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STATISTICAL REVIEW(S)



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Statistical Review and Evaluation CLINICAL STUDIES

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Indication: _____ of fibromyalgia

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Biometrics division: Division of Biometrics II

Statistical reviewer: Joan Buenconsejo, Ph.D.

Concurring reviewers: Dionne Price, Ph.D.

Medical division: Division of Anesthesia, Analgesia, and Rheumatology
Products

Clinical team: Ricardo Dent, M.D.

Celia Winchell, M.D.

Project manager: Parinda Jani

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TABLE OF CONTENTS

1 Executive Summary	6
1.1 Conclusions and recommendations	6
1.2 Brief overview of clinical studies	7
1.3 Statistical issues and findings	10
2 Introduction	13
2.1 Overview	13
2.2 Data sources	15
3 Statistical Evaluation	15
3.1 Evaluation of efficacy	15
3.1.1 Study design and analysis plan	15
3.1.2 Patient characteristics and dispositions	24
3.1.3 Summary of results	30
3.1.3.1 Evaluation of Pain, Patient Global Improvement, FIQ Total Score and FIQ Pain Score in Controlled Studies	30
3.1.3.2 Reviewer's Comments	33
3.1.3.3 Efficacy Conclusion	55
3.2 Evaluation of safety	56
4 Findings in Subgroups and Special Populations	57
4.1 Sex, race and age	57
4.2 Other subgroups and special populations	61
5 Summary and Conclusions	66
5.1 Statistical issues and collective evidence	66
5.2 Conclusions and recommendations	69
6 Labelling	70
7 Appendix	73

List of Tables

Table 1: Description of Fibromyalgia Studies	8
Table 2: Treatment Groups by Study.....	19
Table 3: Analysis of the Primary Efficacy Variable(s) by Study.....	21
Table 4: Efficacy Variables for Study HMEH.....	23
Table 5: Reasons for Discontinuation – Study HMBO	25
Table 6: Reasons for Discontinuation by Visit – Study HMBO	25
Table 7: Reasons for Discontinuation – Study HMCA.....	26
Table 8: Reasons for Discontinuation – Study HMCJ	26
Table 9: Reasons for Discontinuation by Visit – Study HMCA.....	27
Table 10: Reasons for Discontinuation at three months by Visit – Study HMCJ	27
Table 11: Reasons for Discontinuation – Study HMEH (open-label phase)	28
Table 12: Reasons for Discontinuation – Study HMEH (double-blind phase)	28
Table 13: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint and PGI-Improvement at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, F1J-MC-HMCJ, and F1J-MC-HMEF.....	31
Table 14: FIQ Total Score and FIQ Pain Score Mean Change from Baseline to Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, and F1J-MC-HMCJ	32
Table 15: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint: All Randomized Patients by Brief Pain Inventory Response Status at Visit 4 – Double-Blind Study Phase	33
Table 16: Treatment Groups by Study.....	34
Table 17: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, and F1J-MC-HMCJ	36
Table 18: PGI-Improvement at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, and F1J-MC-HMCJ	37
Table 19: Van der Waerden Test for Difference in Distribution: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ	39
Table 20: Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ.....	39
Table 21: Patient Disposition at Six Months	47
Table 22: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months) and PGI Improvement at Endpoint: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ	48
Table 23: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months): All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ	48
Table 24: Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ	49
Table 25: Responder Profile at Endpoint based on responder analysis at three months: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ	50
Table 26: Patient Disposition of responders at 3 months who became non-responders at Six Months – Study HMCJ.....	50
Table 27: Fibromyalgia Impact Questionnaire Total Score Change from Baseline to Endpoint*: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ.....	51
Table 28: Change in CGI-Severity at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ	51
Table 29: Patient Disposition at Endpoint (i.e. Week 52) – Study HMEH.....	52

Table 30: Responder Analysis (> 50% reduction from Week 0) of Brief Pain Inventory Average Pain Score at Endpoint: Study HMEH.....	53
Table 31: Lack of Efficacy at Week 52 (using 50% improvement in pain from baseline to define responder) – Study HMEH	53
Table 32: Responder Analysis (> 30% reduction from Week 0) of Brief Pain Inventory Average Pain Score at Endpoint: Study HMEH.....	54
Table 33: Lack of Efficacy at Week 52 (using 30% improvement in pain from baseline as definition of responder) – Study HMEH	54
Table 34: Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Gender: F1J-MC-HMCJ.....	57
Table 35: Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Race: F1J-MC-HMCA and F1J-MC-HMCJ.....	58
Table 36: Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Age: F1J-MC-HMCA and F1J-MC-HMCJ.....	59
Table 37: PGI-Improvement at Endpoint by Gender: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCJ.....	60
Table 38: PGI-Improvement at Endpoint by Race: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ	60
Table 39: PGI-Improvement at Endpoint by Age: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ	61
Table 40: Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Major Depressive Disorder Status: F1J-MC-HMCA and F1J-MC-HMCJ	62
Table 41: Endpoint Mean Pain Score Analysis: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Major Depressive Disorder Status: F1J-MC-HMCA and F1J-MC-HMCJ	62
Table 42: Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ	63
Table 43: PGI-Improvement at Endpoint by Major Depressive Disorder Status: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ	64
Table 44: Endpoint HAMD17 Total Score Analysis: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Major Depressive Disorder Status: F1J-MC-HMCA and F1J-MC-HMCJ.....	65

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List of Figures

Figure 1: Study Design for HMBO	17
Figure 2: Study Design for HMCA.....	17
Figure 3: Study Design for HMCJ	18
Figure 4: Overall Response Profile for Study HMCA.....	38
Figure 5: Overall Response Profile for Study HMCJ at 3 months.....	38
Figure 6: Weekly Mean Pain Score (Study HMCA).....	40
Figure 7: Weekly Mean Pain Score (Study HMCJ)	41
Figure 8: Continuous Responder Analysis by Week – Study HMCA.....	42
Figure 9: Continuous Responder Analysis by Week – Study HMCJ	43
Figure 10: Proportion of Responders by Week (30% Improvement) – Study HMCA	44
Figure 11: Proportion of Responders by Week (50% Improvement) – Study HMCA	45
Figure 12: Proportion of Responders by Week (30% Improvement) – Study HMCJ.....	45
Figure 13: Proportion of Responders by Week (50% Improvement) – Study HMCJ.....	46
Figure 14: Overall Response Profile for Study HMCJ at 6 months.....	49
Figure 15: Responder Profiles for HMCA	63
Figure 16: Responder Profiles for HMCJ.....	64

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The Applicant, Eli Lilly and Company, seeks to market CYMBALTA for the treatment of fibromyalgia.

The evidence taken collectively from studies reviewed indicated statistical support in favor of duloxetine (60 mg BID, 60 mg QD, or 120 mg QD) treatment over placebo in pain reduction at three months of therapy. There is also evidence that both duloxetine 60 mg QD and duloxetine 120 mg QD are associated with improvements in patient global score at three months of therapy. The evidence supporting the 120 mg dose and the 60 mg BID dose is derived from a single study (Study HMCJ and Study HMCA, respectively).

Based on the weekly responder analyses of the improvement in BPI pain scores, as well as the response profile among responders at Week 12 in Study HMCA and in Study HMCJ, some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Because of multiplicity concerns, there is not enough evidence to support treatment difference in patient global improvement between duloxetine 60 mg BID and placebo (in Study HMCA), as well as no evidence to support treatment difference in pain interference score, FIQ Total score, CGI-Severity score or mental fatigue in all duloxetine dose groups. However, descriptive statistics suggest that the patient global, FIQ total score and CGI-Severity are trending in the direction similar to the primary endpoint. Mental fatigue was not included in my review.

Presence of major depressive disorder was also examined to determine whether it has an impact on patient response. Like the other subgroups studied (age, gender, and race), there were no remarkable effects of MDD

status according to the pain endpoint analysis, as well as patient global improvement score endpoint analysis using different imputation strategies. Because nearly all subjects in each study had no MDD at enrollment (Study HMCA 74%; Study HMCJ 76%), it is difficult to distinguish the possible treatment effects for the subgroups of MDD status.

Lastly, there is not enough evidence to demonstrate that duloxetine-treated patients are associated with significant improvement in pain at six months, when an imputation strategy that correctly assigns a bad score to dropouts is applied (in Study HMCJ). Furthermore, there is no evidence that duloxetine continues to demonstrate a clinically meaningful improvement in the BPI average pain score through 12 months of treatment (based on the result from Study HMEH).

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

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

CYMBALTA (duloxetine hydrochloride) is currently indicated for the _____ of major depressive disorder (MDD), diabetic peripheral neuropathic pain (DPNP), and generalized anxiety disorder in the United States, as well as for the treatment of MDD, DPNP, and stress urinary incontinence in the European Union.

The Applicant, Eli Lilly and Company, seeks to market CYMBALTA for the _____ of fibromyalgia. The dosage form to be used will be the currently marketed CYMBALTA oral capsules. In the proposed product label, it states:

The efficacy of duloxetine in patients who met the American College of Rheumatology (ACR) criteria for fibromyalgia with or without MDD has been evaluated in five studies (see Table 1). Four of the studies (Study HMBO, Study HMCA, Study HMCJ, and Study HMEF) were placebo-controlled and included 876 duloxetine-treated patients and 535 placebo-treated patients. The fifth study was a long-term uncontrolled study (Study HMEH) with 350 duloxetine-treated patients.

The development plan for CYMBALTA (duloxetine hydrochloride) for the _____ of fibromyalgia was previously discussed during several meetings with the US Food and Drug Administration's (FDA's) Division of Anesthesia, Analgesia and Rheumatology Products from 17 October 2002 through 16 May 2007. Advice was also received from the Committee for Medicinal Products for Human Use (CHMP) on 24 October 2004. At the time of initial advice in 2004, both studies HMBO and HMCA had been completed, and thus the advice received formed the basis of the design of the 3 more recent studies HMCJ, HMEF and HMEH. Key elements of the advice received from the agencies which was implemented in these protocols were: 1) enrollment of patients of both genders, 2) utilization of coprimary endpoints measuring both pain and global function, 3) collection of long term data (12-month) for safety and persistence of efficacy, 4) inclusion of a dose lower than 60 mg (for example, 20 mg), 5) stratifying in the randomization for MDD status at baseline, and 6) inclusion of at least one 6-month efficacy study. In a subsequent conversation with the FDA the requirement for a 6-month efficacy study was removed.

Table 1: Description of Fibromyalgia Studies

Study ID	Design/ Control type	Number of subjects by arm entered/ completed	Duration	Gender	Primary Endpoint(s)
HMBO	Parallel, double-blind, placebo-controlled	Randomized: 104 duloxetine, 103 placebo. Completed: 58 duloxetine, 66 placebo.	3 months	Male and female patients	Reduction in FIQ Pain Item and FIQ Total Score
HMCA	Parallel, double-blind, fixed dose, placebo-controlled study	Randomized: 234 duloxetine, 120 placebo. Completed: 148 duloxetine, 68 placebo.	3 months	Female patients	Reduction in average pain item of the BPI scale
HMCJ	Parallel, double-blind, fixed dose, placebo-controlled study	Randomized: 376 duloxetine, 144 placebo Completed 3-month therapy phase: 242 duloxetine, 84 placebo Completed 6-month therapy phase: 206 duloxetine, 72 placebo	3 month therapy phase, 3 month continuation phase	Male and female patients	Reduction in average pain item of the BPI scale and improvement in the PGI-I scale
HMEF	Parallel, double-blind, placebo-controlled study	Randomized: 162 duloxetine, 168 placebo Completed: 101 duloxetine, 103 placebo	6 months	Male and female patients	Reduction in average pain item of the BPI scale and improvement in the PGI-I scale
HMEH	open-label period, followed by a double-blind period.	Randomized: 307 duloxetine Completed: 195 duloxetine (duloxetine 60mg: 71 Duloxetine 120mg: 124)	2 months open label followed by 1 year double-blind	Male and female patients	Safety and tolerability Persistence of efficacy was also assessed

Abbreviations: BID = twice daily; BPI = Brief Pain Inventory; FIQ = Fibromyalgia Impact Questionnaire; HMBO = Study F1J-MC-HMBO; HMCA = Study F1J-MC-HMCA; HMCJ = Study F1J-MC-HMCJ; HMEF = Study F1J-MC-HMEF; HMEH = Study F1J-MC-HMEH; ID = identification; MDD = major depressive disorder; PGI-I = Patient's Global Impressions of Improvement.

Source: Clinical study reports for Study HMBO, Study HMCA, Study HMCJ, Study HMEF, and Study HMEH.

The following is an overview of the four placebo-controlled clinical studies. A more detailed description of the study design can be found in Dr. Ricardo Dent's review. Meanwhile, a more detailed description of the analysis plan can be found in Section 3.1.1:

Study Objective and Efficacy Outcome(s):

Study HMCA, Study HMCJ, and Study HMEF were all Phase 3 placebo-controlled studies and used the same primary efficacy objective; to assess the efficacy of duloxetine on the reduction of pain severity as measured by the average pain item of the Brief Pain Inventory (BPI). Both Study HMCJ and Study HMEF employed a coprimary measure, the Patient's Global Impressions of Improvement (PGI-Improvement) scale, to assess patient-reported improvement. In the case of Study HMCA, PGI-Improvement was a secondary measure. Study HMBO was a Phase 2 fixed-dose study which assessed the efficacy of duloxetine on the reduction of pain severity by both the Fibromyalgia Impact Questionnaire (FIQ) Pain Item and the FIQ Total Score. Brief Pain Inventory and PGI-Improvement were secondary measures.

Duration of Treatment:

Patients were randomized to either duloxetine or placebo for 3 months (Study HMCA and Study HMBO) and 6 months (Study HMCJ and Study HMEF). The primary efficacy measure was evaluated after 3 months of therapy in Study HMBO, Study HMCA, Study HMCJ, and after 6 months of therapy in Study HMEF. In Study HMCJ and Study HMEF, placebo-treated patients were switched to duloxetine at the end of the 6 months randomized phase and patients were treated in an open-label fashion for an additional 6 months.

Treatment Groups:

Duloxetine has previously shown efficacy in MDD and diabetic peripheral neuropathic pain (DPNP) at 60 and 120 mg once daily (QD), and these were also the main doses explored in fibromyalgia. In an attempt to reduce the number of patients dropping out early from these studies, titration schemes were adopted.

In the early Study HMBO, patients were randomized to duloxetine 60 mg twice daily (BID) or placebo. This included 3 titration steps from 20 mg QD to 60 mg BID over the course of 2 weeks.

In Study HMCA, patients were randomized to duloxetine 60 mg QD, 60 mg BID or placebo. Patients assigned to 60 mg QD started immediately on their assigned dose, whereas patients assigned to 60 mg BID received 60 mg QD for the first week.

In Study HMCJ, patients were randomized to duloxetine 20 mg QD, 60 mg QD, 120 mg QD or placebo in a 1:2:2:2 fashion. Based on previous experience in studies of MDD and DPNP, duloxetine 20 mg QD was anticipated to be a suboptimal dose. Thus, while it was included in the fibromyalgia program to confirm the dose range, the exposure in this dose group was restricted by randomizing fewer patients to this dose and, secondly, by titrating all patients in this group to 60 mg QD after 3 months of treatment. For the purposes of the results at 6 months, this dose group is therefore referred to as the 20/60 mg group. Patients assigned to both 60 and 120 mg QD received 30 mg QD for the first week followed by 60 mg QD for a week (120 mg arm).

In Study HMEF patients were randomized to duloxetine 60 mg or placebo for the first 3 months, after which time up-titration to 120 mg QD (blinded) was allowed on an individual basis for the remainder of the study. With an aim to mimic clinical practice, patients were titrated to 120 mg if they did not respond adequately to the 60 mg dose, and clinicians were allowed to reduce the dose to 60 mg if a patient was unable to tolerate 120 mg. The studies employed various ways of titrating patients up to their assigned treatment dose. All patients received 30 mg QD for the first week.

Statistical Analysis:

In general, treatment group differences in continuous measures (i.e. BPI-pain, PGI-improvement, FIQ-pain and FIQ-total) were based on comparisons of least-squares mean (LSMean) change from baseline (or least-squares means at endpoint for the PGI-Improvement) derived from an analysis of covariance model. Mean change analyses were implemented using the last-observation carried forward (LOCF) methodology. Mixed-effects repeated measures modeling (MMRM analysis) was also implemented to provide visit-wise comparisons between groups. Categorical measures (e.g. response rates at 30% or 50%) were compared using Fisher's exact test and/or the Cochran-Mantel-Haenszel (CMH) test for general association (adjusting for investigative sites).

Study HMCJ and Study HMEF included gatekeeper strategies for selected secondary endpoints to adjust for multiplicity-associated with multiple endpoints, doses and time points.

In addition to the placebo-controlled studies, a fifth study, Study HMEH, was conducted to assess longer-term safety and tolerability of duloxetine. A secondary objective was to evaluate the persistence of efficacy over 12 month of treatment. In this study, patients were treated with duloxetine 30 mg QD for 1 week, and 60 mg QD open-label for 7 weeks, at which point they were randomized to receive duloxetine 60 mg or 120 mg QD in a 1:2 fashion for 52 weeks.

The main focus of this statistical review is on the two placebo-controlled studies (HMCA and HMCJ) and the long-term safety study (HMEH). The Applicant included the results from these three studies in their proposed product label.

1.3 STATISTICAL ISSUES AND FINDINGS

During my review of the submission, I identified several issues that warranted further consideration. Statistical issues included the choice of primary analysis population, the appropriateness of the primary method of imputation (i.e. last observation carried forward) and the lack of a multiplicity adjustment on multiple secondary endpoints being tested.

In all studies, the Applicant conducted the primary analyses on all randomized patients who had at least one post-baseline measure, which I termed as modified intent-to-treat population (mITT). This implies that any patients who only had baseline score are not included in the efficacy analyses. Although only a small proportion of patients were excluded in the analyses because of missing post-baseline measures, this post-randomization exclusion may still potentially introduce problems (i.e. bias) to the comparability of the treatment arms. In addition, patients who dropped out prior to the first post-baseline are informative (i.e. their missingness is informative as they may not have even been able to tolerate the treatment for a short time). Therefore, re-analyses of data using all randomized patients were performed. The results from the analyses using all randomized patients were not different from the results generated using the modified ITT population.

The appropriateness of the primary method of imputation (i.e. LOCF) was also an issue identified during the course of my review. The Division of Anesthesia, Analgesia, and Rheumatology Products does not currently support the last observation carried forward (LOCF) approach in settings where treatment-related dropouts due to adverse events may potentially be assigned good scores. The results after applying different imputation strategies such as baseline observation carried forward (BOCF) as well as performing continuous responder analyses suggest that duloxetine 60 mg BID, duloxetine 60 mg QD and duloxetine 120 mg QD are associated with significant improvement in pain over placebo treatment. There is also evidence that duloxetine 120 mg QD and duloxetine 60 mg QD (both from Study HMCJ) are associated with significant improvement in patient global improvement score over placebo treatment.

Lastly, the Applicant failed to adjust for multiplicity when comparing different dose groups (i.e. Study HMCA) or when testing secondary endpoints. The Applicant stated that the purpose of collecting several secondary efficacy outcomes was to confirm the findings of the primary outcome and was not intended to draw conclusions from these secondary efficacy measures. Therefore, they did not have any plan of making adjustments for multiplicity.

Because of the multitude of secondary endpoints (including different dose and outcome measures) they proposed to examine in the protocol, there will be an increased probability of falsely declaring some dose of the treatment to be effective or one treatment to be superior over placebo in some endpoints, particularly when analyses of multiple endpoints were not adjusted for multiplicity. Either multiplicity adjustment should have been applied to these endpoints in order to maintain an overall type 1 error rate, or the results should have been presented descriptively without p-values. Nonetheless, it is difficult to draw conclusions from the analyses of the secondary endpoints as well as to make labeling claims from a statistical point of view because of the multitude of pairwise comparisons being tested unless the treatment effects are strongly different.

Therefore, after careful review of the Applicant's study report as well as re-analyses of all the data in Study HMCA and Study HMCJ, and accounting for all the statistical issues mentioned, the following are the key findings:

1. In Study HMCA,
 - a. There is strong evidence that duloxetine 60 mg BID is associated with significant improvement in pain over placebo treatment. This was supported by the results when different imputation strategies were applied to the data, as well as by the results of the continuous responder analyses.
 - b. There is also some evidence that duloxetine 60 mg QD is associated with improvement in pain over placebo after three months of treatment regardless of imputation strategy.
 - c. Because of multiplicity concerns, there is not enough evidence to support treatment difference in patient global improvement between duloxetine 60 mg BID and placebo or between duloxetine 60 mg QD and placebo. Similarly, there was no evidence to support treatment difference in FIQ Total score.
 - d. Although there is evidence that after three months of treatment, duloxetine 60 mg BID and duloxetine 60 mg QD are superior over placebo in the improvement in pain, the treatment effect from these two dose groups (i.e. once a day (60 mg/day) regimen and twice a day (120 mg/day) regimen) was similar. According to the Applicant, a prior study demonstrated efficacy using duloxetine 60 mg BID; therefore, in this study the 60 mg QD dose was tested to evaluate the dose response relationship. They claimed that duloxetine 60 mg QD could allow ease of use for patients and potentially improve patient drug compliance. Therefore, it is important to assess the risk on each dosing regimen to determine which dosing regimen is more beneficial to patients.
 - e. Descriptive statistics suggest that FIQ total score and CGI-Severity are trending in the direction similar to the primary endpoint. However, there is not evidence to show treatment difference between any of the duloxetine groups and placebo in the improvement from these outcome measures.
 - f. There were no remarkable effects of MDD status according to the pain endpoint analysis, as well as patient global improvement score endpoint analysis using different imputation strategies. Because nearly all subjects (74%) had limited number of patients with MDD at

enrollment, it is difficult to distinguish the possible treatment effects for the subgroups of MDD status. Nonetheless, it appears that both patients with MDD and without MDD showed favorable effect (i.e. improvement) in their endpoint mean pain scores. However, the magnitude of change is greater for patients with MDD.

2. In Study HMCJ,

- a. After three months of treatment, duloxetine 120 mg QD is associated with significant improvement in pain, as well as significant improvement in patient global improvement score over placebo treatment. Like in Study HMCA, these findings were supported by the results when different imputation strategies were applied to the data, as well as by the result of the continuous responder analyses on pain.
- b. Applying the pre-specified gatekeeper strategy, there is evidence that duloxetine 60 mg QD is also associated with improvement in pain, as well as improvement in patient global improvement score, over placebo treatment.
- c. According to the Applicant, the purpose of the inclusion of duloxetine 20 mg QD was to establish duloxetine 60 mg QD as a minimum effective dose. Although this dose was not meant to be included in the analyses and the (adjusted) pairwise comparison test results were not significant, the treatment effect on this dose is almost similar to duloxetine 60 mg QD and duloxetine 120 mg QD in both BPI average pain score and PGI-Improvement score. In fact, the effect of duloxetine 60 mg QD is almost the same as duloxetine 120 mg QD in both BPI average pain score and PGI-Improvement score as well. Therefore, it is difficult to establish that duloxetine 60 mg QD is the minimum effective dose even though duloxetine 20 mg QD is not significant.
- d. There is not enough evidence to show that duloxetine-treated patients are associated with significant improvement in pain at six months, when imputation strategy that correctly assigns a bad score to dropouts was applied.
- e. Like in Study HMCA, descriptive statistics suggest that FIQ total score and CGI-Severity are trending in the direction similar to the primary endpoint. However, there is not evidence to show treatment difference between any of the duloxetine groups and placebo in the improvement from these outcome measures.
- f. There were no remarkable effects of MDD status according to the pain endpoint analysis, as well as patient global improvement score endpoint analysis using different imputation strategies. Because nearly all subjects (76%) had limited number of patients with MDD at enrollment, it is difficult the possible treatment effects for the subgroups of MDD status. Nonetheless, it appears that both patients with MDD and without MDD showed favorable effect (i.e. improvement) in their endpoint mean pain scores. However, the magnitude of change is greater for patients with MDD.

3. In Study HMEH,

- a. Statistically significant persistence of effect was not demonstrated in patients who had at least 50 % reduction on the BPI average pain score at Week 8 of the open-label phase and had remained on duloxetine 60 mg in the 52-week double-blind phase. In fact, when applying an imputation strategy that correctly assigns a bad score to dropouts, less than 50% of those who responded at Week 8 achieved the same level of response at the end of the one-year double-blind phase (i.e. $\geq 50\%$ improvement in pain). Of the approximately 60% who responded at Week 8 but did not respond at Week 52, approximately 25% completed

the study but did not achieve the level of response seen at Week 8 (i.e. $\geq 50\%$ improvement in pain).

- b. Only 20% of the patients who did not respond at Week 8 and were given 120 mg QD during double-blind phase responded at the end of the study. This implies that increasing the dose did not improve their pain response.

2 INTRODUCTION

2.1 OVERVIEW

CYMBALTA (duloxetine hydrochloride) is currently indicated for the treatment of major depressive disorder (MDD), diabetic peripheral neuropathic pain (DPNP), and generalized anxiety disorder in the United States, as well as for the treatment of MDD, DPNP, and stress urinary incontinence in the European Union.

The Applicant, Eli Lilly and Company, seeks to market CYMBALTA for the _____ of fibromyalgia. The dosage form to be used will be the currently marketed CYMBALTA oral capsules. In the proposed product label, it states:

The efficacy of duloxetine in patients who met the American College of Rheumatology (ACR) criteria for fibromyalgia with or without MDD has been evaluated in five studies (see Table 1). Four of the studies (Study HMBO, Study HMCA, Study HMCJ, and Study HMEF) were placebo-controlled and included 876 duloxetine-treated patients and 535 placebo-treated patients. The fifth study was a long-term uncontrolled study (Study HMEH) with 350 duloxetine-treated patients.

The development plan for CYMBALTA (duloxetine hydrochloride) for the _____ of fibromyalgia was previously discussed during several meetings with the US Food and Drug Administration's (FDA's) Division of Anesthesia, Analgesia and Rheumatology Products from 17 October 2002 through 16 May 2007 under IND 63,615. Advice was also received from the Committee for Medicinal Products for Human Use (or better known as CHMP) on 24 October 2004. At the time of initial advice in 2004, both studies HMBO and HMCA had been completed, and thus the advice received formed the basis of the design of the 3 more recent studies HMCJ, HMEF and HMEH. The key milestones in the clinical development program are highlighted in Dr. Dent's review. Statistical issues were discussed during several meetings and key issues are summarized below:

1. End-of-Phase 2 meeting (October 17, 2002)

The Division noted that the primary endpoints must demonstrate statistical significance before consideration can be given to the secondary endpoints and their inclusion in the labeling. Potential secondary efficacy endpoints that are to be included in the package insert, based on statistical significance, must be prespecified in the protocol. A valid structure of hypotheses on both the primary and secondary endpoints can then be imposed and tested for significance, controlling for the overall type I error.

2. End-of-Phase 2 meeting (July 28, 2004)

The Division recommended that for the pain _____ trials need to demonstrate efficacy for pain at the 3- and 6-month timepoints. In the 6-month trial, there should also be evidence that this analgesic

effect is also trending in the right direction at 3 months. The Division is also recommending patient global outcome as coprimary in order to address the issue that _____ measurement of pain severity alone may not adequately and completely reflect the effect of treatment for such a complicated syndrome. _____ the Division is recommending a third co-primary, that is, a validated patient-reported physical function outcome.

3. Addendum to meeting minutes (August 20, 2004)
 - a. The Division clarified that the co-primary endpoints have to achieve statistical significant simultaneously. Therefore, multiplicity adjustments for the co-primary endpoints are not necessary.
 - b. The Division acknowledged that the gatekeeper strategy to the fibromyalgia syndrome appeared reasonable.
 - c. The Division noted that multiplicity adjustment for the statistical tests on pre-selected and agreed-upon secondary endpoints will be necessary.
4. Response to Amendment under serial no. 56 (August 9, 2005)
 - a. The Division noted that Study HMCA may not provide sufficient evidence for a pivotal efficacy study for fibromyalgia syndrome due to the absence of male patients in the study, unless representation of male patients is addressed in another clinical trial.
 - b. For the _____ of fibromyalgia, the Patient's Global Improvement and Fibromyalgia Impact Questionnaire would be considered two additional co-primary outcomes.
5. Special Protocol Assessment under serial no. 61 (January 31, 2005)
 - a. The co-primary endpoints of BPI pain and patient global impression of improvement would be suitable to support an _____
 - b. The Division pointed out that
 - i. The Applicant should demonstrate reduction in pain intensity both clinically and statistically at the landmark (end-of-treatment) endpoint.
 - ii. There is at least 30% improvement in pain relief between baseline and landmark visits, and that this relief is statistically different than placebo/standard of care.
 - c. The Division is unclear at that moment whether a positive result at 3-months in the absence of positive results at 6-months would be sufficient to support an _____
 - d. The Division is unaware of the validation of the Sheehan Disability Scale in patients with fibromyalgia, therefore, the Division is not clear whether this scale or other scales will support an _____
 - e. In terms of planned statistical analysis, the Division noted the following:
 - i. The proposed statistical analysis plan and the multiple testing adjustment method (gatekeeper method) are acceptable. However, it should be noted that if 60 mg were the most effective dose or six months were the most effective time point, the proposed method might miss them.
 - ii. There is discrepancy in the Sponsor's sample size calculation.
 - iii. The Sponsor did not provide methods on how to handle missing values in the primary efficacy analysis
 - iv. The Division recommended that $\alpha \geq 0.1$ be used for testing the center-by-treatment interaction.
 - v. The Sponsor should provide rationale for the proposed dose response analysis and clarify its objectives and associated contrast.
6. Teleconference (June 23, 2006)

The Division notified the Sponsor that six month trials for "pain of fibromyalgia" are not necessary. These trials can be three months in length. If Eli Lilly wishes to modify their protocols, they should do so through a protocol amendment.

7. Type B Teleconference (March 13, 2007) – No statistical issues were discussed.
8. Teleconference (May 16, 2007)
The Division initiated the teleconference to convey information to all FM sponsors regarding changes in recommendations for the development of therapies for FM.
 - a. The division will consider only 1 indication (e.g. no syndrome) and that is " ~~fibromyalgia~~". This requires a single primary of pain and does not require the previously advised 3 co-primaries. The division recognizes that the primary symptom of FM is pain and therefore the treatment of pain is significant impact on treating this disorder.
 - b. The division encourages sponsors to study other endpoints, including sleep, fatigue, for example. The division will allow other endpoints to be included in the clinical trial section of the label with adjustments for multiplicity. Adding that this would allow sponsors to market off of these other endpoints, provided the division agrees with the statistical analyses.
 - c. The FIQ is not the best outcome measure for function in the clinical trial section. SF-36, EuroQUOL may be used (provided meets criteria in #2 above).
 - d. The Division requires 2 studies of 3 month duration (not 6 months as initially conveyed to Lilly).

2.2 DATA SOURCES

This statistical review is based on data submitted in studies HMCA, HMCJ, HMEH and HMBO.

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 of CYMBALTA comprised four double-blind, placebo-controlled studies (conducted from July 2001 to December 2006) and one long-term safety study.

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 HMCA and HMCJ) and on the long term safety study (Study HMEH). Initial review of the Applicant's proposed label includes ~~_____~~. In addition, examination of the Applicant's results for study HMEF indicated that the study failed to show evidence of efficacy. Meanwhile, the results for study HMBO are discussed and included in the review for the reason that this study could provide us additional information on the efficacy of 60 mg BID dose of duloxetine compared to placebo.

According to the Applicant, elements of the study designs that were common across the 5 studies were as follows:

- All studies followed the guidelines for Good Clinical Practice (GCP).
- Patients were required to meet criteria for primary fibromyalgia as defined by the ACR (widespread aching pain in all 4 quadrants of the body and axial skeleton for >3 months duration and ≥ 11 of 18 tender points under digital palpitation examination with an approximate force of 4 kg/cm²).

- Patients were also required to score ≥ 4 on the primary pain severity measures at both screening and baseline for each study (average pain item of the BPI in Study HMCA, Study HMCJ and Study HMEF and the pain intensity item of the FIQ at screening and baseline in Study HMBO).

In addition, patients were excluded from the study if they met any of the following criteria:

- Any current primary Axis I diagnosis other than MDD (except in Study HMEH)
- Pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease (such as osteoarthritis, bursitis, and tendonitis)
- Confirmed current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or infectious arthritis, or an autoimmune disease (for example, systemic lupus erythematosus)
- Use of any excluded medications that could not be discontinued at Visit 1 (excluded medications included but was not limited to narcotics, nonsteroidal anti-inflammatory drugs [NSAIDs], tramadol, triptans, anticonvulsants, and antidepressants).

In the four placebo-controlled studies, patients were evaluated for the presence or absence of major depression by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria at baseline using the Mini International Neuropsychiatric Interview (MINI).

Study HMCA and Study HMCJ were Phase 3 placebo-controlled studies and used the same primary efficacy objective; to assess the efficacy of duloxetine on the reduction of pain severity as measured by the average pain item of the Brief Pain Inventory (BPI). Study HMCJ employed a coprimary measure, the Patient's Global Impressions of Improvement (PGI-Improvement) scale, to assess patient-reported improvement; while in Study HMCA, PGI-Improvement was a secondary measure. Study HMBO was a Phase 2 fixed-dose study which assessed the efficacy of duloxetine on the reduction of pain severity by both the Fibromyalgia Impact Questionnaire (FIQ) Pain Item and the FIQ Total Score. Brief Pain Inventory and PGI-Improvement were secondary measures. Meanwhile, Study HMEH was a Phase 3, outpatient 62-week safety study to evaluate the safety and tolerability of duloxetine at doses up to 120 mg once daily for up to 60 weeks. There was no primary efficacy measure(s) for this study.

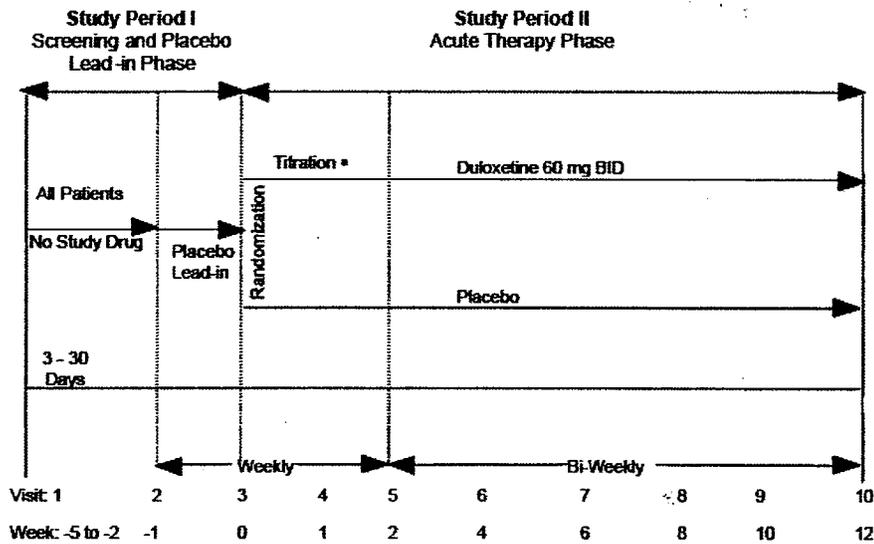
An overview of the study design for Studies HMCA, HMCJ, HMBO and HMEH is as follows:

Duloxetine has previously shown efficacy in MDD and diabetic peripheral neuropathic pain (DPNP) at 60 and 120 mg once daily (QD), and these were also the main doses explored in fibromyalgia. In an attempt to reduce the number of patients dropping out early from these studies, titration schemes were adopted.

In the early Study HMBO, patients (male or female) were randomized in a 1:1 ratio to duloxetine 60 mg twice daily (BID) or placebo for 12 weeks. This included 3 titration steps from 20 mg QD to 60 mg BID over the course of 2 weeks followed by a 10-week fixed dose phase. Random assignment of the patients was stratified into two groups: patients with a current major depressive disorder (MDD) and patients without a current MDD. The study design is illustrated in **Error! Reference source not found.**

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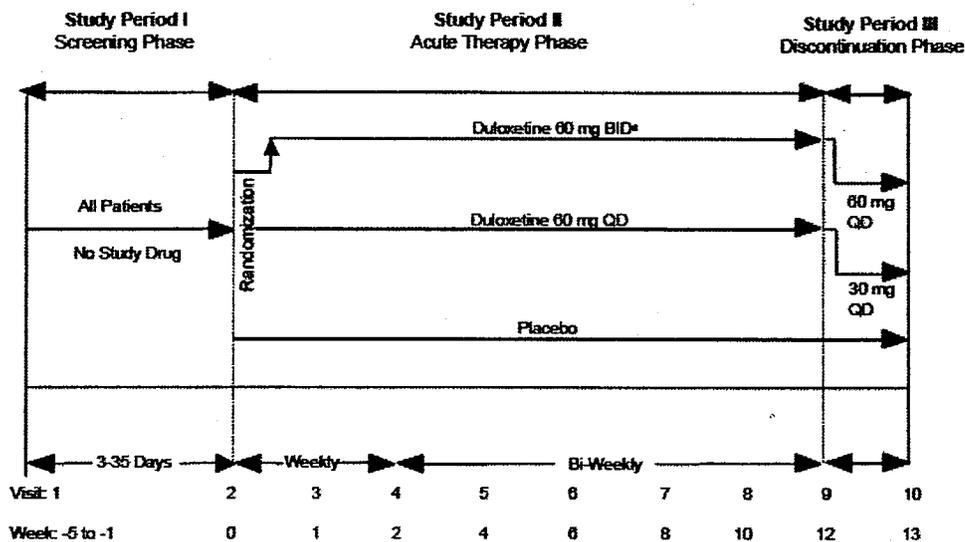
Figure 1: Study Design for HMBO



* Double-blind forced titration from 20 mg QD to 60 mg BID.

In Study HMCA, patients (female only) were randomized in a 1:1:1 ratio to duloxetine 60 mg QD, 60 mg BID or placebo. Patients were treated in a double-blind manner for 12 weeks. Patients assigned to 60 mg QD started immediately on their assigned dose, whereas patients assigned to 60 mg BID received 60 mg QD for the first week. Random assignment of the patients was stratified into two groups: patients with a current major depressive disorder (MDD) and patients without a current MDD. After 12-weeks of treatment, patients entered into a 1-week, double-blind discontinuation phase at which time dosage of study drug was reduced. The study design is illustrated in Figure 2.

Figure 2: Study Design for HMCA

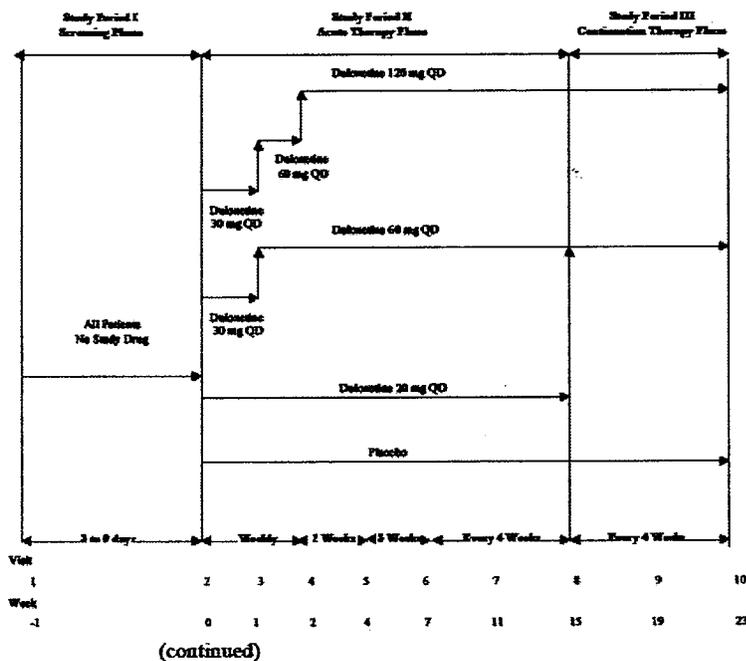


* Initial dosing from 60 mg once daily (QD) for 3 days to 60 mg twice daily (BID).

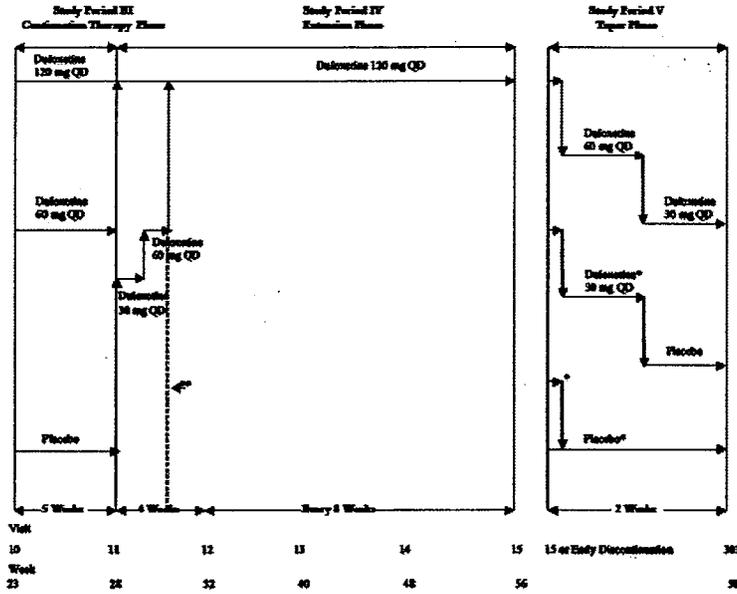
Abbreviations: BID = twice daily, QD = once daily.

In Study HMCJ, patients were randomized to duloxetine 20 mg QD, 60 mg QD, 120 mg QD or placebo in a 1:2:2:2 fashion. Based on previous experience in studies of MDD and DPNP, duloxetine 20 mg QD was anticipated to be a suboptimal dose. Thus, while it was included in the fibromyalgia program to confirm the dose range, the exposure in this dose group was restricted by randomizing fewer patients to this dose and, secondly, by titrating all patients in this group to 60 mg QD after 3 months of treatment. For the purposes of the results at 6 months, this dose group is therefore referred to as the 20/60 mg group. Patients assigned to both 60 and 120 mg QD received 30 mg QD for the first week followed by 60 mg QD for a week (120 mg arm). This study consisted of five study periods: screening, acute therapy phase, continuation therapy phase, taper phase and 28-week extension phase. The design is illustrated in Figure 3.

Figure 3: Study Design for HMCJ



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Abbreviations: QD = once daily.

*To maintain blinding integrity, placebo-treated patients remained on placebo, duloxetine 20 mg-treated patients received placebo, and duloxetine 60 mg-treated patients tapered to 30 mg for 1 week followed by 1 week of placebo if they discontinued early.

**At Week 30 all patients were on 120 mg.

Study HMEH was designed to evaluate the safety and tolerability of duloxetine 60 mg and 120 mg once daily (QD) in patients diagnosed with fibromyalgia. Patients were assigned to duloxetine 30 mg QD for one week, duloxetine 60 mg QD for seven weeks, and then were randomized 2:1 to 120 mg QD and 60 mg QD within response status (defined as $\geq 50\%$ reduction from baseline to Week 8 in the Brief Pain Inventory (BPI) average pain score) for 52 weeks. Patients then entered a two-week taper period.

The following table illustrates the doses that have been studied.

Table 2: Treatment Groups by Study

Study	Dose				
	20 mg QD	60 mg BID	60 mg QD	120 mg QD	Placebo
HMBO		√			√
HMCA		√	√		√
HMCJ	√		√	√	√
HMEH			√	√	

As stated, the exploratory Study HMBO utilized both the FIQ total score and the FIQ pain severity item score as coprimary endpoints. In the 3 subsequent studies (Study HMCA, Study HMCJ, and Study HMEF), the BPI Assessment Scale using the average pain severity (in the 11-point Likert scale; 0 = no pain to 10 = pain as bad as you can imagine), was employed as a primary endpoint. The PGI-Improvement (ranged from 1 = normal or not all ill to 7 = most extremely ill patients) was selected as a coprimary measure (in Study HMCJ and Study HMEF) to ensure that changes seen in the BPI were clinically meaningful for the patient. It was also used as a secondary measure in Study HMBO and Study HMCA.

The following is a summary of the statistical methods used in the analysis of the primary and secondary efficacy variables for Studies HMBO, HMCA, and HMCJ (see also Table 3 and appendix 1 for details of the statistical methods used).

All analyses were conducted on an intent-to-treat basis unless otherwise specified. All randomized patients were included in patient baseline characteristics analyses, while all randomized patients with a baseline and at least 1 post-baseline measurement were included in the efficacy analyses. For study HMCJ, the terms "3- and 6-month therapy phases" refer to the time interval in which active study drugs were administered with a placebo comparator and excludes taper, discontinuation, or placebo lead-in phases.

Except for Study HMBO, treatment group differences in continuous measures were based on comparisons of least-squares mean (LSMean) change from baseline (or least-squares means at endpoint for the PGI Improvement) derived from an analysis of covariance model. In all analyses, "baseline" was defined as the last nonmissing observation across all the visits at or before randomization. Mean change analyses were implemented using the last-observation-carried forward (LOCF) methodology, that is, "endpoint" was defined as the last nonmissing, post-baseline observation across visits with respect to either 3 months or 6 months of treatment. Mixed-effects repeated measures modeling (MMRM analysis) was also implemented to provide visit-wise comparisons between groups. The term "last visit" in the repeated measures analysis denoted the last planned visit in the respective therapy phase (3 months or 6 months) for each protocol, and "last observation" denoted data collected at the last visit for each patient within the therapy phase. In Study HMBO, the null hypothesis of treatment difference was tested by a MMRM analysis for the pain severity (FIQ pain) and FIQ Total scores. Categorical measures were compared using Fisher's exact test and/or the Cochran-Mantel-Haenszel (CMH) test for general association adjusting for investigative sites.

Treatment effects were evaluated through pairwise comparisons with placebo and based on two-sided tests with a significance level of 0.05. A gatekeeper strategy was employed in Study HMCJ for sequentially testing the secondary hypotheses for eligibility for possible inclusion in the label. If the primary hypothesis was statistically significant at the 0.05 two-sided level, the secondary gatekeeper hypotheses were tested. The sequential testing was conducted in the following order:

- the comparison between duloxetine 60 mg QD and placebo on the change from baseline to endpoint on the average pain item of the BPI and the endpoint of PGI-Improvement (3-month comparison)
- the comparison between duloxetine 120 mg QD and placebo on the change from baseline to endpoint on the average pain item of the BPI and the endpoint of PGI-Improvement (6-month comparison)
- the comparison between duloxetine 60 mg QD and placebo on the change from baseline to endpoint on the average pain item of the BPI and the endpoint of PGI-Improvement (6-month comparison)
- the comparison between duloxetine 120 mg QD and placebo on the change from baseline to endpoint on the SDS total score (6-month comparison).
- the comparison between duloxetine 60 mg QD and placebo on the change from baseline to endpoint on the SDS total score (6-month comparison).
- the comparison between duloxetine 120 mg QD and placebo on the change from baseline to endpoint on the SDS total score (3-month comparison)
- the comparison between duloxetine 60 mg QD and placebo on the change from baseline to endpoint on the SDS total score (3-month comparison).

No such strategy was employed in Study HMBO and Study HMCA given that the interests of each study were to evaluate the efficacy of each individual duloxetine dose versus placebo.

Table 3: Analysis of the Primary Efficacy Variable(s) by Study

Study	Analysis	Endpoints	Comparison	Method
HMBO	Co-Primary	(1) FIQ Pain Item Score (2) FIQ Total Score	Duloxetine 60 mg BID versus placebo	Mixed model repeated measures analysis that included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as continuous fixed covariates of baseline score and baseline-by-visit interaction. The unstructured covariance structure was used in the analysis. Repeated measures analysis as described above with the additional terms of the baseline MDD group and the treatment-by-group interaction.
	Secondary	Includes but not limited to: (1) BPI average pain severity score (2) Patient Global Impression of Improvement		
HMCA	Primary	BPI average pain score	Duloxetine 60 mg BID versus placebo	Analysis of covariance model with the terms of treatment, investigator, treatment-by-investigator interaction, and baseline scores.
HMCJ	Co-Primary	(1) BPI average pain (2) PGI Improvement at 3-month acute therapy phase	Duloxetine 120 mg QD versus placebo	Analysis of covariance model with the terms of treatment, investigator, treatment-by-investigator interaction, and baseline BPI pain scores for the analysis on changes on BPI average pain. Analysis of variance model with the terms of treatment, investigator, treatment-by-investigator interaction, and baseline PGI-severity at baseline for the analysis on the endpoint of PGI.

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Because the primary objective of Study HMEH was to assess long-term safety and tolerability, there was no primary efficacy measure(s) for this study. However, persistence of effect was evaluated in patients who remained on 60 mg for 52 weeks after having at least a 50% reduction on the BPI average pain score during the 8 week open label phase in Study HMEH.

The following is a summary of the analysis method used in Study HMEH.

Like Studies HMBO, HMCA, and HMCJ, all analyses were conducted on an intent-to-treat basis. The statistical evaluations of the safety and the efficacy of the study were conducted for both the open-label and double-blind phases, and where indicated, for the overall study and taper phases. For the open-label study phase, "baseline" refers to the last nonmissing observation at or before Visit 2, the visit at which patients were randomized, and "endpoint" refers to the last nonmissing observation at or before Visit 4. For the double-blind phase, "baseline" refers to the last observation at or before Visit 4 for safety measures and at Visit 4 for efficacy measures, and "endpoint" refers to the last nonmissing observation at or before Visit 12. For the overall study phase (combined open-label and double-blind study phases), "baseline" refers to the last nonmissing observation at or before Visit 2, and "endpoint" refers to the last nonmissing observation between the open-label and double-blind therapy phase of study (up to Visit 12).

With-in the open-label study phase, within-group change was evaluated by a Student's t-test to test the null hypothesis of no significant change from baseline. Between-group differences during the double-blind phase were assessed using 2 separate models. The primary model was a fixed-effects ANCOVA model assessing mean change from baseline to endpoint. Main effects for treatment group and investigative site were included, along with the baseline value of the respective measure as a covariate. Treatment-by-investigator interactions also were reported. A likelihood-based, MMRM analysis was used for confirmatory purposes that included the main effects of treatment group, site and visit, baseline value for the respective measure as a covariate, and the baseline-by-visit and treatment-by-visit interactions. Table 4 summarizes the detailed variables for the efficacy measures used in this study.

To evaluate the persistence of the efficacy of duloxetine 60 mg, additional analysis for BPI average pain score was conducted on the patients who had at least a 50% reduction on BPI average pain score at the entry of the double-blind study phase (Visit 4, Week 8) and remained on duloxetine 60 mg in the double-blind study phase. In the analysis, the change from baseline to endpoint on BPI average pain was summarized along with a 90% two-sided confidence interval (CI). When the upper bound of the 90% CI was less than 0.5, the null hypothesis that duloxetine treatment effect on pain reduction on the fibromyalgia patients was not maintained in the 1-year double-blind study phase was rejected at the significance level of 0.05.

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Table 4: Efficacy Variables for Study HMEH

Collected Variable	Derived Variable
<p>1. Change from baseline to endpoint:</p> <p>a. BPI-Severity (for worst pain, least pain, average pain, pain right now) and BPI-Interference (for general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life)</p> <p>b. FIQ total score and pain, tiredness and restedness items</p> <p>c. Mean tender point threshold measure</p> <p>d. # of tender points below the minimum threshold of $\leq 4\text{kg/cm}^2$</p> <p>e. SDS Global Functional Impairment total score</p> <p>f. CGI-Severity</p> <p>2. Observed score from Week 1 to endpoint</p> <p>g. PGI-Improvement</p> <p>3. 50% Response rate</p> <p>h. BPI 24-hour average pain score</p>	<p>a. BPI-Average Interference score is the average of seven interference questions</p> <p>c. The mean of the threshold for all 18 tender points</p> <p>h. Dichotomous variable defined as $\geq 50\%$ decrease in last observation collected during the phase</p> <p style="text-align: center; font-size: 1.2em;">Appears This Way On Original</p>

Abbreviations: # = number, BPI = Brief Pain Inventory, CGI-Severity = Clinical Global Impressions of Severity, PGI-Improvement = Patient's Global Impressions of Improvement, FIQ = Fibromyalgia Impact Questionnaire, SDS = Sheehan Disability Scale.

Sample Size

The sample size for each study was determined based on the following assumptions:

In the Phase 2 study (i.e. Study HMBO), the sample size of 200 patients (i.e. 100 patients per arm) was determined to provide at least 90% power to detect treatment group difference of -1.4 points in pain severity as measured by the 11-point Likert scale using the pain item from the Fibromyalgia Impact Questionnaire (FIQ) using a common standard deviation of 2.4, as well as treatment group difference of 12 points in the FIQ total score assuming a common standard deviation of 15. The sample size was determined using a two-sided test with $\alpha=0.05$ and a discontinuation rate of 35%.

For Study HMCA, the sample size of 345 patients (i.e. 115 patients per arm) was determined to provide at least 80% power to detect a treatment group difference of -1.2 points in the baseline-to-endpoint mean change on Brief Pain Inventory (BPI) average pain score between duloxetine 60 mg BID and placebo. The sample size was determined using a two-sided test with $\alpha=0.05$, assuming a common standard deviation of 2.66 and a discontinuation rate of 30%.

For Study HMCJ, the sample size of 490 patients (i.e. 140 patients each for duloxetine 60 mg QD, duloxetine 120 mg QD, and placebo, and 70 patients for duloxetine 20 mg QD) was determined to provide at least 80% power to detect a treatment group difference between duloxetine 120 mg QD and placebo in the co-primary efficacy measures during the 3-month acute therapy phase. For the BPI average pain score, the study would have at least 85% power to detect the group difference of -1.2 points in the baseline-to-endpoint mean change with a common standard deviation of 2.66. For the PGI-Improvement, the study would have at least 80% power to detect the difference of 0.68 with a

common SD of 1.6 on the endpoint score. The sample size was determined using a two-sided test with $\alpha=0.05$ and a discontinuation rate of 35%.

The sample size of 350 patients for Study HMEH was not based on statistical consideration.

Handling of Missing Data

Analyses for the three placebo-controlled studies, as well as the safety study (Study HMEH) used the last observation carried forward (LOCF) imputation strategy. Mixed-effects repeated measures modeling (MMRM analysis) was also implemented to provide visit-wise comparisons between groups. No other sensitivity analyses were conducted.

Statistical Decision Rule (Multiple Comparisons)

Treatment effects were evaluated through pairwise comparisons of duloxetine with placebo and based on two-sided tests with a significance level of 0.05. A gatekeeper strategy was employed in Study HMCJ for sequentially testing the secondary hypotheses for eligibility for possible inclusion in the label. If the primary hypothesis was statistically significant at the 0.05 level, the secondary gatekeeper hypotheses were tested. No multiplicity adjustments were made in Studies HMBO, HMCA and HMEH.

3.1.2 PATIENT CHARACTERISTICS AND DISPOSITIONS

Patient Disposition

In Study HMBO, a total of 555 patients entered the screening phase of the study. Of these 555 patients, a total of 284 patients failed to meet entry criteria or declined to participate in the study. Of the 271 patients who met entry criteria, 207 patients were randomized to one of two treatment groups: (103 patients in the placebo group and 104 patients in the duloxetine group). Sixty six patients (64%) in the placebo group and 58 patients (56%) in the duloxetine group completed the study. The reason for discontinuation is shown in Table 5. Meanwhile, Table 6 summarizes the discontinuation reason by visit. It appears that a slightly higher proportion of patients in the duloxetine group discontinued early compared to patients in the placebo group. It appears that the rates of discontinuation were homogenous over time in the placebo group.

In Study HMCA, a total of 746 patients entered the screening phase of the study. Of these 746 patients, a total of 354 women met entry criteria and were randomly assigned to one of three treatment groups: (120 patients in the placebo group, 118 patients in the duloxetine 60 QD group and 116 patients in the duloxetine 60 BID group). A total of 216 (61%) women completed the acute therapy phase (placebo=68 [57%]; duloxetine 60 mg QD=77 [65%]; and duloxetine 60 mg BID=71 [61%]), 138 (39%) women discontinued during the acute therapy phase, and 1 woman in the duloxetine 60 mg QD group discontinued during the discontinuation phase. The reason for discontinuation is shown in Table 7. Meanwhile, Table 9 summarizes the discontinuation reason by visit. Like Study HMBO, it appears that slightly higher proportion of patients in the duloxetine groups (i.e. 60 mg QD and 60 mg BID) discontinued early compared to patients in the placebo group, particularly when discontinuation is due to adverse events. However, it is also noticeable that patients in the placebo group who dropped out due to lack of efficacy discontinued early in the trial as well.

In Study HMCJ, a total of 520 patients were randomly assigned to one of three treatment groups: (144 patients in the placebo group, 150 patients in the duloxetine 60 QD group, 147 patients in the duloxetine 120 QD, and 79 patients in the duloxetine 20 QD group). At 3-month therapy phase, a total of 325 (63%) women

completed the acute therapy phase (placebo=84 [58%]; duloxetine 60 mg QD=97 [65%]; duloxetine 120 mg QD = 95 [65%]; and duloxetine 20 mg QD=49 [62%]). The reason for discontinuation is shown in Table 8. Meanwhile, Table 10 summarizes the discontinuation reason by visit up to Month 3. Except for the duloxetine 20 mg QD group, there is no evidence that discontinuation rates are different over time in all treatment groups.

Table 5: Reasons for Discontinuation – Study HMBO

Primary Reason for Discontinuation	Placebo	DLX60BID	Total
	(N=103) n (%)	(N=104) n (%)	(N=207) n (%)
Protocol completed	66 (64%)	58 (56%)	124 (60%)
Adverse event	11 (11%)	18 (17%)	29 (14%)
Unable to contact patient (lost to follow-up)	3 (3%)	6 (6%)	9 (4%)
Personal conflict or other patient decision	9 (9%)	10 (10%)	19 (9%)
Physician decision	0	1 (1%)	1 (1%)
Protocol violation	1 (1%)	2 (2%)	3 (1%)
Lack of efficacy	13 (13%)	9 (9%)	22 (11%)

Source: Study Report – F1J-MC-HMBO page 59

Table 6: Reasons for Discontinuation by Visit – Study HMBO

	Total	Placebo (N=103)			DLX60BID (N=104)			
		AE	LOE	Others	Total	AE	LOE	Others
Visit 4	7%	3%	2%	2%	11%	4%	3%	4%
Visit 5	6%	0%	3%	3%	9%	5%	1%	3%
Visit 6	8%	2%	4%	2%	13%	7%	2%	4%
Visit 7	6%	4%	1%	1%	5%	1%	1%	3%
Visit 8	9%	2%	3%	4%	4%	1%	0%	3%
Visit 9	1%	0%	0%	1%	4%	0%	2%	2%

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Table 7: Reasons for Discontinuation – Study HMCA

Events	PLACEBO (N=120) n(%)	DLX600D (N=118) n(%)	DLX608D (N=116) n(%)	TOTAL (N=354) n(%)
Advs. evt.	14(11.7)	25(21.2)	27(23.3)	66(18.6)
Unable to contact pat(lost to follow-up)	4(3.3)	1(0.8)	5(4.3)	10(2.8)
Personal conflict or other pat decision	1(0.8)	3(2.5)	4(3.4)	8(2.3)
Physician decision	0(0.0)	1(0.8)	0(0.0)	1(0.3)
Noncompl	1(0.8)	3(2.5)	1(0.9)	5(1.4)
Protocol Violation	1(0.8)	0(0.0)	0(0.0)	1(0.3)
Lack of Efficacy	18(15.0)	7(5.9)	4(3.4)	29(8.2)
Withdrawal of informed consent	13(10.8)	1(0.8)	4(3.4)	18(5.1)

p-Values are from Fisher's Exact Test.
 (1) - PLACEBO, (2) - DLX600D, (3) - DLX608D
 Program: RMP.FLJSEHCA.SASPCN(PQNDCHIA) QCA700
 Data: RMP.SAS.FLJM.L.MCHOCASW.FIRML

Source: Study Report – FIJ-MC-HMCA page 65

Table 8: Reasons for Discontinuation – Study HMCJ

Primary Reason for Discontinuation	Treatment	N	n	Percent
DC due to ANY reason	1) PLACEBO	144	60	41.67
	2) DLX200D	79	30	37.97
	3) DLX600D	150	53	35.33
	4) DLX1200D	147	52	35.37
Adverse Event	1) PLACEBO	144	17	11.81
	2) DLX200D	79	8	10.13
	3) DLX600D	150	22	14.67
	4) DLX1200D	147	32	21.77
Lack of Efficacy	1) PLACEBO	144	14	9.72
	2) DLX200D	79	8	10.13
	3) DLX600D	150	11	7.33
	4) DLX1200D	147	6	4.08
Subject Decision	1) PLACEBO	144	10	6.94
	2) DLX200D	79	8	10.13
	3) DLX600D	150	9	6.00
	4) DLX1200D	147	5	3.40
Lost to follow up	1) PLACEBO	144	13	9.03
	2) DLX200D	79	3	3.80
	3) DLX600D	150	7	4.67
	4) DLX1200D	147	7	4.76

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Source: Study Report – FIJ-MC-HMCJ page 80

Table 9: Reasons for Discontinuation by Visit – Study HMCA

	Placebo (N=120)			DLX60QD (N=118)			DLX60BID (N=116)			
	Total	AE	LOE	Total	AE	LOE	Total	AE	LOE	Others
Visit 3	5%	3%	0%	15%	14%	1%	15%	12%	1%	2%
Visit 4	8%	2%	4%	2%	1%	1%	5%	4%	0%	1%
Visit 5	13%	3%	6%	8%	5%	1%	9%	4%	2%	3%
Visit 6	6%	1%	3%	4%	0%	1%	2%	0%	1%	1%
Visit 7	9%	3%	1%	1%	0%	0%	3%	2%	0%	1%
Visit 8	1%	0%	1%	3%	2%	2%	4%	1%	0%	3%
Visit 9	1%	0%	0%	2%	0%	1%	1%	0%	0%	1%
Visit 10	0%	0%	0%	1%	1%	0%	0%	0%	0%	0%

Table 10: Reasons for Discontinuation at three months by Visit – Study HMCJ

	Placebo (N=144)			DLX60QD (N=150)			DLX120QD (N=147)			
	Total	AE	LOE	Total	AE	LOE	Total	AE	LOE	Others
Visit 2	0%	0%	0%	0%	0%	0%	1%	0%	0%	1%
Visit 3	6%	1%	1%	9%	5%	1%	9%	5%	0%	3%
Visit 4	5%	1%	1%	7%	4%	1%	3%	3%	0%	0%
Visit 5	9%	5%	2%	5%	1%	0%	4%	3%	0%	1%
Visit 6	9%	2%	3%	6%	2%	1%	3%	2%	1%	1%
Visit 7	10%	3%	1%	7%	2%	3%	8%	5%	3%	0%
Visit 8	3%	1%	1%	3%	1%	2%	7%	3%	1%	3%

DLX 20/60 QD (N=79)				
Total	AE	LOE	Others	
Visit 2	0%	0%	0%	0%
Visit 3	6%	0%	1%	5%
Visit 4	4%	3%	1%	0%
Visit 5	3%	1%	0%	1%
Visit 6	4%	1%	1%	1%
Visit 7	8%	0%	4%	4%
Visit 8	13%	5%	1%	6%

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Study HMEH comprised four study phases. Three hundred fifty patients entered the open-label phase. Of these 350, 307 patients entered the double-blind study phase of which 104 patients were randomized to duloxetine 60 mg and 203 patients were randomized to duloxetine 120 mg. A total of 195 (64%) completed the study (duloxetine 60 mg = 71 [68%]), and duloxetine 120 mg = 124 [61%]). The reasons for discontinuation during the open-label phase and double-blind phase are shown in Table 11 and Table 12, respectively.

Table 11: Reasons for Discontinuation – Study HMEH (open-label phase)

Primary Reasons For Discontinuation	DLX60QD (N = 350) n (%)
DC due to ANY reason	43 (12.3)
Adverse Event	26 (7.4)
Subject Decision	9 (2.6)
Lost to follow up	4 (1.1)
Protocol Violation	3 (0.9)
Lack of Efficacy	1 (0.3)
Patients Continuing	307 (87.7)

Source: Study Report – FIJ-MC-HMEH page 77

Table 12: Reasons for Discontinuation – Study HMEH (double-blind phase)

Primary Reason for Discontinuation	DLX60QD (N=104) n (%)	DLX120QD (N=203) n (%)	Total (N=307) n (%)
Protocol completed	71 (68%)	124 (39%)	195 (64%)
Adverse event	14 (14%)	34 (17%)	48 (16%)
Lack of efficacy	8 (8%)	20 (10%)	28 (9%)
Unable to contact patient (lost to follow-up)	2 (2%)	3 (2%)	5 (2%)
Personal conflict or other patient decision	2 (2%)	14 (7%)	16 (5%)
Physician decision	3 (3%)	5 (3%)	8 (3%)
Sponsor decision	0	1 (1%)	1 (0%)
Protocol violation	4 (4%)	2 (1%)	6 (2%)

Source: Study Report – FIJ-MC-HMEH page 79

Patient characteristics

Within each study, treatment groups were well-matched for baseline characteristics, including age, sex, race, weight, height, presence of MDD or presence of secondary anxiety disorder. In all four placebo-controlled studies, the majority of the patients were white and female. The total number of males enrolled in all five fibromyalgia studies (including HMEF) was 5%. The minimum age for inclusion in the studies was 18. There was no maximum age limit; however, few patients 65 years of age or older participated in the placebo-controlled studies (8.5%) or the uncontrolled long-term study (5.7%). Patients in these studies were enrolled

from North and South America, Europe, and Asia. Study HMCA, Study HMCJ and Study HMBO were conducted entirely in the United States (US) while Study HMEH was conducted in North and South America, Europe and Asia. The mean baseline BPI scores ranged from 6.1 to 6.5, and the mean FIQ total scores ranged from 49 to 52 on a scale of 0 to 80.

The following is a short summary of patient characteristics taken from the Applicant's individual study reports.

In study HMBO, the majority of patients were white (87%) and female (89%), the age range of the patients was 19 to 80 years, and the median age was 50 years. Thirty eight percent of patients had major depressive episode, while 20% had secondary diagnosis of anxiety. Their mean baseline BPI scores were around 6.1, and the mean FIQ total scores were around 49 on a scale of 0 to 80.

In study HMCA, only women were included in the study. The majority of patients were white (90%), the age range of the patients was 20 to 80 years, and the median age was 51 years. Twenty six percent of patients had major depressive episode, while 10% had secondary diagnosis of anxiety. Their mean baseline BPI scores were around 6.4, and the mean FIQ total scores were around 52 on a scale of 0 to 80.

In study HMCJ, the majority of patients were female (95%) and white (84%), the age range of the patients was 19 to 77 years, and the median age was 53 years. Twenty four percent of patients had major depressive episode, while 6% had secondary diagnosis of anxiety. Forty five percent of patients had previous antidepressant usage. Their mean baseline BPI scores were around 6.5, and the mean FIQ total scores were around 52 on a scale of 0 to 80. Meanwhile, the mean PGI-severity score was about 4 on a scale of 1 to 7.

Among all enrolled patients in Study HMEH, the majority of patients were white (61%) and female (96%). The mean age was 49 years, with a range of 18 to 84 years of age. Their mean baseline BPI scores were around 6.7, and the mean FIQ total scores were around 54 on a scale of 0 to 80. Meanwhile, the mean PGI-severity score was about 4 on a scale of 1 to 7.

Exposure to Study Medication

In Study HMBO, 67% of patients in placebo group and 59% in duloxetine group received at least 63 days (or 9 weeks) of study medication during acute therapy phase. The median durations of exposure were similar for all treatment groups: 81 days in placebo, and 79 days in duloxetine 60 BID group. In general, patients were compliant with study drug administration during the study. In addition, at least 62% in the placebo group and 54% in duloxetine group remained compliant at Visit 10 (i.e. Week 12). According to the Applicant, a patient was considered compliant to study drug at a certain visit if the compliance rate (calculated as percentage of the number of capsules taken between visits divided by the total number of capsules prescribed for that treatment interval) was between 80% and 120% at that visit.

In Study HMCA, 61% of patients in placebo group, 69% patients in the duloxetine 60 QD group, and 66% in duloxetine 60 BID group received at least 63 days (or 9 weeks) of study medication during acute therapy phase. The median durations of exposure were similar for all treatment groups: 86 days in placebo, 88 days in duloxetine 60 QD, and 88 days in duloxetine 60 BID group. However, patients in the duloxetine groups were more likely to have less than 7 days of exposure compared with patients in the placebo group. Patients in the placebo group were more likely to have 21 to 63 days of exposure compared with patients in the duloxetine groups. These differences are due to patients in the duloxetine treatment groups withdrawing because of adverse events during the first weeks of treatment more often than patients in the placebo treatment group. In general, patients were compliant with study drug administration during the study. In addition, at least 55%

in the placebo group, 63% in the duloxetine 60 QD group, and 61% in the duloxetine 60 BID group remained compliant at Visit 9 (i.e. Week 12).

In Study HMCJ, 39% of patients in placebo group, 53% patients in the duloxetine 20 mg QD, 40% in the duloxetine 60 QD group, and 47% in duloxetine 120 QD group received at least 105 days of study medication during the 3-month acute therapy phase. The median durations of exposure were almost similar for all treatment groups: 103 days in placebo, 105 days in duloxetine 20 QD, 104 days in duloxetine 60 QD, and 104 days in duloxetine 120 QD group. In general, patients were compliant with study drug administration during the study. In addition, at least 60% in the placebo group, 70% in the duloxetine 20 QD group, 69% in the duloxetine 60 QD group, and 69% in the duloxetine 120 QD group remained compliant at Visit 8 (i.e. Week 12 of the 3-month therapy phase).

In the open-label phase of Study HMEH, the median duration of exposure was 56 days for all enrolled patients. In the double-blind phase, the median duration of exposure for patients was similar for all treatment groups: duloxetine 60 QD was 364 days and duloxetine 120 mg QD was 362 days. In general, patients were compliant with study drug administration during the study. During the double-blind and taper study phases, a greater rate of noncompliance for the last study visit was observed within the duloxetine 120 mg QD treatment group when compared with duloxetine 60 mg QD treatment group. For all other visits, no difference in treatment compliance was observed between treatment groups.

3.1.3 SUMMARY OF RESULTS

3.1.3.1 Evaluation of Pain, Patient Global Improvement, FIQ Total Score and FIQ Pain Score in Controlled Studies

The primary efficacy analyses in studies HMCA and HMCJ were based on the mean change from baseline to endpoint for the BPI average pain scores. As a coprimary measure to the BPI score in Study HMCJ, the analysis on the endpoint of PGI improvement score was also conducted. Meanwhile, the primary efficacy analyses in study HMBO were based on the mean change from baseline to endpoint for the FIQ total score and for the FIQ pain severity score. BPI average pain scores and PGI improvement scores were also collected in Study HMBO and were part of the pre-specified secondary endpoints. Likewise, PGI improvement scores were also collected in Study HMCA and were part of the pre-specified secondary endpoints. However, none of these studies (Study HMBO and Study HMCA) had a pre-specified procedure to adjust for multiplicity. In fact, only Study HMCJ had a pre-specified sequential testing procedure employing a gatekeeper strategy for secondary endpoints to adjust for multiplicity.

The primary analysis in Study HMCA compared duloxetine 60 mg BID to placebo, while the primary analyses in Study HMCJ compared duloxetine 120 mg QD to placebo. The results for the primary efficacy parameters taken from the Applicant's study reports are summarized in Table 13 and Table 14.

Using the last observation carried forward approach (LOCF), duloxetine 60 mg BID and duloxetine 120 mg QD were associated with significant improvement in pain over placebo treatment in Study HMCA and Study HMCJ, respectively. Duloxetine 120 mg QD was also associated with significant improvement in patient global score over placebo in Study HMCJ using the gatekeeper (step-down) approach. Although no multiplicity adjustment was pre-specified in Study HMCA, it appears that duloxetine 60 mg BID was also associated with significant improvement in patient global score over placebo.

Like the primary analyses, there is also evidence that patients treated with duloxetine 60 mg QD have greater improvement in pain, as well as greater patient global improvement compared to patients treated with placebo in Studies HMCA and HMCJ.

In Study HMBO, using LOCF approach, there is no evidence that duloxetine 60 mg BID was associated with improvement in FIQ Total Score and FIQ Pain Score over placebo (Table 14). In contrast, using the same imputation strategy, there is some evidence that duloxetine 60 mg BID and duloxetine 60 mg QD may be associated with improvements in FIQ Total Score and FIQ Pain Score over placebo in Studies HMCA and HMCJ, although none of the results were adjusted for multiplicity.

Although there is some evidence that patients who received duloxetine at 60 mg BID in Study HMBO have greater improvement in pain, as well as improvement in patient global score over patients who received placebo, the BPI average pain score and PGI-improvement were prespecified secondary endpoints and no adjustments to control the type 1 error were performed.

Table 13: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint and PGI-Improvement at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, F1J-MC-HMCJ, and F1J-MC-HMEF

Study	Treatment Group	BPI Average Pain Score			PGI-I Score	
		Baseline	LSMean Change	p-value ^a	LSMean at Endpoint	p-value ^a
HMBO	Placebo	6.11	-0.67		3.66	
	Duloxetine 60 mg BID	6.13	-1.43	.012	3.18	.034
HMCA	Placebo	6.47	-1.16		3.79	
	Duloxetine 60 mg QD	6.38	-2.39	<.001	3.17	.005
	Duloxetine 60 mg BID	6.36	-2.40	<.001	3.13	.003
HMCJ	Placebo	6.57	-1.38		3.39	
	Duloxetine 20 mg QD	6.74	-1.92	.097	2.85	.009
	Duloxetine 60 mg QD	6.46	-2.00	.022	3.04	.044
	Duloxetine 120 mg QD	6.41	-2.31	<.001	2.89	.004
HMEF	Placebo	6.45	-1.17		3.60	
	Duloxetine 60 mg QD	6.59	-1.50	.209	3.38	.181

Abbreviations: BID = twice daily; BPI = Brief Pain Inventory; HMBO = Study F1J-MC-HMBO; HMCA = Study F1J-MC-HMCA; HMCJ = Study F1J-MC-HMCJ; HMEF = Study F1J-MC-HMEF; LSMean = least-squares mean; PGI-I = Patient's Global Impressions of Improvement; QD = once daily.

^a p-values are from comparisons with placebo.

Source: Clinical Overview page 25

Table 14: FIQ Total Score and FIQ Pain Score Mean Change from Baseline to Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, and F1J-MC-HMCJ

Study	Treatment Group	FIQ Total Score			FIQ Pain score **		
		Baseline	LSMean Change	p-value	Baseline	LSMean Change	p-value
HMBO*	Placebo	50.7	-6.4		7.0	-1.0	
	Duloxetine 60 mg BID	48.9	-10.2	0.080	6.9	-1.6	0.093
HMCA	Placebo	53.0	-8.4		7.2	-1.1	
	Duloxetine 60 mg QD	51.5	-16.7	<0.001	7.0	-2.4	<0.001
	Duloxetine 60 mg BID	52.5	-16.8	<0.001	7.1	-2.4	<0.001
HMCJ	Placebo	52.7	-10.1				
	Duloxetine 20 mg QD	53.7	-14.6	0.040			
	Duloxetine 60 mg QD	51.3	-15.4	0.004			
	Duloxetine 120 mg QD	51.7	-14.5	0.017			

Source: Clinical Study Report, HMBO page 84 and 88; HMCA page 93; HMCJ page 568

* Primary Efficacy endpoints.

** FIQ Pain Scores for Studies HMCA and HMCJ are provided by the reviewer using LOCF

In Study HMEH, patients were randomized to receive either duloxetine 120 mg QD or 60 mg QD at Week 8. This was carried out to patients who responded to treatment (response defined as a $\geq 50\%$ reduction from Week 0 (baseline) to Week 8 in the BPI 24-hour average pain score) as well as to non-responders. Of the 350 patients who entered the open-label phase, 339 patients had a baseline and an endpoint BPI average pain score values, while 43 patients discontinued from the study. Of the 339 patients who had BPI score at baseline and post-baseline, 118 patients (35%) were considered BPI responders at Visit 4 (Week 8). The Applicant evaluated the persistence of the efficacy of duloxetine 60 mg on patients who were responders at Week 8 and remained on duloxetine 60 mg in the double-blind study phase. This was done by evaluating the change from baseline to endpoint on BPI average pain and comparing the upper bound of the 90% two-sided confidence interval to 0.5. The Applicant did not specify the basis of the 0.5 margin. The result of the analysis is summarized in Table 15. The upper bound of the 90% two-sided confidence interval in duloxetine 60 mg QD treatment group within the response status 'yes' was 2.15 which is more than the margin specified by the Applicant (i.e. 0.5). The Applicant's conclusion is that

For persistence of efficacy analysis, mean change in BPI average pain from baseline to endpoint did not reach significance in the initial responders on duloxetine 60 mg QD. However, initial responders began and ended the double-blind study phase with mean BPI average pain scores in the mild range that were well below the mean baseline pain scores at Visit 2. In addition, decreases (improvements) in mean average pain score were observed for non-responders within both treatment groups.

In my opinion, regardless of the basis of this margin, what this implies is that duloxetine treatment effect on pain reduction on the fibromyalgia patients was not maintained in the one-year double-blind study phase. Furthermore, applying mean change from baseline to measure persistence of effect does not appear to be informative. Instead, I believe that looking at the individual level data may provide more meaningful result when studying the persistence of effect, as shown in Section 3.1.3.2.

Table 15: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint: All Randomized Patients by Brief Pain Inventory Response Status at Visit 4 – Double-Blind Study Phase

Table HMEH.11.14. Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint All Randomized Patients by Brief Pain Inventory Response Status at Visit 4 Double-Blind Study Phase

Subgroup	Treatment by Subgroup p-Value	Sub-group p-Value	BPI Response Status at Visit 4	N	Treatment	n	Baseline		Change			p-Value*	
							Mean	SD	Mean	SD	LSMean		SE
BPI Average Pain Score	.995	.397	No	194	1)DLX60QD	66	5.71	1.73	-0.82	2.48	-1.27	0.34	.639
					2)DLX120QD	128	6.03	1.53	-0.88	2.61	-1.10	0.26	
			Yes	1)DLX60QD	36	1.75	1.05	1.36	2.73	1.26	0.45	.939	
				2)DLX120QD	74	2.09	1.20	1.36	2.60	1.22	0.36		

Two-sided 90% CI of LS Means for change from baseline in DLX60QD treatment group within response status 'yes' group: (0.38,2.15).
 N = Number of patients with a baseline and at least one non-missing post baseline value.
 Type III sums of squares from ANCOVA Model = Treatment, Pooled Investigator, and Baseline for within-stratum p-values. Model = Treatment, Pooled Investigator, Baseline, Subgroup, and treatment*subgroup for interaction and subgroup p-values.

Report: RMP.F1J0.EMERSTAT.FINAL (LOBP1321)
 Program: RMP.F1J5EMER.SASPGM (LOBP132)
 Data: RMP.SAS.F1J5.L.WCMEKH.ADS.DBF

3.1.3.2 Reviewer's Comments

When the submitted datasets (raw and derived) were re-analyzed (e.g. patient disposition, demographic and baseline characteristics, primary and secondary endpoints analyses), I identified a few inconsistencies with the results presented in the Study Report; however, the inconsistencies did not affect the overall conclusions. For the most part, I was able to replicate the Applicant's results.

During my evaluation of the submission, I identified several areas that warranted further consideration including the population used to conduct the primary efficacy analysis, the approach to handle missing data, and the multiplicity adjustment.

In all studies, the Applicant conducted the primary analyses on all randomized patients who had at least one post-baseline measure, which I termed as modified intent-to-treat population (mITT). This implies that any patients who only had baseline scores are not included in the efficacy analyses. Although only a small proportion of patients were excluded in the analyses because of missing post-baseline measures, this post-randomization exclusion may still potentially introduce problems (i.e. bias) to the comparability of the treatment arms. Furthermore, patients who dropped out prior to the first post-baseline are informative (i.e. their missingness is informative as they may not have even been able to tolerate the treatment for a short time). Therefore, re-analyses of data using all randomized patients were performed. Results generated from the re-analyses using LOCF, although slightly different, did not affect the Applicant's overall conclusions.

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Table 16: Treatment Groups by Study

Study	Population	Dose			
		20 mg QD	60 mg BID	60 mg QD	120 mg QD
HMBO	mITT		100		102
	ITT		103		102
HMCA	mITT		114	116	118
	ITT		116	117	120
HMCJ	mITT	77		144	142
	ITT	79		150	147

The LOCF method was the primary approach used to impute missing data in all placebo-controlled studies. In general, the LOCF approach applies to data that is considered to be missing completely at random and unrelated to the treatment. However, patients who drop out of the studies due to treatment-related adverse events are not randomly missing but are non-responders. Assigning potentially good scores to patients who drop out for treatment-related adverse events can inflate the treatment effect. The Applicant did not perform any additional sensitivity analyses to handle missing data. Instead, they performed an additional analysis using a mixed model repeated measures approach to evaluate pain and global improvement over time without the intention.

Therefore in my re-analyses, two imputation strategies were applied to missing data in the BPI average pain score, namely baseline observation carried forward (BOCF), and a hybrid LOCF/BOCF. In the hybrid LOCF/BOCF strategy, patients who dropped out of the study due to adverse events were assigned their baseline score, while the remaining patients who dropped out were assigned their last observed score. Furthermore, all randomized patients were included in the analyses. Worst observation carried forward strategies were applied to missing data in the patient global improvement rating score.

In Study HMCA, more than one dose and more than 20 secondary endpoints were explored. In Study HMCJ, although there was a pre-specified gatekeeper strategy to adjust for multiplicity, this strategy did not cover all the secondary endpoints that the Applicant examined. In fact, only the dose (i.e. 60 mg QD), the time (six-month), and the Sheehan Disability scale were included in the gatekeeper strategy. Likewise, in Study HMBO, a multitude of secondary endpoints (that includes BPI average pain score) were studied.

The Applicant stated that the purpose of collecting several secondary efficacy outcomes was to confirm the findings of the primary outcome and was not intended to draw conclusions from these secondary efficacy measures. Therefore, they did not have any plan of making adjustments for multiplicity.

Because of the multitude of secondary endpoints (including different dose and outcome measures) they proposed to examine in the protocol, there will be an increased probability of falsely declaring some dose of the treatment to be effective or one treatment to be superior over placebo in some endpoints, particularly when analyses of multiple endpoints were not adjusted for multiplicity. Furthermore, secondary endpoints can not be validly analyzed if the primary endpoint does not demonstrate clear statistical significant (e.g. Study HMBO). Either multiplicity adjustment (e.g. Bonferroni method which entails dividing the alpha level by the number of pairwise comparisons of interest) should have been applied to Study HMCA and Study HMBO, as well as to Study HMCJ for the other secondary endpoints not included in the gatekeeper strategy, in order to maintain

an overall type 1 error rate, or the results should have been presented descriptively without p-values. Either way, it is difficult to draw conclusions from the analyses of the secondary endpoints as well as to make labeling claims from a statistical point of view because of the multitude of pairwise comparisons being tested and the clinical relevance of these endpoints.

My results for the primary efficacy parameters are summarized in Table 17 and Table 18. Note that in Study HMCJ, there were 24 patients (placebo=3, DLX20QD=9, DLX60QD=4, and DLX120QD=8) that had Visit 8 BPI Average pain score data (i.e. Month 3) but discontinued at Visit 8. Of the 24 patients who dropped out, 11 of these dropped out due to AE. In the re-analyses, all 24 patients' Visit 8 scores were recoded as 'missing'. Imputation techniques were applied to handle the missing data. The results of these re-analyses are provided in this review.

An alternate strategy was also conducted to validate the results treating all 24 patients as missing. In this strategy, only 11 of the patients' Visit 8 scores were recoded as 'missing' (patients who dropped out due to AE). The remaining 13 patients' Visit 8 scores were retained. The result of this new analysis will slightly be affected when LOCF/BOCF imputation is applied since these 13 patients' Visit 8 scores will be used instead of their last observed value before discontinuation. Nonetheless, the results using this new strategy were consistent with the results when the 24 patients' Visit 8 scores were coded as 'missing' using LOCF/BOCF imputation strategy. The results are not shown in this review.

Using the BOCF and the LOCF/BOCF approaches, duloxetine 60 mg BID and duloxetine 120 mg QD were associated with significant improvement in pain over placebo treatment in Study HMCA and Study HMCJ, respectively.

There is also some evidence that duloxetine 60 mg QD was associated with improvement in pain over placebo in Study HMCA regardless of imputation strategy. Because the treatment difference was highly significant (based on unadjusted p-value), this treatment comparison may potentially survive when Bonferroni adjustment is applied.

Using the pre-specified gatekeeper strategy in Study HMCJ, there is evidence that duloxetine 60 mg QD was associated with significant improvement in pain when LOCF/BOCF imputation strategy was applied. However, this was not evident when BOCF imputation strategy was applied to missing data.

As a co-primary measure in Study HMCJ, duloxetine 120 mg QD was also associated with significant improvement in patient global score over placebo. When WOCF was applied to missing data, duloxetine 60 mg QD appeared to be associated with significant improvement in patient global score over placebo, using the pre-specified gatekeeper strategy.

As noted, PGI improvement rating was a pre-specified secondary endpoint in Study HMCA but was not adjusted for multiplicity. However, because the unadjusted p-value was not highly significant, there is little to no evidence of a treatment difference in PGI improvement between duloxetine 60 mg BID and placebo and between duloxetine 60 mg QD and placebo.

Similarly in Study HMBO, because none of the primary endpoints (i.e. FIQ Total and FIQ pain) were significant, and because of the multitude of secondary endpoints being tested, there is no evidence of a treatment difference between duloxetine 60 mg BID and placebo in the improvement of pain and in the improvement in patient global score.

In Study HMCA, although there is evidence that duloxetine 60 mg BID and duloxetine 60 mg QD are superior over placebo in the improvement in pain, the magnitude of the treatment effect on these two dose

groups (i.e. once a day (60 mg/day) regimen and twice a day (120 mg/day) regimen) was similar. In my opinion, the treatment benefit is almost identical, if not better in the 60 mg QD regimen. According to the Applicant, a prior study demonstrated efficacy using duloxetine 60 mg BID; therefore, in this study the 60 mg QD dose was tested to evaluate the dose response relationship. They claimed that duloxetine 60 mg QD could allow ease of use for patients and potentially improve patient drug compliance. Therefore in my opinion, it is important to assess the risk on each dosing regimen to determine which dosing regimen is more beneficial to patients.

In Study HMCJ, according to the Applicant, the purpose of the inclusion of duloxetine 20 mg QD was to establish duloxetine 60 mg QD as a minimum effective dose. Although this dose was not meant to be included in the analyses and the (adjusted) pairwise comparison test results were not significant, the treatment effect on this dose is almost similar to duloxetine 60 mg QD and duloxetine 120 mg QD in both BPI average pain score and PGI-Improvement score. Therefore, it is difficult to establish that duloxetine 60 mg QD is the minimum effective dose even though duloxetine 20 mg QD is not significant. Like in Study HMCA, it is important to assess the risk on each dosing regimen to determine which dosing regimen is more beneficial to patients

Table 17: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, and F1J-MC-HMCJ

Study	Treatment Group	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)	
		Baseline	LSMean Change	p-value	LSMean Change	p-value
HMBO*	Placebo	6.11	-0.7		-0.6	
	Duloxetine 60 mg BID	6.13	-1.2	0.067	-1.2	0.049
HMCA	Placebo	6.52	-0.9		-1.0	
	Duloxetine 60 mg QD	6.37	-2.1	<0.001†	-2.2	<0.001†
	Duloxetine 60 mg BID	6.37	-1.8	0.001	-2.1	<0.001
HMCJ	Placebo	6.58	-1.1		-1.2	
	Duloxetine 20 mg QD	6.77	-1.6	0.135†	-1.9	0.039†
	Duloxetine 60 mg QD	6.49	-1.6	0.065	-1.8	0.036
	Duloxetine 120 mg QD	6.39	-1.7	0.036	-1.8	0.038

†unadjusted p-value.

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Table 18: PGI-Improvement at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMBO, F1J-MC-HMCA, and F1J-MC-HMCJ

Study	Treatment Group	N	PGI Improvement Score (LOCF)		PGI Improvement Score (WOCF)	
			LSMean Change	p-value	LSMean Change	p-value
HMBO*	Placebo	99	3.7		3.8	
	Duloxetine 60 mg BID	95	3.1	0.006	3.2	0.011
HMCA**	Placebo	111	3.8		3.9	
	Duloxetine 60 mg QD	114	3.2	0.005†	3.2	0.002†
	Duloxetine 60 mg BID	111	3.1	0.003†	3.2	0.002†
HMCJ**	Placebo	139	3.4		3.6	
	Duloxetine 20 mg QD	77	2.9	0.012†	3.1	0.010†
	Duloxetine 60 mg QD	143	3.0	0.026	3.1	0.009
	Duloxetine 120 mg QD	142	2.9	0.004	3.0	0.002

*Generalized linear model (GLM) Model: PGIImp=Treatment+Pool Investigator +Treatment*Pool Investigator

**GLM Model: PGIImp=Treatment+Pool Investigator

†unadjusted p-value.

Continuous responder curves for each treatment arm were plotted for Studies HMCA and HMCJ (Figure 4 and Figure 5). In these plots, all patients who drop out of the study are considered non-responders. 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. The curves for the active arms were compared to placebo using the van der Waerden test (Table 19). Note that because there was no treatment effect seen in Study HMBO, this study will not be explored further.

There was a clear separation of curves between duloxetine 60 mg QD and placebo in Study HMCA and duloxetine 120 mg QD and placebo in HMCJ. Like their primary analyses using BOCF and LOCF/BOCF imputation strategies, these differences were also statistically significant. It also appeared that the separation was maintained even when stringent criteria of response were applied (i.e. > 70% improvement in pain).

There is also evidence that duloxetine 60 mg BID in Study HMCA and duloxetine 60 mg QD in Study HMCJ have a higher proportion of responders compared to placebo almost at all levels of response (except when stringent criteria of response were applied; >80% improvement in pain). However, none of these curves were statistically different when multiplicity adjustments were applied. Like in the mean BPI pain analysis, it appears that duloxetine 20 mg QD is almost similar to both duloxetine 60 mg QD and duloxetine 120 mg QD in terms of patient's overall response profile in Study HMCJ. Likewise, in Study HMCA, it appears that the response profile of both duloxetine 60 mg BID and duloxetine 60 mg QD are identical. Therefore, it appears that there is no added benefit to patients taking 120 mg QD or 60 mg QD (or even 60 mg BID) over 20 mg QD.

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Figure 4: Overall Response Profile for Study HMCA

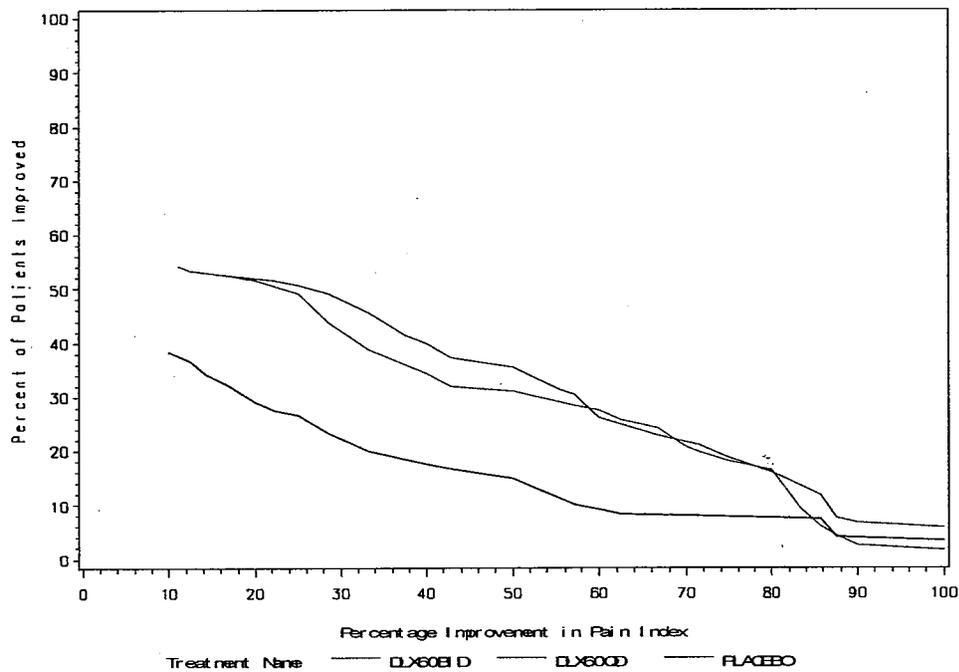


Figure 5: Overall Response Profile for Study HMCJ at 3 months

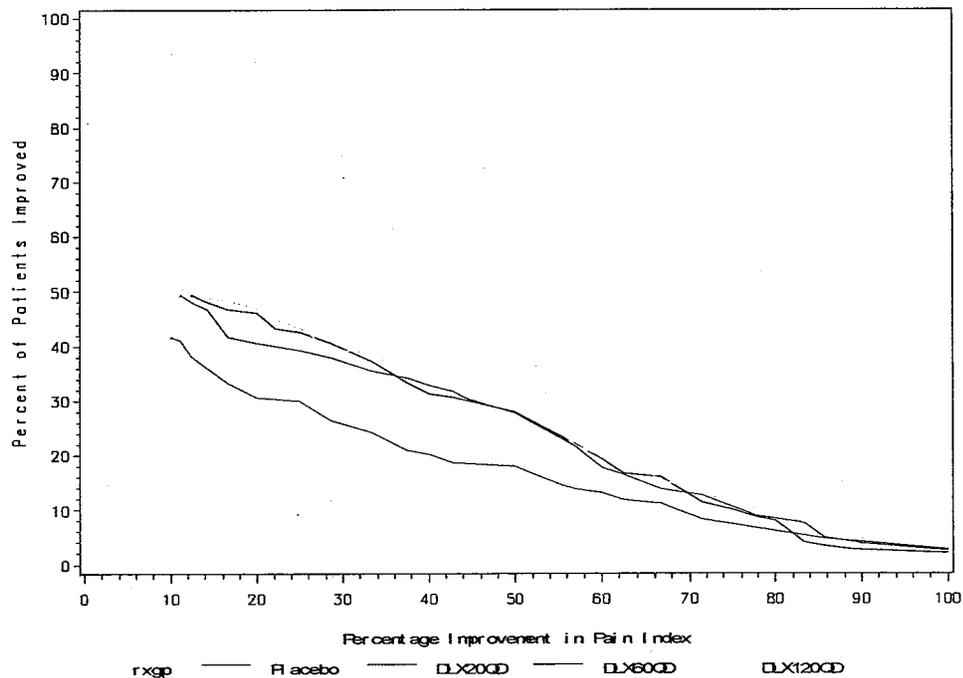


Table 19: Van der Waerden Test for Difference in Distribution: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ

Study	Treatment Group	N	Van der Waerden Test†
HMCA	Placebo	120	
	Duloxetine 60 mg QD	118	0.004
	Duloxetine 60 mg BID	116	0.036
HMCJ	Placebo	144	
	Duloxetine 20 mg QD	79	0.177
	Duloxetine 60 mg QD	150	0.085
	Duloxetine 120 mg QD	147	0.052

† unadjusted p-value

An alternate way to view the treatment effect is to explore the proportion of patients who had at least 30% improvement in pain or at least 50% improvement in pain in Study HMCA and Study HMCJ.

In Table 20, there was consistent evidence that duloxetine 60 mg BID (in Study HMCA) and duloxetine 120 mg QD (in Study HMCJ) were superior to placebo in terms of improvement in pain. The proportion of patients who had at least 30% improvement and at least 50% improvement were higher in the duloxetine group compared to placebo. Although not significant, a similar proportion of patients in the duloxetine 20 mg QD arm had at least 30% improvement and at least 50% improvement compared to duloxetine 60 mg QD and duloxetine 120 mg QD in Study HMCJ. Meanwhile, it appears that a higher proportion of patients in the duloxetine 60 mg QD arm had at least 30% and at least 50% improvement compared to duloxetine 60 mg BID in Study HMCA.

Table 20: Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ

Study	Treatment Group	≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
		N	n(%)	p-value	n(%)	p-value
HMCA	Placebo	120	24 (20%)		18 (15%)	
	Duloxetine 60 mg QD	118	54 (46%)	<0.001	42 (36%)	<0.001
	Duloxetine 60 mg BID	116	45 (39%)	0.002	36 (31%)	0.003
HMCJ	Placebo	144	37 (26%)		26 (18%)	
	Duloxetine 20 mg QD	79	28 (35%)	0.126	22 (28%)	0.089
	Duloxetine 60 mg QD	150	56 (37%)	0.032	42 (28%)	0.043
	Duloxetine 120 mg QD	147	57 (39%)	0.017	44 (30%)	0.018

In examining the raw data for Study HMCA and taking the average pain over time (observed cases only), there is consistent evidence that on average patients treated with duloxetine (60 mg BID and 60 mg QD) have greater improvement in their pain scores compared to patients treated with placebo as early as Week 1 (Figure 6). However, there is also evidence that this improvement seemed to plateau at around Week 4 for duloxetine 60 mg QD and at around Week 6 for duloxetine 60 mg BID. In Study HMCJ, there is also evidence that on average patients treated with duloxetine 60 mg QD and duloxetine 120 mg QD have greater

improvement in pain compared to placebo patients as early as Week 1. However, it appears that patients treated with placebo had some improvements in their pain score over time such that patients in all treatment groups who had Week 11 data (mostly completers) almost had the same average pain score (Figure 7). Note that patients were initially dosed at 30 mg QD in both the duloxetine 60 mg QD and duloxetine 120 mg QD arms during the first week of the double-blind phase. Patients in the duloxetine 120 mg QD were then titrated to 60 mg QD during the second week. Only during the third week did these patients receive their fixed dose of 120 mg QD. So in essence, the early difference could be attributed to the dose of 30 mg QD and patients who could tolerate the drug continued to improve in their pain score up to Week 4 (i.e. second week of fixed dose). However, the pain scores in these patients who tolerated the drug appeared to decline after the second week of fixed dose treatment. Meanwhile, pain scores in patients taking duloxetine 60 mg QD appeared to plateau after the second week of treatment (or first week of fixed dose). They only showed improvement during the first and second week of treatment. It appears that the pain scores among patients taking duloxetine 60 mg QD who tolerated the drug and remained in the study did not improve. Please refer to Reviewer's Continuous Responder Analysis Section below for more explanation.

Figure 6: Weekly Mean Pain Score (Study HMCA)

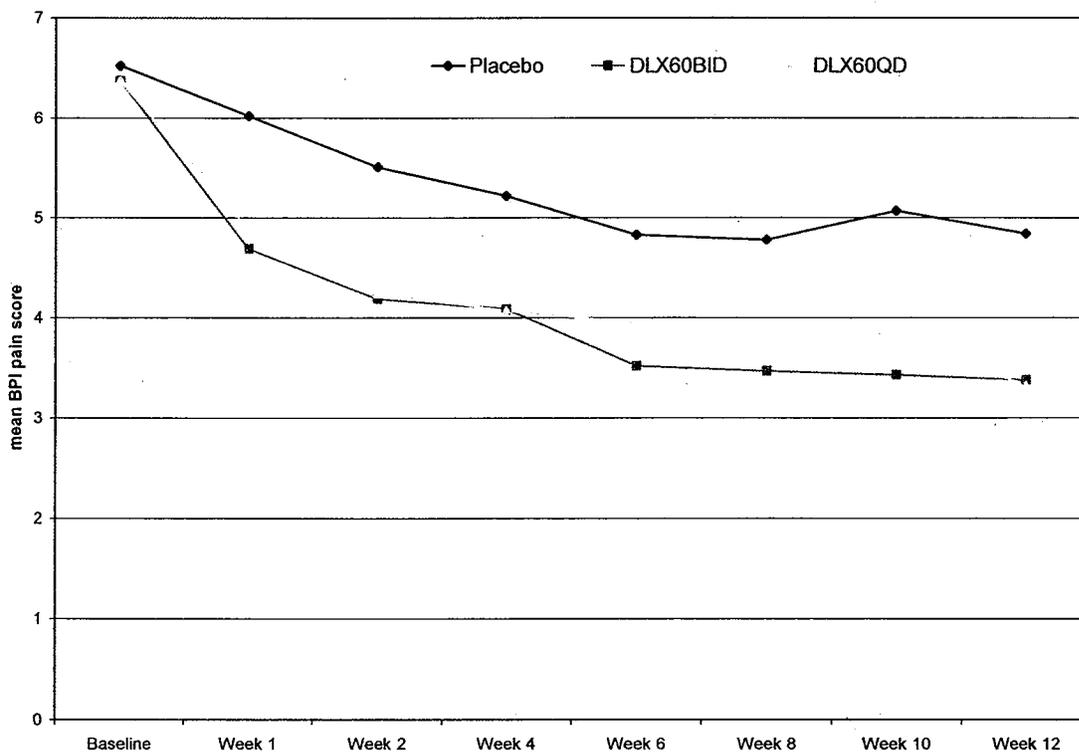
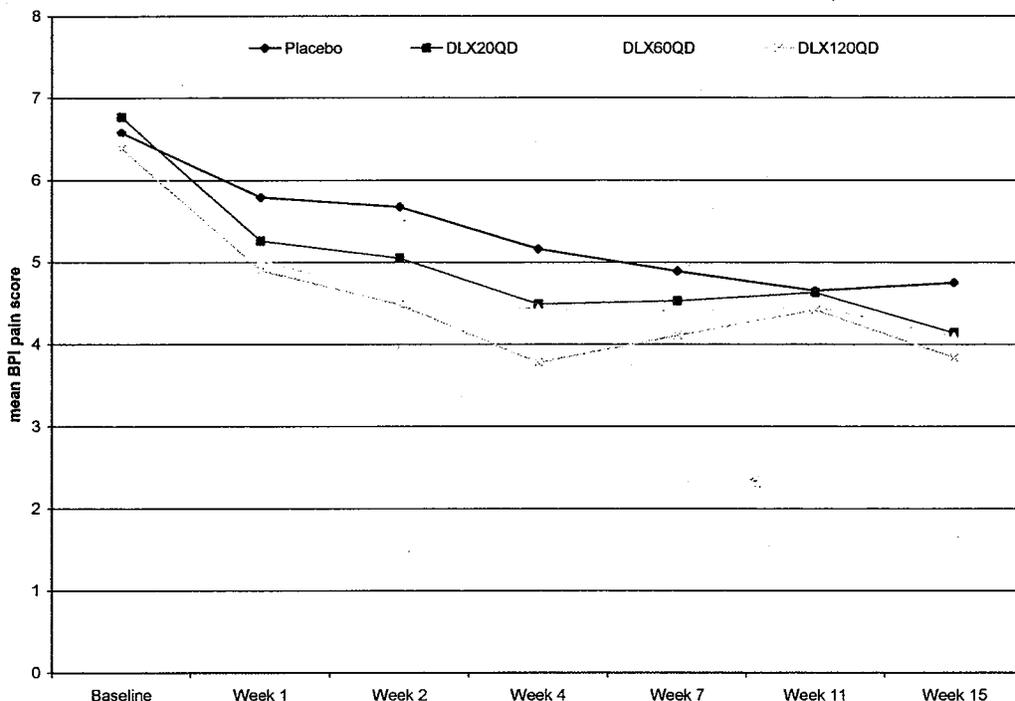


Figure 7: Weekly Mean Pain Score (Study HMCJ)



Continuous responder analyses by week are explored for Studies HMCA and HMCJ (Figure 8 and Figure 9, respectively). In these plots, all patients who drop out of the study are considered non-responders. 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 for Study HMCA, there is clear evidence that a higher proportion of patients treated with duloxetine (60 mg QD and 60 mg BID) responded better compared to the placebo as early as Week 1 and this continues on until Week 12. Again, these patients were not titrated except for patients taking duloxetine 60 mg BID who were initially dosed (for three days) with 60 mg QD.

Meanwhile in Study HMCJ, it is difficult to draw conclusions from data for Week 1 and Week 2 since patients were initially titrated and patients in both duloxetine 60 mg QD and duloxetine 120 mg were taking the same dosing regimen at those times. Therefore, the curves for duloxetine 120 mg QD and duloxetine 60 mg QD are almost overlapping especially at Week 2. It is difficult to attribute the difference in responder curves to any of the dosing regimens at Week 1. However, there is some evidence that a higher proportion of patients treated with duloxetine 60 mg QD experienced a better response to treatment compared to placebo at Week 2 (this includes patients taking duloxetine 120 mg). At Week 3 onwards, only duloxetine 120 mg patients showed consistent evidence of achieving higher levels of pain reduction compared to placebo patients. There is some evidence of a difference in the proportion of responders between duloxetine 60 mg QD and placebo, but this was not consistent over time. This could be attributed to the inclusion of male patients in the study, in which the majority fell in the duloxetine 60 mg QD group (14/28 or 50%). Also, of these 14 male patients, 50% dropped out before Week 12.

Figure 8: Continuous Responder Analysis by Week – Study HMCA

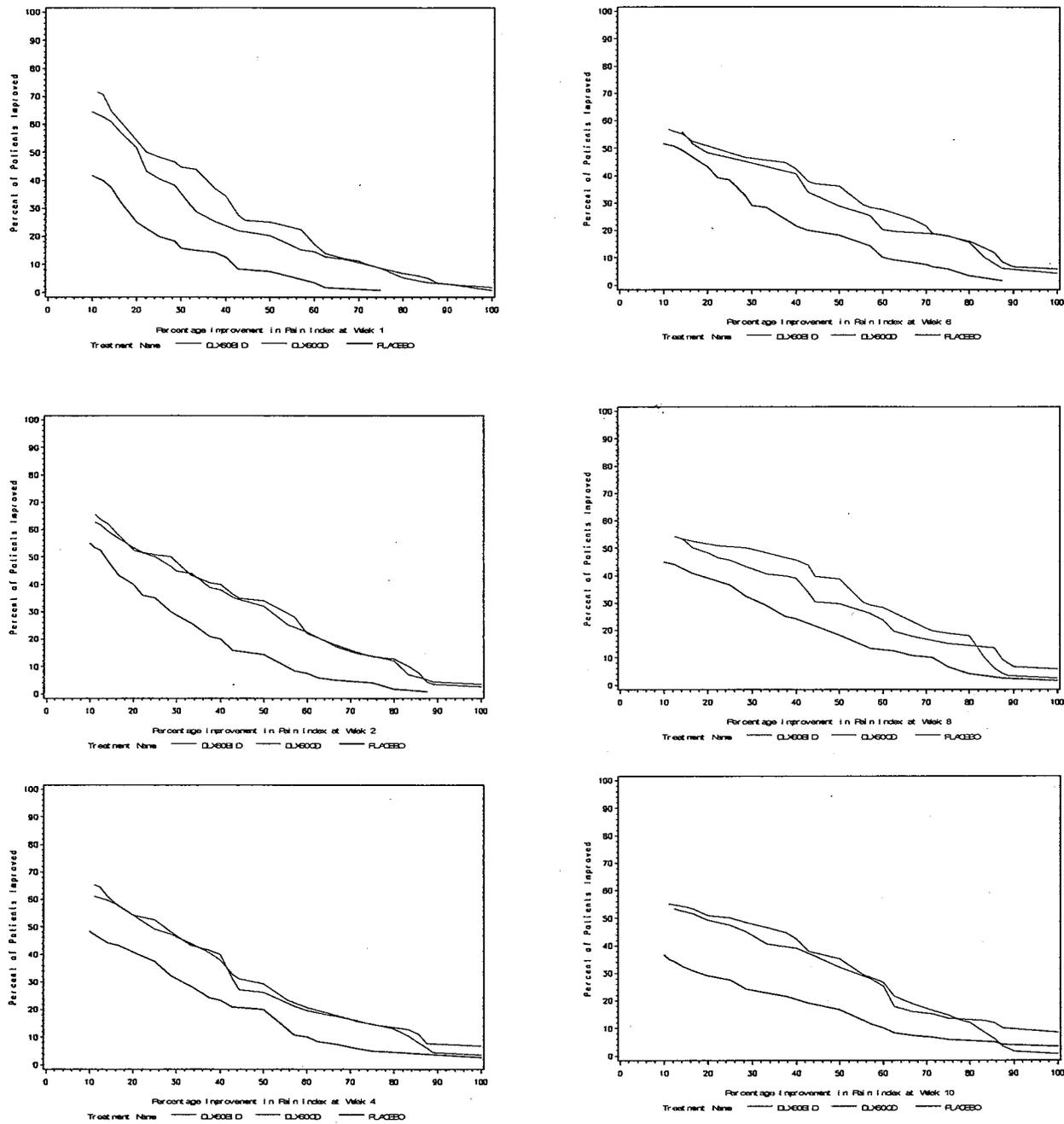
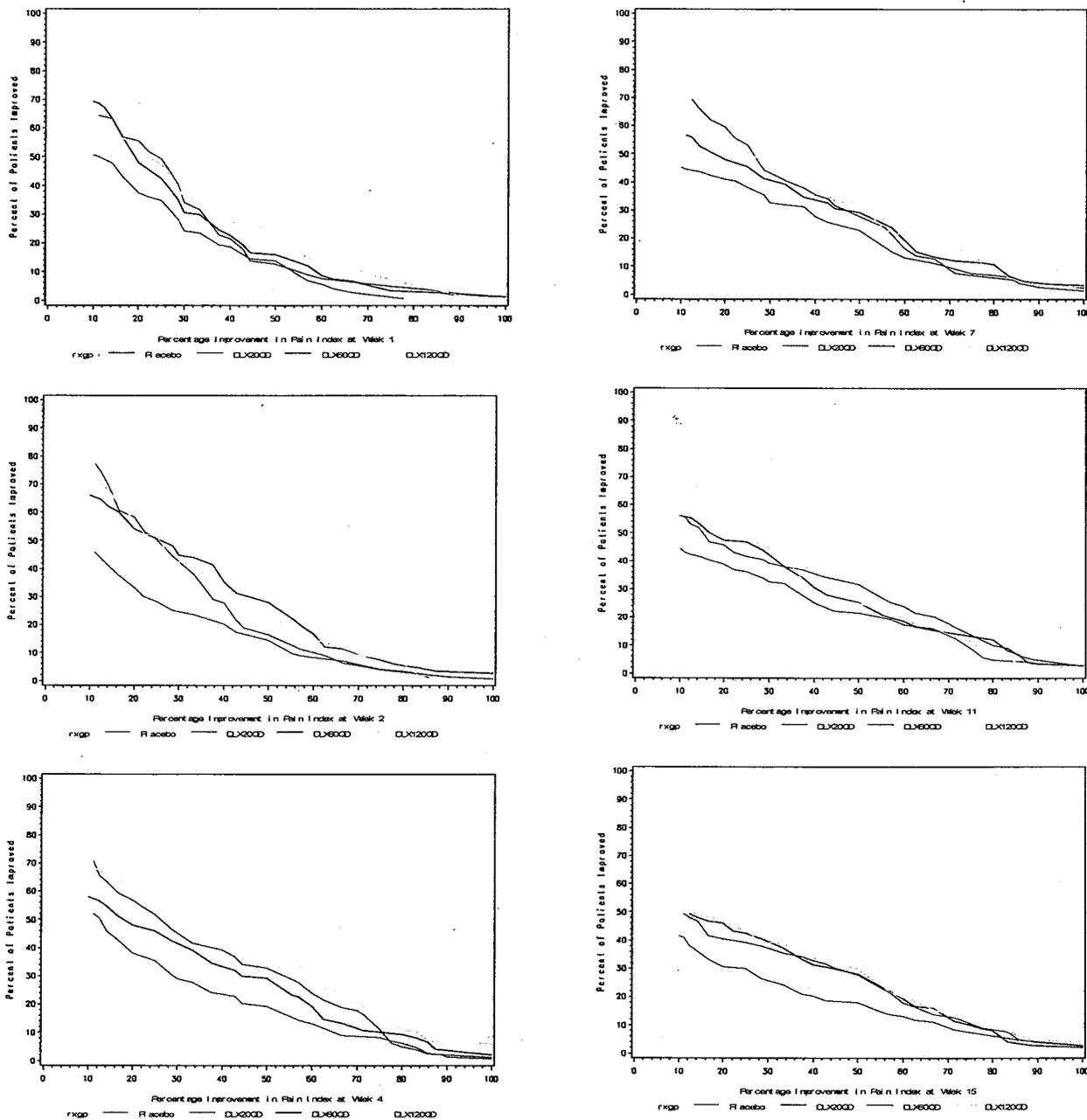


Figure 9: Continuous Responder Analysis by Week – Study HMCJ



An alternate way to view the treatment effect over time is to explore those patients who completed the study and who responded to treatment, either using the 30% responder criteria or 50% responder criteria in Studies HMCA and HMCJ. 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% (or 50%) improvement in pain from baseline over time.

In Study HMCA, a total of 133 patients completed the study and had at least 30% improvement in pain from baseline at the end of the study, and a total of 96 patients had at least 50% improvement. Figure 10 and Figure 11 provide a graphical display of patients who responded to treatment. It appears that most patients receiving duloxetine 60 mg BID achieved the level of response at Visit 5 (Week 4). In contrast, patients receiving duloxetine 60 mg QD appears to benefit even as long as Visit 9 (Week 12). Among patients who responded at Week 12, there is a difference in the proportion of responders as early as Week 1 between the active treatment arms and the placebo.

In Study HMCJ, a total of 178 patients completed the study and had at least 30% improvement in pain from baseline at the end of the study, and a total of 134 patients had at least 50% improvement. Figure 12 and Figure 13 provide a graphical display of patients who responded to treatment. It appears that most patients receiving duloxetine 60 mg QD and duloxetine 120 mg QD continued to achieve the level of response up to Visit 8 (Week 12). Among patients who responded at Week 12, there is a difference in the proportion of responders as early as Week 1 between the active treatment arms and the placebo.

Figure 10: Proportion of Responders by Week (30% Improvement) – Study HMCA

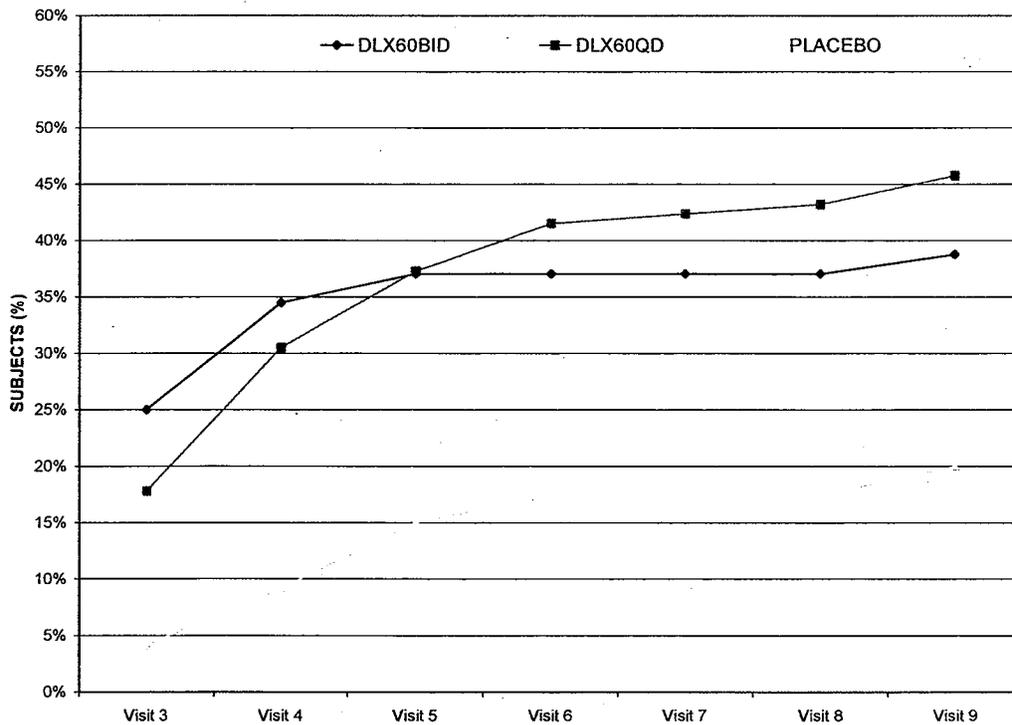


Figure 11: Proportion of Responders by Week (50% Improvement) – Study HMCA

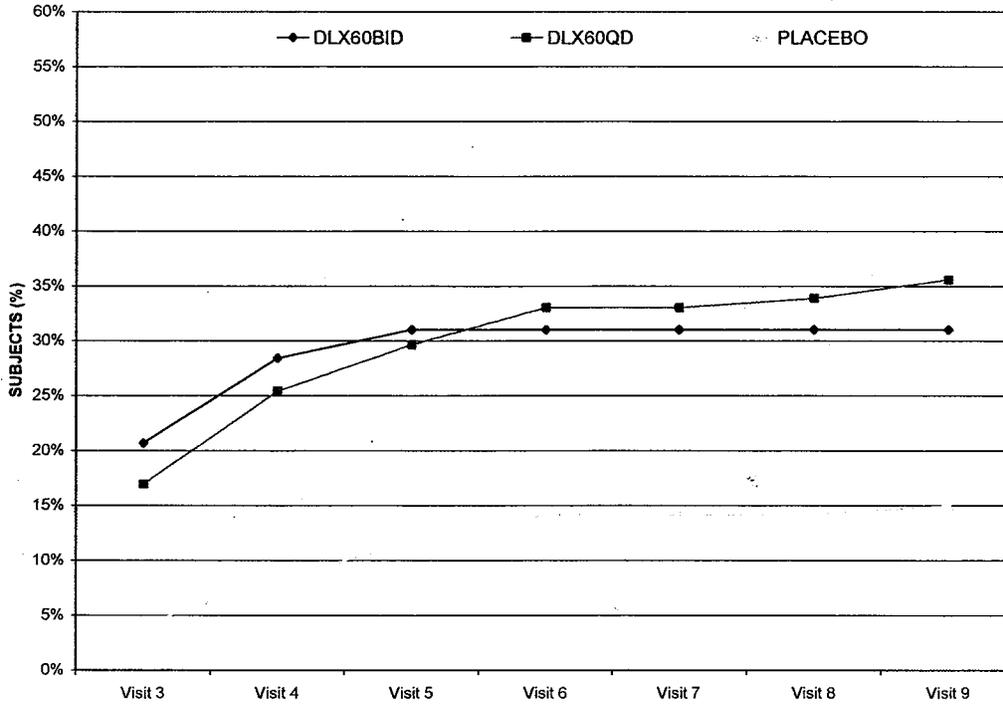


Figure 12: Proportion of Responders by Week (30% Improvement) – Study HMCJ

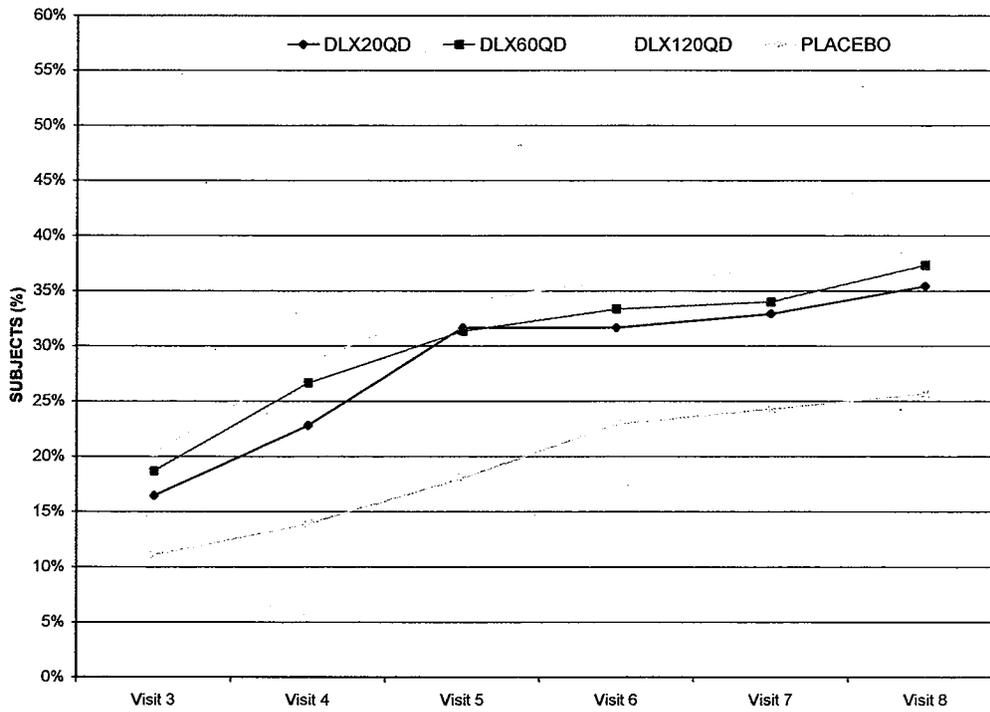
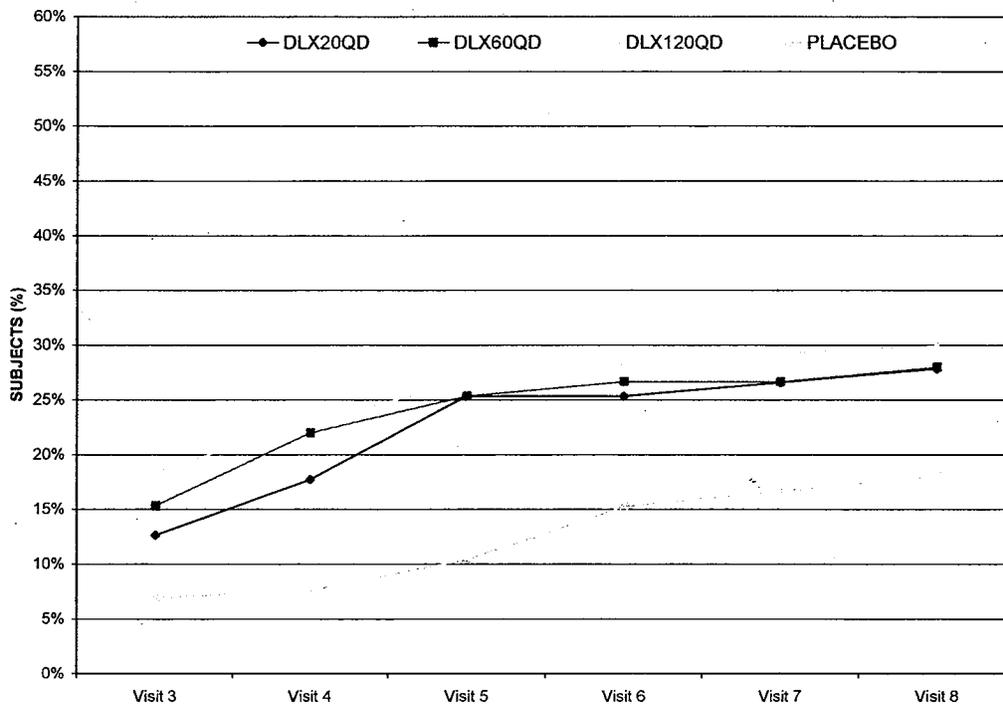


Figure 13: Proportion of Responders by Week (50% Improvement) – Study HMCJ



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As part of the secondary gatekeeper analyses in Study HMCJ, comparisons of duloxetine (120 mg QD and 60 mg QD) and placebo on the change from baseline in BPI average pain score at six months and PGI-Improvement at six months are explored. The following table summarizes the patient disposition (reasons for study discontinuations) at three months of treatment and at six months of treatment (Table 21). Note that patients taking duloxetine 20 mg QD the first three months were titrated to 60 mg QD up to week 28 (month 6). It appears that there were at least 6% to 10% more patients who dropped out at month 6. Most of the dropouts were in the duloxetine 60 mg QD and duloxetine 120 mg QD group. There was a 5% increase in the number of patients dropping out due to AE as well as due to subject decision in the duloxetine 120 mg QD, while the other treatment arms remained fairly the same. Meanwhile, there was a 4% increase in the number of patients dropping out due to lack of efficacy in the duloxetine 60 mg QD group and 4% increase in loss to follow-up in the placebo group.

Table 21: Patient Disposition at Six Months

Study	Treatment Group	N	At 3 months n(%)	At 6 months n(%)
DC due to any reason	Placebo	144	60 (42%)	72 (50%)
	Duloxetine 20 mg QD (60 mg QD after 3 months)	79	30 (38%)	35 (44%)
	Duloxetine 60 mg QD	150	53 (35%)	68 (45%)
	Duloxetine 120 mg QD	147	52 (35%)	68 (46%)
Adverse Events	Placebo	144	17 (12%)	19 (13%)
	Duloxetine 20 mg QD (60 mg QD after 3 months)	79	8 (10%)	9 (11%)
	Duloxetine 60 mg QD	150	22 (15%)	23 (15%)
	Duloxetine 120 mg QD	147	32 (22%)	39 (27%)
Lack of Efficacy	Placebo	144	14 (10%)	16 (11%)
	Duloxetine 20 mg QD (60 mg QD after 3 months)	79	8 (10%)	8 (10%)
	Duloxetine 60 mg QD	150	11 (7%)	15 (10%)
	Duloxetine 120 mg QD	147	6 (4%)	7 (5%)
Subject Decision	Placebo	144	10 (7%)	12 (8%)
	Duloxetine 20 mg QD (60 mg QD after 3 months)	79	8 (10%)	10 (13%)
	Duloxetine 60 mg QD	150	9 (6%)	12 (8%)
	Duloxetine 120 mg QD	147	5 (3%)	10 (7%)
Loss to Follow-Up	Placebo	144	13 (9%)	18 (13%)
	Duloxetine 20 mg QD (60 mg QD after 3 months)	79	3 (4%)	4 (5%)
	Duloxetine 60 mg QD	150	7 (5%)	10 (7%)
	Duloxetine 120 mg QD	147	7 (5%)	8 (5%)

The following table summarizes the results taken from the Applicant's study report. They applied last observation carried forward in handling missing data.

Table 22: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months) and PGI Improvement at Endpoint: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ

Treatment Group	BPI Average Pain Score (LOCF)			PGI-Improvement (LOCF)		
	Baseline	LSMean Change	p-value	Baseline	LSMean Endpoint	p-value
Placebo	6.57	-1.4		4.06	3.4	
Duloxetine 20 mg QD	6.74	-2.3	0.018	4.20	2.8	0.006
Duloxetine 60 mg QD	6.46	-1.9	0.041	3.78	3.1	0.108
Duloxetine 120 mg QD	6.41	-2.1	0.003	3.82	2.9	0.012

Source: Clinical Study Report HMCJ, page 128 and 130

The results for the re-analyses of the mean change from baseline in BPI average pain score at six months for Study HMCJ are summarized in Table 23. Like at three months, there were 11 patients (placebo=2, DLX20/60QD=0, DLX60QD=3, and DLX120QD=6) that had Visit 11 BPI Average pain score data (i.e. Month 6) but discontinued at Visit 11. Of the 11 patients who dropped out, three dropped out due to AE (two patients from DLX120 QD and one subject from placebo). In the re-analyses (Table 23), all 11 patients' Visit 8 scores were recoded as 'missing'. As such, imputation techniques (i.e. BOCF and LOCF/BOCF) were applied to handle the missing data.

The results from these two imputation techniques suggest that patients taking either duloxetine 120 mg QD or duloxetine 60 mg QD had minimal treatment effect (not significant) compared to placebo. When eight of the 11 patients' scores were retained (LOCF/BOCF*), the conclusion remained the same. Because no significant effect was shown in the duloxetine 120 mg QD and 60 mg QD, the PGI improvement score at six months was not examined.

Although it appears that there is significant improvement in pain in the duloxetine 20 mg QD/60 mg QD group compared to placebo at six months, patients taking duloxetine 20 mg QD during the first three months of the study did not show any benefit over placebo. Since the effect was not demonstrated at three months, patients may not have the patience to continue taking the therapy.

Table 23: Brief Pain Inventory Average Pain Score Mean Change from Baseline to Endpoint (Six Months): All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ

Treatment Group	BPI Average Pain Score (BOCF)			BPI Average Pain Score (LOCF/BOCF)		BPI Average Pain Score (LOCF/BOCF)*	
	Baseline	LSMean Change	p-value	LSMean Change	p-value	LSMean Change	p-value
Placebo	6.58	-1.1		-1.2		-1.2	
Duloxetine 20 mg QD/60 mg QD	6.77	-1.9	0.018	-2.2	0.003	-2.2	0.004
Duloxetine 60 mg QD	6.49	-1.4	0.391	-1.7	0.048	-1.7	0.057
Duloxetine 120 mg QD	6.39	-1.4	0.251	-1.7	0.093	-1.6	0.121

* Eight patients who dropped out at Visit 11 retained their Visit 11 score.

Continuous responder curves for each treatment arm were plotted at six months (Figure 14). In this plot, all patients who drop out of the study are considered non-responders. There was a clear separation of curves between duloxetine 20/60 mg QD and placebo. The difference was less evident in duloxetine 60 mg QD and duloxetine 120 mg QD compared to placebo. An alternate way to view the treatment effect is to explore the proportion of patients who had at least 30% improvement in pain or at least 50% improvement in pain at 6 months (Table 24). Except for duloxetine 20/60 mg QD group, it appears that the proportions of responders among the placebo, duloxetine 60 mg QD and duloxetine 120 mg QD groups at 6 months are almost comparable.

Figure 14: Overall Response Profile for Study HMCJ at 6 months

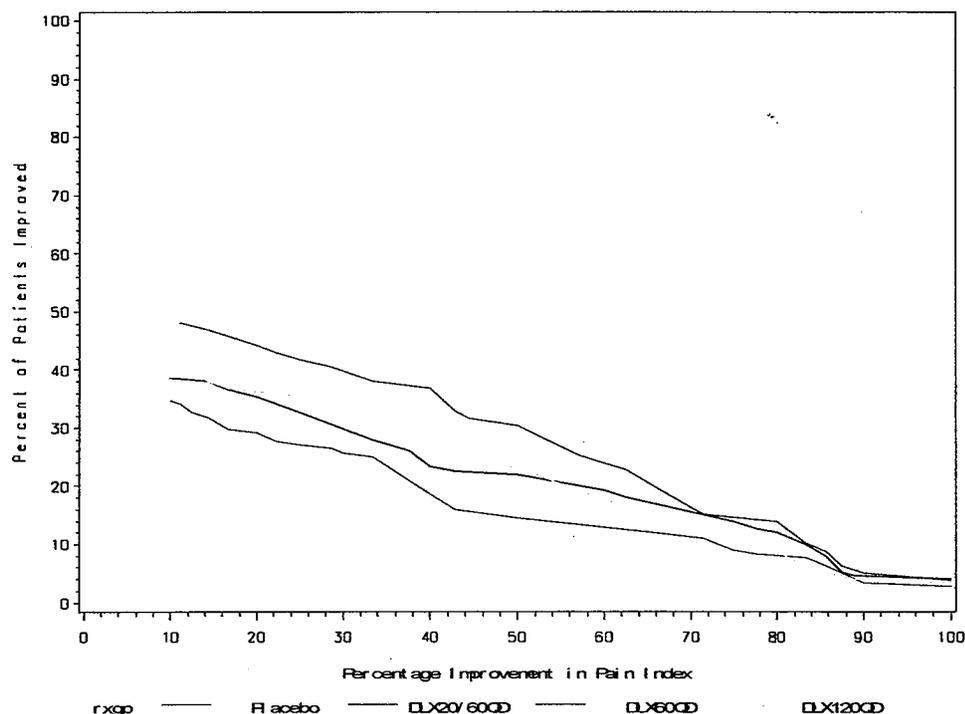


Table 24: Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ

Study	Treatment Group	≥ 30% Improvement in Pain			≥ 50% Improvement in Pain	
		N	n(%)	p-value	n(%)	p-value
HMCJ	Placebo	144	37 (26%)		21 (15%)	
	Duloxetine 20/60 mg QD	79	30 (38%)	0.056	24 (30%)	0.005
	Duloxetine 60 mg QD	150	42 (28%)	0.656	33 (22%)	0.101
	Duloxetine 120 mg QD	147	47 (32%)	0.237	34 (23%)	0.063

In collaboration with Dr. Winchell, we explored the six-month profile of patients who responded and who did not respond at three months (Table 25). Responder is defined as a patient who had at least

30% improvement in pain from baseline. The objective is to determine whether the response at Month 3 was sustained up to Month 6. Thirty four (61%) responders at 3 months in the duloxetine 60 mg QD and 35 (61%) responders at 3 months in the duloxetine 120 mg QD remained responders at 6 months compared to 73% in the placebo group and 79% in the duloxetine 20/60mg QD group.

Of the 22 non-responders at 6 months in the duloxetine 60 mg QD group, 13 patients completed the study but did not achieve the level of response seen at Month 3 (i.e. $\geq 30\%$ improvement in pain). Moreover, three of the 22 patients discontinued due to lack of efficacy (Table 26). Of the 22 non-responders at 6 months in the duloxetine 120 mg QD group, 14 patients completed the study but did not achieve the level of response seen at Month 3 (i.e. $\geq 30\%$ improvement in pain). One of the 22 patients also discontinued due to lack of efficacy.

Table 25: Responder Profile at Endpoint based on responder analysis at three months: All Randomized Patients in the 6-Month Therapy Phase Placebo-Controlled Study: F1J-MC-HMCJ

Treatment Group	Responders at 3 months			NonResponders at 3 months	
	N	Remained Responders at 6 months	Became non-responders at 6 months	N	Became responders at 6 months
Placebo	37	27 (73%)	10 (27%)	107	10 (9%)
Duloxetine 20/60 mg QD	28	22 (79%)	6 (21%)	51	8 (16%)
Duloxetine 60 mg QD	56	34 (61%)	22 (39%)	94	8 (9%)
Duloxetine 120 mg QD	57	35 (61%)	22 (39%)	90	12 (13%)

Table 26: Patient Disposition of responders at 3 months who became non-responders at Six Months – Study HMCJ

Study	Placebo N=10	DLX20/60 mg QD N=6	DLX60 mg QD N=22	DLX120 mg QD N=22
Completed	8 (80%)	5 (83%)	13 (59%)	14 (64%)
Discontinued	2 (20%)	1 (17%)	9 (41%)	8 (36%)
Adverse Events	0	0	0	4 (18%)
Lack of Efficacy	0	0	3 (14%)	1 (5%)
Subject Decision	1 (10%)	1 (17%)	2 (9%)	1 (5%)
Loss to Follow-Up	1 (10%)	0	2 (9%)	0

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Two additional secondary endpoints (FIQ Total Score and Clinical Global Impression of Severity) were examined and reported. As mentioned, it is difficult to draw any conclusions from the analyses of these endpoints because multiplicity adjustments were not applied to these endpoints. Nonetheless, descriptive statistics suggest that FIQ total score and CGI-Severity are trending in the direction similar to the primary endpoint. However, there is not enough evidence to show treatment difference between any of the duloxetine groups and placebo.

Table 27: Fibromyalgia Impact Questionnaire Total Score Change from Baseline to Endpoint*: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ

Study	Treatment Group	FIQ Total Score (BOCF)			FIQ Total Score (LOCF/BOCF)	
		Baseline	LSMean Change	p-value†	LSMean Change	p-value†
HMCA	Placebo	53.1	-6.7		-7.6	
	Duloxetine 60 mg QD	51.4	-13.6	0.001	-14.2	0.002
	Duloxetine 60 mg BID	52.5	-12.9	0.003	-14.3	0.002
HMCJ	Placebo	53.0	-8.0		-9.1	
	Duloxetine 20 mg QD	54.0	-11.1	0.130	-13.3	0.053
	Duloxetine 60 mg QD	51.7	-12.1	0.017	-12.9	0.032
	Duloxetine 120 mg QD	51.7	-11.7	0.030	-12.7	0.048

*negative implies improvement

†unadjusted p-value

Table 28: Change in CGI-Severity at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA, and F1J-MC-HMCJ

Study	Treatment Group	N	CGI Improvement Score (WOCF)		CGI Improvement Score (BOCF)	
			LSMean Change	p-value†	LSMean Change	p-value†
HMCA**	Placebo	120	-0.4		-0.3	
	Duloxetine 60 mg QD	118	-0.8	0.007	-0.8	<0.001
	Duloxetine 60 mg BID	116	-0.8	0.005	-0.7	0.003
HMCJ	Placebo	144	-0.5		-0.6	
	Duloxetine 20 mg QD	79	-0.8	0.063	-0.8	0.068
	Duloxetine 60 mg QD	150	-0.8	0.033	-0.8	0.054
	Duloxetine 120 mg QD	147	-0.9	0.002	-0.9	0.005

* negative implies improvement

†unadjusted p-value

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The reader is referred to Section 3.1.3.1 of this review for the Applicant's report on the results of Study HMEH. The following is a summary of my re-analyses of Study HMEH.

According to the Applicant, of the 339 patients who had BPI score at baseline and post-baseline, 118 patients (35%) were considered BPI responders at Visit 4 (Week 8). My re-analyses of the data showed that, of the 339 patients included in the responder analysis, 13 of these patients did not have Visit 4 (Week 8) data. Three of these 13 patients were classified as responders at Week 8. Redefining the intent-to-treat population to include all patients who had baseline score and to classify these 13 patients as non-responder (for missing Week 8 data), the BPI responders at Week 8 will be 115 patients out of 350 (or 33%), which is not that different from the Applicant's analysis. Thus, I focused on the applicant's results.

Using the result from the Applicant, of the 118 patients who were classified as responders, 112 entered the double-blind phase (i.e. 37 patients remained in the 60 mg QD, while 75 patients received 120 mg QD). Meanwhile, of the 221 who were non-responders, 195 entered the double-blind phase. Therefore, there are total of 307 who entered double-blind phase (203 in the duloxetine 120 mg QD group and 104 patients remained in the duloxetine 60 mg QD group).

As stated in the patient disposition section (Section 3.1.2), 71 (68%) patients in the duloxetine 60 mg QD group completed the double-blind phase (62% from the responder group and 72% from the non-responder group). In the duloxetine 120 mg QD, 124 (61%) completed the double-blind phase (73% responder and 54% non-responder). Table 29 summarizes the patient disposition for Week 8 responders and non-responders at the end of the double-blind phase (i.e. 52 weeks). It appears that majority of the dropouts among responders were due to AE, while AE and lack of efficacy are two reasons why most non-responders at Week 8 were dropping out before Week 52.

Table 29: Patient Disposition at Endpoint (i.e. Week 52) – Study HMEH

Study	Treatment Group	N	Responder at Week 8 n(%)	Non-Responder at Week 8 n(%)
Completed	Duloxetine 120 mg QD	203	55 (73%)	69 (54%)
	Duloxetine 60 mg QD	104	23 (62%)	48 (72%)
Adverse Events	Duloxetine 120 mg QD	203	12 (16%)	22 (17%)
	Duloxetine 60 mg QD	104	6 (16%)	8 (12%)
Lack of Efficacy	Duloxetine 120 mg QD	203	0	20 (16%)
	Duloxetine 60 mg QD	104	4 (11%)	4 (6%)
Subject Decision	Duloxetine 120 mg QD	203	4 (5%)	10 (8%)
	Duloxetine 60 mg QD	104	1 (3%)	1 (1%)
Loss to Follow-Up	Duloxetine 120 mg QD	203	1 (1%)	2 (2%)
	Duloxetine 60 mg QD	104	1 (3%)	1 (1%)
Others	Duloxetine 120 mg QD	203	3 (4%)	5 (4%)
	Duloxetine 60 mg QD	104	2 (5%)	5 (7%)

In the responder analysis from the start of the double-blind phase to the end of the study, the Applicant used LOCF to impute missing data. In the re-analyses, I used a more conservative approach to impute missing data, namely: BOCF and LOCF/BOCF.

Of the 37 patients who responded at Week 8 and who remained in the 60 mg QD group, 14 patients (38%) remained responders at Week 52 using the same criteria of response (i.e. at least 50% improvement in pain from baseline, BOCF). Of the 75 patients who responded at Week 8 and who titrated to 120 mg QD, 34 patients (45%) remained responders at Week 52. In contrast, only 20% of patients who did not respond at Week 8 and were titrated to 120 mg QD responded at Week 52. Thus, increasing the dose did not improve their pain response.

Table 30: Responder Analysis ($\geq 50\%$ reduction from Week 0) of Brief Pain Inventory Average Pain Score at Endpoint: Study HMEH

Study	Treatment Group	Responder at end of Week 8	No. (%) responders at Week 52	Non-responder at end of Week 8	No. (%) responders at Week 52
LOCF	Duloxetine 120 mg QD	75	43 (57%)	128	37 (29%)
	Duloxetine 60 mg QD	37	23 (62%)	67	19 (28%)
BOCF	Duloxetine 120 mg QD	75	34 (45%)	128	26 (20%)
	Duloxetine 60 mg QD	37	14 (38%)	67	17 (25%)
LOCF/BOCF	Duloxetine 120 mg QD	75	37 (49%)	128	32 (25%)
	Duloxetine 60 mg QD	37	19 (51%)	67	19 (28%)

Under BOCF, of the 23 non-responders at 52 weeks in the duloxetine 60 mg QD group, 9 patients completed the study but did not achieve the level of response seen at Week 8 (i.e. $\geq 50\%$ improvement in pain). Moreover, four of the 23 patients discontinued due to lack of efficacy (Table 31). Of the 41 non-responders at 52 weeks in the duloxetine 120 mg QD group, 21 patients completed the study but did not achieve the level of response seen at Week 8 (i.e. $\geq 50\%$ improvement in pain).

Table 31: Lack of Efficacy at Week 52 (using 50% improvement in pain from baseline to define responder) – Study HMEH

	DLX 60 N =104	DLX 120 N =203
Responder at Week 8	37/104 (36%)	75/203 (37%)
Responders who Completed the study Week 52	23/37 (62%)	55/75 (73%)
Responders at Week 52	14/37 (38%)	34/75 (45%)

To be consistent with the definition of responder used in Study HMCJ (see Table 25 to Table 26), we redefined the definition of responders to include patients who had at least 30% improvement in pain at Week 8 and at the end of the study (Week 52). In this new definition, a total of 170 patients responded at the end of Week 8 (56 in the duloxetine 60 mg QD group and 105 in the duloxetine 120 mg QD group). Table 32 summarizes the proportion of responders and non-responders at the end of Week 8 who remained or became responders at the end of 52 weeks. Of the 56 patients who responded at Week 8 and who remained in the 60 mg QD group, 26 patients (46%) remained responders at Week 52 using the same criteria of response (i.e. at least 30% improvement in pain from baseline, BOCF). Of the 105 patients who responded at Week 8 and who titrated to 120 mg QD, 49 patients (47%) remained responders at Week 52. In contrast, only 27% of

patients in the duloxetine 60 mg QD and 26% of patients in the duloxetine 120 mg QD who did not respond at the end of Week 8, responded at Week 52. Thus, increasing the dose did not improve their pain response.

Table 32: Responder Analysis ($\geq 30\%$ reduction from Week 0) of Brief Pain Inventory Average Pain Score at Endpoint: Study HMEH

Study	Treatment Group	Responder at end of Week 8	No. (%) responders at Week 52	Non-responder at end of Week 8	No. (%) responders at Week 52
LOCF	Duloxetine 120 mg QD	105	65 (62%)	98	36 (37%)
	Duloxetine 60 mg QD	56	37 (66%)	48	16 (33%)
BOCF	Duloxetine 120 mg QD	105	49 (47%)	98	25 (26%)
	Duloxetine 60 mg QD	56	26 (46%)	48	13 (27%)
LOCF/BOCF	Duloxetine 120 mg QD	105	55 (52%)	98	32 (33%)
	Duloxetine 60 mg QD	56	32 (57%)	48	15 (31%)

Under BOCF, of the 30 non-responders at 52 weeks in the duloxetine 60 mg QD group, 11 patients completed the study but did not achieve the level of response seen at Week 8 (i.e. $>30\%$ improvement in pain). Moreover, four of the 30 non-responders discontinued due to lack of efficacy (Table 33). Of the 56 non-responders at 52 weeks in the duloxetine 120 mg QD group, 26 patients completed the study but did not achieve the level of response seen at Week 8. Moreover, one of the 56 non-responders discontinued due to lack of efficacy.

Table 33: Lack of Efficacy at Week 52 (using 30% improvement in pain from baseline as definition of responder) – Study HMEH

	DLX 60 N =104	DLX 120 N =203
Responder at Week 8	56/104 (54%)	105/203 (52%)
Responders who Completed the study Week 52	37/56 (66%)	75/105 (71%)
Responders at Week 52	26/56 (46%)	49/105 (47%)

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3.1.3.3 Efficacy Conclusion

In Study HMBO, there is not enough evidence to demonstrate that duloxetine 60 mg BID is superior to placebo in the improvement of pain, in the improvement in patient global score or in the two co-primary endpoints (FIQ Total score and FIQ pain severity score).

In Study HMCA, after three months of treatment, there is strong evidence that duloxetine 60 mg BID is associated with significant improvement in pain over placebo treatment. This was supported by the result when different imputation strategies for missing data were applied to the data, as well as by the result of the continuous responder analyses.

There is also some evidence that duloxetine 60 mg QD is associated with improvement in pain over placebo after three months of treatment regardless of imputation strategy. Because the treatment difference was highly significant (based on unadjusted p-value), this treatment comparison may potentially survive when Bonferroni adjustment is applied.

Because of multiplicity concerns, there is not enough evidence to support treatment difference in patient global improvement between duloxetine 60 mg BID and placebo or between duloxetine 60 mg QD and placebo. Similarly, there was no evidence to support treatment difference in FIQ Total score.

Although there is evidence that after three months of treatment, duloxetine 60 mg BID and duloxetine 60 mg QD are superior over placebo in the improvement in pain, the treatment effect on these two dose groups (i.e. once a day (60 mg/day) regimen and twice a day (120 mg/day) regimen) were similar. According to the Applicant, prior study demonstrated efficacy using duloxetine 60 mg BID; therefore, in this study the 60 mg QD dose was tested to evaluate the dose response relationship. They claimed that duloxetine 60 mg QD could allow ease of use for patients and potentially improve patient drug compliance. Therefore, it is important to assess the risk on each dosing regimen and to evaluate the risks and benefits to determine which dosing regimen is more beneficial to patients.

In Study HMCJ, after three months of treatment, duloxetine 120 mg QD is associated with significant improvement in pain, as well as significant improvement in patient global improvement score over placebo treatment. Like in Study HMCA, these were supported by the results when different imputation strategies for missing data were applied to the data, as well as by the result of the continuous responder analyses on pain. Applying the pre-specified gatekeeper strategy, there is evidence that duloxetine 60 mg QD is also associated with improvement in pain, as well as improvement in patient global improvement score, over placebo treatment.

According to the Applicant, the purpose of the inclusion of duloxetine 20 mg QD was to establish duloxetine 60 mg QD as a minimum effective dose. Although this dose was not meant to be included in the analyses and the (adjusted) pairwise comparison test results were not significant, treatment effect on this dose is almost similar to duloxetine 60 mg QD and duloxetine 120 mg QD in both BPI average pain score and PGI-Improvement score. In fact, the effect of duloxetine 60 mg QD is almost the same as duloxetine 120 mg QD in both BPI average pain score and PGI-Improvement score as well. Therefore, it is difficult to establish that duloxetine 60 mg QD is the minimum effective dose even though duloxetine 20 mg QD is not significant.

The Applicant had a different view on this. They claimed that 60 mg per day is considered the minimum effective dose for the treatment of fibromyalgia. Their argument is described as follows:

A review of the statistically significant efficacy results by dose at the 3 month time point shows that 20 mg did not separate statistically from placebo on many of the efficacy endpoints.

It might be argued that due to the randomization scheme in Study HMCJ, the 20 mg arm had less power to detect statistically significant effects. However, at the 6-month time point, patients in the 20 mg QD dose arm who had their dose titrated to 60 mg QD at 3-months, demonstrated a 49.1% improvement in BPI average pain compared to that seen in the 20 mg QD group at the 3-month point, leading to statistically significant improvements on both coprimary endpoints. In the same timeframe (3 to 6 months) there was an observed minimal 8.1% and 8.9% diminishment in treatment benefit for the 60 mg QD group and 120 mg QD groups, respectively. Thus, despite the lower sample size in this arm, the lack of effect at 3 months was transformed into a significant treatment benefit at 6 months following a dose increase from 20 mg to 60 mg QD, further supporting that a 20 mg dose does not provide optimal pain reduction. On the basis of these observations, 60 mg per day is considered the minimum effective dose for the treatment of fibromyalgia.

In study HMCJ, there was not enough evidence to demonstrate that duloxetine-treated patients are associated with significant improvement in pain at six months, when an imputation strategy that correctly assigns a bad score to dropouts was applied.

Furthermore, applying the method they proposed to examine persistence of effect in Study HMEH, the result was not significant at 52 weeks. When applying an imputation strategy that correctly assigns a bad score to dropouts, less than 50% of those who responded at Week 8 achieve the same level of response at the end of the one-year double-blind phase (i.e. $\geq 50\%$ improvement in pain). Of the approximately 60% who responded at Week 8 but did not respond at Week 52, approximately 25% completed the study but did not achieve the level of response seen at Week 8 (i.e. $\geq 50\%$ improvement in pain). Another important finding from this analysis is that only 20% of the patients who did not respond at Week 8 and were given 120 mg QD during double-blind phase responded at the end of the study. This implies that increasing the dose did not improve their pain response.

3.2 EVALUATION OF SAFETY

Dr. Ricardo Dent reviewed the safety of duloxetine in detail. The reader is referred to Dr. Dent's review for information regarding the adverse event profile.

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4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

Subgroup analyses were conducted separately for each of the two studies (Study HMCA and Study HMCJ), according to the primary endpoint (i.e. pain), as well as to the patient global improvement score. A descriptive summary of the primary endpoint by each subgroup is presented. An ANCOVA analysis adjusting for the interaction term was conducted to explore the relationship between the subgroups and treatment.

4.1 SEX, RACE AND AGE

A descriptive summary of the primary endpoint by age, race, and gender is presented in Table 34 through Table 36 and the patient global improvement score by age, race, and gender is presented in Table 37 through Table 39.

In Study HMCJ, of the 520 randomized in the double-blind phase, 492 (95%) were female, 474 (91%) were between 18 to 64 years of age, and 438 (84%) were white.

Because of the small numbers of males (in HMCJ), of patients over 65 years of age, and of nonwhites in both studies, any claims of parity in terms of patient's sex, age or race are essentially unsupported.

Nonetheless, there were no remarkable effects of gender, or race according to the primary endpoint analysis using either the BOCF or LOCF/BOCF imputation strategy. There is some indication that there may possibly be an effect of age, but because nearly all subjects in these studies were white, under 65 years old, and female, it is impossible to distinguish the possible treatment effects for the subgroups of race, age or sex.

In terms of patient global improvement score, there were also no remarkable effects of age, or gender using either the LOCF or WOCF imputation strategy. There is some indication that there may possibly be an effect of race, but because nearly all subjects in each study were white, under 65 years old, and female, it is impossible to distinguish the possible treatment effects for the subgroups of race, age or sex.

Table 34: Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Gender: F1J-MC-HMCJ

Treatment Group	N	Women		N	Men	
		Baseline	Endpoint Mean		Baseline	Endpoint Mean
BOCF						
Placebo	137	6.6	5.5	7	6.1	5.6
Duloxetine 20 mg QD	76	6.8	5.1	3	6.3	6.3
Duloxetine 60 mg QD	136	6.5	5.0	14	6.2	4.9
Duloxetine 120 mg QD	143	6.4	4.8	4	7.0	4.5
LOCF/BOCF						
Placebo	137	6.6	5.4	7	6.1	5.7
Duloxetine 20 mg QD	76	6.8	4.8	3	6.3	6.3
Duloxetine 60 mg QD	136	6.5	4.9	14	6.2	4.3
Duloxetine 120 mg QD	143	6.4	4.7	4	7.0	4.5

Table 35: Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Race: F1J-MC-HMCA and F1J-MC-HMCJ

Study	Treatment Group	N	White		N	Non-white	
			Baseline	Endpoint Mean		Baseline	Endpoint Mean
BOCF							
HMCA	Placebo	107	6.4	5.5	13	7.8	6.2
	Duloxetine 60 mg QD	106	6.3	4.2	12	7.0	5.8
	Duloxetine 60 mg BID	104	6.2	4.3	12	7.8	6.8
HMCJ	Placebo	119	6.3	5.3	25	7.9	6.4
	Duloxetine 20 mg QD	66	6.6	5.0	13	7.8	5.8
	Duloxetine 60 mg QD	127	6.4	4.8	23	7.0	6.0
	Duloxetine 120 mg QD	126	6.3	4.6	21	7.1	5.9
LOCF/BOCF							
HMCA	Placebo	107	6.4	5.3	13	7.8	6.2
	Duloxetine 60 mg QD	106	6.3	4.1	12	7.0	5.7
	Duloxetine 60 mg BID	104	6.2	4.0	12	7.8	6.3
HMCJ	Placebo	119	6.3	5.2	25	7.9	6.4
	Duloxetine 20 mg QD	66	6.6	4.7	13	7.8	5.5
	Duloxetine 60 mg QD	127	6.4	4.6	23	7.0	5.7
	Duloxetine 120 mg QD	126	6.3	4.6	21	7.1	5.7

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Table 36: Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Age: F1J-MC-HMCA and F1J-MC-HMCJ

Study	Treatment Group	N	Age < 65		Age ≥ 65		
			Baseline	Endpoint Mean	N	Baseline	Endpoint Mean
BOCF							
HMCA	Placebo	109	6.6	5.7	11	5.5	3.6
	Duloxetine 60 mg QD	113	6.4	4.4	5	6.6	1.6
	Duloxetine 60 mg BID	105	6.3	4.4	11	6.6	5.7
HMCJ	Placebo	136	6.6	5.4	8	6.9	6.3
	Duloxetine 20 mg QD	70	6.8	5.3	9	6.2	4.2
	Duloxetine 60 mg QD	135	6.5	4.9	15	6.3	5.2
	Duloxetine 120 mg QD	133	6.3	4.7	14	6.9	6.1
LOCF/BOCF							
HMCA	Placebo	109	6.6	5.6	11	5.5	3.6
	Duloxetine 60 mg QD	113	6.4	4.3	5	6.6	1.6
	Duloxetine 60 mg BID	105	6.3	4.1	11	6.6	6.0
HMCJ	Placebo	136	6.6	5.3	8	6.9	6.4
	Duloxetine 20 mg QD	70	6.8	4.9	9	6.2	4.3
	Duloxetine 60 mg QD	135	6.5	4.8	15	6.3	4.9
	Duloxetine 120 mg QD	133	6.3	4.6	14	6.9	6.0

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Table 37: PGI-Improvement at Endpoint by Gender: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCJ

Study	Treatment Group	Women		Men	
		N	Endpoint Mean	N	Endpoint Mean
LOCF					
HMCJ	Placebo	138	3.0	4	2.5
	Duloxetine 20 mg QD	75	2.9	2	4.0
	Duloxetine 60 mg QD	130	3.1	13	3.2
	Duloxetine 120 mg QD	132	3.5	7	3.7
WOCF					
HMCJ	Placebo	138	3.1	4	2.5
	Duloxetine 20 mg QD	75	3.1	2	4.5
	Duloxetine 60 mg QD	129	3.2	13	3.3
	Duloxetine 120 mg QD	132	3.7	6	3.8

Table 38: PGI-Improvement at Endpoint by Race: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ

Study	Treatment Group	White		Non-White	
		N	Endpoint Mean	N	Endpoint Mean
LOCF					
HMCA	Placebo	100	3.7	11	3.5
	Duloxetine 60 mg QD	103	3.1	11	3.6
	Duloxetine 60 mg BID	99	3.0	12	3.3
HMCJ	Placebo	121	2.9	21	3.3
	Duloxetine 20 mg QD	64	2.9	13	3.2
	Duloxetine 60 mg QD	120	3.1	23	3.3
	Duloxetine 120 mg QD	115	3.6	24	2.7
WOCF					
HMCA	Placebo	100	3.8	11	3.5
	Duloxetine 60 mg QD	103	3.1	11	3.6
	Duloxetine 60 mg BID	99	3.1	12	3.4
HMCJ	Placebo	121	3.1	21	3.4
	Duloxetine 20 mg QD	64	3.1	13	3.3
	Duloxetine 60 mg QD	119	3.2	23	3.4
	Duloxetine 120 mg QD	114	3.8	24	3.0

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Table 39: PGI-Improvement at Endpoint by Age: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ

Study	Treatment Group	Age < 65		Age ≥ 65	
		N	Endpoint Mean	N	Endpoint Mean
LOCF					
HMCA	Placebo	100	3.8	11	2.7
	Duloxetine 60 mg QD	109	3.2	5	1.6
	Duloxetine 60 mg BID	100	3.0	11	3.7
HMCJ	Placebo	129	2.9	13	3.5
	Duloxetine 20 mg QD	68	2.9	9	3.2
	Duloxetine 60 mg QD	128	3.1	15	3.6
	Duloxetine 120 mg QD	131	3.5	8	3.8
WOCF					
HMCA	Placebo	100	3.9	11	2.7
	Duloxetine 60 mg QD	109	3.2	5	1.6
	Duloxetine 60 mg BID	100	3.0	11	3.7
HMCJ	Placebo	129	3.1	13	3.7
	Duloxetine 20 mg QD	68	3.1	9	3.2
	Duloxetine 60 mg QD	127	3.2	15	3.7
	Duloxetine 120 mg QD	130	3.6	8	4.4

4.2 OTHER SUBGROUPS AND SPECIAL POPULATIONS

Presence of major depressive disorder was also examined to determine whether it has an impact on patient response

Like the other subgroups studied, there were no remarkable effects of MDD status according to the pain endpoint analysis, as well as patient global improvement score endpoint analysis using different imputation strategies. Because each study had limited number of patients with MDD at enrollment (Study HMCA 74%; Study HMCJ 76%), it is difficult to distinguish the possible treatment effects for the subgroups of MDD status. Nonetheless, it appears that both patients with MDD and without MDD showed favorable effect (i.e. improvement) in their endpoint mean pain scores (Table 41). However, the magnitude of change is greater for patients with MDD. Accordingly, more patients with MDD meet responder criteria based on magnitude of change from baseline. In addition, patients with MDD were less likely to respond to placebo treatment. Therefore, the comparison between treatment and placebo groups appears to provide evidence of a greater effect of duloxetine in patients with MDD than in patients without (Table 42, Figure 15 and Figure 16).

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Table 40: Endpoint Mean Brief Pain Inventory Average Pain Score: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Major Depressive Disorder Status: F1J-MC-HMCA and F1J-MC-HMCJ

Study	Treatment Group	N	No MDD		N	With MDD	
			Baseline	Endpoint Mean		Baseline	Endpoint Mean
			BOCF				
HMCA	Placebo	88	6.3	5.2	32	7.2	6.4
	Duloxetine 60 mg QD	89	6.3	4.3	29	6.7	4.3
	Duloxetine 60 mg BID	84	6.2	4.5	32	6.8	4.6
HMCJ	Placebo	109	6.4	5.3	35	7.0	6.0
	Duloxetine 20 mg QD	57	6.6	5.1	22	7.2	5.4
	Duloxetine 60 mg QD	115	6.4	4.9	35	6.7	5.1
	Duloxetine 120 mg QD	113	6.3	4.7	34	6.6	5.1
			LOCF/BOCF				
HMCA	Placebo	88	6.3	5.1	32	7.2	6.2
	Duloxetine 60 mg QD	89	6.3	4.3	29	6.7	4.1
	Duloxetine 60 mg BID	84	6.2	4.4	32	6.8	4.0
HMCJ	Placebo	109	6.4	5.2	35	7.0	6.0
	Duloxetine 20 mg QD	57	6.6	4.8	22	7.2	5.0
	Duloxetine 60 mg QD	115	6.4	4.8	35	6.7	4.9
	Duloxetine 120 mg QD	113	6.3	4.7	34	6.6	4.9

Table 41: Endpoint Mean Pain Score Analysis: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Major Depressive Disorder Status: F1J-MC-HMCA and F1J-MC-HMCJ

Study	Treatment Group	N	No MDD		N	With MDD	
			Baseline	LSMean Change *		Baseline	LSMean change *
			BOCF				
HMCA	Placebo	88	6.3	-1.0	32	7.2	-0.7
	Duloxetine 60 mg QD	89	6.3	-1.9	29	6.7	-2.8
	Duloxetine 60 mg BID	84	6.2	-1.6	32	6.8	-2.5
HMCJ	Placebo	109	6.4	-1.1	35	7.0	-1.4
	Duloxetine 20 mg QD	57	6.6	-1.4	22	7.2	-2.0
	Duloxetine 60 mg QD	115	6.4	-1.5	35	6.7	-2.1
	Duloxetine 120 mg QD	113	6.3	-1.6	34	6.6	-2.1
			LOCF/BOCF				
HMCA	Placebo	88	6.3	-1.1	32	7.2	-0.9
	Duloxetine 60 mg QD	89	6.3	-1.9	29	6.7	-3.0
	Duloxetine 60 mg BID	84	6.2	-1.8	32	6.8	-3.1
HMCJ	Placebo	109	6.4	-1.2	35	7.0	-1.3
	Duloxetine 20 mg QD	57	6.6	-1.6	22	7.2	-2.5
	Duloxetine 60 mg QD	115	6.4	-1.6	35	6.7	-2.4
	Duloxetine 120 mg QD	113	6.3	-1.6	34	6.6	-2.2

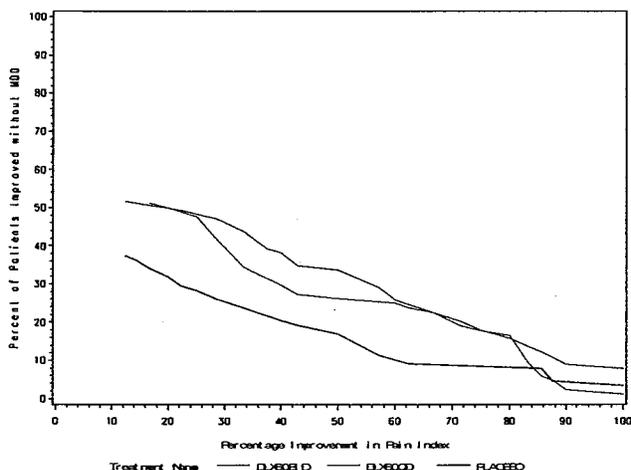
*ANCOVA model including treatment and pooled center as fixed effects, and baseline pain score as covariate

Table 42: Responder Analysis of Brief Pain Inventory Average Pain Score at Endpoint: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: FIJ-MC-HMCA and FIJ-MC-HMCJ

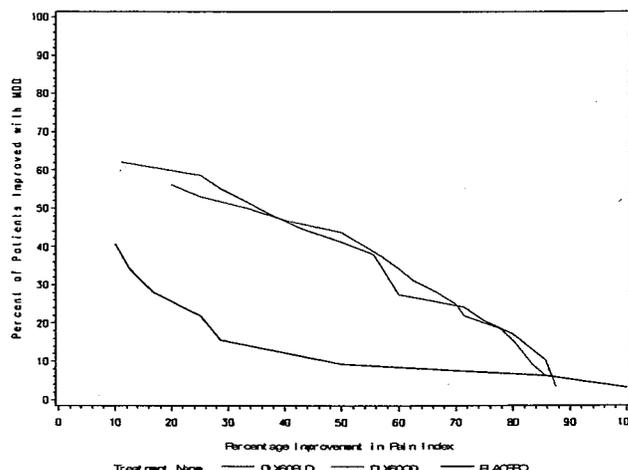
Study	Treatment Group	N	≥ 30% Improvement in Pain n(%)	≥ 50% Improvement in Pain n(%)	
HMCA	Without MDD	Placebo	88	21 (24%)	15 (17%)
		Duloxetine 60 mg QD	89	39 (44%)	30 (34%)
		Duloxetine 60 mg BID	84	29 (35%)	22 (26%)
	With MDD	Placebo	32	3 (9%)	3 (9%)
		Duloxetine 60 mg QD	29	15 (52%)	12 (41%)
		Duloxetine 60 mg BID	32	16 (50%)	14 (44%)
HMCJ	Without MDD	Placebo	109	30 (28%)	22 (20%)
		Duloxetine 20 mg QD	57	19 (33%)	14 (25%)
		Duloxetine 60 mg QD	115	41 (36%)	33 (29%)
		Duloxetine 120 mg QD	113	43 (38%)	34 (30%)
	With MDD	Placebo	35	7 (20%)	4 (11%)
		Duloxetine 20 mg QD	22	9 (41%)	8 (36%)
		Duloxetine 60 mg QD	35	15 (43%)	9 (26%)
		Duloxetine 120 mg QD	34	14 (41%)	10 (29%)

Figure 15: Responder Profiles for HMCA

Without MDD



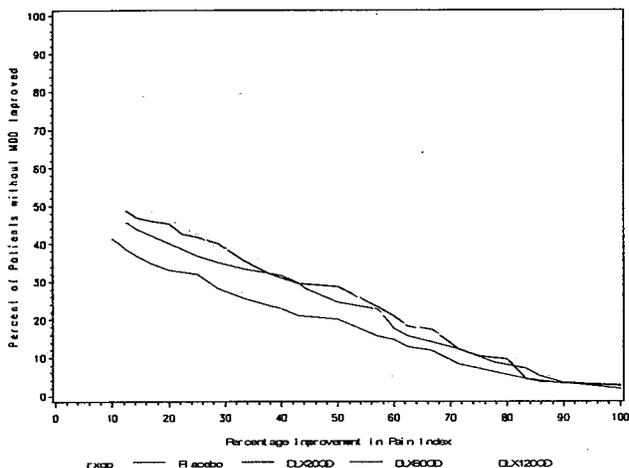
With MDD



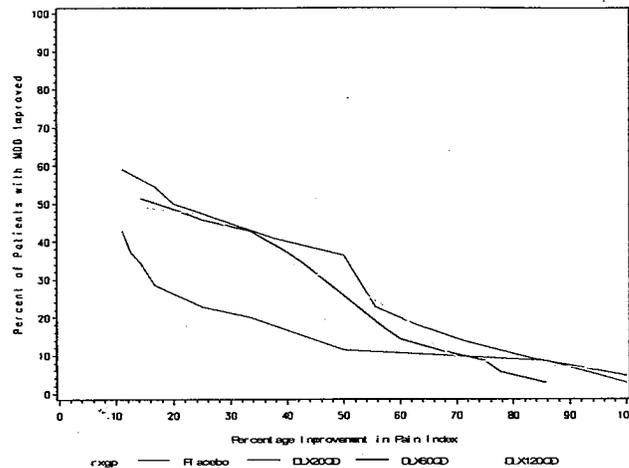
Red: DLX60BID, Blue: DLX60QD, Black: PLACEBO

Figure 16: Responder Profiles for HMCJ

Without MDD



With MDD



Red: Placebo, Blue: DLX20QD, Black: DLX60QD, Yellow: DLX120QD

Table 43: PGI-Improvement at Endpoint by Major Depressive Disorder Status: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies: F1J-MC-HMCA and F1J-MC-HMCJ

Study	Treatment Group	Without MDD		With MDD	
		N	Endpoint Mean	N	Endpoint Mean
		LOCF			
HMCA	Placebo	28	3.9	83	3.6
	Duloxetine 60 mg QD	28	2.9	86	3.2
	Duloxetine 60 mg BID	30	2.6	81	3.2
HMCJ	Placebo	109	3.1	33	2.7
	Duloxetine 20 mg QD	55	3.0	22	2.9
	Duloxetine 60 mg QD	109	3.2	34	2.9
	Duloxetine 120 mg QD	105	3.5	34	3.5
		WOCF			
HMCA	Placebo	28	4.0	83	3.7
	Duloxetine 60 mg QD	28	3.0	86	3.2
	Duloxetine 60 mg BID	30	2.7	81	3.3
HMCJ	Placebo	109	3.2	33	2.8
	Duloxetine 20 mg QD	55	3.2	22	3.0
	Duloxetine 60 mg QD	109	3.3	33	3.0
	Duloxetine 120 mg QD	104	3.7	34	3.6

As mentioned, the Applicant _____ The following was taken

 from the Clinical Overview Section:

As is typical of fibromyalgia trials, approximately 25% of patients entered met criteria for MDD based on the Mini Neuropsychiatric Interview. Although the trials were not powered to demonstrate statistically significant changes in severity of depression based on 17-item Hamilton Depression Rating Scale (HAM-D17) scores, clinically significant improvements were seen in duloxetine 60 and 120 mg treated patients, as compared with placebo-treated patients (difference in LSMeans changes ranging from -1.2 to -3.6). The average baseline HAM-D17 scores ranged from 15 to 16 which correspond to mild depression. Clinically significant changes were seen despite the relatively low baseline HAM-D17 scores (compared to baseline HAM-D17 scores of 17 required for depression trials) which left little room for improvement.

The Applicant did not provide any explanation as to what “clinically significant changes” means. In addition, they did not provide any Tables or Figures or analysis _____. Although the average HAM-D17 total scores for patients with MDD ranged from 15 to 16 at baseline in Study HMCA, the range of HAM-D17 total scores among these patients with MDD are between 2 to 32 at baseline. Thus, some patients in fact had severe depression (HAM-D17 total score ≥ 25)¹ at baseline. Likewise in Study HMCJ, the baseline HAM-D17 total scores for patients with MDD ranged from 3 to 28.

Applying LOCF to missing data, the results for the endpoint analyses are summarized in Table 44. It appears that both patients with MDD and without MDD showed favorable effect (i.e. improvement) in their endpoint HAM-D17 Total Score. Like the mean pain score analysis, the magnitude of change is greater for patients with MDD since they have higher HAM-D17 total score at baseline compared to patients without MDD. The low baseline HAM-D17 total score among patients without MDD left little room for improvement. Therefore, the comparison between treatment and placebo groups appears to provide some evidence of a greater effect of duloxetine in patients with MDD than in patients without. Similar results were found when BOCF or LOCF/BOCF imputation strategies were applied.

Table 44: Endpoint HAM-D17 Total Score Analysis: All Randomized Patients in the 3-Month Therapy Phase Placebo-Controlled Studies by Major Depressive Disorder Status: F1J-MC-HMCA and F1J-MC-HMCJ

Study	Treatment Group	N	Without MDD		N	With MDD	
			Baseline mean (range)	LSMean Change *		Baseline mean (range)	LSMean change *
HMCA	Placebo	88	9.5 (1 – 23)	-1.3	32	16.4 (4 – 26)	-3.9
	Duloxetine 60 mg QD	89	9.6 (2 – 25)	-3.0	29	16.0 (2 – 32)	-6.1
	Duloxetine 60 mg BID	84	10.1 (1 – 23)	-1.9	32	15.4 (4 – 26)	-6.4
HMCJ	Placebo	109	9.1 (0 – 23)	-1.3	35	15.3 (1 – 24)	-4.8
	Duloxetine 20 mg QD	57	8.9 (0 – 22)	-1.7	22	15.1 (6 – 23)	-6.0
	Duloxetine 60 mg QD	115	8.2 (0 – 21)	-2.7	35	15.4 (3 – 28)	-6.6
	Duloxetine 120 mg QD	113	8.1 (0 – 23)	-2.0	34	16.3 (9 – 24)	-7.8

*ANCOVA model including treatment and pooled center as fixed effects, and baseline HAM-D17 total score as covariate

¹ Shelton R.C, et al. Evidence for the efficacy of duloxetine in treating mild, moderate, and severe depression. *Int. Clin. Psychopharmacol.* 2007 Nov;22(6):348-55.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The Applicant conducted three Phase 3 trials, Study HMCA, Study HMCJ, and Study HMEF, as well as one Phase 2 trial (Study HMBO) and a long-term safety trial (Study HMEH) to support the indication of for the of fibromyalgia for duloxetine HCl. The primary focus of this review is on Study HMCA, Study HMCJ and Study HMEH.

Based on my review and analysis of the data, there were several statistical and non-statistical issues warranting further consideration. The issues were discussed in detail in Section 3.1.3.2. The statistical issues were:

1. Primary analysis population used
2. Choice of primary method of imputation (i.e. last observation carried forward)
3. Analyses of multiple secondary endpoints (i.e. multiplicity)

In all studies, the Applicant conducted the primary analyses on all randomized patients who had at least one post-baseline measure, which I termed as modified intent-to-treat population (mITT). This implies that any patients who only had baseline score are not included in the efficacy analyses. Although only a small proportion of patients were excluded in the analyses because of missing post-baseline measures, this post-randomization exclusion may still potentially introduce problems (i.e. bias) to the comparability of the treatment arms. In addition, patients who dropped out prior to the first post-baseline are informative (i.e. their missingness is informative as they may not have even been able to tolerate the treatment for a short time). Therefore, re-analyses of data using all randomized patients were performed. The results from the analyses using all randomized patients were not different from the results generated using the modified ITT population.

The second issue to be considered is the appropriateness of the primary method of imputation (i.e. LOCF). The Division of Anesthesia, Analgesia, and Rheumatology Products does not support the LOCF approach in settings where treatment-related dropouts due to adverse events may potentially be assigned good scores.

Lastly, the Applicant failed to adjust for multiplicity when comparing different dose groups (i.e. Study HMCA) or when testing secondary endpoints. The Applicant stated that the purpose of collecting several secondary efficacy outcomes was to confirm the findings of the primary outcome and was not intended to draw conclusions from these secondary efficacy measures. Therefore, they did not have any plan of making adjustments for multiplicity.

Because of the multitude of secondary endpoints (including different dose and outcome measures) they proposed to examine in the protocol, there will be an increased probability of falsely declaring some dose of the treatment to be effective or one treatment to be superior over placebo in some endpoints, particularly when analyses of multiple endpoints were not adjusted for multiplicity. Either multiplicity adjustments should have been applied to these endpoints in order to maintain an overall type 1 error rate, or present the results descriptively without p-values. Nonetheless, it is difficult to draw conclusions from the analyses of the secondary endpoints as well as to make labeling claims from a statistical point of view because of the multitude of pairwise comparisons being tested.

After re-analyses of all the data in Study HMCA and Study HMCJ, and accounting for all the statistical issues mentioned, the following are the key findings:

1. In Study HMCA,
 - a. There is strong evidence that duloxetine 60 mg BID is associated with significant improvement in pain over placebo treatment. This was supported by the results when different imputation strategies were applied to the data, as well as by the results of the continuous responder analyses.
 - b. There is also some evidence that duloxetine 60 mg QD is associated with improvement in pain over placebo after three months of treatment regardless of imputation strategy.
 - c. Because of multiplicity concerns, there is not enough evidence to support treatment difference in patient global improvement between duloxetine 60 mg BID and placebo or between duloxetine 60 mg QD and placebo. Similarly, there was no evidence to support treatment difference in FIQ Total score.
 - d. Although there is evidence that after three months of treatment, duloxetine 60 mg BID and duloxetine 60 mg QD are superior over placebo in the improvement in pain, treatment effect on these two dose groups (i.e. once a day (60 mg/day) regimen and twice a day (120 mg/day) regimen) were similar. In other words, the treatment benefit is almost identical, if not better in the 60 mg QD regimen. According to the Applicant, a prior study demonstrated efficacy using duloxetine 60 mg BID; therefore, in this study the 60 mg QD dose was tested to evaluate the dose response relationship. They claimed that duloxetine 60 mg QD could allow ease of use for patients and potentially improve patient drug compliance. Therefore, it is important to assess the risk on each dosing regimen to determine which dosing regimen is more beneficial to patients
 - e. Descriptive statistics suggest that FIQ total score and CGI-Severity are trending in the direction similar to the primary endpoint. However, there is not enough evidence to show treatment difference between any of the duloxetine groups and placebo in the improvement from these outcome measures.
 - f. There were no remarkable effects of MDD status according to the pain endpoint analysis, as well as patient global improvement score endpoint analysis using different imputation strategies. Because nearly all subjects (74%) had limited number of patients with MDD at enrollment, it is difficult to distinguish the possible treatment effects for the subgroups of MDD status. Nonetheless, it appears that both patients with MDD and without MDD showed favorable effect (i.e. improvement) in their endpoint mean pain scores. However, the magnitude of change is greater for patients with MDD.
2. In Study HMCJ,
 - a. After three months of treatment, duloxetine 120 mg QD is associated with significant improvement in pain, as well as significant improvement in patient global improvement score over placebo treatment. Like in Study HMCA, these findings were supported by the results when different imputation strategies were applied to the data, as well as by the result of the continuous responder analyses on pain.

- b. Applying the pre-specified gatekeeper strategy, there is evidence that duloxetine 60 mg QD is also associated with improvement in pain, as well as improvement in patient global improvement score, over placebo treatment.
 - c. According to the Applicant, the purpose of the inclusion of duloxetine 20 mg QD was to establish duloxetine 60 mg QD as a minimum effective dose. Although this dose was not meant to be included in the analyses and the (adjusted) pairwise comparison test results were not significant, the treatment effect on this dose is almost similar to duloxetine 60 mg QD and duloxetine 120 mg QD in both BPI average pain score and PGI-Improvement score. In fact, the effect of duloxetine 60 mg QD is almost the same as duloxetine 120 mg QD in both BPI average pain score and PGI-Improvement score as well. Therefore, it is difficult to establish that duloxetine 60 mg QD is the minimum effective dose even though duloxetine 20 mg QD is not significant.
 - d. There is not enough evidence to show that duloxetine-treated patients are associated with significant improvement in pain at six months, when imputation strategy that correctly assigns a bad score to dropouts was applied.
 - e. Like in Study HMCA, descriptive statistics suggest that FIQ total score and CGI-Severity are trending in the direction similar to the primary endpoint. However, there is not enough evidence to show treatment difference between any of the duloxetine groups and placebo in the improvement from these outcome measures.
 - f. There were no remarkable effects of MDD status according to the pain endpoint analysis, as well as patient global improvement score endpoint analysis using different imputation strategies. Because nearly all subjects (76%) had limited number of patients with MDD at enrollment, it is impossible to distinguish the possible treatment effects for the subgroups of MDD status. Nonetheless, it appears that both patients with MDD and without MDD showed favorable effect (i.e. improvement) in their endpoint mean pain scores. However, the magnitude of change is greater for patients with MDD.
3. In Study HMEH,
- a. Statistically significant persistence of effect was not demonstrated in patients who had at least 50 % reduction on the BPI average pain score at Week 8 of the open-label phase and had remained on duloxetine 60 mg in the 52-week double-blind phase. In fact, when applying an imputation strategy that correctly assigns a bad score to dropouts, less than 50% of those who responded at Week 8 achieved the same level of response at the end of the one-year double-blind phase (i.e. $\geq 50\%$ improvement in pain). Of the approximately 60% who responded at Week 8 but did not respond at Week 52, approximately 25% completed the study but did not achieve the level of response seen at Week 8 (i.e. $\geq 50\%$ improvement in pain).
 - b. Only 20% of the patients who did not respond at Week 8 (i.e. $\geq 50\%$ improvement in pain) and were given 120 mg QD during double-blind phase responded at the end of the study. This implies that increasing the dose did not improve their pain response.

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 duloxetine 60 mg BID, duloxetine 60 mg QD, and duloxetine 120 mg QD are efficacious in reducing pain at three months of therapy. There is also evidence that both duloxetine 60 mg QD and duloxetine 120 mg QD are associated with improvements in patient global score at three months of therapy. Because of multiplicity concerns, there is not enough evidence to support treatment difference in patient global improvement between duloxetine 60 mg BID and placebo, as well as no evidence to support treatment difference in FIQ Total score or CGI-Severity score in all duloxetine dose groups. However, descriptive statistics suggest that the patient global, FIQ total score and CGI-Severity are trending in the direction similar to the primary endpoint.

There is not enough evidence to show that duloxetine-treated patients are associated with significant improvement in pain at six months. Furthermore, there is no evidence that duloxetine continues to demonstrate a clinically meaningful improvement in the BPI average pain score through 12 months of treatment.

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Deliberative Process

7 APPENDIX

Appendix 1: Analysis for the Secondary Efficacy Variables

Study HMBO

Efficacy Variable	Derivation	Analysis
1. All postbaseline data in the acute therapy phase for: a. Tender Point Threshold b. FIQ items of Fatigue, Rest and Stiffness c. BPI: Severity and Interference d. CGI – Severity e. BDI-II total score f. BAI total score g. Number of tender points with low threshold	a. 18 individual tender points c. Each severity score, each interference score and the sum of the 7 interference items e. Sum of the 21 items f. Sum of the 21 items g. Number of tender points that had a threshold of ≤ 4 kg/cm ²	Variables 1a to 1g were analyzed by the repeated measures analysis as described in Section 9.7.1.11, Primary Efficacy Analysis.
2. All postbaseline data for PGI-Improvement		Variable 2 was analyzed primarily by a repeated measures analysis. The model was similar to the one described in the Section 9.7.1.11, Primary Efficacy Analysis, with the modifications that there were no baseline and baseline-by-treatment effects in the model. In addition, the observed scores at each postbaseline visit were analyzed by the ANOVA model as described in Section 9.7.1.1, General Considerations.
3. Change from baseline to endpoint: a. FIQ pain score b. Tender Point Threshold c. FIQ items of Fatigue, Rest and Stiffness d. BPI: Severity and Interference e. CGI – Severity f. BDI-II total score g. BAI total score h. # of tender points with low threshold	(refer to the definitions above)	Variables 3a to 3h were analyzed by the ANCOVA models as described in Section 9.7.1.1, General Considerations. Within-group change was analyzed by Student's t-test. The distribution of the residual was checked. When the assumptions of normality and homogeneity were violated, further approaches were taken to explore the nature of the distribution and to make appropriate statistical inferences.

Efficacy Variable	Derivation	Analysis
4. Categorical variable: a. Response rate for FIQ pain score b. Sustained response rate for 24-hour average pain severity	a. Response: at least 30% reduction from baseline to endpoint b. Sustained response: at least 30% reduction from baseline to endpoint; with a 30% reduction from baseline at an earlier than the last visit, and remained at least 20% reduction from baseline in every visit in between, if there were any intervening visits.	For variables 4a to 4b proportions were summarized by treatment group and were analyzed by Fisher's exact test.
5. Time-to-event variable: a. Time-to-sustained response b. Time-to-first 30% reduction in 24-hour average pain severity	a. For the sustained responders defined above, time = date of the visit that the earliest sustained response was observed – the randomization date; for the others, time = date of last visit - the randomization date. b. For the patients with a 30% reduction at a visit in the acute therapy phase, time = date of the visit that the earliest 30% reduction was observed – the randomization date; for the others, time = date of last visit - the randomization date.	For variables 5a and 5b, the Kaplan-Meier survival curves of time-to-event were calculated by treatment group. In the calculation, patients who did not have the event were considered as right-censored observation. The comparison of the survival curves among and between treatment groups was conducted by a log-rank test and the Wilcoxon test (using PROC LIFETEST).

Note: Baseline was defined as the last measurement taken at, or prior to, Visit 3; endpoint was defined as the last nonmissing measurement taken in the acute therapy phase; last visit was defined as the visit where the endpoint was assessed.

Abbreviations: CGI-Severity = Clinical Global Impressions of Severity; PGI-Improvement = Patient Global Impressions of Improvement; BDI-II = Beck Depression Inventory- Second Edition; BAI = Beck Anxiety Inventory; # = Number.

Study HMCA

Efficacy Variable	Derivation and Details	Analysis
1. AUC - pain relief	The relief score at a visit is defined as the BPI average pain score at the particular visit minus the baseline score. The AUC is the sum of each trapezoidal area circumscribed by the sides of relief scores at two consecutive nonmissing visits and the side of days between the two visits.	The AUC will be analyzed by the ANCOVA model as described in Section 9.7.1.1, General Considerations. The distribution of the residuals will be checked. When the assumptions of normality and homogeneity are violated, rank-transformed change scores will be analyzed using an ANOVA model with the terms of treatment and investigator.
2. Change from baseline to endpoint: a. FIQ total score b. BPI: Severity and Interference c. Mean Tender Point Threshold d. Number of tender points with low threshold e. CGI-Severity f. HAMD ₁₇ total score	a. See below for FIQ total derivation. b. BPI severity for worst pain, least pain, and pain right now. BPI interference for general activity, mood, walking normally, normal work, relations with others, sleep, and enjoyment of life. In addition, a mean interference score will be calculated from the seven interference questionnaires. c. Mean of 18 tender point thresholds. d. Number of tender points that have a threshold of ≤ 4.0 kg/cm ² . e. No derivations. f. Sum of 17 HAMD items.	Variables 2a to 2f will be analyzed by the ANCOVA models as described in Section 9.7.1.1, General Considerations. The distribution of the residuals will be checked for all the variables except for CGI-Severity and HAMD ₁₇ total scores, since their distributions have been shown to be normal in many previous clinical studies. When the assumptions of normality and homogeneity are violated, rank-transformed change scores will be analyzed using an ANOVA model with the terms of treatment and investigator.

(continued)

Efficacy Variable	Derivation and Details	Analysis
1. AUC - pain relief	The relief score at a visit is defined as the BPI average pain score at the particular visit minus the baseline score. The AUC is the sum of each trapezoidal area circumscribed by the sides of relief scores at two consecutive nonmissing visits and the side of days between the two visits.	The AUC will be analyzed by the ANCOVA model as described in Section 9.7.1.1, General Considerations. The distribution of the residuals will be checked. When the assumptions of normality and homogeneity are violated, rank-transformed change scores will be analyzed using an ANOVA model with the terms of treatment and investigator.
2. Change from baseline to endpoint: a. FIQ total score b. BPI: Severity and Interference c. Mean Tender Point Threshold d. Number of tender points with low threshold e. CGI-Severity f. HAMD ₁₇ total score	a. See below for FIQ total derivation. b. BPI severity for worst pain, least pain, and pain right now. BPI interference for general activity, mood, walking normally, normal work, relations with others, sleep, and enjoyment of life. In addition, a mean interference score will be calculated from the seven interference questionnaires. c. Mean of 18 tender point thresholds. d. Number of tender points that have a threshold of ≤ 4.0 kg/cm ² . e. No derivations. f. Sum of 17 HAMD items.	Variables 2a to 2f will be analyzed by the ANCOVA models as described in Section 9.7.1.1, General Considerations. The distribution of the residuals will be checked for all the variables except for CGI-Severity and HAMD ₁₇ total scores, since their distributions have been shown to be normal in many previous clinical studies. When the assumptions of normality and homogeneity are violated, rank-transformed change scores will be analyzed using an ANOVA model with the terms of treatment and investigator.

(continued)

<p>3. All baseline and postbaseline data during acute therapy for:</p> <p>a. FIQ total score</p> <p>b. BPI: Severity and Interference</p> <p>c. Mean Tender Point Threshold</p> <p>d. Number of tender points with low threshold</p> <p>e. CGI-Severity</p> <p>f. HAMD₁₇ total score</p>	<p>a. See the following for FIQ total derivation.</p> <p>b. BPI severity for worst pain, least pain, and pain right now. BPI interference for general activity, mood, walking normally, normal work, relations with others, sleep, and enjoyment of life. In addition, a mean interference score will be calculated from the seven interference questionnaires.</p> <p>c. Mean of 18 tender point thresholds.</p> <p>d. Number of tender points that have a threshold of ≤ 4.0 kg/cm².</p> <p>e. No derivations.</p> <p>f. Sum of 17 HAMD items.</p>	<p>Variables 3a to 3f will be analyzed by a repeated measures analysis. The model details will be described in text beneath the table.</p>
<p>4. All postbaseline data for PGI-Improvement</p>		<p>The observed scores at each postbaseline visit as well as the last nonmissing score (defined as endpoint) will be analyzed by the ANOVA model as described in Section 9.7.1.1, General Considerations. In addition, the data will also be analyzed by a repeated measures analysis. The model will be similar to the one used for the variables in the above group, with the modifications that there are no baseline or baseline-by-treatment effects in the model.</p>

(continued)

<p>3. All baseline and postbaseline data during acute therapy for:</p> <p>a. FIQ total score</p> <p>b. BPI: Severity and Interference</p> <p>c. Mean Tender Point Threshold</p> <p>d. Number of tender points with low threshold</p> <p>e. CGI-Severity</p> <p>f. HAMD₁₇ total score</p>	<p>a. See the following for FIQ total derivation.</p> <p>b. BPI severity for worst pain, least pain, and pain right now. BPI interference for general activity, mood, walking normally, normal work, relations with others, sleep, and enjoyment of life. In addition, a mean interference score will be calculated from the seven interference questionnaires.</p> <p>c. Mean of 18 tender point thresholds.</p> <p>d. Number of tender points that have a threshold of ≤ 4.0 kg/cm².</p> <p>e. No derivations.</p> <p>f. Sum of 17 HAMD items.</p>	<p>Variables 3a to 3f will be analyzed by a repeated measures analysis. The model details will be described in text beneath the table.</p>
<p>4. All postbaseline data for PGI-Improvement</p>		<p>The observed scores at each postbaseline visit as well as the last nonmissing score (defined as endpoint) will be analyzed by the ANOVA model as described in Section 9.7.1.1, General Considerations. In addition, the data will also be analyzed by a repeated measures analysis. The model will be similar to the one used for the variables in the above group, with the modifications that there are no baseline or baseline-by-treatment effects in the model.</p>

(continued)

<p>5. Categorical variable: a. Response rate for BPI average pain score b. Sustained response rate for BPI average pain score</p>	<p>a. Response: at least 30% reduction from baseline to endpoint. b. Sustained response: at least 30% reduction from baseline to endpoint; with a 30% reduction from baseline at a visit earlier than the last visit, and reduction from baseline remains at least 20% in every visit in between, if there are any intervening visits.</p>	<p>For variables 5a and 5b, proportions will be summarized by treatment group and will be analyzed by Fisher's exact test.</p>
<p>6. Time-to-event variable a. Time-to-first 30% reduction in BPI average pain score b. Time-to-sustained response</p>	<p>a. For patients with a 30% reduction at a visit in the acute therapy phase, time=date of the visit that the earliest 30% reduction is observed - the randomization date; for others, time=date of last visit - the randomization date. b. For the sustained responder defined above, time=date of the visit which is the earlier visit from which sustained response is observed minus the randomization date; for others, time=date of last visit minus the randomization date.</p>	<p>For variables 6a and 6b, the Kaplan-Meier survival curves of time-to-event will be calculated by treatment group. In the calculation, patients who do not have the event will be considered as right-censored observations. The comparison of the survival curves between treatment groups will be conducted by a log-rank test and the Wilcoxon test (using PROC LIFETEST).</p>

abbreviations: ANCOVA = analysis of covariance; AUC = American College of Rheumatology; BPI = Brief Pain Inventory; CGI-Severity = Clinical Global Impressions of Severity; FIQ = Fibromyalgia Impact Questionnaire; PGI-Improvement = Patient Global Impressions of Improvement; HAMD17 = 17-item Hamilton Depression Rating Scale.

Study HMCJ

Efficacy Variable	Derivation and Details	Analysis
<p>1. Area under the curve of pain relief (AUC)</p>	<p>The relief score at a visit is defined as the BPI average pain score at the particular visit minus the baseline score. The AUC is the sum of each trapezoidal area circumscribed by the relief scores at 2 consecutive nonmissing visits and the days between the 2 visits.</p>	<p>The AUC will be analyzed by the ANCOVA model as described in Section 9.7.1.1 with baseline BPI average pain as a covariate. The distribution of the residuals will be checked. When the assumptions of normality and homogeneity are violated, rank-transformed change scores will be analyzed using an ANOVA model with the terms of treatment and investigator.</p>
<p>2. Change from baseline to endpoint: a. FIQ Total score, physical component, fatigue and rest item b. BPI Severity (except for the average pain item) and Interference c. Mean Tender Point Threshold d. Number of tender points with low threshold e. CGI - Severity f. MFI: General fatigue, Physical fatigue, Mental fatigue, Reduced motivation, and Reduced activity g. HAMD₁₇ total score h. BDI-II total score</p>	<p>a. See text below for FIQ total derivation b. BPI severity for worst pain, least pain, and pain right now. BPI interference for general activity, mood, walking normally, normal work, relations with others, sleep, and enjoyment of life. In addition, a mean interference score will be calculated from the 7 interference questions. c. Mean of 18 tender point thresholds d. Number of tender points that have a low threshold (≤ 4 kg/cm²) f. Each dimension is the sum of 4 items in the group. If 1 or more items are missing for a given dimension, the score for that dimension will be set to missing. g. Sum of 17 HAMD items h. Sum of 21 items</p>	<p>Variables 2a to 2h will be analyzed by the ANCOVA models as described in Section 9.7.1.1, General Considerations. The distribution of the residuals will be checked for the variables obtained from MFI. When the assumptions of normality and homogeneity are violated, rank-transformed change scores will be analyzed using an ANOVA model with the terms of treatment and investigator.</p>

(continued)

Efficacy Variable	Derivation and Details	Analysis
3. All baseline and post-baseline data at the Visits in the acute therapy for: a. FIQ Total score, fatigue and rest item b. BPI: Severity and Interference c. Mean Tender Point Threshold d. Number of tender points with low threshold e. CGI – Severity f. MFI: General fatigue g. PGI ^a h. BDI-II total score	(The same as above)	Variables 3a to 3h will be analyzed by a repeated measures analysis. The model details will be described in text beneath the table.
4. Categorical variable: a. Response rate for BPI average pain score b. Sustained response rate for BPI average pain score	a. Response: at least 50% reduction from baseline to endpoint. b. Sustained response: at least 50% reduction from baseline to endpoint; with a 50% reduction from baseline at an earlier than the last visit, with at least a 30% reduction from baseline at every visit in between, if there are any intervening visits.	For variables 5a to 5b, proportions will be summarized by treatment group and will be analyzed by a Fisher's Exact test.

(continued)

Efficacy Variable	Derivation and Details	Analysis
3. All baseline and post-baseline data at the Visits in the acute therapy for: a. FIQ Total score, fatigue and rest item b. BPI: Severity and Interference c. Mean Tender Point Threshold d. Number of tender points with low threshold e. CGI – Severity f. MFI: General fatigue g. PGI ^a h. BDI-II total score	(The same as above)	Variables 3a to 3h will be analyzed by a repeated measures analysis. The model details will be described in text beneath the table.
4. Categorical variable: a. Response rate for BPI average pain score b. Sustained response rate for BPI average pain score	a. Response: at least 50% reduction from baseline to endpoint. b. Sustained response: at least 50% reduction from baseline to endpoint; with a 50% reduction from baseline at an earlier than the last visit, with at least a 30% reduction from baseline at every visit in between, if there are any intervening visits.	For variables 5a to 5b, proportions will be summarized by treatment group and will be analyzed by a Fisher's Exact test.

(continued)

Efficacy Variable	Derivation and Details	Analysis
5. Time-to-event variable: a. Time-to-first 50% reduction in BPI average pain score b. Time-to-sustained response	a. For the patients with a 50% reduction at a visit in the acute therapy phase, time = date of the visit that the earliest 50% reduction is observed – the randomization date; for the others, time = date of last visit – the randomization date and was censored. b. For the sustained responders defined above, time = date of the visit which is the earliest visit from which the sustained response is observed minus the randomization date; for the others, time = date of last visit minus the randomization date and was censored.	For variables 6a and 6b, the Kaplan-Meier survival curves of time-to-event will be calculated by treatment group. In the calculation, patients who do not have the event will be considered as right-censored observation. The comparison of the survival curves between treatment groups will be conducted by a log-rank test and the stratified log-rank test controlling for investigator (using PROC LIFETEST).

Abbreviations: BPI = Brief Pain Inventory, FIQ = Fibromyalgia Impact Questionnaire, CGI-Severity = Clinical Global Impressions of Severity, MFI = Multidimensional Fatigue Inventory, PGI-Improvement = Patient's Global Impressions of Improvement, HAMDI7 = 17-item Hamilton Depression Rating Scale.

^a PGI-Severity measured at Visit 2 will be used as the continuous covariate in the model.

Note: "Baseline" is defined as the last measurement taken at, or prior to, Visit 2; "endpoint" for 3-month analysis is defined as the last nonmissing measurement taken in the acute therapy phase (at or before Visit 8); "endpoint" for 6-month analysis is defined as the last nonmissing measurement taken in the acute therapy plus continuation therapy phases (at or before Visit 11).

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