



Clinical trial results:

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

Summary

EudraCT number	2018-001615-78
Trial protocol	Outside EU/EEA
Global end of trial date	28 November 2017

Results information

Result version number	v1 (current)
This version publication date	10 June 2018
First version publication date	10 June 2018

Trial information

Trial identification

Sponsor protocol code	14099
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01237587
WHO universal trial number (UTN)	-
Other trial identifiers	Eli Lilly and Company: 14099

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 November 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether duloxetine is safe and effective in the treatment of adolescents with Juvenile Primary Fibromyalgia Syndrome (JPFS).
This trial consists of two distinct study periods. A blinded treatment period of 13 weeks and an open label extension period of 26 weeks.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 128
Country: Number of subjects enrolled	Puerto Rico: 5
Country: Number of subjects enrolled	Argentina: 38
Country: Number of subjects enrolled	India: 13
Worldwide total number of subjects	184
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	184

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

13 week Double-Blind Treatment Phase (Acute Phase), followed by 26 week Open-Label Extension Treatment Phase (Extension Phase), followed by 1 week Taper/Discontinuation Phase.

Pre-assignment

Screening details:

Subjects were evaluated by the investigator to determine if they meet the diagnostic criteria for JPFS, based upon Yunus and Masi's criteria. subjects had undergone a physical examination and multiple screening procedures that need to be assessed prior to initiating a "washout period" for any excluded medications.

Period 1

Period 1 title	Double blind treatment (Acute Phase)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Duloxetine

Arm description:

Participants received flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 13 weeks during double blind treatment period (Acute Phase).

Arm type	Experimental
Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 30 or 60 mg flexible doses of duloxetine capsules orally once daily.

Arm title	Placebo
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Arm description:

Participants received Placebo orally once daily (QD) for 13 weeks during double blind treatment phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo capsules orally once daily.

Number of subjects in period 1	Duloxetine	Placebo
Started	91	93
Received at least one dose of study drug	91	93
Completed	74	75
Not completed	17	18
Parent/Caregiver Decision	2	4
Consent withdrawn by subject	3	4
Adverse event, non-fatal	5	1
Lost to follow-up	2	3
Lack of efficacy	1	3
Protocol deviation	4	3

Period 2

Period 2 title	Open Label Treatment (Extension Phase)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Duloxetine/Duloxetine

Arm description:

Participants received flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 13 weeks during double blind treatment period (Acute Phase) and flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 26 weeks during open label extension treatment period (Extension Phase).

Arm type	Experimental
Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 30 or 60 mg flexible doses of duloxetine capsules orally once daily.

Arm title	Placebo/Duloxetine
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Arm description:

Participants received Placebo orally once daily (QD) for 13 weeks during double blind treatment phase and flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 26 weeks during open label extension treatment period (Extension Phase).

Arm type	Experimental
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Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 30 or 60 mg flexible doses of duloxetine capsules orally once daily.

Number of subjects in period 2	Duloxetine/Duloxetine	Placebo/Duloxetine
Started	74	75
Received at least one dose of study drug	74	75
Completed	56	50
Not completed	18	25
Physician decision	4	4
Consent withdrawn by subject	-	5
Adverse event, non-fatal	5	5
Parent/Guardian Decision	2	4
Sponsor Decision	1	-
Lost to follow-up	4	3
Lack of efficacy	2	4

Period 3

Period 3 title	Taper Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Duloxetine/Duloxetine

Arm description:

Participants who received higher doses of Duloxetine in acute & extension phase received gradually lower doses of duloxetine & participants on lower doses of Duloxetine in acute phase received placebo during 1-week tapering phase.

Arm type	Experimental
Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 30 mg duloxetine capsules orally once daily.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Participants received placebo capsules orally once daily.	
Arm title	Placebo/Duloxetine

Arm description:

Participants who received placebo in acute phase received placebo & participants who received higher doses of Duloxetine in extension phase received gradually lower doses of duloxetine during 1-week tapering phase.

Arm type	Experimental
Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 30 mg duloxetine capsules orally once daily.

Investigational medicinal product name	Duloxetine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 30 mg duloxetine capsules orally once daily.

Number of subjects in period 3^[1]	Duloxetine/Duloxetine	Placebo/Duloxetine
Started	36	44
Completed	31	34
Not completed	5	10
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2
Parent/Guardian Decision	-	2
Sponsor Decision	1	-
Protocol deviation	2	-
Lack of efficacy	2	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who discontinued Acute or Extension phase had an option to enter tapering phase.

Baseline characteristics

Reporting groups

Reporting group title	Duloxetine
Reporting group description:	
Participants received flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 13 weeks during double blind treatment period (Acute Phase).	
Reporting group title	Placebo
Reporting group description:	
Participants received Placebo orally once daily (QD) for 13 weeks during double blind treatment phase.	

Reporting group values	Duloxetine	Placebo	Total
Number of subjects	91	93	184
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	91	93	184
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	15.74	15.33	
standard deviation	± 1.379	± 1.421	-
Gender categorical			
Units: Subjects			
Female	73	65	138
Male	18	28	46
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	36	39	75
Not Hispanic or Latino	54	54	108
Unknown or Not Reported	1	0	1
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	6	7	13
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	7	8	15
White	72	70	142
More than one race	4	6	10
Unknown or Not Reported	1	1	2
Region of Enrollment			

Units: Subjects			
Puerto Rico	2	3	5
Argentina	19	19	38
United States	64	64	128
India	6	7	13
Brief Pain Inventory (BPI) Modified short form (SF) Adolescent version (AV) Average Pain			
BPI Modified SF AV is a scale that measures severity & interference of pain. Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). 4 questions assessing severity for worst pain, least pain, average pain in past 24 hours, & pain right now.			
Units: units on a scale			
arithmetic mean			
standard deviation	±	±	-

Subject analysis sets

Subject analysis set title	Duloxetine - Acute
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received 30 or 60 mg Duloxetine orally once daily (QD) for 13 weeks.	
Subject analysis set title	Placebo - Acute
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received Placebo orally once daily (QD) for 13 weeks.	
Subject analysis set title	Duloxetine/Duloxetine - Extension Phase
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 13 weeks during double blind treatment period (Acute Phase) and flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 26 weeks during open label extension treatment period (Extension Phase).	
Subject analysis set title	Placebo/Duloxetine - Extension Phase
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received Placebo orally once daily (QD) for 13 weeks during double blind treatment phase and flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 26 weeks during open label extension treatment period (Extension Phase).	
Subject analysis set title	Duloxetine - Acute
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received 30 or 60 mg Duloxetine orally once daily (QD) for 13 weeks.	
Subject analysis set title	Placebo - Acute
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received Placebo orally once daily (QD) for 13 weeks.	

Reporting group values	Duloxetine - Acute	Placebo - Acute	Duloxetine/Duloxetine - Extension Phase
Number of subjects	76	76	74
Age categorical			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Region of Enrollment Units: Subjects			
Puerto Rico Argentina United States India			
Brief Pain Inventory (BPI) Modified short form (SF) Adolescent version (AV) Average Pain			
BPI Modified SF AV is a scale that measures severity & interference of pain. Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). 4 questions assessing severity for worst pain, least pain, average pain in past 24 hours, & pain right now.			
Units: units on a scale arithmetic mean standard deviation	±	±	±
Reporting group values	Placebo/Duloxetine - Extension Phase	Duloxetine - Acute	Placebo - Acute
Number of subjects	75	90	91

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	±	±	±
standard deviation			
Gender categorical Units: Subjects			
Female			
Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
Unknown or Not Reported			
Region of Enrollment Units: Subjects			
Puerto Rico			
Argentina			
United States			
India			
Brief Pain Inventory (BPI) Modified short form (SF) Adolescent version (AV) Average Pain			
BPI Modified SF AV is a scale that measures severity & interference of pain. Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). 4 questions assessing severity for worst pain, least pain, average pain in past 24 hours, & pain right now.			
Units: units on a scale			
arithmetic mean		5.7	5.6
standard deviation	±	± 1.37	± 1.55

End points

End points reporting groups

Reporting group title	Duloxetine
Reporting group description: Participants received flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 13 weeks during double blind treatment period (Acute Phase).	
Reporting group title	Placebo
Reporting group description: Participants received Placebo orally once daily (QD) for 13 weeks during double blind treatment phase.	
Reporting group title	Duloxetine/Duloxetine
Reporting group description: Participants received flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 13 weeks during double blind treatment period (Acute Phase) and flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 26 weeks during open label extension treatment period (Extension Phase).	
Reporting group title	Placebo/Duloxetine
Reporting group description: Participants received Placebo orally once daily (QD) for 13 weeks during double blind treatment phase and flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 26 weeks during open label extension treatment period (Extension Phase).	
Reporting group title	Duloxetine/Duloxetine
Reporting group description: Participants who received higher doses of Duloxetine in acute & extension phase received gradually lower doses of duloxetine & participants on lower doses of Duloxetine in acute phase received placebo during 1-week tapering phase.	
Reporting group title	Placebo/Duloxetine
Reporting group description: Participants who received placebo in acute phase received placebo & participants who received higher doses of Duloxetine in extension phase received gradually lower doses of duloxetine during 1-week tapering phase.	
Subject analysis set title	Duloxetine - Acute
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received 30 or 60 mg Duloxetine orally once daily (QD) for 13 weeks.	
Subject analysis set title	Placebo - Acute
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received Placebo orally once daily (QD) for 13 weeks.	
Subject analysis set title	Duloxetine/Duloxetine - Extension Phase
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 13 weeks during double blind treatment period (Acute Phase) and flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 26 weeks during open label extension treatment period (Extension Phase).	
Subject analysis set title	Placebo/Duloxetine - Extension Phase
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants received Placebo orally once daily (QD) for 13 weeks during double blind treatment phase and flexible doses of 30 or 60 milligram (mg) Duloxetine orally once daily (QD) for 26 weeks during open label extension treatment period (Extension Phase).	
Subject analysis set title	Duloxetine - Acute
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received 30 or 60 mg Duloxetine orally once daily (QD) for 13 weeks.

Subject analysis set title	Placebo - Acute
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received Placebo orally once daily (QD) for 13 weeks.

Primary: Change from baseline to 13 week endpoint in Brief Pain Inventory (BPI) modified short form-adolescent version 24 hour average pain severity item

End point title	Change from baseline to 13 week endpoint in Brief Pain Inventory (BPI) modified short form-adolescent version 24 hour average pain severity item
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End point description:

Brief Pain Inventory (BPI) modified short form is a self-reported scale that measures the severity of pain and the interference of pain on function, Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). Severity of pain is measured based on the average pain experienced over the past 24-hours.

Mixed Model Repeated Measure (MMRM) model with terms for treatment, pooled investigator, visit, baseline, treatment by visit, and baseline by visit was used to produce Least Square (LS) means.

Analysis Population Description (APD): All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline BPI average pain score.

End point type	Primary
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End point timeframe:

Baseline, 13 weeks

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	76		
Units: units on a scale				
least squares mean (standard error)	-1.62 (± 0.247)	-0.97 (± 0.244)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.052
Method	Repeated Measures
Parameter estimate	LS mean change difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0

Variability estimate	Standard error of the mean
Dispersion value	0.33

Secondary: Change from baseline to 13 week endpoint in Brief Pain Inventory (BPI) modified short form-Adolescent version severity and interference items

End point title	Change from baseline to 13 week endpoint in Brief Pain Inventory (BPI) modified short form-Adolescent version severity and interference items
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End point description:

The Brief Pain Inventory (BPI) - Modified Short Form Adolescent Version is a self-reported scale that measures the severity of pain and the interference of pain on function. 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.

MMRM model with terms for treatment, pooled investigator, visit, baseline, treatment by visit, and baseline by visit was used to produce LS means.

End point type	Secondary
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End point timeframe:

Baseline, 13 weeks

APD:Analysis population description: All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline BPI severity & interferences items score.

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	76		
Units: units on a scale				
least squares mean (standard error)				
Worst Pain	-1.58 (± 0.270)	-0.90 (± 0.266)		
Least Pain	-1.08 (± 0.239)	-0.47 (± 0.236)		
Pain Right Now	-1.56 (± 0.274)	-1.05 (± 0.271)		
General Activity	-2.00 (± 0.262)	-1.03 (± 0.258)		
Mood	-2.00 (± 0.269)	-1.46 (± 0.265)		
Walking ability	-1.30 (± 0.266)	-1.09 (± 0.262)		
Normal Work	-1.49 (± 0.277)	-1.21 (± 0.274)		
Relations With Other People	-1.87 (± 0.237)	-1.07 (± 0.233)		
Sleep	-1.40 (± 0.343)	-1.05 (± 0.338)		
Enjoyment of Life	-1.76 (± 0.253)	-1.47 (± 0.250)		

School Work	-1.68 (\pm 0.316)	-1.08 (\pm 0.313)		
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Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Worst Pain	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.36

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Least Pain	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.319

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Pain Right Now	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.365

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
General Activity	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.344

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Mood	
Comparison groups	Duloxetine - Acute v Placebo - Acute

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.356

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Walking ability	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.352

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Normal Work	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.371

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Relations With Other	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	0.312

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Sleep	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.443
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	0.55
Variability estimate	Standard error of the mean
Dispersion value	0.454

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
Enjoyment of Life	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.338

Statistical analysis title	Statistical Analysis 11
Statistical analysis description:	
School Work	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.424

Secondary: Maintenance effect in acute phase responders on the Brief Pain Inventory (BPI) modified short form-adolescent version 24 hour average pain severity item

End point title	Maintenance effect in acute phase responders on the Brief Pain Inventory (BPI) modified short form-adolescent version 24 hour average pain severity item
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End point description:

Brief Pain Inventory (BPI) modified short form is a self-reported scale that measures the severity of pain and the interference of pain on function. Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). Severity of pain is measured based on the average pain experienced over the past 24-hours.

Acute phase responders: Participants with $\geq 30\%$ pain reduction from baseline on the BPI average pain severity measure at the last non-missing assessment in acute phase.

APD: All randomized participants in duloxetine only arm with $\geq 30\%$ pain reduction from baseline on the BPI average pain severity measure at the last non-missing assessment in acute phase.

End point type	Secondary
End point timeframe:	
Baseline (Extension Phase), 39 weeks	

End point values	Duloxetine/Duloxetine - Extension Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: units on a scale				
arithmetic mean (standard deviation)	-3.4 (\pm 1.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with greater than or equal to 30% reduction from baseline in BPI 24 hour average pain severity score at 13 weeks

End point title	Number of participants with greater than or equal to 30% reduction from baseline in BPI 24 hour average pain severity score at 13 weeks
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End point description:

Brief Pain Inventory (BPI) modified short form is a self-reported scale that measures the severity of pain and interference of pain on function, Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). Severity of pain is measured based on the average pain experienced over the past 24-hours.

Percent reduction of BPI 24 hour average pain from baseline to last observation carried forward (LOCF).

APD: All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline BPI average pain score.

End point type	Secondary
End point timeframe:	
13 weeks	

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	91		
Units: Participants				
number (not applicable)	47	33		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	Fisher exact

Secondary: Number of participants with greater than or equal to 50% reduction from baseline in BPI 24 hour average pain severity score at 13 weeks

End point title	Number of participants with greater than or equal to 50% reduction from baseline in BPI 24 hour average pain severity score at 13 weeks
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End point description:

Brief Pain Inventory (BPI) modified short form is a self-reported scale that measures the severity of pain and interference of pain on function, Severity scores range from 0 (no pain) to 10 (pain as bad as you can imagine). Severity of pain is measured based on the average pain experienced over the past 24-hours.

Percent reduction of BPI 24 hour average pain from baseline to last observation carried forward (LOCF).

APD:All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline BPI average pain score.

End point type	Secondary
End point timeframe:	
13 weeks	

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	91		
Units: Participants				
number (not applicable)	36	22		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	Fisher exact

Secondary: Change from baseline in Pediatric Pain Questionnaire (PPQ) item scores

End point title	Change from baseline in Pediatric Pain Questionnaire (PPQ) item scores
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End point description:

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). The severity scores range from 0 (no hurting, no discomfort, no pain) to 100 (hurting a whole lot, very uncomfortable, severe pain).

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for treatment, pooled investigator and baseline value.

APD: All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline PPQ score.

End point type	Secondary
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End point timeframe:

Baseline, 13 weeks

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	86		
Units: mm				
least squares mean (standard error)				
Average Pain Score	-11.03 (± 2.982)	-9.41 (± 2.946)		
Worst Pain Score	-14.36 (± 3.367)	-8.46 (± 3.322)		
Pain Score Right Now	-8.99 (± 3.092)	-7.20 (± 3.065)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Average Pain Score	
Comparison groups	Placebo - Acute v Duloxetine - Acute

Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.669
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	5.86

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Worst Pain Score	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.169
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.32
upper limit	2.53

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Pain Score Right Now	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.647
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.53
upper limit	5.94

Secondary: Change from baseline in Clinical Global Impression (CGI) Severity: Overall Illness Score

End point title	Change from baseline in Clinical Global Impression (CGI) Severity: Overall Illness Score
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End point description:

Clinical Global Impression of Severity: Overall Illness (CGI-S: Overall Illness) scale evaluates the severity of the overall illness of JPFS, including all relevant, associated symptoms. The scoring ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). The scoring is based on observed and reported symptoms and behaviors over the past 7 days that are ongoing at the time of the Study Visit.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS mean with terms for treatment, pooled investigator and baseline value.

APD: All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline CGI-S overall illness score.

End point type	Secondary
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End point timeframe:

Baseline, 13 weeks

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	92		
Units: units on a scale				
least squares mean (standard error)	-0.88 (± 0.121)	-0.66 (± 0.118)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.08

Secondary: Change from baseline in Clinical Global Impression (CGI) Severity: Mental illness score

End point title	Change from baseline in Clinical Global Impression (CGI) Severity: Mental illness score
End point description: Clinical Global Impression of Severity: Mental Illness (CGI-S: Mental Illness) scale evaluates the severity of any diagnosed, comorbid Axis I/II condition. The scoring ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). Participants without a diagnosed Axis I/II condition should receive a score of 1 (normal, not at all ill). Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS mean with terms for treatment, pooled investigator and baseline value. APD:All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline CGI-S mental illness score.	
End point type	Secondary
End point timeframe: Baseline, 13 weeks	

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	90	92		
Units: units on a scale				
least squares mean (standard error)	-0.16 (± 0.089)	-0.15 (± 0.087)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.927
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.21

Secondary: Change From Baseline in Functional Disability Inventory Child Form (FDI-Child)

End point title	Change From Baseline in Functional Disability Inventory Child Form (FDI-Child)
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End point description:

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. 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.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for treatment, pooled investigator and baseline value.

APD:All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline FDI child scale score.

End point type	Secondary
End point timeframe:	
Baseline, 13 weeks	

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	88		
Units: units on a scale				
least squares mean (standard error)	-3.97 (\pm 1.038)	-5.00 (\pm 1.021)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.431
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	3.59

Secondary: Change From Baseline in Functional Disability Inventory Parent Form (FDI-Parent)

End point title	Change From Baseline in Functional Disability Inventory Parent Form (FDI-Parent)
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End point description:

Functional Disability Inventory-parent form (FDI-parent) contains the same items as FDI-child, but is reported by parent/legal representative. The total score range from 0 to 60. The higher the score, the more physical trouble or difficulty the child has doing regular activities.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to

produce LS means with terms for treatment, pooled investigator and baseline value.

APD:All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline FDI-parent scale score.

End point type	Secondary
End point timeframe:	
Baseline, 13 weeks	

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	87		
Units: units on a scale				
least squares mean (standard error)	-3.25 (± 1.152)	-4.17 (± 1.139)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.529
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	3.79

Secondary: Change from baseline in Children's Depression Inventory (CDI)

End point title	Change from baseline in Children's Depression Inventory (CDI)
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End point description:

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. 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.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for treatment, pooled investigator and baseline value.

APD:All randomized participants who received at least one dose of study drug and had baseline & at least one post baseline CDI score.

End point type	Secondary
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End point timeframe:

Baseline, 13 weeks

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	89		
Units: units on a scale				
least squares mean (standard error)	-3.28 (\pm 0.682)	-2.45 (\pm 0.674)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.335
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	0.86

Secondary: Change from baseline in Multidimensional Anxiety Scale for Children (MASC)

End point title	Change from baseline in Multidimensional Anxiety Scale for Children (MASC)
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End point description:

Multidimensional Anxiety Scale for Children (MASC) is a self-reported scale developed to assess anxiety in children and adolescents. The MASC consists of 39 items that comprise 4 factors, 3 of which can be separated into 2 sub factors each. Main factors (sub factors) 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 (0-never true about me, 1-rarely true about me, 2- sometimes true about me, 3-often true about me). Total score range from 0 to 117. The higher the total score, the more severe the anxiety. Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for treatment, pooled investigator and baseline value.

End point type	Secondary
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End point timeframe:

Baseline, 13 weeks

End point values	Duloxetine - Acute	Placebo - Acute		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	89		
Units: units on a scale				
least squares mean (standard error)				
Physical Symptoms	-1.39 (± 0.663)	-1.44 (± 0.652)		
Harm Avoidance	-1.34 (± 0.507)	-0.78 (± 0.501)		
Social Anxiety	-1.86 (± 0.497)	-1.42 (± 0.489)		
Separation/Panic	-1.62 (± 0.393)	-1.43 (± 0.389)		
Total Score	-6.21 (± 1.575)	-4.99 (± 1.558)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Physical Symptoms Score	
Comparison groups	Placebo - Acute v Duloxetine - Acute
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.955
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	1.68

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Harm Avoidance	
Comparison groups	Duloxetine - Acute v Placebo - Acute

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.381
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	0.7

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Social Anxiety	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	0.79

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Separation/Panic	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.79

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Total Score	
Comparison groups	Duloxetine - Acute v Placebo - Acute
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.12
upper limit	2.69

Secondary: Change From Baseline to 39 Week Endpoint in Brief Pain Inventory (BPI) Modified Short Form-adolescent Version Severity and Interference Items

End point title	Change From Baseline to 39 Week Endpoint in Brief Pain Inventory (BPI) Modified Short Form-adolescent Version Severity and Interference Items
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End point description:

BPI - Modified Short Form Adolescent Version is a self-reported scale that measures the severity of pain & interference of pain on function. 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. 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, & enjoyment of life. The BPI: Adolescent Version added an eighth interference question to assess interference of pain on school work. Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for pooled investigator and baseline value.

End point type	Secondary
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End point timeframe:

Baseline (extension phase), 39 weeks

APD: Analysis population description: All randomized participants who received at least one dose of study drug & had baseline & at least one post baseline BPI severity & interferences items scores.

End point values	Duloxetine/Duloxetine - Extension Phase	Placebo/Duloxetine - Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	75		
Units: units on a scale				
least squares mean (standard error)				
Worst Pain	-0.65 (± 0.262)	-0.80 (± 0.256)		
Least Pain	-0.29 (± 0.218)	-0.45 (± 0.212)		
Pain Right Now	-0.38 (± 0.259)	-0.29 (± 0.252)		
General Activity	-0.18 (± 0.233)	0.20 (± 0.229)		
Mood	-0.15 (± 0.270)	-0.25 (± 0.258)		
Walking Ability	-0.24 (± 0.260)	-0.21 (± 0.253)		
Normal Work	-0.62 (± 0.231)	-0.32 (± 0.226)		
Relations with Other People	-0.12 (± 0.229)	-0.41 (± 0.222)		
Sleep	-0.63 (± 0.292)	-0.54 (± 0.284)		
Enjoyment of Life	-0.25 (± 0.243)	-0.26 (± 0.236)		
School Work	-0.59 (± 0.278)	-0.06 (± 0.271)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Pediatric Pain Questionnaire (PPQ) item scores

End point title	Change from baseline in Pediatric Pain Questionnaire (PPQ) item scores
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End point description:

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). The severity scores range from 0 (no hurting, no discomfort, no pain) to 100 (hurting a whole lot, very uncomfortable, severe pain).

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for pooled investigator and baseline value.

APD: All randomized participants who received at least one dose of study drug & had baseline & at least one post baseline PPQ measurement.

Baseline for extension phase is defined as the last non-missing value in acute phase.

End point type	Secondary
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End point timeframe:

Baseline (extension phase), 39 weeks

End point values	Duloxetine/Duloxetine - Extension Phase	Placebo/Duloxetine - Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	60		
Units: units on a scale				
least squares mean (standard error)				
Average Pain Score	-10.65 (\pm 3.080)	-6.44 (\pm 3.296)		
Worst Pain Score	-4.15 (\pm 3.127)	-8.06 (\pm 3.677)		
Score Right Now	-4.74 (\pm 3.075)	-6.34 (\pm 3.335)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression (CGI) Severity: Overall Illness Score

End point title	Change From Baseline in Clinical Global Impression (CGI) Severity: Overall Illness Score
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End point description:

Clinical Global Impression of Severity: Overall Illness (CGI-S: Overall Illness) scale evaluates the severity of the overall illness of JPFS, including all relevant, associated symptoms. The scoring ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). The scoring is based on observed and reported symptoms and behaviors over the past 7 days that are ongoing at the time of the Study Visit.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS mean with terms for pooled investigator and baseline value.

APD: All randomized participants who received at least one dose of study drug & had baseline & at least one post baseline CGI overall illness measurement.

Baseline for extension phase is defined as the last non-missing value in acute phase.

End point type	Secondary
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End point timeframe:

Baseline (extension phase), 39 weeks

End point values	Duloxetine/Duloxetine - Extension Phase	Placebo/Duloxetine - Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	75		
Units: units on a scale				
least squares mean (standard error)	-0.67 (\pm 0.125)	-0.67 (\pm 0.121)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression (CGI) Severity: Mental Illness Score

End point title	Change From Baseline in Clinical Global Impression (CGI) Severity: Mental Illness Score
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End point description:

Clinical Global Impression of Severity: Mental Illness (CGI-S: Mental Illness) scale evaluates the severity of any diagnosed, comorbid Axis I/II condition. The scoring ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). Participants without a diagnosed Axis I/II condition should receive a score of 1 (normal, not at all ill).

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS mean with terms for pooled investigator and baseline value.

APD:All randomized participants who received at least one dose of study drug & had baseline & at least one post baseline CGI mental Illness measurement.

Baseline for extension phase is defined as the last non-missing value in acute phase.

End point type	Secondary
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End point timeframe:

Baseline (extension phase), 39 weeks

End point values	Duloxetine/Duloxetine - Extension Phase	Placebo/Duloxetine - Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	75		
Units: units on a scale				
least squares mean (standard error)	-0.20 (\pm 0.104)	-0.24 (\pm 0.101)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Disability Inventory Child Form (FDI-child)

End point title	Change From Baseline in Functional Disability Inventory Child Form (FDI-child)
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End point description:

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. 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.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for pooled investigator and baseline value.

APD:All randomized participants who received at least one dose of study drug & had baseline & at least one post baseline FDI-child measurement.

Baseline for extension phase is defined as the last non-missing value in acute phase.

End point type	Secondary
End point timeframe:	
Baseline (extension phase), 39 weeks	

End point values	Duloxetine/Duloxetine - Extension Phase	Placebo/Duloxetine - Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	60		
Units: units on a scale				
least squares mean (standard error)	-3.49 (\pm 1.227)	-2.27 (\pm 1.327)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Disability Inventory Parent Form (FDI-parent)

End point title	Change From Baseline in Functional Disability Inventory Parent Form (FDI-parent)
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End point description:

Functional Disability Inventory-parent form (FDI-parent) contains the same items as FDI-child, but is reported by parent/legal representative. The total score range from 0 to 60. The higher the score, the more physical trouble or difficulty the child has doing regular activities.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for pooled investigator and baseline value.

APD: All randomized participants who received at least one dose of study drug & had baseline & at least one post baseline FDI-parent measurement.

Baseline for extension phase is defined as the last non-missing value in acute phase.

End point type	Secondary
End point timeframe:	
Baseline (extension phase), 39 weeks	

End point values	Duloxetine/Duloxetine - Extension Phase	Placebo/Duloxetine - Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	60		
Units: units on a scale				
least squares mean (standard error)	-3.49 (\pm 1.227)	-2.27 (\pm 1.327)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children's Depression Inventory (CDI)

End point title	Change From Baseline in Children's Depression Inventory (CDI)
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End point description:

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. 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.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for pooled investigator and baseline value.

APD: All randomized participants who received at least one dose of study drug & had baseline & at least one post baseline CDI measurement.

Baseline for extension phase is defined as the last non-missing value in acute phase.

End point type	Secondary
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End point timeframe:

Baseline (extension phase), 39 weeks

End point values	Duloxetine/Duloxetine - Extension Phase	Placebo/Duloxetine - Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	74		
Units: units on a scale				
least squares mean (standard error)	-0.42 (± 0.703)	-1.41 (± 0.681)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multidimensional Anxiety Scale for Children (MASC)

End point title	Change From Baseline in Multidimensional Anxiety Scale for Children (MASC)
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End point description:

Multidimensional Anxiety Scale for Children (MASC) is a self-reported scale developed to assess anxiety in children and adolescents. The MASC consists of 39 items that comprise 4 factors, 3 of which can be separated into 2 sub factors each. Main factors (sub factors) 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 (0-never true about me, 1-rarely true about me, 2- sometimes true about me, 3-often true about me). Total score range from 0 to 117. The higher the total score, the more severe the anxiety.

Analysis of Covariance (ANCOVA) model with last observation carried forward (LOCF) was used to produce LS means with terms for pooled investigator and baseline value.

Baseline for extension phase is defined as the last non-missing value in acute phase.

End point type	Secondary
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End point timeframe:

Baseline (extension phase), 39 weeks

Analysis population description: All randomized participants who received at least one dose of study drug & had baseline & at least one post baseline MASC measurement.

End point values	Duloxetine/Duloxetine - Extension Phase	Placebo/Duloxetine - Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74	74		
Units: units on a scale				
least squares mean (standard error)				
Physical Symptoms	-0.63 (± 0.715)	-0.92 (± 0.692)		
Harm Avoidance	0.23 (± 0.485)	0.10 (± 0.471)		
Social Anxiety	-0.11 (± 0.487)	-0.02 (± 0.472)		
Separation/Panic	-0.06 (± 0.371)	0.01 (± 0.361)		
Total Score	-0.55 (± 1.478)	-0.78 (± 1.432)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 39 Weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Duloxetine - Acute
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Reporting group description: -

Reporting group title	Placebo - Acute
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Reporting group description: -

Reporting group title	Duloxetine/Duloxetine - Extension
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Reporting group description: -

Reporting group title	Placebo/Duloxetine - Extension
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Reporting group description: -

Reporting group title	Duloxetine/Duloxetine - Taper
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Reporting group description: -

Reporting group title	Placebo/Placebo - Taper
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Reporting group description: -

Serious adverse events	Duloxetine - Acute	Placebo - Acute	Duloxetine/Duloxetine - Extension
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 91 (2.20%)	0 / 93 (0.00%)	3 / 74 (4.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
intentional overdose			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 91 (0.00%)	0 / 93 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
generalised tonic-clonic seizure			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 91 (0.00%)	0 / 93 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
affective disorder			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 91 (0.00%)	0 / 93 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hallucination, auditory			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 91 (0.00%)	0 / 93 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intentional self-injury			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 91 (0.00%)	0 / 93 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal ideation			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 91 (1.10%)	0 / 93 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicide attempt			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 91 (0.00%)	0 / 93 (0.00%)	2 / 74 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 91 (1.10%)	0 / 93 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo/Duloxetine - Extension	Duloxetine/Duloxetine - Taper	Placebo/Placebo - Taper
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Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 75 (4.00%)	0 / 77 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
intentional overdose			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
generalised tonic-clonic seizure			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
affective disorder			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hallucination, auditory			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intentional self-injury			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal ideation			
alternative dictionary used: MedDRA 20.1			

subjects affected / exposed	1 / 75 (1.33%)	0 / 77 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicide attempt			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 75 (0.00%)	0 / 77 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 75 (0.00%)	0 / 77 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Duloxetine - Acute	Placebo - Acute	Duloxetine/Duloxetine - Extension
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 91 (81.32%)	58 / 93 (62.37%)	52 / 74 (70.27%)
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	8 / 91 (8.79%)	9 / 93 (9.68%)	4 / 74 (5.41%)
occurrences (all)	10	13	4
headache			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	13 / 91 (14.29%)	10 / 93 (10.75%)	6 / 74 (8.11%)
occurrences (all)	15	14	8
somnolence			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	8 / 91 (8.79%)	3 / 93 (3.23%)	3 / 74 (4.05%)
occurrences (all)	8	3	3
General disorders and administration site conditions			

fatigue alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	5 / 91 (5.49%) 5	2 / 93 (2.15%) 2	4 / 74 (5.41%) 4
Gastrointestinal disorders abdominal pain alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	0 / 91 (0.00%) 0	2 / 93 (2.15%) 2	0 / 74 (0.00%) 0
abdominal pain upper alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 2	6 / 93 (6.45%) 6	2 / 74 (2.70%) 2
constipation alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 3	2 / 93 (2.15%) 2	2 / 74 (2.70%) 2
nausea alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	23 / 91 (25.27%) 30	14 / 93 (15.05%) 16	10 / 74 (13.51%) 14
vomiting alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	14 / 91 (15.38%) 19	5 / 93 (5.38%) 5	4 / 74 (5.41%) 4
Respiratory, thoracic and mediastinal disorders dysmenorrhoea alternative dictionary used: MedDRA 20.1 subjects affected / exposed ^[1] occurrences (all)	2 / 73 (2.74%) 2	4 / 65 (6.15%) 6	2 / 61 (3.28%) 2
erectile dysfunction alternative dictionary used: MedDRA 20.1 subjects affected / exposed ^[2] occurrences (all)	0 / 18 (0.00%) 0	0 / 28 (0.00%) 0	1 / 13 (7.69%) 1
Psychiatric disorders			

insomnia alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	0 / 91 (0.00%) 0	3 / 93 (3.23%) 3	2 / 74 (2.70%) 2
Infections and infestations gastroenteritis viral alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) nasopharyngitis alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) upper respiratory tract infection alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	5 / 91 (5.49%) 6 8 / 91 (8.79%) 11 6 / 91 (6.59%) 6	0 / 93 (0.00%) 0 2 / 93 (2.15%) 2 2 / 93 (2.15%) 2	1 / 74 (1.35%) 1 3 / 74 (4.05%) 3 6 / 74 (8.11%) 6
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	14 / 91 (15.38%) 14	3 / 93 (3.23%) 5	6 / 74 (8.11%) 6

Non-serious adverse events	Placebo/Duloxetine - Extension	Duloxetine/Duloxetine - Taper	Placebo/Placebo - Taper
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 75 (72.00%)	8 / 77 (10.39%)	0 / 3 (0.00%)
Nervous system disorders			
dizziness alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 4	3 / 77 (3.90%) 3	0 / 3 (0.00%) 0
headache alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 9	1 / 77 (1.30%) 1	0 / 3 (0.00%) 0
somnolence			

alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	1 / 77 (1.30%) 1	0 / 3 (0.00%) 0
General disorders and administration site conditions fatigue alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	0 / 77 (0.00%) 0	0 / 3 (0.00%) 0
Gastrointestinal disorders abdominal pain alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) abdominal pain upper alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) constipation alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) nausea alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) vomiting alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 6 6 / 75 (8.00%) 8 4 / 75 (5.33%) 4 22 / 75 (29.33%) 26 8 / 75 (10.67%) 9	0 / 77 (0.00%) 0 0 / 77 (0.00%) 0 0 / 77 (0.00%) 0 0 / 77 (0.00%) 0 0 / 77 (0.00%) 0	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0
Respiratory, thoracic and mediastinal disorders dysmenorrhoea alternative dictionary used: MedDRA 20.1 subjects affected / exposed ^[1] occurrences (all)	2 / 53 (3.77%) 5	0 / 60 (0.00%) 0	0 / 2 (0.00%) 0

erectile dysfunction alternative dictionary used: MedDRA 20.1 subjects affected / exposed ^[2] occurrences (all)	0 / 22 (0.00%) 0	0 / 17 (0.00%) 0	0 / 1 (0.00%) 0
Psychiatric disorders insomnia alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	0 / 77 (0.00%) 0	0 / 3 (0.00%) 0
Infections and infestations gastroenteritis viral alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) nasopharyngitis alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all) upper respiratory tract infection alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5 4 / 75 (5.33%) 4 4 / 75 (5.33%) 4	0 / 77 (0.00%) 0 1 / 77 (1.30%) 1 1 / 77 (1.30%) 1	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 20.1 subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 9	0 / 77 (0.00%) 0	0 / 3 (0.00%) 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific adverse event, data posted is only for female subjects.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific adverse event, data posted is only for male subjects.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2011	Blood sample draw for pharmacogenomic assessment was moved from visit 8 to visit 1, if not withdrawn at visit 1 then it should be collected at visit 2 or at the earliest possible opportunity.
24 April 2013	Changes to inclusion & exclusion criteria. Discontinuation of patients was modified to include a stipulation that Lilly or its designee must be contacted if patients who do not meet enrollment criteria were inadvertently enrolled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported