	Baseline	65 (42 – 94)	65 (39 – 99)	63 (39 – 90)
3-month landmark*	25 (1 – 52)	25 (1 – 54)	23 (0 – 57)	
Change from Baseline†	40 (18 – 75)	39 (16 – 80)	40 (13 – 81)	
Pain/PGIC (Yes/No)		35 (9%)	33 (8%)	21 (5%)
	Sex (F)	35 (100%)	32 (97%)	20 (95%)
	Race (W)	34 (97%)	31 (94%)	21 (100%)
	Age, in yrs (mean)	51.6 (9.9)	53.5 (9.5)	49.6 (11.6)
	Baseline BDI	14.7 (9.4)	15.0 (9.2)	13.5 (7.6)
	Duration of FMS	9.6 (9.3)	11.2 (8.6)	8.4 (7.2)
	Mean Pain Score (Range) - BOCF			
	Baseline	63 (43 – 91)	63 (42 – 91)	67 (45 – 91)
3-month landmark*	31 (12 – 52)	35 (7 – 55)	34 (4 – 54)	
Change from Baseline†	31 (15 – 60)	27 (14 – 51)	33 (17 – 65)	
Pain/PGIC (No/Yes)		26 (6%)	34 (9%)	31 (8%)
	Sex (F)	26 (100%)	34 (100%)	31 (100%)
	Race (W)	24 (92%)	34 (100%)	29 (94%)
	Age, in yrs (mean)	51.1 (6.0)	51.3 (9.6)	48.6 (10.6)
	Baseline BDI	13.2 (8.1)	15.5 (8.9)	15.0 (9.5)
	Duration of FMS	7.8 (8.1)	8.4 (6.2)	7.8 (6.2)
	Mean Pain Score (Range) - BOCF			
	Baseline	69 (41 – 89)	63 (42 – 99)	66 (43 – 95)
3-month landmark*	58 (17 – 88)	56 (24 – 99)	60 (20 – 95)	
Change from Baseline†	8 (-4 – 24)	5 (-5 – 23)	5 (-7 – 23)	

* No rescue medication restriction and number of observations restriction

† Include rescue medication restriction and number of observations restriction

Aside from pain and global claims, the Applicant is also seeking a function claim. The physical function domain for response analysis was measured using the Physical Component Summary of the Short Form (SF-36 PCS).

The results for the SF-36 PCS responder rate and the primary efficacy parameter for the composite syndrome response using different imputation strategies are summarized in Table 25. At the 3-month landmark visit using BOCF, 9% of placebo patients were defined as composite syndrome responders compared to 15% of milnacipran 100 mg patients and 14% of milnacipran 200 mg patients. Applying the two-step multiplicity adjustment, there is evidence that all pairwise comparisons of single milnacipran dosages to placebo are significant to the treatment of syndrome.

When syndrome was analyzed by itself, using SF-36 PCS responder rate at endpoint, it appears that there is insufficient evidence to show that the proportion of SF-36 PCS responders in the milnacipran group is greater compared to placebo (using BOCF with unadjusted p-value).

Table 25: SF-36 Physical Component Score and Composite Responder Rate for Syndrome for Milnacipran Versus Placebo at the 3-Month Landmark

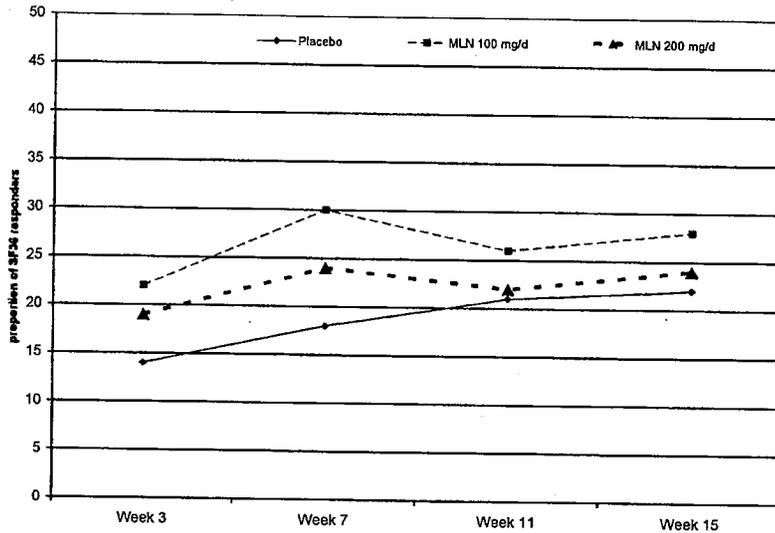
		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Composite: Syndrome				
	LOCF	39 (10%)	65 (16%) 1.82 (1.2, 2.8) p=0.006	65 (16%) 1.90 (1.2, 2.9) p=0.003
	BOCF	35 (9%)	58 (15%) 1.79 (1.1, 2.8) p=0.011	55 (14%) 1.75 (1.1, 2.8) p=0.015
SF-36 PCS Score		N=401	N=399	N=396
	LOCF	102 (25%)	129 (32%) 1.43 (1.0, 2.0) p=0.0297	109 (28%) 1.17 (0.8, 1.6) p=0.3429
	BOCF	86 (21%)	108 (27%) 1.37 (<1.0, 1.9) p=0.0628	89 (22%) 1.10 (0.8, 1.6) p=0.5777
	BOCF*	86 (21%)	108 (27%) 1.37 (<1.0, 1.9) p=0.0628	91 (23%) 1.14 (0.8, 1.6) p=0.4611

*Reviewer's
 Logistic regression with treatment and baseline SF-36 PCS summary score as explanatory variables.
 p-values are unadjusted

The SF-36 PCS was administered to patients at Baseline, weeks 3, 7, 11, and 15 (or early termination before week 15). The results from each week are presented in Figure 11 (see Appendix 5 for the table). Note that unlike the primary endpoint (i.e. composite pain responder), the definition of responder was not restricted to the use of rescue medication or non-allowed narcotic medications.

The proportion of patients achieving at least a six-point change from baseline in SF-36 PCS score appears to be slightly higher in the milnacipran 100 mg/d compared to the placebo group across all weeks. In contrast, the proportion of patients achieving at least a six-point change from baseline in SF-36 PCS score does not appear to differ between the milnacipran 200 mg/d and placebo after week 7.

Figure 11: Change from Baseline SF-36 Physical Component Score Responder Rate (≥ 6) for Milnacipran Versus Placebo by Week (ITT Population) - BOCF



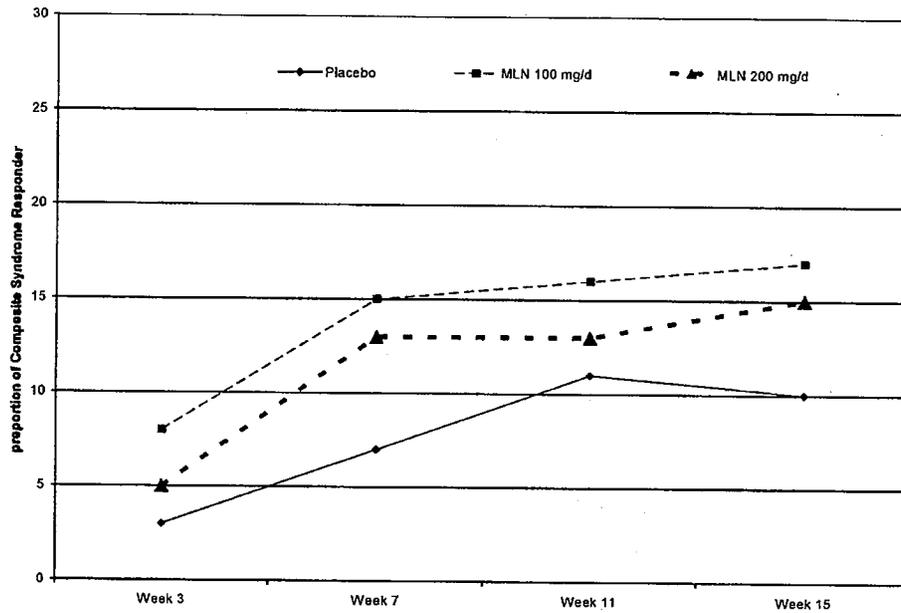
The composite syndrome responder rate was calculated based on the information from the pain only responder, patient global responder, and SF-36 physical component summary score at weeks 3, 7, 11, and 15. The results from each week are summarized in Table 26 and presented graphically in Figure 12. Like the pain responder and global responder, the responder definition for syndrome here is slightly different from the primary endpoint definition, thus the result at Week 15 will be slightly different from the primary endpoint result of syndrome at three months.

A slightly higher proportion of patients in the milnacipran groups achieved the composite syndrome responder criteria starting at Week 7 compared to placebo. However, the difference does not appear to be sustained in the milnacipran 200 mg/d group.

Table 26: Composite Syndrome Responder Rate for Milnacipran Versus Placebo by Week (ITT Population)

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=401	N=399	N=396
Week 3	14 (3%)	31 (8%)	21 (5%)
Week 7	29 (7%)	60 (15%)	53 (13%)
Week 11	44 (11%)	62 (16%)	52 (13%)
Week 15	40 (10%)	66 (17%)	61 (15%)

Figure 12: Composite Syndrome Responder Rate for Milnacipran Versus Placebo by Week (ITT Population)



In summary, there is evidence that all pairwise comparisons of single milnacipran dosages to placebo are significant using the composite pain responder definition as well as using the composite syndrome responder definition. However, the effects on pain and on syndrome based on SF-36 PCS score are not that different between the milnacipran groups and placebo at the end of the 3-month period. There is some evidence, at least in this study that the treatment difference seems to be influenced by the patient global score. It appears that a lower proportion of placebo patients have achieved a 'very much improved' or 'improved' global test at the end of the 3-month period as opposed to the milnacipran groups.

Numerically, there appears to be no difference in the proportion of responders (i.e. composite pain or composite syndrome) between the two milnacipran groups. The response profile between these two milnacipran doses appears to be similar across different range of response.

Although there are some patients who experienced a decrease in pain as early as week 1, the treatment difference did not occur until after the dose titration period ended (i.e. week 3).

3.1.3.1.2 FMS-031

Like Study MLN-MD-02, the primary efficacy parameters for Study FMS-031 were the proportion of patients who satisfied the composite response definition for a treatment of the fibromyalgia syndrome (Syndrome) claim and the proportion of patients who satisfied the composite response definition for a treatment of the pain of fibromyalgia (Pain) claim at the 3-month landmark visit and 6-month landmark visit.

As explained in Section 3.1.1 (Design and Analysis Section), the composite response definition for pain and syndrome were modified under the Uniform Program Analysis (UPA). In addition, the primary method of handling missing data was also modified from “BOCF from visit 0 to visit 7 and LOCF from visit 7 onwards” to “BOCF for missing data”. In the original protocol-specified definition of global improvement, patients were identified as global responder if they achieved “very much improved”, “improved”, or “minimally improved” at the 3-month landmark (or at the 6-month landmark). Under the UPA, a definition of improvement for the global domain was restricted to “very much improved” or “much improved” (i.e., 1 or 2 on the PGIC scale), similar to Study MLN-MD-02. Fibromyalgia Impact Questionnaire Physical Function (FIQ-PF) was used as measure for the physical function improvement in the original protocol. Like the global test, the milnacipran program has adopted a definition of improvement for the physical function domain based on the SF-36-PCS (under UPA).

In this section, the result from the primary analysis using the original protocol-specified definition is presented in Table 27 and Table 28, and the result from the primary analysis using the UPA analysis is presented in Table 29 and Table 30. Following these, the results from all the other analyses will be presented under the UPA.

The following are the results from the original protocol-specified analysis using BOCF.

For the pain claim, 25% of placebo-treated patients and 32% of those treated with milnacipran 200 mg/d were defined as pain (composite) responders at the 3-month landmark (i.e. treatment weeks 14-15). At the six-month landmark (i.e. treatment weeks 26-27), 21% and 27% respectively were classified as responders; however, they were not significantly different.

For the syndrome claim, the responder rates among placebo-treated patients and those treated with milnacipran 200 mg/d at both 3-month landmark (i.e. treatment weeks 14-15) and 6-month landmark (i.e. treatment weeks 26-27) were lower than those for the pain claim and were not significantly different between treatment groups.

Based on the pre-specified stepdown procedure (i.e. eight primary comparisons), only milnacipran 200 mg showed a significant difference compared to placebo in the proportion of pain responders at the 3-month landmark. Because milnacipran 200 mg did not achieve statistical significance compared to placebo on the composite syndrome at the 3-month landmark, none of the other secondary endpoints can be considered or tested for significance.

Table 27: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark – Original Protocol-Specified Analysis (Study FMS-031)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Three-Month Landmark				
IIT		N=223	N=224	N=441
	LOCF	62 (28%)	75 (33%) 1.31 (0.9, 2.0) p=0.1868	154 (35%) 1.41 (<1.0, 2.0) p=0.0584
	BOCF	56 (25%)	72 (32%) 1.43 (0.9, 2.2) p=0.0936	143 (32%) 1.44 (1.0, 2.1) p=0.0489
remove Class 4 (ITT)‡		N=213	N=215	N=429
	LOCF	60 (28%)	75 (35%) 1.38 (0.9, 2.1) p=0.1253	153 (36%) 1.43 (<1.0, 2.0) p=0.0512
	BOCF	54 (25%)	72 (33%) 1.51 (<1.0, 2.3) p=0.0578	143 (33%) 1.48 (1.0, 2.1) p=0.0362
Six-month landmark				
IIT				
	LOCF	56 (25%)	69 (31%) 1.32 (0.9, 2.0) p=0.1964	142 (32%) 1.43 (<1.0, 2.1) p=0.0528
	BOCF	46 (21%)	60 (27%) 1.37 (0.9, 2.1) p=0.1666	119 (27%) 1.44 (<1.0, 2.1) p=0.0667

‡ remove class 4 violators

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

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Table 28: Primary Efficacy Analyses: Composite Syndrome Responder Rates for Milnacipran vs. Placebo at the 3-Month Landmark – Original Protocol-Specified Analysis (Study FMS-031)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Three-Month Landmark				
IIT		N=223	N=224	N=441
	LOCF	45 (20%)	44 (20%) 0.93 (0.6, 1.5) p=0.7811	104 (24%) 1.22 (0.8, 1.8) p=0.3206
	BOCF	39 (17%)	42 (19%) 1.06 (0.6, 1.7) p=0.8153	98 (22%) 1.35 (0.9, 2.0) p=0.1504
remove Class 4 (ITT)‡		N=213	N=215	N=429
	BOCF	38 (18%)	42 (20%) 1.09 (0.7, 1.8) p=0.7448	98 (23%) 1.37 (0.9, 2.1) p=0.1424
Six-month landmark				
IIT				
	LOCF	42 (18%)	44 (20%) 1.03 (0.6, 1.7) p=0.9067	97 (22%) 1.22 (0.8, 1.8) p=0.3317
	BOCF	34 (15%)	38 (17%) 1.07 (0.6, 1.8) p=0.7937	81 (18%) 1.26 (0.8, 2.0) p=0.3082

‡ remove class 4 violators

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

Table 29 presents the Applicant’s summary (under the UPA analysis) of the responder analysis for the treatment of the pain of fibromyalgia using different imputation strategies at the 3-month landmark and at the 6-month landmark. Additional analysis removing patients who had class 4 violations and removing the restrictions to the responder definition were also conducted; the results were found to be consistent with the other analyses.

Table 30 presents the Applicant’s summary (under the UPA analysis) of the responder analysis for the treatment of the syndrome of fibromyalgia using different imputation strategies at the 3-month landmark and at the 6-month landmark. Note that we did not present the result from the analysis when class 4 violators were removed since this did not affect the overall conclusion.

Under LOCF, the last observed scores for patients who dropped out are carried forward at the end of month 3 or end of month 6. Under BOCF, all patients who dropped out are considered nonresponders. At the 6-month landmark, the primary imputation approach used by the Applicant is the LOCF-BOCF approach. In this approach, BOCF is applied to missing data at the 3-month landmark, and LOCF to missing data from 3-month to 6-month landmark.

The pain domain responder was calculated based on at least 30% improvement in pain from baseline at Weeks 14 to 15 and at Weeks 26 to 27, and this was restricted to the use of rescue medication or non-allowed narcotic medications at that time period, as well to number of valid pain assessments at that time period. The global domain responder was calculated based on a “very much improved” or “improved” response at the 3-month visit and at the 6-month visit with rescue medication restrictions at that visit.

As part of an information request, we asked the Applicant to clarify the stepdown approach they applied in the analysis of the primary composite endpoints under the UPA. According to the Applicant,

Based on the agreement with the FDA that the 6-month landmark would not need to be evaluated as part of the primary efficacy evaluation for the MLN clinical program, only the 3-month landmark needs to be considered. If one wishes to adjust for the evaluation of two doses simultaneously, the two-step approach from Study MLN-MD-02 can be applied to the 3-month landmark for Study FMS031.

The Applicant provided a summary of the results and is presented in Table 29 and Table 30 under BOCF. They applied the same logistic regression model used in Study MLN-MD-02. At the 3-month landmark using the two-step approach, there is evidence that all pairwise comparisons of single milnacipran dosages to placebo are significant to the treatment of pain, as well as treatment of syndrome of fibromyalgia.

In their response, the Applicant added that

In the NDA, which evaluated both the 3-month landmark and the 6-month landmark for the UPA analyses, the two-step approach from Study MLN-MD-02 does not apply since it was only intended for a single landmark. Therefore the multiple comparison procedure used for FMS031 in the original statistical analyses (Vol. 1, page 60 of the FMS-031 study report), applies to the UPA analyses.

In summary, the multiple comparison procedure (i.e. eight pairwise comparisons) applies to the UPA analysis.

The following are the results under the UPA analysis using BOCF imputation strategy at the 3-month landmark and the LOCF-BOCF strategy at the 6-month landmark.

I first examined the comparison between milnacipran 200 mg and placebo as it was the first step in the specified multiple comparison procedure. For the pain claim, 19% of placebo-treated patients and 27% of those treated with milnacipran 200 mg/d were defined as pain (composite) responders at the 3-month landmark (i.e. treatment weeks 14-15). At the six-month landmark (i.e. treatment weeks 26-27), 18% and 26% respectively were classified as responders using LOCF-BOCF.

For the syndrome claim, the responder rates among placebo-treated patients and those treated with milnacipran 200 mg/d at both 3-month landmark (i.e. treatment weeks 14-15) and 6-month landmark (i.e. treatment weeks 26-27) were lower than those for the pain claim. Only at the 3-month landmark was milnacipran 200 mg/d significantly different from placebo using BOCF. The Applicant claimed that

The magnitude of difference in response rates between the 100 mg/d and 200 mg/d treatment groups relative to placebo was virtually identical, and the marginally significant p value was due primarily to the smaller sample size in the 100 mg/d treatment group. The greater odds of response with milnacipran 200 mg/d and 100 mg/d response relative to placebo were 54% and 55%, respectively.

In my opinion, it is meaningless to argue what may have caused the marginal p-value in the 100 mg/d treatment group. The confidence interval (CI) in the 100 mg includes the null effect (i.e. 1.0), while the confidence interval for the 200 mg/d treatment group did not include the null effect. For the 100 mg/d arm, the CI includes values that correspond to a more favorable response among placebo patients, while the CI for the 200 mg/d arm indicates that if there is any effect, it could potentially be a small improvement or two times improvement (i.e. between 1.04 to 2.28).

In summary, based on the pre-specified stepdown procedure (i.e. eight primary comparisons) and imputation strategy used by the Applicant, only milnacipran 200 mg showed a significant difference compared to placebo in the treatment of pain of fibromyalgia at the 3-month landmark and at the 6-month landmark, as well as in the treatment of syndrome of fibromyalgia at the 3-month landmark. Because milnacipran 200 mg did not achieve statistical significance compared to placebo on the composite syndrome at the 6-month landmark, none of the other secondary endpoints can be considered or tested for significance. However, like Study MLN-MD-02, the proportion of responders (i.e. composite pain or composite syndrome) between the two milnacipran groups is identical. An important clinical question is whether greater odds of response (about 54%) with milnacipran relative to placebo (or an 8% difference in response rate) are clinically relevant or meaningful, and whether the similarity in the proportion of responder can be disregarded because of lack of statistical evidence in the milnacipran 100 mg/d group.

Table 29: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran versus Placebo at the 3-Month Landmark – UPA Analysis (Study FMS-031)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Three-Month Landmark				
Composite Pain		N=223	N=224	N=441
	LOCF†	50 (22%)	67 (30%) 1.45 (0.9, 2.2) p=0.0895	134 (30%) 1.52 (1.1, 2.2) p=0.0283
	BOCF†	43 (19%)	61 (27%) 1.55 (<1.0, 2.4) p=0.0554	118 (27%) 1.54 (1.0, 2.3) p=0.0323
	BOCF‡	43 (19%)	61 (27%) 1.57 (1.0, 2.4) p=0.0477	118 (27%) 1.54 (1.0, 2.3) p=0.0329
	BOCF§	44 (20%)	62 (28%) 1.55 (<1.0, 2.4) p=0.0540	119 (27%) 1.51 (1.0, 2.2) p=0.0390
Six-month landmark				
		N=223	N=224	N=441
	LOCF	47 (21%)	64 (29%) 1.46 (0.9, 2.3) p=0.0915	128 (29%) 1.56 (1.1, 2.3) p=0.0242
	BOCF†	39 (17%)	53 (24%) 1.41 (0.9, 2.3) p=0.1511	104 (24%) 1.49 (<1.0, 2.3) p=0.0605
	BOCF‡	39 (17%)	53 (24%) 1.46 (0.9, 2.3) p=0.1079	104 (24%) 1.46 (<1.0, 2.2) p=0.0704
	LOCF-BOCF (Sponsor's)	41 (18%)	58 (26%) 1.52 (<1.0, 2.4) p=0.0721	113 (26%) 1.54 (1.0, 2.3) p=0.0341

*implies subjects who dropped out are considered nonresponders

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

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

§ remove ITT restrictions i.e. rescue medication or non-allowed medication, number of valid pain assessments

Table 30: Primary Efficacy Analyses: Composite Syndrome Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark – UPA Analysis (Study FMS-031)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Three-Month Landmark				
Composite Syndrome		N=223	N=224	N=441
	LOCF†	32 (14%)	48 (21%) 1.66 (1.0, 2.8) p=0.0475	98 (22%) 1.76 (1.1, 2.8) p=0.0147
	BOCF†	27 (12%)	44 (20%) 1.84 (1.1, 3.2) p=0.0277	85 (19%) 1.80 (1.1, 2.9) p=0.0175
	BOCF‡	27 (12%)	44 (20%) 1.75 (1.0, 3.0) p=0.0351	85 (19%) 1.75 (1.1, 2.8) p=0.0197
Six-month landmark				
		N=223	N=224	N=441
	LOCF	33 (15%)	45 (20%) 1.34 (0.8, 2.2) p=0.2641	92 (10%) 1.52 (<1.0, 2.4) p=0.0660
	BOCF†	27 (12%)	40 (18%) 1.46 (0.8, 2.5) p=0.1751	73 (17%) 1.47 (0.9, 2.4) p=0.1244
	BOCF‡	27 (12%)	40 (18%) 1.56 (0.9, 2.7) p=0.0999	73 (17%) 1.45 (0.9, 2.3) p=0.1299
	LOCF-BOCF (Sponsor's)	29 (13%)	41 (18%) 1.37 (0.8, 2.4) p=0.245	80 (18%) 1.48 (0.9, 2.4) p=0.105

*implies subjects who dropped out are considered nonresponders

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

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

As part of my exploratory analysis, BOCF is applied to patients who withdrew from the study between the 3-month landmark visit and the 6-month landmark visit. This approach is more appropriate than the LOCF-BOCF analysis conducted by the Applicant because there is no evidence that patients who dropped out between Week 15 to Week 27 were getting better. Based on the disposition (Table 14), 53 more patients dropped out of the study between Week 15 and Week 27. Of the 53 who dropped out, 20 patients dropped out due to AE, 17 patients dropped out due to lack of efficacy, 3 patients dropped out due to non-compliant with protocol requirements, 7 patients dropped out due to patient withdrawal of consent, 1 due to lost to follow-up and 5 dropped out and the reason was categorized as "Other". It was not clearly documented what 'Other' meant. However, since there were only 5 additional patients categorized as 'Other', this should not impact the overall conclusion. Therefore, there is no reason to believe that patients who dropped out during this interval did so because they started to feel better after the first three months of treatment.

The results for the 6-month landmark were slightly different from the pre-specified LOCF-BOCF approach. Under the BOCF approach, milnacipran 200 mg did not show significant difference compared to placebo in the treatment of pain of fibromyalgia at the 6-month landmark. The

confidence interval in the 200 mg includes the null effect (between 0.98 and 2.3). What this implies is that the CI for the 200 mg includes values that correspond to a more favorable response among placebo patients. Thus, only treatment of pain of fibromyalgia at the 3-month landmark achieved statistical significance based on the pre-specified gatekeeping strategy. Similar results were observed when the responder definition was not restricted to the number of days in rescue medication or non-allowed medication, or to the number of valid pain assessments.

Because there is evidence of an increase in the composite response to the treatment of pain in the milnacipran 200 mg group compared to placebo at the 3-month landmark, additional post-hoc analyses were conducted to determine whether there is consistency in results in each domain of the composite pain endpoint (i.e. pain and global test). All subsequent analyses were conducted under the UPA.

Table 31 presents the mean change from baseline to endpoint for the 24-hour recall pain scores and patient global improvement score at the 3-month landmark. There is evidence of slight improvement in PGI score among the milnacipran groups compared to the placebo group. In terms of mean pain score, there is no evidence of a treatment difference in the improvement in pain score between the milnacipran groups and the placebo.

Note that after re-analyzing the data, there were two subjects (ID# 20919 and ID#27013) in the milnacipran 200 mg group that should have been global responders; however, these two subjects did not have any impact on the overall conclusion. Therefore, the Applicant's results are reported in this review.

Table 31: Average Pain Score Mean Change from Baseline to Endpoint and PGI at the 3-month landmark – UPA Analysis (Study FMS-031)

Treatment Group	Pain Score (Using BOCF)			PGI Score (Using LOCF)	
	Baseline	LSMean Change*	p-value†	LSMean Change**	p-value†
Placebo	68.4	12.7		3.5	
Milnacipran 100 mg/d	68.3	14.5	0.3652	3.0	0.0010
Milnacipran 200 mg/d	69.4	15.2	0.1559	3.1	0.0005

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

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

† unadjusted p-value

The following two tables (Table 32 and Table 33) summarize the results for the analyses of the pain responder and global responder using various sensitivity analyses. Because the results are based on post-hoc analyses, no p-values are presented. Instead only the proportion, the odds ratio, and the 95% confidence interval of the odds ratio are presented in the Table.

Using BOCF and the pre-specified logistic regression model, there is insufficient evidence to demonstrate that the proportion of pain responders in the milnacipran group is greater compared to placebo (Table 32). The result is consistent with the result from the analysis of mean change from baseline in pain score. There is also insufficient evidence that the proportion of PGI responders is greater in the milnacipran group compared to the placebo group (Table 33).

Table 32: Pain Only Responder Rate for Milnacipran Versus Placebo at the 3-Month and 6-month Landmark (UPA Analysis) (Study FMS-031)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Three-month landmark				
Pain Only Responder				
	LOCF†	78 (35%)	89 (40%) 1.23 (0.8, 1.8)	185 (42%) 1.36 (<1.0, 1.9)
	BOCF†	62 (28%)	76 (34%) 1.34 (0.9, 2.0)	155 (35%) 1.42 (<1.0, 2.0)
	BOCF‡	62 (28%)	76 (34%) 1.34 (0.9, 2.0)	155 (35%) 1.43 (1.0, 2.0)
	BOCF§	63 (28%)	77 (34%) 1.34 (0.9, 2.0)	156 (35%) 1.40 (<1.0, 2.0)
Six-month landmark				
	BOCF†	52 (23%)	67 (30%) 1.38 (0.9, 2.1)	127 (29%) 1.36 (0.9, 2.0)
	LOCF-BOCF†	57 (26%)	76 (34%) 1.50 (<1.0, 2.3)	143 (32%) 1.41 (<1.0, 2.0)

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

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

§ remove ITT restrictions i.e. rescue medication or non-allowed medication, number of valid pain assessments

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

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Three-month landmark				
PGI Only Responder				
	LOCF	68 (30%)	84 (38%) 1.37 (0.9, 2.0)	171 (39%) 1.44 (1.0, 2.0)
	BOCF*	60(27%)	74 (33%) 1.34 (0.9, 2.0)	145 (33%) 1.33 (0.9, 1.9)
	BOCF§	60 (27%)	75 (33%) 1.37 (0.9, 2.1)	146 (33%) 1.34 (0.9, 1.9)
Six-month landmark				
	BOCF*	55 (25%)	63 (28%) 1.20 (0.8, 1.8)	140 (32%) 1.42 (<1.0, 2.0)
	LOCF-BOCF	60 (27%)	67 (30%) 1.16 (0.8, 1.7)	145 (33%) 1.33 (0.9, 1.9)

*implies subjects who dropped out are considered nonresponders

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

§ remove ITT restrictions i.e. rescue medication or non-allowed medication, number of valid pain assessments

Continuous responder curves for each treatment arm were plotted under the UPA Analysis. The first plot (Figure 13) describes the pain profile for patients who have PGI score equal to 1 (very much improved) or 2 (much improved) at three months (i.e. composite pain definition). The second plot (Figure 14) describes the pain profile for patients who have PGI score greater than 2 at three months. Lastly, the third plot (Figure 15) describes the pain profile regardless of PGI score at three

months (i.e. pain only response profile). In these plots, all patients who drop out of the study are considered nonresponders. These figures were created to provide a visual display of the relative benefit of various doses across the entire range of responses. The x-axis shows the percent reduction in pain from baseline (or improvement) to the end of the study, and the y-axis shows the corresponding percentage of patients achieving that level of pain reduction or greater.

When pain response profile is plotted among patients with good global rating at the 3-month landmark (i.e. less than 3), there is a slight separation of curves between milnacipran 200 mg/d group and placebo, and between milnacipran 100 mg/d and placebo. The response curves between the two milnacipran groups do not appear to be different. All three curves appear to be consistent across different definitions of response.

When pain response profile is plotted among patients with global score greater than 2, there appears to be a higher proportion of patients responding to placebo compared to milnacipran across different definitions of response, particularly when the definition of response is less stringent (i.e. less than 30% improvement).

When all ITT patients are included in the response profile (i.e. pain only responder), there is no clear separation between the milnacipran groups and placebo except in the middle section between 25% to 60% response criteria. It is difficult to conclude whether this is a meaningful separation or not. It does appear that a higher proportion of patients treated with milnacipran achieved at least a 30% or 50% improvement compared to placebo.

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Figure 13: Pain Response Profile for Patients with PGI =1 or PGI=2 (i.e. Composite Pain) – Study FMS-031 (UPA Analysis)

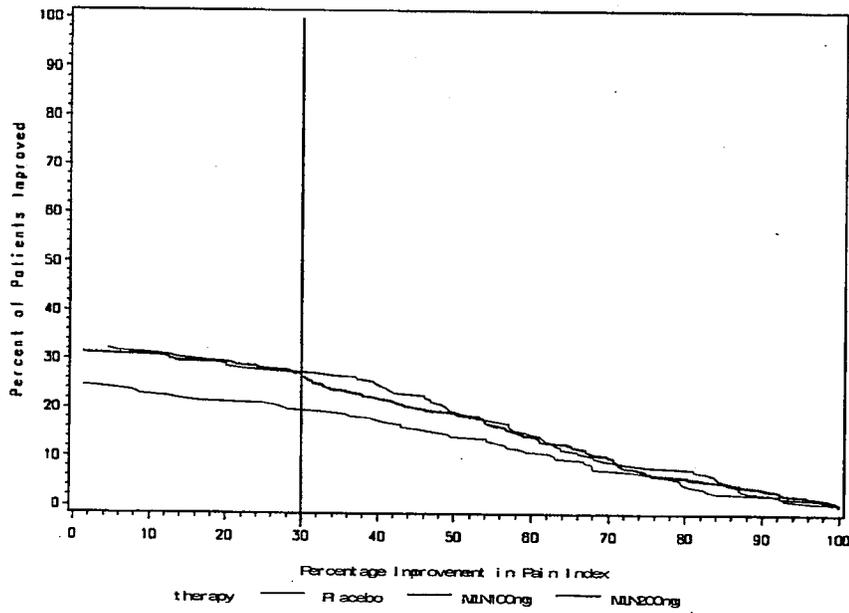


Figure 14: Pain Response Profile for Patients with PGI >2 – Study FMS-031 (UPA Analysis)

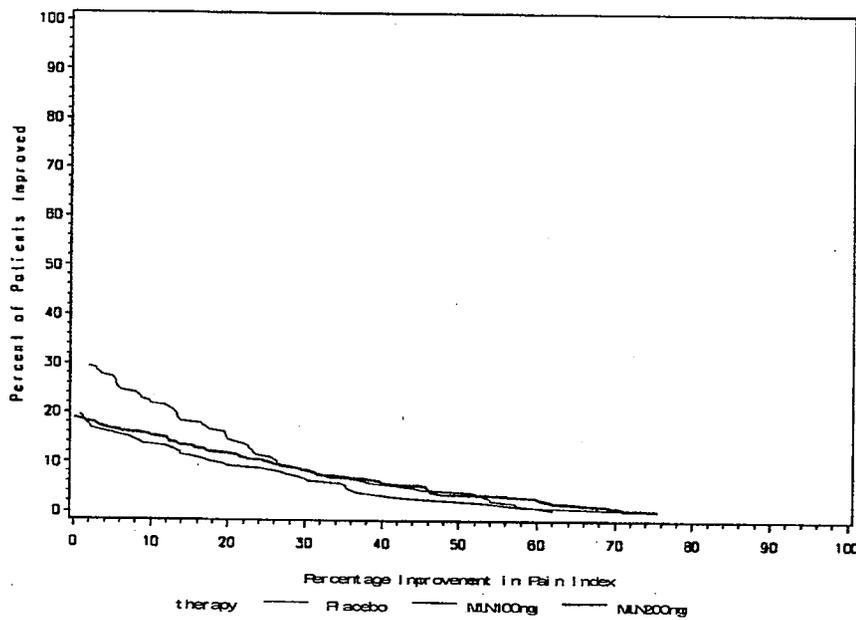
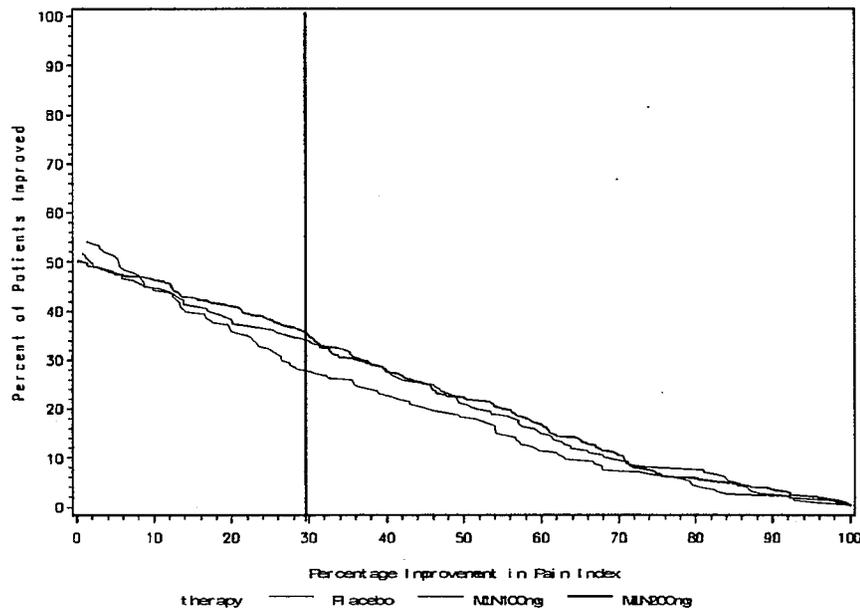


Figure 15: Pain Response Profile – Study FMS-031 (UPA Analysis)

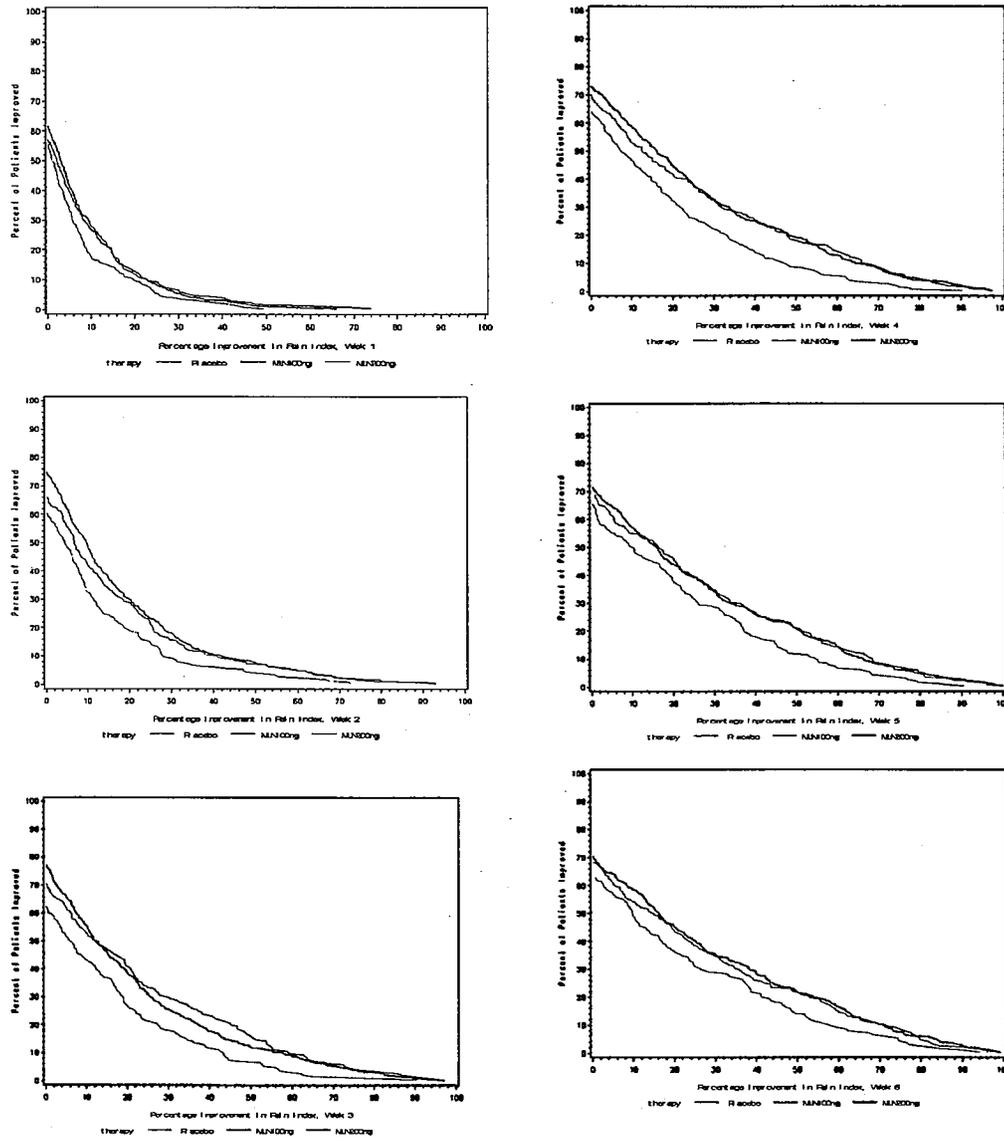


Continuous responder analyses by week are explored in the ITT population (Figure 16). In these plots, all patients who drop out of the study are considered nonresponders. In contrast to the primary endpoint, there were no restrictions in terms of the use of rescue medication or non-allowed narcotic medications and the number of valid pain assessments. Note that these figures were created to provide a visual display of the relative benefit of various doses across the entire range of response, as well over the period of double-blind treatment. The x-axis shows the percent reduction in pain from baseline (or improvement) to endpoint, and the y-axis shows the corresponding percentage of patients achieving that level of pain reduction or greater.

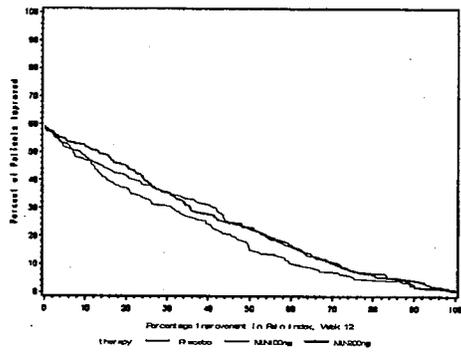
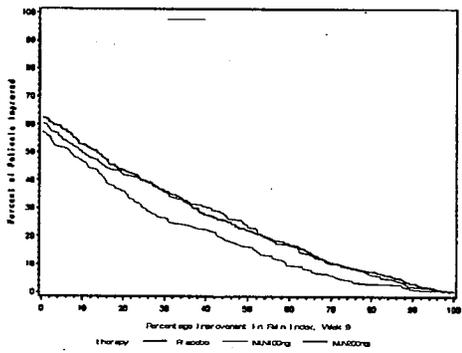
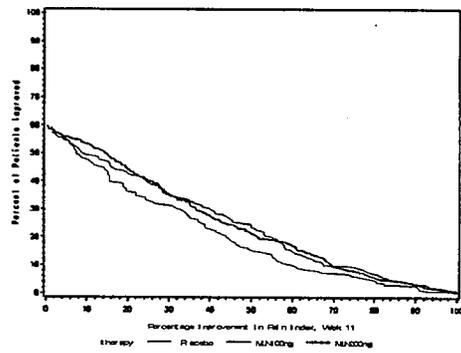
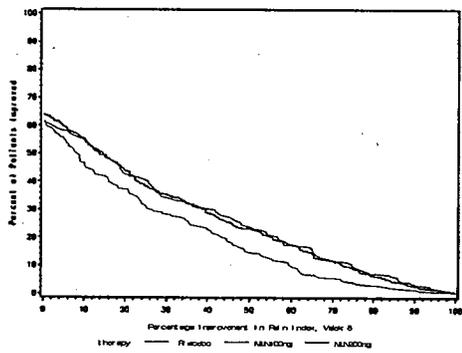
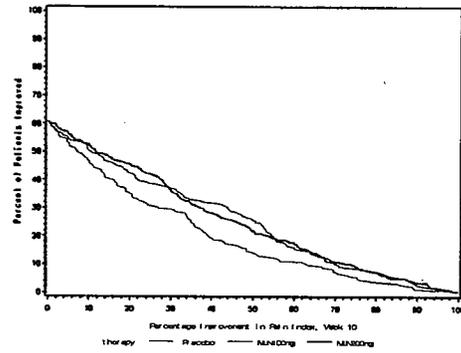
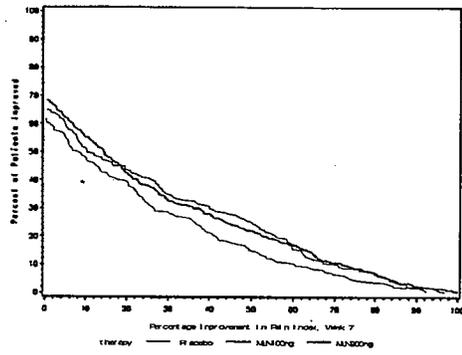
From the plots, there is some evidence that a slightly higher proportion of patients treated with milnacipran responded better compared to the placebo as early as Week 2. The separation is clearer in both milnacipran dose groups compared to placebo at Week 3.

Like Study MLN-MD-02, patients in milnacipran 100 mg/d and milnacipran 200 mg/d are taking the same dosage (i.e. 100 mg/d) at Weeks 1 and 2. Only during week 3 did the milnacipran 200 mg/d group receive their full dose. Thus, it is sensible to observe the separation at Week 3. However, it does not appear that the curves separate consistently over time. Between Weeks 11 to 17, the curves seem to converge a bit across all treatment groups. It seems to separate again between Weeks 18 to 24, until the separation becomes less evident.

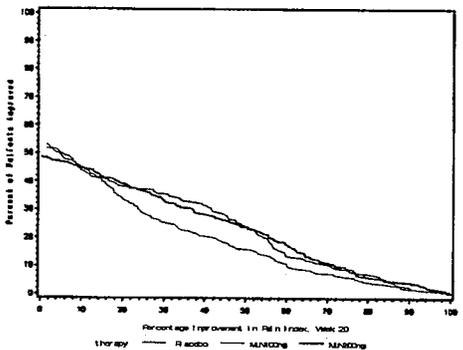
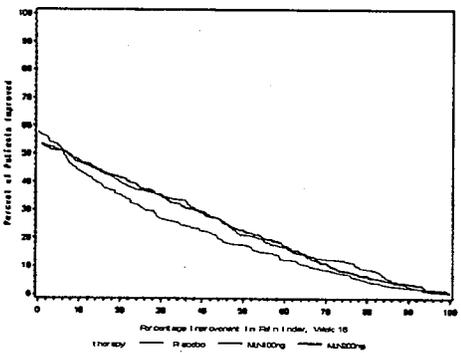
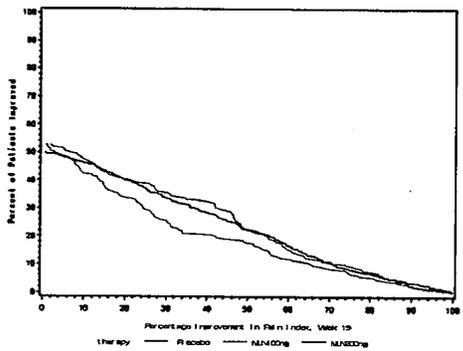
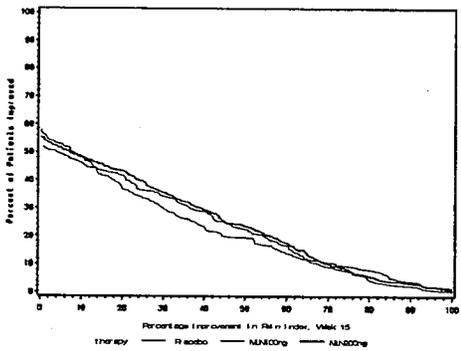
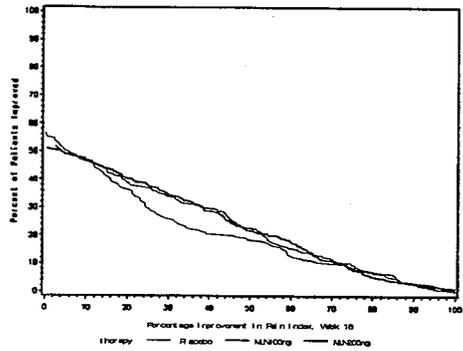
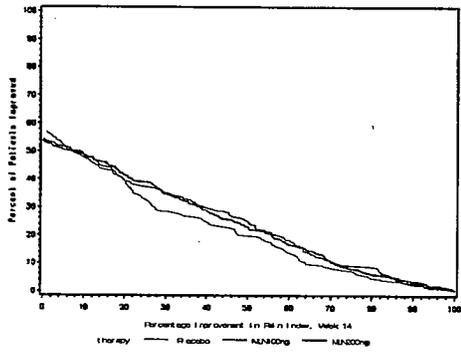
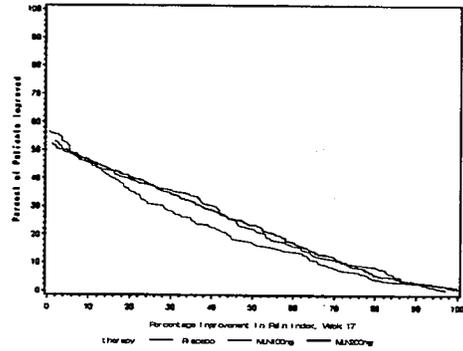
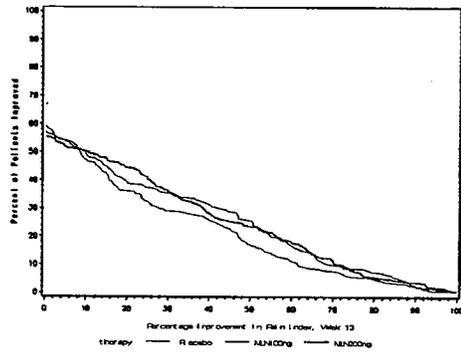
Figure 16: Continuous Responder Analysis (Pain only) by Visit – FMS-031

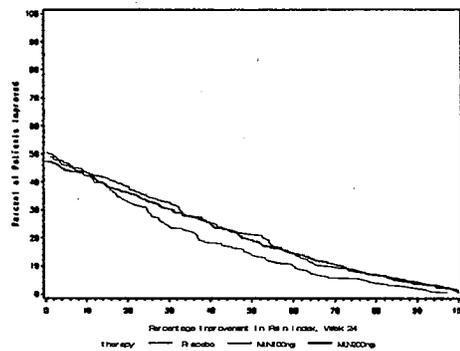
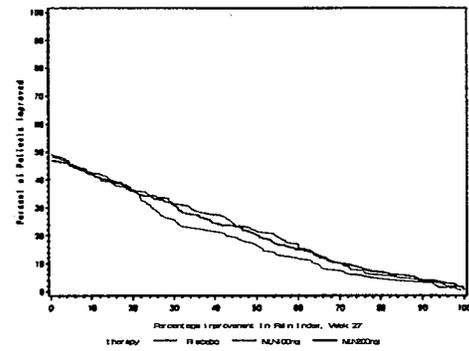
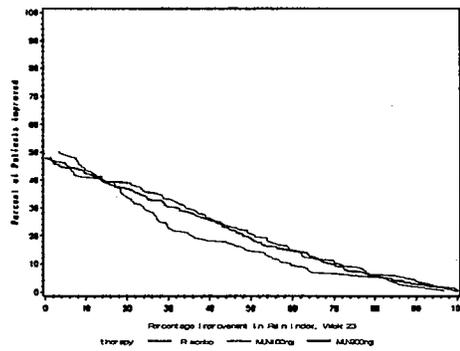
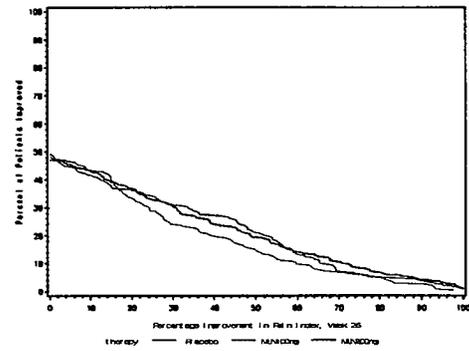
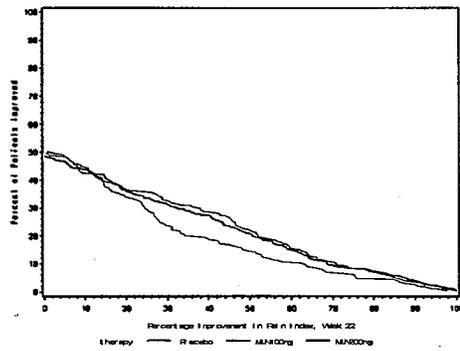
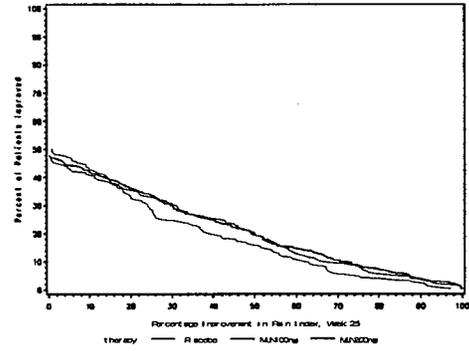
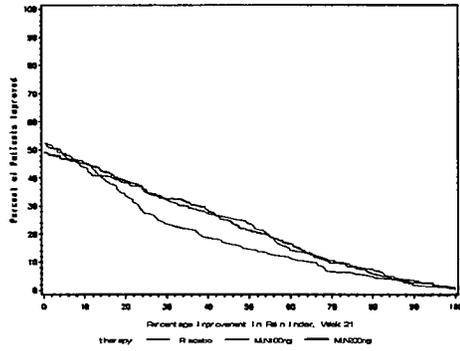


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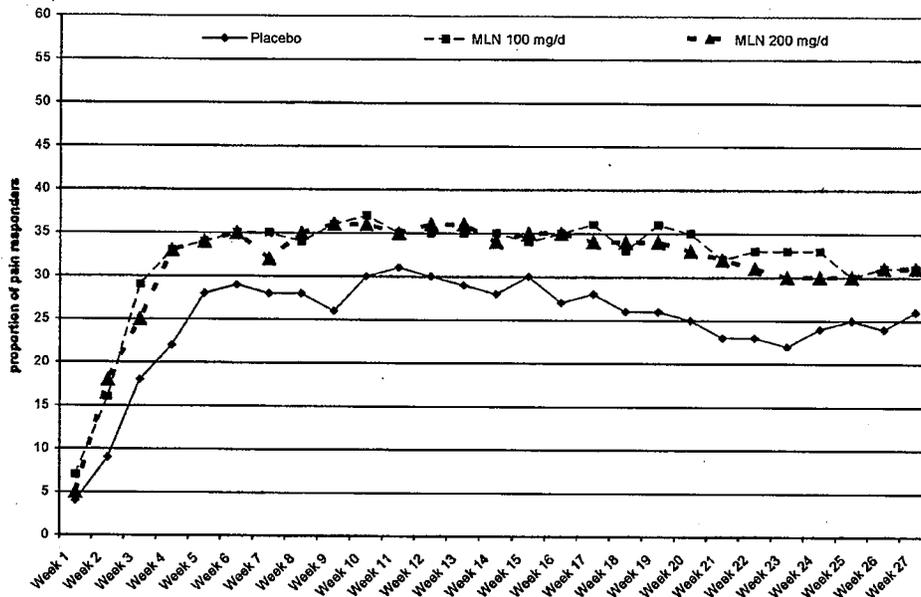




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Figure 17 presents the proportion of patients achieving at least 30% improvement in pain by week. The results are consistent with the continuous responder graphs by week (see also Appendix 6 for the table). A higher proportion of responders appears to occur at Week 3 (milnacipran 200 mg/d versus placebo group), and the difference (although not consistently large) appears to continue until Week 27.

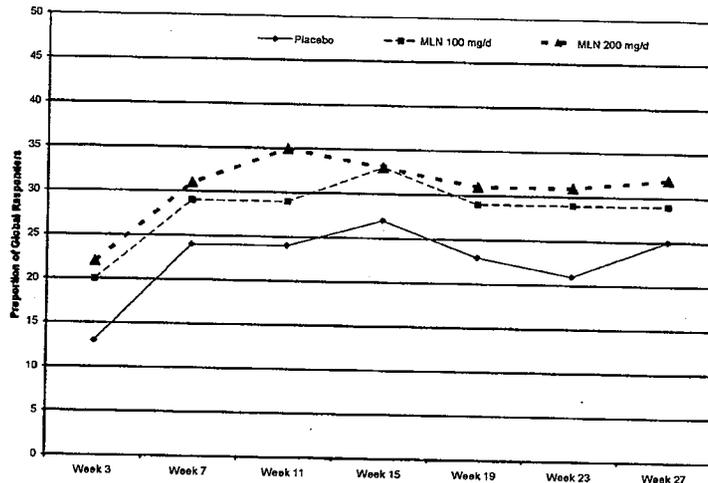
Figure 17: Pain Only Responder Rate ($\geq 30\%$ improvement) for Milnacipran Versus Placebo by Week (UPA) – Study FMS-031



Patient Global Impression of Change scores were collected on weeks 3, 7, 11, 15, 19, 23 and 27. The results using BOCF (i.e. drop outs are considered nonresponder) from each week are presented in Figure 18 (see Appendix 7 for the table). Note that unlike the primary endpoint (i.e. composite pain responder), the definition of responder was not restricted to the use of rescue medication or non-allowed narcotic medications.

As a result of the analysis by week, the proportion of patients achieving at least a “very much improved” or “improved” in global test appears to be consistently higher in the milnacipran groups compared to the placebo group across all weeks.

Figure 18: Patient Global Impression of Change Responder Rate (very much improved or improved) for Milnacipran Versus Placebo by Week (UPA) using BOCF – Study FMS-031

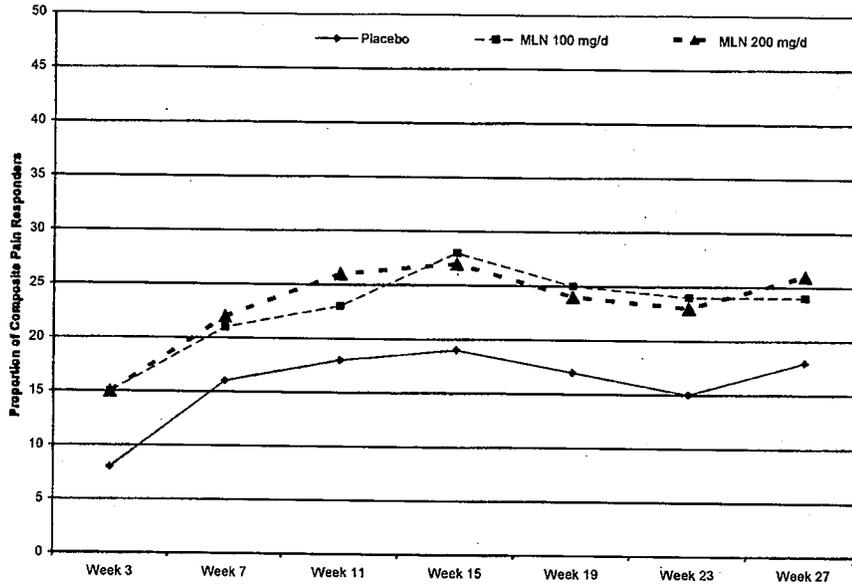


Composite pain responder rate was calculated based on the information from the pain only responder and patient global responder at weeks 3, 7, 11, 15, 19, 23 and 27. The results from each week are summarized in Table 34 and presented graphically in Figure 19. Like the pain responder and global responder, the responder definition is slightly different from the primary endpoint definition, thus the results at Week 15 and Week 27 will be slightly different from the primary endpoint results at three months and at six months. A higher proportion of patients in the milnacipran groups achieved at least 30% improvement in pain and achieved at least a “very much improved” or “improved” in global test compared to placebo starting at Week 3. The difference appears to continue until week 27.

Table 34: Composite Pain Responder Rate for Milnacipran Versus Placebo by Week (UPA Analysis) – Study FMS-031

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=223	N=224	N=441
Week 3	17 (8%)	35 (15%)	65 (15%)
Week 7	36 (16%)	48 (21%)	96 (22%)
Week 11	40 (18%)	52 (23%)	113 (26%)
Week 15	42 (19%)	62 (28%)	118 (27%)
Week 19	37 (17%)	56 (25%)	108 (24%)
Week 23	34 (15%)	54 (24%)	103 (23%)
Week 27	41 (18%)	53 (24%)	113 (26%)

Figure 19: Composite Pain Responder Rate for Milnacipran Versus Placebo by Week (UPA analysis) – Study FMS-031

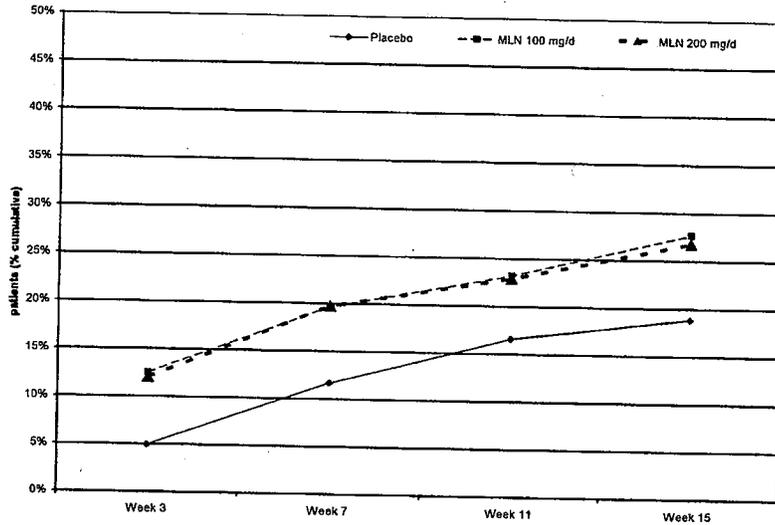


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An alternate way to view the treatment effect over time is to explore those patients who completed the study and who responded to treatment, using the 30% responder criteria. For simplicity, the definition of responder will not be restricted on the use of rescue or non-allowed narcotics, or the number of available pain assessments.

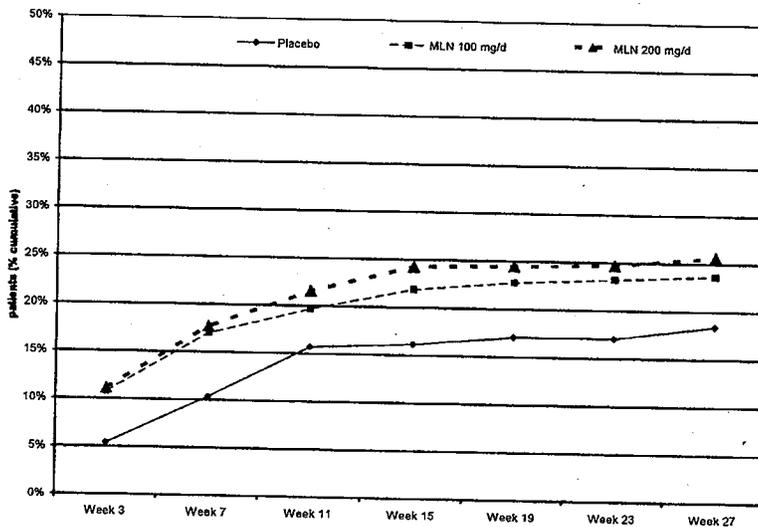
In these plots, we examined when these patients started to respond to treatment. In some cases, patients may respond early and then respond late again while some respond all throughout the study. In this plot, we assume that a subject who responded will respond up to the end of the study. Therefore, the x-axis shows the week the subject responded, and the y-axis shows the corresponding percentage of patients who had at least 30% improvement in pain from baseline over time. A total of 565 (64%) patients completed the 3-month landmark. Of these, 222 patients had at least 30% improvement in pain from baseline at the end of the study and achieved a “very much improved” or “improved” in the global test. Figure 20 provides a graphical display of patients who responded to treatment. It appears that most patients receiving milnacipran (100 mg or 200 mg) continued to benefit until Week 15. Among patients who responded at Week 15, there is a difference in the proportion of responders as early as Week 3 between the active treatment arms and the placebo.

Figure 20: Proportion of Responders by Week ($\geq 30\%$ Improvement in Pain and ≤ 2 in Global) at the 3-month landmark – Study FMS-031



Looking at data up to Week 27, a total of 512 (58%) patients completed the study (27 weeks of treatment). Of these, 207 patients had at least 30% improvement in pain from baseline at the end of the study and achieved a “very much improved” or “improved” in the global test. Figure 21 provides a graphical display of patients who responded to treatment. Like Figure 20, it appears that most patients receiving milnacipran (100 mg or 200 mg) achieved the level of response at Week 15 and seemed to plateau thereafter.

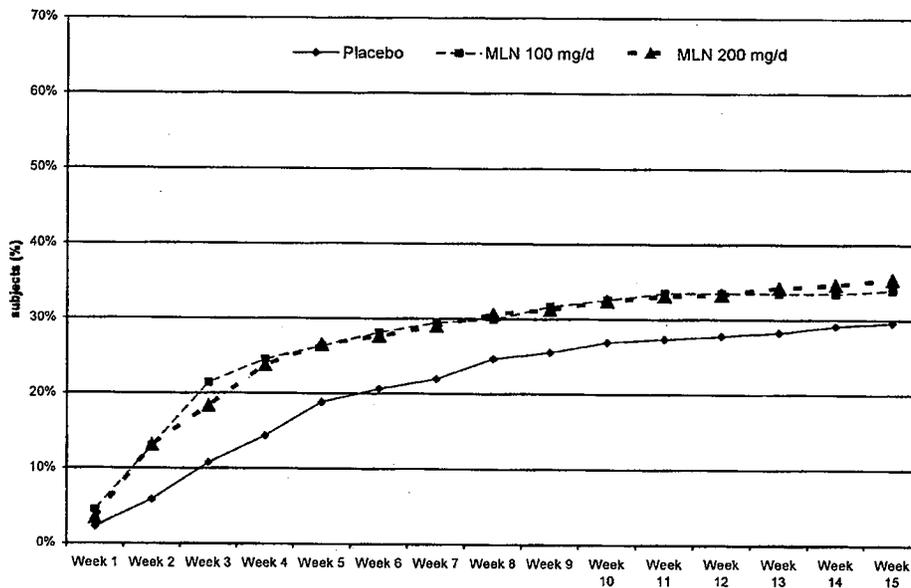
Figure 21: Proportion of Responders by Week ($\geq 30\%$ Improvement in Pain and ≤ 2 in Global) at the 6-month landmark – Study FMS-031



In terms of the pain only responder, of the 565 patients who completed 15 weeks of treatment, 298 patients (53%) had at least 30% improvement in pain score from baseline at the 3-month landmark. Figure 22 provides a graphical display of patients who responded to treatment. It appears that most patients receiving milnacipran (100 mg or 200 mg) continued to achieve the level of pain response up until Week 15. Among patients who responded at Week 15, there is a difference in the proportion of pain responders as early as Week 3 between the active treatment arms and the placebo.

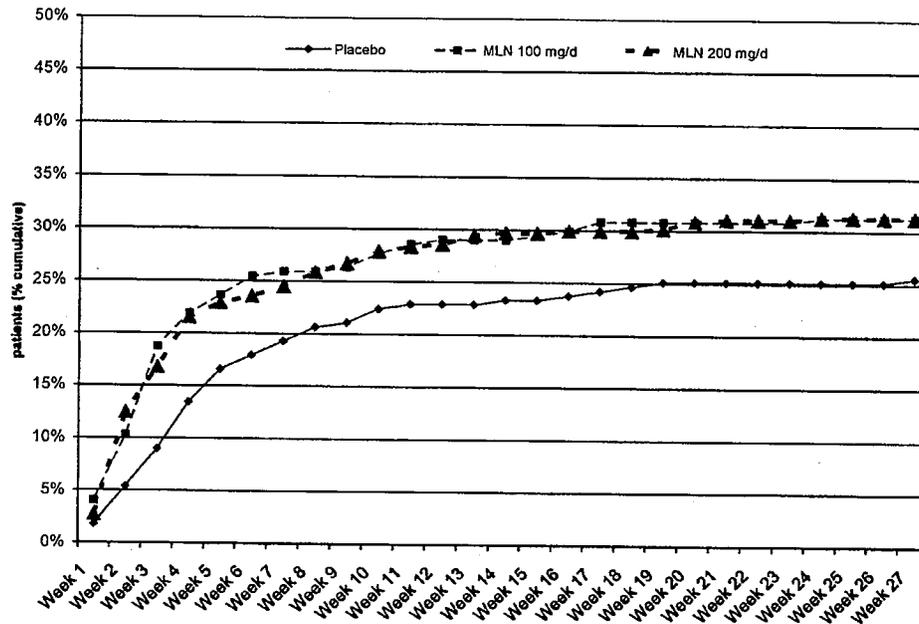
Looking at data up to Week 27, a total of 512 (58%) patients completed the study (27 weeks of treatment). Of these, 265 patients had at least 30% improvement in pain from baseline at the end of the study (27 weeks of treatment). Figure 23 provides a graphical display of patients who responded to treatment. Like Figure 22, it appears that most patients receiving milnacipran (100 mg or 200 mg) achieved the level of response at Week 15 and seemed to plateau thereafter.

Figure 22: Proportion of Responders by Week up to week 15 ($\geq 30\%$ Improvement in Pain) – Study FMS-031



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Figure 23: Proportion of Responders by Week up to week 27 ($\geq 30\%$ Improvement in Pain) – Study FMS-031



Like Study MLN-MD-02, we explored the contribution of pain response and global response to the composite responder. This is done by analyzing patients who met the pain response criteria only, the global response criteria only or both criteria (Table 35). In this analysis, responder is defined with restrictions on the use of rescue medication or non-allowed medication, or on the number of days with valid pain assessments. Therefore, the column “Pain/PGIC (Yes/Yes)” is the result of the primary endpoint (composite pain responder). Adding the column “Pain/PGIC (Yes/Yes)” with the column “Pain/PGIC (Yes/No)” will result in pain only responder at endpoint. Lastly, adding the column “Pain/PGIC (Yes/Yes)” with the column “Pain/PGIC (No/Yes)” will result in global only responder at endpoint. The objective is to determine what may be driving the test of the primary endpoint to be significant.

Based on the result, there is no evidence that treatment difference in the composite response rate can be attributed to one domain, i.e. patients achieving a good global score or patients’ improvement in their pain score. It appears that the proportion of patients achieving 30% improvement in pain but did not meet the criteria on global is similar to the proportion of patients who met the criteria on global test but did not achieve 30% improvement in pain across all treatment groups. Therefore, treatment difference in the composite pain response rate can be attributed to improvement in both pain and global domain.

Table 35: Analysis of Pain and Global Tests (UPA Analysis, BOCF) – Study FMS-031

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

We explored whether there are differences in baseline characteristics among the treatment groups based on their responses to pain and global rating at the 3-month landmark. There appears to be no substantial difference in baseline characteristics among the treatment groups across different responses to pain and global tests. Although there are no differences in endpoint mean pain score and change from baseline score at the 3-month landmark across treatment groups, there appears to be difference across different responses. Like Study MLN-MD-02, it appears that patients have a higher endpoint mean pain score among the discordant pairs (i.e. Pain/PGIC (Yes/No) and Pain/PGIC (No/Yes)) compared to concordant pairs (i.e. Pain/PGIC (Yes/Yes)). However, unlike Study MLN-MD-02, the endpoint mean pain score in the milnacipran 200 mg/d group appears slightly lower compared to placebo in the discordant pairs; while it appears to be slightly higher compared to placebo in the concordant pair.

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Table 36: Analysis of Pain and Global Tests (BOCF) at the 3-month landmark by Baseline Characteristics – Study FMS-031

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

* No rescue medication restriction and number of observations restriction

† Include rescue medication restriction and number of observations restriction

b(4)

Aside from pain and global claims, the Applicant is also seeking The physical function domain for response analysis was measured using the Physical Component Summary of the Short Form (SF-36 PCS).

The results for the SF-36 PCS responder rate and the primary efficacy parameter for the composite syndrome response using different imputation strategies are summarized in Table 30 and Table 37. At the 3-month landmark visit under BOCF, 12% of placebo patients were defined as composite responders compared with 20% of milnacipran 100 mg patients and 19% of milnacipran 200 mg patients. Based on the pre-specified stepdown procedure (i.e. eight primary comparisons), only milnacipran 200 mg showed a significant difference compared to placebo in the treatment of syndrome of fibromyalgia at the 3-month landmark.

When syndrome was analyzed by itself, using SF-36 PCS responder rate at endpoint, it appears that there is insufficient evidence to conclude that the proportion of SF-36 PCS responders in the milnacipran group is greater compared to placebo (using BOCF with unadjusted p-value).

Like the global response, after re-analyzing the data, there were two subjects (ID# 20919 and ID#27013) in the milnacipran 200 mg group that should not have been function responders but were reported as responders; however, since these two subjects did not have any impact on the overall conclusion, the Applicant's results are reported in this review.

Table 37: SF-36 Physical Component Score and Composite Responder Rate for Syndrome for Milnacipran Versus Placebo at the 3-Month Landmark – Study FMS-031

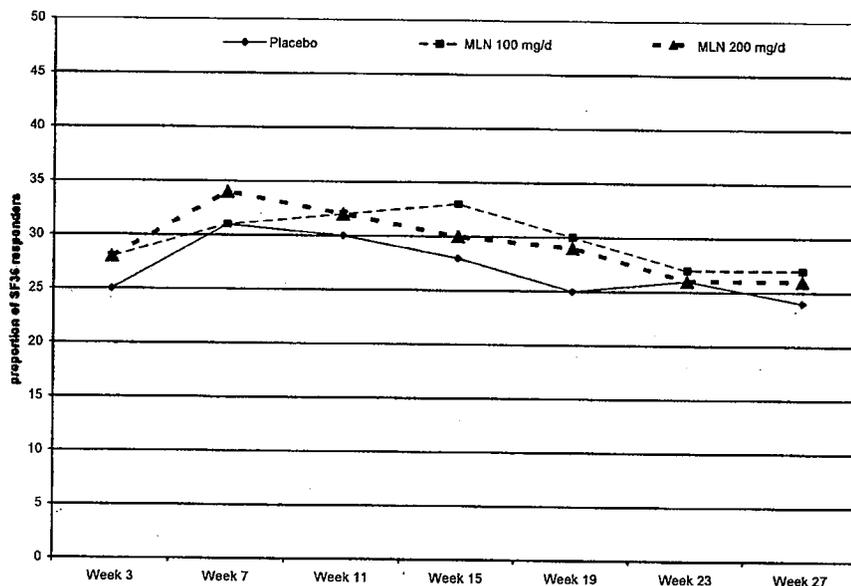
		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Composite: Syndrome		N=223	N=224	N=441
	LOCF†	32 (14%)	48 (21%) 1.66 (1.0, 2.8) p=0.0475	98 (22%) 1.76 (1.1, 2.8) p=0.0147
	BOCF†	27 (12%)	44 (20%) 1.84 (1.1, 3.2) p=0.0277	85 (19%) 1.80 (1.1, 2.9) p=0.0175
SF-36 PCS Score		N=223	N=224	N=441
	LOCF†	75 (34%)	86 (38%) 1.23 (0.8, 1.9) p=0.315	177 (40%) 1.38 (<1.0, 2.0) p=0.075
	BOCF†	61 (27%)	71 (32%) 1.28 (0.8, 2.0) p=0.254	131 (30%) 1.18 (0.8, 1.7) p=0.403

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

The SF-36 PCS was administered to patients at Baseline, weeks 3, 7, 11, 15, 19, 23, and 27 (or early termination before week 27). The results from each week are presented in Figure 24 (see Appendix 8 for the table). Note that unlike the primary endpoint (i.e. composite pain responder), the definition of responder was not restricted to the use of rescue medication or non-allowed narcotic medications.

The proportion of patients achieving at least a six-point change from baseline in SF-36 PCS score does not appear to differ between the milnacipran groups and the placebo group across all weeks.

Figure 24: Change from Baseline SF-36 Physical Component Score Responder Rate (≥ 6) for Milnacipran Versus Placebo by Week (ITT Population) BOCF – Study FMS-031



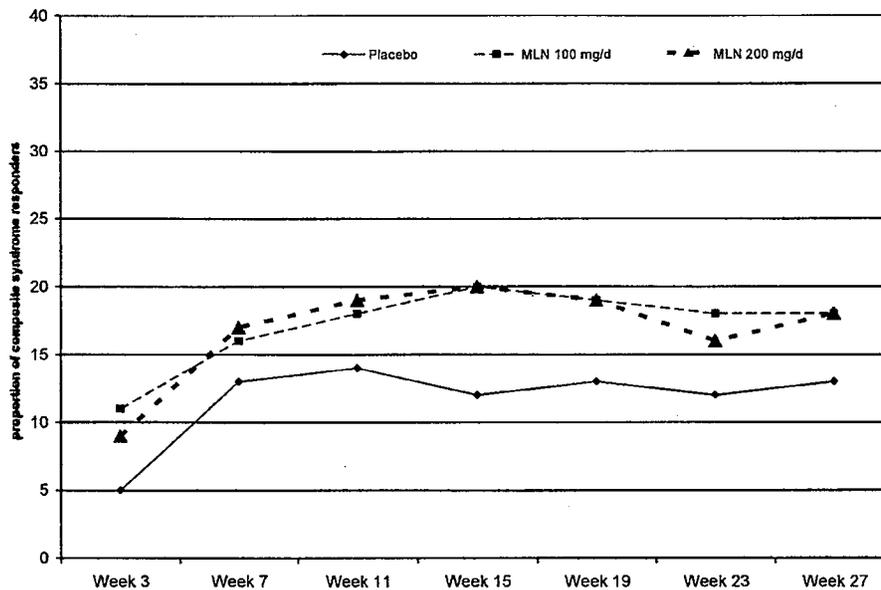
The composite syndrome responder rate was calculated based on the information from the pain only responder, patient global responder, and SF-36 physical component summary score at weeks 3, 7, 11, 15, 19, 23, and 27. The results from each week are summarized in Table 38 and presented graphically in Figure 25. Like the composite pain responder, the responder definition for syndrome here is slightly different from the primary endpoint definition, thus the result at Week 15 and Week 27 will be slightly different from the primary endpoint result of syndrome at three months and at six months.

A slightly higher proportion of patients in the milnacipran groups achieved the composite syndrome responder criteria starting at Week 3 compared to placebo. The difference appears to be sustained in the milnacipran groups until Week 27.

Table 38: Composite Syndrome Responder Rate for Milnacipran Versus Placebo by Week (ITT Population), BOCF – Study FMS-031

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=223	N=224	N=441
Week 3	11 (5%)	24 (11%)	41 (9%)
Week 7	29 (13%)	36 (16%)	76 (17%)
Week 11	32 (14%)	40 (18%)	83 (19%)
Week 15	27 (12%)	45 (20%)	88 (20%)
Week 19	28 (13%)	42 (19%)	83 (19%)
Week 23	27 (12%)	41 (18%)	72 (16%)
Week 27	30 (13%)	41 (18%)	80 (18%)

Figure 25: Composite Syndrome Responder Rate for Milnacipran Versus Placebo by Week (ITT Population)



Because the entry criteria of Study MLN-MD-02 and FMS-031 were slightly different, the Applicant conducted post-hoc analysis by excluding patients with baseline FIQ-PF <4 and baseline BDI score of greater than 25. This is called the UPA population. Of the 888 patients randomized, 715 patients (81%) had baseline BDI ≤ 25 and baseline FIQ-PF ≥ 4. The following (Table 39 and Table 40) are the results of the primary endpoint analysis (composite pain responder and composite syndrome responder) at the 3-month and 6-month landmark under the UPA population using BOCF.

The result appears to be slightly different from the UPA analysis. Since this is a post-hoc analysis, the error rates should be adjusted for this repeat testing; by how much, is a difficult question to answer. Nonetheless, there is evidence that the magnitude of difference in the response rates between the milnacipran groups and the placebo group is relatively similar to that of the UPA analysis. However, the confidence intervals for all the pairwise comparisons of single milnacipran dosages to placebo indicate that the milnacipran groups have greater odds of response (i.e. composite pain and composite syndrome) compared to placebo. Furthermore, similar to the UPA analysis, the proportion of responders between the two milnacipran groups appear to be identical. In contrast to the UPA analysis, in this population, there is also some evidence of a higher proportion of composite pain responders at 6 months in the milnacipran 200 mg dose group compared to the placebo group. Yet again, the error rates are not adjusted for this repeat testing and the evidence may not be well supported.

Table 39: Primary Endpoint at 3 months landmark – UPA Population

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=171	N=189	N=355
Composite Pain†	31 (18%)	52 (28%) 1.73 (1.0, 2.9) p=0.0335	99 (28%) 1.8 (1.1, 2.8) p=0.0152
Composite Syndrome‡	21 (12%)	39 (21%) 2.0 (1.1, 3.8) p=0.0235	73 (21%) 2.1 (1.2, 3.8) p=0.0104
Pain Only Responder‡	47 (27%)	64 (34%) 1.36 (0.9, 2.1) p=0.1808	133 (37%) 1.60 (1.1, 2.4) p=0.0212
PGI Only Responder§	45 (26%)	64 (34%) 1.43 (0.9, 2.3) p=0.1204	125 (35%) 1.52 (1.0, 2.3) p=0.0417
SF36-PCS Responder‡	48 (28%)	62 (33%) 1.31 (0.8, 2.1) p=0.2676	115 (32%) 1.37 (0.9, 2.1) p=0.1590

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

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

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

Table 40: Primary Endpoint at 6 months landmark – UPA Population

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=171	N=189	N=355
Composite Pain†	29 (17%)	46 (24%) 1.58 (0.9, 2.7) p=0.0882	86 (24%) 1.61 (1.0, 2.6) p=0.0488
Composite Syndrome‡	22 (13%)	34 (18%) 1.43 (0.8, 2.6) p=0.2454	62 (17%) 1.5 (0.9, 2.7) p=0.1323
Pain Only Responder‡	37 (22%)	59 (31%) 1.65 (1.0, 2.7) p=0.0389	105 (30%) 1.54 (1.0, 2.4) p=0.0486
PGI Only Responder§	43 (25%)	55 (29%) 1.22 (0.8, 1.9) p=0.4002	119 (34%) 1.50 (<1.0, 2.3) p=0.0521
SF36-PCS Responder‡	44 (26%)	51 (27%) 1.08 (0.7, 1.8) p=0.7736	103 (29%) 1.30 (0.8, 2.0) p=0.2580

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

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

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

In summary, there is evidence that milnacipran 200 mg/day is different from placebo in the treatment of pain using the composite pain responder definition. There is some evidence that milnacipran 200 mg/day is different from placebo in the treatment of syndrome using the composite syndrome responder definition; however, this did not survive the step down procedure when a more conservative strategy is applied to the 6-month landmark on pain. Nonetheless, the proportion of responders (i.e. composite pain or composite syndrome) between the two milnacipran groups is identical. In addition, the response profile between these two milnacipran arms appears to be similar across different range of response.

There is no evidence that the milnacipran 200 mg group is different from placebo in either domain (i.e. pain, global or SF36 PCS). It appears that none of the domains significantly influenced the response individually. Instead, it appears that the response is influenced by the combination of these domains.

Although there are some patients who experienced a decrease in pain as early as week 1, the treatment difference did not occur until after the dose titration period ended (i.e. week 3). Furthermore, it appears that no additional benefit can be seen after Week 15.

3.1.3.1.3 Long-Term Effect/Persistence of Efficacy

In Study FMS-031, patients received 27 weeks of treatment, including the 3-week dose escalation phase. The result for the composite pain responder and composite syndrome responder is summarized in Table 41 using BOCF under the Unified Program Analysis. Although numerically, a higher proportion of patients in the milnacipran groups achieve the composite pain responder criteria as well as the composite syndrome responder criteria compared to the placebo, the confidence interval includes values that correspond to a more favorable response among placebo patients such that the difference in the proportion of response may not be well supported.

Table 41: Primary Efficacy Analyses: Composite Pain Responder Rates for Milnacipran versus Placebo at the 6-Month Landmark – UPA Analysis (Study FMS-031)

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=223	N=224	N=441
Composite Pain†	39 (17%)	53 (24%) 1.41 (0.9, 2.3)	104 (24%) 1.49 (<1.0, 2.3)
Composite Syndrome‡	27 (12%)	40 (18%) 1.46 (0.8, 2.5)	73 (17%) 1.47 (0.9, 2.4)
Pain Only Responder†	52 (23%)	67 (30%) 1.38 (0.9, 2.1)	127 (29%) 1.36 (0.9, 2.0)
PGI Only Responder§	55 (25%)	63 (28%) 1.20 (0.8, 1.8)	140 (32%) 1.42 (<1.0, 2.0)
SF36-PCS Responder‡	53 (24%)	59 (26%) 1.14 (0.7, 1.8)	114 (26%) 1.15 (0.8, 1.7)

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

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

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

The Applicant conducted two long-term extension studies, Studies MLN-MD-04 and Study FMS-034. These two studies extend the findings of the two placebo-controlled studies (Study MLN-MD-02 and Study FMS-031, respectively) for a period of up to 1 year.

The following is a summary of the study design for both Study MLN-MD-04 and Study FMS-034:

Both studies were phase 3, randomized, double-blind, 2-arm, multicenter extension study of the long-term safety and efficacy of milnacipran in patients who successfully completed Study MLN-MD-02 for Study MLN-MD-04 and Study FMS-031 for Study FMS-034. Patients who entered Study MLN-MD-04 received up to 39 weeks of milnacipran therapy. Patients who entered Study FMS-034 received up to 28 weeks of milnacipran therapy. The study consisted of two milnacipran treatment groups: 100 mg/d (50 mg BID) and 200 mg/d (100 mg BID). No patients experienced dose reduction from their final dose in the lead-in studies. Patients who received 200 mg/d in the lead-in studies continued to receive 200 mg/d in the extension studies. Patients who had received either placebo or 100 mg/d of milnacipran during the lead-in studies were randomized in a 1:4 ratio to either 100 mg/d or 200 mg/d of milnacipran in the extension studies. To maintain blinding integrity, sham escalations were performed if no actual dose escalation occurred.

A total of 384 patients were randomized from lead-in Study MLN-MD-02 into this extension study, of whom 32% (124/384) discontinued prematurely. Meanwhile, a total of 449 patients were randomized from lead-in Study FMS-031 into the extension study, with 33% (148/449) discontinued prematurely. The main reason for discontinuation was AE (18% in both studies). Patients who had been treated with placebo in both lead-in studies and then treated with active drug in the extension studies had higher rates of discontinuation because of an AE (placebo to milnacipran 100 mg/d, 22% in Study MLN-MD-04 and 21% in Study FMS-034, placebo to milnacipran 200 mg/d, 27% in Study MLN-MD-04 and 21% in Study FMS-034) than did patients who remained at the same dose of milnacipran.

The primary efficacy parameters in the extension studies were the changes from baseline in VAS assessments of daily and weekly pain recall, Fibromyalgia Impact Questionnaire (FIQ) total score, FIQ-PF subscore; and the PGIC.

The Applicant claimed that treatment with milnacipran 100 mg/d or 200 mg/d for up to 39 weeks in Study MLN-MD-04 and up to 28 weeks in Study FMS-034 maintained the beneficial effects observed in the lead-in studies in pain assessment, PGIC, and physical function (measured by FIQ total score).

In my opinion, it is difficult to assess 'maintenance' when there is no assay sensitivity in the extension study or when there are no pre-defined criteria (e.g. at least X proportion of patients who respond consecutively) that would allow us to determine 'maintenance' of effect. Either a randomized withdrawal study design should be conducted or a placebo-controlled study for up to 52 weeks should be conducted to determine the 'maintenance' or 'persistence' of effect.

3.2 EVALUATION OF SAFETY

Dr. Jane Filie reviewed the safety of milnacipran in detail. The reader is referred to Dr. Filie's review for information regarding the adverse event profile.

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4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

4.1 SEX, RACE AND AGE

Subgroup analyses were conducted with respect to gender, race, and age for the primary efficacy endpoints (i.e. composite pain and composite syndrome) at the 3-month landmark in the ITT population. A descriptive summary of the primary endpoint (i.e. composite syndrome by each subgroup in the pooled data and by individual studies is presented in Appendix 9 to Appendix 17 and graphically illustrated in Figure 26 to Figure 28 for the pooled studies, in Figure 29 to Figure 31 for Study FMS-031 and in Figure 32 to Figure 34 for Study MLN-MD-02.

The female population comprised 96% (2000/2084) of the patients in the pooled ITT population. There were no statistically significant treatment group-by-sex interactions observed for the treatment of either fibromyalgia syndrome or fibromyalgia pain. However, because of the small numbers of male patients in the study sample, any claims in terms of patient's gender are essentially unsupported.

The Applicant stratified the age into two groups: age < 60 years and age ≥ 60 years; 81% of the pooled population was younger than 60 years. There were no statistically significant treatment group-by-age interactions observed for the treatment of either fibromyalgia syndrome or fibromyalgia pain. However, because of the small numbers of patients greater than 60 years of age in the study sample, any claims in terms of patient's age are essentially unsupported.

Like gender, more than 93% of the pooled ITT population was Caucasian. There were no statistically significant treatment group-by-race interactions observed for the treatment of either fibromyalgia syndrome or fibromyalgia pain. However, because of the small numbers of non-Caucasian patients in the study sample, any claims in terms of patient's race are essentially unsupported.

Similar results were observed in Study FMS-031 and Study MLN-MD-02 when subgroup analyses were conducted.

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Figure 26: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Pooled Data

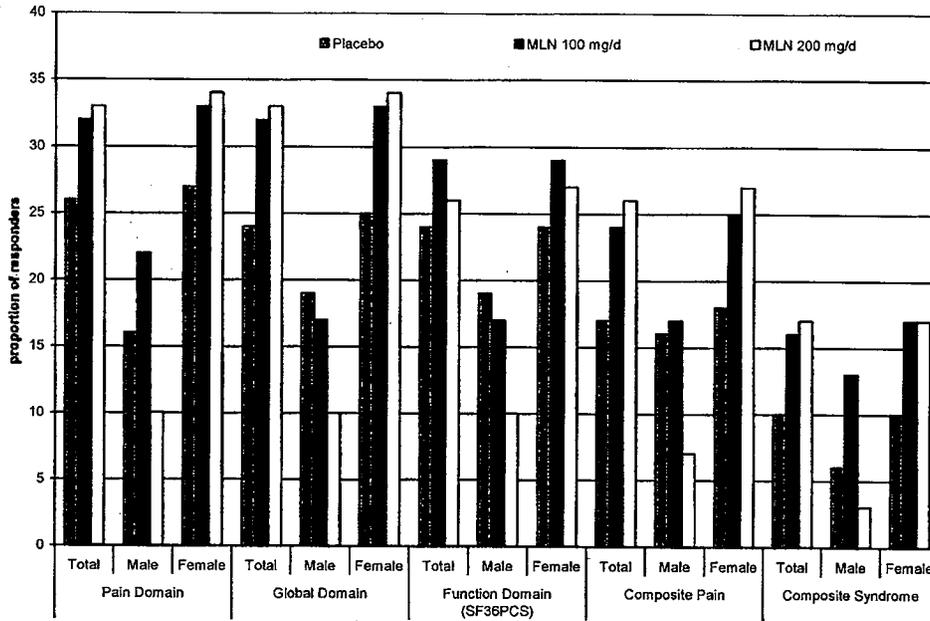


Figure 27: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Pooled Data

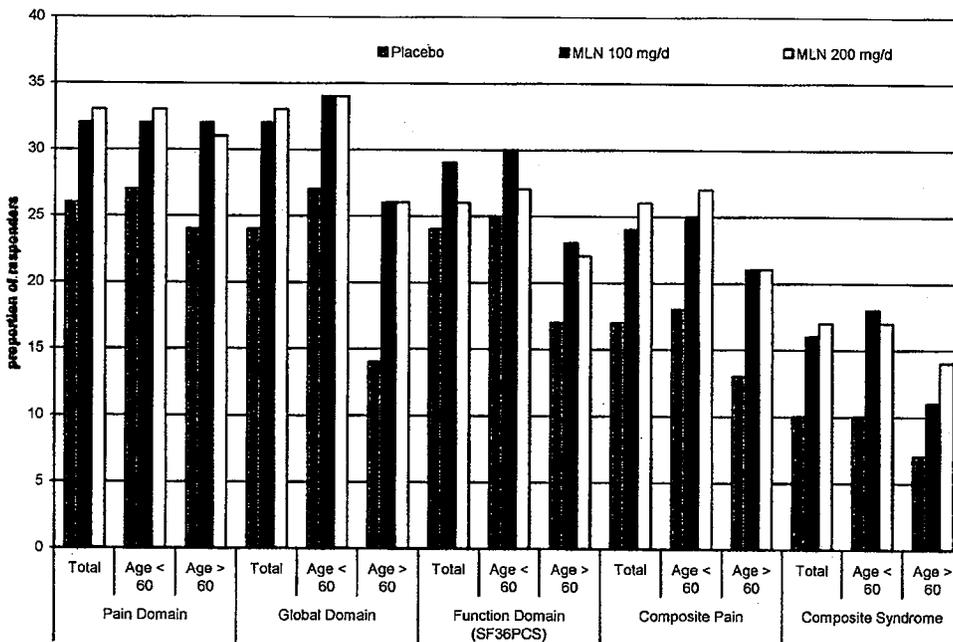


Figure 28: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Pooled Data

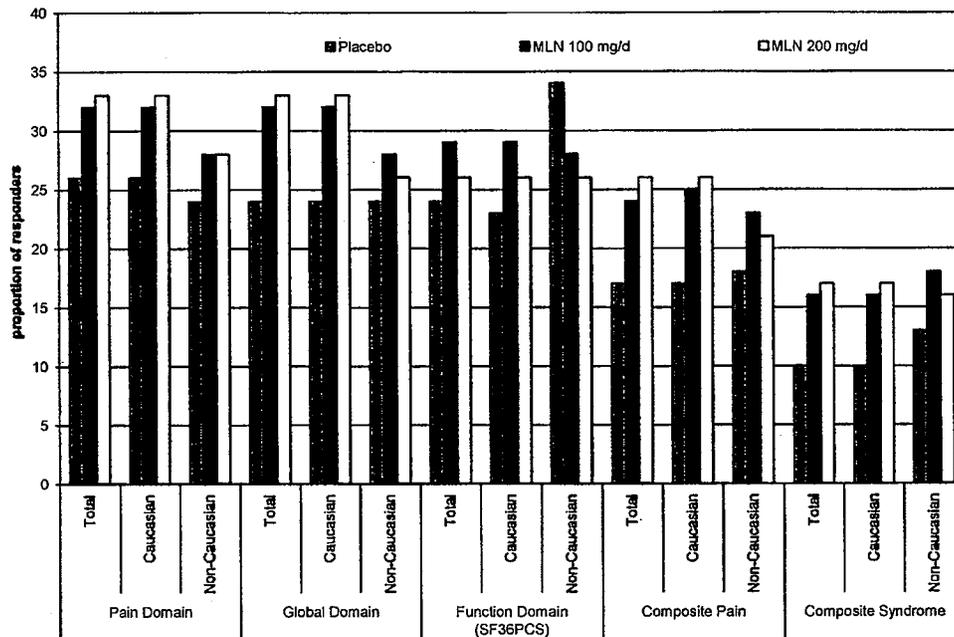


Figure 29: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Study FMS-031

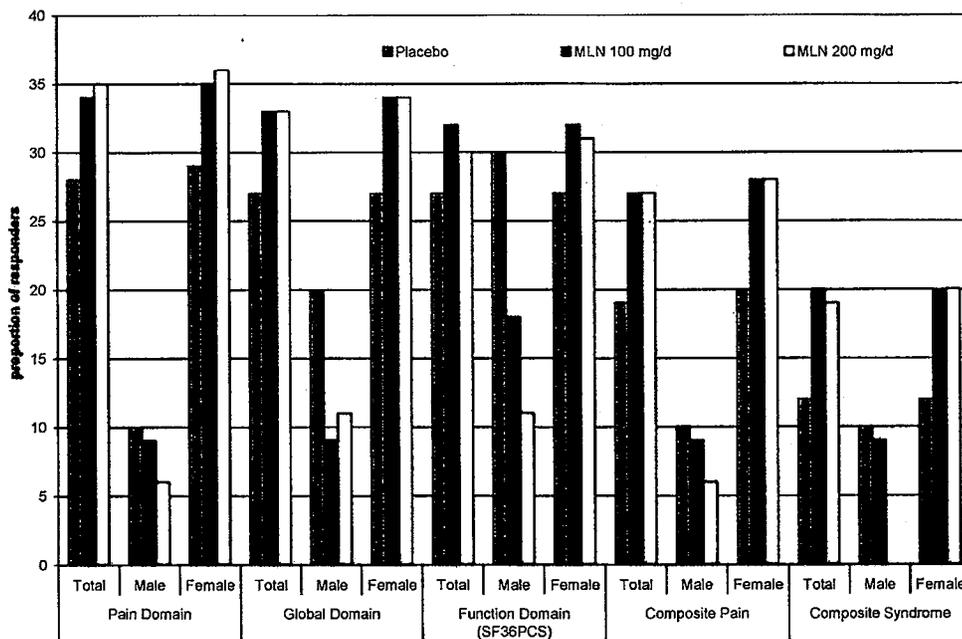


Figure 30: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Study FMS-031

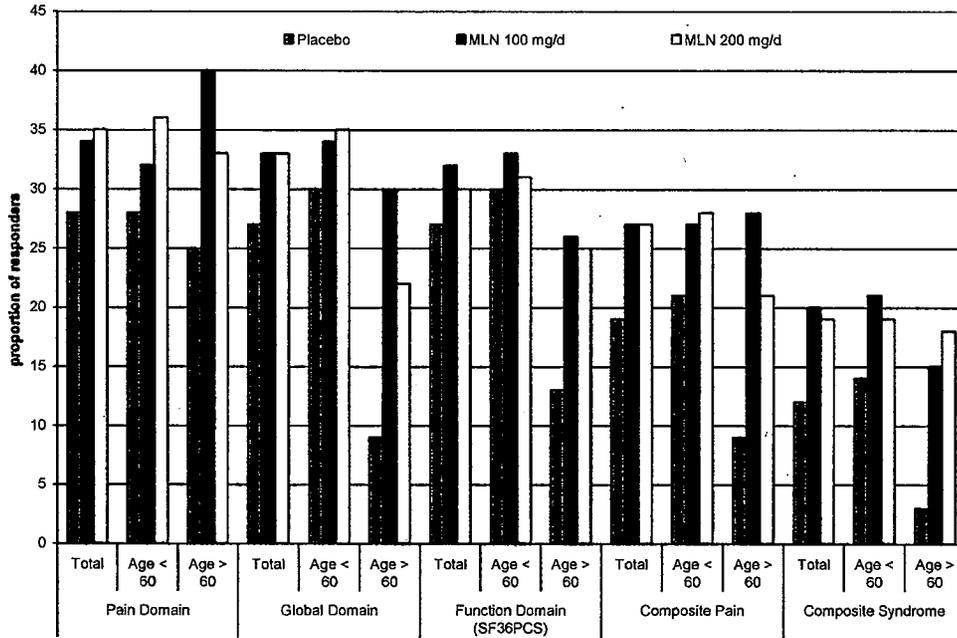


Figure 31: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Study FMS-031

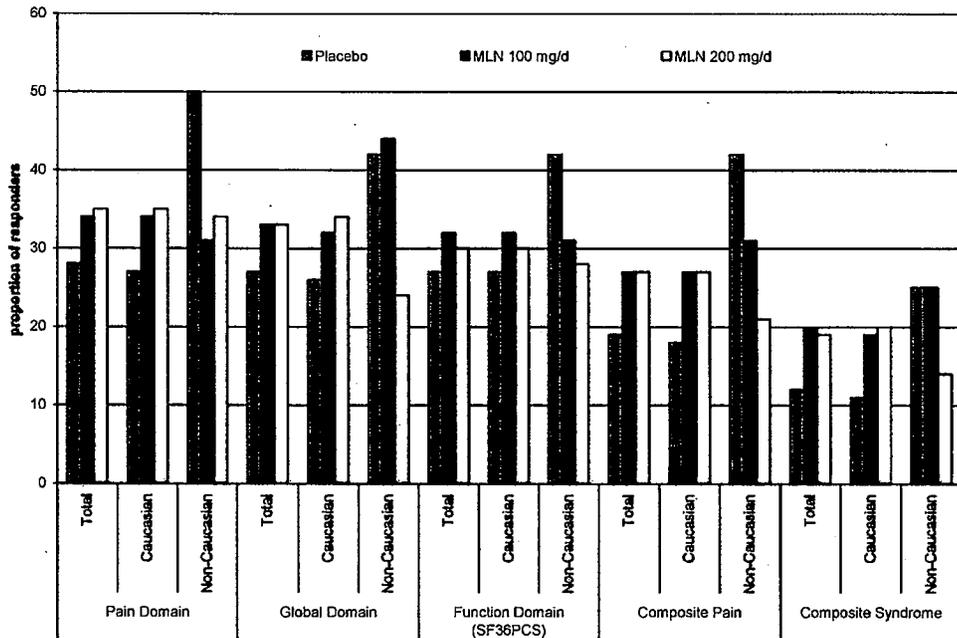


Figure 32: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Study MLN-MD-02

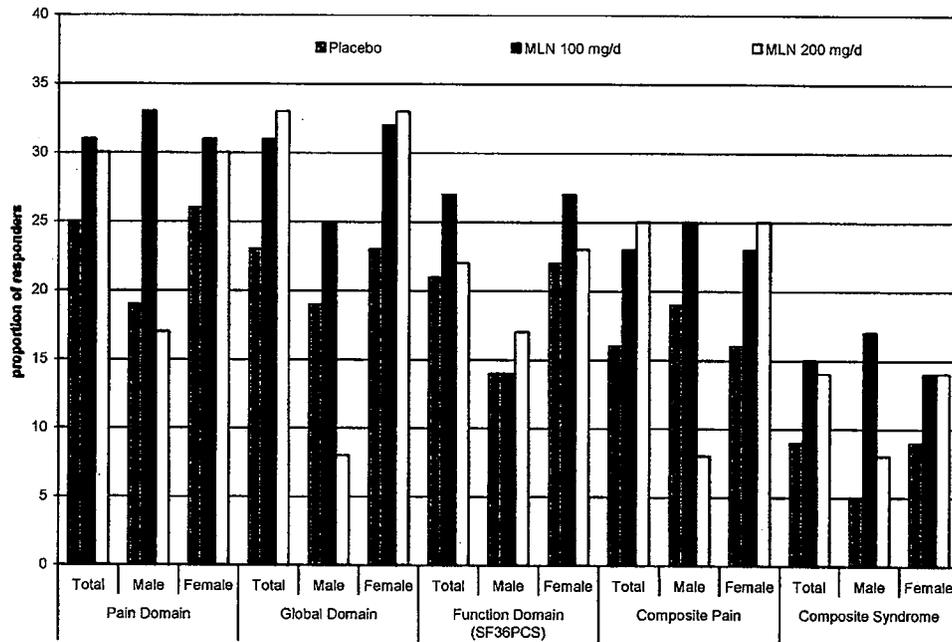


Figure 33: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Study MLN-MD-02

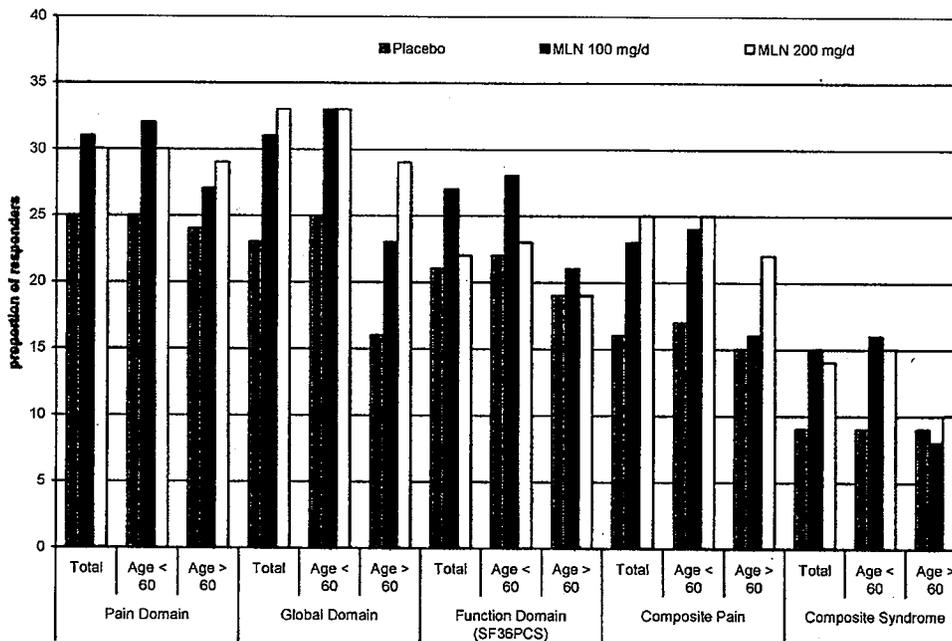
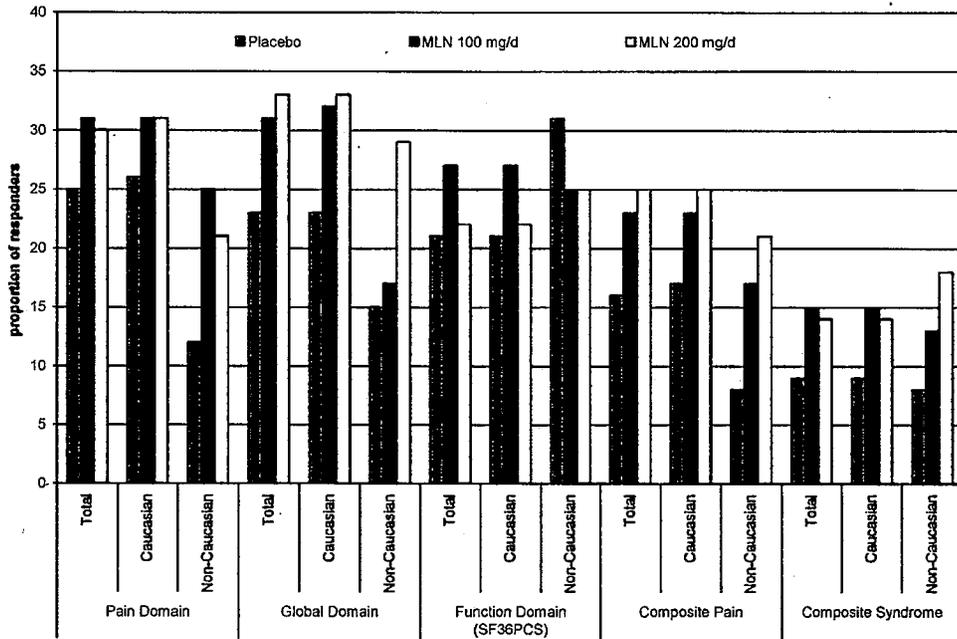


Figure 34: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Study MLN-MD-02



4.2 OTHER SUBGROUPS AND SPECIAL POPULATIONS

In the pooled ITT Population, the mean BDI score at baseline was 14, with 89% (1864/2084) of the population having a baseline score of ≤ 25 . There was no statistically significant treatment group-by-baseline BDI category (BDI ≤ 25 or BDI > 25) interaction at either the 100 mg/d or 200 mg/d dosages for fibromyalgia syndrome or fibromyalgia pain. A summary of results by baseline BDI scores is presented in Appendix 18 to Appendix 20 and graphically in Figure 35 to Figure 37.

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Figure 35: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Pooled Studies

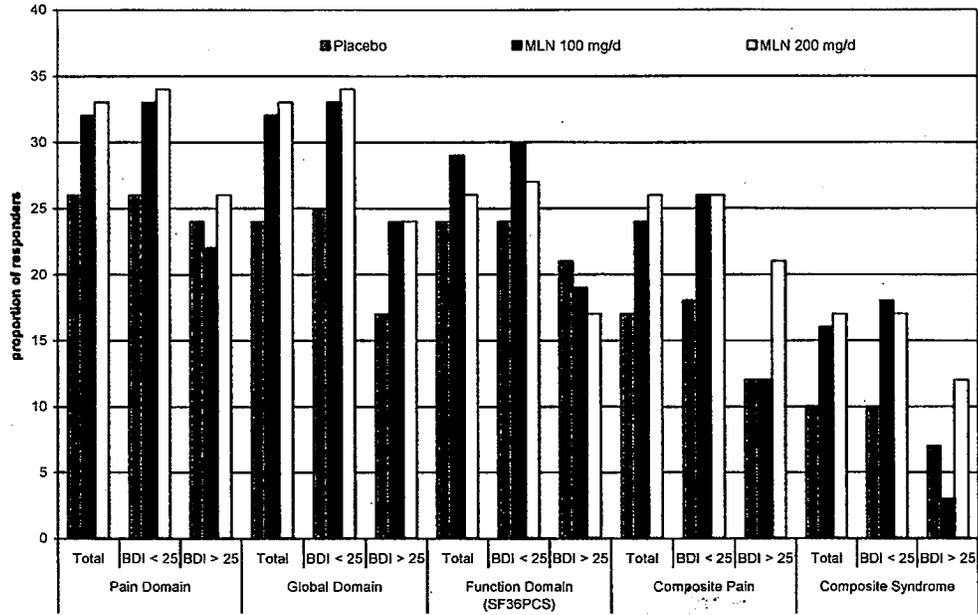


Figure 36: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study FMS-031

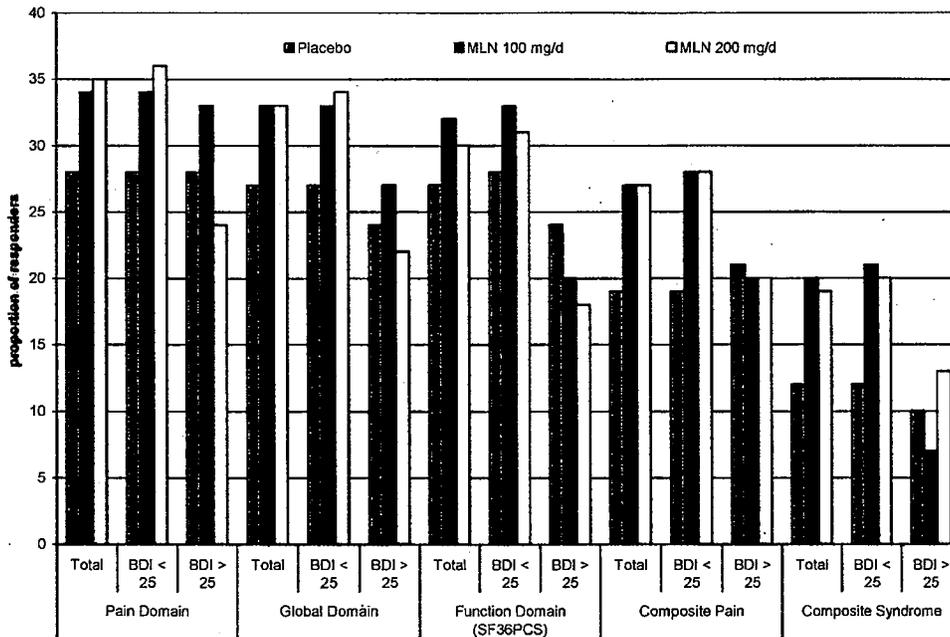
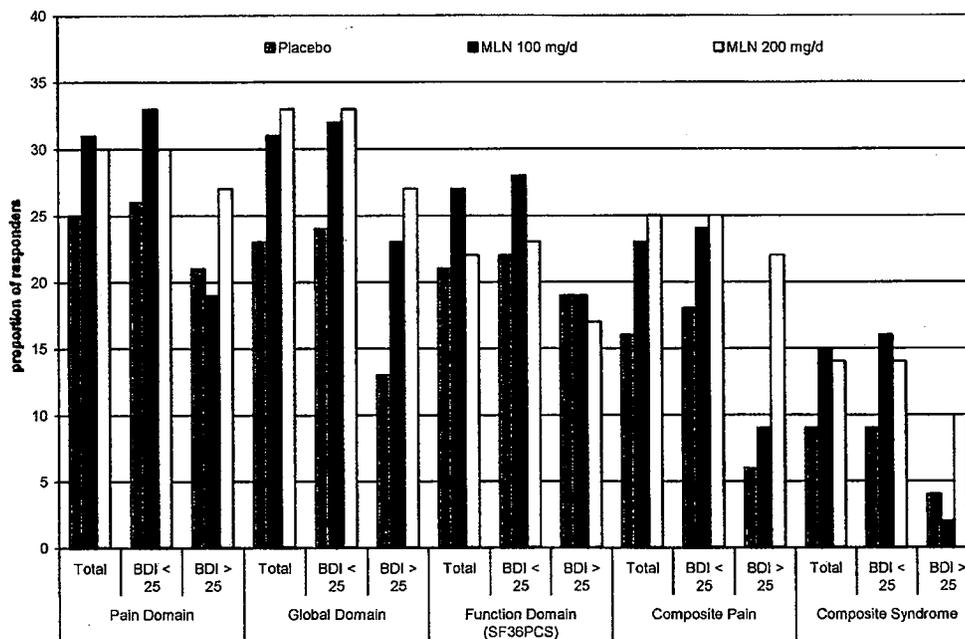


Figure 37: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study MLN-MD-02



We conducted additional analysis by baseline BDI scores categorized into 4 groups (0 to 9 or nondepressed, 10 to 16 as mildly depressed, 17 to 29 as moderately depressed, and 30 or higher as severely depressed). There was no treatment group-by-baseline BDI category interaction for either fibromyalgia syndrome or fibromyalgia pain. A summary of results by baseline BDI scores is presented in Appendix 21 to Appendix 23 and graphically in Figure 38 to Figure 40.

There appears to be a higher proportion of patients responding (on both fibromyalgia syndrome and fibromyalgia pain) to the milnacipran treatment compared to placebo across the baseline BDI strata. In particular, there was no indication that patients with higher BDI scores at baseline responded better than patients with lower scores at baseline.

The Applicant additionally claimed that

In patients with baseline BDI score > 9, the 200 mg/d dose of milnacipran appeared to provide greater response rates and greater odds ratios than the 100 mg/d dose for both fibromyalgia syndrome and fibromyalgia pain. These results support an additional benefit with treatment with 200 mg/d of milnacipran in patients with higher baseline BDI scores.

This statement may be true for the composite endpoints; but this is not consistent when exploring the individual domains/components.

Figure 38: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Pooled Studies

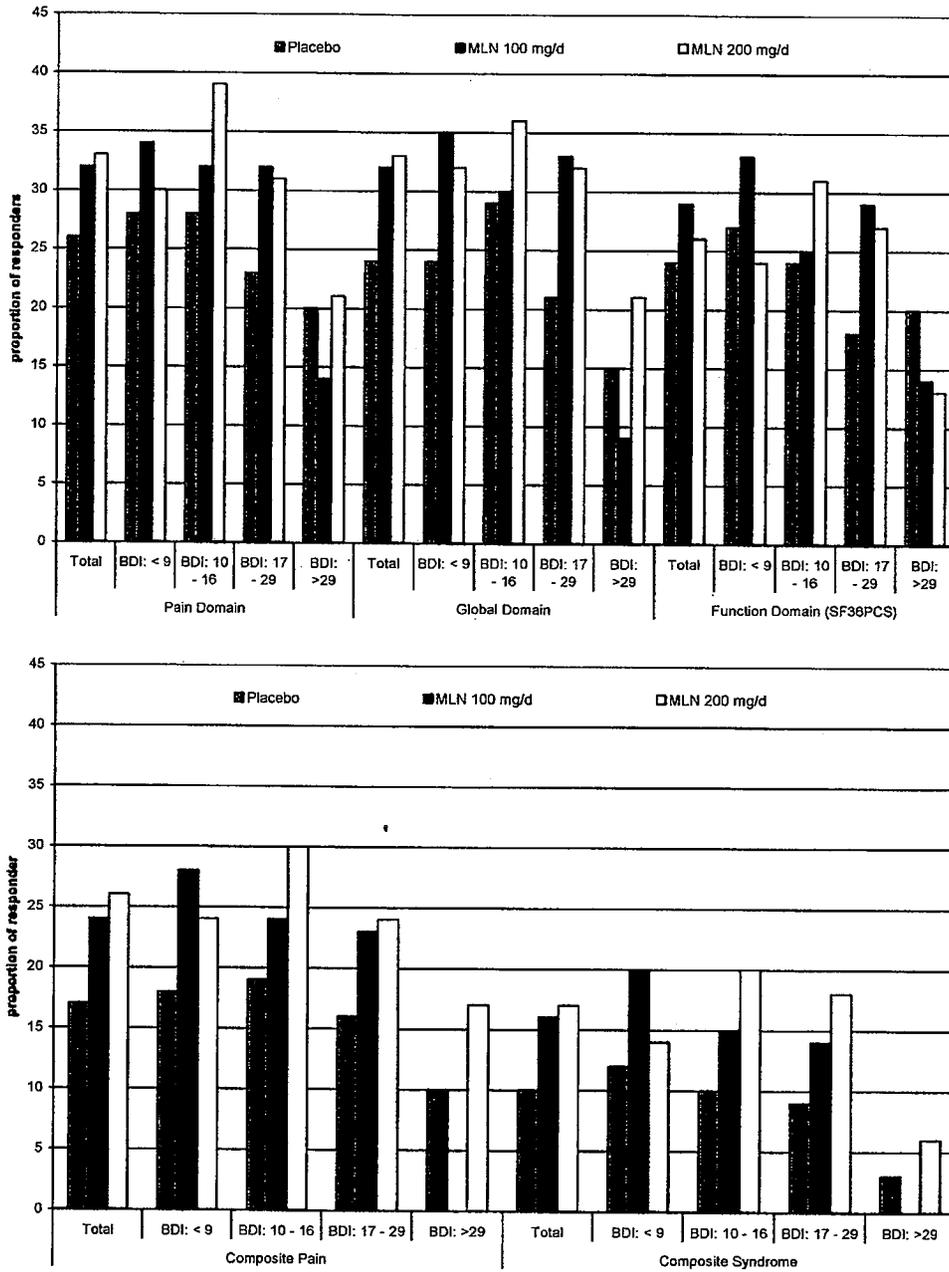


Figure 39: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study FMS-031

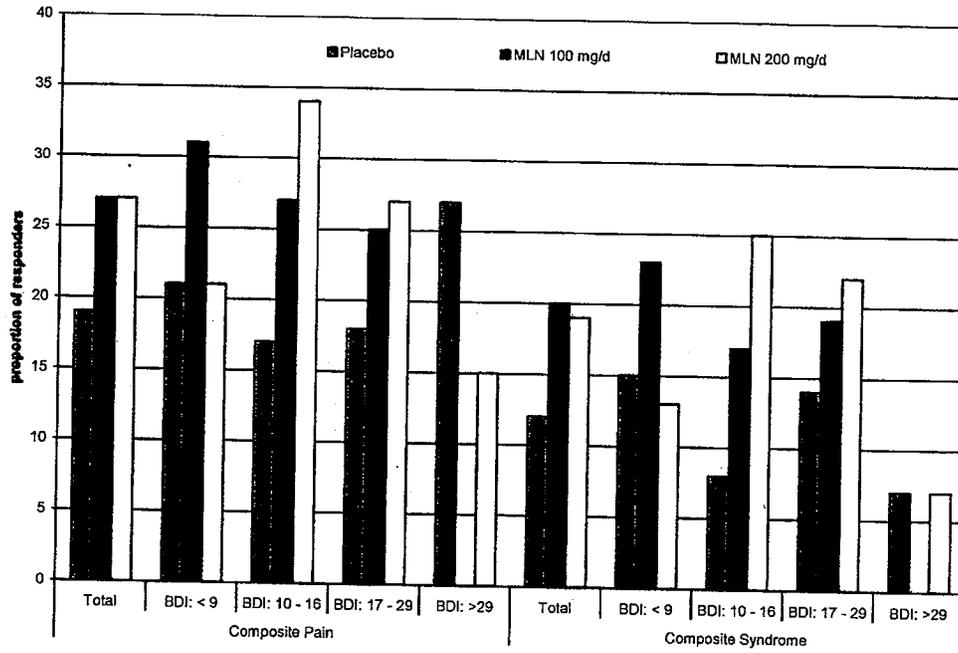
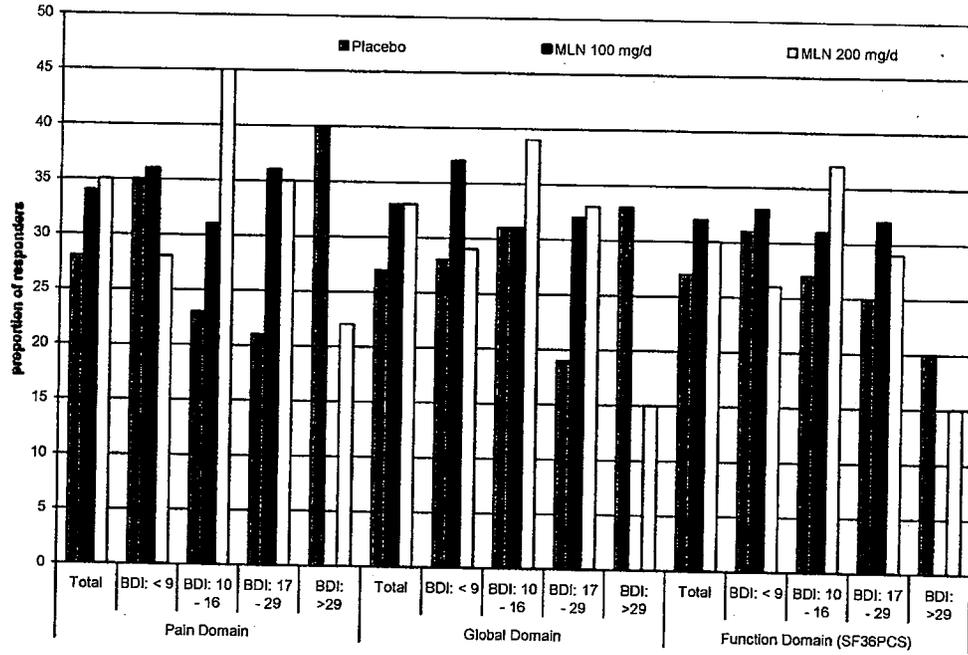
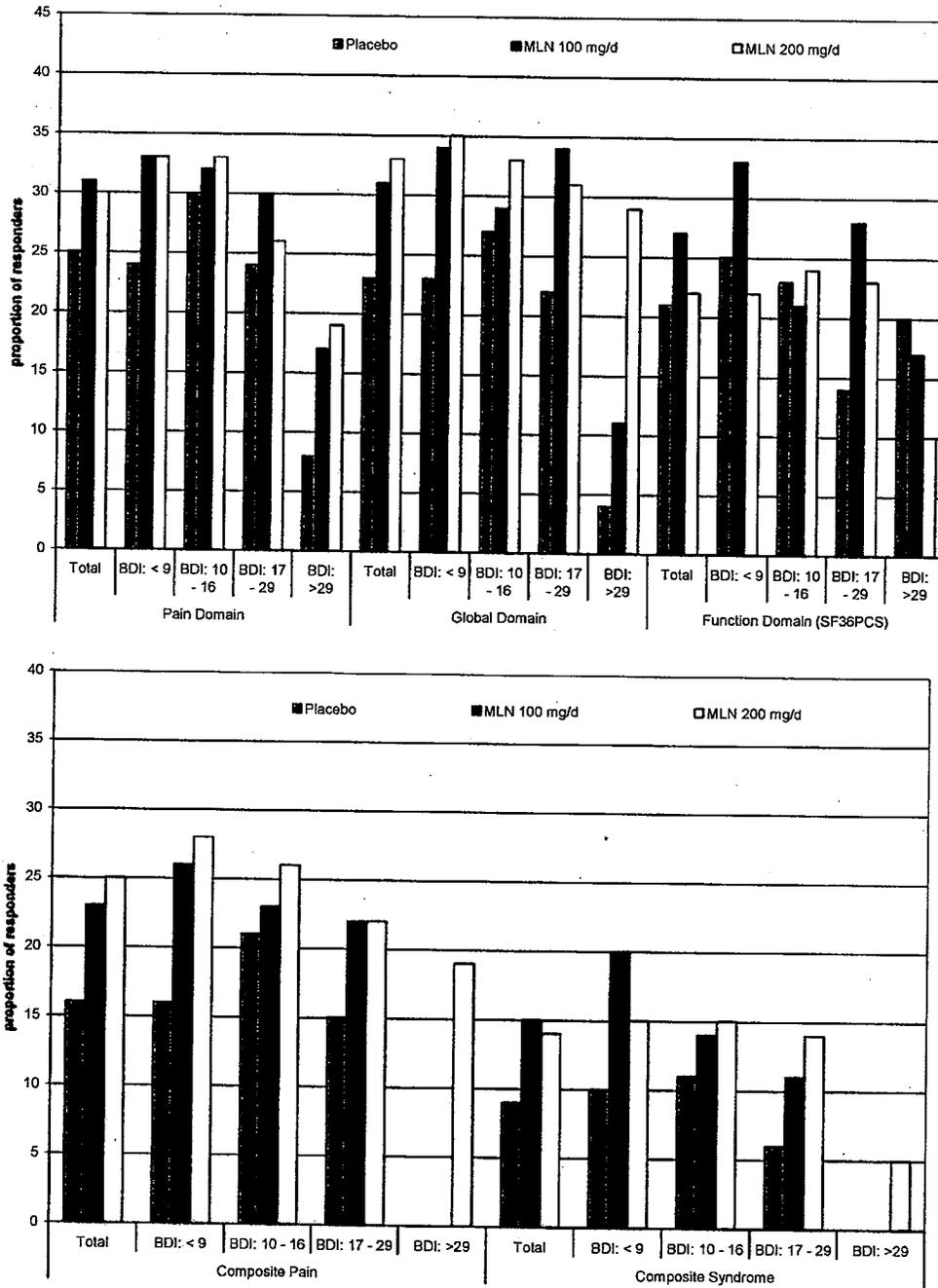


Figure 40: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI Group – Study MLN-MD-02



5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The Applicant conducted two Phase 3 trials, Study MLN-MD-02 and Study FMS-031, and two long-term extension studies (MLN-MD-04 and FMS-034) to support the indication of the treatment of fibromyalgia syndrome for milnacipran HCl. The primary focus of this review is on the two Phase 3 studies.

During my review of the submission, I identified some issues that warranted further consideration and issues that could be resolved by recoding and re-analyzing the data. One statistical issue is the choice of imputation strategy for the 6-month endpoint in Study FMS-031 which was discussed in Section 3.1.3.1. I also identified various discrepancies between the raw and derived datasets. Reasons for most of these discrepancies were found not to affect the overall conclusion.

Based on evidence taken collective from the two Phase 3 studies, milnacipran 200 mg/day is different from placebo in the treatment of pain using the composite pain responder definition and treatment of fibromyalgia syndrome using the composite syndrome responder definition at the 3-month landmark. There is evidence in one study that milnacipran 100 mg/day is different from placebo in the treatment of pain using the composite pain responder definition and treatment of fibromyalgia syndrome using the composite syndrome responder definition at the 3-month landmark. Numerically, there appears to be no difference in the proportion of responders (i.e. composite pain or composite syndrome) between the two milnacipran groups. The response profile between these two milnacipran arms appears to be similar across different range of response.

When the domains (i.e. pain, global and function by SF36-PCS) are analyzed separately, there is no evidence that the milnacipran groups are different from placebo in each domain (i.e. pain, global or SF36 PCS) in Study FMS-031 and in pain and SF36-PCS in Study MLN-MD-02. In Study FMS-031, none of the domains appears to influence the response and instead, it appears that the response is influenced by combination of these domains. Meanwhile, in Study MLN-MD-02, there is some evidence that the treatment difference seems to occur or being driven by the patient global test score. It appears that a lower proportion of placebo patients have achieved a 'very much improved' or 'improved' global test at the end of the 3-month period as opposed to the milnacipran groups.

In summary, 30% to 35% of patients in the milnacipran group will achieve at least a 30% improvement in pain score from baseline at the end of the 3-month landmark compared to 25% to 28% in the placebo group. When patient global is included in the responder definition (i.e. Composite Pain), the proportion of responders of around 30% to 35% becomes 23% to 27% in the milnacipran group and 16% to 19% in the placebo group. When function is included in the responder definition (i.e. Composite Syndrome), the proportion of responder in the milnacipran group is around 14% to 20% and around 9 to 12% in the placebo group. As the responder criteria become more stringent, the proportion of responders also decreases. The important clinical question is whether a quarter of patients who received milnacipran treatment and who responded (based on "composite pain" response criteria) adequate to conclude the efficacy of milnacipran in the treatment of pain.

The 6-month landmark is evaluated in only one study. Although numerically, a higher proportion of patients in the milnacipran groups achieve the composite pain responder criteria as well as the composite syndrome responder criteria compared to the placebo at the 6-month landmark, this evidence was not supported statistically.

In both studies, although there are some patients who experienced a decrease in pain as early as week 1, treatment difference did not occur until after the dose titration period ends (i.e. week 3). Furthermore, from the result of Study FMS-031, it appears that no additional benefit can be seen after Week 15.

5.2 CONCLUSIONS AND RECOMMENDATIONS

In view of the statistical findings generated from the analyses conducted by the Applicant and by me, I conclude that milnacipran 200 mg/d is efficacious treatment of pain using the composite pain responder definition and treatment of fibromyalgia syndrome using the composite syndrome responder definition at the 3-month landmark. There is also evidence that milnacipran 100 mg/day is different from placebo in the treatment of pain using the composite pain responder definition and treatment of fibromyalgia syndrome using the composite syndrome responder definition at the 3-month landmark. The response profiles between the two milnacipran groups are identical across different range of response. When the domains are considered separately, there is no evidence in either Phase 3 study that milnacipran is associated with improvements in pain (i.e. pain domain only) or improvements in function (i.e. function domain only) at three months of therapy. There is some evidence in one study that the treatment difference seems to be influenced by the patient global test score; however this finding is not observed in the other Phase 3 study.

There is not enough evidence to show that milnacipran-treated patients are associated with significant improvement in pain based on the composite pain response criteria or improvement in syndrome based on composite syndrome response criteria at six months or beyond.

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6 LABELING

The following are the proposed changes (and comments) to the label. The recommended edits are based on similar labels for products approved for the treatment of fibromyalgia. My primary recommendations include:

- 1) deletion of the composite syndrome graphs and text since this does not add information beyond the composite pain graph or the pain response profile graph.
- 2) deletion of the text regarding the durability of the response since there is insufficient evidence to show that milnacipran-treated patients are associated with significant improvement in pain based on the composite pain response criteria or improvement in syndrome based on composite syndrome response criteria at six months or beyond.

14. CLINICAL STUDIES

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 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

7 APPENDIX

Appendix 1: Demographic and Baseline Characteristics in Study MLN-MD-02 – Safety Population

Characteristic	Placebo (N=401)	Milnacipran		Total (N=1196)
		100 mg (N=399)	200 mg (N=396)	
Age (yrs), mean ± SD	50.7 ± 10.4	49.5 ± 10.9	50.4 ± 10.6	50.2 ± 10.6
≥ 60 years, %	18.7	18.8	19.7	19.1
Sex, n (%)				
Male	21 (5.2)	12 (3.0)	12 (3.0)	45 (3.8)
Female	380 (94.8)	387 (97.0)	384 (97.0)	1151 (96.2)
Race, n (%)				
Caucasian	375 (93.5)	375 (94.0)	368 (92.9)	1118 (93.5)
Non-Caucasian	26 (6.5)	24 (6.0)	28 (7.1)	78 (6.5)
Weight (lb), mean ± SD	183.9 ± 44.8	179.5 ± 42.2	179.2 ± 41.9	180.8 ± 43.0
FMS Duration (yrs), mean ± SD	9.8 ± 8.5	9.5 ± 8.0	9.9 ± 8.2	9.7 ± 8.2
BDI score, mean ± SD	13.80 ± 8.98	13.60 ± 8.67	14.30 ± 8.69	13.90 ± 8.78
>25, n (%)	47 (11.7)	43 (10.8)	41 (10.4)	131 (11.0)
≤ 25, n (%)	354 (88.3)	356 (89.2)	355 (89.6)	1065 (89.0)

BDI = Beck Depression Inventory. Cross-reference: Table 14.2.1.

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

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

Cross-reference: Table 14.2.4.

Appendix 2: Demographic and Baseline Characteristics in Study FMS-031 – Safety Population

	Placebo (N = 223)	Milnacipran		Total (N = 888)
		100 mg/d (N = 224)	200 mg/d (N = 441)	
Age, y, mean ± SD	49.4 ± 10.1	49.9 ± 10.6	49.2 ± 11.0	49.4 ± 10.7
Sex, n (%)				
Male	10 (4.5)	11 (4.9)	18 (4.3)	39 (4.4)
Female	213 (95.5)	213 (95.1)	423 (95.9)	849 (95.6)
Race, n (%)				
Caucasian	211 (94.6)	208 (92.9)	412 (93.4)	831 (93.6)
Non-Caucasian	12 (5.4)	16 (7.1)	29 (6.6)	57 (6.4)
Weight (lb), mean ± SD	181.9 ± 40.7	180.6 ± 41.4	181.3 ± 44.3	181.5 ± 42.7
FMS Duration, y, mean ± SD	6.0 ± 5.9	5.6 ± 5.3	5.5 ± 5.1	5.6 ± 5.4

FMS = fibromyalgia syndrome.

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

^a From Table 14.4.2.5.11.

^b From Table 14.4.2.5.12.

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

Clinical study report, page 84 – 86

Appendix 3: Pain Only Responder Rate ($\geq 30\%$ improvement) for Milnacipran Versus Placebo
 by Week (ITT Population)

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=401	N=399	N=396
Week 1	22 (5%)	36 (9%)	27 (7%)
Week 2	48 (12%)	92 (23%)	72 (18%)
Week 3	71 (18%)	107 (27%)	105 (27%)
Week 4	86 (21%)	135 (34%)	139 (35%)
Week 5	109 (27%)	136 (34%)	150 (38%)
Week 6	113 (28%)	140 (35%)	144 (36%)
Week 7	110 (27%)	156 (39%)	146 (37%)
Week 8	112 (28%)	142 (36%)	146 (37%)
Week 9	119 (30%)	147 (37%)	150 (38%)
Week 10	126 (31%)	145 (36%)	151 (38%)
Week 11	127 (32%)	139 (35%)	152 (38%)
Week 12	125 (31%)	140 (35%)	146 (37%)
Week 13	116 (29%)	142 (36%)	146 (37%)
Week 14	118 (29%)	131 (33%)	141 (36%)
Week 15	116 (29%)	136 (34%)	138 (35%)
Primary Endpoint (3 months)	101 (25%)	124 (31%) 1.34 (<1.0, 1.8)	119 (30%) 1.28 (0.9, 1.8)

APPEARS THIS WAY
 ON ORIGINAL

Appendix 4: Patient Global Impression of Change Responder Rate (very much improved or improved) for Milnacipran Versus Placebo by Week (ITT Population)

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=401	N=399	N=396
Week 3	52 (13%)	93 (23%)	77 (19%)
Week 7	78 (19%)	119 (30%)	126 (32%)
Week 11	97 (24%)	123 (31%)	123 (31%)
Week 15	95 (24%)	127 (32%)	132 (33%)

Appendix 5: Change from Baseline SF-36 Physical Component Score Responder Rate (≥ 6) for Milnacipran Versus Placebo by Week (ITT Population) - BOCF

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=401	N=399	N=396
Baseline mean SF-36 PCS score	32.1 (7.4)	31.9 (7.5)	32.4 (7.3)
Week 3	58 (14%)	88 (22%)	74 (19%)
Week 7	74 (18%)	118 (30%)	96 (24%)
Week 11	85 (21%)	105 (26%)	87 (22%)
Week 15	88 (22%)	111 (28%)	95 (24%)

APPEARS THIS WAY
 ON ORIGINAL

Appendix 6: Pain Only Responder Rate ($\geq 30\%$ improvement) for Milnacipran Versus Placebo by Week (UPA)

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=223	N=224	N=441
Week 1	8 (4%)	15 (7%)	24 (5%)
Week 2	20 (9%)	35 (16%)	80 (18%)
Week 3	40 (18%)	66 (29%)	112 (25%)
Week 4	50 (22%)	73 (33%)	144 (33%)
Week 5	63 (28%)	76 (34%)	152 (34%)
Week 6	64 (29%)	79 (35%)	153 (35%)
Week 7	63 (28%)	78 (35%)	143 (32%)
Week 8	63 (28%)	76 (34%)	156 (35%)
Week 9	59 (26%)	80 (36%)	159 (36%)
Week 10	66 (30%)	83 (37%)	159 (36%)
Week 11	70 (31%)	78 (35%)	155 (35%)
Week 12	68 (30%)	79 (35%)	157 (36%)
Week 13	64 (29%)	79 (35%)	158 (36%)
Week 14	63 (28%)	78 (35%)	152 (34%)
Week 15	66 (30%)	76 (34%)	156 (35%)
Primary Endpoint (3 months)	62 (28%)	76 (34%) 1.34 (0.9, 2.0) P=0.1578	155 (35%) 1.42 (<1.0, 2.0) p=0.0507
Week 16	60 (27%)	78 (35%)	156 (35%)
Week 17	63 (28%)	80 (36%)	151 (34%)
Week 18	57 (26%)	75 (33%)	151 (34%)
Week 19	57 (26%)	80 (36%)	149 (34%)
Week 20	56 (25%)	79 (35%)	145 (33%)
Week 21	52 (23%)	72 (32%)	143 (32%)
Week 22	52 (23%)	73 (33%)	138 (31%)
Week 23	50 (22%)	74 (33%)	134 (30%)

Week 24	53 (24%)	73 (33%)	133 (30%)
Week 25	55 (25%)	68 (30%)	131 (30%)
Week 26	53 (24%)	69 (31%)	135 (31%)
Week 27	57 (26%)	70 (31%)	138 (31%)
Secondary (6 months)	57 (26%)	76 (34%) 1.50 (<1.0, 2.3) P=0.0524	143 (32%) 1.41 (<1.0, 2.0) p=0.0618

Appendix 7: Patient Global Impression of Change Responder Rate (very much improved or improved) for Milnacipran Versus Placebo by Week (UPA) using BOCF

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=223	N=224	N=441
Week 3	30 (13%)	45 (20%)	95 (22%)
Week 7	53 (24%)	64 (29%)	136 (31%)
Week 11	54 (24%)	65 (29%)	153 (35%)
Week 15	60 (27%)	75 (33%)	146 (33%)
Week 19	52 (23%)	66 (29%)	135 (31%)
Week 23	47 (21%)	66 (29%)	136 (31%)
Week 27	55 (25%)	64 (29%)	142 (32%)

**APPEARS THIS WAY
 ON ORIGINAL**

Appendix 8: Change from Baseline SF-36 Physical Component Score Responder Rate (≥ 6) for Milnacipran Versus Placebo by Week (ITT Population) – BOCF

	Placebo	Milnacipran	
		100 mg/d	200 mg/d
	N=222	N=223	N=440
Baseline mean SF-36 PCS score	31.4 (7.8)	30.8 (7.6)	31.4 (8.0)
Week 3	55 (25%)	62 (28%)	125 (28%)
Week 7	69 (31%)	69 (31%)	151 (34%)
Week 11	66 (30%)	72 (32%)	142 (32%)
Week 15	62 (28%)	74 (33%)	133 (30%)
Week 19	56 (25%)	67 (30%)	127 (29%)
Week 23	57 (26%)	60 (27%)	114 (26%)
Week 27	53 (24%)	60 (27%)	116 (26%)

APPEARS THIS WAY
 ON ORIGINAL

Appendix 9: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Pooled Data

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=624	N=623	N=837
		163 (26%)	200 (32%)	274 (33%)
	Male	N=31	N=23	N=30
		5 (16%)	5 (22%)	3 (10%)
	Female	N=593	N=600	N=807
		158 (27%)	195 (33%)	271 (34%)
Global Domain	Total	N=624	N=623	N=837
		152 (24%)	199 (32%)	274 (33%)
	Male	N=31	N=23	N=30
		6 (19%)	4 (17%)	3 (10%)
	Female	N=593	N=600	N=807
		146 (25%)	195 (33%)	271 (34%)
Function Domain (SF36PCS)	Total	N=624	N=623	N=837
		147 (24%)	179 (29%)	220 (26%)
	Male	N=31	N=23	N=30
		6 (19%)	4 (17%)	3 (10%)
	Female	N=593	N=600	N=807
		141 (24%)	175 (29%)	217 (27%)
Composite Pain Responder	Total	N=624	N=623	N=837
		109 (17%)	152 (24%)	216 (26%)
	Male	N=31	N=23	N=30
		5 (16%)	4 (17%)	2 (7%)
	Female	N=593	N=600	N=807
		104 (18%)	148 (25%)	214 (27%)
Composite Syndrome Responder	Total	N=624	N=623	N=837
		62 (10%)	102 (16%)	140 (17%)
	Male	N=31	N=23	N=30
		2 (6%)	3 (13%)	1 (3%)
	Female	N=593	N=600	N=807
		60 (10%)	99 (17%)	139 (17%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1317, 1323, 1363, and 1369

Appendix 10: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Study FMS-031

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=223	N=224	N=441
		62 (28%)	76 (34%)	155 (35%)
	Male	N=10	N=11	N=18
		1 (10%)	1 (9%)	1 (6%)
	Female	N=213	N=213	N=423
		61 (29%)	75 (35%)	154 (36%)
Global Domain	Total	N=223	N=224	N=441
		60 (27%)	74 (33%)	145 (33%)
	Male	N=10	N=11	N=18
		2 (20%)	1 (9%)	2 (11%)
	Female	N=213	N=213	N=423
		58 (27%)	73 (34%)	143 (34%)
Function Domain (SF36PCS)	Total	N=223	N=224	N=441
		61 (27%)	71 (32%)	131 (30%)
	Male	N=10	N=11	N=18
		3 (30%)	2 (18%)	2 (11%)
	Female	N=213	N=213	N=423
		58 (27%)	69 (32%)	129 (31%)
Composite Pain Responder	Total	N=223	N=224	N=441
		43 (19%)	61 (27%)	118 (27%)
	Male	N=10	N=11	N=18
		1 (10%)	1 (9%)	1 (6%)
	Female	N=213	N=213	N=423
		42 (20%)	60 (28%)	117 (28%)
Composite Syndrome Responder	Total	N=223	N=224	N=441
		27 (12%)	44 (20%)	85 (19%)
	Male	N=10	N=11	N=18
		1 (10%)	1 (9%)	0
	Female	N=213	N=213	N=423
		26 (12%)	43 (20%)	85 (20%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1318, 1324, 1364, and 1370

Appendix 11: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Sex – Study MLN-MD-02

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=401	N=399	N=396
		101 (25%)	124 (31%)	119 (30%)
	Male	N=21	N=12	N=12
		4 (19%)	4 (33%)	2 (17%)
	Female	N=380	N=387	N=384
		97 (26%)	120 (31%)	117 (30%)
Global Domain	Total	N=401	N=399	N=396
		92 (23%)	125 (31%)	129 (33%)
	Male	N=21	N=12	N=12
		4 (19%)	3 (25%)	1 (8%)
	Female	N=380	N=387	N=384
		88 (23%)	122 (32%)	128 (33%)
Function Domain (SF36PCS)	Total	N=401	N=399	N=396
		86 (21%)	108 (27%)	89 (22%)
	Male	N=21	N=12	N=12
		3 (14%)	2 (17%)	1 (8%)
	Female	N=380	N=387	N=384
		83 (22%)	106 (27%)	88 (23%)
Composite Pain Responder	Total	N=401	N=399	N=396
		66 (16%)	91 (23%)	98 (25%)
	Male	N=21	N=12	N=12
		4 (19%)	3 (25%)	1 (8%)
	Female	N=380	N=387	N=384
		62 (16%)	88 (23%)	97 (25%)
Composite Syndrome Responder	Total	N=401	N=399	N=396
		35 (9%)	58 (15%)	55 (14%)
	Male	N=21	N=12	N=12
		1 (5%)	2 (17%)	1 (8%)
	Female	N=380	N=387	N=384
		34 (9%)	56 (14%)	54 (14%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1319, 1325, 1365, and 1371

Appendix 12: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Pooled Data

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=624	N=623	N=837
		163 (26%)	200 (32%)	274 (33%)
	Age < 60	N=517	N=495	N=683
		137 (27%)	159 (32%)	226 (33%)
Global Domain	Age ≥ 60	N=107	N=128	N=154
		26 (24%)	41 (32%)	48 (31%)
	Total	N=624	N=623	N=837
		152 (24%)	199 (32%)	274 (33%)
Function Domain (SF36PCS)	Age < 60	N=517	N=495	N=683
		137 (27%)	166 (34%)	234 (34%)
	Age ≥ 60	N=107	N=128	N=154
		15 (14%)	33 (26%)	40 (26%)
Composite Pain Responder	Total	N=624	N=623	N=837
		147 (24%)	179 (29%)	220 (26%)
	Age < 60	N=517	N=495	N=683
		129 (25%)	149 (30%)	186 (27%)
Composite Syndrome Responder	Age ≥ 60	N=107	N=128	N=154
		18 (17%)	30 (23%)	34 (22%)
	Total	N=624	N=623	N=837
		109 (17%)	152 (24%)	216 (26%)
Composite Syndrome Responder	Age < 60	N=517	N=495	N=683
		95 (18%)	125 (25%)	183 (27%)
	Age ≥ 60	N=107	N=128	N=154
		14 (13%)	27 (21%)	33 (21%)
Composite Syndrome Responder	Total	N=624	N=623	N=837
		62 (10%)	102 (16%)	140 (17%)
	Age < 60	N=517	N=495	N=683
		54 (10%)	88 (18%)	118 (17%)
Composite Syndrome Responder	Age ≥ 60	N=107	N=128	N=154
		8 (7%)	14 (11%)	22 (14%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1317, 1329, 1363, and 1375

Appendix 13: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Study FMS-031

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=223	N=224	N=441
		62 (28%)	76 (34%)	155 (35%)
	Age < 60	N=191	N=171	N=365
		54 (28%)	55 (32%)	130 (36%)
Global Domain	Age ≥ 60	N=32	N=53	N=76
		8 (25%)	21 (40%)	25 (33%)
	Total	N=223	N=224	N=441
		60 (27%)	74 (33%)	145 (33%)
Function Domain (SF36PCS)	Age < 60	N=191	N=171	N=365
		57 (30%)	58 (34%)	128 (35%)
	Age ≥ 60	N=32	N=53	N=76
		3 (9%)	16 (30%)	17 (22%)
Composite Pain Responder	Total	N=223	N=224	N=441
		61 (27%)	71 (32%)	131 (30%)
	Age < 60	N=191	N=171	N=365
		57 (30%)	57 (33%)	112 (31%)
Composite Syndrome Responder	Age ≥ 60	N=32	N=53	N=76
		4 (13%)	14 (26%)	19 (25%)
	Total	N=223	N=224	N=441
		43 (19%)	61 (27%)	118 (27%)
Composite Responder	Age < 60	N=191	N=171	N=365
		40 (21%)	46 (27%)	102 (28%)
	Age ≥ 60	N=32	N=53	N=76
		3 (9%)	15 (28%)	16 (21%)
Composite Syndrome Responder	Total	N=223	N=224	N=441
		27 (12%)	44 (20%)	85 (19%)
	Age < 60	N=191	N=171	N=365
		26 (14%)	36 (21%)	71 (19%)
Composite Responder	Age ≥ 60	N=32	N=53	N=76
		1 (3%)	8 (15%)	14 (18%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1318, 1330, 1364, and 1376

Appendix 14: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Age Group – Study MLN-MD-02

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=401	N=399	N=396
		101 (25%)	124 (31%)	119 (30%)
	Age < 60	N=326	N=324	N=318
		83 (25%)	104 (32%)	96 (30%)
	Age ≥ 60	N=75	N=75	N=78
		18 (24%)	20 (27%)	23 (29%)
Global Domain	Total	N=401	N=399	N=396
		92 (23%)	125 (31%)	129 (33%)
	Age < 60	N=326	N=324	N=318
		80 (25%)	108 (33%)	106 (33%)
	Age ≥ 60	N=75	N=75	N=78
		12 (16%)	17 (23%)	23 (29%)
Function Domain (SF36PCS)	Total	N=401	N=399	N=396
		86 (21%)	108 (27%)	89 (22%)
	Age < 60	N=326	N=324	N=318
		72 (22%)	92 (28%)	74 (23%)
	Age ≥ 60	N=75	N=75	N=78
		14 (19%)	16 (21%)	15 (19%)
Composite Pain Responder	Total	N=401	N=399	N=396
		66 (16%)	91 (23%)	98 (25%)
	Age < 60	N=326	N=324	N=318
		55 (17%)	79 (24%)	81 (25%)
	Age ≥ 60	N=75	N=75	N=78
		11 (15%)	12 (16%)	17 (22%)
Composite Syndrome Responder	Total	N=401	N=399	N=396
		35 (9%)	58 (15%)	55 (14%)
	Age < 60	N=326	N=324	N=318
		28 (9%)	52 (16%)	47 (15%)
	Age ≥ 60	N=75	N=75	N=78
		7 (9%)	6 (8%)	8 (10%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1319, 1331, 1365, and 1377

Appendix 15: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Pooled Data

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=624	N=623	N=837
		163 (26%)	200 (32%)	274 (33%)
	Caucasian	N=586	N=583	N=780
		154 (26%)	189 (32%)	258 (33%)
	Non-caucasian	N=38	N=40	N=57
		9 (24%)	11 (28%)	16 (28%)
Global Domain	Total	N=624	N=623	N=837
		152 (24%)	199 (32%)	274 (33%)
	Caucasian	N=586	N=583	N=780
		143 (24%)	188 (32%)	259 (33%)
	Non-caucasian	N=38	N=40	N=57
		9 (24%)	11 (28%)	15 (26%)
Function Domain (SF36PCS)	Total	N=624	N=623	N=837
		147 (24%)	179 (29%)	220 (26%)
	Caucasian	N=586	N=583	N=780
		134 (23%)	168 (29%)	205 (26%)
	Non-caucasian	N=38	N=40	N=57
		13 (34%)	11 (28%)	15 (26%)
Composite Pain Responder	Total	N=624	N=623	N=837
		109 (17%)	152 (24%)	216 (26%)
	Caucasian	N=586	N=583	N=780
		102 (17%)	143 (25%)	204 (26%)
	Non-caucasian	N=38	N=40	N=57
		7 (18%)	9 (23%)	12 (21%)
Composite Syndrome Responder	Total	N=624	N=623	N=837
		62 (10%)	102 (16%)	140 (17%)
	Caucasian	N=586	N=583	N=780
		57 (10%)	95 (16%)	131 (17%)
	Non-caucasian	N=38	N=40	N=57
		5 (13%)	7 (18%)	9 (16%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1317, 1335, 1363, and 1381

Appendix 16: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Study FMS-031

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=223	N=224	N=441
		62 (28%)	76 (34%)	155 (35%)
	Caucasian	N=211	N=208	N=412
		56 (27%)	71 (34%)	145 (35%)
	Non-caucasian	N=12	N=16	N=29
		6 (50%)	5 (31%)	10 (34%)
Global Domain	Total	N=223	N=224	N=441
		60 (27%)	74 (33%)	145 (33%)
	Caucasian	N=211	N=208	N=412
		55 (26%)	67 (32%)	138 (34%)
	Non-caucasian	N=12	N=16	N=29
		5 (42%)	7 (44%)	7 (24%)
Function Domain (SF36PCS)	Total	N=223	N=224	N=441
		61 (27%)	71 (32%)	131 (30%)
	Caucasian	N=211	N=208	N=412
		56 (27%)	66 (32%)	123 (30%)
	Non-caucasian	N=12	N=16	N=29
		5 (42%)	5 (31%)	8 (28%)
Composite Pain Responder	Total	N=223	N=224	N=441
		43 (19%)	61 (27%)	118 (27%)
	Caucasian	N=211	N=208	N=412
		38 (18%)	56 (27%)	112 (27%)
	Non-caucasian	N=12	N=16	N=29
		5 (42%)	5 (31%)	6 (21%)
Composite Syndrome Responder	Total	N=223	N=224	N=441
		27 (12%)	44 (20%)	85 (19%)
	Caucasian	N=211	N=208	N=412
		24 (11%)	40 (19%)	81 (20%)
	Non-caucasian	N=12	N=16	N=29
		3 (25%)	4 (25%)	4 (14%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1318, 1336, 1364, and 1382

Appendix 17: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Race Group – Study MLN-MD-02

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=401	N=399	N=396
		101 (25%)	124 (31%)	119 (30%)
	Caucasian	N=375	N=375	N=368
		98 (26%)	118 (31%)	113 (31%)
	Non- caucasian	N=26	N=24	N=28
		3 (12%)	6 (25%)	6 (21%)
Global Domain	Total	N=401	N=399	N=396
		92 (23%)	125 (31%)	129 (33%)
	Caucasian	N=375	N=375	N=368
		88 (23%)	121 (32%)	121 (33%)
	Non- caucasian	N=26	N=24	N=28
		4 (15%)	4 (17%)	8 (29%)
Function Domain (SF36PCS)	Total	N=401	N=399	N=396
		86 (21%)	108 (27%)	89 (22%)
	Caucasian	N=375	N=375	N=368
		78 (21%)	102 (27%)	82 (22%)
	Non- caucasian	N=26	N=24	N=28
		8 (31%)	6 (25%)	7 (25%)
Composite Pain Responder	Total	N=401	N=399	N=396
		66 (16%)	91 (23%)	98 (25%)
	Caucasian	N=375	N=375	N=368
		64 (17%)	87 (23%)	92 (25%)
	Non- caucasian	N=26	N=24	N=28
		2 (8%)	4 (17%)	6 (21%)
Composite Syndrome Responder	Total	N=401	N=399	N=396
		35 (9%)	58 (15%)	55 (14%)
	Caucasian	N=375	N=375	N=368
		33 (9%)	55 (15%)	50 (14%)
	Non- caucasian	N=26	N=24	N=28
		2 (8%)	3 (13%)	5 (18%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1319, 1337, 1365, and 1383

Appendix 18: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI – Pooled Data

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=624	N=623	N=837
		163 (26%)	200 (32%)	274 (33%)
	BDI ≤ 25	N=548	N=565	N=751
		145 (26%)	187 (33%)	252 (34%)
	BDI > 25	N=76	N=58	N=86
		18 (24%)	13 (22%)	22 (26%)
Global Domain	Total	N=624	N=623	N=837
		152 (24%)	199 (32%)	274 (33%)
	BDI ≤ 25	N=548	N=565	N=751
		139 (25%)	185 (33%)	253 (34%)
	BDI > 25	N=76	N=58	N=86
		13 (17%)	14 (24%)	21 (24%)
Function Domain (SF36PCS)	Total	N=624	N=623	N=837
		147 (24%)	179 (29%)	220 (26%)
	BDI ≤ 25	N=548	N=565	N=751
		131 (24%)	168 (30%)	205 (27%)
	BDI > 25	N=76	N=58	N=86
		16 (21%)	11 (19%)	15 (17%)
Composite Pain Responder	Total	N=624	N=623	N=837
		109 (17%)	152 (24%)	216 (26%)
	BDI ≤ 25	N=548	N=565	N=751
		100 (18%)	145 (26%)	198 (26%)
	BDI > 25	N=76	N=58	N=86
		9 (12%)	7 (12%)	18 (21%)
Composite Syndrome Responder	Total	N=624	N=623	N=837
		62 (10%)	102 (16%)	140 (17%)
	BDI ≤ 25	N=548	N=565	N=751
		57 (10%)	100 (18%)	130 (17%)
	BDI > 25	N=76	N=58	N=86
		5 (7%)	2 (3%)	10 (12%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1317, 1341, 1363, and 1387

Appendix 19: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI – Study FMS-031

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=223	N=224	N=441
		62 (28%)	76 (34%) 1.34 (0.9, 2.0)	155 (35%) 1.42 (<1.0, 2.0)
	BDI ≤ 25	N=194	N=209	N=396
		54 (28%)	71 (34%) 1.34 (0.9, 2.1)	144 (36%) 1.49 (1.0, 2.2)
	BDI > 25	N=29	N=15	N=45
		8 (28%)	5 (33%) 1.19 (0.3, 4.7)	11 (24%) 0.83 (0.3, 2.4)
Global Domain	Total	N=223	N=224	N=441
		60 (27%)	74 (33%)	145 (33%)
	BDI ≤ 25	N=194	N=209	N=396
		53 (27%)	70 (33%)	135 (34%)
	BDI > 25	N=29	N=15	N=45
		7 (24%)	4 (27%)	10 (22%)
Function Domain (SF36PCS)	Total	N=223	N=224	N=441
		61 (27%)	71 (32%)	131 (30%)
	BDI ≤ 25	N=194	N=209	N=396
		54 (28%)	68 (33%)	123 (31%)
	BDI > 25	N=29	N=15	N=45
		7 (24%)	3 (20%)	8 (18%)
Composite Pain Responder	Total	N=223	N=224	N=441
		43 (19%)	61 (27%)	118 (27%)
	BDI ≤ 25	N=194	N=209	N=396
		37 (19%)	58 (28%)	109 (28%)
	BDI > 25	N=29	N=15	N=45
		6 (21%)	3 (20%)	9 (20%)
Composite Syndrome Responder	Total	N=223	N=224	N=441
		27 (12%)	44 (20%)	85 (19%)
	BDI ≤ 25	N=194	N=209	N=396
		24 (12%)	43 (21%)	79 (20%)
	BDI > 25	N=29	N=15	N=45
		3 (10%)	1 (7%)	6 (13%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1318, 13242 1364, and 1388

Appendix 20: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI – Study MLN-MD-02

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=401	N=399	N=396
		101 (25%)	124 (31%)	119 (30%)
	BDI ≤ 25	N=354	N=356	N=355
		91 (26%)	116 (33%)	108 (30%)
	BDI >25	N=47	N=43	N=41
		10 (21%)	8 (19%)	11 (27%)
PGI Domain	Total	N=401	N=399	N=396
		92 (23%)	125 (31%)	129 (33%)
	BDI ≤ 25	N=354	N=356	N=355
		86 (24%)	115 (32%)	118 (33%)
	BDI >25	N=47	N=43	N=41
		6 (13%)	10 (23%)	11 (27%)
Function Domain	Total	N=401	N=399	N=396
		86 (21%)	108 (27%)	89 (22%)
	BDI ≤ 25	N=354	N=356	N=355
		77 (22%)	100 (28%)	82 (23%)
	BDI >25	N=47	N=43	N=41
		9 (19%)	8 (19%)	7 (17%)
Composite Pain	Total	N=401	N=399	N=396
		66 (16%)	91 (23%)	98 (25%)
	BDI ≤ 25	N=354	N=356	N=355
		63 (18%)	87 (24%)	89 (25%)
	BDI >25	N=47	N=43	N=41
		3 (6%)	4 (9%)	9 (22%)
Composite Syndrome	Total	N=401	N=399	N=396
		35 (9%)	58 (15%)	55 (14%)
	BDI ≤ 25	N=354	N=356	N=355
		33 (9%)	57 (16%)	51 (14%)
	BDI >25	N=47	N=43	N=41
		2 (4%)	1 (2%)	4 (10%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1319, 1343, 1365, and 1389

Appendix 21: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI – Pooled Data

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=624	N=623	N=837
		163 (26%)	200 (32%)	274 (33%)
	BDI: 0 – 9	N=226	N=230	N=264
		63 (28%)	78 (34%)	79 (30%)
	BDI: 10 – 16	N=206	N=183	N=291
		57 (28%)	58 (32%)	113 (39%)
	BDI: 17 – 29	N=152	N=188	N=234
		35 (23%)	61 (32%)	72 (31%)
	BDI: 30 – 63	N=40	N=22	N=48
	8 (20%)	3 (14%)	10 (21%)	
Global Domain	Total	N=624	N=623	N=837
		152 (24%)	199 (32%)	274 (33%)
	BDI: 0 – 9	N=226	N=230	N=264
		55 (24%)	80 (35%)	84 (32%)
	BDI: 10 – 16	N=206	N=183	N=291
		59 (29%)	55 (30%)	105 (36%)
	BDI: 17 – 29	N=152	N=188	N=234
		32 (21%)	62 (33%)	75 (32%)
	BDI: 30 – 63	N=40	N=22	N=48
	6 (15%)	2 (9%)	10 (21%)	
Function Domain (SF36PCS)	Total	N=624	N=623	N=837
		147 (24%)	179 (29%)	220 (26%)
	BDI: 0 – 9	N=226	N=230	N=264
		62 (27%)	76 (33%)	63 (24%)
	BDI: 10 – 16	N=206	N=183	N=291
		50 (24%)	45 (25%)	89 (31%)
	BDI: 17 – 29	N=152	N=188	N=234
		27 (18%)	55 (29%)	62 (27%)
	BDI: 30 – 63	N=40	N=22	N=48
	8 (20%)	3 (14%)	6 (13%)	

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Composite Pain Responder	Total	N=624	N=623	N=837
		109 (17%)	152 (24%)	216 (26%)
	BDI: 0 – 9	N=226	N=230	N=264
		41 (18%)	64 (28%)	64 (24%)
	BDI: 10 – 16	N=206	N=183	N=291
		40 (19%)	44 (24%)	87 (30%)
	BDI: 17 – 29	N=152	N=188	N=234
	24 (16%)	44 (23%)	57 (24%)	
	BDI: 30 – 63	N=40	N=22	N=48
		4 (10%)	0	8 (17%)
Composite Syndrome Responder	Total	N=624	N=623	N=837
		62 (10%)	102 (16%)	140 (17%)
	BDI: 0 – 9	N=226	N=230	N=264
		26 (12%)	47 (20%)	36 (14%)
	BDI: 10 – 16	N=206	N=183	N=291
		21 (10%)	28 (15%)	59 (20%)
	BDI: 17 – 29	N=152	N=188	N=234
	14 (9%)	27 (14%)	42 (18%)	
	BDI: 30 – 63	N=40	N=22	N=48
		1 (3%)	0	3 (6%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1317 and 1363

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Appendix 22: Responder Analysis for the Treatment of the Syndrome or Treatment of the Pain of Fibromyalgia during Treatment Weeks 14-15 (BOCF) by Baseline BDI – Study FMS-031

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Pain Domain	Total	N=223	N=224	N=441
		62 (28%)	76 (34%)	155 (35%)
	BDI: 0 – 9	N=80	N=84	N=141
		28 (35%)	30 (36%)	39 (28%)
	BDI: 10 – 16	N=71	N=64	N=150
		16 (23%)	20 (31%)	67 (45%)
PGI Domain	Total	N=223	N=224	N=441
		60(27%)	74 (33%)	145 (33%)
	BDI: 0 – 9	N=80	N=84	N=141
		22 (28%)	31 (37%)	41 (29%)
	BDI: 10 – 16	N=71	N=64	N=150
		22 (31%)	20 (31%)	59 (39%)
Function Domain	Total	N=223	N=224	N=441
		61 (27%)	71 (32%)	131 (30%)
	BDI: 0 – 9	N=80	N=84	N=141
		25 (31%)	28 (33%)	36 (26%)
	BDI: 10 – 16	N=71	N=64	N=150
		19 (27%)	20 (31%)	55 (37%)
BDI: 17 – 29	Total	N=57	N=72	N=123
		12 (21%)	26 (36%)	43 (35%)
	BDI: 30 – 63	N=15	N=4	N=27
		6 (40%)	0 (0%)	6 (22%)
	BDI: 17 – 29	N=57	N=72	N=123
		11 (19%)	23 (32%)	41 (33%)
BDI: 30 – 63	Total	N=15	N=4	N=27
		5 (33%)	0 (0%)	4 (15%)
	BDI: 17 – 29	N=57	N=72	N=123
		14 (25%)	23 (32%)	36 (29%)
	BDI: 30 – 63	N=15	N=4	N=27
		3 (20%)	0 (0%)	4 (15%)

		Placebo	Milnacipran	
			100 mg/d	200 mg/d
Composite Pain	Total	N=401	N=399	N=396
		66 (16%)	91 (23%)	98 (25%)
	BDI: 0 – 9	N=146	N=146	N=123
		24 (16%)	38 (26%)	34 (28%)
	BDI: 10 – 16	N=135	N=119	N=141
		28 (21%)	27 (23%)	36 (26%)
	BDI: 17 – 29	N=95	N=116	N=111
		14 (15%)	26 (22%)	24 (22%)
	BDI: 30 – 63	N=25	N=18	N=21
		0 (0%)	0 (0%)	4 (19%)
Composite Syndrome	Total	N=401	N=399	N=396
		35 (9%)	58 (15%)	55 (14%)
	BDI: 0 – 9	N=146	N=146	N=123
		14 (10%)	28 (20%)	18 (15%)
	BDI: 10 – 16	N=135	N=119	N=141
		15 (11%)	17 (14%)	21 (15%)
	BDI: 17 – 29	N=95	N=116	N=111
		6 (6%)	13 (11%)	15 (14%)
	BDI: 30 – 63	N=25	N=18	N=21
		0 (0%)	0 (0%)	1 (5%)

Source: Summary of Clinical Efficacy – Module 2.7 page 1319 and 1343

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number: NDA 22-256
Drug Name: Milnacipran
Indication(s): 26 Week Carcinogenicity in TG.rasH2 Mice
Applicant: Forest Research Institute
Harborside Financial Center, Plaza V, Jersey City, NJ 07311

Test Facility: C J
E J

Documents Reviewed: Electronic submission, Dated: Dec. 18, 2007
Data submitted electronically

b(4)

Review Priority: Standard

Biometrics Division: Division of Biometrics -6
Statistical Reviewer: Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer: Karl Lin, Ph.D.

Medical Division: Division of Anesthesia, Analgesia, and Rheumatology Products
Reviewing Pharmacologist: Elizabeth Bolan, Ph.D.
Project Manager: Diana Walker

Keywords: Carcinogenicity, Dose response

Table of Contents

1.....	Background	3
1.1. Design		3
1.2. Sponsor's analyses		3
1.2.1. Survival analysis		3
1.2.2. Tumor data analysis		3
1.3. Reviewer's analyses		4
1.3.1. Survival analysis		4
1.3.2. Tumor data analysis		4
2.....	Summary	5
3.....	Appendix	7
4.....	References:	11

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1. Background

In this submission the sponsor included a report of an animal carcinogenicity study in mice. This study was intended to assess the carcinogenic potential of Milnacipran in Tg.rassH2 mice when administered orally by gavage at appropriate drug levels for 26 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Bolan.

1.1. Design

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group and one positive control group. One hundred and twenty five Tg.rassH2 mice of each sex were randomly allocated to treated and control groups in equal size of 25 animals. The dose levels for treated groups were 25, 50, and 125 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The controls received the vehicle (sterile water for injection) by gavage, while the positive control received urethane.

All animals were observed twice daily for morbidity and mortality. A detailed hands-on examination was performed for the detection of abnormal mass growth at the time animals were weighed (on Test Day 1) and weekly thereafter. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

1.2. Sponsor's analyses

1.2.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method. Evaluations of trend and heterogeneity of survival data were performed using the Cox-Tarone binary regression on life tables and Gehan-Breslow nonparametric methods. Day 184 was treated as the end of the study for both the males and females. Continuity-corrected, two-sided tail probabilities for trend and group comparisons were evaluated at the 5% significance level.

Sponsor's findings: Sponsor's analysis showed survival rates of 24/25, 25/25, 24/25, and 22/25 in vehicle control, low, medium, and high dose groups, respectively in males and 23/25, 25/25, 24/25, and 23/25, in vehicle control, low, medium, and high dose groups, respectively in females. The positive control had survival rates of 4/25 and 5/25 on day 104. All other animals in this group were moribund sacrifice during Days 94-115. Sponsor concluded that there was no statistically significant treatment related effect on the survival in either sex.

1.2.2. Tumor data analysis

The sponsor chose neoplastic lesions for statistical analyses if the incidence in at least one treated group for each sex was increased or decreased by at least one occurrence over that of the vehicle control group. The occult tumors (incidental alone or incidental and fatal combined) were analyzed by asymptotic fixed interval-based prevalence test (Peto et al., 1980). The cut-off points for the interval-based test were Days 0-85, 86-184, and terminal sacrifice. In the case of sparse tables (<5), the exact form of the above analysis was used. The benign and malignant neoplastic lesions were evaluated individually as well as combined, where appropriate. Analysis of the combination of benign and malignant lesions was performed following the methods suggested by McConnell et al (1986). One-sided test for trend was evaluated at $p < 0.05$ for all tumors in this study. All statistical analyses were performed in two sets: one consisting of comparison of the

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Sex: Female		0 mg	25 mg	50 mg	125 mg	P_Value	P_Value	P_Value	P_Value
Organ Name	Tumor Name	Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
		N=25	N=25	N=25	N=25	Dos Resp	C vs. L	C vs. M	C vs. H
Whole_Body	Hemangioma/ Hemangiosarcoma	0	0	2	3	0.025	1.000	0.266	0.133

Reviewer's test results showed a statistically significant dose response relationship in incidence of whole body hemangioma/hemangiosarcoma in females.

2. Summary

In this submission the sponsor included a report of an animal carcinogenicity study in mice. This study was intended to assess the carcinogenic potential of Milnacipran in Tg.rassH2 mice when administered orally by gavage at appropriate drug levels for 26 weeks.

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group and one positive control group. One hundred and twenty five Tg.rassH2 mice of each sex were randomly allocated to treated and control groups in equal size of 25 animals. The dose levels for treated groups were 25, 50, and 125 mg/kg/day. The controls received the vehicle (sterile water for injection) by gavage, while the positive control received urethane.

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Tests did not show statistically significant dose response relationship in mortality in either sex. Pairwise comparisons did not show statistically significantly higher mortality in any of the treated groups compared to the vehicle control. The positive control showed statistically significant higher mortality compared to the vehicle control or any of the treated groups. Tests showed a statistically significant dose response relationship in incidence of whole body hemangioma/ hemangiosarcoma in females.

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Concur: Karl Lin, Ph.D.
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3. Appendix

**Table 1A: Mortality Data Analysis All Dose Groups
Male Mouse**

Test	Chi-Square	DF	Pr >
			Chi-Square
Log-Rank	4.1829	3	0.2424
Wilcoxon	4.2856	3	0.2322

Pairwise comparisons

P(Cont VS. Low Dose Group)= 0.3173
P(Cont VS. Medium Dose Group)= 0.9885
P(Cont VS. High Dose Group)= 0.2874

**Table 1B: Mortality Data Analysis All Dose Groups
Female Mouse**

Test	Chi-Square	DF	Pr >
			Chi-Square
Log-Rank	2.2986	3	0.5128
Wilcoxon	2.3163	3	0.5094

Pairwise comparisons

P(Cont VS. Low Dose Group)= 0.1531
P(Cont VS. Medium Dose Group)= 0.5396
P(Cont VS. High Dose Group)= 0.9834

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**Table 2A: Dose Response Relationship Test and Pairwise Comparisons
Using Poly-3 test
Male Mouse**

Organ Name	Tumor Name	0 mg	25 mg	50 mg	125 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=25	Low N=25	Med N=25	High N=25				
whole_body	Hemangeoma/ Hemangiosarcoma	2	1	3	3	0.238	0.500	0.500	0.480
bone	hemangiosarcoma	0	0	0	1	0.229	.	.	0.468
cavity, nasal	hemangiosarcoma sarcoma	0	1	0	0	0.479	.	.	.
		0	0	0	1	0.237	.	.	.
harderian gland	adenoma	0	1	0	0	0.479	.	.	.
liver	hemangiosarcoma	1	0	0	0	0.740	0.500	0.490	0.468
		1	2	0	1	0.495	.	.	.
		0	1	0	0	0.479	.	.	.
lungs with bron	adenoma carcinoma hemangiosarcoma	1	0	0	0	0.740	.	.	.
		1	0	0	0	0.740	.	.	.
		1	0	0	0	0.740	.	.	.
seminal vesicle	hemangiosarcoma	1	0	0	0	0.740	0.500	0.490	0.468
skin	hemangiosarcoma papilloma	0	0	1	1	0.174	.	0.500	0.479
		0	0	0	2	0.051	.	.	0.214
spleen	hemangiosarcoma	1	0	0	1	0.420	0.500	0.490	0.734
testes	hemangiosarcoma	0	0	2	0	0.468	.	0.235	.

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**Table 2B: Dose Response Relationship Test and Pairwise Comparisons
Using Poly-3 test
Female Mouse**

Organ Name	Tumor Name	0 mg	25 mg	50 mg	125 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=25	Low N=25	Med N=25	High N=25	Dos Resp	C vs. L	C vs. M	C vs. H
whole_Body	Hemangeoma/ Hemangiosarcoma	0	0	2	3	0.025	.	0.266	0.133
harderian gland	adenoma	0	1	0	0	0.500	.	.	.
	carcinoma	0	0	1	0	0.250	.	.	.
lungs with bron	adenoma	2	1	1	2	0.448	.	.	.
lymph node, man	hemangiosarcoma	0	0	0	1	0.250	.	.	.
lymph node, med	hemangiosarcoma	0	0	1	0	0.250	.	.	.
salivary glands	hemangiosarcoma	0	0	1	0	0.247	.	0.521	.
skin	hemangiosarcoma	0	0	0	1	0.258	.	.	0.521
	squamous cell carcin	0	1	0	0	0.500	0.521	.	.
spleen	lymphoma	1	0	1	1	0.436	0.510	0.255	0.755
thymus	lymphoma	0	0	0	1	0.250	.	.	0.511
vagina	hemangiosarcoma	0	0	0	1	0.250	.	.	0.511

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Figure 1A: Kaplan Meier Curve Male Mice
Mortality Data Analysis All Dose Groups

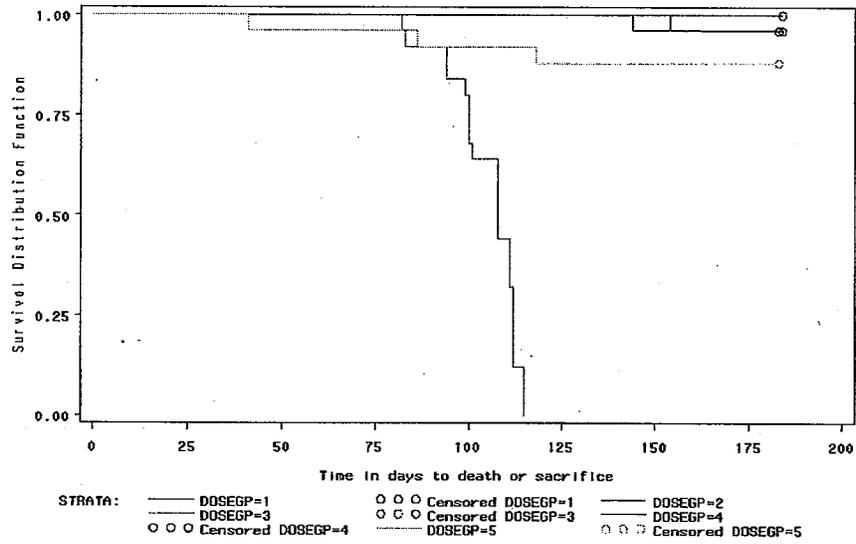
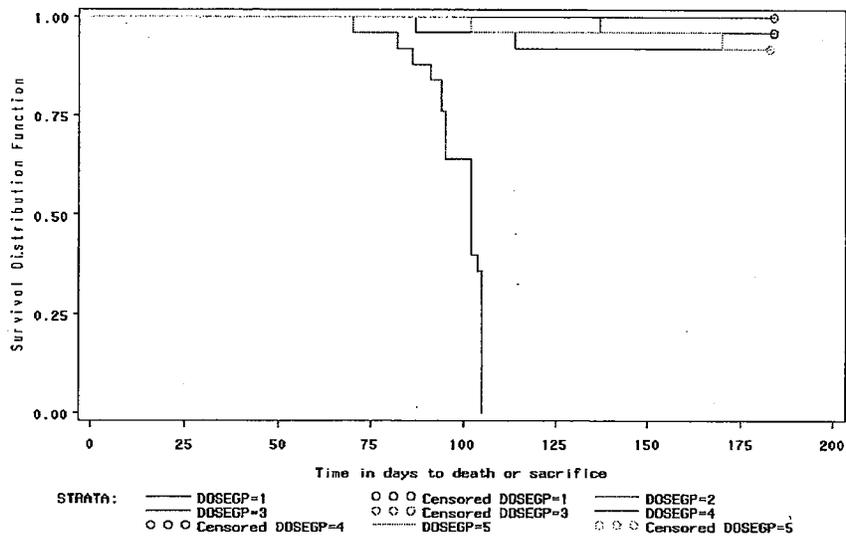


Figure 1B: Kaplan Meier Curve Female Mice
Mortality Data Analysis All Dose Groups



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Karl Lin
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