Clinical trial results:
A randomized, double-blind study comparing the efficacy and safety of trazodone OAD and venlafaxine XR in the treatment of patients with Major Depressive Disorder

Summary

EudraCT number	2011-005878-37
Trial protocol	IT AT CZ ES SK RO
Global end of trial date	25 April 2014

Results information

Result version number	v2 (current)
This version publication date	18 August 2018
First version publication date	12 August 2015
Version creation reason	• Changes to summary attachments A summary of results is uploaded replacing the CSR.
Summary attachment (see zip file)	Synopsis (2011_005878-37.pdf)

Trial information

Trial identification

Sponsor protocol code	039(C)SC11063

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02086929
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACRAF SpA
Sponsor organisation address	Piazzale della stazione, s.n.c., S.Palomba- Pomezia (Rome), Italy, 00071
Public contact	Clinical Trial Application Unit, ANGELINI ACRAF SpA, +39 0691045335, ctaunit@angelini.it
Scientific contact	Clinical Trial Application Unit, ANGELINI ACRAF SpA, +39 0691045432, ctaunit@angelini.it

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	07 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of trazodone OAD vs venlafaxine XR after an 8-week treatment period in patients with major depressive disorder (MDD).

Protection of trial subjects:

The study was performed in accordance with the protocol and the European Community CPMP guidelines of GCP for Trials on Medicinal Products [CPMP/ICH/135/1995] and applicable regulatory requirements. The study was in keeping with the requirements of the "Declaration of Helsinki" as adopted by the 18th World Medical Association (WMA) General Assembly in 1964 and with the subsequent revisions.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	21 December 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	Slovakia: 75
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Czech Republic: 72
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	Romania: 110
Worldwide total number of subjects	321
EEA total number of subjects	321

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)	304
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male and female 18-75 years, outpatients, MDD according o DMS-IV criteria, 17- item HAMD score >= 18, discontinuation of antidepressantsor proibited medications (wash out) for a period specif to taper schedule (based on 5 elimination half-life of the used medication).

Period 1

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

Blinding implementation details:

To maintain the blinding conditions of the study, trazodone OAD tablets and venlafaxine XR capsules were inserted into capsules having identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trazodone OAD

Arm description:

Trazodone once a daily administration

Arm type	Experimental
Investigational medicinal product name	Trazodone
Investigational medicinal product code	039
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One trazodone OAD 150mg tablet daily for 1 week (dose- titration) followed by one trazodone OAD 300 mg tablet daily for 8 weeks.
After 3 and 5 weeks of treatment for non-responding patients dose increases (in increments of 75 mg/day) till to reach the maximum of 450 mg/day.
According to the maximum dosage taken by the patients at the end of Treatment Phase, a 1 to 3 weeks of Tapering Period was planned for no responders.

Arm title	Venlafaxine

Arm description:

Venlafaxine XR

Arm type	Active comparator
Investigational medicinal product name	Venlafaxine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Venlafaxine XR 75 mg/die for 8 weeks. After 3 and 5 weeks of treatment for non-responding patients, dose increases (in increments of 75 mg/day) till to reach the maximum of 225 mg/day.

Number of subjects in period 1	Trazodone OAD	Venlafaxine
Started	165	156
Completed	117	121
Not completed	48	35
Consent withdrawn by subject	15	11
Adverse event, non-fatal	25	15
IMP not available	1	-
Lack of efficacy	2	2
Protocol deviation	5	7

Baseline characteristics

Reporting groups	
Reporting group title	Trazodone OAD
Reporting group description: Trazodone once a daily administration	
Reporting group title	Venlafaxine
Reporting group description: Venlafaxine XR	

Reporting group values	Trazodone OAD	Venlafaxine	Total
Number of subjects	165	156	321
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	157	147	304
From 65-84 years	8	9	17
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.8	47.9	
standard deviation	± 11.38	± 11.41	-
Gender categorical Units: Subjects			
Female	120	121	241
Male	45	35	80

End points

End points reporting groups	
Reporting group title	Trazodone OAD
Reporting group description: Trazodone once a daily administration	
Reporting group title	Venlafaxine
Reporting group description: Venlafaxine XR	

Primary: Change in HAMD-17 total score frome baseline at Visit 9/ITT	
End point title	Change in HAMD-17 total score frome baseline at Visit 9/ITT
End point description: The primary efficacy measurement was the comparison of HAMD-17 scores reported at the Visit 9 with those reported at the baseline.	
End point type	Primary
End point timeframe: At Visit 2 (baseline) and Visit 9 (Day 56).	

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	152		
Units: score on a scale				
arithmetic mean (standard deviation)	-12.9 (± 6.82)	-14.7 (± 6.56)		

Statistical analyses

Statistical analysis title	Change HAMD-17 total score from baseline V9/ITT
Statistical analysis description: Change HAMD-17 total score from baseline and at V9 in the ITT (LOCF) population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.01
Method	ANCOVA

Primary: Change in HAMD-17 total score frome baseline at Visit 9/PP	
End point title	Change in HAMD-17 total score frome baseline at Visit 9/PP

End point description:

The primary efficacy measurement was the comparison of HAMD-17 scores reported at the Visit 9 with those reported at the baseline

End point type	Primary

End point timeframe:

At Visit 2 (baseline) and Visit 9 (Day 56).

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	127		
Units: score on a scale				
arithmetic mean (standard deviation)	-15.4 (± 5.32)	-16.4 (± 5.39)		

Statistical analyses

Statistical analysis title	Change HAMD-17 total score from baseline V9/PP

Statistical analysis description:

Change HAMD-17 total score from baseline at V9 in the PP population

Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.056
Method	ANCOVA

Secondary: Change in MADRS score frome baseline at Visit 9/ITT

End point title	Change in MADRS score frome baseline at Visit 9/ITT

End point description:

Mean change from baseline (Visit 2-D0) in MADRS score at Visit 9 (D56).

End point type	Secondary

End point timeframe:

At Visit 2 (baseline)and Visit 9 (Day 56).

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	151		
Units: score on a scale				
arithmetic mean (standard deviation)	-14.4 (± 7.65)	-16.9 (± 7.65)		

Statistical analyses

Statistical analysis title	Change MADRS score from baseline V9/ITT
Statistical analysis description: Change MADRS score from baseline at V9 in the ITT population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.003
Method	ANCOVA

Secondary: Change in MADRS score frome baseline at Visit 9/PP	
End point title	Change in MADRS score frome baseline at Visit 9/PP
End point description: Mean change from baseline (Visit 2-D0) in MADRS score at Visit 9 (D56).	
End point type	Secondary
End point timeframe: At Visit 2 (baseline) and Visit 9 (Day 56).	

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	127		
Units: score on a scale				
arithmetic mean (standard deviation)	-17.1 (± 6.01)	-18.6 (± 6.58)		

Statistical analyses

Statistical analysis title	Change MADRS score from baseline V9/PP
Statistical analysis description: Change MADRS score from baseline at V9 in the PP population	
Comparison groups	Trazodone OAD v Venlafaxine

Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.018
Method	ANCOVA

Secondary: CGI-Severity of Illness/baseline-V9/ITT

End point title	CGI-Severity of Illness/baseline-V9/ITT

End point description:

The distribution of CGI-S (Clinical Global Impression-Severity of illness) and the change from baseline. The CGI-S was evaluated with a seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

End point type	Secondary

End point timeframe:

At Visit 2 (baseline) to Visit 9(Day 56).

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	152		
Units: score on a scale				
arithmetic mean (standard deviation)	-1.8 (± 1.16)	-2.1 (± 1.17)		

Statistical analyses

Statistical analysis title	Change CGI-S total score from baseline V9/ITT

Statistical analysis description:

Change CGI-S total score from baseline at V9 in the ITT (LOCF) population

Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.032
Method	ANCOVA

Secondary: CGI-Severity of Illness/baseline-V9/PP

End point title	CGI-Severity of Illness/baseline-V9/PP

End point description:

End point type	Secondary

End point timeframe:

At Visit 2 (baseline) to Visit 9 (Day 56).

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	127		
Units: score on a scale				
arithmetic mean (standard deviation)	-2.1 (± 1.06)	-2.3 (± 1.02)		

Statistical analyses

Statistical analysis title	Change CGI-S total score from baseline V9/PP
Statistical analysis description:	
Change CGI-S total score from baseline at V9 in PP population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.056 [1]
Method	ANCOVA

Notes:

[1] - Not significant

Secondary: CGI-Global improvement V9/ITT

End point title	CGI-Global improvement V9/ITT
End point description:	
The CGI-G was evaluated with a seven-point scale: 1=very much improved; 2=much improved; 3=minimaly improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.	
End point type	Secondary
End point timeframe:	
At Visit 9 (D56)	

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	152		
Units: score on a scale				
arithmetic mean (standard deviation)	2 (± 1.12)	1.7 (± 0.99)		

Statistical analyses

Statistical analysis title	CGI-G total score V9/ITT

Statistical analysis description:	
CGI- Global Improvement total score at V9 in the ITT (LOCF) population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0088
Method	ANOVA

Secondary: CGI-Global improvement V9/PP

End point title	CGI-Global improvement V9/PP
End point description:	
End point type	Secondary
End point timeframe:	
At Visit 9 (D56)	

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	127		
Units: score on a scale				
arithmetic mean (standard deviation)	1.7 (± 0.82)	1.5 (± 0.72)		

Statistical analyses

Statistical analysis title	CGI-G total score V9/PP
Statistical analysis description:	
CGI- Global Improvement total score at V9 in the PP population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0383
Method	ANOVA

Secondary: HAMD-17 responder rates V9/ITT

End point title	HAMD-17 responder rates V9/ITT
End point description:	
Responders were defined as patients with at least 50% decrease with respect to baseline on the HAMD score at Visit 9 (D56).	
End point type	Secondary

End point timeframe:
AT visit 9 /D56)

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	152		
Units: percent				
number (not applicable)	65.4	76.3		

Statistical analyses

Statistical analysis title	HAMD- 17 responder rates V9/ITT
Statistical analysis description: HAMD-17 responder rates at V9 for ITT (LOCF) population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0396
Method	Cochran-Mantel-Haenszel

Secondary: HAMD-17 responder rates V9/PP

End point title	HAMD-17 responder rates V9/PP
End point description:	
End point type	Secondary
End point timeframe: At Visit 2 (D0) and Visit 9 (D56)	

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	127		
Units: percent				
number (not applicable)	82.8	87.4		

Statistical analyses

Statistical analysis title	HAMD- 17 responder rates V9/PP
Statistical analysis description:	
HAMD-17 responder rates at V9 for PP population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2097 [2]
Method	Cochran-Mantel-Haenszel

Notes:
[2] - Not significant

Secondary: HAMD-17 remitter rates V9/ ITT

End point title	HAMD-17 remitter rates V9/ ITT
End point description:	
Remitters were defined as patients with HAMD score ≤ 7 at Visit 9 (D56)	
End point type	Secondary
End point timeframe:	
At the Visit 9 (D56)	

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	152		
Units: percent				
number (not applicable)	37.7	52		

Statistical analyses

Statistical analysis title	HAMD- 17 remitter rates V9/ITT
Statistical analysis description:	
HAMD-17 remitter rates at V9 for ITT (LOCF) population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0068
Method	Cochran-Mantel-Haenszel

Secondary: HAMD-17 remitter rates V9/ PP

End point title	HAMD-17 remitter rates V9/ PP
End point description:	

End point type	Secondary
End point timeframe: At the Visit 9 (D56)	

End point values	Trazodone OAD	Venlafaxine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	127		
Units: percent				
number (not applicable)	48.4	60.6		

Statistical analyses

Statistical analysis title	HAMD- 17 remitter rates V9/PP
Statistical analysis description: HAMD- 17 remitter rates V9 in the PP population	
Comparison groups	Trazodone OAD v Venlafaxine
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.013
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the ICF signature until 30 days after the last IMP administration.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Venlafaxine
Reporting group description: -	
Reporting group title	Trazodone OAD
Reporting group description: Trazodone once a day	

Serious adverse events	Venlafaxine	Trazodone OAD	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 156 (0.64%)	3 / 165 (1.82%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Mental impairment			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			

subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Venlafaxine	Trazodone OAD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 156 (46.79%)	83 / 165 (50.30%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cerebellopontine angle tumour			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Thyroid neoplasm			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 156 (1.28%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Orthostatic hypotension			
subjects affected / exposed	1 / 156 (0.64%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 156 (1.92%)	7 / 165 (4.24%)	
occurrences (all)	3	7	
Influenza like illness			
subjects affected / exposed	1 / 156 (0.64%)	1 / 165 (0.61%)	
occurrences (all)	1	1	

Oedema peripheral			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Swelling			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Ejaculation delayed			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 156 (0.64%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
Dry throat			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Rhinorrhoea			

subjects affected / exposed	3 / 156 (1.92%)	0 / 165 (0.00%)	
occurrences (all)	3	0	
Throat tightness			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Yawning			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Depression			
subjects affected / exposed	2 / 156 (1.28%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Derealisation			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Disturbance in sexual arousal			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Hypersomnia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Initial insomnia			
subjects affected / exposed	5 / 156 (3.21%)	0 / 165 (0.00%)	
occurrences (all)	5	0	
Insomnia			
subjects affected / exposed	3 / 156 (1.92%)	5 / 165 (3.03%)	
occurrences (all)	3	5	
Major depression			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	

Nervousness			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Suicide attempt			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Tension			
subjects affected / exposed	5 / 156 (3.21%)	0 / 165 (0.00%)	
occurrences (all)	6	0	
Terminal insomnia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 156 (0.00%)	2 / 165 (1.21%)	
occurrences (all)	0	2	
Electrocardiogram QT prolonged			
subjects affected / exposed	6 / 156 (3.85%)	9 / 165 (5.45%)	
occurrences (all)	6	9	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 156 (1.28%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Glucose urine present			

subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Urine output increased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Medication error			
subjects affected / exposed	3 / 156 (1.92%)	3 / 165 (1.82%)	
occurrences (all)	3	3	
Overdose			
subjects affected / exposed	2 / 156 (1.28%)	2 / 165 (1.21%)	
occurrences (all)	2	2	
Cardiac disorders			
Palpitations			
subjects affected / exposed	9 / 156 (5.77%)	3 / 165 (1.82%)	
occurrences (all)	9	4	
Tachycardia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	6 / 156 (3.85%)	17 / 165 (10.30%)	
occurrences (all)	6	18	
Dysgeusia			
subjects affected / exposed	1 / 156 (0.64%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	17 / 156 (10.90%)	10 / 165 (6.06%)	
occurrences (all)	19	11	
Hydrocephalus			

subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Mental impairment			
subjects affected / exposed	0 / 156 (0.00%)	2 / 165 (1.21%)	
occurrences (all)	0	2	
Sedation			
subjects affected / exposed	0 / 156 (0.00%)	4 / 165 (2.42%)	
occurrences (all)	0	4	
Somnolence			
subjects affected / exposed	0 / 156 (0.00%)	14 / 165 (8.48%)	
occurrences (all)	0	14	
Syncope			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	4 / 156 (2.56%)	0 / 165 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Diplopia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Mydriasis			

subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Photophobia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 156 (0.00%)	2 / 165 (1.21%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	1 / 156 (0.64%)	2 / 165 (1.21%)	
occurrences (all)	1	2	
Breath odour			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	3 / 156 (1.92%)	2 / 165 (1.21%)	
occurrences (all)	3	2	
Dental caries			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	4 / 156 (2.56%)	3 / 165 (1.82%)	
occurrences (all)	5	3	
Dry mouth			
subjects affected / exposed	3 / 156 (1.92%)	11 / 165 (6.67%)	
occurrences (all)	3	11	
Dyspepsia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	

Nausea			
subjects affected / exposed	22 / 156 (14.10%)	10 / 165 (6.06%)	
occurrences (all)	23	10	
Vomiting			
subjects affected / exposed	2 / 156 (1.28%)	2 / 165 (1.21%)	
occurrences (all)	2	2	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	5 / 156 (3.21%)	3 / 165 (1.82%)	
occurrences (all)	5	3	
Psoriasis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 156 (0.00%)	2 / 165 (1.21%)	
occurrences (all)	0	2	
Urinary retention			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 156 (0.64%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Myalgia			

subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Sensation of heaviness			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Chronic hepatitis C			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 156 (0.64%)	2 / 165 (1.21%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
Pyelonephritis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 156 (1.28%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	1 / 156 (0.64%)	1 / 165 (0.61%)	
occurrences (all)	1	1	
Vaginal infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	2	
Viral infection			
subjects affected / exposed	1 / 156 (0.64%)	0 / 165 (0.00%)	
occurrences (all)	2	0	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	2 / 156 (1.28%)	0 / 165 (0.00%)	
occurrences (all)	2	0	
Increased appetite			
subjects affected / exposed	0 / 156 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2012	The substantial amendment no. 1/0 (June 28th, 2012) proposed changes as requested by the Voluntary Harmonized Procedure (VHP). It aimed to introduce further safety precautions in terms of study procedures and selection of study population. Additional procedures (haematology and serum chemistry tests) for the safety monitoring of the patients were implemented at visit 4 and visit 6. A new inclusion criteria limiting the enrolment to patients ≤75 years and a new exclusion criteria avoiding the enrolment of subjects with high blood pressure were introduced.
10 October 2012	The substantial amendment no. 2 (October 10th, 2012) was made to submit an updated version of the IMPD (Investigational Medicianl Product Dossier). The new IMPD (Ver. 2.0 of October 9th, 2012) included new stability data on the IMPs derived from previously planned stability studies.
07 June 2013	The amendment no. 3/0 (June 7th, 2013) proposed changes regarding the IMPD and IB. The new IMPD (Ver. 3.0 of June 3rd, 2013) included changes related to IMPs storage condition, Marketing Authorization status of trazodone OAD in Europe and long term stability studies. The new IB (ver. 7.0 of March 26th, 2013) included changes related to non-clinical pharmacological data and post-marketing experience in USA. The new data did not impact on the safety profile of the trazodone and on the information to be given to the patients..
10 June 2013	The Amendment no. 4/0 (June 10th, 2013) proposed changes to the Study Protocol, Study Synopsis, Information sheet/Informed Consent, Letter to the General Practitioner. Relevant sections of these documents included changes regarding Sponsor Personnel, contact details of a vendor, side effects, special warnings and precautions for use of the reference product (venlafaxine) accordingly to the new SPC approved in April 2013 in Italy. The amendment included also an updated version of the IB (ver. 7.0 of March 26th, 2013).
24 February 2014	The Amendment no. 5/0 (February 24th, 2014) proposed to replace the Principal Investigator of an Italian site. This Amendment was applied only to the Italian site which it refers to.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported