Clinical trial results:
LY2216684 Compared to Placebo as Adjunctive Therapy to SSRI in the Prevention of Symptom Re-emergence in Major Depressive Disorder

Summary

EudraCT number	2010-024632-42
Trial protocol	DE BE SK GR ES IT
Global end of trial date	14 November 2013

Results information

Result version number	v1 (current)
This version publication date	06 March 2018
First version publication date	06 March 2018

Trial information

Trial identification

Sponsor protocol code	H9P-MC-LNBN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01299272
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Alias: 14310

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the maintenance of efficacy of LY2216684 compared with placebo as adjunctive therapy to selective serotonin reuptake inhibitors (SSRIs) as measured by the time-to-symptom reemergence among participants with major depressive disorder (MDD) who met randomization criteria with adjunctive LY2216684 during the stabilization period.

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:

SSRI: Participants were treated with one of the following SSRIs that has been approved for MDD treatment within the participating country: escitalopram, citalopram, sertraline, fluoxetine, paroxetine, and fluvoxamine; and has been treated with their SSRI at least 6 weeks prior to Visit 2 with at least the last 4 consecutive weeks at a stable optimized dose prior to Visit 2. The SSRI prescribed, including dose, should be consistent with labeling guidelines within the participating country.

Evidence for comparator: -

Actual start date of recruitment	12 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Argentina: 62
Country: Number of subjects enrolled	Croatia: 9
Country: Number of subjects enrolled	France: 61
Country: Number of subjects enrolled	Germany: 73
Country: Number of subjects enrolled	Greece: 43
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Mexico: 63
Country: Number of subjects enrolled	Puerto Rico: 77
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Russian Federation: 96
Country: Number of subjects enrolled	Slovakia: 65
Country: Number of subjects enrolled	Spain: 43
Country: Number of subjects enrolled	Turkey: 30

Country: Number of subjects enrolled	United States: 535
Worldwide total number of subjects	1249
EEA total number of subjects	368

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1175
From 65 to 84 years	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All enrolled participants entered the Acute Open-label (OL) Period. At Week 8, if remission criteria were met, participants entered the Stabilization OL Period. At Week 20, if randomization criteria were met, participants entered the 24-week Double-blind Randomized Withdrawal Period. Those who discontinued early entered the Discontinuation Period.

Period 1

Period 1 title	Acute open-label (OL) period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LY2216684 + SSRI (Acute open-label period)

Arm description:

Flexible dose of 12 or 18 milligrams (mg) LY2216684, administered orally, once daily (QD) for 8 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI).

Arm type	Experimental
Investigational medicinal product name	LY2216684
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a selective serotonin SSRI.

Number of subjects in period 1	LY2216684 + SSRI (Acute open-label period)
Started	1249
Entered Discontinuation (DC) Period	271 [1]
Completed	835
Not completed	414
Consent withdrawn by subject	56
Physician decision	5
Adverse event, non-fatal	140
Sponsor Decision	13
Lost to follow-up	14
Remission Criteria Not Met	140
Lack of efficacy	10
Protocol deviation	36

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants who discontinued the Acute OL Period had the option to enter the DC Period.

Period 2

Period 2 title	stabilization open-label (OL) period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LY2216684 + SSRI (stabilization open-label period)

Arm description:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD for an additional 12 weeks.

Arm type	Experimental
Investigational medicinal product name	LY2216684
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD for an additional 12 weeks.

Number of subjects in period 2	LY2216684 + SSRI (stabilization open-label period)
Started	835
Entered Discontinuation (DC) Period	164 [2]
Completed	586
Not completed	249
Consent withdrawn by subject	42
Physician decision	3
Adverse event, non-fatal	42
Sponsor Decision	12
Randomization Criteria Not Met	80
Reemergence of Study Condition Symptoms	6

Lost to follow-up	9
Lack of efficacy	11
Protocol deviation	44

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants who discontinued the Stabilization OL Period had the option to enter the DC Period.

Period 3

Period 3 title	Double-blind (DB) Randomized Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)

Arm description:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD, for 12 weeks. At 20 weeks, participants meeting criteria for randomization continued at their current dose of LY2216684 and SSRI, orally, QD, for an additional 24 weeks.

Arm type	Experimental
Investigational medicinal product name	LY2216684
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD, for 12 weeks. At 20 weeks, participants meeting criteria for randomization continued at their current dose of LY2216684 and SSRI, orally, QD, for an additional 24 weeks.

Arm title	Placebo + SSRI (Double-blind Randomized Withdrawal Period)

Arm description:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD, for 12 weeks. At 20 weeks, participants meeting criteria for randomization were switched from LY2216684 to Placebo and continued at their current SSRI dose, orally, QD, for an additional 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD, for 12 weeks. At 20 weeks, participants meeting criteria for randomization were

switched from LY2216684 to Placebo and continued at their current SSRI dose, orally, QD, for an additional 24 weeks.

Number of subjects in period 3	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)
Started	294	292
Entered Taper Discontinuation Period	129 [3]	0 [4]
Entered Abrupt Discontinuation Period	132 [5]	268
Completed	224	234
Not completed	70	58
Consent withdrawn by subject	22	15
Physician decision	2	1
Adverse event, non-fatal	8	9
Sponsor Decision	1	1
Reemergence of Study Condition Symptoms	4	10
Lost to follow-up	5	5
Lack of efficacy	20	10
Protocol deviation	8	7

Notes:

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants who completed or discontinued the DB Period were randomized to the taper DC Period.Participants who completed or discontinued the DB Period were randomized to the abrupt DC Period.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants who completed or discontinued the DB Period entered the DC Period.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Participants who completed or discontinued the DB Period were randomized to the taper DC Period. Participants who completed or discontinued the DB Period were randomized to the abrupt DC Period.

Baseline characteristics

Reporting groups	
Reporting group title	Acute open-label (OL) period
Reporting group description: All enrolled participants.	

Reporting group values	Acute open-label (OL) period	Total	
Number of subjects	1249	1249	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	47.4		
standard deviation	± 12.54	-	
Gender, Male/Female Units: Participants			
Female	917	917	
Male	332	332	
Region of Enrollment Units: Subjects			
United States	535	535	
Slovakia	65	65	
Greece	43	43	
Spain	43	43	
Turkey	30	30	
Russian Federation	96	96	
Italy	44	44	
France	61	61	
Mexico	63	63	
Puerto Rico	77	77	
Argentina	62	62	
Belgium	11	11	
Croatia	9	9	
Romania	19	19	
Germany	73	73	
Korea, Republic of	18	18	
Race Units: Subjects			
American Indian or Alaska Native	50	50	
Asian	21	21	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	99	99	
White	1066	1066	
More than one race	13	13	
Unknown or Not Reported	0	0	
Ethnicity			

Units: Subjects			
Hispanic or Latino	254	254	
Not Hispanic or Latino	622	622	
Unknown or Not Reported	373	373	

End points

End points reporting groups

Reporting group title	LY2216684 + SSRI (Acute open-label period)

Reporting group description:

Flexible dose of 12 or 18 milligrams (mg) LY2216684, administered orally, once daily (QD) for 8 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI).

Reporting group title	LY2216684 + SSRI (stabilization open-label period)

Reporting group description:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD for an additional 12 weeks.

Reporting group title	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)

Reporting group description:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD, for 12 weeks. At 20 weeks, participants meeting criteria for randomization continued at their current dose of LY2216684 and SSRI, orally, QD, for an additional 24 weeks.

Reporting group title	Placebo + SSRI (Double-blind Randomized Withdrawal Period)

Reporting group description:

Flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD, for 12 weeks. At 20 weeks, participants meeting criteria for randomization were switched from LY2216684 to Placebo and continued at their current SSRI dose, orally, QD, for an additional 24 weeks.

Subject analysis set title	All Enrolled Participants
Subject analysis set type	Full analysis

Subject analysis set description:

All enrolled participants started on a flexible dose of 12 or 18 mg LY2216684, administered orally, QD for 8 weeks, adjunctive to a SSRI. At 8 weeks, participants meeting remission criteria continued on the same, stable dose of LY2216684 and SSRI, orally, QD, for an additional 12 weeks. At 20 weeks, participants meeting criteria for randomization either 1) continued at their current dose of LY2216684 and SSRI, orally, QD, for an additional 24 weeks or 2) were switched from LY2216684 to Placebo and continued at their current SSRI dose, orally, QD, for an additional 24 weeks.

Primary: Percentage of Participants who meet criteria for re-emergence of depressive symptoms estimated by Kaplan-Meier product limit method (Double-blind Randomized Withdrawal Period)

End point title	Percentage of Participants who meet criteria for re-emergence of depressive symptoms estimated by Kaplan-Meier product limit method (Double-blind Randomized Withdrawal Period)

End point description:

Participants meeting any of the following criteria were determined as having major depressive disorder symptom re-emergence: 1) a Montgomery-Asberg Depression Rating Scale (MADRS) total score greater ≥14 or a Clinical Global Impressions of Severity (CGI-S) increase of 2 or more points from Week 18 at 2 consecutive visits or 2) discontinuation due to lack of efficacy/worsening of depression/suicidality. Time from randomization to the first visit at which the participant met the reemergence criteria was calculated. The percentage of participants who meet criteria was estimated using the Kaplan-Meier product limit method. The MADRS is a rating scale for severity of depressive mood symptoms and has a 10-item checklist with items rated on a scale of 0-6, for a total score range of 0 (low severity) to 60 (high severity). CGI-S measures severity of depression at the time of assessment compared with the start of treatment. Scores range from 1 (normal, not at all ill) to 7 (extremely ill).

End point type	Primary

End point timeframe:

Randomization up to 44 weeks

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294[1]	292[2]		
Units: percentage of participants				
number (not applicable)	10.43	8.24		

Notes:

[1] - All randomized participants.

[2] - All randomized participants.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period) v Placebo + SSRI (Double-blind Randomized Withdrawal Period)
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.485
Method	Logrank

Secondary: Percentage of participants with re-emergence of depressive symptoms (Double-blind Randomized Withdrawal Period)

End point title	Percentage of participants with re-emergence of depressive symptoms (Double-blind Randomized Withdrawal Period)

End point description:

Participants meeting any of the following criteria were determined as having major depressive disorder symptom re-emergence: 1) a Montgomery-Asberg Depression Rating Scale (MADRS) total score greater ≥14 or a Clinical Global Impressions of Severity (CGI-S) increase of 2 or more points from Week 18 at 2 consecutive visits or 2) discontinuation due to lack of efficacy/worsening of depression/suicidality. The percentage of participants with re-emergence of depressive symptoms was calculated by dividing the number of participants who meet any of the criteria by the total number of participants analyzed, multiplied by 100. The MADRS is a rating scale for severity of depressive mood symptoms and has a 10-item checklist with items rated on a scale of 0-6, for a total score range of 0 (low severity) to 60 (high severity). CGI-S measures severity of depression at the time of assessment compared with the start of treatment. Scores range from 1 (normal, not at all ill) to 7 (extremely ill).

End point type	Secondary

End point timeframe:

Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294[3]	292[4]		
Units: percentage of participants				
number (not applicable)	9.9	8.2		

Notes:

[3] - All randomized participants.

[4] - All randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in the Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscale scores at Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in the Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscale scores at Week 44 (double-blind randomized withdrawal period)

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire with 2 subscales: anxiety and depression. Each item is rated on a 4-point scale (0-3), giving maximum scores of 21 for anxiety and depression. Scores of 11 or more on either subscale are considered to be a 'significant' case of psychological morbidity, while scores of 8-10 represent 'borderline' and 0-7 represent 'normal'. Least Squares (LS) means were calculated using a mixed model repeated measures (MMRM) analysis which included terms for the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline subscale score and baseline subscale score-by-visit interaction. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	286	285		
Units: units on a scale				
least squares mean (standard error)				
HADS Anxiety Subscale Score	0 (± 0.22)	0.15 (± 0.22)		
HADS Depression Subscale Score	-0.18 (± 0.23)	0.15 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in the Clinical Global Impression of Severity (CGI-S) scores at Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in the Clinical Global Impression of Severity (CGI-S) scores at Week 44 (double-blind randomized withdrawal period)

End point description:

The Clinical Global Impression of Severity (CGI-S) instrument is used to record the severity of mental illness at the time of assessment. Scores range from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). Least Squares (LS) means were calculated using a mixed model repeated measures (MMRM) analysis which included terms for the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline CGI-S score and baseline CGI-S score-by-visit interaction. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	290	292		
Units: units on a scale				
least squares mean (standard error)	0.01 (± 0.05)	0 (± 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and individual item scores at week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and individual item scores at week 44 (double-blind randomized withdrawal period)

End point description:

MADRS is a rating scale for severity of depressive mood symptoms. The MADRS has 10-item checklist (sadness [apparent], sadness [reported], inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts). Items are rated on a scale of 0-6, for a total score range of 0 (low severity of depressive symptoms) to 60 (high severity of depressive symptoms). Least Squares (LS) means were calculated using a mixed model repeated measures (MMRM) analysis which includes terms for the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline MADRS total score (individual item score) and baseline MADRS total score (individual item score)-by-visit interaction. Analysis population included all randomized participants who have non-missing values at the

time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	290	292		
Units: units on a scale				
least squares mean (standard error)				
MADRS Total Score	0.4 (± 0.33)	0.34 (± 0.33)		
Item 1: Apparent Sadness	0.09 (± 0.05)	0.08 (± 0.05)		
Item 2: Reported Sadness	0.09 (± 0.06)	0.05 (± 0.06)		
Item 3: Inner Tension	0.06 (± 0.07)	0.14 (± 0.06)		
Item 4: Reduced Sleep	-0.02 (± 0.07)	-0.06 (± 0.07)		
Item 5: Reduced Appetite	0 (± 0.04)	0 (± 0.04)		
Item 6: Concentration Difficulties	0.07 (± 0.06)	0.08 (± 0.06)		
Item 7: Lassitude	0.02 (± 0.06)	0.07 (± 0.06)		
Item 8: Inability to Feel	0 (± 0.05)	-0.05 (± 0.05)		
Item 9: Pessimistic Thoughts	-0.01 (± 0.05)	-0.02 (± 0.04)		
Item 10: Suicidal Thoughts	0.02 (± 0.02)	0.01 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in the Sheehan Disability Scale (SDS) items at Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in the Sheehan Disability Scale (SDS) items at Week 44 (double-blind randomized withdrawal period)

End point description:

The Sheehan Disability Scale (SDS) is completed by the participant and used to assess the effect of the participant's symptoms on their work (work/school impairment score), social life (social life/leisure activities impairment score), and family life (family life/home responsibilities impairment score). Each item is measured on a 0 (not at all) to 10 (extremely) point scale with higher values indicating greater disruption. Least Squares (LS) means were calculated using a mixed model repeated measures (MMRM) analysis which included terms for the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	289		
Units: units on a scale				
least squares mean (standard error)				
Work Impairment Score (n=198, 212)	-0.24 (± 0.17)	0.02 (± 0.17)		
Social Life Impairment Score (n=286, 286)	-0.17 (± 0.14)	-0.15 (± 0.14)		
Family Life Impairment Score (n=286, 286)	-0.26 (± 0.14)	-0.08 (± 0.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in the Fatigue Associated with Depression (FAsD) average score, experience subscale score, and impact subscale score at Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in the Fatigue Associated with Depression (FAsD) average score, experience subscale score, and impact subscale score at Week 44 (double-blind randomized withdrawal period)

End point description:

The FAsD is a 13-item participant-rated scale.Items 1-6 ask how often participants(pts) experience different aspects of fatigue with responses from 1(never) to 5(always).Items 7-13 ask how often fatigue impacts various aspects of pts lives with responses from 1(not at all) to 5(very much).The experience subscale score is derived by taking mean of Items 1-6.The impact subscale score is derived by taking mean of applicable Items 7-13.The average score is mean of applicable Items 1-13.Item 12 applies only to pts with a spouse or significant other and Item 13 applies to pts who had job or went to school. LS means were calculated using a MMRM analysis which included terms for the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	286[5]	286[6]		

Units: units on a scale				
least squares mean (standard error)				
FAsD Experience Subscale Score	-0.05 (± 0.05)	0.05 (± 0.05)		
FAsD Impact Subscale Score	-0.06 (± 0.05)	-0.01 (± 0.05)		
FAsD Average Score	-0.05 (± 0.05)	0.02 (± 0.05)		

Notes:

[5] - Participants with non-missing values at time of randomization, at least one post-randomization value
[6] - Participants with non-missing values at time of randomization, at least one post-randomization value

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in the Arizona Sexual Experiences (ASEX) Questionnaire at Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in the Arizona Sexual Experiences (ASEX) Questionnaire at Week 44 (double-blind randomized withdrawal period)

End point description:

Arizona Sexual Experiences (ASEX) Questionnaire is a 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Each item is rated from 1 (extremely) to 6 (no/never). Possible total scores ranged from 5 to 30, with the higher scores indicating more sexual dysfunction. Least Squares (LS) means were calculated using a mixed model repeated measures (MMRM) analysis which included terms for the fixed categorical effects of treatment, country, visit, treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline ASEX total score and baseline ASEX total score-by-visit interaction. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	277		
Units: units on a scale				
least squares mean (standard error)	-0.39 (± 0.33)	-0.08 (± 0.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in the EuroQol Questionnaire-5 Dimension (EQ-5D) index scores, visual analog scale up to Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in the EuroQol Questionnaire-5 Dimension (EQ-5D) index scores, visual analog scale up to Week 44 (double-blind randomized withdrawal period)

End point description:

The profile allows participants(pts) to rate their health state in 5 health domains: mobility,self-care,usual activities,pain/discomfort,and mood using a 3-level scale(no problem,some problems, and major problems).These dimensions are converted into weighted health-state index scores according to United States(US),United Kingdom(UK) population-based algorithms.The US and UK based index scores range from -0.11 to 1.0(where score of 1.0 indicates perfect health)and from -0.59(severe problems in all 5 dimensions) to 1.0(no problem in any dimension)respectively.The VAS consists of pts rating their current health state from 0(worst imaginable health state) to 100(best imaginable health).LS means calculated using analysis of ANCOVA model with main effects of treatment,country,baseline score.Analysis population included all randomized pts who have non-missing values at time of randomization and at least one post-randomization value.Last observation carried forward(LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Randomization, up to Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	285		
Units: units on a scale				
least squares mean (standard error)				
EQ-5D US (n=278, 284)	0.01 (± 0.01)	0.01 (± 0.01)		
EQ-5D UK (n=278, 284)	0.01 (± 0.02)	0.01 (± 0.02)		
VAS (n=278, 285)	1.87 (± 1.39)	0.61 (± 1.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment-emergent suicidal ideation and behaviors assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) (double-blind randomized withdrawal period)

End point title	Number of participants with treatment-emergent suicidal ideation and behaviors assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) (double-blind randomized withdrawal period)

End point description:

The Columbia-Suicide Severity Rating Scale (C-SSRS) captures occurrence, severity, and frequency of suicide-related thoughts and behaviors. Suicidal ideation is defined as a "yes" answer to any 1 of 5 suicidal ideation questions, which includes a wish to be dead and 4 different categories of active suicidal ideation. Suicidal behavior is defined as a "yes" answer to any of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Suicidal ideation and behavior are defined as treatment-emergent (TE) if not present during the period up through randomization. A summary of serious and other non-serious adverse events regardless of causality is located in the Reported Adverse Event module. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization through Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	292		
Units: participants				
number (not applicable)				
TE Suicidal Ideation (n=291, 292)	5	4		
TE Suicidal Behavior (n=277, 278)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and individual item scores up to Week 8 (acute open-label period)

End point title	Change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and individual item scores up to Week 8 (acute open-label period)

End point description:

Montgomery-Asberg Depression Rating Scale (MADRS) is a rating scale for severity of depressive mood symptoms. The MADRS has a 10-item checklist (sadness [apparent], sadness [reported], inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts). Items are rated on a scale of 0-6, for a total score range of 0 (low severity of depressive symptoms) to 60 (high severity of depressive symptoms). Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 8

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1214			
Units: units on a scale				
arithmetic mean (standard deviation)				
MADRS Total Score	-13.21 (± 8.3)			

Item 1: Apparent Sadness	-1.82 (± 1.37)			
Item 2: Reported Sadness	-1.86 (± 1.39)			
Item 3: Inner Tension	-1.24 (± 1.37)			
Item 4: Reduced Sleep	-1.29 (± 1.57)			
Item 5: Reduced Appetite	-0.65 (± 1.47)			
Item 6: Concentration Difficulties	-1.49 (± 1.43)			
Item 7: Lassitude	-1.74 (± 1.44)			
Item 8: Inability to Feel	-1.65 (± 1.42)			
Item 9: Pessimistic Thoughts	-1.23 (± 1.28)			
Item 10: Suicidal Thoughts	-0.24 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and individual item scores up to Week 20 (stabilization open-label period)

End point title	Change from Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score and individual item scores up to Week 20 (stabilization open-label period)

End point description:

Montgomery-Asberg Depression Rating Scale (MADRS) is a rating scale for severity of depressive mood symptoms. The MADRS has a 10-item checklist (sadness [apparent], sadness [reported], inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts). Items are rated on a scale of 0-6, for a total score range of 0 (low severity of depressive symptoms) to 60 (high severity of depressive symptoms). Analysis population included all randomized participants who have non-missing values at Week 8 and at least one post-Week 8 value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Week 8, up to Week 20

End point values	LY2216684 + SSRI (stabilization open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	812			
Units: units on a scale				
arithmetic mean (standard deviation)				
MADRS Total Score	-0.38 (± 6.09)			
Item 1: Apparent Sadness	-0.01 (± 1.01)			
Item 2: Reported Sadness	-0.08 (± 1.15)			
Item 3: Inner Tension	-0.05 (± 1.18)			
Item 4: Reduced Sleep	-0.12 (± 1.28)			
Item 5: Reduced Appetite	0 (± 0.89)			
Item 6: Concentration Difficulties	-0.06 (± 1.19)			
Item 7: Lassitude	0.02 (± 1.19)			

Item 8: Inability to Feel	-0.09 (± 1.08)			
Item 9: Pessimistic Thoughts	-0.04 (± 0.87)			
Item 10: Suicidal Thoughts	0.03 (± 0.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) total score at Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) total score at Week 44 (double-blind randomized withdrawal period)

End point description:

Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) is a 7-item participant-rated questionnaire pertaining to a participant's cognitive and physical well-being. It assesses motivation, wakefulness, energy, focus, recall, word-finding difficulty, and mental acuity. Each item is scored on a 6-point scale ranging from 1 (greater than normal) to 6 (totally absent). Total score is reported and ranges from 7 to 42, with higher scores indicating greater impairment. Least Squares (LS) means were calculated using a mixed model repeated measures (MMRM) analysis which included terms for the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline CPFQ total score and baseline CPFQ total score-by-visit interaction. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	286	286		
Units: units on a scale				
least squares mean (standard error)	-0.27 (± 0.31)	-0.05 (± 0.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 8 in the Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscale scores up to Week 20 (stabilization open-label period)

End point title	Change from Week 8 in the Hospital Anxiety and Depression

	Scale (HADS) depression and anxiety subscale scores up to Week 20 (stabilization open-label period)

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire with 2 subscales: anxiety and depression. Each item is rated on a 4-point scale (0-3), giving maximum scores of 21 for anxiety and depression. Scores of 11 or more on either subscale are considered to be a 'significant' case of psychological morbidity, while scores of 8-10 represent 'borderline' and 0-7 represent 'normal'. Analysis population included all randomized participants who have non-missing values at Week 8 and at least one post-Week 8 value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Week 8, up to Week 20

End point values	LY2216684 + SSRI (stabilization open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	781			
Units: units on a scale				
arithmetic mean (standard deviation)				
HADS Anxiety Subscale Score	-0.77 (± 3.73)			
HADS Depression Subscale Score	-0.74 (± 3.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscale scores up to Week 8 (acute open-label period)

End point title	Change from baseline in the Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscale scores up to Week 8 (acute open-label period)

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire with 2 subscales: anxiety and depression. Each item is rated on a 4-point scale (0-3), giving maximum scores of 21 for anxiety and depression. Scores of 11 or more on either subscale were considered to be a 'significant' case of psychological morbidity, while scores of 8-10 represent 'borderline' and 0-7 represent 'normal'. Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 8

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1199			
Units: units on a scale				
arithmetic mean (standard deviation)				
HADS Anxiety Subscale Score (n=1198) HADS Depression Subscale Score (n=1199)	-3.02 (± 3.92) -3.98 (± 4.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Clinical Global Impression of Severity (CGI-S) scores up to Week 8 (acute open-label period)

End point title	Change from baseline in the Clinical Global Impression of Severity (CGI-S) scores up to Week 8 (acute open-label period)

End point description:

The Clinical Global Impression of Severity (CGI-S) instrument is used to record the severity of mental illness at the time of assessment. Scores range from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 8

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1214			
Units: units on a scale				
arithmetic mean (standard deviation)	-1.51 (± 1.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 8 in the Fatigue Associated with Depression (FAsD) average score, experience subscale score, and impact subscale score up to Week 20 (stabilization open-label period)

End point title	Change from Week 8 in the Fatigue Associated with Depression (FAsD) average score, experience subscale score, and impact

	subscale score up to Week 20 (stabilization open-label period)

End point description:

The Fatigue Associated with Depression (FAsD) is a 13-item participant-rated scale. Items 1-6 ask how often participants experience different aspects of fatigue with responses from 1 (never) to 5 (always). Items 7-13 ask how often fatigue impacts various aspects of the participant's lives with responses from 1 (not at all) to 5 (very much). The experience subscale score is derived by taking the mean of Items 1-6. The impact subscale score is derived by taking the mean of applicable Items 7-13. The average score is the mean of applicable Items 1-13. Item 12 applies only to participants with a spouse or significant other and Item 13 applies to participants who had a job or who went to school. Analysis population included all randomized participants who have non-missing values at Week 8 and at least one post-Week 8 value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Week 8, up to Week 20

End point values	LY2216684 + SSRI (stabilization open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	781			
Units: units on a scale				
arithmetic mean (standard deviation)				
FAsD Experience Subscale Score	-0.22 (± 0.93)			
FAsD Impact Subscale Score	-0.15 (± 0.87)			
FAsD Average Score	-0.19 (± 0.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 8 in the Clinical Global Impression of Severity (CGI-S) scores up to Week 20 (stabilization open-label period)

End point title	Change from Week 8 in the Clinical Global Impression of Severity (CGI-S) scores up to Week 20 (stabilization open-label period)

End point description:

The Clinical Global Impression of Severity (CGI-S) instrument is used to record the severity of mental illness at the time of assessment. Scores range from 1 (normal, not at all ill) to 7 (among the most extremely ill participants). Analysis population included all randomized participants who have non-missing values at Week 8 and at least one post-Week 8 value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Week 8, up to Week 20

End point values	LY2216684 + SSRI (stabilization open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	812			
Units: units on a scale				
arithmetic mean (standard deviation)	-0.25 (± 0.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Fatigue Associated with Depression (FAsD) average score, experience subscale score, and impact subscale score up to Week 8 (acute open-label period)

End point title	Change from Baseline in the Fatigue Associated with Depression (FAsD) average score, experience subscale score, and impact subscale score up to Week 8 (acute open-label period)

End point description:

The FAsD is a 13-item participant-rated scale.Items 1-6 ask how often participants(pts) experience different aspects of fatigue with responses from 1(never) to 5(always).Items 7-13 ask how often fatigue impacts various aspects of pts lives with responses from 1(not at all) to 5(very much).The experience subscale score is derived by taking mean of Items 1-6.The impact subscale score is derived by taking mean of applicable Items 7-13.The average score is mean of applicable Items 1-13.Item 12 applies only to pts with a spouse or significant other and Item 13 applies to pts who had job or went to school. Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 8

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1166			
Units: units on a scale				
arithmetic mean (standard deviation)				
FAsD Experience Subscale Score (n=1166)	-0.82 (± 0.99)			
FAsD Impact Subscale Score (n=1164)	-0.88 (± 1.03)			
FAsD Average Score (n=1164)	-0.85 (± 0.93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Sheehan Disability Scale (SDS) items up to Week 8 (acute open-label period)

End point title	Change from baseline in the Sheehan Disability Scale (SDS) items up to Week 8 (acute open-label period)

End point description:

The Sheehan Disability Scale (SDS) is completed by the participant and used to assess the effect of the participant's symptoms on their work (work/school impairment score), social life (social life/leisure activities impairment score), and family life (family life/home responsibilities impairment score). Each item is measured on a 0 (not at all) to 10 (extremely) point scale with higher values indicating greater disruption. Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 8

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1197			
Units: units on a scale				
arithmetic mean (standard deviation)				
Work Impairment Score (n=757)	-2.17 (± 2.65)			
Social Life Impairment Score (n=1197)	-2.38 (± 2.85)			
Family Life Impairment Score (n=1197)	-2.16 (± 2.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 8 in the Sheehan Disability Scale (SDS) items up to Week 20 (stabilization open-label period)

End point title	Change from Week 8 in the Sheehan Disability Scale (SDS) items up to Week 20 (stabilization open-label period)

End point description:

The Sheehan Disability Scale (SDS) is completed by the participant and used to assess the effect of the participant's symptoms on their work (work/school impairment score), social life (social life/leisure activities impairment score), and family life (family life/home responsibilities impairment score). Each item is measured on a 0 (not at all) to 10 (extremely) point scale with higher values indicating greater disruption. Analysis population included all randomized participants who have non-missing values at Week 8 and at least one post-Week 8 value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Week 8, up to Week 20

End point values	LY2216684 + SSRI (stabilization open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	781			
Units: units on a scale				
arithmetic mean (standard deviation)				
Work Impairment Score (n=567)	-0.58 (± 2.61)			
Social Life Impairment Score (n=781)	-0.47 (± 2.54)			
Family Life Impairment Score (n=781)	-0.5 (± 2.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the EuroQol Questionnaire-5 Dimension (EQ-5D) index scores, visual analog scale up to Week 20 (open-label period)

End point title	Change from baseline in the EuroQol Questionnaire-5 Dimension (EQ-5D) index scores, visual analog scale up to Week 20 (open-label period)

End point description:

The EQ-5D, a health-related, quality-of-life instrument, contains 2 parts: a health status profile and a visual analog scale (VAS). The profile allows participants to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and mood using a 3-level scale (no problem, some problems, and major problems). These dimensions are converted into weighted health-state index scores according to United States (US) and United Kingdom (UK) population-based algorithms. The US and UK based index scores range from -0.11 to 1.0 (where a score of 1.0 indicates perfect health) and from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension), respectively. The VAS consists of participants rating their current health state from 0 (worst imaginable health state) to 100 (best imaginable health).Analysis population included all randomized pts who have non-missing values at baseline and at least one post-baseline value.LOCF methodology used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 20

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	779			
Units: units on a scale				
arithmetic mean (standard deviation)				
EQ-5D US (n=773)	0.15 (± 0.19)			
EQ-5D UK (n=773)	0.21 (± 0.29)			

VAS (n=779)	18.07 (± 22.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) total score at Week 20 (open-label period)

End point title	Change from baseline in the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) total score at Week 20 (open-label period)

End point description:

Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) is a 7-item participant-rated questionnaire pertaining to a participant's cognitive and physical well-being. It assesses motivation, wakefulness, energy, focus, recall, word-finding difficulty, and mental acuity. Each item is scored on a 6-point scale ranging from 1 (greater than normal) to 6 (totally absent). Total score is reported and ranges from 7 to 42, with higher scores indicating greater impairment. Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 20

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1167			
Units: units on a scale				
arithmetic mean (standard deviation)	-6.68 (± 7.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment-emergent suicidal ideation and behaviors assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) (open-label period)

End point title	Number of participants with treatment-emergent suicidal ideation and behaviors assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) (open-label period)

End point description:

The Columbia-Suicide Severity Rating Scale (C-SSRS) captures occurrence, severity, and frequency of suicide-related thoughts and behaviors. Suicidal ideation is defined as a "yes" answer to any 1 of 5 suicidal ideation questions, which included a wish to be dead and 4 different categories of active suicidal

ideation. Suicidal behavior is defined as a "yes" answer to any of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Suicidal ideation and behavior are defined as treatment-emergent (TE) if not present at baseline. A summary of serious and other non-serious adverse events regardless of causality is located in the Reported Adverse Event module. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value. All participants who have non-missing values at baseline and at least one post-baseline value.

End point type	Secondary

End point timeframe:

Baseline through Week 20

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1216			
Units: participants				
number (not applicable)				
TE Suicidal Ideation (n=1216) TE Suicidal Behavior (n=1124)	66 5			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Arizona Sexual Experiences (ASEX) Questionnaire up to Week 20 (open-label period)

End point title	Change from baseline in the Arizona Sexual Experiences (ASEX) Questionnaire up to Week 20 (open-label period)

End point description:

Arizona Sexual Experiences (ASEX) Questionnaire is a 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Each item is rated from 1 (extremely) to 6 (no/never). Possible total scores ranged from 5 to 30, with the higher scores indicating more sexual dysfunction. Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 20

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1115			
Units: units on a scale				
arithmetic mean (standard deviation)	-1.78 (± 4.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in blood pressure up to Week 20 (open-label period)

End point title	Change from baseline in blood pressure up to Week 20 (open-label period)

End point description:

Blood pressure measurements were taken 3 times at each visit in a sitting position. The average of the 3 values was used for analysis. Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 20

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1214			
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic blood pressure	2.3 (± 11.95)			
Diastolic blood pressure	2.81 (± 8.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in pulse rate at Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in pulse rate at Week 44 (double-blind randomized withdrawal period)

End point description:

Pulse rate measurements were collected when the participant was in a sitting position. Least Squares (LS) means were calculated using a mixed model repeated measures (MMRM) analysis which included terms for the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	292		
Units: beats per minute (bpm)				
least squares mean (standard error)	-2.54 (± 0.74)	-10.76 (± 0.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization in blood pressure at Week 44 (double-blind randomized withdrawal period)

End point title	Change from randomization in blood pressure at Week 44 (double-blind randomized withdrawal period)

End point description:

Blood pressure measurements were taken 3 times at each visit in a sitting position. The average of the 3 values was used for analysis. Least Squares (LS) means were calculated using a mixed model repeated measures (MMRM) analysis which included terms for the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. Analysis population included all randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Secondary

End point timeframe:

Randomization, Week 44

End point values	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	292		
Units: millimeters of mercury (mmHg)				
least squares mean (standard error)				
Systolic blood pressure	-0.2 (± 0.75)	-4.19 (± 0.75)		
Diastolic blood pressure	0.24 (± 0.55)	-4.18 (± 0.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in pulse rate up to Week 20 (open-label period)

End point title	Change from baseline in pulse rate up to Week 20 (open-label period)

End point description:

Pulse measurements were collected when the participant was in a sitting position. Analysis population included all randomized participants who have non-missing values at baseline and at least one post-baseline value. Last observation carried forward (LOCF) methodology was used.

End point type	Secondary

End point timeframe:

Baseline, up to Week 20

End point values	LY2216684 + SSRI (Acute open-label period)			
Subject group type	Reporting group			
Number of subjects analysed	1214			
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)	10.8 (± 12.47)			

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:

H9P-MC-LNBN

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	LY2216684 + SSRI (Stabilization Open- label Period)

Reporting group description:

Same, stable dose of LY2216684 as in the Acute Open-label Period, orally, once daily (QD) for 12 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI). Includes all participants who completed the Acute Open-label Period and did not discontinue for the reason 'Lost to Follow-up' at the first post-baseline visit during the Stabilization Open-label Period.

Reporting group title	LY2216684 + SSRI (Acute Open-label Period)

Reporting group description:

Flexible dose of 12 or 18 milligrams (mg) LY2216684, administered orally, once daily (QD) for 8 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI). Includes all enrolled participants who did not discontinue for the reason 'Lost to Follow-up' at the first post-baseline visit during the Acute Open-label Period.

Reporting group title	LY2216684 + SSRI (Randomized Abrupt Discontinuation Period)

Reporting group description:

Placebo, orally, once daily (QD) for 2 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI).
Includes all randomized participants who abruptly discontinued LY2216684 after completion of or early withdrawal from the Double-blind Randomized Withdrawal Period and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation Period visit.

Reporting group title	Placebo + SSRI (Abrupt Discontinuation Period)

Reporting group description:

Placebo, orally, once daily (QD) for 2 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI). Includes all randomized participants who discontinued placebo after completion of or early withdrawal from the Double-blind Randomized Withdrawal Period and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation Period visit.

Reporting group title	LY2216684 + SSRI (Nonrandomized Abrupt Discontinuation Period)

Reporting group description:

Placebo, orally, once daily (QD) for 2 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI).
Includes all non-randomized participants who discontinued early from either Open-label Period and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation Period visit.

Reporting group title	Placebo + SSRI (Double-blind Randomized Withdrawal Period)

Reporting group description:

Placebo, orally, once daily (QD) for 24 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI).
Includes randomized participants who did not discontinue for the reason 'Lost to Follow-up' at the first post-randomization visit during the Double-blind Randomized Withdrawal Period.

Reporting group title	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)

Reporting group description:

Same, stable dose of LY2216684 as in the Stabilization Open-label Period, orally, once daily (QD) for 24 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI). Includes randomized participants who did not discontinue for the reason 'Lost to Follow-up' at the first post-randomization visit during the

Double-blind Randomized Withdrawal Period.

Reporting group title	LY2216684 + SSRI (Randomized Tapered Discontinuation Period)

Reporting group description:

12 milligrams (mg) LY2216684 for 4 days, 6 mg LY2216684 for 4 days, then placebo for 6 days, orally, once daily (QD), adjunctive to a selective serotonin reuptake inhibitor (SSRI). Includes all randomized participants who tapered discontinuation of LY2216684 after completion of or early withdrawal from the Double-blind Randomized Withdrawal Period and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation Period visit.

Serious adverse events	LY2216684 + SSRI (Stabilization Open-label Period)	LY2216684 + SSRI (Acute Open-label Period)	LY2216684 + SSRI (Randomized Abrupt Discontinuation Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 831 (1.81%)	19 / 1244 (1.53%)	0 / 132 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
angiomyolipoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
breast cancer			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholesteatoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
metastases to liver			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 831 (0.12%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	2 / 1244 (0.16%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
hysterectomy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[1]	1 / 641 (0.16%)	0 / 914 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
abortion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[2]	1 / 641 (0.16%)	0 / 914 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blighted ovum			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[3]	0 / 641 (0.00%)	1 / 914 (0.11%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
vaginal polyp			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed[4]	1 / 641 (0.16%)	0 / 914 (0.00%)	0 / 105 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
alcohol abuse			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 831 (0.12%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
major depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
self injurious behaviour			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal behaviour			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 831 (0.12%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal ideation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 831 (0.12%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicide attempt			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 831 (0.24%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
blood creatine phosphokinase increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 831 (0.12%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood glucose increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
intentional overdose			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 831 (0.12%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
poisoning			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 831 (0.12%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
road traffic accident			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tendon rupture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
myocardial infarction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ventricular extrasystoles			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 831 (0.12%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
convulsion			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
encephalopathy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoaesthesia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
colitis ischaemic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intestinal obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 831 (0.12%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	3 / 1244 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oesophageal spasm			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vomiting			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	3 / 1244 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
nephrolithiasis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 831 (0.12%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intervertebral disc disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
osteoarthritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 831 (0.12%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
diverticulitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 831 (0.12%)	0 / 1244 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ketosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 831 (0.00%)	1 / 1244 (0.08%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo + SSRI (Abrupt Discontinuation Period)	LY2216684 + SSRI (Nonrandomized Abrupt Discontinuation Period)	Placebo + SSRI (Double-blind Randomized Withdrawal Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 267 (0.75%)	8 / 434 (1.84%)	6 / 292 (2.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
angiomyolipoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
breast cancer			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholesteatoma			
alternative dictionary used:			

MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
metastases to liver			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 267 (0.37%)	0 / 434 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
hysterectomy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[1]	0 / 212 (0.00%)	0 / 307 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
abortion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[2]	0 / 212 (0.00%)	0 / 307 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blighted ovum			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[3]	0 / 212 (0.00%)	1 / 307 (0.33%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
vaginal polyp			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[4]	0 / 212 (0.00%)	0 / 307 (0.00%)	0 / 226 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
alcohol abuse			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
major depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

self injurious behaviour			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal behaviour			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal ideation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 267 (0.37%)	0 / 434 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicide attempt			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
blood creatine phosphokinase increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood glucose increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

intentional overdose			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
poisoning			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
road traffic accident			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tendon rupture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
myocardial infarction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ventricular extrasystoles			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
convulsion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
encephalopathy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoaesthesia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
colitis ischaemic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intestinal obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oesophageal spasm			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vomiting			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
nephrolithiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intervertebral disc disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
osteoarthritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	1 / 292 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
diverticulitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ketosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	0 / 292 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	LY2216684 + SSRI (Randomized Tapered Discontinuation Period)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 294 (0.68%)	2 / 128 (1.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
angiomyolipoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast cancer			
alternative dictionary used:			

MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholesteatoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to liver			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
hysterectomy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[1]	0 / 223 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
abortion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[2]	0 / 223 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blighted ovum			
alternative dictionary used:			

MedDRA 16.1			
subjects affected / exposed[3]	0 / 223 (0.00%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
vaginal polyp			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[4]	1 / 223 (0.45%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
alcohol abuse			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

major depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
self injurious behaviour			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suicidal behaviour			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suicidal ideation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suicide attempt			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
blood creatine phosphokinase increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood glucose increased			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
intentional overdose			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
poisoning			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
road traffic accident			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tendon rupture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 294 (0.34%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
myocardial infarction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tachycardia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ventricular extrasystoles			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
convulsion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
encephalopathy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoaesthesia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis ischaemic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal spasm			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
nephrolithiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intervertebral disc disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteoarthritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
diverticulitis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ketosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 294 (0.00%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects has been adjusted accordingly.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects has been adjusted accordingly.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects has been adjusted accordingly.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects has been adjusted accordingly.

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

Non-serious adverse events	LY2216684 + SSRI (Stabilization Open-label Period)	LY2216684 + SSRI (Acute Open-label Period)	LY2216684 + SSRI (Randomized Abrupt Discontinuation Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 831 (13.48%)	505 / 1244 (40.59%)	4 / 132 (3.03%)
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	8 / 831 (0.96%)	83 / 1244 (6.67%)	1 / 132 (0.76%)
occurrences (all)	8	86	1
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	53 / 831 (6.38%)	111 / 1244 (8.92%)	4 / 132 (3.03%)
occurrences (all)	54	128	5
Gastrointestinal disorders			
constipation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	14 / 831 (1.68%)	132 / 1244 (10.61%)	0 / 132 (0.00%)
occurrences (all)	14	134	0
dry mouth			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	10 / 831 (1.20%)	80 / 1244 (6.43%)	0 / 132 (0.00%)
occurrences (all)	10	81	0
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	18 / 831 (2.17%)	147 / 1244 (11.82%)	1 / 132 (0.76%)
occurrences (all)	21	155	1
Skin and subcutaneous tissue disorders			
hyperhidrosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	23 / 831 (2.77%)	215 / 1244 (17.28%)	0 / 132 (0.00%)
occurrences (all)	24	228	0

Non-serious adverse events	Placebo + SSRI (Abrupt Discontinuation Period)	LY2216684 + SSRI (Nonrandomized Abrupt Discontinuation	Placebo + SSRI (Double-blind Randomized Withdrawal Period)

		Period)	
Total subjects affected by non-serious adverse events subjects affected / exposed	16 / 267 (5.99%)	32 / 434 (7.37%)	21 / 292 (7.19%)
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 267 (1.50%)	4 / 434 (0.92%)	4 / 292 (1.37%)
occurrences (all)	4	4	4
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	11 / 267 (4.12%)	24 / 434 (5.53%)	13 / 292 (4.45%)
occurrences (all)	16	30	13
Gastrointestinal disorders			
constipation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	0 / 434 (0.00%)	2 / 292 (0.68%)
occurrences (all)	0	0	2
dry mouth			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	1 / 434 (0.23%)	0 / 292 (0.00%)
occurrences (all)	0	1	0
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 267 (1.87%)	8 / 434 (1.84%)	5 / 292 (1.71%)
occurrences (all)	6	10	5
Skin and subcutaneous tissue disorders			
hyperhidrosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 267 (0.00%)	5 / 434 (1.15%)	1 / 292 (0.34%)
occurrences (all)	0	5	1

Non-serious adverse events	LY2216684 + SSRI (Double-blind Randomized Withdrawal Period)	LY2216684 + SSRI (Randomized Tapered Discontinuation Period)	
Total subjects affected by non-serious adverse events subjects affected / exposed	37 / 294 (12.59%)	9 / 128 (7.03%)	

Nervous system disorders dizziness alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) headache alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	 3 / 294 (1.02%) 3 18 / 294 (6.12%) 24	 1 / 128 (0.78%) 1 7 / 128 (5.47%) 10	
Gastrointestinal disorders constipation alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) dry mouth alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) nausea alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	 4 / 294 (1.36%) 5 3 / 294 (1.02%) 3 7 / 294 (2.38%) 7	 0 / 128 (0.00%) 0 0 / 128 (0.00%) 0 3 / 128 (2.34%) 3	
Skin and subcutaneous tissue disorders hyperhidrosis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	 8 / 294 (2.72%) 8	 0 / 128 (0.00%) 0	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25894953