Clinical trial results:
A Randomized, Placebo-Controlled, Double-Blind Study of LY2216684 Fixed-Dose 12 milligrams (mg) and 18 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	2010-021214-39
Trial protocol	LV
Global end of trial date	21 October 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-LNBM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01173601
WHO universal trial number (UTN)	-
Other trial identifiers	Tral Alias: 11316

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, United States,
Public contact	Available Mon - Fri 9 AM - 5 PM Eastern time (UTC/GMT - 5 hours, EST), Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM Eastern time (UTC/GMT - 5 hours, 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	21 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to assess whether at least 1 dose of LY2216684 (12 milligrams [mg] or 18 mg once daily) is superior to placebo once daily in the adjunctive treatment of participants with major depressive disorder (MDD) who were identified as partial responders to an adequate course of treatment with a selective serotonin reuptake inhibitor (SSRI) during an 8-week, double-blind, acute adjunctive treatment phase.

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:

Selective Serotonin Reuptake Inhibitor (SSRI): Participants were 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 prescribed, including dose, was maintained consistently with labeling guidelines within the participating country.

Evidence for comparator: -

Actual start date of recruitment	16 December 2010
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	United States: 594
Country: Number of subjects enrolled	Poland: 220
Country: Number of subjects enrolled	Ukraine: 134
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	South Africa: 77
Country: Number of subjects enrolled	Latvia: 85
Country: Number of subjects enrolled	Japan: 270
Worldwide total number of subjects	1416
EEA total number of subjects	305

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)	1363
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First 3 weeks was double-blind adjunctive placebo lead-in Confirmation Phase during which participants(pts) continued SSRI with adjunctive placebo. If randomization criteria were met, pts were randomized to receive LY2216684 12 mg, 18 mg, or 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	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Arm title	Placebo + SSRI (Pre-Randomized Participants)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo taken by mouth once daily for 11 weeks.

Number of subjects in period 1	Placebo + SSRI (Pre-Randomized Participants)
Started	1416
Entered Discontinuation Phase	21 [1]
Completed	1328
Not completed	88
Physician decision	3
Consent withdrawn by subject	25
Adverse event, non-fatal	23
Sponsor Decision	6
Lost to follow-up	7
Lack of efficacy	9
Protocol deviation	15

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 mg LY2216684 + SSRI (Randomized Participants)

Arm description:

LY2216684: 12 milligrams (mg), administered orally, once daily for 8 weeks, adjunctive to a 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:

Double-blind Study of LY2216684 Fixed-dose 12 mg and 18 mg Once Daily as Adjunctive Treatment for Patients With Major Depressive Disorder Who Are Partial Responders to Selective Serotonin Reuptake Inhibitor Treatment.

Arm title	18 mg LY2216684 + SSRI (Randomized Participants)

Arm description:

LY2216684: 12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a 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:

12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a SSRI

Arm title	Placebo + SSRI (Randomized Participants)

Arm description:

Placebo: Administered orally, once daily for 8 weeks, adjunctive to a 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 taken by mouth once daily for 11 weeks.

Arm title	Placebo + SSRI (Non-Randomized Participants)

Arm description:	
Placebo: Administered orally, once daily for 8 weeks	
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 taken by mouth once daily for 11 weeks.	

Notes:

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

Justification: Period 1 is the confirmatory phase, baseline and analytical data is based on Period 2 (Adjunctive phase).

Number of subjects in period 2[3]	12 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)
Started	231	230	240
Entered Taper Discontinuation Phase	100 [4]	107 [5]	0 [6]
Entered Abrupt Discontinuation Phase	100 [7]	108 [8]	221
Completed	196	197	210
Not completed	35	33	30
Physician decision	2	-	2
Consent withdrawn by subject	9	7	5
Adverse event, non-fatal	10	15	7
Sponsor Decision	-	-	2
Lost to follow-up	3	-	2
Lack of efficacy	10	6	8
Protocol deviation	1	5	4

Number of subjects in period 2[3]	Placebo + SSRI (Non-Randomized Participants)
Started	627
Entered Taper Discontinuation Phase	0 [9]
Entered Abrupt Discontinuation Phase	586
Completed	559
Not completed	68
Physician decision	1
Consent withdrawn by subject	24
Adverse event, non-fatal	14
Sponsor Decision	6
Lost to follow-up	9
Lack of efficacy	9
Protocol deviation	5

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: Participants who completed the AT Phase or discontinued early entered the taper DC phase or abrupt DC phase.

[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 the AT Phase or discontinued early entered the taper DC phase or abrupt DC phase.

[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 the AT Phase or discontinued early entered the taper DC (discontinuation) phase or abrupt DC phase.

[6] - 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 the AT Phase or discontinued early entered the taper DC phase or abrupt DC phase.

[7] - 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 the AT Phase or discontinued early entered the taper DC phase or abrupt DC phase.

[8] - 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 the AT Phase or discontinued early entered the taper DC phase or abrupt DC phase.

[9] - 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 the AT Phase or discontinued early entered the taper DC phase or abrupt DC phase.

Baseline characteristics

Reporting groups	
Reporting group title	12 mg LY2216684 + SSRI (Randomized Participants)
Reporting group description:	
LY2216684: 12 milligrams (mg), administered orally, once daily for 8 weeks, adjunctive to a SSRI	
Reporting group title	18 mg LY2216684 + SSRI (Randomized Participants)
Reporting group description:	
LY2216684: 12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a SSRI	
Reporting group title	Placebo + SSRI (Randomized Participants)
Reporting group description:	
Placebo: Administered orally, once daily for 8 weeks, adjunctive to a SSRI	
Reporting group title	Placebo + SSRI (Non-Randomized Participants)
Reporting group description:	
Placebo: Administered orally, once daily for 8 weeks	

Reporting group values	12 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)
Number of subjects	231	230	240
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	44.95	46.06	44.38
standard deviation	± 12.38	± 12.82	± 10.6
Gender, Male/Female Units:			
Male	86	81	85
Female	145	149	155
Region of Enrollment Units: Subjects			
United States	73	76	74
Poland	46	52	51
Ukraine	33	29	29
Russian Federation	6	6	6
South Africa	10	9	10
Latvia	16	14	17
Japan	47	44	53
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	47	45	56
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	14	14	19
White	164	170	164
More than one race	5	1	0

Unknown or Not Reported	1	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	7	7
Not Hispanic or Latino	181	172	188
Unknown or Not Reported	41	51	45

Reporting group values	Placebo + SSRI (Non-Randomized Participants)	Total	
Number of subjects	627	1328	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	44.73		
standard deviation	± 11.89	-	
Gender, Male/Female Units:			
Male	176	428	
Female	451	900	
Region of Enrollment Units: Subjects			
United States	318	541	
Poland	63	212	
Ukraine	36	127	
Russian Federation	15	33	
South Africa	44	73	
Latvia	34	81	
Japan	117	261	
Race Units: Subjects			
American Indian or Alaska Native	2	2	
Asian	121	269	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	65	112	
White	429	927	
More than one race	9	15	
Unknown or Not Reported	1	3	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	28	51	
Not Hispanic or Latino	520	1061	
Unknown or Not Reported	79	216	

End points

End points reporting groups

Reporting group title	Placebo + SSRI (Pre-Randomized Participants)
Reporting group description: -	
Reporting group title	12 mg LY2216684 + SSRI (Randomized Participants)
Reporting group description:	
LY2216684: 12 milligrams (mg), administered orally, once daily for 8 weeks, adjunctive to a SSRI	
Reporting group title	18 mg LY2216684 + SSRI (Randomized Participants)
Reporting group description:	
LY2216684: 12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a SSRI	
Reporting group title	Placebo + SSRI (Randomized Participants)
Reporting group description:	
Placebo: Administered orally, once daily for 8 weeks, adjunctive to a SSRI	
Reporting group title	Placebo + SSRI (Non-Randomized Participants)
Reporting group description:	
Placebo: Administered orally, once daily for 8 weeks	
Subject analysis set title	12 mg LY2216684 + SSRI (Randomized Participants)
Subject analysis set type	Full analysis
Subject analysis set description:	
LY2216684: 12 milligrams (mg), administered orally, once daily for 8 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI)	
Subject analysis set title	18 mg LY2216684 + SSRI (Randomized Participants)
Subject analysis set type	Full analysis
Subject analysis set description:	
LY2216684: 12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a SSRI	
Subject analysis set title	Placebo + SSRI (Randomized Participants)
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo: Administered orally, once daily for 8 weeks, adjunctive to a SSRI	
Subject analysis set title	Placebo + SSRI (Non-Randomized Participants)
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo: Administered orally, once daily for 8 weeks, adjunctive to a SSRI	
Subject analysis set title	LY2216684 + SSRI
Subject analysis set type	Full analysis
Subject analysis set description:	
LY2216684: fixed doses of 12 milligrams (mg) administered orally, once daily for 8 weeks, adjunctive to a selective serotonin reuptake inhibitor (SSRI) or 12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a SSRI	

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. 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. 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	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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: units on a scale				
least squares mean (standard error)	-8.47 (± 0.52)	-8.7 (± 0.53)	-7.77 (± 0.51)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	12 mg LY2216684 + SSRI (Randomized Participants) v Placebo + SSRI (Randomized Participants)
Number of subjects included in analysis	470
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.338 [2]
Method	Mixed models analysis

Notes:

[2] - In order to test the primary outcome between each LY2216684 dose and placebo while controlling the overall Type I error at 0.05, the significance level was a priori partitioned equally between the 2 LY2216684 dose-placebo comparisons at 0.025.

Statistical analysis title	Statistical Analysis 2
Comparison groups	18 mg LY2216684 + SSRI (Randomized Participants) v Placebo + SSRI (Randomized Participants)
Number of subjects included in analysis	470
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.201 [3]
Method	Mixed models analysis

Notes:

[3] - In order to test the primary outcome between each LY2216684 dose and placebo while controlling the overall Type I error at 0.05, the significance level was a priori partitioned equally between the 2 LY2216684 dose-placebo comparisons at 0.025.

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

End point title	Change from Randomization to Week 8 in Sheehan Disability Scale (SDS) Global Functional Impairment Scale[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 Function Impairment Score is the sum of the 3 items, and scores ranged from 0 to 30 with higher values indicating 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	222	236	
Units: units on a scale				
least squares mean (standard error)	-5.36 (± 0.44)	-5.27 (± 0.44)	-4.47 (± 0.43)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization to Week 8 in Fatigue Associated with Depression (FAsD) Impact Subscale Score

End point title	Change from Randomization to Week 8 in 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. 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	221	236	
Units: units on a scale				
least squares mean (standard error)	-0.74 (± 0.06)	-0.66 (± 0.06)	-0.53 (± 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 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 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. 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%. 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 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: percentage of participants				
number (not applicable)	27.83	26.96	26.67	

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. 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%. Analysis population included all randomized participants with a baseline and at least one post-baseline value.

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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: percentage of participants				
number (not applicable)	16.96	19.13	19.58	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization to Week 8 in Hospital and Anxiety and Depression Scale (HADS) Anxiety Subscale Score

End point title	Change from Randomization to Week 8 in 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 (0-3), 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 8-10 represent 'borderline' and 0-7 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. Analysis population included all randomized participants with a baseline and at least one post-baseline 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	239	
Units: units on a scale				
least squares mean (standard error)	-1.97 (± 0.22)	-2.05 (± 0.22)	-1.85 (± 0.22)	

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. 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%. 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 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: percentage of participants				
number (not applicable)	30.43	34.35	27.08	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Randomization to Week 8 in Hospital Anxiety and Depression Scale (HADS) depression subscale score

End point title	Change from Randomization to Week 8 in 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 (0-3), 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 8-10 represent 'borderline' and 0-7 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	239	
Units: units on a scale				
least squares mean (standard error)	-3.19 (± 0.26)	-3.38 (± 0.27)	-2.76 (± 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: units on a scale				
least squares mean (standard error)	-1.01 (± 0.07)	-1.08 (± 0.07)	-0.95 (± 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: units on a scale				
least squares mean (standard error)				
Apparent sadness	-1.18 (± 0.08)	-1.04 (± 0.08)	-1.01 (± 0.08)	
Reported sadness	-1.21 (± 0.08)	-1.2 (± 0.08)	-1 (± 0.08)	
Inner tension	-0.71 (± 0.07)	-0.74 (± 0.07)	-0.65 (± 0.07)	
Reduced sleep	-0.97 (± 0.09)	-0.94 (± 0.09)	-0.83 (± 0.08)	
Reduced appetite	-0.82 (± 0.08)	-0.74 (± 0.08)	-0.75 (± 0.08)	

Concentration difficulties	-0.88 (± 0.08)	-1.01 (± 0.08)	-0.94 (± 0.08)	
Lassitude	-1.04 (± 0.08)	-1.12 (± 0.08)	-0.89 (± 0.08)	
Inability to feel	-1.05 (± 0.08)	-1.07 (± 0.08)	-0.9 (± 0.08)	
Pessimistic thoughts	-0.77 (± 0.07)	-0.74 (± 0.07)	-0.74 (± 0.07)	
Suicidal thoughts	-0.09 (± 0.03)	-0.13 (± 0.03)	-0.15 (± 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 Sheehan Disability Scale (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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	222	236	
Units: units on a scale				
least squares mean (standard error)				
Work impairment score (n=149, 145, 167)	-1.77 (± 0.19)	-1.74 (± 0.2)	-1.44 (± 0.19)	
Social life impairment score (n=224, 222, 236)	-1.85 (± 0.16)	-1.81 (± 0.16)	-1.64 (± 0.16)	
Family life impairment score (224, 222, 236)	-1.72 (± 0.16)	-1.71 (± 0.16)	-1.43 (± 0.15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization to Week 8 in Fatigue Associated with Depression (FAsD) Average Score and Experience Subscale Score

End point title	Change From Randomization to Week 8 in 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. 6 of the 13 items ask how often participants experience different aspects of fatigue with responses from 1 (never) to 5 (always). 7 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. LS means were calculated using MMRM adjusting for treatment, investigator, visit, baseline score, treatment-by-visit and baseline score-by-visit. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	221	236	
Units: units on a scale				
least squares mean (standard error)				
Average score	-0.69 (± 0.05)	-0.67 (± 0.05)	-0.57 (± 0.05)	
Experience score	-0.66 (± 0.06)	-0.67 (± 0.06)	-0.6 (± 0.05)	

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)[15]

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 the 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	222	236	
Units: units on a scale				
least squares mean (standard error)	12.201 (± 1.218)	12.762 (± 1.225)	9.756 (± 1.188)	

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)[16]

End point description:

The Q-LES-Q-SF is a self-administered 16-item questionnaire that measures 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	222	236	
Units: percentage of maximum possible				

score				
least squares mean (standard error)	10.51 (± 0.98)	9.93 (± 0.98)	8.47 (± 0.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Treatment Emergent (TE) Suicidal Ideation and Behaviors Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Percentage of 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 (SI) was defined as a 'yes' answer to any 1 of 5 SI questions, which included a wish to be dead and 4 different categories of active SI. 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.SI and behavior are defined as 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 at risk, multiplied by 100%. 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 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: percentage of participants				
number (not applicable)				
TE of suicidal ideation (n=230, 230, 240)	3.91	3.91	3.33	
TE of suicidal behavior (n=209, 214, 226)	0	0.47	0.44	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization to Week 8 in Arizona Sexual Experiences

(ASEX) Scale

End point title	Change From Randomization to Week 8 in 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]) to 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	222	220	233	
Units: units on a scale				
least squares mean (standard error)	-1.32 (± 0.26)	-1.27 (± 0.26)	-0.79 (± 0.25)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization to Week 8 in Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

End point title	Change From Randomization to Week 8 in 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224	222	236	
Units: units on a scale				
least squares mean (standard error)	-4.7 (± 0.37)	-4.41 (± 0.38)	-3.79 (± 0.36)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization to Week 8 in Blood Pressure (BP)

End point title	Change From Randomization to Week 8 in Blood Pressure

End point description:

Blood pressure (BP) measurements were collected when the participant was in a sitting position. Three measurements of sitting BP 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. 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, 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: millimeters of mercury (mmHg)				
least squares mean (standard error)				
Sitting systolic BP	2.11 (± 0.57)	3.18 (± 0.57)	0.02 (± 0.55)	
Sitting diastolic BP	3.57 (± 0.43)	4 (± 0.43)	0.66 (± 0.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Participants Experiencing Treatment-Emergent Adverse Events as a Function of CYP2D6 Phenotype

End point title	The Percentage of Participants Experiencing Treatment-Emergent Adverse Events as a Function of CYP2D6 Phenotype[21]

End point description:

Treatment-emergent adverse events (TEAEs) were events that first occurred or worsened during the treatment phase. CYP2D6 functional phenotype was classified as poor metabolizer (PM) or non-poor metabolizer (non-PM). The percentage of participants who reported the TEAE is presented for each phenotype classification. Only TEAEs for which there was a statistically significant treatment-by-SSRI therapy interaction were included: tinnitus and influenza. A summary of serious and other non-serious adverse events regardless of causality is located in the Report of Adverse Events module. Analysis population included all randomized patients who do not discontinue from the study for the reason 'Lost to follow-up' at the first post-baseline visit.

End point type	Secondary

End point timeframe:

Through 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	140	157	
Units: percentage of participants				
number (not applicable)				
Tinnitus non-PM (n=144, 140, 157)	0	0	1.27	
Tinnitus PM (n=77, 83, 76)	0	3.61	0	
Influenza non-PM (n=144, 140, 157)	1.39	0	0.64	
Influenza PM (n=77, 83, 76)	0	2.41	0	

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 pharmacokinetics assessment. 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:

1 week, 4 weeks, and 8 weeks

End point values	LY2216684 + SSRI			
Subject group type	Subject analysis set			
Number of subjects analysed	442			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
12 mg dose (n=427) 18 mg dose (n=202)	37.8 (± 20.7) 55.3 (± 30.4)			

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[22]

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. 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, 8 weeks

Notes:

[22] - 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 mg LY2216684 + SSRI (Randomized Participants)	18 mg LY2216684 + SSRI (Randomized Participants)	Placebo + SSRI (Randomized Participants)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	230	230	240	
Units: beats per minute (bpm)				
least squares mean (standard error)	8.66 (± 0.64)	9.12 (± 0.64)	-1.41 (± 0.62)	

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-LNBM

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

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 participants 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	12 mg LY2216684 + SSRI (Randomized) AT Phase

Reporting group description:

LY2216684: 12 milligrams (mg), administered orally, once daily for 8 weeks, adjunctive to a SSRI, during the adjunctive treatment phase.
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	18 mg LY2216684 + SSRI (Randomized) AT Phase

Reporting group description:

LY2216684: 12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a SSRI, during the adjunctive treatment phase.
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 SSRI, during the adjunctive treatment phase
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 SSRI, during the adjunctive treatment phase.
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) Discontinuation Phase

Reporting group description:

Placebo: Administered orally, once daily for 8 weeks, adjunctive to a SSRI, during the adjunctive treatment phase.
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	18 mg LY2216684 + SSRI (Taper Discontinuation Phase)

Reporting group description:

LY2216684: 12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a SSRI, during the adjunctive treatment phase
Includes all randomized participants who tapered discontinuation of 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 mg LY2216684 + SSRI (Abrupt Discontinuation Phase)

Reporting group description:

LY2216684: 12 milligrams (mg), administered orally, once daily for 8 weeks, adjunctive to a SSRI
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 mg LY2216684 + SSRI (Taper Discontinuation Phase)

Reporting group description:

LY2216684: 12 milligrams (mg), administered orally, once daily for 8 weeks, adjunctive to a SSRI
Includes all randomized participants who tapered discontinuation of 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	18 mg LY2216684 + SSRI (Abrupt Discontinuation Phase)

Reporting group description:

LY2216684: 12 mg, administered orally, once daily for 1 week, followed by 18 mg, administered orally, once daily for 7 weeks, adjunctive to a SSRI, during the adjunctive treatment phase
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) Discontinuation Phase

Reporting group description:

Placebo: Administered orally, once daily for 8 weeks, adjunctive to a SSRI, during the adjunctive treatment phase.
Includes all randomized participants who 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) Discontinuation Phase

Reporting group description:

Placebo: Administered orally, once daily for 8 weeks, adjunctive to a SSRI, during the adjunctive treatment phase.
Includes all non-randomized participants who 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	12 mg LY2216684 + SSRI (Randomized) AT Phase	18 mg LY2216684 + SSRI (Randomized) AT Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 1413 (0.14%)	3 / 231 (1.30%)	2 / 230 (0.87%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
blood pressure increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	0 / 230 (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
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	0 / 230 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
colon cancer metastatic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	0 / 230 (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 carcinoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 1413 (0.07%)	0 / 231 (0.00%)	0 / 230 (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
Vascular disorders			
arteriosclerosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	1 / 230 (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
Gastrointestinal disorders			
gastritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	1 / 231 (0.43%)	0 / 230 (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
oesophageal achalasia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 1413 (0.07%)	1 / 231 (0.43%)	0 / 230 (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
Hepatobiliary disorders			
cholecystitis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	0 / 230 (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
cholelithiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	0 / 230 (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			
depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	1 / 230 (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
suicidal ideation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	1 / 231 (0.43%)	0 / 230 (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
suicide attempt			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	0 / 230 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
sialoadenitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 1413 (0.00%)	0 / 231 (0.00%)	0 / 230 (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) Discontinuation Phase
Total subjects affected by serious			

adverse events			
subjects affected / exposed	1 / 240 (0.42%)	5 / 627 (0.80%)	1 / 20 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
blood pressure increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	1 / 627 (0.16%)	0 / 20 (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
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	1 / 627 (0.16%)	0 / 20 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
colon cancer metastatic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	1 / 627 (0.16%)	0 / 20 (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
oesophageal carcinoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	0 / 627 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
arteriosclerosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	0 / 627 (0.00%)	0 / 20 (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
Gastrointestinal disorders			
gastritis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 240 (0.00%)	0 / 627 (0.00%)	0 / 20 (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 achalasia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	0 / 627 (0.00%)	0 / 20 (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
Hepatobiliary disorders			
cholecystitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	0 / 627 (0.00%)	0 / 20 (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
cholelithiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	1 / 627 (0.16%)	0 / 20 (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			
depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	0 / 627 (0.00%)	0 / 20 (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	0 / 240 (0.00%)	0 / 627 (0.00%)	0 / 20 (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 16.1			

subjects affected / exposed	1 / 240 (0.42%)	0 / 627 (0.00%)	0 / 20 (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			
sialoadenitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	1 / 627 (0.16%)	0 / 20 (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	18 mg LY2216684 + SSRI (Taper Discontinuation Phase)	12 mg LY2216684 + SSRI (Abrupt Discontinuation Phase)	12 mg LY2216684 + SSRI (Taper Discontinuation Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 107 (0.93%)	1 / 108 (0.93%)	1 / 100 (1.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
blood pressure increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
colon cancer metastatic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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 carcinoma			
alternative dictionary used:			

MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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
Vascular disorders			
arteriosclerosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 107 (0.93%)	0 / 108 (0.00%)	0 / 100 (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
Gastrointestinal disorders			
gastritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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 achalasia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	1 / 108 (0.93%)	0 / 100 (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
Hepatobiliary disorders			
cholecystitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholelithiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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			
depression			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
sialoadenitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (0.00%)	0 / 100 (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	18 mg LY2216684 + SSRI (Abrupt Discontinuation Phase)	Placebo + SSRI (Randomized) Discontinuation Phase	Placebo + SSRI (Non-randomized) Discontinuation Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	1 / 585 (0.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
blood pressure increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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
electrocardiogram qt prolonged			
alternative dictionary used:			

MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
colon cancer metastatic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	1 / 585 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oesophageal carcinoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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
Vascular disorders			
arteriosclerosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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
Gastrointestinal disorders			
gastritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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 achalasia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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
Hepatobiliary disorders			

cholecystitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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
cholelithiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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			
depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (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 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
sialoadenitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 108 (0.00%)	0 / 221 (0.00%)	0 / 585 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo + SSRI (Pre-randomized) CF Phase	12 mg LY2216684 + SSRI (Randomized) AT Phase	18 mg LY2216684 + SSRI (Randomized) AT Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	240 / 1413 (16.99%)	71 / 231 (30.74%)	73 / 230 (31.74%)
Cardiac disorders			
tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 1413 (0.28%)	16 / 231 (6.93%)	23 / 230 (10.00%)
occurrences (all)	4	16	24
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	45 / 1413 (3.18%)	8 / 231 (3.46%)	12 / 230 (5.22%)
occurrences (all)	48	9	13
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	116 / 1413 (8.21%)	22 / 231 (9.52%)	18 / 230 (7.83%)
occurrences (all)	136	28	18
Reproductive system and breast disorders			
erectile dysfunction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[1]	3 / 447 (0.67%)	2 / 86 (2.33%)	1 / 81 (1.23%)
occurrences (all)	3	2	1
Gastrointestinal disorders			
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	55 / 1413 (3.89%)	11 / 231 (4.76%)	17 / 230 (7.39%)
occurrences (all)	57	11	21
Skin and subcutaneous tissue disorders			
hyperhidrosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	17 / 1413 (1.20%)	19 / 231 (8.23%)	16 / 230 (6.96%)
occurrences (all)	17	20	16
Infections and infestations			

nasopharyngitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	43 / 1413 (3.04%)	18 / 231 (7.79%)	10 / 230 (4.35%)
occurrences (all)	45	18	10

Non-serious adverse events	Placebo + SSRI (Randomized) AT Phase	Placebo + SSRI (Non-randomized) AT Phase	Placebo + SSRI (Pre-randomized) Discontinuation Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 240 (15.00%)	100 / 627 (15.95%)	3 / 20 (15.00%)
Cardiac disorders			
tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 240 (0.00%)	3 / 627 (0.48%)	0 / 20 (0.00%)
occurrences (all)	0	4	0
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 240 (2.08%)	13 / 627 (2.07%)	0 / 20 (0.00%)
occurrences (all)	10	16	0
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	14 / 240 (5.83%)	39 / 627 (6.22%)	3 / 20 (15.00%)
occurrences (all)	16	47	3
Reproductive system and breast disorders			
erectile dysfunction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[1]	0 / 85 (0.00%)	2 / 176 (1.14%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 240 (0.42%)	13 / 627 (2.07%)	0 / 20 (0.00%)
occurrences (all)	1	13	0
Skin and subcutaneous tissue disorders			
hyperhidrosis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 240 (0.83%)	6 / 627 (0.96%)	0 / 20 (0.00%)
occurrences (all)	2	6	0
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	15 / 240 (6.25%)	34 / 627 (5.42%)	0 / 20 (0.00%)
occurrences (all)	15	37	0

Non-serious adverse events	18 mg LY2216684 + SSRI (Taper Discontinuation Phase)	12 mg LY2216684 + SSRI (Abrupt Discontinuation Phase)	12 mg LY2216684 + SSRI (Taper Discontinuation Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 107 (17.76%)	17 / 108 (15.74%)	15 / 100 (15.00%)
Cardiac disorders			
tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 107 (0.93%)	0 / 108 (0.00%)	0 / 100 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	8 / 107 (7.48%)	3 / 108 (2.78%)	5 / 100 (5.00%)
occurrences (all)	11	3	5
headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	10 / 107 (9.35%)	13 / 108 (12.04%)	7 / 100 (7.00%)
occurrences (all)	18	29	9
Reproductive system and breast disorders			
erectile dysfunction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed[1]	0 / 37 (0.00%)	0 / 37 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	6 / 107 (5.61%)	2 / 108 (1.85%)	1 / 100 (1.00%)
occurrences (all)	6	2	1

Skin and subcutaneous tissue disorders hyperhidrosis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	 4 / 107 (3.74%) 7	 0 / 108 (0.00%) 0	 1 / 100 (1.00%) 1
Infections and infestations nasopharyngitis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	 2 / 107 (1.87%) 2	 3 / 108 (2.78%) 3	 2 / 100 (2.00%) 2

Non-serious adverse events	18 mg LY2216684 + SSRI (Abrupt Discontinuation Phase)	Placebo + SSRI (Randomized) Discontinuation Phase	Placebo + SSRI (Non-randomized) Discontinuation Phase
Total subjects affected by non-serious adverse events subjects affected / exposed	 18 / 108 (16.67%)	 39 / 221 (17.65%)	 106 / 585 (18.12%)
Cardiac disorders tachycardia alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	 0 / 108 (0.00%) 0	 0 / 221 (0.00%) 0	 0 / 585 (0.00%) 0
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 / 108 (2.78%) 4 10 / 108 (9.26%) 14	 7 / 221 (3.17%) 9 26 / 221 (11.76%) 36	 34 / 585 (5.81%) 42 69 / 585 (11.79%) 108
Reproductive system and breast disorders erectile dysfunction alternative dictionary used: MedDRA 16.1 subjects affected / exposed[1] occurrences (all)	 0 / 38 (0.00%) 0	 0 / 81 (0.00%) 0	 0 / 168 (0.00%) 0
Gastrointestinal disorders			

nausea alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	5 / 108 (4.63%) 7	4 / 221 (1.81%) 4	19 / 585 (3.25%) 21
Skin and subcutaneous tissue disorders hyperhidrosis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	1 / 108 (0.93%) 3	1 / 221 (0.45%) 1	3 / 585 (0.51%) 3
Infections and infestations nasopharyngitis alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all)	3 / 108 (2.78%) 3	11 / 221 (4.98%) 11	10 / 585 (1.71%) 10

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This event is gender specific and that's why the total number of subjects exposed in this reporting group is less than the total number of subjects exposed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2012	Moved Fatigue Associated with Depression (FAsD) subscale from the secondary gatekeeper objective to additional secondary objective; changed statistical methodology; added information on potential interim analysis; Updated the details of how the sample size and power calculations are provided to ERBs.
02 August 2012	Added language for "re-screening"; 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