



Clinical trial results:

F1J-MC-HMFN (a) An Open-Label Study of Tolerability, Safety, and Pharmacokinetics of Duloxetine in the Treatment of Children and Adolescents with Major Depressive Disorder

Summary

EudraCT number	2017-000211-16
Trial protocol	Outside EU/EEA
Global end of trial date	22 September 2008

Results information

Result version number	v1 (current)
This version publication date	16 April 2017
First version publication date	16 April 2017

Trial information

Trial identification

Sponsor protocol code	F1J-MC-HMFN
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00529789
WHO universal trial number (UTN)	-
Other trial identifiers	Trial ID: 11664

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, 1 877-CTLILLY,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559,

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	22 September 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 September 2008
Global end of trial reached?	Yes
Global end of trial date	22 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of your participation in this study is to help answer the following research question, and not to provide you treatment for your condition. Whether duloxetine once daily orally is tolerated and safe, in children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with Major Depressive Disorder.

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	31 August 2007
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: 72
Worldwide total number of subjects	72
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)	31
Adolescents (12-17 years)	41
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Period I was a 2-week Screening/Washout Phase. Period II was a 10-week Dose-Titrating with Pharmacokinetic Sampling Phase. Period III was an 8-week Safety and Tolerability Phase. Period IV was a 3-month Extended Safety and Tolerability Phase. Period V was a 2-week Taper Phase. Results presented are for combined Periods II/III and Period IV.

Period 1

Period 1 title	Study Period II/III
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Duloxetine
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Arm description:

20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks;
If patient is ≤ 40 kilograms (kg), initial dose is 20 mg, then titrated up.
If patient is >40 kg, initial dose is 30 mg, then titrated up.

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:

A dose range of 20 - 120 milligrams (mg) Duloxetine every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is ≤ 40 kilograms (kg), initial dose is 20 mg, then titrated up. If patient is >40 kg, initial dose is 30 mg, then titrated up.

Number of subjects in period 1	Duloxetine
Started	72
Completed	48
Not completed	24
Parent/Caregiver Decision	9
Consent withdrawn by subject	1
Physician decision	3
Adverse event, non-fatal	3
Lost to follow-up	3
Lack of efficacy	2
Protocol deviation	3

Period 2

Period 2 title	Study Period IV
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Duloxetine
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Arm description:

20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is ≤ 40 kilograms (kg), initial dose is 20 mg, then titrated up. If patient is >40 kg, initial dose is 30 mg, then titrated up.

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:

A dose range of 20 - 120 milligrams (mg) Duloxetine every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is ≤ 40 kilograms (kg), initial dose is 20 mg, then titrated up. If patient is >40 kg, initial dose is 30 mg, then titrated up.

Number of subjects in period 2	Duloxetine
Started	48
Completed	42
Not completed	6
Parent/Caregiver Decision	1
Adverse event, non-fatal	1
Lost to follow-up	3
Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	Duloxetine
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Reporting group description:

20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks;

If patient is ≤40 kilograms (kg), initial dose is 20 mg, then titrated up.

If patient is >40 kg, initial dose is 30 mg, then titrated up.

Reporting group values	Duloxetine	Total	
Number of subjects	72	72	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	31	31	
Adolescents (12-17 years)	41	41	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	12.5		
standard deviation	± 2.9	-	
Gender categorical			
Units: Subjects			
Female	35	35	
Male	37	37	
Region of Enrollment			
Units: Subjects			
United States	72	72	
Race/Ethnicity			
Units: Subjects			
African	17	17	
Caucasian	42	42	
East Asian	1	1	
Hispanic	11	11	
Native American	1	1	
Tobacco Use			
Tobacco use was based on cotinine level.			
Units: Subjects			
No	70	70	
Yes	1	1	
Not Available	1	1	

Body Mass Index (BMI)			
Body mass index is an estimate of body fat based on body weight divided by height squared.			
Units: Subjects			
arithmetic mean	23.7		
standard deviation	± 6.4	-	

End points

End points reporting groups

Reporting group title	Duloxetine
Reporting group description: 20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is ≤40 kilograms (kg), initial dose is 20 mg, then titrated up. If patient is >40 kg, initial dose is 30 mg, then titrated up.	
Reporting group title	Duloxetine
Reporting group description: 20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is ≤40 kilograms (kg), initial dose is 20 mg, then titrated up. If patient is >40 kg, initial dose is 30 mg, then titrated up.	
Subject analysis set title	Duloxetine Dose 20mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Summary of observed plasma concentrations of duloxetine 20 mg.	
Subject analysis set title	Duloxetine Dose 30mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Summary of observed plasma concentrations of duloxetine 30 mg.	
Subject analysis set title	Duloxetine Dose 60mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Summary of observed plasma concentrations of duloxetine 60 mg.	
Subject analysis set title	Duloxetine Dose 90mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Summary of observed plasma concentrations of duloxetine 90 mg.	
Subject analysis set title	Duloxetine Dose 120mg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Summary of observed plasma concentrations of duloxetine 120 mg.	

Primary: Number of Participants with Emergence of Suicidal Ideation During Period II/III

End point title	Number of Participants with Emergence of Suicidal Ideation During Period II/III ^[1]
End point description: Emergence of Any Suicidal Ideation: Item 13 of Children's Depression Rating Scale-Revised (CDRS-R) has possible scores of 1 (no thoughts of suicide) to 7 (contemplation of suicide). Emergence of suicidal ideation was defined as an increase in severity of suicidal ideation for those patients who did not have suicidal ideation at baseline (Week 0).	
End point type	Primary
End point timeframe: Baseline to 18 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: participants				
number (not applicable)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Emergence of Suicidal Ideation During Period IV

End point title	Number of Participants with Emergence of Suicidal Ideation During Period IV ^[2]
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End point description:

Emergence of Any Suicidal Ideation: Item 13 of Children's Depression Rating Scale-Revised (CDRS-R) has possible scores of 1 (no thoughts of suicide) to 7 (contemplation of suicide). Emergence of suicidal ideation was defined as an increase in severity of suicidal ideation for those patients who did not have suicidal ideation at baseline (Week 0).

End point type	Primary
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End point timeframe:

Week 0 and Between 18 and 30 Weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) During Period II/III

End point title	Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) During Period II/III ^[3]
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End point description:

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. Some questions are yes/no and some are on a scale of 1 (low severity) to 5 (high severity). Completed suicide and non-fatal suicide events are yes/no questions and results presented are the number of participants with these events. Worsening of suicidal ideation was an increase in severity of suicidal ideation from baseline.

End point type	Primary			
End point timeframe:				
Baseline to 18 Weeks				
Notes:				
[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.				
Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.				
End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: participants				
number (not applicable)				
Completed Suicide	0			
Non-fatal Suicide Event	1			
Worsening of Suicidal Ideation	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) During Period IV

End point title	Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) During Period IV ^[4]			
End point description:				
The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. Some questions are yes/no and some are on a scale of 1 (low severity) to 5 (high severity). Completed suicide and non-fatal suicide events are yes/no questions and results presented are the number of participants with these events. Worsening of suicidal ideation was an increase in severity of suicidal ideation from baseline.				
End point type	Primary			
End point timeframe:				
Between 18 and 30 Weeks				
Notes:				
[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.				
Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.				
End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	45 ^[5]			
Units: participants				
number (not applicable)				
Completed suicide	0			
Non-fatal suicide event	0			
Worsening of Suicidal Ideation	1			

Notes:

[5] - Number of enrolled patients with baseline and post-baseline values in Period IV.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant Vital Sign Values at Any Time During Period II/III

End point title	Number of Participants Meeting Criteria for Potentially Clinically Significant Vital Sign Values at Any Time During Period II/III ^[6]
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End point description:

Total number of patients with any abnormal post-baseline value, based on all values at scheduled and unscheduled visits. Criteria: High Diastolic Blood Pressure = increase of at least 5 mmHg to a value above the 95th percentile; High Systolic Blood Pressure = increase of at least 5 mmHg to a value above the 95th percentile; High Pulse = increase of at least 25 to a value of at least 110.

End point type	Primary
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End point timeframe:

Baseline to 18 Weeks

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: participants				
number (not applicable)				
High Diastolic Blood Pressure	22			
High Systolic Blood Pressure	25			
High Pulse	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant Vital Sign Values at Any Time During Period IV

End point title	Number of Participants Meeting Criteria for Potentially Clinically Significant Vital Sign Values at Any Time During Period IV ^[7]
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End point description:

Total number of patients with any abnormal post-baseline value, based on all values at scheduled and unscheduled visits. Criteria: High Diastolic Blood Pressure = increase of at least 5 mmHg to a value above the 95th percentile; High Systolic Blood Pressure = increase of at least 5 mmHg to a value above the 95th percentile; High Pulse = increase of at least 25 to a value of at least 110.

End point type	Primary
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End point timeframe:

Between 18 and 30 Weeks

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: participants				
number (not applicable)				
High Diastolic Blood Pressure	3			
High Systolic Blood Pressure	1			
High Pulse	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant (PCS) Laboratory Analyte Values at Any Time During Period II/III

End point title	Number of Participants Meeting Criteria for Potentially Clinically Significant (PCS) Laboratory Analyte Values at Any Time During Period II/III ^[8]
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End point description:

The results shown are for all laboratory analytes where PCS criteria were met, based on criteria used for adult studies. Criteria: High Alanine transaminase (>165 Units/Liter [U/L]); High Creatine Phosphokinase (females: >507 U/L; males: >594 U/L); Low Glucose (<2.498 millimoles/L); Low Hematocrit (females: <0.32; males <0.37); Low Hemoglobin (females <5.896 millimoles/L [mmol/L] iron; males <7.137 mmol/L iron); High Inorganic Phosphorus (>1.776 millimoles/L); Low Leukocyte Count (<2.8 X10⁹/L).

Number of patients with baseline (and none abnormal) and post-baseline values, based on all values at scheduled and unscheduled visits

End point type	Primary
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End point timeframe:

Baseline to 18 Weeks

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: participants				
number (not applicable)				
High Alanine Transaminase (N=69)	1			
High Creatine Phosphokinase (N=69)	6			

Low Glucose (N=69)	1			
Low Hematocrit (N=60)	8			
Low Hemoglobin (N=67)	1			
High Inorganic Phosphorus (N=62)	16			
Low Leukocyte Count (N=68)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant (PCS) Laboratory Analyte Values at Any Time During Period IV

End point title	Number of Participants Meeting Criteria for Potentially Clinically Significant (PCS) Laboratory Analyte Values at Any Time During Period IV ^[9]
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End point description:

The results shown are for all laboratory analytes where PCS criteria were met, based on criteria used for adult studies. Criteria: High Alkaline Phosphatase (>420 Units/Liter [U/L]); Low Hematocrit (females <0.32; males <0.37); High Inorganic Phosphorus (>1.776 millimoles/L).

Total number of patients with baseline (and none abnormal) and post-baseline values in Period IV, based on all values at scheduled and unscheduled visits.

End point type	Primary
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End point timeframe:

Between 18 and 30 Weeks

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: participants				
number (not applicable)				
High Alkaline Phosphatase (N=42)	1			
Low Hematocrit (N=39)	1			
High Inorganic Phosphorus (N=39)	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant Electrocardiograms at Any Time in Period II/III

End point title	Number of Participants Meeting Criteria for Potentially Clinically Significant Electrocardiograms at Any Time in Period II/III ^[10]
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End point description:

Total number of patients with any abnormal post-baseline values, based on all values at scheduled and unscheduled visits. Criteria: High QRS Interval = ≥ 100 milliseconds (msec); High QTc Bazette's or Fredericia's correction - Female = ≥ 470 msec; High QTc Bazette's or Fredericia's correction - Male = ≥ 450 msec.

Number of patients with baseline (and none abnormal) and post-baseline values, based on all values at scheduled and unscheduled visits

End point type	Primary
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End point timeframe:

Baseline to 18 Weeks

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: participants				
number (not applicable)				
High QRS Interval (N=63)	1			
High QTc Bazette's Correction (N=64)	2			
High QTc Fredericia's Correction (N=65)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Potentially Clinically Significant Electrocardiograms at Any Time in Period IV

End point title	Number of Participants with Potentially Clinically Significant Electrocardiograms at Any Time in Period IV ^[11]
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End point description:

Total number of patients with any abnormal post-baseline values, based on all values at scheduled and unscheduled visits. Criteria: High QRS Interval = ≥ 100 milliseconds (msec); High QTc Bazette's or Fredericia's correction - Female = ≥ 470 msec; High QTc Bazette's or Fredericia's correction - Male = ≥ 450 msec.

Number of patients with baseline (and none abnormal) and post-baseline values, based on all values at scheduled and unscheduled visits.

End point type	Primary
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End point timeframe:

Between 18 and 30 Weeks

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

End point values	Duloxetine			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: participants				
number (not applicable)				
High QRS Interval (N=39)	1			
High QTc Bazette's Correction (N=41)	1			
High QTc Fredericia's Correction (N=41)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose

End point title	Pharmacokinetics: Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose
End point description:	Plasma samples were obtained at steady state, and approximately 95% of duloxetine concentrations were within the 24 hour dosing interval.
End point type	Secondary
End point timeframe:	Weeks 2, 4, 6, 8, 10, 14, 18

End point values	Duloxetine Dose 20mg	Duloxetine Dose 30mg	Duloxetine Dose 60mg	Duloxetine Dose 90mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	53	41	33
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	15.2 (± 12)	20.8 (± 21.2)	41.1 (± 34.7)	57.6 (± 43.2)

End point values	Duloxetine Dose 120mg			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	77.6 (± 54.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to 18 Weeks and 30 Weeks in Clinical Global Impressions of Severity Scale (CGI-S)

End point title	Change from Baseline to 18 Weeks and 30 Weeks in Clinical Global Impressions of Severity Scale (CGI-S)
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End point description:

Measures severity of illness at the time of assessment compared with start of treatment. Scores range from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). Baseline is the same timepoint (Week 0) for both comparisons, but due to differences in number of patients in both periods (II/III vs IV), the baseline values may be slightly different.

18 Week results are for all enrolled patients with a baseline and at least one non-missing post-baseline value; 30 Week results are for the enrolled patients with a baseline and at least one non-missing post-baseline value in Period IV. Last observation carried forward.

End point type	Secondary
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End point timeframe:

Week 0 (Baseline), 18 Weeks, 30 Weeks

End point values	Duloxetine	Duloxetine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72 ^[12]	45 ^[13]		
Units: units on a scale				
arithmetic mean (standard deviation)				
18 Week Baseline	4.5 (± 0.58)	0 (± 0)		
18 Week Change from Baseline	-2.11 (± 1.17)	0 (± 0)		
30 Week Baseline	0 (± 0)	4.5 (± 0.59)		
30 Week Change from Baseline	0 (± 0)	-2.7 (± 1.07)		

Notes:

[12] - All enrolled patients with a baseline and at least 1 non-missing post-baseline value at 18 Weeks.

[13] - All enrolled patients with a baseline and at least 1 non-missing post-baseline value at 30 Weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to 18 Weeks and 30 Weeks in Children's Depression Rating Scale-Revised (CDRS-R) Total Score

End point title	Change from Baseline to 18 Weeks and 30 Weeks in Children's Depression Rating Scale-Revised (CDRS-R) Total Score
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End point description:

Measures presence and severity of depression. Consists of 17 items scored on a 1-5 or 1-7 scale. A rating of 1 indicates normal, thus the minimum score is 17. The maximum score is 113. In general, scores below 20 indicate an absence of depression; scores of 20 or 30 indicate borderline depression; scores of 40 to 60 indicate moderate depression. Baseline is the same timepoint (Week 0) for both comparisons, but due to differences in number of patients in both periods (II/III vs IV), the baseline values may be slightly different.

18 Week results are for all enrolled patients with a baseline and at least one non-missing post-baseline value; 30 Week results are for the enrolled patients with a baseline and at least one non-missing post-baseline value in Period IV. Last observation carried forward.

End point type	Secondary
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End point timeframe:

Week 0 (Baseline), 18 Weeks, 30 Weeks

End point values	Duloxetine	Duloxetine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72 ^[14]	45 ^[15]		
Units: units on a scale				
arithmetic mean (standard deviation)				
18 Week Baseline	61.69 (± 8.98)	0 (± 0)		
18 Week Change from Baseline	-32.11 (± 12.92)	0 (± 0)		
30 Week Baseline	0 (± 0)	61.8 (± 9.28)		
30 Week Change from Baseline	0 (± 0)	-38.8 (± 11.14)		

Notes:

[14] - All enrolled patients with a baseline and at least one post-baseline value at 18 Weeks.

[15] - All enrolled patients with a baseline and at least one post-baseline value at 30 Weeks.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Adverse Events Leading to Discontinuation

End point title	Adverse Events Leading to Discontinuation
End point description:	A listing of adverse events leading to discontinuation from the study. Abbreviation in data table: ADHD = Attention-Deficit/Hyperactivity Disorder.
End point type	Other pre-specified
End point timeframe:	
Week 0 (Baseline) to 30 Weeks	

End point values	Duloxetine	Duloxetine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	48		
Units: participants				
number (not applicable)				
Nausea	1	0		
Worsening of ADHD	1	0		
Rash	1	0		
Irritability	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

F1J-MC-HMFN

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	Duloxetine-SPII-III
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Reporting group description: -

Reporting group title	Duloxetine-SPIV
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Reporting group description: -

Serious adverse events	Duloxetine-SPII-III	Duloxetine-SPIV	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 72 (6.94%)	0 / 48 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
depression			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 72 (1.39%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oppositional defiant disorder			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 72 (1.39%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
self injurious behaviour			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 72 (2.78%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

suicidal ideation alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 72 (1.39%) 0 / 1 0 / 0	0 / 48 (0.00%) 0 / 0 0 / 0	
Infections and infestations gastroenteritis viral alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 72 (1.39%) 0 / 1 0 / 0	0 / 48 (0.00%) 0 / 0 0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Duloxetine-SPII-III	Duloxetine-SPIV	
Total subjects affected by non-serious adverse events subjects affected / exposed	57 / 72 (79.17%)	21 / 48 (43.75%)	
General disorders and administration site conditions fatigue alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all) irritability alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 5 2 / 72 (2.78%) 2	2 / 48 (4.17%) 2 1 / 48 (2.08%) 1	
Reproductive system and breast disorders menstruation delayed alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all) ovarian cyst alternative dictionary used: MedDRA 11.0	0 / 72 (0.00%) 0	1 / 48 (2.08%) 1	

subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	1 / 48 (2.08%) 1	
Respiratory, thoracic and mediastinal disorders			
asthma exercise induced alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	1 / 48 (2.08%) 1	
cough alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 3	1 / 48 (2.08%) 1	
pharyngolaryngeal pain alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 3	1 / 48 (2.08%) 1	
respiratory tract congestion alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	0 / 48 (0.00%) 0	
rhinorrhoea alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 5	1 / 48 (2.08%) 1	
Psychiatric disorders			
aggression alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 48 (2.08%) 1	
anxiety alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	0 / 48 (0.00%) 0	
bruxism alternative dictionary used: MedDRA 11.0			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 72 (4.17%)</p> <p>3</p>	<p>1 / 48 (2.08%)</p> <p>1</p>	
<p>insomnia</p> <p>alternative dictionary used: MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 72 (4.17%)</p> <p>3</p>	<p>1 / 48 (2.08%)</p> <p>1</p>	
<p>libido increased</p> <p>alternative dictionary used: MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 72 (0.00%)</p> <p>0</p>	<p>1 / 48 (2.08%)</p> <p>1</p>	
<p>oppositional defiant disorder</p> <p>alternative dictionary used: MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 72 (2.78%)</p> <p>2</p>	<p>0 / 48 (0.00%)</p> <p>0</p>	
<p>restlessness</p> <p>alternative dictionary used: MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 72 (2.78%)</p> <p>2</p>	<p>1 / 48 (2.08%)</p> <p>1</p>	
<p>suicidal ideation</p> <p>alternative dictionary used: MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 72 (1.39%)</p> <p>1</p>	<p>1 / 48 (2.08%)</p> <p>1</p>	
<p>Investigations</p> <p>white blood cell count decreased</p> <p>alternative dictionary used: MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 72 (1.39%)</p> <p>1</p>	<p>1 / 48 (2.08%)</p> <p>1</p>	
<p>Injury, poisoning and procedural complications</p> <p>excoriation</p> <p>alternative dictionary used: MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 72 (2.78%)</p> <p>2</p> <p>skin laceration</p> <p>alternative dictionary used: MedDRA 11.0</p>	<p>1 / 48 (2.08%)</p> <p>1</p>	

subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 3	1 / 48 (2.08%) 1	
Cardiac disorders palpitations alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	1 / 48 (2.08%) 1	
Nervous system disorders dizziness alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all) headache alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all) migraine alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all) sedation alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all) somnolence alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all) tremor alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)	7 / 72 (9.72%) 7 10 / 72 (13.89%) 13 1 / 72 (1.39%) 1 7 / 72 (9.72%) 7 7 / 72 (9.72%) 8 0 / 72 (0.00%) 0	0 / 48 (0.00%) 0 0 / 48 (0.00%) 0 1 / 48 (2.08%) 1 1 / 48 (2.08%) 1 2 / 48 (4.17%) 2 1 / 48 (2.08%) 1	
Eye disorders myopia alternative dictionary used: MedDRA 11.0			

subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	1 / 48 (2.08%) 1	
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	6 / 72 (8.33%)	0 / 48 (0.00%)	
occurrences (all)	8	0	
constipation			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 72 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
diarrhoea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 72 (2.78%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
dry mouth			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 72 (5.56%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
flatulence			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 72 (2.78%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
nausea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	18 / 72 (25.00%)	1 / 48 (2.08%)	
occurrences (all)	20	1	
vomiting			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	10 / 72 (13.89%)	1 / 48 (2.08%)	
occurrences (all)	13	1	
Skin and subcutaneous tissue disorders			
hyperhidrosis			
alternative dictionary used: MedDRA 11.0			

subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 48 (2.08%) 1	
Infections and infestations			
ear infection			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 72 (2.78%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
gastroenteritis viral			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 72 (4.17%)	1 / 48 (2.08%)	
occurrences (all)	3	1	
influenza			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 72 (4.17%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
nasopharyngitis			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	9 / 72 (12.50%)	0 / 48 (0.00%)	
occurrences (all)	9	0	
pharyngitis streptococcal			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 72 (1.39%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
sinusitis			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 72 (2.78%)	1 / 48 (2.08%)	
occurrences (all)	2	1	
upper respiratory tract infection			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 72 (2.78%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 11.0			

subjects affected / exposed	4 / 72 (5.56%)	1 / 48 (2.08%)	
occurrences (all)	4	1	
obesity			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 72 (1.39%)	1 / 48 (2.08%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported