Trial record **1 of 1** for: HMGO

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A Study of the Neurobiology of Depression

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ClinicalTrials.gov Identifier: NCT01051466

Recruitment Status : Completed
First Posted : January 18, 2010
Results First Posted : April 2, 2014
Last Update Posted : October 10, 2014

Sponsor:
Eli Lilly and Company

Information provided by (Responsible Party):
Eli Lilly and Company

Study Details | Tabular View | Study Results | Disclaimer
How to Read a Study Record

Study Type	Interventional
Study Design	

	Allocation: Non-Randomized; Intervention Model: Parallel Assignment; Masking: None (Open Label); Primary Purpose: Basic Science
Conditions	Major Depressive Disorder Healthy Participants
Intervention	Drug: Duloxetine
Enrollment	60

Participant Flow

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Recruitment Details	
Pre-assignment Details	

Arm/Group Title	Duloxetine	Healthy Participants
Arm/Group Description	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.

	tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	
Period Title: **Overall Study**		
Started	32	28
Completed	24	23
Not Completed	8	5
Reason Not Completed		
Adverse Event	1	0
Lost to Follow-up	1	1
Withdrawal by Subject	5	1
Entry Criteria Not Met	0	3
Physician Decision	1	0

Baseline Characteristics

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Arm/Group Title	Duloxetine	Healthy Participants	Total
Arm/Group Description	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult	Total of all reporting groups

		the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.	
Overall Number of Baseline Participants		32	28	60
▼ Baseline Analysis Population Description		All enrolled participants.		
Age, Continuous				

Mean (Standard Deviation) Unit of measure: Years				
	Number Analyzed	32 participants	28 participants	60 participants
		40.21 (11.23)	39.19 (9.41)	39.74 (10.35)
Sex: Female, Male Measure Type: Count of Participants Unit of measure: Participants				
	Number Analyzed	32 participants	28 participants	60 participants
	Female	13 40.6%	14 50.0%	27 45.0%
	Male	19 59.4%	14 50.0%	33 55.0%
Race/Ethnicity, Customized Measure Type: Number Unit of measure: Participants	Number Analyzed	32 participants	28 participants	60 participants
White		18	16	34
Asian		10	4	14
Black		4	8	12
Region of Enrollment Measure Type: Number				

Unit of measure: Participants				
United Kingdom	Number Analyzed	32 participants	28 participants	60 participants
		32	28	60

Outcome Measures

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1. Primary Outcome

Title	Change From Baseline to 12-Week Endpoint in the Functional Magnetic Resonance Imaging (fMRI) Mean Blood Oxygenation-Level-Dependent (BOLD) Response in the Amygdalae
Description	Functional MRI or fMRI is a functional neuroimaging procedure that uses MRI technology to measure brain activity by detecting associated changes in blood flow. When an area of the brain is in use, blood flow to that region increases. The activation in response to the processing of sad faces was measured by the percentage of signal change in BOLD response from before to after sad faces processing. The percentage of signal change was calculated by taking the difference between BOLD response after sad faces processing and BOLD response before sad faces processing and dividing by BOLD response before sad face processing, then multiplying by 100. BOLD signals were measured using arbitrary magnetic resonance units. Amygdala BOLD activation was calculated as an average between the left amygdala activation and right amygdala activation. Least squares (LS) mean was calculated using mixed-model repeated measures (MMRM) adjusted for group, visit, group-by-visit, and baseline value.
Time Frame	Baseline, Week 12

Outcome Measure Data

Analysis Population Description

Enrolled participants who had baseline and at least 1 post-baseline activation (BOLD response) observation.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.
Overall Number of Participants Analyzed	28	28
Least Squares Mean (Standard Error)		

Unit of Measure: percentage of signal change		
	-0.01 (0.13)	-0.16 (0.13)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.457
	Comments	The significance level was 0.05 for a 2-sided test.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

2. Secondary Outcome

Title	Change From Baseline to 12-Week Endpoint in Activation [Blood Oxygenation-Level-Dependent (BOLD) Response to Implicit Processing of Sad Faces] for Each of the 3 Brain Regions
▼ Description	Functional magnetic resonance imaging (fMRI) is a functional neuroimaging procedure that uses MRI technology to measure brain activity by detecting associated changes in blood flow. When an area of the brain is in use, blood flow to that region increases. The activation in response to the processing of sad faces in each brain region (anterior cingulate, left amygdala and right amygdala) was measured by the percentage of signal change in BOLD response. The percentage of signal change was calculated by taking the difference between BOLD response after sad faces processing and BOLD response before sad faces processing and dividing by BOLD response before sad face processing, then multiplying by 100. BOLD signals were measured using arbitrary magnetic resonance units. Least squares (LS) mean was calculated using mixed-model repeated

	measures (MMRM) adjusted for group, visit, group-by-visit, and baseline value.
Time Frame	Baseline, Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled participants who had baseline and at least 1 post-baseline activation (BOLD response) observation, excluding 3 healthy participants who did not meet entry criteria.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.

Overall Number of Participants Analyzed	28	25
Least Squares Mean (Standard Error) Unit of Measure: percentage of signal change		
Anterior Cingulate	0.13 (0.09)	0.20 (0.09)
Left Amygdala	-0.04 (0.16)	-0.26 (0.16)
Right Amygdala	0.03 (0.12)	-0.09 (0.12)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.627
	Comments	The p-value is for change from baseline activation (BOLD response) in the anterior cingulate.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 2

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.338
	Comments	The p-value is for change from baseline activation

		(BOLD response) in the left amygdala.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 3

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.518
	Comments	The p-value is for change from baseline activation (BOLD response) in the right amygdala.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

3. Secondary Outcome

Title	Change From Baseline to 12-Week Endpoint in Volume of Subgenual Anterior Cingulate, Amygdalae, and Hippocampus
▼ Description	The volume of specific brain regions is obtained using a structural magnetic resonance imaging (sMRI) procedure in which high-resolution spoiled gradient recall images are acquired in coronal brain slices. Least squares (LS) mean was calculated using mixed-model repeated measures (MMRM) adjusted for group, visit, group-by-visit, and baseline value.
Time Frame	Baseline, Week 12

▼ Outcome Measure Data

▼ Analysis Population Description

Enrolled participants who had baseline and at least 1 post-baseline observation for the volume of specific brain regions, excluding 3 healthy participants who did not meet entry criteria.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.
Overall Number of Participants Analyzed	28	24
Least Squares Mean (Standard Error) Unit of Measure: cubic millimeters (mm^3)		
	-188.27 (112.37)	175.22 (116.14)

Subgenual Anterior Cingulate		
Left Amygdalae	-23.68 (15.25)	4.20 (15.59)
Right Amygdalae	-33.38 (17.83)	23.86 (18.40)
Left Hippocampus	-13.56 (23.53)	18.52 (24.37)
Right Hippocampus	-14.70 (19.19)	21.80 (19.66)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.030
	Comments	The p-value is for change from baseline volume in the subgenual anterior cingulate.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 2

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.208
	Comments	The p-value is for change from baseline volume in the left amygdalae.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 3

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.031
	Comments	The p-value is for change from baseline volume in the right amygdalae.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 4

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.350
	Comments	The p-value is for change from baseline volume in the left hippocampus.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 5

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.191
	Comments	The p-value is for change from baseline volume in the right hippocampus.

	Method	Mixed Models Analysis
	Comments	[Not Specified]

4. Secondary Outcome

Title	Translocation of Gs Alpha (Gsα) From Lipid Rafts in the Cell Membranes of Red Blood Cells (RBCs), White Blood Cells (WBCs) and Platelets Compared With Baseline
▼ Description	Gsα is a membrane-associated protein that couples receptors for neurotransmitters like serotonin to allow them to send messages between nerve cells - a process that may be altered during depression and antidepressant treatment. Gsα localization in the cholesterol-rich (lipid rafts) and cholesterol-poor regions of cell membranes of RBCs and platelets was measured with quantitative Western blots and reported as the ratio of Gsα (absorbance units) in Triton X-100 (TX-100) over Triton X-114 (TX-114), 2 detergents that discriminate between lipid raft and non-raft membrane domains. Translocation of Gsα was measured as the change from baseline in Gsα localization. Translocation of Gsα from lipid rafts in the cell membranes of WBCs was not analyzed due to technical laboratory issues. Least squares (LS) mean was calculated using mixed-model repeated measures (MMRM) adjusted for group, visit, group-by-visit, and baseline value.
Time Frame	Baseline, Weeks 1, 8, and 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled participants who had a baseline and at least 1 post-baseline Gsα localization observation, excluding 3 healthy participants who did not meet entry criteria. No participants were analyzed for the translocation of Gsα from lipid rafts in the cell membranes of WBCs.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder	Healthy participants: Participants who successfully

	(MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.
Overall Number of Participants Analyzed	23	22
Least Squares Mean (Standard Error) Unit of Measure: Ratio		
RBCs, Week 1 (n=23, 22)	0.51 (0.21)	0.09 (0.22)
RBCs, Week 8 (n=23, 22)	-0.01 (0.14)	-0.15 (0.14)
	0.36 (0.26)	0.10 (0.26)

RBCs, Week 12 (n=23, 22)		
Platelets, Week 1 (n=23, 20)	-0.63 (0.46)	-0.69 (0.49)
Platelets, Week 8 (n=23, 20)	-1.16 (0.42)	-0.92 (0.44)
Platelets, Week 12 (n=23, 20)	-0.52 (5.40)	7.93 (5.40)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.174
	Comments	The p-value is for Gsα translocation in RBCs at Week 1.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 2

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.488
	Comments	The p-value is for Gsα translocation in RBCs at Week 8.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 3

Statistical Analysis Overview	Comparison Group Selection	Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.480
	Comments	The p-value is for Gsα translocation in RBCs at Week 12.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 4

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.925
	Comments	The p-value is for Gsα translocation in platelets at Week 1.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 5

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.697
	Comments	The p-value is for Gsα translocation in platelets at Week 8.

	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 6

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.276
	Comments	The p-value is for Gsα translocation in platelets at Week 12.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

5. Secondary Outcome

Title	Gs Alpha (Gsα)-Activated Adenylyl Cyclase
▼ Description	Gsα is a membrane-associated protein that couples receptors for neurotransmitters like serotonin to allow them to send messages between nerve cells - a process that may be altered during depression and antidepressant treatment. Adenylyl cyclase is activated by Gsα, and when Gsα is translocated from lipid rafts it more effectively activates adenylyl cyclase. Gsα-activated adenylyl cyclase was not analyzed due to technical laboratory issues.
Time Frame	Baseline and Weeks 1, 8, and 12

Outcome Measure Data Not Reported

6. Secondary Outcome

Title	Change From Baseline to 12-Week Endpoint in Brain-Derived Neurotrophic Factor (BDNF) and the Precursor of BDNF (proBDNF)
▼ Description	

	There is evidence that stress may decrease BDNF expression, while antidepressant treatment reverses or blocks these effects. BDNF is a protein that occurs naturally and supports the survival and growth of some nerve cells in the brain. proBDNF is a precursor of BDNF. Least squares (LS) mean was calculated using mixed-model repeated measures (MMRM) adjusted for group, visit, group-by-visit, and baseline value.
Time Frame	Baseline, Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled participants who had baseline and at least 1 post-baseline BDNF or proBDNF observation, excluding 3 healthy participants who did not meet entry criteria.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.

	tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	
Overall Number of Participants Analyzed	23	21
Least Squares Mean (Standard Error) Unit of Measure: nanograms per milliliter (ng/mL)		
BDNF (n=23, 21)	6.61 (23.38)	10.57 (22.80)
proBDNF (n=13, 17)	-5.67 (12.77)	-9.37 (9.36)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.904
	Comments	The p-value is for change from baseline BDNF.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 2

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
	P-Value	0.819

	Statistical Test of Hypothesis	Comments	The p-value is for change from baseline proBDNF.
		Method	Mixed Models Analysis
		Comments	[Not Specified]

7. Secondary Outcome

Title	Change From Baseline to 12-Week Endpoint in Brain-Derived Neurotrophic Factor (BDNF) and the Precursor of BDNF (proBDNF) Receptors
▼ Description	There is evidence that stress may decrease BDNF expression, while antidepressant treatment reverses or blocks these effects. BDNF is a protein that occurs naturally and supports the survival and growth of some nerve cells in the brain. proBDNF is a precursor of BDNF. Tropomyosin receptor kinase B (trkB) is a receptor for BDNF, and pan-neurotrophin receptor p75 (p75NTR) is a receptor for proBDNF. p75NTR was not analyzed due to technical laboratory issues. Least squares (LS) mean was calculated using mixed-model repeated measures (MMRM) adjusted for group, visit, group-by-visit, and baseline value.
Time Frame	Baseline, Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled participants who had baseline and at least 1 post-baseline trkB observation, excluding 3 healthy participants who did not meet entry criteria. No participant was analyzed for the change from baseline in p75NTR receptors.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler

	dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.
Overall Number of Participants Analyzed	24	21
Least Squares Mean (Standard Error) Unit of Measure: picograms per milligram (pg/mg)		
	52.1 (41.08)	-8.9 (36.25)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
	P-Value	0.070

	Statistical Test of Hypothesis	Comments	The p-value is for change from baseline trkB.
		Method	Mixed Models Analysis
		Comments	[Not Specified]

8. Secondary Outcome

Title	Change From Baseline to 12-Week Endpoint in Proinflammatory Cytokines [Tumor Necrosis Factor Alpha (TNFα), Interleukin 1 (IL-1), and Interleukin 6 (IL-6)]
▼ Description	Cytokines are naturally produced and regulate responses to inflammation. Proinflammatory cytokines like TNFα, IL-1, and IL-6 increase inflammation in the body. Least squares (LS) mean was calculated using mixed-model repeated measures (MMRM) adjusted for group, visit, group-by-visit, and baseline value.
Time Frame	Baseline, Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled participants who had baseline and at least 1 post-baseline cytokine observation (TNFα, IL-1, or IL-6), excluding 3 healthy participants who did not meet entry criteria.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy

	Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	participants did not receive study drug.
Overall Number of Participants Analyzed	28	22
Least Squares Mean (Standard Error) Unit of Measure: picograms per milliliter (pg/mL)		
Cytokine TNFα	-0.04 (0.78)	0.25 (0.81)
Cytokine IL-1	-0.08 (2.53)	4.01 (2.64)
Cytokine IL-6	-0.61 (0.69)	-0.52 (0.71)

▼ Statistical Analysis 1

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.797
	Comments	

		The p-value is for change from baseline cytokine TNFα.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 2

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.269
	Comments	The p-value is for change from baseline cytokine IL-1.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

▼ Statistical Analysis 3

Statistical Analysis Overview	Comparison Group Selection	Duloxetine, Healthy Participants
	Comments	[Not Specified]
	Type of Statistical Test	Superiority or Other
	Comments	[Not Specified]
Statistical Test of Hypothesis	P-Value	0.925
	Comments	The p-value is for change from baseline cytokine IL-6.
	Method	Mixed Models Analysis
	Comments	[Not Specified]

9. Secondary Outcome

Title	17-Item Hamilton Depression Rating Scale (HAMD17)
▼ Description	

	The HAMD17 is a standardized instrument consisting of 17 items used to measure the severity of major depressive disorder (MDD) and improvements in depression symptoms. Each item was evaluated and scored using either a 5-point scale of 0 (not present/absent) to 4 (very severe) or a 3-point scale of 0 (not present/absent) to 2 (marked). Higher scores indicated greater symptom severity. The total score was the sum of the scores from HAMD17 Items 1 through 17 and could have ranged from 0 (not at all depressed) to 52 (severely depressed).
Time Frame	Baseline and up to Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled participants who had a baseline and at least 1 post-baseline HAMD17 observation. Last observation carried forward (LOCF) was utilized when calculating the Week 12 endpoint outcome.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg	Healthy participants: Participants who successfully completed screening, were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.

	QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	
Overall Number of Participants Analyzed	29	14
Mean (Standard Deviation) Unit of Measure: units on a scale		
Baseline	22.4 (2.66)	0.5 (1.34)
Week 12	8.5 (6.60)	0.5 (1.40)

10. Secondary Outcome

Title	Percentage of Participants With 17-Item Hamilton Depression Rating Scale (HAMD17) Response
▼ Description	HAMD17 response is defined as a >50% reduction in HAMD17 total score from baseline. The HAMD17 is a standardized instrument consisting of 17 items used to measure the severity of major depressive disorder (MDD) and improvements in depression symptoms. Each item was evaluated and scored using either a 5-point scale of 0 (not present/absent) to 4 (very severe) or a 3-point scale of 0 (not present/absent) to 2 (marked). Higher scores indicated greater symptom severity. The total score was the sum of the scores from HAMD17 Items 1 through 17 and could have ranged from 0 (not at all depressed) to 52 (severely depressed). The percentage of participants with a HAMD17 response was calculated as the number of participants with a >50% reduction in HAMD17 total score from baseline divided by the number of participants who had a HAMD17 observation at Week 12 then multiplied by 100.

Time Frame	Baseline, up to Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled MDD participants who had a baseline and at least 1 post-baseline HAMD17 observation. Last observation carried forward (LOCF) was utilized when calculating the Week 12 endpoint outcome.

Arm/Group Title	Duloxetine
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.
Overall Number of Participants Analyzed	29
Measure Type: Number Unit of Measure: percentage of participants	
	72.4

11. Secondary Outcome

Title	Percentage of Participants With 17-Item Hamilton Depression Rating Scale (HAMD17) Remission
▼ Description	

	HAMD17 remission is defined as a HAMD17 total score of ≤7 at Week 12 (endpoint). The HAMD17 is a standardized instrument consisting of 17 items used to measure the severity of major depressive disorder (MDD) and improvements in depression symptoms. Each item was evaluated and scored using either a 5-point scale of 0 (not present/absent) to 4 (very severe) or a 3-point scale of 0 (not present/absent) to 2 (marked). Higher scores indicated greater symptom severity. The total score was the sum of the scores from HAMD17 Items 1 through 17 and could have ranged from 0 (not at all depressed) to 52 (severely depressed). The percentage of participants with remission was calculated as the number of participants with a HAMD17 total score of ≤7 divided by the number of participants who had a HAMD17 observation at Week 12 then multiplied by 100.
Time Frame	Baseline, up to Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled MDD participants who had a baseline and at least 1 post-baseline HAMD17 observation. Last observation carried forward (LOCF) was utilized when calculating the Week 12 endpoint outcome.

Arm/Group Title	Duloxetine
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.
	29

Overall Number of Participants Analyzed	
Measure Type: Number Unit of Measure: percentage of participants	
	62.1

12. Secondary Outcome

Title	Sheehan Disability Scale (SDS)
▼ Description	The SDS is a participant-rated questionnaire used to assess the effect of the participant's symptoms on work/school (Item 1), social life/leisure activities (Item 2), and family/home management (Item 3). Each item was rated on a visual analog scale (VAS) from 0 (not at all) to 10 (very severely). The SDS Global Functional Impairment Score (SDS Global Score) was the sum of the 3 items and could have ranged from 0 (unimpaired) to 30 (highly impaired). Higher values indicated higher functional impairment in the participant's work/social/family life.
Time Frame	Baseline and up to Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled participants who had baseline and at least 1 post-baseline SDS observation. Last observation carried forward (LOCF) was utilized when calculating the Week 12 endpoint outcome.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received	Healthy participants: Participants who successfully completed screening were matched by age, gender, and

	60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.
Overall Number of Participants Analyzed	27	25
Mean (Standard Deviation) Unit of Measure: units on a scale		
Baseline	19.3 (5.41)	0.2 (0.80)
Week 12	9.4 (7.72)	0.0 (0.00)

13. Secondary Outcome

Title	Clinical Global Impressions of Severity Scale (CGI-S)
▼ Description	

	The CGI-S measures severity of illness at the time of assessment. Scores can range from 1 (normal, not at all ill) to 7 (among the most extremely ill participants).
Time Frame	Baseline and up to Week 12

▼ Outcome Measure Data

▼ Analysis Population Description

Enrolled participants who had baseline and at least 1 post-baseline CGI-S observation. Last observation carried forward (LOCF) was utilized when calculating the Week 12 endpoint outcome.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally	Healthy participants: Participants who successfully completed screening were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.

	complete a 2-week dose down-titration taper.	
Overall Number of Participants Analyzed	29	25
Mean (Standard Deviation) Unit of Measure: units on a scale		
Baseline	4.4 (0.56)	1.0 (0.00)
Week 12	2.2 (1.08)	1.0 (0.00)

14. Secondary Outcome

Title	Patient's Global Impressions of Improvement (PGI-I) Scale
▼ Description	The PGI-I scale measures the participant's perception of improvement at the time of assessment compared with the start of treatment. Scores can range from 1 (very much better) to 7 (very much worse).
Time Frame	Baseline, up to Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled MDD participants who had at least 1 post-baseline PGI-I observation. Last observation carried forward (LOCF) was utilized when calculating the Week 12 endpoint outcome. PGI-I observations were not completed for healthy participants.

Arm/Group Title	Duloxetine
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed

	between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.
Overall Number of Participants Analyzed	29
Mean (Standard Deviation) Unit of Measure: units on a scale	
	2.6 (1.24)

15. Secondary Outcome

Title	Hamilton Anxiety Rating Scale (HAMA)
▼ Description	The 14-item HAMA is used to assess the severity of anxiety. The investigator talked to the participant about their symptoms over the previous week. Each item was scored using a 5-point scale (0 = not present to 4 = very severe). Total HAMA scores could have ranged from 0 (normal) to 56 (severe).
Time Frame	Baseline and up to Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Enrolled participants who had a baseline and at least 1 post-baseline HAMA observation. Last observation carried forward (LOCF) was utilized when calculating the Week 12 endpoint outcome.

Arm/Group Title	Duloxetine	Healthy Participants
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for	Healthy participants: Participants who successfully completed screening were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was

	12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.	measured by the Wechsler Adult Intelligence Scale - Third United Kingdom (UK) Edition (WAIS-III^UK). Healthy participants did not receive study drug.
Overall Number of Participants Analyzed	29	25
Mean (Standard Deviation) Unit of Measure: units on a scale		
Baseline	21.1 (5.78)	0.4 (0.87)
Week 12	9.6 (7.25)	0.4 (0.96)

16. Secondary Outcome

Title	Incidence of Suicidal Behavior and Suicidal Ideation as Measured by the Columbia Suicide Severity Rating Scale (C-SSRS)
▼ Description	The C-SSRS captures the occurrence, severity, and frequency of treatment-emergent suicide-related thoughts and behaviors.

	Suicidal ideation is defined as a "yes" answer to any 1 of 5 suicidal ideation questions: wish to be dead, and 4 different categories of active suicidal ideation. Suicidal behavior is defined as a "yes" answer to any 1 of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Treatment-emergent outcomes were the worsening or new occurrence of suicidal behaviors or ideation during treatment compared with baseline.
Time Frame	Baseline through Week 12

▼ Outcome Measure Data

▼ Analysis Population Description
Participants with MDD who had a baseline and at least 1 post-baseline C-SSRS assessment. Healthy participants did not have a C-SSRS assessment post baseline.

Arm/Group Title	Duloxetine
▼ Arm/Group Description:	Duloxetine: Participants with major depressive disorder (MDD), who successfully completed screening, received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and tolerability of the participant to the dose. At study completion, participants could optionally complete a 2-week dose down-titration taper.
Overall Number of Participants Analyzed	29
Measure Type: Number Unit of Measure: participants	

Treatment-emergent suicidal ideation	5
Treatment-emergent suicidal behavior	0

Adverse Events

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Time Frame	[Not Specified]
Adverse Event Reporting Description	[Not Specified]

Arm/Group Title	Duloxetine	Healthy Participants
Arm/Group Description	Duloxetine: Participants with major depressive disorder (MDD) received 60 milligrams (mg) up to 120 mg orally, once daily (QD) for 12 weeks. The initial starting dose was 60 mg duloxetine QD for the first 8 weeks. Then, remitters [defined as participants with a 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤7] continued on 60 mg duloxetine QD, while non-remitters (HAMD17 total score >7) could have their duloxetine dose flexed between 60 mg QD up to 120 mg QD, based on the clinical judgment of the Principal Investigator and	Healthy participants: Participants were matched by age, gender, and intelligence quotient (IQ) to participants with MDD. IQ was measured by the Wechsler Adult Intelligence Scale - Third United Kingdom Edition (WAIS-III UK). Healthy participants did not receive study drug.

	tolerability of the participant to the dose.	

All-Cause Mortality

	Duloxetine		Healthy Participants	
	Affected / at Risk (%)		Affected / at Risk (%)	
Total	--/--		--/--	

Serious Adverse Events

	Duloxetine		Healthy Participants	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	1/32 (3.13%)		0/28 (0.00%)	
Eye disorders				
Retinal pigment epitheliopathy †1	1/32 (3.13%)	1	0/28 (0.00%)	0

† Indicates events were collected by systematic assessment
1 Term from vocabulary, MedDRA 15.1

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	3%

	Duloxetine		Healthy Participants	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	32/32 (100.00%)		11/28 (39.29%)	
Blood and lymphatic system disorders				
Microcytic anaemia †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Cardiac disorders				
Palpitations †1	2/32 (6.25%)	2	0/28 (0.00%)	0
Ear and labyrinth disorders				
Motion sickness †1	1/32 (3.13%)	1	0/28 (0.00%)	0

Tinnitus [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Endocrine disorders				
Hypothyroidism [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Eye disorders				
Eye pain [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Eye pruritus [†1]	0/32 (0.00%)	0	1/28 (3.57%)	1
Lacrimation increased [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Vision blurred [†1]	2/32 (6.25%)	2	0/28 (0.00%)	0
Gastrointestinal disorders				
Abdominal discomfort [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Abdominal distension [†1]	1/32 (3.13%)	1	1/28 (3.57%)	1
Constipation [†1]	7/32 (21.88%)	7	0/28 (0.00%)	0
Diarrhoea [†1]	7/32 (21.88%)	7	0/28 (0.00%)	0
Dry mouth [†1]	8/32 (25.00%)	8	0/28 (0.00%)	0
Dyspepsia [†1]	2/32 (6.25%)	2	1/28 (3.57%)	1
Epigastric discomfort [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Irritable bowel syndrome [†1]	0/32 (0.00%)	0	1/28 (3.57%)	1
Nausea [†1]	20/32 (62.50%)	23	0/28 (0.00%)	0
Salivary hypersecretion [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Vomiting [†1]	7/32 (21.88%)	9	0/28 (0.00%)	0
General disorders				
Asthenia [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Chest pain [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Fatigue [†1]	6/32 (18.75%)	6	0/28 (0.00%)	0
Feeling hot [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Influenza like illness [†1]	2/32 (6.25%)	2	0/28 (0.00%)	0
Irritability [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Pyrexia [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Sluggishness [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Thirst [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Immune system disorders				
Allergy to animal [†1]	0/32 (0.00%)	0	1/28 (3.57%)	1
Seasonal allergy [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0

Infections and infestations				
Ear infection [†1]	1/32 (3.13%)	1	1/28 (3.57%)	2
Gastroenteritis [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Nasopharyngitis [†1]	5/32 (15.63%)	7	3/28 (10.71%)	3
Viral upper respiratory tract infection [†1]	1/32 (3.13%)	2	0/28 (0.00%)	0
Injury, poisoning and procedural complications				
Post procedural complication [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Procedural dizziness [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Procedural pain [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Tendon injury [†1]	0/32 (0.00%)	0	1/28 (3.57%)	1
Tooth fracture [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Investigations				
Alanine aminotransferase increased [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Aspartate aminotransferase increased [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Blood alkaline phosphatase increased [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Blood creatine phosphokinase increased [†1]	2/32 (6.25%)	2	0/28 (0.00%)	0
Gamma-glutamyltransferase increased [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Gastric ph decreased [†1]	1/32 (3.13%)	1	0/28 (0.00%)	0
Metabolism and nutrition disorders				
Decreased appetite [†1]	9/32 (28.13%)	9	0/28 (0.00%)	0
Food craving [†1]	2/32 (6.25%)	2	0/28 (0.00%)	0
Increased appetite [†1]	2/32 (6.25%)	2	0/28 (0.00%)	0
Musculoskeletal and connective tissue disorders				

Arthralgia †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Back pain †1	3/32 (9.38%)	4	0/28 (0.00%)	0
Joint stiffness †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Muscle spasms †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Muscle twitching †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Myalgia †1	2/32 (6.25%)	2	1/28 (3.57%)	1
Pain in extremity †1	1/32 (3.13%)	2	0/28 (0.00%)	0
Pain in jaw †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Nervous system disorders				
Balance disorder †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Disturbance in attention †1	2/32 (6.25%)	2	0/28 (0.00%)	0
Dizziness †1	9/32 (28.13%)	11	0/28 (0.00%)	0
Dysgeusia †1	2/32 (6.25%)	2	0/28 (0.00%)	0
Headache †1	11/32 (34.38%)	18	4/28 (14.29%)	8
Hypersomnia †1	2/32 (6.25%)	2	0/28 (0.00%)	0
Myoclonus †1	1/32 (3.13%)	2	0/28 (0.00%)	0
Nervous system disorder †1	0/32 (0.00%)	0	1/28 (3.57%)	1
Paraesthesia †1	2/32 (6.25%)	3	0/28 (0.00%)	0
Somnolence †1	4/32 (12.50%)	5	0/28 (0.00%)	0
Syncope †1	2/32 (6.25%)	2	0/28 (0.00%)	0
White matter lesion †1	0/32 (0.00%)	0	1/28 (3.57%)	1
Psychiatric disorders				
Abnormal dreams †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Anorgasmia †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Anxiety †1	3/32 (9.38%)	3	0/28 (0.00%)	0
Bruxism †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Insomnia †1	9/32 (28.13%)	9	0/28 (0.00%)	0
Libido decreased †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Obsessive-compulsive disorder †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Sleep disorder †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Suicidal ideation †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Renal and urinary disorders				

Chromaturia †1	2/32 (6.25%)	2	0/28 (0.00%)	0
Dysuria †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Micturition disorder †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Pollakiuria †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Urinary hesitation †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Reproductive system and breast disorders				
Ejaculation delayed †1	1/19 (5.26%)	1	0/14 (0.00%)	0
Ejaculation disorder †1	1/19 (5.26%)	1	0/14 (0.00%)	0
Erectile dysfunction †1	1/19 (5.26%)	1	0/14 (0.00%)	0
Respiratory, thoracic and mediastinal disorders				
Cough †1	2/32 (6.25%)	2	0/28 (0.00%)	0
Dry throat †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Dyspnoea †1	2/32 (6.25%)	2	0/28 (0.00%)	0
Nasal polyps †1	0/32 (0.00%)	0	1/28 (3.57%)	1
Sneezing †1	0/32 (0.00%)	0	1/28 (3.57%)	1
Yawning †1	7/32 (21.88%)	7	0/28 (0.00%)	0
Skin and subcutaneous tissue disorders				
Eczema †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Hyperhidrosis †1	2/32 (6.25%)	2	0/28 (0.00%)	0
Pruritus †1	1/32 (3.13%)	1	0/28 (0.00%)	0
Psoriasis †1	1/32 (3.13%)	1	0/28 (0.00%)	0

† Indicates events were collected by systematic assessment

1 Term from vocabulary, MedDRA 15.1

Limitations and Caveats

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Three healthy participants were identified as not meeting inclusion/exclusion criteria after enrollment. They were discontinued and excluded from secondary outcome analyses, but included in participant flow, primary outcome analyses, and safety.

More Information

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Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact

Name/Title:	Chief Medical Officer
Organization:	Eli Lilly and Company
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Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Fu CH, Costafreda SG, Sankar A, Adams TM, Rasenick MM, Liu P, Donati R, Maglanoc LA, Horton P, Marangell LB. Multimodal functional and structural neuroimaging investigation of major depressive disorder following treatment with duloxetine. BMC Psychiatry. 2015 Apr 14;15:82. doi: 10.1186/s12888-015-0457-2.

Responsible Party:	Eli Lilly and Company
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