Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-Controlled, Relapse Prevention Study With Vilazodone in Patients With Major Depressive Disorder

Summary

EudraCT number	2012-001950-25
Trial protocol	DE FI BG
Global end of trial date	11 October 2014

Results information

Result version number	v1 (current)
This version publication date	18 November 2017
First version publication date	18 November 2017

Trial information

Trial identification

Sponsor protocol code	VLZ-MD-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01573598
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Forest Laboratories Inc, an Affilate of Allergan plc; Allergan Limited
Sponsor organisation address	Allergan Limited Marlow International The Parkway, Marlow, United Kingdom, SL7 1YL
Public contact	Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com
Scientific contact	Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com

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	17 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2014
Global end of trial reached?	Yes
Global end of trial date	11 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy, safety, and tolerability of vilazodone relative to placebo in the prevention of depression relapse in patients with major depressive disorder

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Finland: 41
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Serbia: 39
Country: Number of subjects enrolled	Ukraine: 15
Country: Number of subjects enrolled	United States: 384
Worldwide total number of subjects	563
EEA total number of subjects	125

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)	539
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The 1-2 week Screening/Wash-Out Phase was followed by the 8 week Run-In Phase of open-label treatment with vilazodone 40 mg/day. The Run-In phase included 1213 patients. The Run-In Phase was followed by the 12-week open-label Stabilization Phase; 879 patients entered the Stabilization Phase. Subsequently, 563 patients were randomized.

Period 1

Period 1 title	Double-Blind (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules from Week 22 through Week 50.

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:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules from Week 22 through Week 50.

Arm title	Vilazodone 20 mg

Arm description:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for Weeks 21 through 49, vilazodone 10 mg for Week 49, and matching placebo for Week 50.

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

Dosage and administration details:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for Weeks 21 through 49, vilazodone 10 mg for Week 49, and matching placebo for Week 50.

Arm title	Vilazodone 40 mg

Arm description:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 to 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and

matching placebo for Week 50.

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

Dosage and administration details:

Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 to 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and matching placebo for Week 50.

Number of subjects in period 1	Placebo	Vilazodone 20 mg	Vilazodone 40 mg
Started	192	185	186
Completed	136	119	121
Not completed	56	66	65
Consent withdrawn by subject	17	16	9
Adverse event, non-fatal	2	4	1
Other Reasons	4	4	5
Lost to follow-up	3	10	11
Relapse Event	23	20	25
Protocol deviation	7	12	14

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules from Week 22 through Week 50.	
Reporting group title	Vilazodone 20 mg
Reporting group description:	
Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for Weeks 21 through 49, vilazodone 10 mg for Week 49, and matching placebo for Week 50.	
Reporting group title	Vilazodone 40 mg
Reporting group description:	
Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 to 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and matching placebo for Week 50.	

Reporting group values	Placebo	Vilazodone 20 mg	Vilazodone 40 mg
Number of subjects	192	185	186
Age categorical Units: Subjects			
Adults (18-64 years)	184	174	181
From 65-84 years	8	11	5
Age Continuous | Units: years			
arithmetic mean	46.7	45.2	43.8
standard deviation	± 11.9	± 12.6	± 12.0
Gender categorical Units: Subjects			
Female	116	113	126
Male	76	72	60

Reporting group values	Total		
Number of subjects	563		
Age categorical Units: Subjects			
Adults (18-64 years)	539		
From 65-84 years	24		
Age Continuous | Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	355		
Male	208		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules from Week 22 through Week 50.	
Reporting group title	Vilazodone 20 mg
Reporting group description:	
Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 through 20, vilazodone 20 mg for Weeks 21 through 49, vilazodone 10 mg for Week 49, and matching placebo for Week 50.	
Reporting group title	Vilazodone 40 mg
Reporting group description:	
Vilazodone 10 mg for Week 1, vilazodone 20 mg for Week 2, vilazodone 40 mg for Weeks 3 to 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and matching placebo for Week 50.	

Primary: Time to First Relapse During the Double-Blind Treatment Phase (DBP)

End point title	Time to First Relapse During the Double-Blind Treatment Phase (DBP)[1]
End point description:	
Relapse is defined as meeting any 1 or more of the following: 1) Montgomery-Åsberg Depression Rating Scale (MADRS) score of ≥ 18 and meeting criteria for a major depressive episode (MDE) per the MDE Checklist; 2) MADRS total score (from 0 [absence of symptoms] to 60 [maximum severity] ≥ 18 at 2 consecutive visits (where the second visit is in the 7-14 day period after the first visit); 3) Discontinuation for insufficient therapeutic response during the DBP. Insufficient therapeutic response is defined by: a) The inability to continue in the study due to worsening of depression, as determined by a need for change in pharmacological treatment and an increase in Clinical Global Impressions–Severity (CGI-S) score (from 0 [normal state] to 7 [among the most extremely ill] of ≥ 2 compared with that obtained at Week 20; b) Need for hospitalization due to worsening of depression.	
End point type	Primary
End point timeframe:	
Randomization date (Week 20) to the relapse date, up to 28 weeks (Week 48)	

Notes:

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

End point values	Placebo	Vilazodone 20 mg	Vilazodone 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190[2]	185[3]	186[4]	
Units: Days				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)	

Notes:

[2] - No differences between treatment groups; 999 represents N/A

[3] - No differences between treatment groups; 999 represents N/A

[4] - No differences between treatment groups; 999 represents N/A

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored from informed consent signature to the end of study for each subject.

Adverse event reporting additional description:

The Run-In Phase (RIP) Safety Population consists of all screened pts who have a screening number, signed informed consent, and who took at least 1 dose of open-label vilazodone during the RIP of the study. The Double-blind (DB) Safety Population consists of all randomized pts who took at least 1 dose of DB investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo - Double Blind Phase

Reporting group description:

Vilazodone 20 mg taken orally once per day the first 4 days of Week 21, vilazodone 10 mg for the last 3 days of Week 21, and matched placebo capsules taken orally once per day from Weeks 22 through Week 50.

Reporting group title	Vilazodone 40 mg - Double Blind Phase

Reporting group description:

Vilazodone 40 mg taken orally once per day for Weeks 3 through 48, vilazodone 20 mg for the first 4 days of Week 49, vilazodone 10 mg for the last 3 days of Week 49, and matching placebo for Week 50.

Reporting group title	Vilazodone 20 mg - Double Blind Phase

Reporting group description:

Vilazodone 20 mg taken orally once per day for Weeks 21 through 48, vilazodone 10 mg for Week 49, and matching placebo for Week 50.

Serious adverse events	Placebo - Double Blind Phase	Vilazodone 40 mg - Double Blind Phase	Vilazodone 20 mg - Double Blind Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 192 (2.08%)	1 / 186 (0.54%)	5 / 185 (2.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neoplasm			
subjects affected / exposed	0 / 192 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 192 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Urine output decreased			
subjects affected / exposed	1 / 192 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 192 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
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			
Hypoaesthesia			
subjects affected / exposed	0 / 192 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical radiculopathy			
subjects affected / exposed	1 / 192 (0.52%)	0 / 186 (0.00%)	0 / 185 (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			
Chest pain			
subjects affected / exposed	1 / 192 (0.52%)	0 / 186 (0.00%)	0 / 185 (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			
Melaena			
subjects affected / exposed	1 / 192 (0.52%)	0 / 186 (0.00%)	0 / 185 (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			
Pneumothorax			
subjects affected / exposed	0 / 192 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 192 (0.00%)	1 / 186 (0.54%)	0 / 185 (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
Obstructive uropathy			
subjects affected / exposed	0 / 192 (0.00%)	1 / 186 (0.54%)	0 / 185 (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			
Suicidal ideation			
subjects affected / exposed	0 / 192 (0.00%)	0 / 186 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 192 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Musculoskeletal and connective tissue disorders			
Fibromyalgia			
subjects affected / exposed	1 / 192 (0.52%)	0 / 186 (0.00%)	0 / 185 (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
Intervertebral disc displacement			
subjects affected / exposed	1 / 192 (0.52%)	0 / 186 (0.00%)	0 / 185 (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

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

Non-serious adverse events	Placebo - Double Blind Phase	Vilazodone 40 mg - Double Blind Phase	Vilazodone 20 mg - Double Blind Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 192 (53.65%)	115 / 186 (61.83%)	101 / 185 (54.59%)
Investigations			

Weight increased			
subjects affected / exposed	4 / 192 (2.08%)	10 / 186 (5.38%)	7 / 185 (3.78%)
occurrences (all)	4	10	8
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 192 (4.69%)	18 / 186 (9.68%)	15 / 185 (8.11%)
occurrences (all)	11	26	20
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 192 (4.69%)	15 / 186 (8.06%)	13 / 185 (7.03%)
occurrences (all)	11	16	13
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 192 (7.29%)	15 / 186 (8.06%)	16 / 185 (8.65%)
occurrences (all)	16	20	19
Upper respiratory tract infection			
subjects affected / exposed	12 / 192 (6.25%)	10 / 186 (5.38%)	12 / 185 (6.49%)
occurrences (all)	16	11	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2012	(1) add recurrent depression as an inclusion criteria; (2) change the inclusion MADRS score to 26; (3) add AE assessment at Visit 1; (4) allow for changes in MADRS scores during the Screening Period; (5) change the relapse criteria and add Major Depressive Episode Checklist; (6) add justification of the use of the placebo arm in relapse prevention; (7) revise 3 exclusion criteria; (8) delete a laboratory test from the Chemistry panel; (9) add washout language; (10) add the MADRS at every visit; (11) revise the efficacy analyses section to clarify relapse criteria; (12) add the description of the MMRM approach for analysis of additional efficacy parameters; (13) adjust the assumption on relapse event rates and recalculating the power of the study; (14) update Gastrointestinal and Sedatives/Hypnotics medications
21 May 2013	change the developmental phase of the trial for Non-US countries from Phase 4 to Phase 3
27 January 2014	(1) clarify the approximate number of planned enrolled patients; (2) revise the language in the introduction related to the IB version date and adverse reactions in previous trials; (3) correct a discrepancy regarding down-titration duration at the beginning of the DBP; (4) perform an administrative update to exclusion criteria to accommodate for Non-US sites; (5) clarify open-label down-taper language; (6) update the list of anti-insomnia agents; (7) clarify the definition of CGI-S and correct the training requirements; (8) update the relapse assumptions; (9) update hypnotics and antineoplastic medications
29 September 2014	(1) add the description of sensitivity analyses on the primary efficacy parameter in response to FDA statistical comments; (2) delete the protocol deviation section; (3) add a stratification factor of US/non-US category in the primary efficacy analysis based on a FDA statistical comment; (4) add summaries on exposure, concomitant medication, and safety parameters during RIP and SP combined based on RIP Safety Population; (5) modify protocol deviation language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported