Title: Effect of Duloxetine 30/ 60 mg Once Daily versus Placebo in Adolescents with Juvenile Primary Fibromyalgia Syndrome.

NCT ID: NCT01237587

Document Approval Date: 25 Oct 2010

1. Protocol F1J-MC-HMGW
Effect of Duloxetine 30/60 mg Once Daily versus Placebo in Adolescents with Juvenile Primary Fibromyalgia Syndrome

Confidential Information

Duloxetine (LY248686)

Phase IIIb, randomized, double-blind, placebo-controlled, 13-week clinical trial to assess the efficacy and safety of duloxetine 30/60 mg QD compared to placebo in adolescents with Juvenile Primary Fibromyalgia Syndrome. Continued efficacy and safety of duloxetine 30/60 mg QD will be assessed in a 26-week, open-label treatment extension period.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol Approved by Lilly: 25 Oct 2010

2. Synopsis

Study Rationale

There is little published research on Juvenile Primary Fibromyalgia Syndrome (JPFS), yet available literature suggests this condition is associated with significant morbidity and disability in adolescents. Prevalence rates in some countries are estimated from 1.2% to 6.2%, with the rate in the United States not known. To date, there are no published drug efficacy studies in this population, nor is there a drug approved for FM or JPFS in the adolescent age range.

Duloxetine is approved for the management of fibromyalgia (FM) in adults. Upon approval of that indication, the US Food and Drug Administration (FDA), under the Pediatric Research Equity Act (PREA), required Lilly to conduct a deferred study to assess safety and effectiveness of duloxetine in pediatric patients with FM aged 13 to 17 years. Specific facets of this protocol and study design were employed to address the requirements of that deferred research.

Clinical Protocol Synopsis: Study F1J-MC-HMGW

<table>
<tr><td colspan="2">Name of Investigational Product:
Duloxetine (LY248686)</td></tr>
<tr><td colspan="2">Title of Study: Effect of Duloxetine 30/ 60 mg Once Daily versus Placebo in Adolescents with Juvenile Primary Fibromyalgia Syndrome</td></tr>
<tr><td>Number of Planned Patients/Subjects:
Entered: 300
Enrolled/Randomized: 210
Completed (Acute Period): 163</td><td>Phase of Development: Phase 3b</td></tr>
<tr><td colspan="2">Length of Study:
Planned first patient visit: February 2011
Planned last patient visit (Acute Period): September 2014
Planned last patient visit (Extension Period): April 2015</td></tr>
<tr><td colspan="2">Objectives:
The primary objective is to evaluate the efficacy of duloxetine 30/60 mg once daily (QD) compared with placebo on the reduction of average pain severity as measured by the Brief Pain Inventory (BPI) – Modified Short Form: Adolescent Version 24-hour average pain severity rating (for simplicity, it is referred to as the BPI average pain severity here after) during a 13-week, double-blind treatment phase in adolescents (aged 13 to 17 years) with Juvenile Primary Fibromyalgia Syndrome (JPFS).
The secondary objectives of the study are:
To evaluate the efficacy of duloxetine 30/60 mg QD compared with placebo for the treatment of JPFS in adolescents during a 13-week, double-blind treatment phase, as assessed by the change from baseline on the following measures:
Brief Pain Inventory (BPI) Modified Short Form: Adolescent Version severity (worst pain, least pain, pain right now) and interference.
Response to treatment, as defined by a 30% and 50% reduction in the BPI average pain severity.
Pediatric Pain Questionnaire (PPQ) pain right now, and worst pain and average pain items.
Clinical Global Impression of Severity, Overall (CGI-Severity: Overall) scale.</td></tr>
</table>

- Clinical Global Impression of Severity for Mental Illness (CGI-Severity: Mental Illness) scale.
- Functional Disability Inventory-child version scale (FDI-child).
- Functional Disability Inventory-parent version scale (FDI-parent).
- Children's Depression Inventory (CDI).
- Multidimensional Anxiety Scale for Children (MASC).

- To evaluate the safety and tolerability of duloxetine 30/60 mg QD compared with placebo for the treatment of JPFS in adolescents during a 13-week, double-blind treatment phase.
- To evaluate the efficacy and safety of duloxetine 30/60 mg QD during a 26-week, open-label, extension treatment phase, as assessed by the following:
  - Maintenance effect of duloxetine 30/60 mg QD during the open-label extension treatment phase. Maintenance effect will be assessed using the BPI average pain severity in only the acute phase responders (defined as those patients with ≥30% pain reduction from baseline on the BPI average pain severity measure).
  - Effect of duloxetine 30/60 mg QD during extension treatment phase as measured by the following: BPI, PPQ, CGI-Severity: Overall, CGI-Severity: Mental Illness, FDI-child, FDI-parent, CDI, and MASC.
  - Safety of duloxetine 30/60 mg QD during extension treatment phase.

The exploratory objectives of the study are:

- To evaluate the correlation between BPI severity pain items and PPQ pain items.
- To evaluate the appropriateness of the American College of Rheumatology (ACR) fibromyalgia (FM) criteria in an adolescent population.

Study Design: This is a Phase 3b study of duloxetine versus placebo for the treatment of JPFS in adolescents. The study consists of 4 periods: Period I is a 1-week screening period; Period II is a 13-week, double-blind, placebo-controlled treatment period of duloxetine 30/60 mg QD; Period III is a 26-week, open-label extension period of flexible duloxetine 30/60 mg QD; Period IV is a 1-week drug tapering period.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Main inclusion criteria:

- Male and female outpatients aged 13 through 17 years.
- Meet criteria for JPFS as defined by Yunus and Masi (1985).
- Score of ≥4 on BPI average pain severity (Item 3) at Visit 1 and Visit 2.

Main exclusion criteria:

- Pain symptoms related to traumatic injury, past surgery, structural bone or joint disease (such as bursitis, tendonitis), or regional pain syndrome that will interfere with interpretation of outcome measures.
- Current or previous diagnosis of rheumatologic disorder, rheumatoid arthritis (RA), inflammatory arthritis, or infectious arthritis, or an autoimmune disease (for example, systemic lupus erythematosus).
- Have a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I condition, currently or within the past year, except major depressive disorder (MDD) and/or generalized anxiety disorder (GAD), adjustment disorder or specific

phobias with primary investigator approval.

- Have a current secondary DSM-IV Axis I condition of attention-deficit/hyperactivity disorder (ADHD) that requires pharmacologic treatment.
- Have any ***lifetime*** DSM-IV Axis I diagnosis of psychosis, bipolar disorder, or schizoaffective disorder.
- Have a family history of 1 or more first-degree relatives (parents or siblings) with diagnosed bipolar I disorder.
- Have a history of substance abuse or dependence within the past 6 months, excluding nicotine and caffeine.
- Have any DSM-IV Axis II disorder which, in the judgment of the investigator, would interfere with compliance with the study protocol.
- Have a significant suicide attempt within 1 year of Visit 1 or are currently at suicidal risk in the opinion of the investigator (Columbia-Suicide Severity Rating Scale [C-SSRS] criteria to help).
- Have been treated with duloxetine within the past 6 months.
- Have had prior nonresponse or inadequate tolerance to duloxetine.
- Body weight <20 kg at any screening period visit.
- Have initiated, stopped, or changed the type or intensity of psychotherapy within 3 months prior to Visit 1. Patients who anticipate a change to psychotherapy (start, stop, or change in type, intensity, or frequency) during study Period II will be excluded.
- Have a history of seizure disorder (other than febrile seizures).
- Have uncontrolled narrow-angle glaucoma.
- Have acute liver injury (such as hepatitis) or severe cirrhosis (Child-Pugh Class C).
- Have serious or unstable medical illness.
- Are pregnant or breast-feeding.
- Are taking any excluded medications (eg. stimulants, antidepressants) that cannot be discontinued at Visit 1.

Investigational Product, Dosage and Mode of Administration:
Duloxetine 30 or 60 mg QD by mouth.

Planned Duration of Treatment:
Screening period: approximately 1 week, depending on length of medication washout period
Double-blind treatment period: 13 weeks
Open-label extension treatment period: 26 weeks (6 months)
Drug taper period: 1 week

Reference Therapy, Dose and Mode of Administration:
Matched placebo capsules given QD by mouth.

Criteria for Evaluation:

Efficacy:

- Brief Pain Inventory (BPI) Modified Short Form: Adolescent Version
- Pediatric Pain Questionnaire (PPQ)
- Clinical Global Impression of Severity, Overall (CGI-Severity: Overall)
- Clinical Global Impression of Severity for Mental Illness (CGI-Severity: Mental Illness)
- Functional Disability Inventory-child version (FDI-child)
- Functional Disability Inventory-parent version (FDI-parent)
- Children's Depression Inventory (CDI)
- Multidimensional Anxiety Scale for Children (MASC)

Safety:

- Treatment-emergent adverse events (TEAEs)
- Vital signs, height, and weight
- Electrocardiograms (ECGs)
- Rates and reasons for early discontinuation
- Laboratory measurements
- Suicide risk and suicide-related events (behavior and/or ideation) as assessed by the C-SSRS.

Statistical Methods:

This is a randomized, double-blind, parallel, placebo-controlled comparison trial with 4 study periods (screening period, double-blind treatment period, open-label extension period, drug taper period) to assess the efficacy and safety of duloxetine 30/60 mg QD in this adolescent population. Approximately 210 patients will be randomized in a 1:1 ratio to the duloxetine and placebo treatment groups. This study will assess the difference of the mean change in BPI average pain severity from baseline to the last time point (Visit 8, Week 13) in Study Period II between treatment groups. Assuming that there will be some missing post-baseline data, this sample size will provide at least 80% power to detect the treatment difference with α=.05. All the parameters used in the sample size calculations were based on the mixed model repeated measures (MMRM) analysis of data from 3-month, placebo-controlled, acute treatment period in 2 adult FM studies: Study F1J-MC-HMCA and Study F1J-MC-HMCJ.

All analyses will be conducted on an intent-to-treat basis. Treatment and interaction effects will be evaluated based on a 2-sided significance level of 0.05. No adjustments for multiple comparisons will be made. Unless otherwise specified, when a total score is calculated from individual items, it will be considered missing if any of the individual items are missing. When an average score is computed from individual items, it is calculated from nonmissing values.

A restricted maximum likelihood-based, MMRM analysis will be used to analyze the primary efficacy variable (change from baseline in BPI average pain rating). An analysis of covariance (ANCOVA) model with terms for treatment, investigator, and continuous covariate of baseline BPI average pain severity will also be used to test treatment difference for the primary efficacy variable (using last-observation-carried-forward [LOCF] approach and baseline-observation-carried-forward [BOCF] approach). The significance of treatment-by-investigator interaction will be evaluated in a separate model when it is necessary. Type III sum of squares from least-squares means will be used for statistical comparison using analysis of variance (ANOVA) or ANCOVA models when no interaction terms are involved. Type II sum of squares will be used for the LSMeans when an interaction term is included.

ANCOVA and MMRM models similar to those described above will be used to analyze change from baseline for continuous secondary efficacy measures. Treatment differences for categorical efficacy variables will be evaluated using Fisher's exact test.

Analyses of categorical safety variables (adverse events, treatment-emergent changes in vital signs, and labs) will be conducted using Fisher's exact test. Continuous safety data will be analyzed using ANOVA or ANCOVA model.

In the double-blind treatment period, duloxetine will be compared with placebo using statistical inference. In the open-label extension period, descriptive statistics will be used to summarize data for patients who entered the open-label period.

3. Table of Contents

Effect of Duloxetine 30/60 mg Once Daily versus Placebo in Adolescents with Juvenile Primary Fibromyalgia Syndrome

Section **Page**

Table of Contents (concluded)

Attachment **Page**

4. Abbreviations and Definitions

Term	Definition
ACR	American College of Rheumatology
ADHD	attention-deficit/hyperactivity disorder
adolescent	Aged 13 to 17 years
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ANCOVA	analysis of covariance
ANOVA	analysis of variance
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
blinding	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the [subject/patient] are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
BOCF	Baseline observation carried forward
BPI	Brief Pain Inventory
electronic case report form (eCRF)	Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CDI	Children's Depression Inventory
CGI-Severity	Clinical Global Impression of Severity
clinical research physician (CRP)	Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CNS	Central nervous system

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
CRF	case report form
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
DCAE	Discontinuation due to adverse event
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	Electrocardiogram
end of study (trial)	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
ethical review board (ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
FDA	US Food and Drug Administration
FDI	Functional Disability Inventory
FM	Fibromyalgia
GAD	Generalized anxiety disorder
GCP	Good clinical practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation

interim analysis	Interim analysis typically refers to an analysis of clinical trial data that is conducted prior to completion of all phases of a study and its full reporting database. For the purpose of this study, the Interim Analysis section of the protocol (12.2.10) describes the planned analysis of data that will be performed upon completion of the double-blind treatment period (Study Period II). For that analysis, the database will be locked and the unblended data will be analyzed and reported. It will be considered the final data lock/analysis for Study Period I-II.
investigational product (IP)	Study drug/medication provided for this clinical trial (duloxetine and/or placebo).
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IVRS	Interactive Voice Response System
JPFS	Juvenile Primary Fibromyalgia Syndrome
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical trial.
LOCF	Last observation carried forward
LS	least squares
MAOI	Monoamine oxidase inhibitor
MASC	Multidimensional Anxiety Scale for Children
MDD	Major depressive disorder
MINI-KID	Mini International Neuropsychiatric Interview for children and adolescents
MMRM	Mixed model repeated measures
NCS	Not clinically significant
NSAID	non-steroidal anti-inflammatory drug
OTC	Over-the-counter
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PI	principal investigator
PPQ	Pediatric Pain Questionnaire
PREA	Pediatrics Research Equity Act

PRO	Patient-reported outcome
QD	Once daily
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAS	Statistical application software
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
TPO	Third Party Organization
treatment-emergent adverse event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment
TSH	Thyroid-stimulating hormone
UDS	urine drug screen
ULN	upper limit of normal
VAS	Visual Analog Scale

Effect of Duloxetine 30/60mg Once Daily versus Placebo in Adolescents with Juvenile Primary Fibromyalgia Syndrome

5. Introduction

Fibromyalgia (FM) is a common condition in adults that is often challenging to treat. It is defined by the American College of Rheumatology (ACR) as widespread pain, with a duration of at least 3 months, in combination with tenderness at 11 or more of 18 specific sites on the body (Wolfe et al. 1990).

Fibromyalgia can also be observed in adolescents. Some authors have published specific diagnostic criteria for Juvenile Primary Fibromyalgia Syndrome (JPFS) that are derived from the ACR criteria but require fewer tender point sites (at least 4 out of the 18). These criteria also include other features such as chronic anxiety, fatigue, and sleep troubles (Yunus and Masi 1985).

Currently, there is very little published research on JPFS, but available scientific literature suggests that JPFS often leads to substantial morbidity and disability. For example, adolescents with JPFS report significantly greater functional disability and a greater number of school absences than those with other rheumatic diseases, such as juvenile rheumatoid arthritis (RA) or lupus (Varni et al. 2002). The presence of high levels of pain and disability at this critical developmental stage places adolescents with JPFS at a greater risk for long-term social and occupational difficulties.

Small, uncontrolled studies from Israel, Mexico, and Italy have estimated that the prevalence rate of JPFS in school children ranges from 1.24% to 6.20%, with girls making up the majority of cases, but those data are only indicative and need to be confirmed by larger adequate studies (Buskila et al. 1993; Clark et al. 1998; Sardini et al. 1996). Information from a national registry in the United States indicates that JPFS accounts for about 7.7% of new patient diagnoses in pediatric rheumatology settings (Siegel et al. 1998). However, the prevalence of JPFS in children and adolescents in the general population of the United States is still not available. The mean age of onset of JPFS is 12 years. To date, there is no published clinical trial that studied drug efficacy in this population, nor is there a drug approved or marketed for FM in this population.

As in adults, children and adolescents with FM commonly report depressive symptoms, and depression and anxiety disorders are common comorbid disorders (Gedalia et al. 2000, Mikkelsson 1999). The duloxetine studies in adults with FM allowed major depressive disorder (MDD) comorbidity because of its high prevalence (26% to 31% of adult FM patients suffer also from MDD [Russell et al. 2008]). In adolescents, empirical experience suggests the high prevalence of the MDD and the anxiety disorders comorbidity. Duloxetine has demonstrated efficacy in FM, MDD, and general anxiety disorder (GAD) in adults. No study has been conducted with duloxetine in children or adolescents with GAD. There is 1 completed open-label duloxetine study in children and adolescents with MDD, and it suggests clinical benefit of

duloxetine in those patients (March et al. 2009). The current duloxetine study will enroll patients with JPFS, including those with comorbid primary diagnoses of MDD and/or GAD.

At the time of approval of duloxetine for the management of FM, the US Food and Drug Administration (FDA), under the Pediatric Research Equity Act (PREA), required Lilly to conduct a deferred FM study to assess safety and effectiveness of duloxetine in pediatric patients with FM aged 13 to 17 years. Based on the above considerations, Lilly has designed this randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of duloxetine in this population. Safety/tolerability will be assessed based on clinical judgment and comparison to the known safety profile of duloxetine that has been observed in adult patients with FM and adolescents with other conditions such as MDD.

More detailed information about the known benefits and risks of duloxetine may be found in the Investigator's Brochure (IB).

6. Objectives

6.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of duloxetine 30/60 mg once daily (QD) compared with placebo on the reduction of average pain severity as measured by the Brief Pain Inventory (BPI) – Modified Short Form: Adolescent Version 24-hour average pain severity rating (for simplicity, it is referred to as the BPI average pain severity hereafter) during a 13-week, double-blind treatment phase in adolescents (aged 13 to 17 years) with JPFS, as defined by Yunus and Masi (Yunus and Masi 1985).

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of duloxetine 30/60 mg QD in the treatment of adolescents with JPFS during a 13-week, double-blind treatment phase, based on the improvement of the following measures:
    - Brief Pain Inventory (BPI) Modified Short Form: Adolescent Version severity (worst pain, least pain, pain right now) and interference.
    - Response to treatment, as defined by a 30% and 50% reduction in the BPI average pain severity.
    - Pediatric Pain Questionnaire (PPQ) pain right now, worst pain and average pain items.
    - Clinical Global Impression of Severity, overall (CGI-Severity: Overall) scale.
    - Clinical Global Impression of Severity for Mental Illness (CGI-Severity: Mental Illness) scale.
    - Functional Disability Inventory - child version scale (FDI-child).
    - Functional Disability Inventory - parent version scale (FDI-parent).
    - Children's Depression Inventory (CDI).
    - Multidimensional Anxiety Scale for Children (MASC).
- To evaluate the safety and tolerability of duloxetine 30/60 mg QD in the treatment of adolescents with JPFS during a 13-week, double-blind treatment phase.
- To evaluate the efficacy and safety of duloxetine 30/60 mg QD during a 26-week, open-label, extension treatment phase, as assessed by the following:
    - Maintenance effect of duloxetine 30/60 mg QD during the open-label extension treatment phase. Maintenance effect will be assessed using the BPI average pain severity in only the acute phase responders (defined as those patients with ≥30% pain reduction from baseline on the BPI average pain severity measure).

- Effect of duloxetine 30/60 mg QD during an extension treatment phase as measured by the following: BPI, PPQ, CGI-Severity: Overall, CGI-Severity: Mental Illness, FDI-child, FDI-parent, CDI, and MASC.
- Safety of duloxetine 30/60 mg QD during an extension treatment phase.

6.3. Exploratory Objectives

Exploratory objectives of the study are as follows:

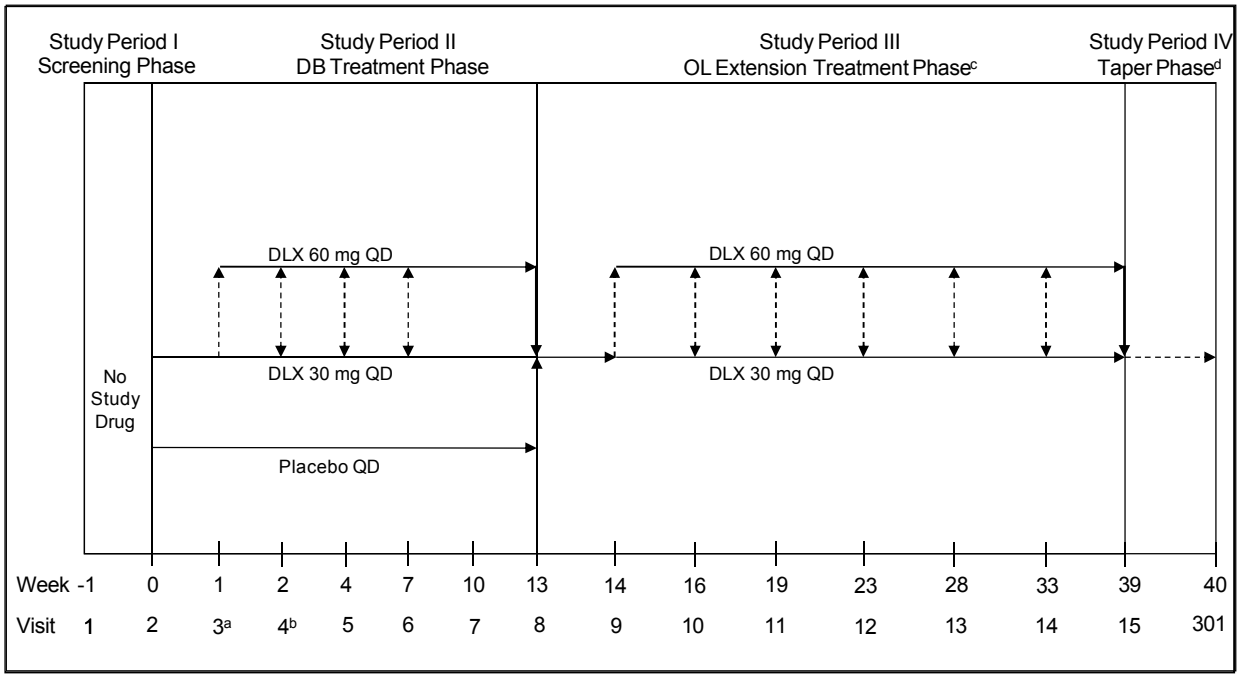
- To evaluate the correlation between BPI pain severity items and PPQ pain items.
- To evaluate the appropriateness of the ACR FM criteria (Wolfe 1990) in an adolescent population.

7. Investigational Plan

7.1. Summary of Study Design

Study F1J-MC-HMGW (HMGW) is a Phase 3b, multicenter, randomized clinical trial of duloxetine versus placebo for the treatment of JPFS in adolescents. The study design includes 4 study periods. Following Study Period I (screening phase), eligible patients enter Study Period II, the acute 13-week parallel, randomized, double-blind, placebo-controlled treatment period of duloxetine 30/60 mg QD. Upon completion of the 13-week double-blind period, patients enter Study Period III, a 26-week, open-label extension phase of duloxetine 30/60 mg QD. A 1-week drug taper period (Study Period IV) is required for all patients who discontinue for any reason between Visit 4 to Visit 8 during Study Period II, or who complete/discontinue Study Period III on duloxetine 60 mg QD. .

Figure HMGW.1 illustrates the study design.



Abbreviations: DB = double-blind; DLX = duloxetine; OL = open-label; QD = once-daily

[a] After Visit 3, patients increased to 60 mg duloxetine can have their dose decreased 1 time, at a scheduled or unscheduled Visit. Once 60 mg dose is decreased to 30 mg, it cannot be increased again during Study Period II.

[b] At Visits 4 through 8, patients randomized to placebo or DLX 30 mg who discontinue prior to entering the open-label extension treatment period (Study Period III) will receive placebo in the drug taper period.

[c] At Visits 9 through 14 in Study Period III, dose increases are permitted at scheduled visits (to a maximum dose of 60 mg QD) and dose decreases are permitted at scheduled or unscheduled visits (to a minimum dose of 30 mg QD).

[d] Patients who complete/discontinue Study Period III on DLX 30 mg do not need to enter the drug taper period.

Figure HMGW.1. Illustration of study design for Protocol F1J-MC-HMGW.

7.1.1. Study Period I – Screening Phase

Study Period I (Visit 1 to Visit 2) is a screening phase in which patients will be screened for study entry eligibility.

At or before Visit 1, the study and its potential risks will be explained to patients and parents/legal representatives. The parent/legal representative will then sign and date the informed consent form (ICF), and the patient will sign and date the assent document. The ICF must be signed before any study procedures are conducted and before patients discontinue any excluded medications. Patients will then be assigned a patient number and undergo screening.

Visit 1 procedures typically require more than 1 day to complete. At Visit 1, patients will be evaluated by the investigator to determine if they meet the diagnostic criteria for JPFS, based upon Yunus and Masi's criteria. Patients will undergo a physical examination and multiple screening procedures that need to be assessed prior to initiating a "washout period" for any excluded medications. This information will be evaluated to ensure consistency with study inclusion and exclusion criteria. See Attachment 1 for a complete list of Visit 1 procedures.

If a study patient is taking medication(s) at Visit 1 that are excluded by this protocol, the patient must complete a washout period for the excluded medications. The length of the washout period must allow adequate time for the medication(s) to be eliminated from the patient's body (generally about 5 half-lives), and may range from 2 to 28 days. The medication washout period must be completed before performing 3 specific Visit 1 procedures: 1) blood chemistries, 2) electrocardiogram (ECG), and 3) urine drug screen (UDS). The overall period of time to complete all Visit 1 procedures, including medication washout, should not exceed 30 days. The day on which the last Visit 1 procedure is completed (for example, scheduled laboratory tests and ECG) will be considered the date of Visit 1. All criteria for enrollment, including the results of ECG, safety, and laboratory analyses, must be reviewed by the principal investigator (PI) prior to enrollment at Visit 2. Patients who do not meet entry criteria (inclusion and exclusion criteria) at Visit 2 will not be enrolled into the study. Visit 2 should be scheduled 5 to 9 days after completion of Visit 1 procedures.

7.1.2. Study Period II – Double-Blind Treatment Phase

Study Period II (Visit 2 to Visit 8) is a 13-week, randomized, double-blind treatment phase. During Study Period II, patients will initially have visits weekly (Visits 3 and 4), then biweekly (Visit 5), and then every 3 weeks (Visits 6 to 8).

At Visit 2, patients who met entry criteria in Study Period I will be randomized in a 1:1 ratio to duloxetine or placebo by a computer-generated random sequence using an interactive voice response system (IVRS). All patients will receive investigational product beginning at Visit 2 and will be instructed to start taking their investigational product the morning after Visit 2.

Patients randomly assigned to placebo will remain on placebo throughout Study Period II.

Patients randomly assigned to the duloxetine treatment group will remain on duloxetine throughout Study Period II. Duloxetine patients will initially take a 30 mg QD dose of duloxetine for 1 week. Starting at Visit 3 through Visit 6, the dose can be increased from 30 mg QD to 60 mg QD. By Visit 4, comorbid MDD and/or GAD patients receiving a 30-mg QD dose should be increased to a 60-mg QD dose, unless the patient is experiencing significant intolerance to the 30-mg dose. Beginning at Visit 7, no dose increases can be made.

Dose-escalation criteria for all patients is based on investigator's clinical judgment of the following:

1) Patient has inadequate treatment response to the 30-mg dose
2) Patient has adequate tolerability to 30-mg dose.
3) For patients diagnosed with comorbid MDD and/or GAD at baseline, the 30-mg dose should be increased to 60 mg, unless the patient is experiencing significant intolerance to the 30-mg dose.

Dose adjustments are to be performed through dispensing the appropriate investigational product packaging at the site. Dose increases can only occur at scheduled study visits. The maximum dose level permitted for this study is 60 mg QD. If necessary due to intolerability, for those patients on a 60-mg QD dose, a one-time dose decrease to 30 mg may occur at a scheduled or unscheduled visit. In order to determine whether a dose decrease is needed, the patient must return to the study site for assessment. If a determination is made at the site to decrease the patient's dose, then a new investigational product package will be dispensed using the IVRS. Once the 60-mg dose is decreased to 30 mg, it cannot be increased again during Study Period II. At the unscheduled visits, procedures are to be performed as indicated in the Study Schedule (Attachment 1). All dosing modifications in this Study Period are implemented in a blinded manner using IVRS.

If the patient has already had their 1 dose decrease, and at a subsequent time cannot tolerate the investigational product dose well enough to remain compliant, the patient should be discontinued.

It is unknown if duloxetine is efficacious in treating MDD or GAD in this adolescent population. The investigator is responsible for assessing the patient's mental status at each visit. The CGI-Severity of Mental Illness will be administered at every visit during Study Period II.

See Attachment 1 for the timing of events and the measures to be assessed.

7.1.3. Study Period III – Open-Label Extension Treatment Phase

Study Period III is a 26-week, open-label extension treatment phase. Patients initially have visits weekly (Visits 8 to 9), then biweekly (Visits 9 to 10), then every 3 to 6 weeks (Visits 10 to 15).

Patients randomized to either the duloxetine or placebo treatment groups during Study Period II will enter Study Period III on a 30-mg dose of duloxetine for 1 week. The duloxetine dose may be increased to 60 mg QD only at a scheduled Visit starting at Visit 9 (Week 14). As in Study Period II, additional dose-escalation consideration should be given to all patients with comorbid

MDD and/or GAD at study entry. At Visit 9, the comorbid MDD and/or GAD patients should have their 30-mg dose increased to 60 mg, unless the patient is experiencing significant intolerance to the 30-mg dose.

From Visit 9 to Visit 14, dose modifications are allowed, and patients must return to the study site for assessment of all dose changes. Dose increases (up to 60 mg QD) are only permitted at scheduled visits. Dose decreases (down to 30 mg QD) are permitted at either scheduled or unscheduled visits. Dose adjustments are to be based on the investigator's clinical judgment of treatment response and tolerability at the patient's current dose. Procedures will be performed as indicated in the Study Schedule (Attachment 1).

7.1.4. Study Period IV – Taper/Discontinuation Phase

Study Period IV is a 1-week taper phase to minimize the occurrence of discontinuation-emergent adverse events (AEs). Patients who complete Study Period III or discontinue after Visit 9 of Study Period III while on duloxetine 60 mg QD, will receive duloxetine 30 mg QD for 1 week. The 1-week taper is not required for patients in Study Period III who complete or discontinue early on a 30-mg QD dose of duloxetine .

Patients who discontinue between Visits 4 to 8 of Study Period II should enter into the 1-week drug taper period. However, tapering of IP should be based on the investigator's determination of safety for his or her patient. Patients on duloxetine 60 mg QD will receive 30 mg QD for 1 week. Patients on duloxetine 30 mg QD will receive placebo for 1 week. Patients on placebo will receive placebo for 1 week. The 1-week taper is implemented in a blinded manner using the IVRS. The taper period is not required for patients who discontinue at Visit 3 and therefore have not received 2 weeks of treatment.

See Attachment 1 for the timing of events and the measures to be assessed.

7.2. Discussion of Design and Control

The study is designed based on the current knowledge of duloxetine safety and efficacy in FM and relevant clinical practice.

The screening period is intended for diagnosing and assessing the patient for possible inclusion in the study and for providing an adequate washout period for excluded medications, which is consistent with periods typical of clinical practice.

Double-blind, placebo-controlled studies are the standard used to assess efficacy in randomized clinical studies. The 13-week treatment period allows a sufficient amount of time to demonstrate efficacy of treatment, while keeping patients on placebo for as short a time as possible.

The 26-week, open-label period will allow for patients initially randomized to placebo during Study Period II to have the opportunity to receive benefit from treatment.

A 1-week tapering period will allow adequate time to gradually decrease the dose and minimize discontinuation symptoms.

8. Study Population

Entered patients who meet all of the inclusion criteria and are not excluded by exclusion criteria will proceed to Visit 2. At Visit 2, patients who are not excluded will be randomized and proceed to Visit 3.

8.1. Inclusion Criteria

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

[1] Outpatient male or female aged 13 to 17 years at the time of screening. Patients cannot turn 18 before the date of Visit 1 completion.

[2] Meet criteria for primary JPFS as defined by Yunus and Masi (1985).

[3] Have a score of ≥4 on Brief Pain Inventory (BPI) average pain severity (Item 3) at Visit 1 and Visit 2.

[4] Female patients must have a negative serum pregnancy test during screening. Furthermore, female patients must agree to abstain from sexual activity or to use a reliable method of birth control as determined by the investigator during the study. Examples of reliable birth control methods include: the use of oral contraceptives (for 3 months prior to study enrollment); 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.

[5] Patient's parent/legal representative and patient are judged to be reliable by the investigator to keep all appointments for clinical visits, tests, and procedures required by the protocol.

[6] Patient's parent/legal representative and patient, if capable, must have a degree of understanding such that they can communicate intelligently with the investigator and study coordinator.

[7] Patients must be capable of swallowing investigational product whole (without, for example, chewing, crushing, dissolving, or dividing the investigational product).

[8] Patients must have venous access sufficient to allow blood sampling and be compliant with blood draws as per the protocol.

8.1.1. Disease Diagnostic Criteria

Patients must have a diagnosis of JPFS. The diagnosis of JPFS, as defined by Yunus and Masi (1985), requires the following 3 criteria to be met:

1) generalized musculoskeletal aching at 3 or more sites for 3 or more months in the absence of an underlying condition
2) the presence of at least 3 or more of the following 10 features present: chronic anxiety or tension, fatigue, poor sleep, chronic headaches, irritable bowel syndrome, subjective soft tissue swelling, numbness, pain modulation by physical activities, pain modulation by weather factors, and pain modulation by anxiety/stress
3) 5 or more typical tender points. Note that 4 tender points will satisfy diagnostic criteria provided that the patient has 5 of the 10 features listed under Criterion 2 above.

8.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[9] Are children of investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[10] Are children of Lilly employees or employees of the designated Clinical Research Organization assisting with the conduct of the study.

[11] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational drug or device or off-label use of a drug or device (other than the investigational product/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[12] Have previously completed or withdrawn from this study or any other study investigating duloxetine.

[13] Have a known hypersensitivity to duloxetine or any of the inactive ingredients, or have frequent or severe allergic reactions to multiple medications.

[14] Have been treated with duloxetine within the last 6 months.

[15] Will not likely benefit from duloxetine treatment, in the opinion of the investigator or have had prior nonresponse or inadequate tolerance to duloxetine for any clinical use.

[16] Have pain symptoms related to traumatic injury, past surgery, structural bone or joint disease (such as bursitis, tendonitis), or regional pain syndrome that, in the opinion of the investigator, will interfere with interpretation of outcome measures.

[17] Currently have evidence of rheumatologic disorder or have a current or previous diagnosis of rheumatoid arthritis, inflammatory arthritis, or infectious arthritis, or an autoimmune disease (for example, systemic lupus erythematosus).

[18] Have a DSM-IV Axis I condition, currently or within the past year, except major depressive disorder (MDD) and/or generalized anxiety disorder (GAD), adjustment disorder or specific phobias with primary investigator approval.

[19] Have a current secondary DSM-IV Axis I condition of attention-deficit/hyperactivity disorder that requires pharmacologic treatment.

[20] Have any ***lifetime*** DSM-IV Axis I diagnosis of psychosis, bipolar disorder, or schizoaffective disorder.

[21] Have any DSM-IV Axis II disorder which, in the judgment of the investigator, would interfere with protocol compliance.

[22] Have a history of substance abuse or dependence within the past 6 months, excluding nicotine and caffeine.

[23] Have a positive urine drug screen (UDS) for any substances of abuse or excluded medication. Note: If the patient has a positive urine drug screen at Visit 1 for an excluded medication that may not have had an adequate washout period, a re-test may be performed and evaluated prior to Visit 2.

[24] Have a family history of 1 or more first-degree relatives (parents or siblings) with diagnosed bipolar I disorder (assessed by family member interview).

[25] Have a significant suicide attempt within 1 year of Visit 1 or are currently at suicidal risk in the opinion of the investigator. Note: Suicidal risk assessment should be facilitated by the Columbia-Suicide Severity Rating Scale (C-SSRS). Patients answering "yes" to any of the questions about active suicidal ideation/intent/behaviors occurring within the past 6 months must be excluded (C-SSRS Suicide Ideation section - Questions 4 and 5; C-SSRS Suicidal Behavior section, any of the suicide behaviors questions).

[26] Have a body weight <20 kg at any screening period visit.

[27] Have initiated, stopped, or changed the type or intensity of psychotherapy within 3 months prior to Visit 1. Patients who anticipate a change to psychotherapy (start, stop, or change in type, intensity, or frequency) during study Period II are excluded.

[28] Have a history of seizure disorder (other than febrile seizures)

[29] Are taking any excluded medications (for example, stimulants, antidepressants) that cannot be discontinued at Visit 1.

[30] Have had treatment with fluoxetine within 30 days prior to Visit 1.

[31] Have had treatment with a monoamine oxidase inhibitor (MAOI) within 14 days of Visit 1; or the potential need to use an MAOI during the study or within 5 days of discontinuation of investigational product.

[32] Have abnormal thyroid-stimulating hormone (TSH) concentrations. **Note:** Patients previously diagnosed with hypothyroidism, who have been treated on a stable dose of thyroid supplement for at least the past 3 months and have medically appropriate TSH concentrations (on replacement therapy the TSH value may be below the reference range), and are clinically euthyroid may participate in the study.

[33] Have uncontrolled narrow-angle glaucoma.

[34] Have acute liver injury (such as hepatitis) or severe cirrhosis (Child-Pugh Class C).

[35] Have a serious or unstable medical illness, including any cardiovascular, hepatic, renal, respiratory, hematologic, endocrinologic, or neurologic disease, or clinically significant laboratory abnormality or electrocardiogram (ECG) result that is not stabilized or is anticipated to require hospitalization within 6 months, or would compromise participation in the study in the opinion of the investigator. A serious or unstable medical condition is one that, in the judgment of the investigator, is likely to require intervention, hospitalization, or use of excluded medications during the course of the study.

[36] Have initiated or discontinued hormone therapy within the previous 3 months.

[37] Female patients who are either pregnant, nursing or have recently given birth.

8.2.1. Exclusion Criteria for Regions with Prevalence of Chronic Hepatitis B Virus

[38] History of hepatic dysfunction, current jaundice, or positive Hepatitis B surface antigen (Dane particle) (HBsAg) or positive Hepatitis C antibody (HCV-Ab). Note: only for regions as determined by the Center for Disease Control (CDC 2010) with a prevalence of chronic hepatitis B virus (HBV).

[39] Patients with an alanine transaminase (ALT) ≥2 times the upper limit of normal (ULN) based on central lab reference range.

8.2.2. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [9] and [10] reduce the potential bias that may be introduced at the study site.

Exclusion Criterion [11] eliminates drugs that cannot be mapped to a standard drug dictionary, or for which little data are known to analyze the potential relationship of AEs or drug interactions.

Exclusion Criteria [16] and [17] are intended to avoid other confounding pain conditions or rheumatologic diagnoses and exclude patients with rheumatologic disorders.

Exclusion Criteria [18], [20], [21], and [24] are intended to avoid confounding psychiatric diagnoses and exclude patients with serious mental diseases.

Exclusion Criterion [15] is intended to avoid enrolling patients with a history of JPFS who have been nonresponsive to drug treatment or are unable to tolerate drug treatment.

Exclusion Criterion [27] is intended to avoid other therapy that can confound the evaluation of treatment response.

Exclusion Criteria [30] and [31] are intended to prevent the development of serotonin syndrome.

Exclusion Criteria [12], [14] and [15] reduce potential bias in patients who have been exposed to duloxetine.

Exclusion Criteria [22] and [23] are intended to exclude patient that are likely to use central nervous system-active drugs that might confound efficacy and safety assessments. Exclusion Criteria [19] and [29] eliminates patients likely to use central nervous system (CNS)-active drugs that might adversely affect the safety assessments of duloxetine or place patients at an increased risk of AEs due to drug-drug interactions.

Exclusion Criteria [13], [25], [26], [28], [33], [34], and [37] are intended to avoid any potential safety issues. Exclusion Criterion [35] excludes patients who have significant medical conditions or diseases that are unrelated to therapy but may need to be treated during the course of the study by an excluded medication or procedure.

Exclusion Criterion [32] is intended to exclude patients with thyroid disease, which may confound symptomatology.

Exclusion Criterion [36] is intended to prevent patients enrolling in the study who present with potentially confounding symptoms resulting from hormone imbalance.

8.3. Discontinuations

8.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient is discontinued from the study, and Lilly or its designee must be contacted.

In addition, patients will be discontinued from the investigational product and/or from the study in the following circumstances.

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- The investigator decides that the patient should be withdrawn. If this decision is made because of a serious adverse event or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Section 10.2 Safety Evaluations.

- The patient, patient's parent/legal representative, or attending physician requests that the patient be withdrawn from the study.
- The patient for any reason, requires 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 occurs prior to introduction of the new agent.
- The investigator or Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.
- If the patient becomes pregnant.
- If the patient's body weight decreases to <20 kg.

In addition, patients may be discontinued in the following circumstances:

- If an exclusion criterion develops after investigational product initiation, Lilly or its designee will be contacted to determine the appropriate evaluation and follow-up, which may include discontinuation of the patient.
- If the patient is unable to tolerate the investigational product as judged by the investigator, the investigators should use clinical judgment on whether to continue or decrease investigational product dose, or discontinue the patient's participation in the study.
- If the patient is significantly noncompliant with investigational product or study procedures, they should be discontinued from the study.
- The patient, for any reason, requires treatment with another therapeutic excluded of concomitant use with duloxetine for the trial. In this case, Lilly or its designee should be contacted and the patient may be discontinued.

Patients who discontinue the investigational product and/or study early will have end-of-therapy and/or end-of-study procedures performed as shown in the Study Schedule (Attachment 1).

8.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8.3.3. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Treatments Administered

During Study Period II (Double-Blind Treatment Period), patients will be randomly assigned to duloxetine or placebo to be taken once daily (QD), preferably in the morning. Patients assigned to duloxetine will begin at 30 mg QD for 1 week. Starting at Visit 3, through Visit 6, the dose may be increased to 60 mg QD. Dose escalation should follow GCP. Dose increases can only occur at scheduled study visits (Visits 3, 4, 5, or 6). Additional dose-escalation consideration should be given to all patients with comorbid MDD/GAD at study entry. At Visit 4, patients with comorbid MDD/GAD on a 30-mg QD dose should have their dose increased to 60 mg QD, unless the patient is experiencing significant intolerance to the 30-mg dose. If necessary, due to intolerability, a one-time dose decrease (down to 30 mg QD) may occur at scheduled or unscheduled visits. To determine whether a dose decrease is needed, the patient must return to the study site for assessment. If a determination is made at the site to decrease the patient's dose, a new investigational product package will be dispensed using the IVRS. A dose decrease can occur anytime throughout the course of Study Period II (to a minimum dose of 30 mg QD). Once a patient's dose has been decreased, it cannot be increased again in Study Period II.

During Study Period III (Open-Label Extension Treatment Period), patients who were randomized to either the duloxetine or placebo treatment groups during Study Period II will receive a 30-mg QD dose of duloxetine for 1 week. The duloxetine dose may be increased to 60 mg QD only at scheduled Visits starting at Visit 9 As in Study Period II, additional dose-escalation consideration should be given to all patients with comorbid MDD/GAD at study entry. At Visit 9, patients with comorbid MDD/GAD should have their 30-mg dose increased to 60 mg, unless the patient is experiencing significant intolerance to the 30-mg dose. From Visit 9 to Visit 14, dose modifications are allowed, and patients must return to the study site for assessment of all dose changes. Dose increases (up to 60 mg QD) are only permitted at scheduled visits. Dose decreases (down to 30 mg QD) are permitted at either scheduled or unscheduled visits. Dose increases or decreases are to be based on the investigator's clinical judgment of treatment response and tolerability at the patient's current dose. Patients unable to tolerate a 30-mg dose should be discontinued from this study. Patients discontinuing the study between Visits 9 to 15 on duloxetine 30 mg QD do not need to enter the drug taper period.

The investigator or his/her designee is responsible for explaining the correct use of the investigational product(s) to the patient and patient's parent/legal representative, verifying that instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

Patients and patient's parent/legal representative will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product, so that the situation can be assessed.

9.2. Materials and Supplies

Lilly will provide the following investigational products:

- 30-mg capsules of duloxetine hydrochloride
- placebo capsules identical in appearance to duloxetine capsules

Investigational product will be dispensed to patients at the study site. Investigational product will be labeled with a unique identifier for drug accountability. Investigational product packaging will contain a sufficient quantity of investigational product to last to the next visit and additional capsules to allow for sufficient investigational product in case of a longer visit window.

9.3. Method of Assignment to Treatment

After the informed consent form (ICF) is signed and dated, a patient is considered to be "entered" into the study and will be assigned a patient number. Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an IVRS. The IVRS will be used to assign investigational product packages containing double-blind investigational product to each patient during Study Period II, and open-label investigational product during Study Period III. Site personnel will confirm that they have located the correct investigational product packages by entering a confirmation number found on the investigational product packages into the IVRS.

To achieve between-group comparability for site factor, the randomization will be stratified by site.

9.4. Rationale for Selection of Doses in the Study

The two doses of duloxetine, 30 mg and 60 mg QD, administered orally, were selected based on the recommended adult dose and current clinical and pharmacokinetic data. For adults, the recommended dose of duloxetine is 60 mg administered QD, with treatment initiating at a 30-mg QD dose for 1 week. Some adults respond to the 30-mg starting dose.

Study F1J-MC-HMFN (HMFN) is an open-label study of duloxetine safety and pharmacokinetics in children and adolescents with MDD. The pharmacokinetic results from Study HMFN suggest that differential dosing based on age or body weight is not warranted. The range of duloxetine concentrations in children (7 through 11 years) and adolescents (12 through 17 years) are similar to those observed in adults, with median values being lower in pediatric patients than in adults. Therefore, differential dosing in the pediatric population compared with the adult population may not be warranted.

9.5. Selection and Timing of Doses

At Visit 2, patients will be instructed to take the investigational product starting the day after Visit 2. The investigational product should be taken QD, preferably in the morning. Patients will take a 30-mg dose QD from the day after Visit 2 to Visit 3; and either a 30-mg or a 60-mg

dose QD from Visit 3 to Visit 8 during Study Period II. Dose changes will occur as described in Section 7.1.

Starting at Visit 8, patients completing Study Period II will be allowed to enter the open-label extension treatment period (Study Period III) and will begin receiving duloxetine 30 mg QD for 1 week, preferably in the morning. The duloxetine dose may be increased to 60 mg QD starting at Visit 9. From Visit 9 to Visit 14, dose increases are permitted at scheduled visits (to a maximum dose of 60 mg QD) and dose decreases are permitted at scheduled or unscheduled visits (to a minimum dose of 30 mg QD). Dose adjustments are to be based on the investigator's clinical judgment of treatment response and tolerability at the patient's current dose.

9.6. Continued Access to Investigational Product

Investigational product will not be provided after the conclusion of the study as it is commercially available in the countries where this study will be conducted.

9.7. Blinding

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for adverse events may be performed through an IVRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IVRS.

The investigator should make every effort to contact the Lilly clinical research physician (CRP) prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly CRP for the patient to continue in the study.

9.8. Concomitant Therapy

In general, concomitant medications with primarily CNS activity are not allowed in this study. Ongoing use of nonsteroidal anti-inflammatory drugs (NSAIDs) is allowed during the study, in accordance with the guidelines specified on the HMGW List of Concomitant Medications that is provided with this protocol. Site personnel should call a designated representative with any questions regarding medications not specifically cited in the list of excluded medications. Patient's parent/legal representative must sign the ICF before patients stop any excluded medications. Any changes in the list of allowed/not allowed medications will be communicated to investigators and will not constitute a protocol amendment.

All nonstudy medications taken during the study will be recorded on the case report form (CRF), including the administration date and dosage. Patients will be instructed to consult with the investigator or study coordinator at the site before taking any new prescribed medications, over-the-counter (OTC) medications, or supplements/herbal preparations.

For a detailed list of specifically excluded medications, see the HMGW List of Concomitant Medications that is provided to the sites with the protocol and is updated as necessary by Lilly.

If any changes to the list are made after the protocol has been approved by Lilly, an ERB, or a regulatory agency, these changes will not be considered modifications to the protocol, but the HMGW List of Concomitant Medications will be updated to provide this information.

Patients who are taking any disallowed medications at the time of screening will need to undergo a washout period prior to completing Visit 1. Ongoing use of NSAIDs is allowed during the study, in accordance with the guidelines specified on the HMGW List of Concomitant Medications that is provided with this protocol. After Visit 2, episodic use of some analgesics is allowed for break-through pain, acute injury, or surgery. Episodic use is defined as no more than 3 consecutive days and no more than 20 cumulative days during Study Period II (Visit 2 to Visit 8), and 3 consecutive days and no more than 40 cumulative days during Study Period III. Analgesics, including acetaminophen and herbal remedies/medicines, are not provided by the sponsor.

9.9. Treatment Compliance

Each patient and parent/legal representative should be instructed to return all investigational product packaging and material to the study site at each visit. The study site will keep a record of all drug dispensed and returned throughout the study. The study site will return all investigational product packaging and unused investigational product for all patients, following completion of drug accountability procedures by Lilly or designee. Patient compliance with investigational product will be assessed at each visit after Visit 2. Compliance will be assessed by direct questioning and counting returned capsules. Compliance with the prescribed regimen will be recorded in the CRF.

During Study Periods II and III, compliance for each visit interval is defined as taking between 80% and 120% of the prescribed capsules of investigational product. If a patient is not compliant during an interval, the patient and parent/legal representative will be counseled regarding the importance of compliance in this study. The patient may be discontinued at this time if, in the opinion of the investigator, the patient is deemed unlikely to become compliant and data obtained from the patient will be unreliable. The second time that a patient is noncompliant with his or her dosage schedule; he or she must be discontinued from the study unless noncompliance results from unforeseen circumstances (for example, a blizzard or illness). In such instances, the Lilly CRP or designee who is responsible for monitoring the study may grant permission for the patient to continue.

In addition, patients who are consistently noncompliant with having their laboratory tests done or their procedures completed as indicated in the Study Schedule (Attachment 1), or who do not

attend visits within the stated study intervals, may be deemed noncompliant by Lilly or investigator and may be discontinued from the study.

10. Efficacy, Health Outcome/Quality of Life Measures, and Safety Evaluations, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

The Brief Pain Inventory (BPI) – Modified Short Form: Adolescent Version. The primary efficacy measure for this study is the BPI "24-hour average pain severity" item (Question 3) of the BPI (Cleeland and Ryan 1994), while the other 3 BPI pain severity items and the interference items will be considered secondary efficacy measures (see Section 10.1.2 below). The BPI is a self-reported scale that measures the severity of pain and the interference of pain on function. For the BPI 24-hour average pain item, the ratings range from 0 (no pain) to 10 (pain as severe as you can imagine). The BPI average pain severity item was selected as the primary outcome measure based on past experience with this measure in adult duloxetine FM clinical trials.

10.1.2. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1).

- **The Brief Pain Inventory (BPI) - Modified Short Form: Adolescent Version** (Severity and Interference) is a self-reported scale that measures the severity of pain and the interference of pain on function (Cleeland and Ryan 1994). The Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). There are 4 questions assessing the severity for worst pain, least pain, average pain in the past 24 hours (which is the primary efficacy measure), and the pain right now. The Interference scores range from 0 (does not interfere) to 10 (completely interferes). There are 7 original questions assessing the interference of pain in the past 24 hours on the following: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The BPI: Adolescent Version added an eighth interference question to assess interference of pain on school work. This scale has not been formally validated in adolescents.
- **The Pediatric Pain Questionnaire (PPQ)** is a self-reported scale that measures the severity for "pain now," worst pain, and average pain in the past week with 100 mm VAS (Visual Analog Scale) (Varni et al. 1987). The severity scores range from 0 (no hurting, no discomfort, no pain) to 100 (hurting a whole lot, very uncomfortable, severe pain). The PPQ has been formally validated in adolescents.

- **The Clinical Global Impression of Severity: Overall (CGI-Severity: Overall)** scale evaluates the severity of overall illness at the time of assessment (Guy 1976). The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-Severity: Overall must be administered by a study physician in the presence of the patient or after having been in the presence of the patient.
- **The Clinical Global Impression of Severity: Mental Illness (CGI-Severity: Mental)** scale evaluates the severity of mental illness at the time of assessment (Guy 1976). The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-Severity: Mental must be administered by a study physician in the presence of the patient or after having been in the presence of the patient
- **Functional Disability Inventory-child form (FDI-child)** is a self-reported scale to assess the physical trouble or difficulty the child has doing regular activities (Walker and Greene 1991). This scale contains 15 items. Each item is scored on a 0- to-4-point scale (0 = no trouble, 1 = a little trouble, 2 = some trouble, 3 = a lot of trouble, 4 = impossible). The total score ranges from 0 to 60. The higher the score, the more physical trouble or difficulty the child has doing regular activities.
- **Functional Disability Inventory-parent form (FDI-parent)** contains the same items as FDI-child, but is reported by parent/legal representative (Walker and Greene 1991). The total score range from 0 to 60. The higher the score, the more physical trouble or difficulty the child has doing regular activities.
- **Children's Depression Inventory (CDI)** is modeled after the Beck Depression Inventory and is a 27-item self-reported, symptom-oriented scale designed for school-aged children and adolescents (Kovacs 1985). Each item is scored on a 0-to-2-point scale (in increasing severity) and thus the total score ranges from 0 to 54. The higher the score, the more severe the depression.
- **Multidimensional Anxiety Scale for Children (MASC)** is a self-reported scale developed to assess anxiety in children and adolescents (March et al. 1997). The MASC consists of 39 items that comprise 4 factors, 3 of which can be separated into 2 subfactors each. Main factors (subfactors) include: 1) physical symptoms (tense/restless and somatic/autonomic); 2) social anxiety (humiliation/rejection and public performance fears); 3) harm avoidance (perfectionism and anxious coping); and 4) separation anxiety. Each item is scored on a 0-to-3-point scale. Total score range from 0 to 117. The higher the total score, the more severe the anxiety.

10.2. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the patient to discontinue before completing the study. The

patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Patients with clinically relevant abnormal ECGs or laboratory findings should be followed at the discretion of the investigator until resolved or explained. Weight and vital signs will be measured at each visit throughout the study, preferably at the same time each visit. Height will be measured by stadiometer three times during the study as indicated in the Study Schedule (Attachment 1). All measurements will be made without shoes and after the removal of any heavy personal items (such as large jewelry, wallets, or coats). Preferably, the same observer should measure the patients throughout the study using the same instruments.

Instruments used for measuring height and weight must be in compliance with the study sites' institutional calibration standards. Compliance with institutional calibration(s) guidelines must be appropriately documented.

If a suicide-related event is identified at any time during the study, a thorough evaluation should be performed by a study physician and appropriate medical care should be provided. In some patients taking antidepressants, worsening of depression, suicidal events (suicidal thinking and/or behavior), or unusual changes in behavior have been reported, especially at the beginning of the drug therapy, at the time of dose changes, or early after treatment discontinuation. It is important that parent/legal representatives and patients are instructed to notify their doctor immediately if the patient has any distressing thoughts or feelings at any time.

10.2.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to investigational product or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via CRF.

Any clinically significant findings from ECGs, labs, vital sign measurements, and other procedures that result in a diagnosis should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and/or investigational product via CRF.

Study site personnel must alert Lilly or its designee within 24 hours of the investigator **unblinding** a patient's treatment group assignment for any reason.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.2.1.1. Serious Adverse Events

Serious adverse event (SAE) collection begins after the patient has signed informed consent and has received investigational product. If a patient experiences an SAE after signing informed consent, but prior to receiving investigational product, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a Sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events occurring after a patient has taken the last dose of investigational product will be collected for 30 days after the last dose of investigational product, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either investigational product, or drug delivery system, or a protocol procedure.

10.2.2. Other Safety Measures

10.2.2.1. Columbia Suicide Severity Rating Scale and Self-Harm Follow-up Form

The Columbia Suicide Severity Rating Scale (C-SSRS) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The tool was developed by the Columbia group (Posner 2007) to prospectively categorize suicide related events.

Suicide-related events (behavior and/or ideations) will be assessed and evaluated at every visit with the administration of the C-SSRS. The Self-Harm Follow-up Form will be completed at any visit, including baseline visit, when a suicidal or nonsuicidal self-injurious behavior is identified. If a suicide-related event is identified at any time during the study, a thorough evaluation should be performed by a study physician and appropriate medical care should be provided.

10.2.2.2. Clinical Laboratory Tests

Standard clinical laboratory tests will be performed at times specified in the Study Schedule (Attachment 1).

Investigators must document their review of each laboratory report. To ensure patient safety during this study, laboratory values that fall outside a clinically accepted reference range, or values that differ significantly from previous values, must be evaluated and commented on by the investigator by marking each value clinically significant (CS) or not clinically significant (NCS).

10.2.2.3. Vital Signs Data

A comprehensive physical examination will be performed at Visit 1.

Blood pressure and pulse will be collected in triplicate at every visit, with readings at least 3 minutes apart. Prior to taking the blood pressure reading, the patient should be seated in a calm, quiet location for at least 5 minutes or until the investigator believes the patient is sufficiently relaxed.

Investigators will use the following guidelines when measuring vital signs:

- Use the same arm for blood pressure collection throughout the study.
- Measure blood pressure and pulse before any blood draws.
- Support arm with cuff at approximately the heart level.
- Ensure blood pressure cuff length is >2/3 circumference of arm size. (Note: a larger or smaller cuff may be required for larger and smaller patients).

10.2.2.4. Electrocardiograms

Twelve-lead ECGs will be obtained according to the Study Schedule (Attachment 1). Triplicate ECGs will be collected approximately 1 minute apart as specified in Attachment 1. Subjects

must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

The ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, for immediate patient management and to determine whether the patient meets entry criteria. If a clinically significant increase in the corrected QT (QTc) interval from baseline is present, then the investigator should assess the patient for symptoms (such as palpitations, near syncope, syncope).

The ECGs will subsequently be electronically transmitted via modem to the centralized ECG vendor designated by Lilly. The centralized ECG vendor's cardiologist will then complete the ECG overread. The central ECG vendor's overread will be used for data analysis and report writing purposes.

After the overread ECG is returned from the centralized ECG vendor, the investigator or qualified designee is responsible for determining if any change to the patient management is needed and must document his/her review.

If there are differences in ECG interpretation between the investigator or qualified designee and the ECG vendor cardiologist, the investigator or qualified designee's interpretation will prevail for study entry and immediate patient management purposes, and the ECG vendor cardiologist's interpretation will prevail for data analysis purposes.

The investigator (or qualified designee) must document his/her review of one of the replicate ECGs printed at the time of collection, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

10.2.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP, will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review trends and laboratory analytes.

In the event that safety monitoring uncovers a potential safety signal, experts outside of the study team will be asked to evaluate the data.

10.2.4. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.3. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 3 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. Fewer invasive sampling may actually occur, but this will not require a protocol amendment.

10.3.1. Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry, hematology, and urinalysis panels, will be collected non-fasting and analyzed. A serum pregnancy test will be performed (if applicable). All clinical laboratory tests will be analyzed by a central laboratory. Attachment 2 lists the specific tests that will be performed for this study.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

Approximately 5 to 10 mL of blood for serum and plasma will be collected by venipuncture per the Study Schedule (Attachment 1). See Attachment 3 for the summary of sample amounts.

Approximately 40 mL of urine will be collected.

Supplies required for the collection and shipment of the patients' stored samples will be supplied by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

10.3.2. Exploratory Work

10.3.2.1. Pharmacogenetic Evaluations

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease

etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow, a 10-mL blood sample will be collected for potential pharmacogenetic analysis. It is a one-time collection, as noted in the Study Schedule (Attachment 1).

Samples will be stored and analysis may be performed on genetic variants thought to play a role in catecholamine signaling including, but not limited to, catechol-O-methyltransferase to evaluate their association with observed clinical outcomes to duloxetine.

In the event of an unexpected AE or the observation of unusual response, the samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY248686. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

Samples will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator site personnel.

10.4. Appropriateness of Measurements

All safety and efficacy assessments have been well documented and are generally regarded as reliable, accurate, and relevant in this patient population.

11. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the CRF or paper documentation provided by the patient or parent/legal representative will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient or parent/legal representative may include, for example, a rating scale to collect patient-reported outcome (PRO) measures.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Approximately 210 patients will be randomized in a 1:1 ratio to the duloxetine and placebo treatment groups. This study is to assess the difference of the mean change in BPI average pain severity from baseline to the last time point (Visit 8, Week 13) in Study Period II between treatment groups. Assuming that there will be some missing post-baseline data, this sample size will provide at least 80% power to detect the treatment difference with α=.05. All the parameters used in the sample size calculations were based on the MMRM analysis of data from 3-month, placebo-controlled, acute treatment period in 2 adult FM studies: Study F1J-MC-HMCA and Study F1J-MC-HMCJ.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

All analyses will be conducted on an intent-to-treat basis, meaning that data will be analyzed by the treatment groups to which patients are randomly assigned, even if the patient does not take the assigned treatment, does not receive the correct treatment, or does not comply with the protocol.

Treatment effects and interaction effects will be evaluated based on a 2-sided significance level of 0.05. No adjustments for multiple comparisons will be made.

A repeated measures analysis refers to a restricted maximum likelihood-based, mixed-effects repeated measures analysis, using all the longitudinal observations at each post-baseline visit.

Unless otherwise specified, when an ANOVA model is used to analyze a continuous variable, the model will contain the terms of treatment and investigator. The significance of treatment-by-investigator interaction will be evaluated in a separated model when it is necessary. Similar logic is 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 (LSMeans) will be used for the statistical comparisons using ANOVA or ANCOVA when there is no interaction term involved. For the ANOVA or ANCOVA models where the interaction term is included, the Type II sum-of-squares for the LSMeans will be employed.

Unless otherwise specified, when a total score is calculated from individual items, it will be considered missing if any of the individual items are missing; when an average score is computed from individual items, it is calculated from nonmissing values.

Unless otherwise specified, for all analyses for Study Period II, baseline is defined as the last nonmissing observation at or before the randomization visit (Visit 2). For analyses using the last-observation-carried-forward (LOCF) approach, endpoint is defined as the last nonmissing observation obtained from Visit 3 through Visit 8.

In some analyses for Study Period II, the baseline-observation-carried-forward (BOCF) endpoint is specified. The BOCF endpoint is defined as follows:

- For randomized patients who complete the treatment period (that is, complete the scheduled Visit 8), the BOCF endpoint is defined as the last nonmissing observation, or for randomized patients who discontinue early (that is, do not complete the scheduled Visit 8) but with at least one non-missing baseline value, the BOCF endpoint is defined as the baseline value.

In Study Period II, all patients who randomized to duloxetine will be considered as being in duloxetine treatment group, and duloxetine will be compared with placebo using statistical inference. In Study Period III, descriptive statistics will be used to summarize for patients who entered Study Period III. The treatment groups for Study Period III will be defined as follows: placebo/duloxetine (PLA/DLX) for those who are randomized to placebo during Study Period II and who enter Study Period III taking duloxetine, and DLX/DLX for those who are randomized to duloxetine during Study Period II and who enter Study Period III taking duloxetine.

When investigator sites are used in an analysis, investigators with fewer than 2 patients randomized to placebo and 2 patients randomized to duloxetine (each patients has nonmissing BPI average pain severity score) will be pooled within countries for statistical analysis purposes. If the pooled site still has fewer than 2 patients randomized to placebo and 2 patients randomized to duloxetine, these sites will be pooled with the next smallest site in the same country, or if there are none, then the next smallest site in the study overall in another country.

Categorical comparisons between treatment groups will be performed using Fisher's exact test.

Any changes to the analysis plan, both those prior to unblinding the data and those subsequent to unblinding, will be documented and justified in the final study report. Exploratory analyses of the data will be conducted as deemed appropriate.

SAS software will be used to perform all statistical analyses. Statistical analysis of this study will be the responsibility of Eli Lilly and Company or designee.

12.2.2. Patient Disposition

Patient disposition (reasons for discontinuation from the study) will be summarized overall and by visit for each treatment group. The reasons for discontinuation will be compared between treatment groups using Fisher's exact test in Study Period II. Reasons for discontinuation in Study Period III will be summarized by treatment groups.

12.2.3. Patient Characteristics

Patient demographics (age, gender, racial origin, country, body mass index [BMI], height, and weight), duration of fibromyalgia and baseline efficacy measures (BPI average pain severity, PPQ average pain rating, CGI-Severity, FDI-child, FDI-parent) will be summarized for all randomized patients for Study Period II and all patients who entered the extension period for Study Period III. In addition, baseline assessment for depression (CDI) will be summarized by MDD and non-MDD status, and baseline assessment for anxiety (MASC) will be summarized by

GAD and non-GAD status for all randomized patients for Study Period II and all patients who entered extension period for Study Period III. For Study Period II, the baseline comparability among treatment groups will be examined using an ANOVA model with the terms of treatment and investigator for continuous measures, and using Fisher's exact test for categorical data. Patient characteristics in Study Period III will be summarized by treatment groups without statistical comparison.

12.2.4. Concomitant Therapy

Previous medications for the treatment of FM, MDD, and GAD will be summarized by treatment group. The frequency of concomitant medication usage during the double-blind treatment period will also be summarized by treatment group and the comparison will be conducted using Fisher's exact test for Study Period II. Concomitant therapy in Study III will be summarized by treatments groups without any statistical comparison.

12.2.5. Treatment Compliance

A patient will be considered to be compliant with investigational product for each visit interval if they take between 80% and 120% of investigational product capsules prescribed for that interval. Overall compliance is defined as having been compliant at all visits. The percentage of patients who are compliant at each visit and overall will be summarized by treatment group for Study Period II and III.

12.2.6. Primary Outcome and Methodology

The primary objective of this study is to assess the efficacy of duloxetine 30/60 mg QD versus placebo in the treatment of adolescents with JPFS.

The primary efficacy measure is the BPI average pain severity in Study Period II. The primary efficacy analysis will be the contrast between duloxetine and placebo at the last visit in Study Period II (Visit 8, Week 13) from a MMRM analysis on change from baseline in the BPI average pain severity. The model for this analysis will include the fixed class effects of treatment, investigative site, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value and baseline value-by-visit interaction. The Kenward-Roger (Kenward and Roger, 1997) approximation will be used to estimate denominator degrees of freedom. An unstructured covariance structure will be used to model the within-patient errors. If the default Newton-Raphson algorithm used by SAS PROC MIXED does not converge, then the Fisher scoring algorithm will be applied. If the model with unstructured covariance structure fails to converge, the sandwich estimator (Diggle et al. 1994; Lu and Mehrotra, 2010) will be used to estimate the standard errors of the fixed effects parameters and the model will be fit using covariance structures of the following order until convergence is met:

1. heterogeneous toeplitz type = toeph
2. heterogeneous autoregressive (1st order) type = arh(1)
3. heterogeneous compound symmetric type = cs(h)
4. toeplitz type = toep
5. autoregressive (1st order) type = ar(1)
6. compound symmetric type = cs

When the sandwich estimator is used, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions. SAS® PROC MIXED will be used to perform the analysis. In addition, sensitivity analysis will also be performed to address the impact of missing data on the primary efficacy analysis. The intent of this sensitivity analysis is to compare the results from assuming Missing at Random (MAR) versus Missing Not at Random (MNAR) and to check for consistency of treatment contrasts. More details will be described in the Statistical Analysis Plan (SAP).

12.2.7. Efficacy Analyses

Table HMGW.1 presents the additional analyses for the primary efficacy variable and the analyses for the secondary efficacy variables in Study Period II, either collected directly from CRFs or derived from raw observations.

Descriptive statistics will be used to summarize these variables, as applicable, by treatment group (PLA/DLX and DLX/DLX) during Study Period III. The details of baseline definition of the secondary efficacy measures for Study Period III will be discussed in SAP. Maintenance effect of duloxetine 30/60 mg QD during Study Period III will be assessed using the BPI average pain severity in only the acute phase responders (defined as those patients with ≥30% pain reduction from baseline on the BPI average pain severity measure). The null hypothesis that the treatment effect of duloxetine was not maintained during the extension treatment phase was tested using T-test by evaluating if upper bound of the 97.5% CI of the change from baseline to endpoint for patients in the extension treatment phase who responded to duloxetine 30 mg QD to 60 mg QD in Study Period II (acute phase duloxetine responders) is less than or equal to the pre-specified margin of 1.5. In this analysis, baseline was defined as the last non-missing observation during Visit 3 to Visit 8, and endpoint was defined as the last non-missing observation in the Study Period III. The non-inferiority margin of 1.5 is chosen based on past experience from duloxetine Diabetic Peripheral Neuropathic Pain (DPNP) study F1J-MC-HMEM and Chronic Low Back Pain (CLBP) study F1J-MC-HMEN, both of those studies used 1.5 as margin to assess maintenance of effect under duloxetine 60/120 mg treatment as measured by 24-hour average pain in 0-10 scale.

Table HMGW.1. Secondary Efficacy Analysis

Efficacy Variable	Derivation and Details	Analysis
1. Area under the curve of pain relief (AUC) a. BPI average pain severity	The relief score at a visit is defined as the BPI average pain score at the particular visit minus the baseline score. The area under the curve of relief (AUC) is the sum of each trapezoidal area circumscribed by the sides of relief scores at two consecutive nonmissing visits and the side of days between the two visits.	Variable 1.a will be analyzed by the ANCOVA model described in Section 12.2.1 (using baseline BPI average pain severity as covariate)
2. Change from baseline to LOCF endpoint: a. BPI worst pain, least pain, average pain, and pain right now; BPI-Interference items b. PPQ average pain, pain right now, and worst pain rating c. CGI-S: Mental Illness d. CGI-S: Overall e. FDI-child f. FDI-parent g. CDI h. MASC	a-d. eCRF data. e-f. FDI total score is the sum of 15 individual item scores. g. CDI total score is the sum of 27 individual item scores. h. MASC physical symptoms, social anxiety, harm avoidance and separation anxiety subscale scores and total score.	The Variable 2.a to 2.h will be analyzed by the ANCOVA models as described in Section 12.2.1
3. Change from baseline to BOCF endpoint: a. BPI average pain severity b. PPQ average pain rating	a-b. eCRF data.	The Variable 3.a to 3.b will be analyzed by the ANCOVA models as described in Section 12.2.1
4. Change from baseline to each post-baseline visit: a. BPI worst pain, least pain, and pain right now; BPI-Interference items b. CGI-Severity: Overall and CGI-Severity: Mental Health	a-b. eCRF data.	Variables 4.a to 4.b will be analyzed by a repeated measures analysis as described in Section 12.2.1

Table HMGW.1. Analysis for the Secondary Efficacy Variables (concluded)

5. Categorical variable: a. 30% Response rate (LOCF) b. 30% Response rate (BOCF) c. 50% Response rate (LOCF) d. 50% Response rate (BOCF) e. Sustained response rate (LOCF) f. Cumulative distribution of BPI average pain score reduction	a-b. Response: at least 30% reduction from baseline to endpoint (LOCF or BOCF) for BPI average pain score. c-d. Response: at least 50% reduction from baseline to endpoint (LOCF or BOCF) for BPI average pain score. e. Sustained response: at least 30% reduction from baseline to endpoint; with a 30% reduction from baseline at an earlier visit than the last visit, and remains at least 20% reduction from baseline in every visit in between, if there are any intervening visits (based on BPI average pain score). f. The percentage of patients who have reached each threshold of BPI average pain reduction from baseline to BOCF endpoint (from >0% to 100% with a 10% increase) will be calculated. Discontinued patients will be considered as "no change".	For Variables 5.a to 5.e, proportions will be summarized by treatment group and will be analyzed by a Fisher's exact test. For Variable 5.f, the treatment group difference in the empirical cumulative distribution of the percentage pain reduction will be evaluated using Van der Waerden test.
6. Time to event variable: a. Time to first 30% reduction in BPI average pain score b. Time to first 50% reduction in BPI average pain score c. Time to sustained response	a. For the patients with a 30% reduction at a visit in the treatment phase, time = days from the date of the visit that the earliest 30% reduction is observed to the randomization date. b. For the patients with a 50% reduction at a visit in the treatment phase, time = days from the date of the visit that the earliest 30% reduction is observed to the randomization date. c. For the sustained responders defined above, time = the days from the date of the visit which is the earlier visit from which the sustained response is observed to the randomization date	For Variables 6.a to 6.c, the Kaplan-Meier survival curves of time to event will be calculated by treatment group. In the calculation, patients who do not have the event will be considered as right-censored observation. The comparison of the survival curves between treatment groups will be conducted by a log-rank test and stratified log-rank test controlling for pooled investigator.

Abbreviations: ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; BPI = Brief Pain Inventory; CDI = Children's Depression Inventory; CGI-S = Clinical Global Impressions of Severity; eCRF = electronic case report form; FDI = Functional Disability Inventory; LOCF = last observation carried forward; MASC = Multidimensional Anxiety Scale for Children; PPQ = Pediatric Pain Questionnaire.

12.2.8. Safety Analyses

Safety will be assessed by summarizing and analyzing treatment-emergent AEs, SAEs, death, rates and reasons for discontinuation, laboratory measurements, vital signs, height, weight, and

ECGs. In addition, suicide risk and suicide-related events (behavior and/or ideation) will be assessed by the C-SSRS. The safety analyses will be conducted for both Study Period II and Study Period III. In Study Period II, duloxetine will be compared with placebo using statistical inference. In Study Period III, descriptive statistics will be used to summarize for patients who entered Study Period III. The details of baseline definition of the safety measures for Study Period III will be discussed in SAP.

Categorical Safety Variables

Comparisons between treatment groups for all categorical safety measures will be made by Fisher's exact test.

Treatment-emergent adverse events (TEAEs) are the reported events that first occurred or worsened during the treatment period. For each AE, the severity level is recorded according to the patient's or investigator's perceived severity of the event (mild, moderate, severe, or more severe than baseline), the category of 'more severe than baseline' only applies to the AE with baseline severity of severe and worsened during the study. The incidence rates of TEAEs will be analyzed by Fisher's exact test. Moreover, TEAEs will be summarized by their maximum severity and system organ class and analyzed by Fisher's exact test.

The death, SAEs, and AEs reported as reasons for discontinuation (DCAE) will be summarized by treatment group and compared among the treatment groups using Fisher's exact tests.

For laboratory measurements, the incidence rates of treatment-emergent abnormally high or low laboratory values at endpoint will be assessed using Fisher's exact test. A "treatment-emergent high value at endpoint" is 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 at endpoint" is 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.

Categorical analysis of weight will be performed and treatment difference will be assessed using Fisher's exact test.

The incidence of patients meeting criteria for potentially clinically significant (PCS) changes in vital signs, and incidence of patients with sustained elevation in blood pressure, as defined in the SAP, will be compared between treatment groups. Patients with abnormal vital signs baseline assessment will be excluded from the analysis of that measure.

The incidence of patients meeting criteria for PCS changes in ECG intervals and heart rate, as defined in the SAP, will also be compared between treatment groups.

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment. In particular, for each of the following suicide-related events, the number and percent of patients with the event will be enumerated by treatment: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, nonspecific active suicidal thoughts, and wish to be dead. In addition, the number and percent of patients who

experienced at least one of various composite measures will be presented. These include suicidal acts (completed suicide and nonfatal suicidal attempts), suicidal behavior (suicidal acts, interrupted attempts, aborted attempts, and preparatory acts or behavior), treatment-emergent suicidal ideation, or treatment-emergent suicidal behavior. Fisher's exact test will be used for treatment comparisons. For each event, p-values will only be displayed if at least 4 events occurred in at least 1 treatment group.

Continuous Safety Measures

Mean change from baseline to endpoint in laboratory analytes will be assessed using the ANOVA model (see Section 12.2.1). Rank-transformed data will be used for the laboratory analysis.

Change from baseline to endpoint in vital signs, ECGs, and weight/height will be analyzed using the ANCOVA model with baseline safety value as covariate.

Time to Event

Time to event data for important safety endpoints (such as DCAE, onset of the important TEAEs) will be analyzed combining data from Study Period II and Study Period III for patients who received duloxetine at anytime during the entire study. Details of the analysis will be provided in the SAP.

Analysis of Drug Taper Period

Similar to the Double-Blind Treatment Period, patient disposition, deaths, SAEs, and taper-emergent AEs will be summarized by treatment groups and analyzed using Fisher's exact test.

Taper-emergent AEs are defined as the new or worsened events reported at Visit 301 compared with events reported at baseline (baseline is the last 2 visits before Visit 301).

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group.

Change from baseline (last nonmissing value before Visit 301) to endpoint in vital signs and weight in the taper period will be analyzed using the ANCOVA model (see Section 12.2.1).

12.2.9. Subgroup Analyses

Table HMGW.2 lists the subgroup analysis variables by which the analyses for the BPI average pain severity will be conducted for Study Period II.

Table HMGW.2. Definition of Subgroup Variables

Subgroup Variable Categories	Categories
1. Gender	1. Female or Male
2. Race Origin	2. White American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander Multiple
3. Baseline Pain Severity	3. ≤6 vs. >6 on BPI average pain severity at baseline
4. Family history of Fibromyalgia	4. Yes/No
5. Onset age of Fibromyalgia (yr.)	5. ≤12 vs. >12
6. Comorbid MDD	6. Yes/No
7. Comorbid GAD	7. Yes/No
8. Country	8. Country name

Abbreviations: BPI = Brief Pain Inventory; MDD = major depressive disorder; GAD = generalized anxiety disorder; vs. = versus.

To analyze a specific subgroup's impact, change from baseline to endpoint (LOCF and BOCF) in BPI average pain will be analyzed using an ANCOVA model with all the terms described generally in Section 12.2.1 with additional terms of the subgroup and the subgroup-by-treatment interaction. The primary statistical test will be for the treatment-by-subgroup interaction, which will be tested at the significance level of 0.05.

Furthermore, treatment group differences will be evaluated within each category of a subgroup regardless of the significance level of the treatment-by-subgroup interaction. For the subgroup of Race Origin, all the categories that have <10% of the patients in the study will be combined in the analysis.

Subgroup analysis for other efficacy and safety variables will be conducted as deemed appropriate and necessary.

12.2.10. Interim Analyses

An analysis of data will be performed when all patients have completed or discontinued early from Study Period II. For this analysis, the database will be locked and unblinded data from Study Period I Study Period II will be analyzed and reported. This is considered the final data lock for the Study Period II, and will not be considered an interim analysis that requires a formal

data monitoring committee (DMC) and no further adjustment to the final analysis significance level is needed.

The remainder of the analyses will be performed when all patients have completed Study Period IV or have been discontinued from the study.

If an unplanned interim analysis is deemed necessary, the appropriate Lilly regulatory scientist will be consulted to determine whether it is necessary to amend the protocol.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The informed consent form (ICF) will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly must agree with all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations and performed in accordance with a written process approved by Lilly.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly. The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

The study site's ERB(s) should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae.

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) the ICH GCP Guideline [E6]
3) applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Eli Lilly and Company certifies that this study is being conducted under an active US investigational drug application (IND 63,615) at clinical sites within the United States. All investigators (at IND and non-IND sites) are expected to comply with GCP and all applicable local clinical trial regulations.

All or some of the obligations of the sponsor will be assigned to a third party organization (TPO).

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with experience in treating FM will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each PI will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

An experienced investigator will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14. References

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Attachment 1. Protocol HMGW Study Schedule

Study Schedule, Protocol F1J-MC-HMGW

Study Period	**I**	**II**							**III**							**IV[a]**	**Unschld[b]**	**ET/ DSC**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**301**	**Unschld**	**ET/ DSC**
Week of Treatment	**–1**	**0**	**1**	**2**	**4**	**7**	**10**	**13**	**14**	**16**	**19**	**23**	**28**	**33**	**39**	**40**	**n/a**	**n/a**
Days from Visit 2	**-9 to -5**	**n/a**	**5 to 9**	**12 to 16**	**26 to 30**	**47 to 51**	**68 to 72**	**89 to 93**	**96 to 100**	**110 to 114**	**131 to 135**	**157 to 165**	**192 to 200**	**227 to 235**	**269 to 277**	**278 to 282**	**n/a**	**n/a**
Informed Consent/assent	X																	
Clinical Assessments																		
Demographics	X																	
Psychiatric, medical, drug, and family history	X																	
Previous treatment for fibromyalgia	X																	
Psychotherapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Physical therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Habits	X							X							X			X
Physical Exam	X																	
Date of first menses	X							X							X			X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Summary/Disposition								X							X	X		X
Diagnostic Measurements																		
MINI-Kid	X																	
Yunus and Masi	X							X							X			X
ACR Criteria	X							X							X			X

Study Schedule for F1J-MC-HMGW (continued)

Study Period	I	II							III							IV[a]	Unschld[b]	ET/ DSC
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**301**	**Unschld**	**ET/ DSC**
Week of Treatment	**–1**	**0**	**1**	**2**	**4**	**7**	**10**	**13**	**14**	**16**	**19**	**23**	**28**	**33**	**39**	**40**	**n/a**	**n/a**
Days from Visit 2	**-9 to -5**	**n/a**	**5 to 9**	**12 to 16**	**26 to 30**	**47 to 51**	**68 to 72**	**89 to 93**	**96 to 100**	**110 to 114**	**131 to 135**	**157 to 165**	**192 to 200**	**227 to 235**	**269 to 277**	**278 to 282**	**n/a**	**n/a**
Investigational Product																		
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense investigational product		X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]		X[c]	X[d]
Drug return/accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Date of first dose			X															
Date of last dose																X		X
Efficacy Measures																		
BPI: Adolescent Version	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
CGI-Severity: Overall		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
CGI-Severity: Mental Illness		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pediatric Pain Questionnaire	X	X						X							X			X
Functional Disability Inventory-Child		X			X			X							X			X
Functional Disability Inventory-Parent		X			X			X							X			X
Children's Depression Inventory		X			X			X		X		X			X			X
Multidimensional Anxiety Scale for Children		X			X			X		X		X			X			X

Study Schedule for F1J-MC-HMGW (continued)

Study Period	I	II							III							IV[a]	Unschld[b]	ET/ DSC
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	301	Unschld	ET/ DSC
Week of Treatment	–1	0	1	2	4	7	10	13	14	16	19	23	28	33	39	40	n/a	n/a
Days from Visit 2	-9 to -5	n/a	5 to 9	12 to 16	26 to 30	47 to 51	68 to 72	89 to 93	96 to 100	110 to 114	131 to 135	157 to 165	192 to 200	227 to 235	269 to 277	278 to 282	n/a	n/a
Laboratory Tests																		
Pregnancy test[e]	X																	
TSH	X																	
Chemistry panel, non-fasting[f]	X					X		X		X		X			X			X
HbA1c	X							X							X			X
Hematology	X					X		X		X		X			X			X
UDS[e]	X																	
Urinalysis	X							X							X			X
Pharmacogenomic sample[g]								X										
Safety																		
Vital signs (Sitting HR and BP) [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[i]	X							X				X			X			X
C-SSRS/ Self Harm Supplement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self Harm Follow-up Form[j]																		
Height	X							X							X			X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Events/ Pre-existing Conditions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Schedule for F1J-MC-HMGW (concluded)

Abbreviations: ACR = American College of Rheumatology; AE = adverse event; BP = Blood Pressure; BPI = Brief Pain Inventory; CGI-Severity = Clinical Global Impressions of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; DSC = discontinuation; ET = Early Termination; HR = Heart Rate; IVRS = Interactive Voice Response System; MINI = Mini International Neuropsychiatric Interview; n/a= not applicable; TSH = Thyroid-Stimulating hormone; UDS = Urine Drug Screen; Unschld - Unscheduled

[a] Drug taper period should be completed for patients discontinuing at or after Visit 4 in Study Period II. Patients discontinuing the study between Visits 9-15 on duloxetine 30 mg QD do not need to enter the drug taper period.

[b] Unscheduled visits can occur anytime. Patients must come in the office for an unscheduled visit and be assessed by the primary investigator.

[c] Investigational product dispensed only if a dose decrease occurs at an unscheduled visit during Study Period II, but not dispensed during Study Period III.

[d] Investigational product dispensed only if patient entering drug taper period. Patients discontinuing the study between Visits 9-15 on duloxetine 30 mg QD do not need to enter the drug taper period.

[e] May be repeated at the investigator's discretion throughout trial.

[f] Hepatic serologies collected at baseline for hepatitis endemic countries and may also be collected for hepatic monitoring follow-up.

[g] Pharmacogenomic sample may be collected at with blood draws scheduled at a later Visit if necessary.

[h] Blood pressure and pulse will be collected in triplicate at each visit. Readings should be taken approximately 3 minutes apart.

[i] Three ECGs will be collected approximately 1 minute apart at these visits.

[j] The Self-Harm Follow-up Form will be completed at any visit when a suicidal or non-suicidal self-injurious behavior is identified.

Attachment 2. Protocol HMGW Clinical Laboratory Tests

Clinical Laboratory Tests, Non-Fasting

Hematology:	**Clinical Chemistry**:
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Bicarbonate
Mean cell hemoglobin (MCH)	Chloride
Mean cell hemoglobin concentration (MCHC)	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Neutrophils, segmented	Albumin
Neutrophils, juvenile (bands)	Alkaline phosphatase
Lymphocytes	Gamma-glutamyl transferase (GGT)
Monocytes	Alanine aminotransaminase (ALT/SGPT)
Eosinophils	Aspartate transaminase (AST/SGOT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Serum Creatinine
Cell morphology	Uric acid
	Phosphorus
Urinalysis:	Calcium
Color	Glucose, non-fasting
Specific gravity	Total Protein
pH	Albumin
Protein	Total Cholesterol
Glucose	Triglycerides
Ketones	Creatine kinase (CK)
Blood	
Nitrate	**Thyroid Function Test:**
Urine leukocyte esterase	Thyroid stimulating hormone (TSH)[a]
Serum Pregnancy Test (females only)	**Urine Drug Screen[b]**
$HgbA_{1C}$	**Serologies as appropriate[c,d]**
	Prothrombin Time (PT) as appropriate[e]

[a] If TSH level is outside normal range, patient is excluded. Patients previously diagnosed with hyperthyroidism or hypothyroidism that have taken a stable dose of thyroid supplement for at least the past 3 months, have medically appropriate TSH concentrations, and are clinically euthyroid will be permitted to enroll in the study. One retest is allowed at the investigator's discretion.

[b] UDS may be repeated at investigator discretion throughout the trial

[c] Serologies collected at baseline for hepatitis endemic regions: Hepatitis B surface antigen, Hepatitis C antibody.

[d] Serologies collected with hepatic follow-up: Hepatitis B surface antigen (HBsAg); Hepatitis B core antibody (HBcAb); Hepatitis B core IgM antibody [HBV-Ab (IgM)]; Hepatitis C antibody (HCV-Ab); Hepatitis A IgM antibody [HAV-Ab (IgM)]; Hepatitis E virus IgM antibody is collected with hepatic alert for endemic areas.

[e] Prothrombin time (PT) collected with hepatic follow up as appropriate

Attachment 3. Protocol HMGW Sampling Summary

This table summarizes the maximum number of samples by venipuncture and blood volumes for all sampling (screening, standard laboratory, pharmacogenetic) and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol F1J-MC-HMGW Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Screening tests[a]	Blood	5 mL	2[b]	10 mL[b]
Standard laboratory tests[a]	Blood	5 mL	6	30 mL
Pharmacogenetic sample	Blood	10 mL	1	10 mL
Total Blood		20 mL		50 mL

[a] Additional samples may be drawn if needed for safety purposes.

[b] An additional sample is required for hepatitis endemic regions. The maximum total amount would then be 15mL.