CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-733

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

NDA:	21-733
Name of Drug:	Cymbalta (Duloxetine HCl)
Indication:	—
Sponsor:	Eli Lilly
Documents Reviewed:	Study Reports and the data submitted to Electronic Document Room: \\CDSESUB1\N21733\N_000\2004-03-02
Dates:	Stamp: 3/2/2004; Assigned: 6/1/2004; PDUFA: 8/31/04
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Key Words: NDA, Clinical Studies, Missing data

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1. EXECUTIVE SUMMARY OF STATISTICAL REVIEW

1.1 Conclusion and Recommendations

This application reports two double-blind, randomized, and placebo-controlled studies to support the efficacy of duloxetine for the — Both studies demonstrated significant pain reduction on the weekly 24-hour average pain score (primary efficacy) in diabetic patients treated with fixed-doses of duloxetine 60 mg BID, and duloxetine 60 mg QD. Both doses of duloxetine were superior to placebo, with duloxetine 60 mg BID numerically superior to 60 mg QD. Despite significant dropouts related to adverse events in the duloxetine treated patients (13%) compared to placebo patients (6%), both intent-to-treat and evaluable patient analysis consistently demonstrated effectiveness of both doses of duloxetine in treating pain. Analysis of secondary efficacy measures also supported the effectiveness of duloxetine compared to placebo. From a statistical perspective, this application provided adequate efficacy data to support the purported indication.

1.2 Overview of the Clinical Program and Studies Reviewed

The sponsor's clinical program included two studies: a phase II (HMAW) and a Phase III (HMAV) study. Both studies were double-blind, randomized, and placebo-controlled that followed identical protocol, varying only in doses. Study HMAW had four arms: duloxetine 60 mg QD, 60 mg BID, 20 mg QD, and placebo; and study HMAV had three arms: duloxetine 60 mg BID, 60 mg QD, and placebo. Studies were conducted in the US, Puerto Rico, Argentina, and Canada. Patients with pain present for at least 6 months were enrolled in a 12–week acute therapy phase (double-blind) followed by an open-label extension phase to assess additional safety parameters. The objective was to demonstrate that duloxetine 60 mg BID and 60 mg QD were superior to placebo in treating patients with diabetic neuropathic pain during the acute phase of the study. The primary efficacy measure was weekly mean of the 24-hour average pain severity score recorded daily on an 11-point Likert scale. The secondary measures included response rate as measured by ≥30% reduction from baseline, Clinical Global Impressions of Severity (CGI-Severity), Patients Global Impressions of improvement (PGI-Improvement), Brief Pain Inventory (BPI), weekly means of worst pain and nightly pain, health outcomes as determined using the short form–36 and Euro–Qol questionnaire. The primary endpoint was the change from baseline to endpoint in weekly 24-hour average pain scores. The protocol specified statistical analysis methods included analysis of covariance (ANCOVA) and repeated measures model for the continuous data, and Fisher's exact test for categorical data. The sponsor's analysis used intent-to-treat principle that included last observation carried forward approach for missing data. The repeated measure model also provided weekly efficacy results for patients with non-missing pain score.

1.3 Principal Findings

A total of 334 and 457 patients were enrolled in Study HMAV and study HMAW, respectively. Patients were randomized equally to duloxetine and placebo groups. Demographic and baseline characteristics of patients were similar between Duloxetine and placebo patients across both studies. Significant treatment-by-center interaction was noted in study HMAV that was due to opposite treatment effect (placebo more effective than test drug) seen in one center. Exclusion of 17 patients from this center showed no further interaction and the test results remained the same without compromising the power of the test. Based on the sponsor's data and our independent analyses, the efficacy results could be summarized as follows:

(1) Duloxetine 60 mg BID and 60 mg QD demonstrated significant ($p<.001$) pain reduction (from baseline to endpoint) on the weekly 24-hour average pain score compared to placebo in both studies. Both doses of duloxetine also demonstrated similar efficacy starting at week 1 of treatment and maintained throughout 12 weeks of treatment.

(2) Primary efficacy analysis using two statistical methods – ANCOVA and Repeated measures models adjusting for baseline pain score, center, center by treatment interaction, and concomitant acetaminophen use as factors, produced similar results.

(3) Results of our analysis of primary efficacy treating dropouts as "non-responders" were no different than the sponsor's last post-baseline carried forward approach.

(4) Although there was a trend for duloxetine 60 mg BID to be numerically more effective than 60 mg QD, no statistically significant differences in efficacy between the two doses were noted.

(5) Responder analysis showed that 65–70% of duloxetine 60 mg BID treated patients achieved ≥30% reduction in pain from baseline to endpoint compared to 40–47% of placebo patients.

(6) Efficacy of duloxetine was similar in men and women, in younger and older patients, and in Caucasian and other races. Within each stratum of the above subgroups, duloxetine remained superior to placebo in treating pain.

2. INTRODUCTION

The sponsor, Eli Lilly, seeks approval for duloxetine for the [redacted]. Diabetic neuropathy is a peripheral neuropathy resulting from nerve damage, and typically associated with pain that is variable in severity. Duloxetine has also been studied as an antidepressant and as a treatment for stress urinary incontinence.

This review will focus on the evidence concerning efficacy only. Details of safety data can be found in clinical reviewer's report.

2.1 Proposed Indication

[redacted]

2.2 Materials Reviewed

The materials reviewed included the final study reports, summary of integrated efficacy report and study data submitted in the electronic document room: \\CDSESUB1\N21733\N_000\2004-03-02

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Approach to the Review

Our approach in this review is first to replicate the Sponsor's results using similar statistical methods. Secondly, we will focus on the handling of missing data due to early dropouts, since it was a concern raised by the clinical reviewer. Overall dropout rates were similar across treatment groups, but significantly more dropouts related to adverse events were observed in the duloxetine treated groups than in the placebo group, thereby raising the possibility of non-ignorable missing pattern. The sponsor carried forward (LOCF) the last non-missing pain score for the dropouts and included them in the intent-to-treat analysis population. Apart from shortcomings of LOCF, imputing the last post-baseline for the endpoint may have systematically biased the result upward. We will use a more conservative approach by treating missing post-baseline weekly pain score as 'no improvements' as opposed to carrying forward the last post-baseline score. In the following section, first we highlight the study features including design and statistical methods employed, followed by comparison of efficacy results between sponsor's and our analysis.

3.1.2 Description of Studies

Two clinical studies referred as "acute phase studies", varying only in the dosages, but identical otherwise, were carried out to support this indication. Key design features of these studies are highlighted in Table 3.1. Both studies had also an open-label extension (not shown here) phase that collected mostly safety data and limited efficacy data. Our review addresses evidence concerning efficacy from the data submitted from the acute phase of the studies.

Table 3.1
Summary of Design: Acute Phase Studies

Study # (Phase)	Location	Design	Treatment Groups (n)	Efficacy Measures	Statistical Methods
HMAW (Acute Phase II)	US, Puerto Rico, Canada and Argentina	Double-blind, parallel, Placebo-controlled, 12 week randomized study.	Dulox. 20 mg QD (n=115) Dulox. 60 mg QD (n=114) Dulox. 60 mg BID (n=113) *Placebo (n=115)*	Primary 24-hour average pain severity Secondary - *Response(≥30% reduction)* in pain from baseline - Sustained Response - 24-hour worst pain severity - Night pain severity - Brief pain index - Clinical Global impression of severity - Health outcomes - Depression/Anxiety	Primary Method Repeated Measures Secondary Method Analysis of Covariance
HMAV (Acute Phase III)	US, Puerto Rico	Double-blind, parallel, Placebo-controlled, 12 week randomized study	Dulox. 60 mg QD (n=114) Dulox. 60 mg BID (n=112) Placebo (n 108)	Same as above	Primary Method Analysis of Covariance Secondary Method Repeated Measures

Design: As noted in Table 3.1, both studies were similar in design and duration of treatment except study HMAW had an additional arm for lower dose of duloxetine 20 mg QD. Patients who were at least 18 years of age and presented with a pain of ≥4 due to bilateral peripheral neuropathy for at least six months, were randomized to following treatment groups: duloxetine 20 mg QD, duloxetine 60 mg once daily (QD), duloxetine mg twice daily (BID), or placebo. Following three weeks of screening period, patients were treated in a double-blind manner for 13 weeks. The first 12 weeks of double-blind phase was considered the "acute" therapy phase. Patients who completed 13-week double-blind period were re-randomized to treatment with duloxetine 60 mg BID or routine care for an additional 52 weeks of open-label extension therapy for safety monitoring purposes.
The objective of the trials was to compare the efficacy of duloxetine versus placebo with respect to a single primary endpoint and several secondary endpoints.

Endpoint(s): The primary efficacy endpoint was the change from baseline to endpoint (non-missing post-baseline score during the acute phase of the treatment) in weekly mean of 24-hour average pain, collected in a daily diary by patients on an 11-point Likert scale (0=no pain to

10=worst pain). The secondary endpoint(s) were the change from baseline to endpoint in the following outcomes:

- Response (at least ≥30% reduction from baseline to endpoint) and sustained response (at least ≥30% reduction for at least 2 weeks and 20% reduction maintained between every week thereafter) rates.
- Weekly means of night and worst daily pain from the daily diary
- Brief pain Inventory (BPI) of Severity and Interference: Measured by patient on an ordinal scale ranging from 0 (no pain) to 10 (pain as bad as one can imagine).
- Clinical Global Impression of Severity (CGI-Severity): Administered by a physician investigator with score ranging from 1 (normal) to 7 (most severe illness).
- Patient Global Impression of Improvement (PGI-Improvement): Completed by the patient with a score ranging from 1 (normal) to 7 (most severe illness).
- Sensor portion of the Short-Form McGill Pain Questionnaire (SF-MPQ): Completed by the clinician using 11 pain descriptors with scores ranging from 0 (none) to 3 (severe).

Secondary objectives also included the evaluation of changes in the following three patient-reported health and mood/anxiety outcomes:

- 36-item Short-Form Health Survey (SF-36)
- EQ-5D version of the Euro-Qol Questionnaire
- Resource Utilization Questionnaire
- Hamilton depression scale measuring depression symptom severity using 17-item scale score each ranging from 0 (no depression) to 52 (severely depressed).
- Beck Depression Inventory-II (BDI-II)
- Beck Anxiety Inventory (BAI)
- Allodynia Measures: Measuring a painful reaction to a normally non-painful stimulus.

Sample size: Both studies were designed to enroll 110 per arm (for a total of 440 patients in study HMAW and 330 patients in study HMAV, respectively) to detect (with at least 90% power) a treatment group difference of -1.20 points based on the primary endpoint.

Statistical Methods: Analysis of covariance (ANCOVA) model was used to analyze differences between treatment groups in weekly 24-hour average pain score mean change from baseline. The model included terms for treatment, center, treatment by center interaction, and the baseline pain score. A likelihood based mixed-effects repeated measures (MMRM) model was also used to analyze both primary and secondary endpoints. Fisher's exact test was used to test for differences in the sustained response rate between treatment groups.
Multicenter: Centers with less than 12 randomized patients were pooled into one center within a country.

Multiple Comparisons/Multiplicity: The per-protocol plan was a single comparison between duloxetine 60 mg BID and placebo in mean change on the primary efficacy measure with error controlled at α=0.05. Secondary measures were considered supportive to confirm the primary outcome, and therefore the protocol had no plan for making adjustments for multiplicity.

Data Sets Analyzed: All analyses were conducted based on intent-to-treat principle i.e., analyzed by the treatment groups to which patients were randomized. For efficacy analysis, patients were included in the analysis if they had baseline and at least one post-baseline pain score.

3.1.3 Comments on the Methods of Analysis

Sample size for the pivotal trials was adequate for the rejection of the null hypothesis of no treatment differences between duloxetine dose groups and placebo. The statistical model chosen appeared appropriate, although it was unclear why the Sponsor planned a priori to use ANOVA for primary efficacy in study HMAV (Phase 3), and mixed-effect repeated measures model in study HMAW.

3.1.4 Study Results

3.1.4.1 Patient Disposition

Table 3.1.4.1 summarizes the patient disposition during the acute phases. Eighty–six (26%) patients in study HMAV and 113 (25%) patients in study HMAW discontinued prematurely, with a significantly higher number in duloxetine group discontinuing early compared to placebo. In addition, seven (2%) patients in study HMAV and 13 (3%) patients in study HMAW, respectively had no post–baseline pain score.

3.1.4.2 Baseline Characteristics

Demographic: The baseline demographic characteristics such as age, gender, ethnicity, height, weight, type of diabetes mellitus, and duration of diabetic neuropathy were similar between duloxetine dose groups and placebo in both studies.

Pain Severity: There were no important differences among treatment groups with regards to baseline pain severity as measured by 24-hour average pain, 24-hour worst pain, or night pain except for Brief Pain Inventory (BPI), where BPI scores for duloxetine patients were higher than placebo patients.
Similarly, no significant differences between treatment groups were noted with regards to baseline Mood and general illness assessed by Hamilton score, and CGI severity.

Table 3.1.4.1
Patient Disposition: Studies HMAW and HMAV

	Study HMAW					Study HMAV			
	Placebo	DLX20QD	DLX60QD	DLX60BID	Total	Placebo	DLX60QD	DLX60BID	Total
Patients Randomized	115	115	114	113	457	108	114	112	334
Discontinued* (Acute Phase):	28 (24%)	24 (21%)	28 (24%)	33 (29%)	113 (25%)	23(21%)	29(25%)	34(30%)	86(26%)
Due to AE		5(4%)	15 (13%)	22 (19%)	48 (10%)	8 (7%)	17(15%)	20 (18%)	45(14%)
Lack of	6 (5%)	2 (1.7%)	1 (<1%)	2 (<2%)	9 (2%)	5 (4 6%)	1 (<1%)	3 (2.7%)	9(3%)
Efficacy	4 (3.5%)	17 (15%)	12 (10%)	9 (8%)	56 (12%)	10 (9%)	11 (10%)	11 (10%)	32(9%)
Others**	18 (16%)								
No post-baseline	4	4	1	4	13 (3%)	2	4	1	7(2%)
ITT* Population	111	111	112	109	443 (97%)	106	110	111	327(98%
Completer's (Acute Phase)	87	91	86	80	344(75%)	85	85	78	248(74%

* Contributed efficacy data
**: Other: Protocol Violation, Entry Criteria not met, Personal decision etc.
a: Excluding Patients with no post-baseline
Source: Table ISE 5.3, 5.8

3.1.4.3 Analysis Population

Sponsor's intent-to-treatment population (327 and 443 in HMAV and HMAW, respectively) included all patients randomized with at least one post-baseline pain score. Patients with no post-baseline data were excluded. Baseline to endpoint (12 week) analysis was based on last observation carried forward (LOCF) approach. Evaluable or analysis (by study week) population was also used in the efficacy analysis.

3.1.4.4 Primary Efficacy

24-Hour Average Pain: The primary measure of efficacy was the change from baseline to endpoint (12 weeks) in weekly 24-hour average pain scores based on patient–reported pain marked as 0= no pain to 10=worst pain on an 11-point Likert scale. The primary test of treatment differences was analysis of covariance (ANCOVA) and Mixed Model Repeated Measures (MMRM) analysis with treatment, center, treatment by center interaction, and baseline pain score as factors. As mentioned earlier, the Sponsor performed analysis using both ANCOVA and MMRM interchangeably, ANCOVA as primary method in study HMAV and MMRM in study HMAW. No rationale was given for the preference; presumably it was performed to replicate the results.

The results of primary efficacy analysis for both studies, verified by our own analysis, are shown in Table 3.1.4.2. In both studies, duloxetine 60 mg QD and duloxetine 60 mg BID were statistically superior (p<.001) to placebo. In study HMAV, however, a significant (p=.007) treatment-by-center interaction was noted due to opposite treatment effect (no reduction in pain for duloxetine patients while pain for placebo patients was improved) seen in one particular center involving 17 patients. A separate analysis excluding this center involving 17 patients showed no further treatment-by-center interaction (p=.113) and duloxetine remained superior to placebo. In study HMAW, no significant treatment-by-center interaction was observed in either ANCOVA or MMRM analysis.

Figure HMVa.11.1 and HMAW.11.1 (copied from the Sponsor's study reports) shows the plot of changes in least square means from repeated measure model by week of treatment. Repeated measures analysis also showed significant (p<.001; Figure HMVAa.11.1 and HMAW.11.1, Appendix) duloxetine effect over placebo in reducing the 24-hour average pain starting from week 1 of treatment. This analysis could also be seen as "Evaluable" analysis, since missing values were not imputed. Both methods showed consistent superiority of duloxetine over placebo during the 12 weeks of treatment period.

We performed analysis using "worst case" scenario, i.e., treating missing as "no improvement". Our analyses showed no significant treatment by center interaction in either study (p=.07 in study HMAV, p=.112 in study HMAW). The treatment differences between both doses of duloxetine 60 mg BID vs. placebo remained statistically significant. Analysis on percent change from baseline in 24-hour average pain showed similar efficacy.

Data from both studies consistently demonstrated superiority of duloxetine doses over placebo in reducing pain.

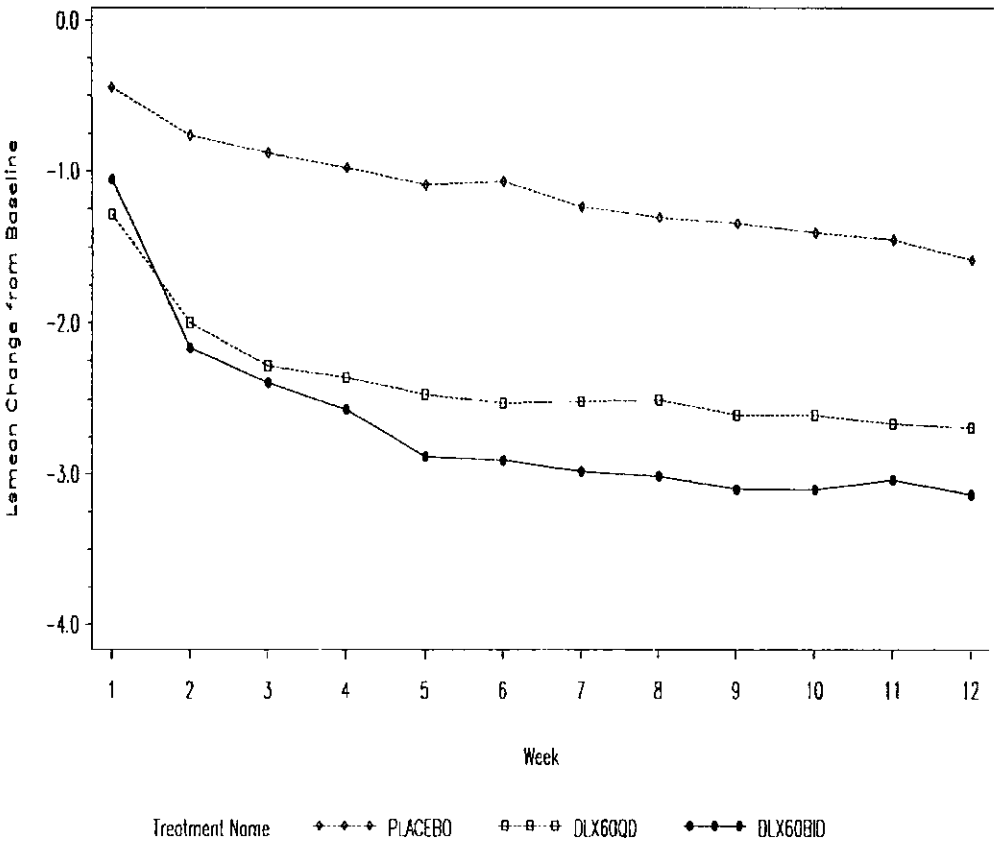
Table 3.1.4.2
Primary Efficacy: 24-hour Average Pain Score Change from Baseline to Endpoint: Intent-to-treat Population*

Study	Treatment Groups	N	24-Hour Average Pain Score			P-value (Pair-wise comparison)		
			Baseline Mean	LS Mean **	SE	Placebo vs. DLX20QD	Placebo vs. DLX60QD	Placebo vs. DLX60BID
HMAV	1) Placebo	106	5.8	-1.4	0.23			
	2) DLX60QD	110	6.1	-2.7	0.22	--	<.001	--
	3) DLX60BID	111	6.2	-2.8	0.23		--	<.001
HMAW	1) Placebo	111	5.7	-1.9	0.22			
	2) DLX20QD	111	5.8	-2.3	0.21	0.13	--	--
	3) DLX60QD	112	6.0	-2.9	0.22	--	<.001	--
	4) DLX60BID	109	5.8	-3.2	0.23	--	--	<.001

* Excluding patients with no post-baseline score and Last observation carried forward
** Estimates from ANCOVA model in Study HMAV and from Repeated Measures Analysis in Study HMAW
Source: Table HMAW 11.8, Page 87 and Table HMAV 11.9, Page 118

Weekly 24-hour Average Pain Score
Least Square Mean Changes from Repeated Measures Analysis
All Randomized Patients
F1J-MC-HMAV(A) Acute Therapy Phase

NL



Model: change from baseline in WKAVRGPS=THERAPY WEEK POOLINV THERAPY*WEEK BASELINE BASELINE*WEEK
Covariance Structure: Unstructured
Program: RMP.F1JSHMAV.SASPGM(PLAPSA1A) RMGCA700
Data: RMP.SAS.F1JM.LMCHMAVSW.INTRIMA1

Figure HMAVa.11.1. 24-hour average pain score least-squares mean change from repeated measures analysis of change by visit for all randomized patients in acute therapy phase.

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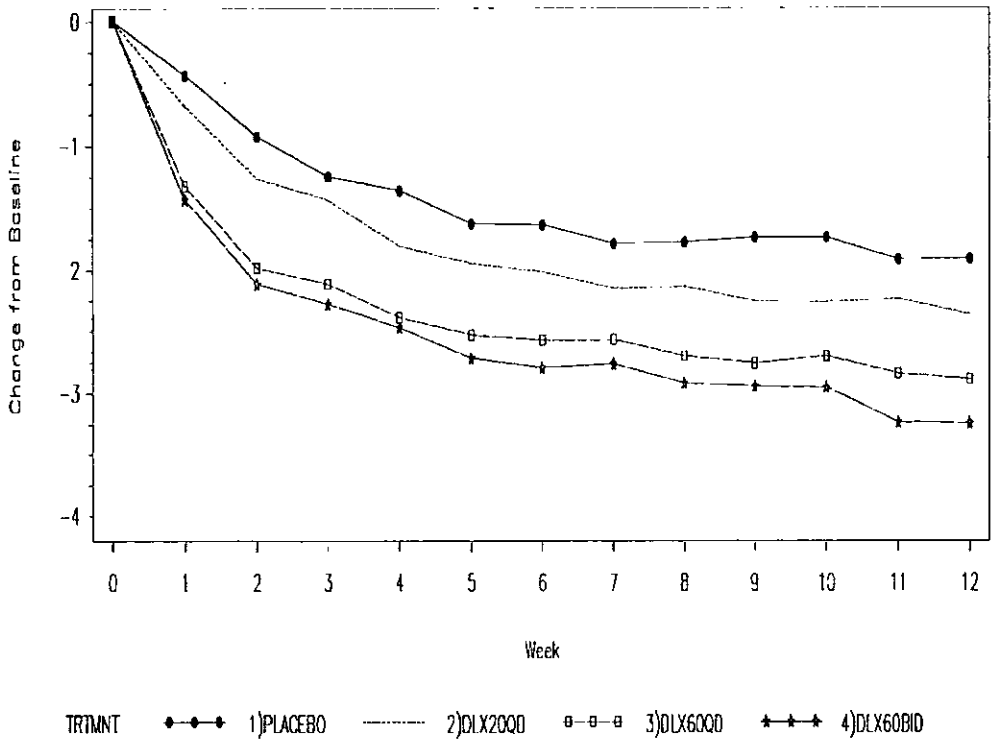
24 Hour Average Pain Severity
Plot of Least Square Mean Change from Baseline
All Randomized Patients
F1J-MC-HMAW Acute Therapy Phase



Model: change from baseline in: VIAVRGPS=trtmnt poolinv visit trtmnt*visit basval basval*visit; cov. structure=UN
Note: At Week 0, value 0 was assigned
Program: RMP.F1JSHMAW.SASPGM(RMPLTS1A) QCA700
Data: RMP.SAS.F1JM.MCHMAWSW.INTRIM1

Figure HMAW.11.1. Plot of mean change on 24-hour average pain severity for all randomized patients in acute therapy phase of Study HMAW.

3.1.4.5 Effect of Concomitant Acetaminophen/Analgesic Use

The treatment group differences on pain reduction were evaluated after accounting for the concomitant effect of acetaminophen/analgesic use. The weekly average dose of acetaminophen taken for relief of DNP was recorded in the patient diary. When acetaminophen was added as a factor in the ANCOVA model, the treatment effects between duloxetine 60 mg BID and placebo remained statistically significant ($p<.001$) in both studies. In addition path analyses were performed to test the change on 24-hour average pain by controlling for the improvement on mood and anxiety (in Study HMAW), or by controlling for mood improvement alone (Study HMAV). Results of Sponsor's path analyses showed that indirect effect on reduction in pain through the improvement on mood and anxiety accounted for only 11% for duloxetine 60 mg BID in study HMAW (Phase 2). No indirect effect was noted in Phase 3 study HMAV.

3.1.4.6 Secondary Efficacy

Response/Sustained Response: The responder analysis was not pre-specified in the protocol; rather, it was an ad hoc analysis based on the primary efficacy. Response was defined when there was a 30% reduction in pain for the first time during the acute phase of the study. The sustained response was defined as 30% reduction from baseline to endpoint with a corresponding 30% reduction from baseline at a visit at least 2-weeks prior to the last visit, and at least 20% reduction maintained at every visit in between. Table 3.1.4.3 summarizes the responder analysis results across both studies. Significantly ($p<.02$) higher percentages (63–69%) of duloxetine patients achieved more than 30% reduction in pain compared to placebo (41–47%). Sustained response was also achieved by more than 50% of the duloxetine patients compared to more than 30% of the placebo patients.

Table 3.1.4.3
24-hour Average Pain Severity Response Rate at Endpoint: Intent-to-treat Population

Study	Treatment Groups	N	Response (≥30% Reduction)		Sustained Response	
			n (%)	P-value* vs. Placebo	n (%)	P-value*
HMAV						
	Placebo	106	44(41%)	--	36(34%)	--
	DLX60QD	110	69(63%)	.003	59(53%)	.004
	DLX60BID	111	77(69%)	<.001	69(62%)	<.001
HMAW						
	Placebo	111	52(47%)	--	37(33%)	--
	DLX20QD	111	57(51%)	.59	51(46%)	.07
	DLX60QD	112	72(64%)	.01	63(56%)	<.001
	DLX60BID	109	71(65%)	.007	61(56%)	.001

* Fisher's exact P-value, Source: ISE Table 5.5, 5.6, 5.10, and 5.11

Additional Secondary Efficacy Measures: Both ANCOVA and MMRM were used to test the treatment differences between duloxetine and placebo with respect to several secondary efficacy measures. The p-value from ANCOVA for the comparison of duloxetine doses versus placebo

are summarized in Table 3.1.4.4. MMRM produced similar p-values.

For most of the secondary measures, the duloxetine 60 mg BID and 60 mg QD were significantly superior to placebo.

Table 3.1.4.4
Secondary Efficacy Measures: ITT Population

	Study HMAW			Study HMAV	
Secondary Measures	DLX20QD vs. Placebo	DLX60QD vs. Placebo	DLX60BID vs. Placebo	DLX60QD vs. Placebo	DLX60BID vs. Placebo
24-hour Worst Pain Score	P=.047	P<.001	P<.001	P<.001	P<.001
24-hour Night Pain Score	P=.65	P=.014	P<.001	P=<.001	P<.001
BPI Worst Pain Severity	P=.226	P<.01	P<.001	P<.001	P<.001
BPI Average Pain Severity	P=.372	P=.013	P=.002	P<.001	P<.001
CGI Severity	P<.05	P<.001	P<.001	P<.01	P=.014
PGI Improvement	P=.64	P<.02	P<.01	P<.001	P<.005
McGill Pain Score	P=.043	P=.001	P<.001	P=.001	P=.001
HAMD17	--	--	--	P=.98	P=.02
SF-MPQ	p=.80	p=.065	p=.065	P<.001	P=.003

* From ANCOVA

3.2 EVALUATION OF SAFETY

There were significant changes in liver function parameters for duloxetine patients compared to placebo patients. One patient had a QTc>512 msec. More details on safety data can be found in the clinical reviewer's report.

3.3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The efficacy in subgroups defined by age (<65 vs. ≥65), gender, ethnicity, and duration of diabetic neuropathy (≤2 years vs. >2 years) was evaluated using data from both studies combined. There were no statistically significant therapy-by-subgroup interactions observed for the above subgroups. The efficacy was similar in younger and older patients, in men and women, and Caucasian and patients of other ethnicity. Within each stratum, duloxetine remained superior to placebo in treating pain.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

The impact of missing data related to adverse events, center-by-treatment interaction, and concomitant medications were examined in this review. There was a significant dropout related to adverse event in the duloxetine treated groups compared to the placebo groups. The sponsor carried forward their last post-baseline values to the endpoint in the intent-to-treat analysis population. We looked at this more conservatively by treating the missing post-baseline scores as 'no improvements' and compared the results using similar statistical methods. We didn't find any treatment-by-center interaction. However, in Sponsor's analysis a significant treatment-by-center interaction was seen in study HMAV, which was due to opposite treatment effect in one center involving 17 patients. Analysis excluding that particular center did not alter the efficacy conclusion. Concomitant medication (analgesic use during the treatment) appeared to have minimal independent effect on the efficacy results. Overall, the Sponsor made a good effort to resolve the above minor issues.

4.2 Conclusions and Recommendations

This review evaluated the efficacy data from two studies to support the safety and efficacy of duloxetine 60 mg BID compared to placebo for the treatment of diabetic neuropathic pain (DNP) in diabetic patients with persistent pain for at least six months. Studies HMAV and HMAW were conducted in the US, Canada, Puerto Rico, and Argentina. Both studies were powered (with 90% power) adequately to detect treatment group differences in change from baseline to endpoint on the weekly 24-hour average pain score between study drug and placebo. Studies were identical in design: double-blind, placebo-controlled, randomized; varying only in an extra dose arm in study HMAW, for duration of 12 weeks of acute phase followed by an open-label extension phase. The protocol had no a priori plan for interim look or adjustment for multiple comparison or multiplicity. Statistical methods employed were appropriate.

Both studies HMAV and HMAW showed an effect that was clearly statistically significant. Duloxetine 60 mg BID or QD was superior to placebo in reducing weekly pain using either ITT or evaluable population, regardless of whether missing pain score was carried forward by last post-baseline or treating missing as no improvement. Superiority of duloxetine 60 mg doses over placebo was also demonstrated with regards to several secondary efficacy endpoints. From a statistical perspective, this application provided adequate efficacy data to support the purported indication.

Mahboob Sobhan, Ph.D.
Reviewing Statistician, HFD-715

Table HMAVa.11.11. 24-Hour Average Pain Score
Repeated Measures Analysis
All Randomized Patients
Acute Therapy Phase

Therapy	Visit(Week)	N	LSMean	LSMean Change	SE	T	DDF	Within p-Value	Pairwise p-Value vs. 1)	vs. 2)
1) PLACEBO	4(1)	106	5.63	-0.45	0.12			<.001		
2) DLX60QD		109	4.79	-1.28	0.12	-4.97	311	<.001	<.001	
3) DLX60BID		111	5.02	-1.06	0.12	-3.62	310	<.001	<.001	.171
1) PLACEBO	5(2)	101	5.31	-0.76	0.18			<.001		
2) DLX60QD		102	4.07	-2.00	0.18	-5.03	311	<.001	<.001	
3) DLX60BID		98	3.91	-2.16	0.18	-5.66	315	<.001	<.001	.503
1) PLACEBO	6(3)	98	5.19	-0.88	0.19			<.001		
2) DLX60QD		97	3.79	-2.28	0.19	-5.40	303	<.001	<.001	
3) DLX60BID		95	3.68	-2.39	0.19	-5.79	305	<.001	<.001	.673
1) PLACEBO	6(4)	98	5.10	-0.98	0.20			<.001		
2) DLX60QD		96	3.72	-2.36	0.19	-5.08	306	<.001	<.001	
3) DLX60BID		94	3.51	-2.57	0.20	-5.81	308	<.001	<.001	.441
1) PLACEBO	7(5)	94	4.98	-1.09	0.20			<.001		
2) DLX60QD		93	3.60	-2.47	0.20	-5.00	297	<.001	<.001	
3) DLX60BID		88	3.19	-2.88	0.20	-6.45	301	<.001	<.001	.136
1) PLACEBO	7(6)	92	5.01	-1.07	0.20			<.001		
2) DLX60QD		91	3.55	-2.52	0.20	-5.31	292	<.001	<.001	
3) DLX60BID		86	3.17	-2.91	0.20	-6.64	296	<.001	<.001	.166

95% CI at last visit: 2vs1(-1.71,-0.5); 3vs1(-2.16,-0.94); 3vs2(-1.05,0.16)
Model WKAVRGPS=trtmnt week poolinv trtmnt*week basval basval*week; Cov. Structure=Unstructured
T and DDF refers to contrasts with Placebo; w/in p-values are from t-tests for LSMean change
Program: RMP.F1JSHMAV.SASPGM(RMAPSA1A) QCA700
Data: RMP.SAS.F1JM.L.MCHMAVSW.INTRIMA1

Table HMAVa.11.11. 24-Hour Average Pain Score
Repeated Measures Analysis
All Randomized Patients
Acute Therapy Phase (Concluded)

Therapy	Visit(Week)	N	LSMean	LSMean Change	SE	T	DDF	Within p-Value	Pairwise p-Value vs. 1)	vs. 2)
1) PLACEBO	8(7)	91	4.84	-1.23	0.21			<.001		
2) DLX60QD		93	3.56	-2.51	0.21	-4.40	293	<.001	<.001	
3) DLX60BID		85	3.09	-2.98	0.21	-5.94	298	<.001	<.001	.110
1) PLACEBO	8(8)	88	4.77	-1.30	0.22			<.001		
2) DLX60QD		92	3.57	-2.50	0.21	-3.99	290	<.001	<.001	
3) DLX60BID		83	3.06	-3.01	0.22	-5.62	295	<.001	<.001	.092
1) PLACEBO	9(9)	88	4.73	-1.34	0.21			<.001		
2) DLX60QD		89	3.47	-2.60	0.21	-4.33	287	<.001	<.001	
3) DLX60BID		83	2.97	-3.10	0.21	-5.97	291	<.001	<.001	.090
1) PLACEBO	9(10)	85	4.67	-1.40	0.22			<.001		
2) DLX60QD		86	3.47	-2.60	0.21	-3.99	284	<.001	<.001	
3) DLX60BID		78	2.97	-3.10	0.22	-5.58	289	<.001	<.001	.100
1) PLACEBO	10(11)	84	4.62	-1.45	0.22			<.001		
2) DLX60QD		87	3.41	-2.66	0.22	-3.92	285	<.001	<.001	
3) DLX60BID		81	3.04	-3.04	0.22	-5.07	290	<.001	<.001	.231
1) PLACEBO	10(12)	82	4.49	-1.59	0.22			<.001		
2) DLX60QD		86	3.38	-2.69	0.22	-3.60	283	<.001	<.001	
3) DLX60BID		77	2.94	-3.13	0.22	-4.98	289	<.001	<.001	.149

95% CI at last visit: 2vs1(-1.71,-0.5); 3vs1(-2.15,-0.94); 3vs2(-1.05,0.16)
Model WKAVRGPS=trtmnt week poolinv trtmnt*week basval basval*week; Cov. Structure=Unstructured
T and DDF refers to contrasts with Placebo; w/in p-values are from t-tests for LSMean change
Program: RMP.F1JSHMAV.SASPGM(RMAPSA1A) QCA700
Data: RMP.SAS.F1JM.L.MCHMAVSW.INTRIMA1

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Table HMAW.11.7. 24-Hour Average Pain Score
Repeated Measures Analysis
All Randomized Patients
Acute Therapy Phase

Therapy	Visit(Week)	N	LSMean	LSMean Change	SE	T	DDF	w/in p-Val	Pairwise p-Val vs. 1)	vs. 2)	vs. 3)
1)PLACEBO	3(1)	111	5.46	-0.43	0.14			.002			
2)DLX20QD		111	5.21	-0.68	0.14	-1.36	427	<.001	.173		
3)DLX60QD		112	4.57	-1.33	0.13	-4.87	427	<.001	<.001	<.001	
4)DLX60BID		109	4.46	-1.43	0.14	-5.43	427	<.001	<.001	<.001	.556
1)PLACEBO	4(2)	108	4.97	-0.93	0.18			<.001			
2)DLX20QD		107	4.63	-1.27	0.19	-1.35	413	<.001	.178		
3)DLX60QD		105	3.91	-1.99	0.18	-4.21	416	<.001	<.001	.004	
4)DLX60BID		96	3.78	-2.11	0.19	-4.65	422	<.001	<.001	<.001	.623
1)PLACEBO	5(3)	107	4.65	-1.25	0.19			<.001			
2)DLX20QD		106	4.46	-1.44	0.19	-0.73	402	<.001	.467		
3)DLX60QD		101	3.78	-2.11	0.19	-3.31	408	<.001	.001	.010	
4)DLX60BID		93	3.62	-2.28	0.20	-3.88	414	<.001	<.001	.002	.541
1)PLACEBO	6(4)	102	4.54	-1.36	0.20			<.001			
2)DLX20QD		103	4.09	-1.81	0.20	-1.64	396	<.001	.102		
3)DLX60QD		96	3.51	-2.38	0.20	-3.73	403	<.001	<.001	.036	
4)DLX60BID		92	3.43	-2.47	0.20	-3.98	406	<.001	<.001	.018	.767

95% CI at visit 14: 2vs1(-1.04,0.13); 3vs1(-1.57,-0.38); 4vs1(-1.94,-0.73); 3vs2(-1.12,0.07); 4vs2(-1.48,-0.28); 4vs3(-0.96,0.25)
Model VIAVRGPS=trtmnt visit poolinv trtmnt*visit basval basval*visit; Cov. Structure=Unstructured
T and DDF refers to contrasts with Placebo; w/in p-values are from t-tests for LSMean change
Program: RMP.F1JSHMAW.SASPGM(RMVIAS1A) QCA700
Data: RMP.SAS.F1JM.MCHMAWSW.INTRIM1

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Table HMAW.11.7. 24-Hour Average Pain Score
Repeated Measures Analysis
All Randomized Patients
Acute Therapy Phase (Continued)

Therapy	Visit(Week)	N	LSMean	LSMean Change	SE	T	DDF	w/in p-Val	Pairwise p-Val vs. 1)	vs. 2)	vs. 3)
1)PLACEBO	7(5)	96	4.27	-1.63	0.20			<.001			
2)DLX20QD		100	3.95	-1.95	0.20	-1.17	383	<.001	.245		
3)DLX60QD		94	3.37	-2.53	0.20	-3.22	389	<.001	.001	.039	
4)DLX60BID		87	3.18	-2.72	0.21	-3.84	394	<.001	<.001	.007	.509
1)PLACEBO	8(6)	96	4.26	-1.64	0.21			<.001			
2)DLX20QD		101	3.88	-2.02	0.21	-1.30	379	<.001	.196		
3)DLX60QD		95	3.33	-2.57	0.21	-3.16	385	<.001	.002	.061	
4)DLX60BID		86	3.10	-2.79	0.22	-3.85	390	<.001	<.001	.010	.458
1)PLACEBO	9(7)	92	4.11	-1.79	0.22			<.001			
2)DLX20QD		98	3.75	-2.15	0.21	-1.20	380	<.001	.229		
3)DLX60QD		93	3.33	-2.57	0.22	-2.57	385	<.001	.010	.166	
4)DLX60BID		83	3.13	-2.76	0.23	-3.17	391	<.001	.002	.046	.524
1)PLACEBO	10(8)	91	4.12	-1.78	0.21			<.001			
2)DLX20QD		98	3.76	-2.13	0.21	-1.22	379	<.001	.223		
3)DLX60QD		91	3.20	-2.70	0.21	-3.12	385	<.001	.002	.055	
4)DLX60BID		84	2.98	-2.92	0.22	-3.81	390	<.001	<.001	.009	.467

95% CI at visit 14: 2vs1(-1.04,0.13); 3vs1(-1.57,-0.38); 4vs1(-1.94,-0.73); 3vs2(-1.12,0.07); 4vs2(-1.48,-0.28); 4vs3(-0.96,0.25)
Model VIAVRGPS=trtmnt visit poolinv trtmnt*visit basval basval*visit; Cov. Structure=Unstructured
T and DDF refers to contrasts with Placebo; w/in p-values are from t-tests for LSMean change
Program: RMP.F1JSHMAW.SASPGM(RMVIAS1A) QCA700
Data: RMP.SAS.F1JM.MCHMAWSW.INTRIM1

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Table HMAW.11.7. 24-Hour Average Pain Score
Repeated Measures Analysis
All Randomized Patients
Acute Therapy Phase (Concluded)

Therapy	Visit(Week)	N	LSMean	LSMean Change	SE	T	DDF	w/in p-Val	Pairwise p-Val vs. 1)	vs. 2)	vs. 3)
1)PLACEBO	11(9)	89	4.15	-1.74	0.21			<.001			
2)DLX20QD		93	3.64	-2.26	0.21	-1.75	378	<.001	.081		
3)DLX60QD		87	3.14	-2.75	0.22	-3.41	384	<.001	<.001	.093	
4)DLX60BID		84	2.95	-2.94	0.22	-3.97	387	<.001	<.001	.024	.544
1)PLACEBO	12(10)	90	4.16	-1.74	0.22			<.001			
2)DLX20QD		93	3.64	-2.26	0.21	-1.76	380	<.001	.079		
3)DLX60QD		88	3.20	-2.70	0.22	-3.20	385	<.001	.002	.145	
4)DLX60BID		82	2.95	-2.95	0.22	-3.96	388	<.001	<.001	.025	.419
1)PLACEBO	13(11)	88	3.98	-1.92	0.21			<.001			
2)DLX20QD		90	3.66	-2.24	0.21	-1.08	373	<.001	.280		
3)DLX60QD		88	3.06	-2.84	0.22	-3.09	377	<.001	.002	.043	
4)DLX60BID		81	2.66	-3.24	0.22	-4.34	380	<.001	<.001	.001	.196
1)PLACEBO	14(12)	88	3.99	-1.91	0.22			<.001			
2)DLX20QD		91	3.53	-2.36	0.21	-1.52	376	<.001	.130		
3)DLX60QD		88	3.01	-2.89	0.22	-3.24	380	<.001	.001	.082	
4)DLX60BID		80	2.66	-3.24	0.23	-4.34	383	<.001	<.001	.004	.251

95% CI at visit 14: 2vs1(-1.04,0.13); 3vs1(-1.57,-0.38); 4vs1(-1.94,-0.73); 3vs2(-1.12,0.07); 4vs2(-1.48,-0.28); 4vs3(-0.96,0.25)
Model VIAVRGPS=trtmnt visit poolinv trtmnt*visit basval basval*visit; Cov. Structure=Unstructured
T and DDF refers to contrasts with Placebo; w/in p-values are from t-tests for LSMean change
Program: RMP.F1JSHMAW.SASPGM(RMVIAS1A) QCA700
Data: RMP.SAS.F1JM.MCHMAWSW.INTRIM1

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S. Edward Nevius
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