1. Title Page

Clinical Study Report: Duloxetine Hydrochloride 60 mg or 120 mg Once Daily Compared with Placebo in Patients with Generalized Anxiety Disorder

LY248686 (Duloxetine Hydrochloride)
Generalized Anxiety Disorder

A multicenter, 9-week, double-blind, randomized, placebo-controlled, Phase 3 study to test the efficacy of duloxetine 60 mg QD and 120 mg once daily (QD) versus placebo in the treatment of generalized anxiety disorder (GAD) as measured by reduction of the mean change in anxiety symptoms on the Hamilton Anxiety Rating Scale (HAMA) total score in patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria for GAD.

Eli Lilly and Company
Protocol F1J-MC-HMBR
Phase 3
First patient enrolled (assigned to therapy): 06 July 2004
Last patient completed: 29 September 2005
Date of report: 02 March 2006

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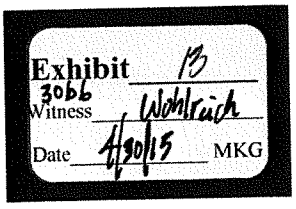
Responsible Medical Officer: Michael Detke MD, PhD
Eli Lilly and Company

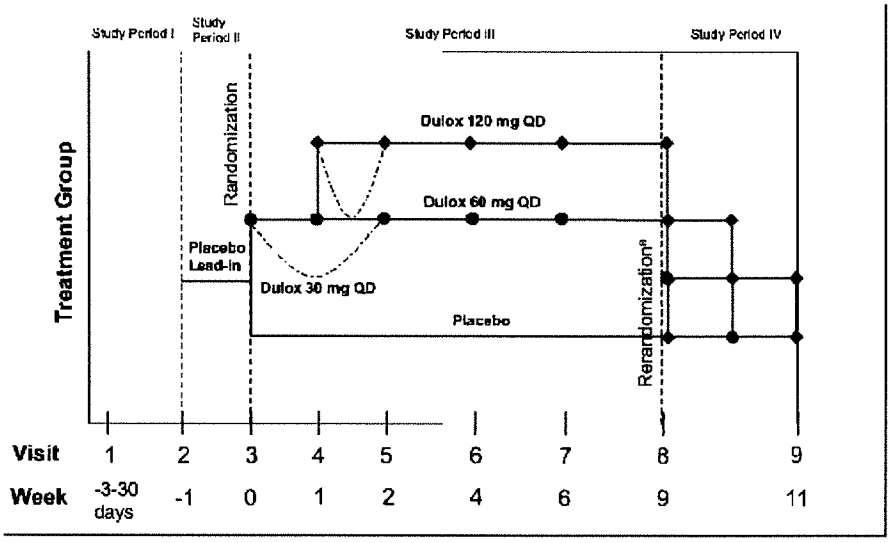


9. Investigational Plan

9.1. Overall Study Design and Plan: Description

Study F1J-MC-HMBR was a multi-center, randomized, double-blind, placebo-controlled Phase 3 study with a single-blind placebo lead-in designed to assess the acute effects of 60 mg once daily (QD) and 120 mg QD doses of duloxetine in the treatment of generalized anxiety disorder (GAD). Patients who met criteria for GAD as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) were eligible to participate in this study. Following a 3- to 30-day screening phase and a 5- to 9-day single-blind placebo lead-in, eligible patients were randomly assigned at Visit 3 to receive treatment with duloxetine 60 mg QD, duloxetine 120 mg QD, or placebo in a 1:1:1 ratio. Approximately 480 patients (160 per treatment group) were planned to be randomly assigned to double-blind treatment. The study design, illustrated in Figure HMBR.9.1, consisted of four study periods.

Figure HMBR.9.1 presents the study design.



Abbreviations: Dulox – duloxetine, QD – once daily.

a One-half of the patients in the duloxetine 60 mg QD and duloxetine 120 mg QD treatment groups started on placebo immediately following Visit 8, whereas the other half of the patients in these treatment groups tapered off duloxetine.

Figure HMBR.9.1. Study design for Study F1J-MC-HMBR.

9.2. Discussion of Study Design, Including the Choice of Control Groups

Study HMBR was a multi-center, randomized, double-blind, placebo-controlled Phase 3 study with a single-blind placebo lead-in consisting of up to 9 weeks of therapy with three treatment groups.

This study was designed to assess the efficacy of duloxetine in the treatment of anxiety in patients with GAD. Because patients diagnosed with anxiety disorders are responsive to placebo, placebo was used as the comparator for duloxetine during the acute therapy phase, despite the risk of a possible worsening of symptoms. There have been estimates of placebo response rates in GAD clinical trials as high as 67% (Loebel et al. 1986). In addition, non-specific treatment effects, such as time (Schweizer and Rickels 1997; Emilien et al. 1998), interaction with a medical professional, or regression to the mean in patients who began the study with more severe symptoms of illness, are associated with improvement in most placebo-treated patients. Patients were allowed to discontinue participation at any time for any reason, including non-response or an inadequate response. Thus, the risk was minimized that GAD symptoms in these patients would worsen during this placebo-controlled study.

Double-blind, placebo-controlled studies are the standard used to assess efficacy in randomized clinical trials of anti-anxiety agents. A duration of at least 8 to 12 weeks is often necessary to adequately assess efficacy.

9.3. Selection of Study Population

Patients enrolled in this study met the DSM-IV criteria for GAD. Patients had a disease severity of at least moderate intensity as defined by a Hospital Anxiety and Depression Scale (HADS) anxiety subscale score of ≥10 and a Covi Anxiety Scale (CAS) score ≥9. No item in the Raskin Depression Scale (RDS) scale was >3. The CAS score was greater than the RDS score. In addition, patients had a Clinical Global Impressions of Severity (CGI-Severity) score ≥4 at Visit 1 and Visit 2.

The Mini-International Neuropsychiatric Interview (MINI) was used to establish the diagnosis and exclude other psychiatric illnesses at Visit 1. The MINI is a standardized diagnostic interview based on DSM-IV criteria. Patients with comorbid social phobia or specific phobia were allowed to participate in the study provided that GAD was the primary diagnosis, defined as the symptoms of GAD being more prominent than the symptoms of Social Phobia or Specific Phobia.

9.3.1. Inclusion Criteria

Patients were eligible to be included in the study only if they met **all** of the following criteria:

[1] Were male and female outpatients at least 18 years of age, presenting with GAD based on the disease diagnostic criteria. Suffered from GAD and not from an adjustment disorder or anxiety disorder not otherwise specified. The symptoms of GAD were not situational in nature.

[2] Were females of childbearing potential (not surgically sterilized and between menarche and 1 year postmenopause) who were not breastfeeding; tested negative for pregnancy at the time of enrollment based on a serum pregnancy test; and agreed to use a reliable method of birth control (for example, use of oral contraceptives or Norplant®; a reliable barrier method of birth control: diaphragms with contraceptive jelly; cervical caps with contraceptive jelly; condoms with contraceptive foam; intrauterine devices; partner with vasectomy; or abstinence) during the study and for 1 week following the last dose of study drug.

[3] Had a CGI-Severity score ≥4 at Visit 1 and Visit 2.

[4] At Visit 1, patient had a CAS score ≥9, no item in the RDS was >3, and the CAS score was greater than the RDS score.

[5] Had HADS anxiety subscale score ≥10 at Visit 1.

9.3.2. Exclusion Criteria

Patients were excluded from the study for **any** of the following reasons:

[6] Were investigator site personnel directly affiliated with the study, or were immediate family of investigator site personnel directly affiliated with the study. Immediate family was defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[7] Were employed by Lilly or Boehringer Ingelheim (BI) (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly or BI employees may participate in Lilly-sponsored clinical trials, but were not permitted to participate at a Lilly facility. Immediate family was defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[8] Had received treatment within the last 30 days with a drug (not including study drug) that had not received regulatory approval for any indication at the time of study entry.

[9] Had previously completed or withdrawn from this study or any other study investigating duloxetine or had previously been treated with duloxetine.

[10] Any current DSM-IV Axis I diagnosis other than GAD.

- Patients diagnosed with major depressive disorder (MDD) within the past 6 months at the time of study entry.
- Patients diagnosed with panic disorder, post-traumatic stress disorder, or an eating disorder within the past year at the time of study entry.
- Obsessive-compulsive disorder, bipolar affective disorder, psychosis, factitious disorder, or somatoform disorders during their lifetime.

[11] The presence of an Axis II disorder or history of antisocial behavior, which, in the judgment of the investigator, would interfere with compliance with the study protocol.

[12] History of alcohol or any psychoactive substance abuse or dependence (as defined in the DSM-IV) within the past 6 months at the time of study entry.

[13] Excessive use of caffeine, in the opinion of the investigator. **Note:** Tapering of caffeine-containing substances was permitted during the screening period as long as stabilization at a permitted level of use for 7 days had been established before Visit 2.

[14] A positive urine drug screen for any non-prescribed substance at Visit 1.

[15] Benzodiazepine use 14 days prior to Visit 2.

[16] Patients judged clinically at serious suicidal risk at the time of study entry, or patients who, in the opinion of the investigator, were poor medical or psychiatric risks for study completion.

[17] Serious medical illness, including any cardiovascular, hepatic, renal, respiratory, hematologic, endocrinologic, or neurologic disease, or clinically significant laboratory abnormality that was not stabilized or was anticipated to require hospitalization within 6 months at the time of study entry, in the opinion of the clinical investigator. Clinically significant laboratory abnormalities were those that, in the judgment of the investigator, indicated a serious medical problem.

[18] Acute liver injury (such as hepatitis) or severe (Child-Pugh Class C) cirrhosis.

[19] Abnormal thyroid-stimulating hormone (TSH) concentrations (outside the reference range of the performing laboratory). **Note:** Patients previously diagnosed with hyperthyroidism or hypothyroidism who had been treated on a stable dose of thyroid supplement for at least the past 3 months at the time of study entry, had medically appropriate TSH concentrations, and were clinically euthyroid were allowed.

[20] Initiation of psychotherapy, change in intensity of psychotherapy or other non-drug therapies (such as acupuncture or hypnosis) within 6 weeks prior to enrollment or at any time during the study.

[21] Taking any excluded medication within 7 days prior to Visit 2.

[22] Treatment with a monoamine oxidase inhibitor (MAOI) or fluoxetine within 30 days of Visit 2 or potential need to use an MAOI during the study or within 5 days of discontinuation of study drug.

[23] Lack of response to two or more adequate trials of antidepressants and/or benzodiazepines at a clinically appropriate dose for a minimum of 4 weeks.

[24] History of severe allergies, hypersensitivity to duloxetine or to any of the inactive ingredients; multiple adverse drug reactions; transcranial magnetic stimulation (TMS); history of seizures; or history of psychosurgery or electroconvulsive therapy (ECT) within 12 months at the time of study entry.

[25] Patients with uncontrolled narrow-angle glaucoma.

9.3.3. Removal of Patients from Therapy or Assessment

The criteria for enrollment were followed explicitly. If a patient who did not meet enrollment criteria was inadvertently enrolled, that patient was discontinued from the study and Lilly or its designee was contacted. An exception may have been granted in very rare circumstances where there was a compelling safety reason to allow the patient to continue. In these rare cases, the investigator obtained documented approval from Lilly to allow the patient to continue in the study.

In addition, patients were discontinued from the study in the following circumstances:

- The investigator decided that the patient should be withdrawn from the study. If this decision was because of a serious adverse event or a clinically significant laboratory value, the study drug was to be discontinued and appropriate measures were to be taken. Lilly or its designee was to be notified immediately.
- The patient or attending physician requested that the patient be withdrawn from the study.
- The patient, for any reason, required treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurred immediately upon introduction of the new agent.
- The patient was deemed by the investigator or Lilly to be noncompliant with protocol requirements.

- The investigator or Lilly, for any reason, stopped the study or stopped the patient's participation in the study.
- The patient became pregnant.

Patients who discontinued the study early had procedures performed as shown in Protocol Attachment HMBR.1 (Study Schedule).

Note: If the patient discontinued before taking any study drug, a physical examination was not repeated as part of the early discontinuation procedures.

9.4. Treatments

9.4.1. Treatments Administered

Study HMBR involved a comparison of duloxetine 60 mg once daily (QD) and duloxetine 120 mg QD with placebo. Placebo was given at Visit 2. Duloxetine 60 mg QD, duloxetine 120 mg QD, or placebo was given to eligible patients for approximately 9 weeks beginning at Visit 3. A 2-week drug-tapering phase began at the completion of Visit 8. Study drug was administered orally.

The investigator or his/her designee was responsible for explaining the correct use of the investigational agent(s) to the patient and study personnel, verifying that instructions were followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to Lilly at the end of the study.

Table HMBR.9.1 demonstrates the treatment regimens to be used in Study HMBR.

Table HMBR.9.1. Treatment Regimens

Study Period	Blinding	Treatment	Dosage Form and Strength	Frequency	Dose Duration	Packaging
Placebo lead-in phase	Single-blind	Placebo	Placebo capsules	4 placebo capsules QD	5- to 9-days	Blister cards
Acute Treatment phase	Double-blind	60 mg QD duloxetine	30 mg duloxetine capsules and placebo capsules	2 duloxetine 30 mg capsules and 2 placebo capsules QD	9 weeks	Blister cards
		120 mg QD duloxetine	30 mg duloxetine capsules and placebo capsules	2 duloxetine 30 mg capsules and 2 placebo capsules QD for 1 week, followed by 4 duloxetine 30 mg capsules QD	9 weeks	Blister cards
		Placebo	Placebo capsules	4 placebo capsules QD	9 weeks	Blister cards
Drug-Tapering Phase	Double-blind	60 mg QD duloxetine re-randomized to 30 mg QD or placebo	30 mg duloxetine capsules and placebo capsules or placebo capsules	1 duloxetine 30 mg capsule and 3 placebo capsules QD or placebo capsules QD	2 weeks	Blister cards
		120 mg QD duloxetine re-randomized to 60 mg QD followed by 30 mg QD or placebo	30 mg duloxetine capsules and placebo capsules or placebo capsules	2 duloxetine 30 mg capsules and 2 placebo capsules QD followed by 1 duloxetine 30 mg capsule and 3 placebo capsules QD or placebo capsules QD	2 weeks	Blister cards
		Placebo	Placebo capsules	4 placebo capsules QD	2 weeks	Blister cards

Abbreviations: QD = once daily.

9.4.2. Identity of Investigational Products

Capsules containing duloxetine and placebo were identical in appearance. Study medication was dispensed to patients at the study site. All study medication was packaged in blister packets. The blister packets were labeled with a unique identifier for drug accountability. Patients were given a sufficient number of capsules to supply the required doses for the duration of the visit interval.

Appendix 16.1.6 provides additional information concerning lot numbers for the study drug used in this study.

Clinical trial materials were labeled according to the country's regulatory requirements. Table HMBR.9.2 lists the materials and supplies to be used in Study HMBR.

Table HMBR.9.2. Materials and Supplies

Study Drug	Dose Strength	Source	Dose Form	Packaging
Duloxetine	120 mg QD	Eli Lilly & Company Indianapolis, IN	Capsules	Blister Packs
Duloxetine	60 mg QD	Eli Lilly & Company Indianapolis, IN	Capsules	Blister Packs
Placebo	N/A	Eli Lilly & Company Indianapolis, IN	Capsules	Blister Packs

Abbreviations: N/A – not applicable; QD – once daily.

9.4.3. Method of Assigning Patients to Treatment Groups

A patient number was assigned to each patient after the informed consent document (ICD) was signed and dated. The identification number and the patient's initials appeared on all patient-related documents. Randomization occurred at Visit 3. To achieve a relative balance across treatment with regard to baseline severity of GAD, treatment assignment was given randomly by the stratum determined by patients' Hamilton Anxiety Rating Scale (HAMA) total score at Visit 3 (<22 or ≥ 22) within each study site.

Assignment to treatment groups was determined by a computer-generated random sequence using an interactive voice response system (IVRS). Site personnel confirmed that they had located the correct blister card by entering a confirmation number found on the card into the IVRS.

Appendix 16.1.7 provides a listing of the randomization codes, patient identifiers, and treatment assignments.

9.4.4. Selection of Doses in the Study

There were previously no studies of duloxetine in the treatment of GAD. The safety and efficacy of other drugs with similar mechanisms of action has been studied in patients with GAD. In these studies, a safe and effective dose of selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs), similar to that found to be safe and effective in MDD trials, was used. Safety and efficacy results in the GAD trials were comparable to those previously observed in MDD trials.

A similar strategy was used to determine rationale for the selection of the optimal dose range of duloxetine for the treatment of GAD. Based upon the results observed in duloxetine studies, the dose range used in the safe and effective treatment of patients with MDD was also used in the treatment of patients with GAD. Duloxetine was safe and effective in the treatment of patients with MDD at doses of 60 mg QD to 120 mg twice daily (BID). The selection of duloxetine doses was made based on tolerance and exposure levels seen in Phase 3 studies as well as safety and efficacy data from studies with duloxetine.

9.4.5. Selection and Timing of Dose for Each Patient

An IVRS was used to assign a study drug package number for each patient at Visit 2 through Visit 8. Beginning at Visit 2, all patients were instructed to take study medication once daily for the remainder of the study. Patients began taking study medication the day after Visit 2. At all subsequent visits, patients took their regularly scheduled dose prior to the visit.

Patients took 4 capsules, preferably in the morning (without regard to meals), throughout the study. If unable to tolerate the randomized dose, patients were instructed to decrease to 2 capsules in the morning; however, patients increased to 4 capsules by Visit 5. Study drug was swallowed whole. Capsules were not crushed or broken.

9.4.6. Blinding

This was a double-blind study. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. Unblinding did not occur until the reporting database was validated and locked for final statistical analysis. Database lock occurred on 16 November 2005.

All study drugs used were identical in color, shape, smell, and taste. Emergency codes, generated by a computer drug-labeling system, were available to the principal investigator (PI). These codes, which revealed the patient's treatment group when opened, could be opened during the study only if the choice of follow-up treatment depended on the patient's therapy assignment. The PI was instructed to make every effort to contact the Lilly clinical research physician (CRP) before unblinding a patient's treatment assignment. If a patient's treatment assignment was unblinded, the Lilly CRP

was to be notified immediately by telephone. After the study, the PI was to return all sealed and any opened codes. If a PI, site personnel performing assessments, or patient was unblinded, the patient was to be discontinued from the study unless there were ethical reasons to have the patient remain in the study. In these special cases, the PI was to obtain specific approval from Lilly's CRP for the patient to continue in the study.

Three patients' treatment assignments were unblinded by the investigator prior to datalock on 16 November 2005; Patient 202-2222 (DLX60QD), Patient 204-2410 (Placebo), and Patient 210-2103 (DLX120QD). Patient 202-2222 was unblinded and subsequently discontinued from the study after completing Visit 7. Patient 204-2410 discontinued from the study after completing Visit 6 and unblinding occurred after the patient had discontinued treatment. Patient 210-2103 was unblinded and subsequently discontinued from the study after completing Visit 8. The sites indicated that they inadvertently unblinded treatment assignment on these patients. It was not clear if the patients last visit data was collected before unblinding; therefore additional analyses were conducted on the primary efficacy measure excluding these three patients. The findings of the study were not impacted due to the unblinding (Table HMBR.14.44).

9.4.7. Prior and Concomitant Therapy

All medications (other than study drug) taken during the study were recorded on the case report form (CRF) or as designated by the protocol. Patients were instructed to consult with the investigator or study coordinator at the site before taking any new medications or supplements. Any use of excluded medication was a violation of the protocol and was documented. Section 10.2 provides a discussion of important protocol violations.

9.4.8. Treatment Compliance

Investigators assessed compliance with the required study drug regimen at each visit, from Visit 3 through Visit 9. Compliance was assessed by direct questioning and by counting returned study drug. All unused study drug was returned to Lilly. Compliance for each visit interval was defined as taking at least 80% and not more than 120% of the study drug dosage prescribed for that interval. Noncompliant patients were discontinued from the study. Any deviation from the prescribed dosage regimen (whether or not the patient was deemed noncompliant) required explanatory documentation.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Study Schedule

The following efficacy measures were collected at the times shown in Table HMBR.9.4 (Study Schedule). Appendix 16.1.2 contains a sample CRF.

- The Hamilton Anxiety Rating Scale (HAMA, Hamilton 1959)
- Hospital Anxiety and Depression Scale (HADS)
- HAMA Factors and Individual Items
- Clinical Global Impressions of Improvement (CGI-Improvement) scale
- Patient Global Impressions of Improvement (PGI-Improvement) scale
- Visual Analog Scale (VAS) for Pain
- Symptom Questionnaire-Somatic Subscale (SQ-SS).

The following health outcome measures were collected at the times shown in Table HMBR.9.4 (Study Schedule):

- Sheehan Disability Scale (SDS)
- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
- EuroQol Questionnaire – 5 Day (EQ-5D).

The following safety measurements were collected at the times shown in Table HMBR.9.4 (Study Schedule):

- **Adverse Events (AEs):** During the study, AEs were collected at every visit, regardless of relationship to study drug. These events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities® (MedDRA®) terms by blinded Lilly clinical personnel.
- **Concomitant Therapies:** Concomitant therapies taken during the study were recorded.
- **Laboratory Data:** During the study, standard laboratory tests, including chemistry, hematology, and urinalysis panels, were collected at regular intervals. A urine drug screen, thyroid function test, and pregnancy test (if applicable) were completed at baseline.
- **Vital Signs:** During the study, vital signs, including blood pressure (systolic and diastolic), pulse rate, weight, and height, were collected at regular intervals.
- **Electrocardiograms (ECGs):** An ECG was collected at baseline end of acute therapy phase, or study discontinuation. .

Table HMBR.9.3. Study Schedule, Protocol F1J-MC-HMBR

	Study Period I	Study Period II	Study Period III						Study Period IV	Early D/C
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**Visits 3-8**
Week Relative to Randomization		-1	0	1	2	4	6	9	11	
Informed consent obtained	X									
Patient number assigned	X									
Medical history	X									
Medication history	X									
Pre-Existing conditions	X									
Demographics	X									
Patient habits										
Alcohol use		X						X		X
Smoking		X								
Psychiatric assessment (MINI)	X									
Covi Anxiety Scale	X									
Raskin Depression Scale	X									
CGI-Severity	X	X								
HADS	X		X					X		X
Physical examination	X									
Weight		X						X		X
Height		X								
Vital signs	X	X	X	X	X	X	X	X	X	X
ECG (12-lead)		X						X		X

(continued)

Table HMBR.9.3. Study Schedule, Protocol F1J-MC-HMBR (continued)

	Study Period I	Study Period II	Study Period III						Study Period IV	Early D/C
Visit Week Relative to Randomization	**V1**	**V2** -1	**V3** 0	**V4** 1	**V5** 2	**V6** 4	**V7** 6	**V8** 9	**V9** 11	**Visits 3-8**
Concomitant meds	X	X	X	X	X	X	X	X	X	X
Laboratory analyses										
Clinical chemistry	X					X		X	X	X
Hematology	X							X	X	X
$HgbA_{1c}$	X							X		X
Urinalysis	X									
Thyroid function	X									
Urine drug screen	X									
Serum pregnancy[a]	X									
Patient assigned to treatment group			X					X		
Medication dispensed		X	X	X	X	X	X	X		
Study drug compliance			X	X	X	X	X	X	X	X
HAMA		X	X	X	X	X	X	X		X
CGI-Improvement				X	X	X	X	X		X[b]
PGI-Improvement				X	X	X	X	X		X[b]

(continued)

Table HMBR.9.3. Study Schedule, Protocol F1J-MC-HMBR (concluded)

	Study Period I	Study Period II	Study Period III						Study Period IV	Early D/C
Visit Week Relative to Randomization	V1	V2 -1	V3 0	V4 1	V5 2	V6 4	V7 6	V8 9	V9 11	Visits 3-8
VAS		X	X	X	X	X	X	X		X
SQ-SS			X			X		X		X
SDS			X					X		X
Q-LES-Q-SF			X					X		X
EQ-5D			X					X		X
Adverse events		X	X	X	X	X	X	X	X	X
Patient Summary									X	X

Abbreviations: CGI-Improvement = Clinical Global Impressions of Improvement Scale; CGI-Severity = Clinical Global Impressions of Severity Scale; D/C = discontinuation; ECG = electrocardiogram; EQ-5D = EuroQol Questionnaire 5 Day; HADS = Hospital Anxiety and Depression Scale; HAMA = Hamilton Anxiety Rating Scale; MINI = Mini-International Neuropsychiatric Interview; PGI-Improvement = Patient Global Impressions of Improvement; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; SDS = Sheehan Disability Scale; SQ-SS = Symptom Questionnaire Somatic Subscale; V = visit; VAS = Visual Analog Scale; X = performed at this visit.

[a] Females of childbearing potential only.

[b] Collect only if patient discontinues at Visit 4 through Visit 8. Do not collect if patient discontinues at Visit 3.

9.5.2. Appropriateness of Measurements

The efficacy and safety assessments used in this study have been well documented and are generally regarded as reliable, accurate, and relevant.

9.5.3. Primary Efficacy Variable

The HAMA is a clinician-administered rating scale used to assess the severity of anxiety, its improvement during the course of treatment, and the timing of such improvement (Riskind et al. 1987). The scale consists of 14 items, which provide an overall measure of general anxiety, including psychic anxiety and somatic anxiety. Each item is rated on a 5-point scale of 0 (not present) to 4 (very severe). The HAMA total score is the sum of the 14 items and ranges from 0 to 56. Higher scores indicate a greater degree of symptom severity.

9.5.4. Drug Concentration Measurements

Drug concentration measurements were not assessed in this study.

9.6. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives did the following:

- provided instructional material to the study sites, as appropriate
- sponsored a start-up training session to instruct the investigators and study coordinators
- made periodic visits to the study sites
- were available for consultation and stayed in contact with study site personnel by mail, telephone, and/or fax
- reviewed and evaluated CRF data and used standard computer edits to detect errors in data collection
- conducted a quality review of the reporting database.

A central laboratory was used to maintain consistency of methods and to combine laboratory data across study sites and/or across studies. (See Appendix 16.1.10 for reference ranges.)

To ensure the safety of patients in the study and to ensure accurate, complete, and reliable data, the investigator kept records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.

Lilly or its representative periodically checked a sample of the patient data recorded against source documents at the study site.

Quintiles audited the study (Appendix 16.1.8).

9.7. Statistical Methods and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

The protocol for this study was approved on 04 February 2004 and was amended on 27 October 2004 and 08 September 2005. Section 9.8 provides further details about protocol amendments. The statistical analysis plan (SAP), which supersedes the statistical plans described in the protocol, was approved on 15 November 2005. The collection database, which contains data collected on the CRFs and other source data (GLS data, which are laboratory and electrocardiogram results and comments), was validated and subsequently locked for analysis on 16 November 2005. The analyses presented in this report are based on data contained in the Analysis Data Sets (ADS, also referred to as the reporting database), an archived production database used for analysis purposes, which contains source data and derived data. The programs used to create the reporting database from the collection database were validated and put into production on 15 November 2005. The reporting database was created on 17 November 2005. After this date, some programming errors were detected. The programs to create the reporting database were updated due to these errors and were put back into production on 16 December 2005. The collection database (source data) remained unchanged.

This section addresses the statistical analyses planned before unblinding, as described in the protocol and SAP. Section 9.8 addresses changes made to the planned statistical analyses after unblinding.

9.7.1.1. General Considerations

All analyses were conducted on an intent-to-treat (ITT) basis, meaning that data was analyzed by the treatment groups to which patients were randomly assigned, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not comply with the protocol.

Treatment effects were evaluated based on a two-sided significance level of 0.05 and interaction effects at 0.05. No adjustments for multiple comparisons were made. No justification was made for any of the pairwise comparisons, given that the interests of the study were to evaluate each individual duloxetine dose versus placebo in terms of efficacy.

Unless otherwise specified, when an analysis of variance (ANOVA) model was used to analyze a continuous efficacy variable, the model contained the main effects of treatment and investigator. Similar logic was applied to an analysis of covariance (ANCOVA) model, which, in general, refers to the ANOVA model with baseline values added as a covariate. Type III sum-of-squares for the least-squares means (LSMean) was used for the statistical comparison using ANOVA or ANCOVA. Unless otherwise specified, pairwise comparisons were always performed when evaluating efficacy measures.

Unless otherwise specified, in all the analyses for the acute therapy phase, "baseline" refers to the last non-missing observation at or before randomization visit (Visit 3), and "endpoint" refers to the last non-missing observation in the acute therapy phase (at or before Visit 8).

Changes made to the data analysis methods as described in the protocol, with the exception of the change to the primary efficacy analysis, did necessitate a protocol amendment. All changes to the analysis plan, after unblinding the data, are documented and justified in this final clinical study report.

Additional exploratory analyses of the data were conducted as deemed appropriate. Statistical analysis of this protocol was the responsibility of Eli Lilly and Company. SAS® software was used to perform all statistical analyses.

9.7.1.2. Adjustments for Covariates

An ANCOVA, which is an ANOVA model with baseline values added as a covariate, was used.

9.7.1.3. Handling of Dropouts or Missing Data

When computing total, factor, or subscale scores for selected efficacy and health outcome measures with missing items, the following procedures were used:

- If ≤20% of the items were missing, the mean score for all other items was imputed as the score for the missing item(s) when computing the total, factor, or subscale score.
- If >20% of the items were missing, then the total, factor, or subscale score was considered missing.

This imputation method was used for the following questionnaires: HAMA, HADS, Q-LES-Q-SF, and the SQ-SS. The HAMA total score that was calculated via this imputation method was considered the primary outcome. Any variables that were calculated based upon HAMA total score used this imputed score (examples include response criteria, remission criteria, and sustained improvement criteria).

Sensitivity analysis on the imputation methods was performed on the primary endpoint only (HAMA total score) as follows:

- Method 1: If any of the individual items on the HAMA were missing, then the HAMA total score was considered missing.
- If ≤1% of the data differed between the primary method of imputation and Method 1, no additional sensitivity analyses were performed. Otherwise, an additional method was done.

- Method 2: If ≤20% of the items were missing, then the item(s) score(s) from the previous visit(s) was used as the score for the missing item(s) when computing the total score. If >20% of the items were missing, then the total score was considered missing.

9.7.1.4. Multicenter Studies

All investigative sites with fewer than 12 randomly assigned patients with non-missing change scores on HAMA total were pooled together within each country and considered a single site for analyses. If this resulted in a site still having fewer than 12 patients, these sites were pooled together with the next smallest site in that country.

9.7.1.5. Multiple Comparisons/Multiplicity

The primary efficacy analysis was the comparison of duloxetine 60 mg QD placebo in change from baseline to endpoint on the HAMA total score.

A gatekeeper strategy (Westfall and Krishen 2001) was employed for testing the secondary gatekeeper hypothesis.

No adjustments for multiple comparisons were made.

9.7.1.6. Use of an "Efficacy Subset" of Patients

No "efficacy subset" analysis was performed.

9.7.1.7. Patient Disposition

Reasons for discontinuation from the study were summarized for all study phases. The reasons for study discontinuation during the acute therapy phase were compared between treatment groups using Fisher's exact test.

9.7.1.8. Patient Characteristics

Standard baseline characteristics of gender, age, and origin were summarized for all randomly assigned patients in the double-blind acute therapy phase. Baseline psychiatric and other symptom measurements (HAMA, HADS, CGI-Severity scale, VAS, and SQ-SS) were summarized for all randomly assigned patients in the 9-week, double-blind, acute therapy phase. Alcohol consumption and smoking status at baseline were also summarized. Comparisons among treatment groups were performed using Fisher's exact test for categorical data and an ANOVA model for continuous data.

9.7.1.9. Treatment Compliance

A patient was defined to be compliant at a visit if he/she has taken at least 80% and not more than 120% of the study drug dosage prescribed for that interval. A patient was considered overall compliant for the double-blind treatment phase if all nonmissing visit wise compliance data from Visit 4 through Visit 8 indicated compliance. Proportions of

patients compliant by visit and overall were compared among treatment groups during the 9-week, double-blind acute therapy phase using Fisher's exact test.

9.7.1.10. Concomitant Therapy

Previous drug therapy for treatment of GAD was compared among treatment groups using Fisher's exact test. The percentage of patients who took benzodiazepine prior to study entry were summarized and analyzed by Fisher's exact test. Concomitant medications used during the double-blind acute therapy phase were compared among treatment groups using Fisher's exact test. Concomitant medications used during the drug-tapering phase were summarized by treatment group.

9.7.1.11. Efficacy Analyses

The primary efficacy analysis was the comparison of duloxetine 120 mg QD with placebo in mean change from baseline to endpoint in the HAMA total score for the double-blind acute therapy phase. The treatment group differences were evaluated using the ANCOVA model as specified in Section 9.7.1.1, General Considerations.

9.7.1.11.1. Secondary Efficacy Analyses

9.7.1.11.1.1. Secondary Gatekeeper Analyses

A gatekeeper strategy (Westfall and Krishen 2001) was employed for testing the secondary gatekeeper hypothesis to be eligible for possible inclusion in the label. The secondary gatekeeper objective for the study was to evaluate the efficacy of duloxetine 120 mg QD compared with placebo during a 9-week, double-blind, acute therapy phase on the improvement on the Sheehan Disability Scale (SDS) Global Functional Impairment score (Sheehan 1983).

Treatment group differences were evaluated using the ANCOVA model as specified in Section 9.7.1.1, General Considerations.

9.7.1.11.1.2. Additional Secondary Analyses

Table HMBR.9.5 lists the variables and which were either collected directly from the CRFs or derived from the raw observations, and the corresponding analyses on those variables.

Table HMBR.9.4. Secondary Efficacy Variables and Their Derivation

Efficacy Variable	Derivation	Analysis
1. Change from baseline to endpoint: a. HADS subscales (depression and anxiety). b. HAMA factor scores and individual items. c. VAS scores (average pain, shoulder pain, back pain). d. SQ-SS total score.	HADS Anxiety Subscale score: The sum of the odd-numbered items. Depression Subscale score: The sum of the even-numbered items. HAMA: Psychic Anxiety Factor Score: The sum of items 1 through 6, and 14. Somatic Anxiety Factor Score: The sum of items 7 through 13. HAMA individual items. VAS: The six questions regarding the experience of overall pain, headache, back pain, shoulder pain, pain interference with daily activities, and proportion of the day with pain. SQ-SS total score: The sum of 23 items.	Variables as classified by 1a to 1d were analyzed by the ANCOVA models as described in Section 9.7.1.1, General Considerations.

(continued)

Table HMBR.9.4. Secondary Efficacy Variables and Their Derivation (continued)

2. Change from baseline to the observation at each postbaseline visit in the acute therapy phase (by Visit 8) for: a. HAMA total score. b. HADS subscale (depression and anxiety). c. HAMA factor scores. d. VAS scores (average pain, shoulder pain, back pain, etc). e. SQ-SS total score.	See definitions above	Variables 2a to 2e were analyzed by a repeated measures analysis. The model details are described in text beneath these tables.
3. Endpoint and all postbaseline data for: a. CGI-Improvement. b. PGI-Improvement.		The endpoint scores were analyzed by the ANOVA model as described in Section 9.7.1.1, General Considerations. All the data collected during the post-baseline visits were analyzed by a repeated measures analysis. The model was similar to the one used for the variables in the above group, with the modifications that there are no baseline effects in the model.

(continued)

Table HMBR.9.4. Secondary Efficacy Variables and Their Derivation (concluded)

4. Categorical variable: a. Response rate at endpoint. b. Remission rate at endpoint. c. Sustained Improvement	a. Response: at least 50% reduction from baseline to endpoint on HAMA total score b. Remission: HAMA total score ≤7 at endpoint (Ballenger 1999). c. Sustained Improvement: will be defined with 2 time points. 1) overall sustained improvement: at least a 30% improvement (reduction) on the HAMA total score from baseline to endpoint, at an earlier visit prior to the last visit of the study period, and at all visits in between. 2) 30% improvement on the HAMA total score from baseline to Week 1 and sustained through the last visit of the study period.	For variables 4a and 4c, treatment group differences were analyzed by using a Cochran-Mantel-Haenszel (CMH) test controlling for Investigator.
5. Time-to-event variable: a. Time-to-first 50% reduction in HAMA total score. b. Time-to-first remitted HAMA total score. c. Time to sustained improvement (onset of action)	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. b. For the patients with a HAMA total score ≤ 7 (remitted score) at a visit, time = date of the visit that the earliest remitted HAMA total is observed the randomization date; for the others, time = date of last visit - the randomization date. c. For the patients with at least a 30% improvement (reduction) on the HAMA total score from baseline to endpoint, at an earlier visit prior to the last visit of the study period, and at all visits in between., time=date of the earliest visit at which sustained 30% improvement on HAMA total score is observed– the randomization date; for the others, time=date of last visit - the randomization date.	For variables 5a and 5c, 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 between treatment groups was conducted by a log-rank test and the stratified log-rank test controlling for investigator (Using PROC LIFETEST).

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CGI-Improvement = Clinical Global Impressions of Improvement Scale; CMH = Cochran-Mantel-Haenszel test; HADS = Hospital Anxiety and Depression Scale; HAMA = Hamilton Anxiety Rating Scale; PGI-Improvement = Patient Global Impressions of Improvement; SQ-SS = Symptom Questionnaire Somatic Subscale; VAS = Visual Analog Scale.

Note: Baseline is defined as the last measurement taken at, or prior to, randomization (Visit 3); endpoint is defined as the last nonmissing measurement taken in the acute therapy phase (at or before Visit 8); last visit is defined as the visit where the endpoint is assessed.

A repeated measures analysis refers to a maximum likelihood-based, mixed-effects repeated measures analysis using all the longitudinal observations at each postbaseline visit. The model included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline score and baseline-by-visit interaction. The unstructured covariance structure was used to model the within-patient errors. If the unstructured covariance matrix led to a lack of convergence, Akaike's Information Criteria was used to select the best fitting covariance structure based on the analysis for the primary efficacy measure, the HAMA total score. The Kenward-Roger method was used to estimate denominator degrees of freedom. Type III sum-of-squares for the LSMean was used. Analyses were implemented using SAS PROC MIXED (Version 8.0). When analyzing efficacy variables using the repeated measures analysis, the treatment group contrasts at the last visit of the acute therapy phase (Visit 8) were primary, and those at earlier postbaseline visits were secondary.

9.7.1.12. Health Outcomes/Quality-of-Life (QoL) Analyses

Patient self-reported health outcomes were assessed in the double-blind acute therapy phase by the SDS, the Q-LES-Q-SF, and the EQ-5D. The SDS analysis was analyzed using an ITT analysis. To be included in the ITT analysis, patients must have had a baseline observation and at least one postbaseline observation. Baseline was defined as the last nonmissing observation from Visit 1 to Visit 3. Endpoint was defined as the last nonmissing observation in the acute therapy phase (at or before Visit 8). The Q-LES-Q-SF and the EQ-5D were analyzed using a completers analysis. To be included in the completers analysis, patients must have had a baseline observation and have completed the acute therapy phase (that is, endpoint is the Visit 8 observation).

The SDS scores assessed the global functional impairment, work/school impairment, social life/leisure activities impairment, and family life/home responsibilities impairment. Change from baseline to endpoint in the SDS impairment scores was evaluated using the ANCOVA model (see Section 9.7.1.1). The SDS global functional impairment score was defined as the sum of the three areas. If an area score was missing for a patient (for example, work/school), the value was imputed using the average of other two scores; if two areas were missing the scores, the global score was considered missing.

Change from baseline to endpoint in Q-LES-Q SF total score was evaluated using the ANCOVA model (see Section 9.7.1.1).

The EQ-5D questionnaire, developed by the EuroQol Group (a network of international, multilingual, multidisciplinary researchers), consisted of 5 items: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, as well as a visual analog scale to rate global health-related quality of life. For each item, patients chose one of the three options that best described their status. The three options, which reflected increasing degrees of difficulty, were coded as 1, 2, and 3. Scores from the five items formed a five-digit code that described the respondent's health state. This five-digit code was then converted to a weighted index (called EQ-5D index) using population values provided by

the EuroQol Group. The change from baseline to endpoint in EQ-5D index and the VAS global health-related quality of life were analyzed using the ANCOVA model (see Section 9.7.1.1).

9.7.1.13. Safety Analyses

Safety analyses included all randomly assigned patients. For change from baseline to endpoint analysis, all randomly assigned patients with a baseline and at least one postbaseline visit were included.

9.7.1.13.1. Acute Therapy Phase

When evaluating safety data, the overall treatment group comparison served the purpose of assessing the significance of the findings; and thus, was primarily reported. Pairwise comparisons between each duloxetine treatment group and the placebo group were also reported when they were necessary for the safety evaluations.

Categorical Safety Variables

Treatment group differences in the incidence rates of serious adverse events were evaluated using Fisher's exact test.

The adverse events reported as reasons for discontinuation were summarized by treatment group and compared among the treatment groups using Fisher's exact tests. Pairwise comparisons using Fisher's exact test were also conducted.

Treatment-emergent adverse events (TEAEs; also called treatment-emergent signs and symptoms [TESS]) are the reported events that first occurred or worsened during the treatment period. For each TEAE, the severity level was recorded according to the patient's or physician's perceived severity of the event (mild, moderate, or severe). The incidence rates of TEAEs was analyzed by Fisher's exact tests for the overall comparison as well as for the pairwise comparisons. Moreover, treatment-emergent adverse events were summarized by their maximum severity as reported while on treatment and analyzed by a Fisher's exact test.

The incidence rates of treatment-emergent abnormal, high, or low laboratory values at endpoint were assessed using Fisher's exact test. A treatment-emergent abnormal value was defined as a change from normal at all baseline visits to abnormal at endpoint. A treatment-emergent high value was defined as a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at endpoint. A treatment-emergent low value was defined as a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at endpoint.

The incidence of treatment-emergent abnormal electrocardiograms (ECGs) was compared between treatment groups using Fisher's exact test.

A patient was considered to have sustained blood pressure elevation during the acute therapy phase if either of the following criteria were met:

- Sitting diastolic blood pressure ≥90 mm Hg and increase from baseline (defined as the highest of all the measures taken at or before randomization) of ≥10 mm Hg for 3 consecutive visits, **or**
- Sitting systolic blood pressure ≥140 mm Hg and increase from baseline (defined as the highest of all the measures taken at or before randomization) of ≥10 mm Hg for 3 consecutive visits.

The percentage of patients having sustained blood pressure elevation was analyzed using Fisher's exact test to evaluate treatment group differences, including overall and pairwise.

The percentage of patients in each of the fasting glucose categories was compared using a Cochran-Mantel-Haenszel test using Row Mean Score Differ for overall p-value (Table HMBR.9.5).

Table HMBR.9.5. Changes in Fasting Glucose

Analyte	Change from Baseline to Endpoint Categories
Fasting glucose	<–0.0 > 0.0 to <–0.5 >.50 to <–1.5 mmol/L (9-27mg/dl) >1.5 mmol/L to <= 2.5 mmol/L (28 - 45 mg/dl) >2.5mmol/L to < =3.5 mmol/L (46 - 63 mg/dl) >3.5 mmol/L to <=4.5 mmol/L (64 - 81 mg/dl) > 4.5 to <=5.5 mmol/L (82 - 99mg/dl) > 5.5 mmol/L (100mg/dl)

Continuous Safety Measures

Mean changes from baseline to endpoint in laboratory analytes, vital signs, weight, and ECG parameters were assessed using the ANOVA model (see Section 9.7.1.1). Rank transform data was used for the laboratory analysis. Raw values were used for the analysis of vital signs, weight, and ECG intervals unless normality assumptions appeared to be violated.

9.7.1.13.2. Drug-Tapering Phase

Duloxetine-treated patients who entered the study drug tapering phase were re-randomly assigned into 4 treatment groups in a double-blind fashion, while placebo-treated patients continued with placebo with blinding maintained. The following safety parameters were collected in this phase: the reason for discontinuation, the incidence of serious adverse events, adverse events reported as reasons for discontinuation, and discontinuation-emergent adverse events (those that first occurred or worsened in the taper phase). Vital signs and weight were also collected.

All the safety parameters assessed in this phase were tabulated by treatment groups.

To evaluate the overall impact of dose of duloxetine and the method of stopping, those safety parameters were also analyzed using a two-way model with the factor of dose (duloxetine 60 mg QD or duloxetine 120 mg QD) and stopping method (abrupt or stepwise). The dose-by-method interaction term was also included in the model. Data from placebo patients was excluded from this type of analysis. To perform the analyses, categorical variables were assessed using a logistic regression model, while continuous variables were evaluated using a two-way ANOVA model.

Moreover, pairwise comparison between each duloxetine treatment group and placebo were analyzed, and between the two treatment groups split after the re-randomization was performed. For those analyses, categorical variables were analyzed by Fisher's exact test. Change from baseline (the last non-missing observation at or before Visit 8) to endpoint (Visit 9) on vital signs and weight was assessed using the ANOVA model (as specified in Section 9.7.1.1).

9.7.1.14. Subgroup Analyses

Table HMBR.9.6 lists the subgroups by which the subgroup analyses for HAMA total score were conducted.

Table HMBR.9.6. Definition of Subgroup Variables

Subgroup Variable	Categories
1. Age	1. <55 or ≥55
2. Gender	2. Female or Male
3. Race origin	3. Caucasian African Descent East/Southeast Asian Western Asian Hispanic Other
4. Severity stratification at baseline	4. HAMA total <22 or >= 22
5. Previous benzodiazepine use	5. Yes or No

Abbreviations: HAMA = Hamilton Anxiety Rating Scale.

To analyze the subgroup impact, the relevant subgroup and the subgroup-by-treatment interaction was added to the ANCOVA model. The treatment-by-subgroup interaction was tested at the significance of 0.05. Treatment group differences were evaluated within each category of the subgroup regardless of whether the interaction was statistically significant.

The treatment-by investigator-was evaluated by using the model described above.

Change from baseline to endpoint on HAMA total was also analyzed for each investigational site using the model described above.

9.7.2. Determination of Sample Size

Approximately 480 patients were estimated to have been enrolled in either the placebo, the duloxetine 60 mg once daily (QD), or the duloxetine 120 mg QD treatment groups. With 160 patients per treatment group, this study had approximately 80% power to detect a treatment group difference of -2.0 points in the baseline-to-endpoint mean change on the HAMA total score between duloxetine 120 mg QD and placebo. The sample size was determined using a two-sided test with significance level of $\alpha = 0.05$, assuming a common standard deviation of 6.0 and that 10% of the patients would miss postbaseline data on the HAMA total score.

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

Appendix 16.1.1 contains the protocol and the two protocol amendments for this study. All changes to the study can be found in these documents.

9.8.2. Changes in the Planned Analyses

Additional analyses added after datalock:

- The table showing the frequency of patients who adjusted their dose during the first 2 weeks of the study treatment was added.
- The table showing the analysis of the primary efficacy measure excluding three patients (Patient 202-2222, Patient 204-2410, and Patient 210-2103) was added because the treatment assignments for these three patients were unblinded prior to datalock.

Analyses deleted after datalock:

- The table showing the change from baseline to endpoint during drug-tapering phase for laboratory values based upon 3 randomized treatment groups was deleted.
- The table showing adverse events reported as reason for discontinuation by decreasing frequency using logistic regression analysis was deleted.
- The table showing discontinuation-emergent adverse events by preferred term by decreasing frequency based upon 3 randomized treatment groups was deleted.
- The table showing adverse events reported as reason for discontinuation by decreasing frequency based upon 3 randomized treatment groups was deleted.
- The Fisher's exact test was removed from the table showing the categorical analysis for laboratory values; only summary results were presented.

- The table showing serious adverse events by decreasing frequency during drug-tapering phase based upon 3 randomized treatment groups was deleted.
- The table showing serious adverse events by decreasing frequency during the drug-tapering phase based upon the method of study drug discontinuation only reports overall p-values; pairwise p-values were deleted.
- The table showing adverse events reported as reason for discontinuation by decreasing frequency by drug-tapering dose only reports overall p-values; pairwise p-values were deleted.

Table HMBR.14.21 summarizes treatment-emergent adverse events by preferred term with decreasing frequency within each system organ class.

Table HMBR.14.22 shows treatment-emergent adverse events (using the MedDRA preferred term as the event descriptor) by maximum severity within system organ class. The majority of the events were categorized as moderate or mild.

Table HMBR.14.23 shows treatment-emergent adverse events by gender. The TEAEs that occurred with significant treatment-group differences with duloxetine 60 mg QD-treated patients experiencing the highest percentage of events compared with placebo-treated patients for female patients were the following: nausea, dry mouth, fatigue, insomnia, constipation, vomiting and anorexia. The TEAEs that occurred with significant treatment-group differences with duloxetine 120 mg QD-treated patients experiencing the highest percentage of events compared with placebo-treated patients for female patients were the following: nausea, dizziness, dry mouth, fatigue, insomnia, constipation, hyperhidrosis, sedation and vomiting. The TEAEs that occurred with significant treatment-group differences with duloxetine 60 mg QD-treated patients experiencing the highest percentage of events compared with placebo-treated patients for male patients were the following: nausea and fatigue. The TEAEs that occurred with significant treatment-group differences with duloxetine 120 mg QD-treated patients the highest percentage of events compared with placebo-treated patients for male patients were the following: nausea, dizziness and fatigue.

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12.2.2.2. Display of Adverse Events: Drug-Tapering Phase

Table HMBR.12.4 summarizes discontinuation-emergent adverse events by MedDRA preferred term in order of decreasing frequency. There was no statistical significance among the study drug stopping method (taper compared with abrupt) during the drug-tapering phase. These findings show that there were not increased adverse events in patients who tapered the medication compared with patients who abruptly discontinued the medication using a Logistic Regression Analysis.

Table HMBR.12.5. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency – Logistic Regression Analysis
All Duloxetine Patients Entering Drug-Tapering Phase
Drug-Tapering Phase

Event	DLX60QD -Abrupt (N=71) n(%)	DLX60QD -Taper (N=64) n(%)	DLX120QD -Abrupt (N=58) n(%)	DLX120QD -Taper (N=66) n(%)	Total (N=259) n(%)	p-Value*
PATIENTS WITH >=1 DISCONTINUATION-EMERGENT EVENT	22(31.0%)	20(31.3%)	21(36.2%)	16(24.2%)	79(30.5%)	.830
Dizziness	7(9.9%)	9(14.1%)	5(8.6%)	7(10.6%)	28(10.8%)	
Headache	4(5.6%)	4(6.3%)	6(10.3%)	4(6.1%)	18(6.9%)	
Insomnia	1(1.4%)	3(4.7%)	3(5.2%)	3(4.5%)	10(3.9%)	
Nausea	3(4.2%)	3(4.7%)	2(3.4%)	0(0.0%)	8(3.1%)	
Paraesthesia	3(4.2%)	1(1.6%)	2(3.4%)	1(1.5%)	7(2.7%)	
Irritability	3(4.2%)	1(1.6%)	0(0.0%)	2(3.0%)	6(2.3%)	
Anxiety	2(2.8%)	2(3.1%)	0(0.0%)	1(1.5%)	5(1.9%)	
Hyperhidrosis	2(2.8%)	1(1.6%)	0(0.0%)	1(1.5%)	4(1.5%)	
Tremor	1(1.4%)	1(1.6%)	1(1.7%)	1(1.5%)	4(1.5%)	
Vertigo	1(1.4%)	2(3.1%)	0(0.0%)	1(1.5%)	4(1.5%)	
Palpitations	2(2.8%)	0(0.0%)	1(1.7%)	0(0.0%)	3(1.2%)	
Abnormal dreams	0(0.0%)	0(0.0%)	1(1.7%)	1(1.5%)	2(0.8%)	
Back pain	1(1.4%)	0(0.0%)	1(1.7%)	0(0.0%)	2(0.8%)	
Feeling hot and cold	0(0.0%)	1(1.6%)	0(0.0%)	1(1.5%)	2(0.8%)	
Nasopharyngitis	2(2.8%)	0(0.0%)	0(0.0%)	0(0.0%)	2(0.8%)	
Nightmare	0(0.0%)	1(1.6%)	1(1.7%)	0(0.0%)	2(0.8%)	
Tachycardia	1(1.4%)	0(0.0%)	1(1.7%)	0(0.0%)	2(0.8%)	
Vision blurred	1(1.4%)	0(0.0%)	1(1.7%)	0(0.0%)	2(0.8%)	
Acute sinusitis	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	

MedDRA Version: 8
N=Number of re-randomized duloxetine patients entering drug-tapering phase
n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using logistic regression with treatment, stopping method and treatment*stopping method in the model.
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD21)
Program: RMP.F1JSHMBR.SASPGM(FQAESD2)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.5. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency – Logistic Regression Analysis
All Duloxetine Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Event	DLX60QD -Abrupt (N=71) n(%)	DLX60QD -Taper (N=64) n(%)	DLX120QD -Abrupt (N=58) n(%)	DLX120QD -Taper (N=66) n(%)	Total (N=259) n(%)	p-Value*
Agitation	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Allergic sinusitis	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	
Asthenia	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.4%)	
Blood creatine increased	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.4%)	
Blood creatine phosphokinase increased	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.4%)	
Blood pressure increased	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	
Chest pain	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	
Cluster headache	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	
Depression	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Diarrhoea	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Dysaesthesia	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Dysarthria	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	
Dyspepsia	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.4%)	
Feeling abnormal	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Formication	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Hepatic enzyme increased	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Hot flush	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.4%)	
Influenza	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Irritable bowel syndrome	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.4%)	
Migraine	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.4%)	
Muscle twitching	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.4%)	

MedDRA Version: 8
N=Number of re-randomized duloxetine patients entering drug-tapering phase
n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using logistic regression with treatment, stopping method and treatment*stopping method in the model.
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD21)
Program: RMP.F1JSHMBR.SASPGM(FQAESD2)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.5. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency – Logistic Regression Analysis
All Duloxetine Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Concluded)

Event	DLX60QD -Abrupt (N=71) n(%)	DLX60QD -Taper (N=64) n(%)	DLX120QD -Abrupt (N=58) n(%)	DLX120QD -Taper (N=66) n(%)	Total (N=259) n(%)	p-Value*
Myalgia	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	
Oral dysaesthesia	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Postnasal drip	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	
Rhinitis allergic	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Sedation	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Shoulder pain	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.4%)	
Sinusitis	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.4%)	
Tinnitus	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.4%)	
Tooth fracture	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)	

MedDRA Version: 8
N=Number of re-randomized duloxetine patients entering drug-tapering phase
n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using logistic regression with treatment, stopping method and treatment*stopping method in the model.
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD21)
Program: RMP.F1JSHMBR.SASPGM(FQAESD2)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.5 summarizes discontinuation-emergent adverse events by MedDRA preferred term in order of decreasing frequency by drug-tapering dose during the drug-tapering phase. Dizziness and headache were the most commonly reported discontinuation-emergent adverse events in the drug-tapering phase.

Table HMBR.12.6. Discontinuation-Emergent Adverse Events Preferred Term by Decreasing Frequency by Drug-Tapering Dose All Patients Entering Drug-Tapering Phase Drug-Tapering Phase

Event	1) PLACEBO (N=130) n(%)	2) DLX60QD -Abrupt (N=71) n(%)	3) DLX60QD -Taper (N=64) n(%)	4) DLX120QD -Abrupt (N=58) n(%)	5) DLX120QD -Taper (N=66) n(%)	Total (N=389) n(%)
PATIENTS WITH >=1 DISCONTINUATION-EMERGENT EVENT	21(16.2%)	22(31.0%)	20(31.3%)	21(36.2%)	16(24.2%)	100(25.7%)
Dizziness	2(1.5%)	7(9.9%)	9(14.1%)	5(8.6%)	7(10.6%)	30(7.7%)
Headache	4(3.1%)	4(5.6%)	4(6.3%)	6(10.3%)	4(6.1%)	22(5.7%)
Insomnia	1(0.8%)	1(1.4%)	3(4.7%)	3(5.2%)	3(4.5%)	11(2.8%)
Nausea	0(0.0%)	3(4.2%)	3(4.7%)	2(3.4%)	0(0.0%)	8(2.1%)
Irritability	1(0.8%)	3(4.2%)	1(1.6%)	0(0.0%)	2(3.0%)	7(1.8%)
Paraesthesia	0(0.0%)	3(4.2%)	1(1.6%)	2(3.4%)	1(1.5%)	7(1.8%)
Anxiety	1(0.8%)	2(2.8%)	2(3.1%)	0(0.0%)	1(1.5%)	6(1.5%)
Hyperhidrosis	0(0.0%)	2(2.8%)	1(1.6%)	0(0.0%)	1(1.5%)	4(1.0%)
Tremor	0(0.0%)	1(1.4%)	1(1.6%)	1(1.7%)	1(1.5%)	4(1.0%)
Vertigo	0(0.0%)	1(1.4%)	2(3.1%)	0(0.0%)	1(1.5%)	4(1.0%)
Nasopharyngitis	1(0.8%)	2(2.8%)	0(0.0%)	0(0.0%)	0(0.0%)	3(0.8%)
Palpitations	0(0.0%)	2(2.8%)	0(0.0%)	1(1.7%)	0(0.0%)	3(0.8%)
Abnormal dreams	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	1(1.5%)	2(0.5%)
Back pain	0(0.0%)	1(1.4%)	0(0.0%)	1(1.7%)	0(0.0%)	2(0.5%)
Blood creatine phosphokinase increased	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	2(0.5%)
Diarrhoea	1(0.8%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	2(0.5%)
Feeling hot and cold	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%)	1(1.5%)	2(0.5%)
Influenza	1(0.8%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	2(0.5%)
Nightmare	0(0.0%)	0(0.0%)	1(1.6%)	1(1.7%)	0(0.0%)	2(0.5%)
Tachycardia	0(0.0%)	1(1.4%)	0(0.0%)	1(1.7%)	0(0.0%)	2(0.5%)
Vision blurred	0(0.0%)	1(1.4%)	0(0.0%)	1(1.7%)	0(0.0%)	2(0.5%)

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.6. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

	p-Values*						
Event	Overall	1 vs. 2	1 vs. 3	1 vs. 4	1 vs. 5	2 vs. 3	2 vs. 4
PATIENTS WITH >=1 DISCONTINUATION-EMERGENT EVENT	.016	.019	.024	.004	.181	1.00	.576
Dizziness	.005	.010	<.001	.030	.007	.595	1.00
Headache	.360	.457	.443	.071	.446	1.00	.343
Insomnia	.159	1.00	.106	.088	.112	.345	.326
Nausea	.021	.043	.035	.094		1.00	1.00
Irritability	.265	.127	.552	1.00	.263	.621	.252
Paraesthesia	.091	.043	.330	.094	.337	.621	1.00
Anxiety	.474	.285	.254	1.00	1.00	1.00	.501
Hyperhidrosis	.201	.124	.330		.337	1.00	.501
Tremor	.362	.353	.330	.309	.337	1.00	1.00
Vertigo	.169	.353	.108		.337	.603	1.00
Nasopharyngitis	.405	.285	1.00	1.00	1.00	.498	.501
Palpitations	.134	.124		.309		.498	1.00
Abnormal dreams	.210			.309	.337		.450
Back pain	.264	.353		.309		1.00	1.00
Blood creatine phosphokinase increased	.878	1.00	1.00	1.00	1.00		
Diarrhoea	.543	1.00	1.00	.523	1.00		.450
Feeling hot and cold	.320		.330		.337	.474	
Influenza	.543	1.00	1.00	.523	1.00		.450
Nightmare	.159		.330	.309		.474	.450
Tachycardia	.264	.353		.309		1.00	1.00
Vision blurred	.264	.353		.309		1.00	1.00

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.6. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

	p-Values*			
Event	2 vs. 5	3 vs. 4	3 vs. 5	4 vs. 5
PATIENTS WITH >=1 DISCONTINUATION-EMERGENT EVENT	.447	.572	.435	.171
Dizziness	1.00	.404	.602	.769
Headache	1.00	.516	1.00	.513
Insomnia	.352	1.00	1.00	1.00
Nausea	.245	1.00	.116	.217
Irritability	1.00	1.00	1.00	.498
Paraesthesia	.620	.604	1.00	.599
Anxiety	1.00	.497	.616	1.00
Hyperhidrosis	1.00	1.00	1.00	1.00
Tremor	1.00	1.00	1.00	1.00
Vertigo	1.00	.497	.616	1.00
Nasopharyngitis	.497			
Palpitations	.497	.475		.468
Abnormal dreams	.482	.475	1.00	1.00
Back pain	1.00	.475		.468
Blood creatine phosphokinase increased	.482		1.00	1.00
Diarrhoea		.475		.468
Feeling hot and cold	.482	1.00	1.00	1.00
Influenza		.475		.468
Nightmare		1.00	.492	.468
Tachycardia	1.00	.475		.468
Vision blurred	1.00	.475		.468

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1J0.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.6. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Event	1) PLACEBO (N=130) n(%)	2) DLX60QD -Abrupt (N=71) n(%)	3) DLX60QD -Taper (N=64) n(%)	4) DLX120QD -Abrupt (N=58) n(%)	5) DLX120QD -Taper (N=66) n(%)	Total (N=389) n(%)
Abdominal pain	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Acute sinusitis	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Agitation	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Allergic sinusitis	0(0.0%)	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Asthenia	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.3%)
Blood creatine increased	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.3%)
Blood pressure increased	0(0.0%)	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Bronchitis	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Chest pain	0(0.0%)	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Cluster headache	0(0.0%)	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Cough	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Depression	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Dysaesthesia	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Dysarthria	0(0.0%)	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Dyspepsia	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.3%)
Ear infection	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Feeling abnormal	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Formication	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Hepatic enzyme increased	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Hot flush	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.3%)
Irritable bowel syndrome	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.3%)
Measles	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Migraine	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.3%)
Muscle twitching	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	1(0.3%)
Myalgia	0(0.0%)	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.6. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

		p-Values*					
Event	Overall	1 vs. 2	1 vs. 3	1 vs. 4	1 vs. 5	2 vs. 3	2 vs. 4
Abdominal pain	1.00	1.00	1.00	1.00	1.00		
Acute sinusitis	.149			.309			.450
Agitation	.149			.309			.450
Allergic sinusitis	.666	.353				1.00	1.00
Asthenia	.314		.330			.474	
Blood creatine increased	.483				.337		
Blood pressure increased	.666	.353				1.00	1.00
Bronchitis	1.00	1.00	1.00	1.00	1.00		
Chest pain	.666	.353				1.00	1.00
Cluster headache	.666	.353				1.00	1.00
Cough	1.00	1.00	1.00	1.00	1.00		
Depression	.149			.309			.450
Dysaesthesia	.149			.309			.450
Dysarthria	.666	.353				1.00	1.00
Dyspepsia	.314		.330			.474	
Ear infection	1.00	1.00	1.00	1.00	1.00		
Feeling abnormal	.149			.309			.450
Formication	.149			.309			.450
Hepatic enzyme increased	.149			.309			.450
Hot flush	.483				.337		
Irritable bowel syndrome	.314		.330			.474	
Measles	1.00	1.00	1.00	1.00	1.00		
Migraine	.314		.330			.474	
Muscle twitching	.314		.330			.474	
Myalgia	.666	.353				1.00	1.00

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.6. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

	p-Values*			
Event	2 vs. 5	3 vs. 4	3 vs. 5	4 vs. 5
Abdominal pain				
Acute sinusitis		.475		.468
Agitation		.475		.468
Allergic sinusitis	1.00			
Asthenia		1.00	.492	
Blood creatine increased	.482		1.00	1.00
Blood pressure increased	1.00			
Bronchitis				
Chest pain	1.00			
Cluster headache	1.00			
Cough				
Depression		.475		.468
Dysaesthesia		.475		.468
Dysarthria	1.00			
Dyspepsia		1.00	.492	
Ear infection				
Feeling abnormal		.475		.468
Formication		.475		.468
Hepatic enzyme increased		.475		.468
Hot flush	.482		1.00	1.00
Irritable bowel syndrome		1.00	.492	
Measles				
Migraine		1.00	.492	
Muscle twitching		1.00	.492	
Myalgia	1.00			

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBP

Table HMBR.12.6. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Event	1) PLACEBO (N=130) n(%)	2) DLX60QD -Abrupt (N=71) n(%)	3) DLX60QD -Taper (N=64) n(%)	4) DLX120QD -Abrupt (N=58) n(%)	5) DLX120QD -Taper (N=66) n(%)	Total (N=389) n(%)
Myocardial infarction	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Oedema peripheral	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Oral dysaesthesia	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Piloerection	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Pollakiuria	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Postnasal drip	0(0.0%)	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Rhinitis allergic	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Seasonal allergy	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Sedation	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Shoulder pain	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.3%)
Sinusitis	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	1(0.3%)
Tearfulness	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
Tinnitus	0(0.0%)	0(0.0%)	0(0.0%)	1(1.7%)	0(0.0%)	1(0.3%)
Tooth fracture	0(0.0%)	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)
White blood cell count decreased	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.3%)

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.6. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

	p-Values*						
Event	Overall	1 vs. 2	1 vs. 3	1 vs. 4	1 vs. 5	2 vs. 3	2 vs. 4
Myocardial infarction	1.00	1.00	1.00	1.00	1.00		
Oedema peripheral	1.00	1.00	1.00	1.00	1.00		
Oral dysaesthesia	.149			.309			.450
Piloerection	1.00	1.00	1.00	1.00	1.00		
Pollakiuria	1.00	1.00	1.00	1.00	1.00		
Postnasal drip	.666	.353				1.00	1.00
Rhinitis allergic	.149			.309			.450
Seasonal allergy	1.00	1.00	1.00	1.00	1.00		
Sedation	.149			.309			.450
Shoulder pain	.483				.337		
Sinusitis	.483				.337		
Tearfulness	1.00	1.00	1.00	1.00	1.00		
Tinnitus	.149			.309			.450
Tooth fracture	.666	.353				1.00	1.00
White blood cell count decreased	1.00	1.00	1.00	1.00	1.00		

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.6. Discontinuation-Emergent Adverse Events
Preferred Term by Decreasing Frequency by Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Concluded)

	p-Values*			
Event	2 vs. 5	3 vs. 4	3 vs. 5	4 vs. 5
Myocardial infarction				
Oedema peripheral				
Oral dysaesthesia		.475		.468
Piloerection				
Pollakiuria				
Postnasal drip	1.00			
Rhinitis allergic		.475		.468
Seasonal allergy				
Sedation		.475		.468
Shoulder pain	.482		1.00	1.00
Sinusitis	.482		1.00	1.00
Tearfulness				
Tinnitus		.475		.468
Tooth fracture	1.00			
White blood cell count decreased				

MedDRA Version: 8
N=Number of patients entering drug-tapering phase, n=Number of patients with discontinuation-emergent adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQAESD31)
Program: RMP.F1JSHMBR.SASPGM(FQAESD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.7 presents SAEs that occurred during the drug-tapering phase by drug-tapering dose. One placebo-treated patient experienced an SAE during the drug-tapering phase.

Table HMBR.12.8. Serious Adverse Events by Decreasing Frequency By Drug-Tapering Dose
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase

Adverse Event	1) PLACEBO (N=142) n(%)	2) DLX60QD -Taper (N=64) n(%)	3) DLX60QD -Abrupt (N=71) n(%)	4) DLX120QD -Taper (N=66) n(%)	5) DLX120QD -Abrupt (N=58) n(%)	Total (N=401) n(%)	p-Value*
PATIENTS WITH >=1 SERIOUS ADVERSE EVENT	1(0.7%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	1.00
Myocardial infarction	1(0.7%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)	1.00

MedDRA Version: 8
N = Number of patients entering drug-tapering phase, n = Number of patients with a serious adverse event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQSAED31)
Program: RMP.F1JSHMBR.SASPGM(FQSAED3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.12.9 presents AEs reported as reason for discontinuation by drug-tapering dose for all patients entering the drug-tapering phase of the study. Only 3 patients discontinued due to an adverse event (1 placebo, 1 duloxetine 60 mg QD-abrupt, and 1 duloxetine 120 mg QD-taper).

Table HMBR.12.10. Adverse Events Reported as Reason for Discontinuation By Decreasing Frequency By Drug-Tapering Dose All Patients Entering Drug-Tapering Phase Drug-Tapering Phase

Event	1) PLACEBO (N=130) n(%)	2) DLX60QD -Taper (N=64) n(%)	3) DLX60QD -Abrupt (N=71) n(%)	4) DLX120QD -Taper (N=66) n(%)	5) DLX120QD -Abrupt (N=58) n(%)	Total (N=389) n(%)	p-Value*
PATIENTS DISCONTINUED FOR ANY AE	1(0.8)	0(0.0)	1(1.4)	1(1.5)	0(0.0)	3(0.8)	1.00
Dizziness	0(0.0)	0(0.0)	0(0.0)	1(1.5)	0(0.0)	1(0.3)	.483
Myocardial infarction	1(0.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.3)	1.00
Paraesthesia	0(0.0)	0(0.0)	1(1.4)	0(0.0)	0(0.0)	1(0.3)	.666

MedDRA Version: 8
N = Number of patients entering drug-tapering phase, n = Number of patients with event
*Frequencies are analyzed using a Fisher's exact test
Report: RMP.F1JO.HMBRSTAT.FINAL(FQDISD51)
Program: RMP.F1JSHMBR.SASPGM(FQDISD5)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

12.4.2.1.3. Liver Function Tests

Table HMBR.14.27 summarizes treatment-emergent abnormal bilirubin for patients with treatment-emergent abnormal liver function tests. One hundred and twenty total patients experienced a treatment-emergent abnormal liver function test but all patients had normal bilirubin..

12.4.2.1.4. Analysis of Fasting Glucose

Table HMBR.14.28 summarizes the mean change from baseline to endpoint results of fasting glucose. No statistically significant differences between treatment groups were observed in the acute therapy phase.

Table HMBR.14.29 summarizes the mean change from baseline to maximum value results of fasting glucose. No statistically significant differences between treatment groups were observed in the acute therapy phase.

Table HMBR.14.30 summarizes the categorical analysis of fasting glucose. No statistically significant differences between treatment groups were observed in the acute therapy phase.

12.4.2.1.5. Analysis of HbA1c and Lipid Profile

Table HMBR.14.31 summarizes the mean changes from baseline to endpoint for HbA1c and lipids. No statistically significant differences between treatment groups were observed in the acute therapy phase.

Table HMBR.14.32 summarizes the incidence of treatment-emergent abnormal HbA1c and lipids during the acute therapy phase. There was a statistically significant greater percentage of duloxetine 60 mg QD-treated patients with high LDL cholesterol compare with placebo-treated patients.

Section 14 contains listings for low abnormal chemistry laboratory values (Table HMBR.14.35); high abnormal chemistry laboratory values (Table HMBR.14.36); low abnormal hematology laboratory values (Table HMBR.14.37); high abnormal hematology laboratory values (Table HMBR.14.38); and abnormal categorical laboratory values (Table HMBR.14.39).

12.4.2.2. Laboratory Values - Drug-Tapering Phase

12.4.2.2.1. Analysis of Chemistry Analytes

Table HMBR.14.33 summarizes treatment-emergent labs for chemistry analytes. No statistically significant differences between treatment groups were observed.

12.4.2.2.2. Analysis of Hematology Analytes

Table HMBR.14.34 summarizes treatment-emergent labs for hematology analytes. No statistically significant differences between treatment groups were observed.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1. Vital Signs

12.5.1.1. Vital Signs and Weight: Acute Therapy Phase

Table HMBR.12.14 summarizes the mean change from baseline to endpoint analysis for vital signs and weight.

Compared with placebo-treated patients, duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean increase in pulse rate and sitting diastolic blood pressure. Duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean increase in pulse rate compared to patients treated with duloxetine 60 mg QD-treated patients.

Table HMBR.14.40 summarizes the mean change from baseline to maximum value analysis for vital signs and weight. No statistically significant differences between treatment groups were observed in the acute therapy phase.

Table HMBR.14.41 summarizes the mean change from baseline to minimum value analysis for vital signs and weight in the acute therapy phase. Placebo-treated patients had a greater mean decrease in sitting diastolic blood pressure compared with duloxetine 120 mg QD-treated patients.

12.5.1.2. Vital Signs: Drug-Tapering Phase

Table HMBR.14.42 summarizes the mean change from baseline to endpoint analysis for vital signs. No statistically significant differences between stopping methods (abrupt compared with taper) were observed.

Table HMBR.14.43 summarizes the mean change from baseline to endpoint analysis by drug-tapering dose for vital signs and weight. No statistically significant differences between treatment groups were observed.

12.5.2. Electrocardiograms

12.5.2.1. ECGs – Acute Therapy Phase

Duloxetine 60 mg QD- and duloxetine 120 mg QD-treated patients experienced a statistically significantly greater mean decrease in QT interval and a statistically significantly greater mean increase in QTc Bazetts interval and heart rate compared with placebo-treated patients. Duloxetine 120 mg QD-treated patients also experienced a statistically significantly greater mean increase in QTc regression interval compared with placebo-treated patients (Table HMBR.12.16). No treatment group differences were observed for QTc Fridericia's interval.

No other differences in ECG parameters were statistically significant between treatment groups. Based on these data, it would appear that duloxetine prolongs cardiac repolarisation. This appears to be a spurious finding for which there is no ready explanation. After extensive investigation of duloxetine for multiple indications, no evidence of QTc prolongation was found. In addition, no QTc prolongation was detected in a high dose clinical pharmacology study where extensive ECG data were collected under tightly controlled conditions.

12.6. Safety Conclusions

There were no patient deaths in this study. Duloxetine was well tolerated and safely administered in patients with GAD during this study. The safety profile of duloxetine in this GAD study is similar to that observed in previous duloxetine studies of patients with major depressive disorder (MDD) and diabetic peripheral neuropathic pain (DPNP). No new safety concerns were noted during this study. No patient deaths occurred in the either study phase.

12.6.1. Acute Therapy Phase

A total of 386 patients reported at least one TEAE during the acute therapy phase. No patient deaths occurred during the acute-therapy phase and one placebo-treated patient reported a SAE. Overall 96 patients discontinued due to an adverse event (4 placebo-treated patients; 19 duloxetine 60-mg treated patients; and 26 120-mg duloxetine treated patients). The majority of the adverse events were categorized as moderate or mild.

Although there were some statistically significant changes in analyte concentrations, vital signs, and ECGs between placebo and both duloxetine treatment groups during the acute therapy phase, none of these mean changes in analyte concentrations are of sufficient magnitude to have clinical relevance.

No statistically significant differences between treatment groups in hematology analytes. were observed.

12.6.2. Drug-Taper Phase

A total of 79 patients experienced a discontinuation-emergent adverse event in the drug-taper phase. There was no statistical significance among the stopping methods (abrupt compared with taper) during the drug-tapering phase. These findings show that there were not increased adverse events in abrupt-discontinuation patients compared with taper-discontinuation patients using a logistic regression analysis.

No deaths occurred during the drug-tapering phase and one placebo-treated patient reported a SAE. Three patients discontinued during the drug-taper phase (1 placebo treated, 1 60 mg QD, and 1 120 mg QD).

Overall statistically significantly more duloxetine treated (both 60 mg and 120 mg in both the taper and abrupt groups) patients reported DEAEs compared with placebo. Among duloxetine treatment groups (both duloxetine 60 mg QD patients who tapered and abruptly discontinued and duloxetine120 mg QD treated patients who tapered and abruptly) there were no statistically significant differences.

No statistically significant differences between treatment groups were observed for chemistry or hematology analytes or vital signs during the drug-taper phase.

Table HMBR.14.42. Vital Signs and Weight
Mean Change from Baseline to Endpoint
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase

PULSE RATE

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
DLX60QD -Taper	63	72.60	10.65	72.0	49.0	100.0	74.95	11.44	74.0	53.0	104.0	2.35	8.74	1.0	-20.0	25.0
DLX60QD -Abrupt	70	73.47	10.02	72.0	56.0	98.0	74.54	10.82	72.0	54.0	112.0	1.07	9.32	0.5	-20.0	24.0
DLX120QD -Taper	66	74.33	9.11	76.0	52.0	90.0	72.86	9.11	72.0	56.0	95.0	-1.47	7.27	-1.0	-18.0	13.0
DLX120QD -Abrupt	58	73.12	9.79	72.5	56.0	108.0	74.14	11.17	72.0	59.0	108.0	1.02	9.71	1.0	-28.0	24.0

Main Effects (Type II SS) Raw Data

Therapy	F=1.94	df=1,225	p=0.165
Investigator	F=1.28	df=28,225	p=0.167
DISCMETHOD	F=0.17	df=1,225	p=0.681

Interaction Effects (Type II SS) Raw Data

Therapy*DISCMETHOD	F=3.93	df=1,225	p=0.049

Least Squares Means for Change from Baseline

Taper	0.55	(SE= 0.81)
Abrupt	1.09	(SE= 0.82)
DLX60QD	1.58	(SE= 0.80)
DLX120QD	0.06	(SE= 0.83)

Pairwise Comparison of LS Means

Abrupt - Taper	diff= 0.54	Two-sided 95% CI :	(-1.64 , 2.72)	t= 0.49	p=0.628
DLX120QD - DLX60QD	diff=-1.52	Two-sided 95% CI :	(-3.71 , 0.67)	t=-1.36	p=0.174

Type II Sums of Squares from two-way ANOVA: Model=Treatment , PINVID, DISCMETHOD, TRT*DISCMETHOD
DISCMETHOD refers to the re-randomization method in the drug-tapering phase for duloxetine patients.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
Report: RMP.F1JO.HMBRSTAT.FINAL(LOVITD21)
Program: RMP.F1JSHMBR.SASPGM(LOVITD2)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.42. Vital Signs and Weight
Mean Change from Baseline to Endpoint
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

SYSTOLIC BLOOD PRESSURE(SITTING)

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
DLX60QD -Taper	63	124.98	15.80	123.0	90.0	170.0	126.57	17.44	121.0	96.0	195.0	1.59	11.25	0.0	-30.0	45.0
DLX60QD -Abrupt	70	123.76	15.00	123.0	90.0	168.0	124.09	13.11	125.0	100.0	165.0	0.33	9.92	0.0	-28.0	35.0
DLX120QD -Taper	66	125.03	14.44	122.0	90.0	176.0	127.29	17.75	124.5	85.0	177.0	2.26	10.37	0.0	-20.0	30.0
DLX120QD -Abrupt	58	123.74	13.48	120.5	94.0	160.0	125.97	15.92	124.5	100.0	168.0	2.22	11.66	0.0	-25.0	30.0

Main Effects (Type II SS) Raw Data
Therapy F=0.23 df=1,225 p=0.631
Investigator F=1.27 df=28,225 p=0.172
DISCMETHOD F=0.17 df=1,225 p=0.679

Interaction Effects (Type II SS) Raw Data
Therapy*DISCMETHOD F=0.20 df=1,225 p=0.651

Least Squares Means for Change from Baseline
Taper 2.31 (SE= 0.99)
Abrupt 1.77 (SE= 1.01)
DLX60QD 1.70 (SE= 0.98)
DLX120QD 2.37 (SE= 1.02)

Pairwise Comparison of LS Means
Abrupt - Taper diff=-0.54 Two-sided 95% CI : (-3.21 , 2.14) t=-0.40 p=0.692
DLX120QD - DLX60QD diff= 0.67 Two-sided 95% CI : (-2.02 , 3.36) t= 0.49 p=0.626

Type II Sums of Squares from two-way ANOVA: Model=Treatment , PINVID, DISCMETHOD, TRT*DISCMETHOD
DISCMETHOD refers to the re-randomization method in the drug-tapering phase for duloxetine patients.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
Report: RMP.F1JO.HMBRSTAT.FINAL(LOVITD21)
Program: RMP.F1JSHMBR.SASPGM(LOVITD2)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DSF

Table HMBR.14.42. Vital Signs and Weight
Mean Change from Baseline to Endpoint
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Concluded)

DIASTOLIC BLOOD PRESSURE(SITTING)

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
DLX60QD -Taper	63	77.83	9.99	78.0	60.0	100.0	78.40	11.01	80.0	60.0	110.0	0.57	8.09	0.0	-20.0	20.0
DLX60QD -Abrupt	70	77.69	11.94	77.5	50.0	101.0	78.39	10.43	78.0	60.0	112.0	0.70	7.71	0.0	-15.0	20.0
DLX120QD -Taper	66	79.48	10.97	80.0	60.0	106.0	79.21	10.30	80.0	60.0	102.0	-0.27	6.20	0.0	-12.0	15.0
DLX120QD -Abrupt	58	77.83	9.73	79.5	52.0	100.0	77.62	9.57	77.0	60.0	100.0	-0.21	8.25	0.0	-15.0	17.0

Main Effects (Type II SS) Raw Data

Therapy	F=0.88	df=1,225	p=0.350
Investigator	F=1.02	df=28,225	p=0.447
DISCMETHOD	F=0.02	df=1,225	p=0.875

Interaction Effects (Type II SS) Raw Data

Therapy*DISCMETHOD	F=0.02	df=1,225	p=0.886

Least Squares Means for Change from Baseline

Taper	0.80	(SE= 0.70)
Abrupt	0.65	(SE= 0.72)
DLX60QD	1.18	(SE= 0.70)
DLX120QD	0.27	(SE= 0.73)

Pairwise Comparison of LS Means

Abrupt - Taper	diff=-0.15	Two-sided 95% CI : (-2.05 , 1.76)	t=-0.15	p=0.880
DLX120QD - DLX60QD	diff=-0.91	Two-sided 95% CI : (-2.83 , 1.01)	t=-0.93	p=0.351

Type II Sums of Squares from two-way ANOVA: Model=Treatment , PINVID, DISCMETHOD, TRT*DISCMETHOD
DISCMETHOD refers to the re-randomization method in the drug-tapering phase for duloxetine patients.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
Report: RMP.F1JO.HMBRSTAT.FINAL(LOVITD21)
Program: RMP.F1JSHMBR.SASPGM(LOVITD2)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.43. Vital Signs and Weight
Mean Change from Baseline to Endpoint by Drug-Tapering Dose
Duloxetine Patients Entering Drug-Tapering Phase
Drug-Tapering Phase

PULSE RATE

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1)PLACEBO	130	71.55	10.13	72.0	48.0	104.0	73.13	10.36	72.0	48.0	104.0	1.58	9.22	0.0	-30.0	36.0
2)DLX60QD -Taper	63	72.60	10.65	72.0	49.0	100.0	74.95	11.44	74.0	53.0	104.0	2.35	8.74	1.0	-20.0	25.0
3)DLX60QD -Abrupt	70	73.47	10.02	72.0	56.0	98.0	74.54	10.82	72.0	54.0	112.0	1.07	9.32	0.5	-20.0	24.0
4)DLX120QD -Taper	66	74.33	9.11	76.0	52.0	90.0	72.86	9.11	72.0	56.0	95.0	-1.47	7.27	-1.0	-18.0	13.0
5)DLX120QD -Abrupt	58	73.12	9.79	72.5	56.0	108.0	74.14	11.17	72.0	59.0	108.0	1.02	9.71	1.0	-28.0	24.0

Main Effects (Type III SS) Raw Data
Therapy F=1.56 df=4,354 p=0.184
Investigator F=1.43 df=28,354 p=0.077

Least Squares Means for Change from Baseline
1)PLACEBO 1.65 (SE= 0.80)
2)DLX60QD-Taper 2.38 (SE= 1.14)
3)DLX60QD-Abrupt 0.88 (SE= 1.08)
4)DLX120QD-Taper -1.19 (SE= 1.11)
5)DLX120QD-Abrupt 1.37 (SE= 1.20)

Pairwise Comparison of LS Means

DLX60QD-Taper - PLACEBO	diff= 0.73	Two-sided 95% CI : (-1.96 , 3.41)	t= 0.53	p=0.595
DLX60QD-Abrupt - PLACEBO	diff=-0.77	Two-sided 95% CI : (-3.38 , 1.83)	t=-0.58	p=0.560
DLX120QD-Taper - PLACEBO	diff=-2.85	Two-sided 95% CI : (-5.50 , -0.19)	t=-2.11	p=0.035
DLX120QD-Abrupt - PLACEBO	diff=-0.28	Two-sided 95% CI : (-3.05 , 2.48)	t=-0.20	p=0.842
DLX60QD-Abrupt - DLX60QD-Taper	diff=-1.50	Two-sided 95% CI : (-4.55 , 1.55)	t=-0.97	p=0.334
DLX120QD-Taper - DLX60QD-Taper	diff=-3.57	Two-sided 95% CI : (-6.66 , -0.48)	t=-2.27	p=0.024
DLX120QD-Abrupt - DLX60QD-Taper	diff=-1.01	Two-sided 95% CI : (-4.20 , 2.18)	t=-0.62	p=0.535
DLX120QD-Taper - DLX60QD-Abrupt	diff=-2.07	Two-sided 95% CI : (-5.10 , 0.96)	t=-1.35	p=0.179
DLX120QD-Abrupt - DLX60QD-Abrupt	diff= 0.49	Two-sided 95% CI : (-2.63 , 3.62)	t= 0.31	p=0.757
DLX120QD-Abrupt - DLX120QD-Taper	diff= 2.56	Two-sided 95% CI : (-0.59 , 5.72)	t= 1.60	p=0.111

Type III Sums of Squares from ANOVA: Model=Treatment and PINVID.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
Report: RMP.F1JO.HMBRSTAT.FINAL(LOVITD31)
Program: RMP.F1JSHMBR.SASPGM(LOVITD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.43. Vital Signs and Weight
Mean Change from Baseline to Endpoint by Drug-Tapering Dose
Duloxetine Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

SYSTOLIC BLOOD PRESSURE(SITTING)

	Baseline						Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1)PLACEBO	130	126.38	14.06	125.5	90.0	174.0	127.14	13.89	125.0	100.0	178.0	0.75	11.42	0.0	-30.0	43.0
2)DLX60QD -Taper	63	124.98	15.80	123.0	90.0	170.0	126.57	17.44	121.0	96.0	195.0	1.59	11.25	0.0	-30.0	45.0
3)DLX60QD -Abrupt	70	123.76	15.00	123.0	90.0	168.0	124.09	13.11	125.0	100.0	165.0	0.33	9.92	0.0	-28.0	35.0
4)DLX120QD -Taper	66	125.03	14.44	122.0	90.0	176.0	127.29	17.75	124.5	85.0	177.0	2.26	10.37	0.0	-20.0	30.0
5)DLX120QD -Abrupt	58	123.74	13.48	120.5	94.0	160.0	125.97	15.92	124.5	100.0	168.0	2.22	11.66	0.0	-25.0	30.0

Main Effects (Type III SS) Raw Data

Therapy	F=0.27	df=4,354	p=0.897
Investigator	F=1.12	df=28,354	p=0.305

Least Squares Means for Change from Baseline

1)PLACEBO	0.57	(SE= 0.99)
2)DLX60QD-Taper	1.54	(SE= 1.42)
3)DLX60QD-Abrupt	0.72	(SE= 1.34)
4)DLX120QD-Taper	1.95	(SE= 1.38)
5)DLX120QD-Abrupt	1.80	(SE= 1.49)

Pairwise Comparison of LS Means

DLX60QD-Taper - PLACEBO	diff= 0.97	Two-sided 95% CI :	(-2.37 , 4.31)	t= 0.57	p=0.569
DLX60QD-Abrupt - PLACEBO	diff= 0.15	Two-sided 95% CI :	(-3.10 , 3.39)	t= 0.09	p=0.929
DLX120QD-Taper - PLACEBO	diff= 1.38	Two-sided 95% CI :	(-1.92 , 4.68)	t= 0.82	p=0.411
DLX120QD-Abrupt - PLACEBO	diff= 1.23	Two-sided 95% CI :	(-2.21 , 4.67)	t= 0.70	p=0.482
DLX60QD-Abrupt - DLX60QD-Taper	diff=-0.82	Two-sided 95% CI :	(-4.61 , 2.97)	t=-0.43	p=0.670
DLX120QD-Taper - DLX60QD-Taper	diff= 0.41	Two-sided 95% CI :	(-3.43 , 4.26)	t= 0.21	p=0.833
DLX120QD-Abrupt - DLX60QD-Taper	diff= 0.26	Two-sided 95% CI :	(-3.71 , 4.23)	t= 0.13	p=0.897
DLX120QD-Taper - DLX60QD-Abrupt	diff= 1.24	Two-sided 95% CI :	(-2.53 , 5.00)	t= 0.65	p=0.519
DLX120QD-Abrupt - DLX60QD-Abrupt	diff= 1.08	Two-sided 95% CI :	(-2.80 , 4.97)	t= 0.55	p=0.584
DLX120QD-Abrupt - DLX120QD-Taper	diff=-0.15	Two-sided 95% CI :	(-4.08 , 3.78)	t=-0.08	p=0.940

Type III Sums of Squares from ANOVA: Model=Treatment and PINVID.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
Report: RMP.F1JO.HMBRSTAT.FINAL(LOVITD31)
Program: RMP.F1JSHMBR.SASPGM(LOVITD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.43. Vital Signs and Weight
Mean Change from Baseline to Endpoint by Drug-Tapering Dose
Duloxetine Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Concluded)

DIASTOLIC BLOOD PRESSURE(SITTING)

	Baseline					Endpoint					Change				
	N	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
1)PLACEBO	130	76.48	9.25	78.0	55.0	96.0	77.50	9.70	80.0	50.0	98.0	1.02	8.16	0.0	-20.0	35.0
2)DLX60QD -Taper	63	77.83	9.99	78.0	60.0	100.0	78.40	11.01	80.0	60.0	110.0	0.57	8.09	0.0	-20.0	20.0
3)DLX60QD -Abrupt	70	77.69	11.94	77.5	50.0	101.0	78.39	10.43	78.0	60.0	112.0	0.70	7.71	0.0	-15.0	20.0
4)DLX120QD -Taper	66	79.48	10.97	80.0	60.0	106.0	79.21	10.30	80.0	60.0	102.0	-0.27	6.20	0.0	-12.0	15.0
5)DLX120QD -Abrupt	58	77.83	9.73	79.5	52.0	100.0	77.62	9.57	77.0	60.0	100.0	-0.21	8.25	0.0	-15.0	17.0

Main Effects (Type III SS) Raw Data

Therapy	F=0.34	df=4,354	p=0.849
Investigator	F=0.86	df=28,354	p=0.674

Least Squares Means for Change from Baseline

1)PLACEBO	1.00	(SE= 0.71)
2)DLX60QD-Taper	0.77	(SE= 1.01)
3)DLX60QD-Abrupt	0.75	(SE= 0.96)
4)DLX120QD-Taper	-0.02	(SE= 0.99)
5)DLX120QD-Abrupt	-0.20	(SE= 1.06)

Pairwise Comparison of LS Means

DLX60QD-Taper - PLACEBO	diff=-0.22	Two-sided 95% CI : (-2.61 , 2.17)	t=-0.18	p=0.854
DLX60QD-Abrupt - PLACEBO	diff=-0.24	Two-sided 95% CI : (-2.56 , 2.07)	t=-0.21	p=0.836
DLX120QD-Taper - PLACEBO	diff=-1.02	Two-sided 95% CI : (-3.38 , 1.34)	t=-0.85	p=0.395
DLX120QD-Abrupt - PLACEBO	diff=-1.20	Two-sided 95% CI : (-3.66 , 1.26)	t=-0.96	p=0.338
DLX60QD-Abrupt - DLX60QD-Taper	diff=-0.02	Two-sided 95% CI : (-2.73 , 2.69)	t=-0.02	p=0.988
DLX120QD-Taper - DLX60QD-Taper	diff=-0.80	Two-sided 95% CI : (-3.54 , 1.95)	t=-0.57	p=0.568
DLX120QD-Abrupt - DLX60QD-Taper	diff=-0.97	Two-sided 95% CI : (-3.81 , 1.86)	t=-0.68	p=0.500
DLX120QD-Taper - DLX60QD-Abrupt	diff=-0.78	Two-sided 95% CI : (-3.47 , 1.92)	t=-0.57	p=0.571
DLX120QD-Abrupt - DLX60QD-Abrupt	diff=-0.95	Two-sided 95% CI : (-3.73 , 1.83)	t=-0.67	p=0.500
DLX120QD-Abrupt - DLX120QD-Taper	diff=-0.18	Two-sided 95% CI : (-2.99 , 2.63)	t=-0.12	p=0.901

Type III Sums of Squares from ANOVA: Model=Treatment and PINVID.
Note: N=Number of patients with a baseline and at least one non-missing post-baseline data.
Report: RMP.F1JO.HMBRSTAT.FINAL(LOVITD31)
Program: RMP.F1JSHMBR.SASPGM(LOVITD3)
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.33. Laboratory Values – Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase

Lab Analyte	Direction	Therapy	N	n	(%)
ALKALINE PHOSPHATASE	High	PLACEBO	110	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	51	2	(3.9)
	Low	PLACEBO	112	3	(2.7)
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	51	0	
ALT/SGPT	High	PLACEBO	94	3	(3.2)
		DLX60QD-Taper	42	3	(7.1)
		DLX60QD-Abrupt	39	0	
		DLX120QD-Taper	43	5	(11.6)
		DLX120QD-Abrupt	46	8	(17.4)
	Low	PLACEBO	111	1	(0.9)
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	52	0	
AST/SGOT	High	PLACEBO	98	2	(2.0)
		DLX60QD-Taper	44	3	(6.8)
		DLX60QD-Abrupt	44	0	
		DLX120QD-Taper	45	1	(2.2)
		DLX120QD-Abrupt	46	4	(8.7)

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD11)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.33. Laboratory Values – Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
AST/SGOT	Low	PLACEBO	108	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	52	0	
BICARBONATE, HCO3	High	PLACEBO	109	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	52	0	
	Low	PLACEBO	109	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	51	0	
BILIRUBIN, TOTAL	High	PLACEBO	104	2	(1.9)
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	51	0	
		DLX120QD-Abrupt	51	0	
	Low	PLACEBO	98	0	
		DLX60QD-Taper	47	1	(2.1)
		DLX60QD-Abrupt	44	0	
		DLX120QD-Taper	50	1	(2.0)
		DLX120QD-Abrupt	48	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD11)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.33. Laboratory Values – Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
CALCIUM	High	PLACEBO	111	2	(1.8)
		DLX60QD-Taper	48	1	(2.1)
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	49	0	
	Low	PLACEBO	112	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	51	0	
CHLORIDE	High	PLACEBO	113	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	51	0	
	Low	PLACEBO	113	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	52	0	
CHOLESTEROL	High	PLACEBO	105	2	(1.9)
		DLX60QD-Taper	41	0	
		DLX60QD-Abrupt	42	1	(2.4)
		DLX120QD-Taper	49	2	(4.1)
		DLX120QD-Abrupt	43	1	(2.3)

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD11)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.33. Laboratory Values – Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
CHOLESTEROL	Low	PLACEBO	98	1	(1.0)
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	39	1	(2.6)
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	48	0	
CREATINE PHOSPHOKINASE	High	PLACEBO	97	7	(7.2)
		DLX60QD-Taper	37	3	(8.1)
		DLX60QD-Abrupt	34	4	(11.8)
		DLX120QD-Taper	38	1	(2.6)
		DLX120QD-Abrupt	39	5	(12.8)
	Low	PLACEBO	110	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	51	0	
CREATININE	High	PLACEBO	110	1	(0.9)
		DLX60QD-Taper	49	2	(4.1)
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	51	0	
		DLX120QD-Abrupt	50	0	
	Low	PLACEBO	112	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	51	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD11)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DSP

Table HMBR.14.33. Laboratory Values – Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
GGT (GGPT/SGGT/YGGT)	High	PLACEBO	102	1	(1.0)
		DLX60QD-Taper	44	0	
		DLX60QD-Abrupt	46	0	
		DLX120QD-Taper	47	1	(2.1)
		DLX120QD-Abrupt	48	1	(2.1)
	Low	PLACEBO	113	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	52	0	
INORGANIC PHOSPHORUS	High	PLACEBO	112	0	
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	51	0	
	Low	PLACEBO	106	1	(0.9)
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	50	1	(2.0)
POTASSIUM	High	PLACEBO	112	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	52	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD11)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.33. Laboratory Values – Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
POTASSIUM	Low	PLACEBO	113	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	52	0	
SODIUM	High	PLACEBO	108	1	(0.9)
		DLX60QD-Taper	49	1	(2.0)
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	52	1	(1.9)
		DLX120QD-Abrupt	48	0	
	Low	PLACEBO	113	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	52	1	(1.9)
TOTAL PROTEIN	High	PLACEBO	112	1	(0.9)
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	48	0	
	Low	PLACEBO	112	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	51	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD11)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.33. Laboratory Values – Chemistry Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Concluded)

Lab Analyte	Direction	Therapy	N	n	(%)
UREA NITROGEN	High	PLACEBO	109	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	48	1	(2.1)
		DLX120QD-Taper	54	1	(1.9)
		DLX120QD-Abrupt	50	1	(2.0)
	Low	PLACEBO	112	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	51	0	
URIC ACID	High	PLACEBO	100	4	(4.0)
		DLX60QD-Taper	47	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	53	0	
		DLX120QD-Abrupt	49	2	(4.1)
	Low	PLACEBO	111	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	49	0	
		DLX120QD-Taper	54	1	(1.9)
		DLX120QD-Abrupt	48	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD11)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.34. Laboratory Values – Hematology Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase

Lab Analyte	Direction	Therapy	N	n	(%)
ANISOCYTOSIS	Abnormal	PLACEBO	97	0	
		DLX60QD-Taper	41	0	
		DLX60QD-Abrupt	45	1	(2.2)
		DLX120QD-Taper	40	1	(2.5)
		DLX120QD-Abrupt	43	1	(2.3)
BASOPHILS	High	PLACEBO	112	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	50	0	
	Low	PLACEBO	112	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	50	0	
EOSINOPHILS	High	PLACEBO	112	0	
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	46	0	
		DLX120QD-Taper	51	1	(2.0)
		DLX120QD-Abrupt	49	0	
	Low	PLACEBO	112	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	50	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD21)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.34. Laboratory Values – Hematology Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
ERYTHROCYTE COUNT	High	PLACEBO	112	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	50	0	
	Low	PLACEBO	107	3	(2.8)
		DLX60QD-Taper	48	3	(6.3)
		DLX60QD-Abrupt	45	0	
		DLX120QD-Taper	51	1	(2.0)
		DLX120QD-Abrupt	47	1	(2.1)
HEMATOCRIT	High	PLACEBO	109	1	(0.9)
		DLX60QD-Taper	48	0	
		DLX60QD-Abrupt	45	1	(2.2)
		DLX120QD-Taper	52	1	(1.9)
		DLX120QD-Abrupt	49	0	
	Low	PLACEBO	111	2	(1.8)
		DLX60QD-Taper	48	0	
		DLX60QD-Abrupt	46	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	50	0	
HEMOGLOBIN	High	PLACEBO	110	0	
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	52	1	(1.9)
		DLX120QD-Abrupt	50	1	(2.0)

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD21)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.34. Laboratory Values – Hematology Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
HEMOGLOBIN	Low	PLACEBO	110	3	(2.7)
		DLX60QD-Taper	48	0	
		DLX60QD-Abrupt	47	1	(2.1)
		DLX120QD-Taper	52	1	(1.9)
		DLX120QD-Abrupt	49	1	(2.0)
LEUKOCYTE COUNT	High	PLACEBO	105	1	(1.0)
		DLX60QD-Taper	48	1	(2.1)
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	47	1	(2.1)
	Low	PLACEBO	109	1	(0.9)
		DLX60QD-Taper	50	1	(2.0)
		DLX60QD-Abrupt	44	0	
		DLX120QD-Taper	50	1	(2.0)
		DLX120QD-Abrupt	47	0	
LYMPHOCYTES	High	PLACEBO	109	2	(1.8)
		DLX60QD-Taper	48	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	49	0	
	Low	PLACEBO	111	0	
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	51	0	
		DLX120QD-Abrupt	50	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD21)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.34. Laboratory Values – Hematology Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
LYMPHOCYTES, ATYPICAL	High	PLACEBO	101	1	(1.0)
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	43	0	
		DLX120QD-Abrupt	47	0	
	Low	PLACEBO	101	0	
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	44	0	
		DLX120QD-Abrupt	48	0	
MACROCYTOSIS	Abnormal	PLACEBO	111	0	
		DLX60QD-Taper	47	2	(4.3)
		DLX60QD-Abrupt	46	1	(2.2)
		DLX120QD-Taper	49	2	(4.1)
		DLX120QD-Abrupt	47	2	(4.3)
MEAN CELL HEMOGLOBIN (MCH)	High	PLACEBO	110	1	(0.9)
		DLX60QD-Taper	46	0	
		DLX60QD-Abrupt	45	0	
		DLX120QD-Taper	49	0	
		DLX120QD-Abrupt	50	1	(2.0)
	Low	PLACEBO	112	0	
		DLX60QD-Taper	48	0	
		DLX60QD-Abrupt	48	1	(2.1)
		DLX120QD-Taper	51	0	
		DLX120QD-Abrupt	50	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD21)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.34. Laboratory Values – Hematology Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)	High	PLACEBO	112	0	
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	50	0	
	Low	PLACEBO	112	0	
		DLX60QD-Taper	48	0	
		DLX60QD-Abrupt	46	1	(2.2)
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	49	0	
MEAN CELL VOLUME (MCV)	High	PLACEBO	105	2	(1.9)
		DLX60QD-Taper	43	3	(7.0)
		DLX60QD-Abrupt	41	1	(2.4)
		DLX120QD-Taper	45	0	
		DLX120QD-Abrupt	43	3	(7.0)
	Low	PLACEBO	111	0	
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	47	1	(2.1)
		DLX120QD-Taper	51	0	
		DLX120QD-Abrupt	49	0	
MICROCYTOSIS	Abnormal	PLACEBO	98	0	
		DLX60QD-Taper	46	0	
		DLX60QD-Abrupt	45	0	
		DLX120QD-Taper	42	0	
		DLX120QD-Abrupt	46	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD21)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.34. Laboratory Values – Hematology Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Continued)

Lab Analyte	Direction	Therapy	N	n	(%)
MONOCYTES	High	PLACEBO	112	0	
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	51	0	
		DLX120QD-Abrupt	50	0	
	Low	PLACEBO	111	2	(1.8)
		DLX60QD-Taper	50	0	
		DLX60QD-Abrupt	47	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	49	0	
NEUTROPHILS, SEGMENTED	High	PLACEBO	107	1	(0.9)
		DLX60QD-Taper	48	1	(2.1)
		DLX60QD-Abrupt	46	1	(2.2)
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	47	1	(2.1)
	Low	PLACEBO	106	5	(4.7)
		DLX60QD-Taper	50	1	(2.0)
		DLX60QD-Abrupt	43	1	(2.3)
		DLX120QD-Taper	49	1	(2.0)
		DLX120QD-Abrupt	47	0	
PLATELET COUNT	High	PLACEBO	99	0	
		DLX60QD-Taper	48	0	
		DLX60QD-Abrupt	41	0	
		DLX120QD-Taper	51	1	(2.0)
		DLX120QD-Abrupt	45	1	(2.2)

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD21)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF

Table HMBR.14.34. Laboratory Values – Hematology Analytes
Treatment-Emergent Abnormal Labs at Any Time
Covance Reference Ranges
All Patients Entering Drug-Tapering Phase
Drug-Tapering Phase (Concluded)

Lab Analyte	Direction	Therapy	N	n	(%)
PLATELET COUNT	Low	PLACEBO	110	0	
		DLX60QD-Taper	49	0	
		DLX60QD-Abrupt	48	0	
		DLX120QD-Taper	52	0	
		DLX120QD-Abrupt	48	0	
RBC MORPHOLOGY	Abnormal	PLACEBO	114	0	
		DLX60QD-Taper	51	0	
		DLX60QD-Abrupt	50	0	
		DLX120QD-Taper	54	0	
		DLX120QD-Abrupt	52	0	

N = Number of patients with a baseline and postbaseline measurement
n = Number of patients with an abnormal postbaseline measurement
Output: RMP.F1JO.HMBRSTAT.FINAL(FQLABD21)
Program: RMP.F1JSHMBR.SASPGM()
Data: RMP.SAS.F1JS.L.MCHMBR.ADS.DBF