Clinical trial results:
A Randomized, Placebo-Controlled, Double-Blind Study of LY2216684 Flexible-Dose 12 mg to 18 mg Once Daily and LY2216684 Fixed-Dose 6 mg Once Daily as Adjunctive Treatment for Patients with Major Depressive Disorder Who Are Partial Responders to Selective Serotonin Reuptake Inhibitor Treatment

Summary

EudraCT number	2010-021215-16
Trial protocol	CZ FI SK HU
Global end of trial date	13 August 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-LNBQ

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01187407
WHO universal trial number (UTN)	-
Other trial identifiers	Eli Lilly and Company: 12182

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Centre, 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 8772854559,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess whether LY2216684 (12 mg to 18 mg flexible dose QD) is superior to placebo QD in the adjunctive treatment of patients with Major Depressive Disorder who were identified as partial responders to an adequate course of treatment with an SSRI during an 11-week, double-blind, acute adjunctive treatment 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:

Subjects are being treated with one of the following SSRIs that have been approved for MDD treatment within the participating country: escitalopram, citalopram, sertraline, fluoxetine, paroxetine, and fluvoxamine; and have 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 should be prescribed, including dose, in a manner consistent with labeling guidelines within the participating country.

Evidence for comparator: -

Actual start date of recruitment	04 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Croatia: 53
Country: Number of subjects enrolled	United States: 750
Country: Number of subjects enrolled	Czech Republic: 258
Country: Number of subjects enrolled	Slovakia: 146
Country: Number of subjects enrolled	Finland: 116
Country: Number of subjects enrolled	Japan: 117
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Romania: 31
Worldwide total number of subjects	1480
EEA total number of subjects	613

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)	1390
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First 3 weeks of study was double-blind Confirmation Phase during which participants (pts) continued to receive their SSRI with adjunctive placebo. If randomization criteria were met, pts were randomized to adjunctive LY2216684 or adjunctive placebo. If criteria were not met, pts continued on placebo and remained in the study to maintain the blind.

Period 1

Period 1 title	Confirmation (CF) Phase, 3 Weeks
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Arm title	Placebo + SSRI (Pre-randomized Participants)

Arm description:

Placebo: administered orally, once daily (QD) for 3 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI)

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

Dosage and administration details:

Placebo tablets are given orally to the participants.

Number of subjects in period 1	Placebo + SSRI (Pre-randomized Participants)
Started	1480
Entered Discontinuation (DC) Phase	25 [1]
Completed	1390
Not completed	90
Physician decision	2
Consent withdrawn by subject	29
Adverse event, non-fatal	29
Sponsor Decision	4
Lost to follow-up	9
Lack of efficacy	4
Protocol deviation	13

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 CF Phase had the option to enter the DC phase. Participants who completed the CF Phase entered the AT Phase.

Period 2

Period 2 title	Adjunctive Treatment (AT) Phase, 8 Weeks
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	12 or 18 mg LY2216684 + SSRI (Randomized Participants)

Arm description:

LY2216684: flexible dose of 12 or 18 milligrams (mg), administered orally, QD for 8 weeks, adjunctive to an SSRI

Arm type	Experimental
Investigational medicinal product name	LY2216684
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LY2216684: flexible dose of 12 or 18 milligrams (mg), administered orally

Arm title	6 mg LY2216684 + SSRI (Randomized Participants)

Arm description:

LY2216684: fixed dose of 6 mg, administered orally, QD for 8 weeks, adjunctive to an SSRI

Arm type	Experimental
Investigational medicinal product name	LY2216684
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LY2216684: fixed dose of 6 mg, administered orally, QD for 8 weeks, adjunctive to an SSRI.

Arm title	Placebo + SSRI (Randomized Participants)

Arm description:

Placebo: administered orally, QD for 8 weeks, adjunctive to an SSRI

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

Dosage and administration details:

Placebo: administered orally, QD for 8 weeks, adjunctive to an SSRI

Arm title	Placebo + SSRI (Non-randomized Participants)

Arm description:

Placebo: administered orally, QD for 8 weeks, adjunctive to an SSRI

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

Dosage and administration details:

Placebo: administered orally, QD for 8 weeks, adjunctive to an SSRI

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is confirmatory phase, baseline characteristics & endpoints are reported for reporting groups in period 2."

Number of subjects in period 2[3]	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)
Started	232	226	231
Entered Discontinuation (DC) Phase	212	215	220
Completed	196	191	202
Not completed	36	35	29
Consent withdrawn by subject	9	9	11
Physician decision	-	-	1
Adverse event, non-fatal	13	6	5
Sponsor Decision	2	2	2
Lost to follow-up	3	5	2
Lack of efficacy	3	8	5
Protocol deviation	6	5	3

Number of subjects in period 2[3]	Placebo + SSRI (Non-randomized Participants)
Started	701
Entered Discontinuation (DC) Phase	660
Completed	626
Not completed	75
Consent withdrawn by subject	22
Physician decision	2
Adverse event, non-fatal	12
Sponsor Decision	7
Lost to follow-up	9
Lack of efficacy	13
Protocol deviation	10

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline period includes only the adjunctive treatment phase.

Baseline characteristics

Reporting groups	
Reporting group title	12 or 18 mg LY2216684 + SSRI (Randomized Participants)
Reporting group description:	
LY2216684: flexible dose of 12 or 18 milligrams (mg), administered orally, QD for 8 weeks, adjunctive to an SSRI	
Reporting group title	6 mg LY2216684 + SSRI (Randomized Participants)
Reporting group description:	
LY2216684: fixed dose of 6 mg, administered orally, QD for 8 weeks, adjunctive to an SSRI	
Reporting group title	Placebo + SSRI (Randomized Participants)
Reporting group description:	
Placebo: administered orally, QD for 8 weeks, adjunctive to an SSRI	
Reporting group title	Placebo + SSRI (Non-randomized Participants)
Reporting group description:	
Placebo: administered orally, QD for 8 weeks, adjunctive to an SSRI	

Reporting group values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)
Number of subjects	232	226	231
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	46.63	47.06	47.3
standard deviation	± 12	± 12.76	± 12.1
Gender, Male/Female Units: Subjects			
Male	83	73	75
Female	149	153	156
Region of Enrollment Units: Subjects			
United States	103	98	104
CzechRepublic	44	44	46
Slovakia	33	35	34
Finland	18	12	17
Croatia	9	10	7
Japan	20	23	19
Hungary	2	2	1
Romania	3	2	3
Ethnicity Units: Subjects			
Hispanic or Latino	11	9	14
Not Hispanic or Latino	183	181	178
Unknown or Not Reported	38	36	39
Race Units: Subjects			

American Indian or Alaska Native	1	0	3
Asian	21	26	20
Native Hawaiian or Pacific Islander	0	0	0
Black or African American	16	25	18
White	192	173	186
More than one race	2	2	3
Unknown or Not Reported	0	0	1

Reporting group values	Placebo + SSRI (Non-randomized Participants)	Total	
Number of subjects	701	1390	
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	46.35		
standard deviation	± 12.42	-	
Gender, Male/Female Units: Subjects			
Male	236	467	
Female	465	923	
Region of Enrollment Units: Subjects			
United States	377	682	
CzechRepublic	119	253	
Slovakia	39	141	
Finland	61	108	
Croatia	26	52	
Japan	53	115	
Hungary	3	8	
Romania	23	31	
Ethnicity Units: Subjects			
Hispanic or Latino	49	83	
Not Hispanic or Latino	562	1104	
Unknown or Not Reported	90	203	
Race Units: Subjects			
American Indian or Alaska Native	4	8	
Asian	54	121	
Native Hawaiian or Pacific Islander	0	0	
Black or African American	63	122	
White	572	1123	
More than one race	8	15	
Unknown or Not Reported	0	1	

End points

End points reporting groups

Reporting group title	Placebo + SSRI (Pre-randomized Participants)
Reporting group description:	
Placebo: administered orally, once daily (QD) for 3 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI)	
Reporting group title	12 or 18 mg LY2216684 + SSRI (Randomized Participants)
Reporting group description:	
LY2216684: flexible dose of 12 or 18 milligrams (mg), administered orally, QD for 8 weeks, adjunctive to an SSRI	
Reporting group title	6 mg LY2216684 + SSRI (Randomized Participants)
Reporting group description:	
LY2216684: fixed dose of 6 mg, administered orally, QD for 8 weeks, adjunctive to an SSRI	
Reporting group title	Placebo + SSRI (Randomized Participants)
Reporting group description:	
Placebo: administered orally, QD for 8 weeks, adjunctive to an SSRI	
Reporting group title	Placebo + SSRI (Non-randomized Participants)
Reporting group description:	
Placebo: administered orally, QD for 8 weeks, adjunctive to an SSRI	
Subject analysis set title	LY2216684
Subject analysis set type	Full analysis
Subject analysis set description:	
LY2216684: flexible dose of 12 or 18 milligrams (mg) or fixed dose of 6 mg, administered orally, once daily (QD)	

Primary: Change From Randomization to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score

End point title	Change From Randomization to Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score[1]

End point description:

The MADRS is a rating scale for severity of depressive mood symptoms. The MADRS had 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 were rated on a scale of 0 to 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 mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline score, treatment-by-visit, and baseline score-by-visit.

All randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

End point type	Primary

End point timeframe:

Randomization, 8 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	228	
Units: units on a scale				
least squares mean (standard error)	-9.36 (± 0.55)	-9.59 (± 0.55)	-9.36 (± 0.54)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + SSRI (Randomized Participants) v 12 or 18 mg LY2216684 + SSRI (Randomized Participants)
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.997 [2]
Method	Mixed models analysis

Notes:

[2] - Primary comparison

Statistical analysis title	Statistical Analysis 2
Comparison groups	6 mg LY2216684 + SSRI (Randomized Participants) v Placebo + SSRI (Randomized Participants)
Number of subjects included in analysis	449
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769 [3]
Method	Mixed models analysis

Notes:

[3] - Secondary comparison.

Secondary: Change From Randomization to Week 8 in the Sheehan Disability Scale (SDS) Global Functional Impairment Score

End point title	Change From Randomization to Week 8 in the Sheehan Disability Scale (SDS) Global Functional Impairment Score[4]

End point description:

The SDS was completed by the participant and used to assess the effect of the participant's symptoms on their work (Item 1), social (Item 2), and family life (Item 3). Each item is measured on a 0 (not at all) to 10 (extremely) point scale with higher values indicating greater disruption. The Global Functional Impairment Score is the sum of the 3 items, and scores ranged from 0 to 30 with higher values indicating greater disruption in the participant's work life (work/school impairment score), social life (social life/leisure activities impairment score), and family life (family life/home responsibilities impairment score). Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline score, treatment-by-visit, and baseline score-by-visit.

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, 8 weeks

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	210	221	
Units: units on a scale				
least squares mean (standard error)	-5.43 (± 0.43)	-6.29 (± 0.44)	-4.3 (± 0.43)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization to Week 8 in the Fatigue Associated With Depression (FAsD) Impact Subscale Score

End point title	Change From Randomization to Week 8 in the Fatigue Associated With Depression (FAsD) Impact Subscale Score[5]

End point description:

The FAsD is a participant-rated scale with a total of 13 items. Six of the 13 items ask how often participants experience different aspects of fatigue with responses from 1 (never) to 5 (always). Seven of the 13 items ask how often fatigue impacts various aspects of the participant's lives with responses from 1 (not at all) to 5 (very much). The impact subscale score was derived by taking the mean of Items 7 through 13 (applicable items only). Item 12 applied only to participants with a spouse or significant other and Item 13 applied to participants who had a job or who went to school. The FAsD impact subscale score ranges from 1 to 5. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline subscale score, treatment-by-visit, and baseline subscale score-by-visit.

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, 8 weeks

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	210	221	
Units: units on a scale				
least squares mean (standard error)	-0.71 (± 0.06)	-0.67 (± 0.06)	-0.56 (± 0.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving a Montgomery-Asberg Depression Rating Scale (MADRS) total score of less than or equal to 10 up to week 8

End point title	Percentage of participants achieving a Montgomery-Asberg Depression Rating Scale (MADRS) total score of less than or equal to 10 up to week 8[6]

End point description:

A MADRS total score of less than or equal to 10 was defined as remission criteria. The MADRS is a rating scale for severity of depressive mood symptoms. The MADRS had 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 were rated on a scale of 0 to 6, for a total score range of 0 (low severity of depressive symptoms) to 60 (high severity of depressive symptoms). Percentage of participants was calculated by dividing the number of participants who meet criteria for remission by the total number of participants analyzed, multiplied by 100%.

All randomized participants who have non-missing values at the 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 8 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	228	
Units: percentage of participants				
number (not applicable)	26.84	29.41	26.32	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving a Montgomery-Asberg Depression Rating Scale (MADRS) total score of less than or equal 10 for at least 2 consecutive measurements, including the participant's last measurement

End point title	Percentage of participants achieving a Montgomery-Asberg Depression Rating Scale (MADRS) total score of less than or

	equal 10 for at least 2 consecutive measurements, including the participant's last measurement[7]

End point description:

A MADRS total score of less than or equal to 10 for at least 2 consecutive measurements, including the participant's last measurement was defined as remission criteria at last 2 consecutive visits. The MADRS is a rating scale for severity of depressive mood symptoms. The MADRS had 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 were rated on a scale of 0 to 6, for a total score range of 0 (low severity of depressive symptoms) to 60 (high severity of depressive symptoms). Percentage of participants was calculated by dividing the number of participants who meet criteria for remission at last 2 consecutive visits by the total number of participants analyzed, multiplied by 100%.

All randomized participants who have non-missing values at the time of randomization and at least one post-randomization value.

All random

End point type	Secondary

End point timeframe:

Randomization up to 8 weeks

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	228	
Units: percentage of participants				
number (not applicable)	17.75	19	14.47	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in the Hospital and Anxiety and Depression Scale (HADS) anxiety subscale score

End point title	Change from randomization to week 8 in the Hospital and Anxiety and Depression Scale (HADS) anxiety subscale score[8]

End point description:

The HADS is a 14-item questionnaire with 2 subscales: anxiety and depression. Each item was rated on a 4-point scale (0 to 3), giving maximum scores of 21 for anxiety and depression subscale. Scores of 11 or more on either subscale were considered to be a significant 'case' of psychological morbidity, while scores of 8 to 10 represent 'borderline' and scores of 0 to 7 represent 'normal'. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline subscale score, treatment-by-visit, and baseline subscale score-by-visit.

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, 8 weeks

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	220	228	
Units: units on a scale				
least squares mean (standard error)	-2.24 (± 0.24)	-2.64 (± 0.24)	-2.05 (± 0.24)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who have a greater than or equal to 50 percent improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from randomization up to week 8

End point title	Percentage of participants who have a greater than or equal to 50 percent improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from randomization up to week 8[9]

End point description:

A greater than or equal to 50 percent improvement (that is, a decrease from baseline) in the MADRS total score was defined as response criteria. The MADRS is a rating scale for severity of depressive mood symptoms. The MADRS had 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 were rated on a scale of 0 to 6, for a total score range of 0 (low severity of depressive symptoms) to 60 (high severity of depressive symptoms). Percentage of participants was calculated by dividing the number of participants meeting response criteria at last visit by the total number of participants analyzed, multiplied by 100%.

All randomized participants who have non-missing values at the 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 8 weeks

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	221	228	
Units: percentage of participants				
number (not applicable)	30.74	30.84	32.46	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in the Hospital Anxiety and Depression Scale (HADS) depression subscale score

End point title	Change from randomization to week 8 in the Hospital Anxiety and Depression Scale (HADS) depression subscale score[10]

End point description:

The HADS is a 14-item questionnaire with 2 subscales: anxiety and depression. Each item was rated on a 4-point scale (0 to 3), giving maximum scores of 21 for anxiety and depression subscale. Scores of 11 or more on either subscale were considered to be a significant 'case' of psychological morbidity, while scores of 8 to 10 represent 'borderline' and scores of 0 to 7 represent 'normal'. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline subscale score, treatment-by-visit, and baseline subscale score-by-visit.

Change from randomization to week 8 in the Hospital Anxiety and Depression Scale (HADS) depression subscale score

End point type	Secondary

End point timeframe:

Randomization, 8 weeks

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	220	228	
Units: units on a scale				
least squares mean (standard error)	-3.4 (± 0.26)	-3.62 (± 0.27)	-2.55 (± 0.26)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in Clinical Global Impressions of Severity (CGI-S)

End point title	Change from randomization to week 8 in Clinical Global Impressions of Severity (CGI-S)[11]

End point description:

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 (among the most extremely ill participants). Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline score, treatment-by-visit, and baseline score-by-visit

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, 8 weeks

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	220	228	
Units: units on a scale				
least squares mean (standard error)	-1.2 (± 0.08)	-1.2 (± 0.08)	-1.14 (± 0.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) individual items

End point title	Change from randomization to week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) individual items[12]

End point description:

The MADRS is a rating scale for severity of depressive mood symptoms. The MADRS had 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 were rated on a scale of 0 to 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 mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline item score, treatment-by-visit and baseline item score-by-visit.

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, 8 weeks

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	220	228	
Units: units on a scale				
least squares mean (standard error)				
Apparent sadness (n=231, 220, 228)	-1.34 (± 0.08)	-1.25 (± 0.08)	-1.26 (± 0.08)	
Reported sadness (n=231, 219, 228)	-1.41 (± 0.09)	-1.31 (± 0.09)	-1.26 (± 0.09)	
Inner tension (n=231, 220, 228)	-0.96 (± 0.08)	-0.91 (± 0.08)	-0.07 (± 0.08)	
Reduced sleep (n=231, 220, 228)	-0.82 (± 0.09)	-0.96 (± 0.09)	-0.92 (± 0.09)	
Reduced appetite (n=231, 220, 228)	-0.57 (± 0.08)	-0.67 (± 0.08)	-0.71 (± 0.08)	
Concentration difficulties (n=231, 220, 228)	-1.13 (± 0.08)	-1.14 (± 0.08)	-0.98 (± 0.08)	
Lassitude (n=231, 220, 228)	-1.15 (± 0.09)	-1.07 (± 0.09)	-1.16 (± 0.09)	
Inability to feel (n=231, 220, 228)	-1.11 (± 0.09)	-1.3 (± 0.09)	-1.14 (± 0.09)	
Pessimistic thoughts (n=231, 220, 228)	-0.84 (± 0.07)	-0.82 (± 0.07)	-0.91 (± 0.07)	
Suicidal thoughts (n=231, 220, 228)	-0.17 (± 0.03)	-0.19 (± 0.03)	-0.17 (± 0.03)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in Sheehan Disability Scale (SDS) items

End point title	Change from randomization to week 8 in Sheehan Disability Scale (SDS) items[13]

End point description:

The SDS was 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 mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline item score, treatment-by-visit, and baseline item score-by-visit.

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, 8 weeks

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	210	221	
Units: units on a scale				
least squares mean (standard error)				
Work impairment score (n=151, 138, 145)	-1.81 (± 0.19)	-1.93 (± 0.2)	-1.32 (± 0.19)	
Social life impairment score (n= 225, 210, 221)	-1.79 (± 0.16)	-2.11 (± 0.16)	-1.52 (± 0.16)	
Family life impairment score (n=225, 210, 221)	-1.75 (± 0.15)	-2.16 (± 0.15)	-1.47 (± 0.15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in The Fatigue Associated with Depression (FAsD) average score and experience subscale score

End point title	Change from randomization to week 8 in The Fatigue Associated with Depression (FAsD) average score and experience subscale score[14]

End point description:

The FAsD is a participant-rated scale with a total of 13 items. Six of the 13 items ask how often participants experience different aspects of fatigue with responses from 1 (never) to 5 (always). Seven of the 13 items 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 was derived by taking the mean of Items 1 through 6, and the average score was the mean of Items 1 through 13 (derived by taking the mean of all applicable items for each participant). Item 12 applied only to participants with a spouse or significant other and Item 13 applied to participants who had a job or who went to school. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline score, treatment-by-visit, and baseline score-by-visit.

End point type	Secondary

End point timeframe:

Randomization, 8 weeks

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	210	221	
Units: units on a scale				
least squares mean (standard error)				
FAsD average score	-0.67 (± 0.05)	-0.68 (± 0.06)	-0.53 (± 0.05)	
FAsD experience score	-0.63 (± 0.06)	-0.67 (± 0.06)	-0.5 (± 0.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)

End point title	Change from randomization to week 8 in the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)[15]

End point description:

The Q-LES-Q-SF is a self-administered 16 item questionnaire measuring degree of enjoyment and satisfaction experienced in various areas of daily life during the past week on a 5-point Likert scale (1=very poor and 5=very good). The total raw score is the sum of Items 1 to 14 and ranges from 14 to 70. The raw scores are converted to and expressed as the percentage of the maximum possible score. Higher scores indicate higher levels of enjoyment/satisfaction. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline score, treatment-by-visit, and baseline score-by-visit.

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, 8 weeks

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	210	221	
Units: percentage of maximum possible score				
least squares mean (standard error)	10.54 (± 1)	10.5 (± 1.02)	8.74 (± 0.99)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in the EuroQol Questionnaire-5 Dimension (EQ-5D)

End point title	Change from randomization to week 8 in the EuroQol Questionnaire-5 Dimension (EQ-5D)[16]

End point description:

The EQ-5D Visual Analog Scale is a generic, multidimensional, health-related, quality-of-life instrument. Overall health state score is self-reported using a visual analogue scale, marked on a scale of 0 to 100 with 0 representing worst imaginable health state and 100 representing best imaginable health state. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline score, treatment-by-visit, and baseline score-by-visit.

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, 8 weeks

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	210	229	
Units: units on a scale				
least squares mean (standard error)	11.457 (± 1.218)	11.895 (± 1.239)	9.53 (± 1.207)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with treatment-emergent (TE) suicidal ideation and behaviors assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Percentage of participants with treatment-emergent (TE) suicidal ideation and behaviors assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)[17]

End point description:

The C-SSRS captured occurrence, severity, and frequency of suicide-related thoughts and behaviors. Suicidal ideation was 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 was 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. Percentage of participants was calculated by dividing the number of participants with suicide-related TE events by the total number of participants analyzed, multiplied by 100%. A summary of serious and other non-SAE, regardless of causality, is located in the Reported Adverse Event module.

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 8 weeks

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	221	228	
Units: percentage of participants				
number (not applicable)				
TE suicidal ideation (n=232, 221, 228)	5.17	3.62	4.39	
TE suicidal behavior (n=203, 198, 202)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in the Arizona Sexual Experiences (ASEX) scale

End point title	Change from randomization to week 8 in the Arizona Sexual Experiences (ASEX) scale[18]

End point description:

The ASEX scale was used to assess sexual functioning in both males and females. The ASEX total score for the male and female version was calculated as the sum of the responses (rated from 1 [extremely] to 6 [no/never]) of the 5 items of the ASEX scale. Total scores ranged from 5 to 30, with higher scores indicating greater sexual dysfunction. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline score, treatment-by-visit, and baseline score-by-visit.

Change from randomization to week 8 in the Arizona Sexual Experiences (ASEX) scale

End point type	Secondary

End point timeframe:

Randomization, 8 weeks

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	209	220	
Units: units on a scale				
least squares mean (standard error)	-1.62 (± 0.29)	-1.29 (± 0.29)	-0.97 (± 0.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

End point title	Change from randomization to week 8 in the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)[19]

End point description:

The 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 was scored on a 6-point scale ranging from 1 (greater than normal) to 6 (totally absent). Total scores ranged from 7 to 42. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline score, treatment-by-visit, and baseline score-by-visit.

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, 8 weeks

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225	210	221	
Units: units on a scale				
least squares mean (standard error)	-4.74 (± 0.38)	-4.67 (± 0.39)	-3.64 (± 0.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in blood pressure

End point title	Change from randomization to week 8 in blood pressure[20]

End point description:

Blood pressure measurements were collected when the participant was in a sitting position. Three measurements of sitting blood pressure collected at approximately 1-minute intervals at every visit were

averaged and used as the value for the visit. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline value, treatment-by-visit, and baseline value-by-visit.

Change from randomization to week 8 in blood pressure.

End point type	Secondary

End point timeframe:

Randomization, 8 weeks

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	220	228	
Units: millimeters of mercury (mmHg)				
least squares mean (standard error)				
Systolic blood pressure	1.64 (± 0.62)	2.93 (± 0.63)	0.78 (± 0.62)	
Diastolic blood pressure	3.46 (± 0.49)	4.47 (± 0.5)	1.01 (± 0.49)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomization to week 8 in pulse rate

End point title	Change from randomization to week 8 in pulse rate[21]

End point description:

Pulse measurements were collected when the participant was in a sitting position. Least Squares (LS) means were calculated using mixed model repeated measures (MMRM) adjusting for treatment, investigator, visit, baseline value, treatment-by-visit, and baseline value-by-visit.

Change from randomization to week 8 in pulse rate

End point type	Secondary

End point timeframe:

Randomization, 8 weeks

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are being reported for all randomized participants per the protocol or Statistical Analysis Plan.

End point values	12 or 18 mg LY2216684 + SSRI (Randomized Participants)	6 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	220	228	
Units: beats per minute (bpm)				
least squares mean (standard error)	9.26 (± 0.65)	7.32 (± 0.66)	-1.03 (± 0.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Plasma concentrations of LY2216684

End point title	Pharmacokinetics: Plasma concentrations of LY2216684

End point description:

A validated bioanalytical assay was used to determine plasma LY2216684 concentrations.

Participants exposed to LY2216684 with evaluable plasma concentration values. Samples with concentrations below the lower quantification limit (BQL) of the assay were treated as missing values for the analysis and samples with incomplete dosing information were not included in the pharmacokinetic assessment.

End point type	Secondary

End point timeframe:

Pre-randomization, 1 week, 4 weeks, and 8 weeks

End point values	LY2216684			
Subject group type	Subject analysis set			
Number of subjects analysed	400			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
6-mg dose (n=197)	17 (± 10.2)			
12-mg dose (n=197)	32.2 (± 21.1)			
18-mg dose (n=136)	52.4 (± 34.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo + SSRI (Pre-randomized) - CF Phase

Reporting group description:

Placebo: administered orally, once daily for 3 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI) Includes all enrolled who did not discontinue for the reason 'Lost to Follow-up' at the first post-baseline visit during the Confirmation (CF) Phase.

Reporting group title	6 mg LY2216684 + SSRI (Randomized) - AT Phase

Reporting group description:

LY2216684: fixed dose of 6 milligrams (mg), administered orally, once daily for 8 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 Adjunctive Treatment (AT) Phase.

Reporting group title	12 or 18 mg LY2216684 + SSRI (Randomized) - AT Phase

Reporting group description:

LY2216684: flexible dose of 12 or 18 milligrams (mg), administered orally, once daily for 8 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 Adjunctive Treatment (AT) Phase.

Reporting group title	Placebo + SSRI (Randomized) - AT Phase

Reporting group description:

Placebo: administered orally, once daily for 8 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 Adjunctive Treatment (AT) Phase.

Reporting group title	Placebo + SSRI (Non-randomized) - AT Phase

Reporting group description:

Placebo: administered orally, once daily for 8 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI) Includes all non-randomized participants who did not discontinue for the reason 'Lost to Follow-up' at the first post-randomization visit during the Adjunctive Treatment (AT) Phase.

Reporting group title	Placebo + SSRI (Pre-randomized) - DC Phase

Reporting group description:

No study drug was administered. Participants were to maintain their selective serotonin reuptake inhibitor (SSRI) treatment at a stable dose for 1 week. Includes all enrolled participants who abruptly discontinued placebo after early withdrawal during the Confirmation (CF) Phase and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation (DC) Phase visit.

Reporting group title	6 mg LY2216684 + SSRI (Randomized) - DC Phase

Reporting group description:

No study drug was administered. Participants were to maintain their selective serotonin reuptake inhibitor (SSRI) treatment at a stable dose for 1 week. Includes all randomized participants who abruptly discontinued LY2216684 either at the end of the study or after early withdrawal from the study and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation (DC) Phase visit.

Reporting group title	12 or 18 mg Flex-dose LY2216684 - DC Phase

Reporting group description:

No study drug was administered. Participants were to maintain their selective serotonin reuptake inhibitor (SSRI) treatment at a stable dose for 1 week. Includes all randomized participants who abruptly discontinued LY2216684 either at the end of the study or after early withdrawal from the study and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation (DC) Phase visit.

Reporting group title	Placebo + SSRI (Randomized) - DC Phase

Reporting group description:

No study drug was administered. Participants were to maintain their selective serotonin reuptake inhibitor (SSRI) treatment at a stable dose for 1 week. Includes all randomized participants who abruptly discontinued placebo either at the end of the study or after early withdrawal from the study and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation (DC) Phase visit.

Reporting group title	Placebo + SSRI (Non-randomized) - DC Phase

Reporting group description:

No study drug was administered. Participants were to maintain their selective serotonin reuptake inhibitor (SSRI) treatment at a stable dose for 1 week. Includes all non-randomized participants who abruptly discontinued placebo either at the end of the study or after early withdrawal from the study and who did not discontinue for the reason 'Lost to Follow-up' at the Discontinuation (DC) Phase visit.

Serious adverse events	Placebo + SSRI (Pre-randomized) - CF Phase	6 mg LY2216684 + SSRI (Randomized) - AT Phase	12 or 18 mg LY2216684 + SSRI (Randomized) - AT Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 1476 (0.47%)	1 / 223 (0.45%)	2 / 232 (0.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
accidental overdose			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	0 / 232 (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			
atrial fibrillation			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	2 / 1476 (0.14%)	0 / 223 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
syncope			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	0 / 232 (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
General disorders and administration site conditions			
inflammation			

alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
cervical dysplasia			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed[1]	1 / 979 (0.10%)	1 / 152 (0.66%)	0 / 149 (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
fibrocystic breast disease			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	0 / 232 (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
metrorrhagia			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed[2]	0 / 979 (0.00%)	0 / 152 (0.00%)	0 / 149 (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			
acute respiratory failure			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	0 / 232 (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			
mania			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 1476 (0.07%)	0 / 223 (0.00%)	0 / 232 (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
suicidal ideation			

alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	2 / 1476 (0.14%)	0 / 223 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicide attempt			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	0 / 232 (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			
osteoarthritis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 1476 (0.07%)	0 / 223 (0.00%)	0 / 232 (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
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diverticulitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	0 / 232 (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
mastitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	0 / 232 (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 16.0			

subjects affected / exposed	0 / 1476 (0.00%)	0 / 223 (0.00%)	0 / 232 (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	Placebo + SSRI (Randomized) - AT Phase	Placebo + SSRI (Non-randomized) - AT Phase	Placebo + SSRI (Pre-randomized) - DC Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 231 (0.87%)	5 / 699 (0.72%)	3 / 25 (12.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
accidental overdose			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	1 / 699 (0.14%)	0 / 25 (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
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	0 / 699 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
syncope			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	0 / 699 (0.00%)	0 / 25 (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
General disorders and administration site conditions			
inflammation			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	0 / 699 (0.00%)	0 / 25 (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			
cervical dysplasia			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed[1]	0 / 156 (0.00%)	0 / 464 (0.00%)	0 / 16 (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
fibrocystic breast disease			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	1 / 699 (0.14%)	0 / 25 (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
metrorrhagia			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed[2]	1 / 156 (0.64%)	0 / 464 (0.00%)	0 / 16 (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			
acute respiratory failure			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	1 / 699 (0.14%)	0 / 25 (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			
mania			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	0 / 699 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicidal ideation			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	0 / 699 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
suicide attempt			

alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	1 / 699 (0.14%)	0 / 25 (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
Musculoskeletal and connective tissue disorders			
osteoarthritis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 231 (0.43%)	0 / 699 (0.00%)	0 / 25 (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
Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	0 / 699 (0.00%)	0 / 25 (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
diverticulitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	1 / 699 (0.14%)	0 / 25 (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
mastitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 231 (0.00%)	1 / 699 (0.14%)	0 / 25 (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 16.0			
subjects affected / exposed	0 / 231 (0.00%)	1 / 699 (0.14%)	0 / 25 (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	6 mg LY2216684 + SSRI (Randomized)	12 or 18 mg Flex-dose LY2216684 -	Placebo + SSRI (Randomized) - DC

	- DC Phase	DC Phase	Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 213 (0.94%)	0 / 212 (0.00%)	1 / 220 (0.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
accidental overdose			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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			
atrial fibrillation			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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			
syncope			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	1 / 213 (0.47%)	0 / 212 (0.00%)	0 / 220 (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
General disorders and administration site conditions			
inflammation			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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			
cervical dysplasia			
alternative dictionary used: MedDRA 16.0			

subjects affected / exposed[1]	1 / 148 (0.68%)	0 / 133 (0.00%)	0 / 145 (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
fibrocystic breast disease			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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
metrorrhagia			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed[2]	0 / 148 (0.00%)	0 / 133 (0.00%)	0 / 145 (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			
acute respiratory failure			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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			
mania			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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
suicide attempt			
alternative dictionary used: MedDRA 16.0			

subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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			
osteoarthritis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	1 / 220 (0.45%)
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			
appendicitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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
diverticulitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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
mastitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (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	Placebo + SSRI (Non-randomized) - DC Phase		
Total subjects affected by serious			

adverse events			
subjects affected / exposed	2 / 659 (0.30%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
accidental overdose			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 659 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 659 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
syncope			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 659 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
inflammation			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 659 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
cervical dysplasia			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed[1]	0 / 441 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
fibrocystic breast disease			

alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	1 / 659 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
metrorrhagia				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed[2]	0 / 441 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
acute respiratory failure				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	0 / 659 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
mania				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	0 / 659 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
suicidal ideation				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	0 / 659 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
suicide attempt				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	0 / 659 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				

osteoarthritis				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	0 / 659 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
appendicitis				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	0 / 659 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
diverticulitis				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	0 / 659 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
mastitis				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	1 / 659 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
pneumonia				
alternative dictionary used: MedDRA 16.0				
subjects affected / exposed	1 / 659 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	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 is gender specific AE, number reported includes only the female subjects.

[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 is gender specific AE, number reported includes only the female subjects.

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

Non-serious adverse events	Placebo + SSRI (Pre-randomized) - CF Phase	6 mg LY2216684 + SSRI (Randomized) - AT Phase	12 or 18 mg LY2216684 + SSRI (Randomized) - AT Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	231 / 1476 (15.65%)	39 / 223 (17.49%)	57 / 232 (24.57%)
Cardiac disorders			
tachycardia			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	6 / 1476 (0.41%)	5 / 223 (2.24%)	12 / 232 (5.17%)
occurrences (all)	6	5	12
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	112 / 1476 (7.59%)	15 / 223 (6.73%)	14 / 232 (6.03%)
occurrences (all)	127	18	15
Gastrointestinal disorders			
nausea			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	77 / 1476 (5.22%)	12 / 223 (5.38%)	12 / 232 (5.17%)
occurrences (all)	80	13	17
Skin and subcutaneous tissue disorders			
hyperhidrosis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	34 / 1476 (2.30%)	7 / 223 (3.14%)	18 / 232 (7.76%)
occurrences (all)	35	8	19
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	35 / 1476 (2.37%)	7 / 223 (3.14%)	12 / 232 (5.17%)
occurrences (all)	35	7	12

Non-serious adverse events	Placebo + SSRI (Randomized) - AT Phase	Placebo + SSRI (Non-randomized) - AT Phase	Placebo + SSRI (Pre-randomized) - DC Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 231 (16.45%)	115 / 699 (16.45%)	0 / 25 (0.00%)
Cardiac disorders			
tachycardia			
alternative dictionary used: MedDRA 16.0			

subjects affected / exposed	0 / 231 (0.00%)	2 / 699 (0.29%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	22 / 231 (9.52%)	61 / 699 (8.73%)	0 / 25 (0.00%)
occurrences (all)	33	81	0
Gastrointestinal disorders			
nausea			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	9 / 231 (3.90%)	25 / 699 (3.58%)	0 / 25 (0.00%)
occurrences (all)	10	41	0
Skin and subcutaneous tissue disorders			
hyperhidrosis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	4 / 231 (1.73%)	11 / 699 (1.57%)	0 / 25 (0.00%)
occurrences (all)	4	11	0
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	7 / 231 (3.03%)	27 / 699 (3.86%)	0 / 25 (0.00%)
occurrences (all)	7	27	0

Non-serious adverse events	6 mg LY2216684 + SSRI (Randomized) - DC Phase	12 or 18 mg Flex-dose LY2216684 - DC Phase	Placebo + SSRI (Randomized) - DC Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 213 (10.33%)	18 / 212 (8.49%)	17 / 220 (7.73%)
Cardiac disorders			
tachycardia			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	0 / 213 (0.00%)	0 / 212 (0.00%)	0 / 220 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 16.0			
subjects affected / exposed	19 / 213 (8.92%)	13 / 212 (6.13%)	14 / 220 (6.36%)
occurrences (all)	19	14	14

Gastrointestinal disorders nausea alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all)	4 / 213 (1.88%) 4	2 / 212 (0.94%) 2	2 / 220 (0.91%) 2
Skin and subcutaneous tissue disorders hyperhidrosis alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all)	0 / 213 (0.00%) 0	4 / 212 (1.89%) 4	0 / 220 (0.00%) 0
Infections and infestations nasopharyngitis alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all)	1 / 213 (0.47%) 1	1 / 212 (0.47%) 1	2 / 220 (0.91%) 2

Non-serious adverse events	Placebo + SSRI (Non-randomized) - DC Phase		
Total subjects affected by non-serious adverse events subjects affected / exposed	64 / 659 (9.71%)		
Cardiac disorders tachycardia alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all)	0 / 659 (0.00%) 0		
Nervous system disorders headache alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all)	47 / 659 (7.13%) 54		
Gastrointestinal disorders nausea alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all)	13 / 659 (1.97%) 13		
Skin and subcutaneous tissue disorders hyperhidrosis alternative dictionary used: MedDRA 16.0			

subjects affected / exposed occurrences (all)	7 / 659 (1.06%) 7		
Infections and infestations nasopharyngitis alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all)	 5 / 659 (0.76%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2011	1.Clarification that the GRID-HAMD17, SAFER criteria, and evaluation of assessed by central rater at Visit 1. 2.Clarification added to exclusion criterion. 3.Added allowance of episodic use of specified benzodiazepines; 4.Added clarifying language regarding timing and assessment of vitals and body weight, PCS criteria for blood pressure, and C-SSRS assessment.
01 May 2012	1.Updated planned LPV. 2.Moved FAsD subscale from secondary gatekeeper objective to additional secondary objective. 3.Updated statistical methodology section. 4.Updated details of how the sample size and power calculations are provided to ERBs
02 August 2012	1.Added language for "re-screening"; 2.Made modifications to interim analysis based on regulatory input and updated statistical methods.

Notes:

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/27035159