Clinical trial results:
Efficacy and safety of tianeptine oral administration (25 to 50 mg/day) in elderly patients suffering from Major Depressive Disorder.
A 8-week, randomized, double-blind, flexible-dose, parallel groups, placebo-controlled, international, multicentre study with escitalopram as active control, followed by an optional double-blind extension treatment period of 16 weeks.

Summary

EudraCT number	2012-005612-26
Trial protocol	SK FI EE BG
Global end of trial date	13 January 2016

Results information

Result version number	v1 (current)
This version publication date	15 October 2016
First version publication date	15 October 2016

Trial information

Trial identification

Sponsor protocol code	CL3-01574-237

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50, rue Carnot, Suresnes, France,
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier (I.R.I.S.), +33 1 55 72 43 66, clinicaltrials@servier.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2016
Global end of trial reached?	Yes
Global end of trial date	13 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the antidepressant efficacy of an 8-week tianeptine oral administration in elderly out-patients suffering from Major Depressive Disorder compared to placebo. The assay sensitivity will be evaluated comparing escitalopram to placebo.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	28 October 2013
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	France: 12
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Mexico: 43
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Slovakia: 37
Country: Number of subjects enrolled	Bulgaria: 26

Country: Number of subjects enrolled	Estonia: 29
Country: Number of subjects enrolled	Finland: 89
Worldwide total number of subjects	311
EEA total number of subjects	242

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)	0
From 65 to 84 years	310
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Investigators were General Practitioners, specialists in psychiatry.

Pre-assignment

Screening details:

Male or female out-patients, ≥ 65-year old, fulfilling DSM-IV-TR criteria for a moderate to severe episode of a recurrent major depressive disorder, with Hamilton depression rating scale 17 items (HAM-D) total score ≥ 22 and clinical global impression (CGI) severity of illness score ≥ 4.

Period 1

Period 1 title	Double-blind treatment period of 8 weeks
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Tianeptine

Arm description:

All patients received 25 mg/day of tianeptine during the first 2 weeks of treatment. At W2, patients with insufficient clinical improvement according to a blind pre-determined clinical improvement criterion received 50 mg/day. After W2, the 25 mg or 50 mg dose was maintained up to W8.

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

Dosage and administration details:

Capsules of 12.5 or 25 mg of tianeptine, taken orally twice daily (one capsule in the morning and one capsule in the evening before meals).
For patients receiving tianeptine 25 mg daily at inclusion (W0), a potential adjustment to 50 mg daily might occur at Week-2 (W2) using pre-determined fixed criterion, in double-blind conditions (neither the investigator, neither the sponsor staff, nor the patients knew whether the dose had been increased) in case of insufficient improvement of depressive symptoms. Patients with sufficient improvement remained on tianeptine 25 mg daily. During tapering period, dose of tianeptine was unchanged.

Arm title	Escitalopram

Arm description:

All patients received a starting dosage of 5 mg/day during the first 2 weeks of treatment. At W2, all patients increased to 10 mg/day (mandatory adjustment). At the end of the study or in case of premature study withdrawal after W2, all patients received 5 mg/day for the last week (tapering period).

Arm type	Active control to assay sensitivity
Investigational medicinal product name	Escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsule of 5 mg or 10 mg of escitalopram or placebo, taken orally twice daily (one escitalopram capsule in the morning and one placebo capsule in the evening before meals). Patients received 5 mg daily from W0 to W2, then 10 mg daily from W2. A one-week tapering period at 5 mg/day was planned to avoid

possible withdrawal reactions.

Arm title	Placebo

Arm description:

Potential or mandatory dose increase (tianeptine and escitalopram groups, respectively) and dose decrease (escitalopram group) were in blind condition.

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

Dosage and administration details:

One capsule taken orally twice daily (one capsule in the morning and one capsule in the evening before meals).

Number of subjects in period 1	Tianeptine	Escitalopram	Placebo
Started	105	99	107
Completed	97	88	91
Not completed	8	11	16
Adverse event, non-fatal	3	6	6
Non medical reasons	3	2	5
Lack of efficacy	2	2	5
Protocol deviation	-	1	-

Period 2	
Period 2 title	Optional extension period of 16 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes

Arm title	Tianeptine

Arm description:

To continue in the optional extension period, patients had to be responder to treatment according to HAM-D total score at W8 (decrease from baseline in HAM-D total score of at least 50%). At W12, only patients with a Clinical Global Impression (CGI) global improvement (item 2) ≤ 2 could continue in the optional extension period up to W24.

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

Dosage and administration details:

Capsules of 12.5 or 25 mg of tianeptine, taken orally twice daily (one capsule in the morning and one capsule in the evening before meals).
The tianeptine dose fixed in blind condition at W2 according to clinical improvement (25 mg/day or 50 mg/day)remained unchanged during the optional extension period. The dose of tianeptine was unchanged during the tapering period (end of the study or in case of premature study discontinuation).

Arm title	Escitalopram

Arm description:

To continue in the optional extension period, patients had to be responder to treatment according to HAM-D total score at W8 (decrease from baseline in HAM-D total score of at least 50%). At W12, only patients with a Clinical Global Impression (CGI) global improvement (item 2) ≤ 2 could continue in the optional extension period up to W24.

Arm type	Active control to assay sensitivity
Investigational medicinal product name	Escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsule of 5 mg or 10 mg of escitalopram or placebo, taken orally twice daily (one escitalopram capsule in the morning and one placebo capsule in the evening before meals).
During the optional extension period, the patients received 10 mg/day. A one-week tapering period at 5 mg/day was planned to avoid possible withdrawal reactions at the end of the study or in case of premature study discontinuation.

Arm title	Placebo

Arm description:

To continue in the optional extension period, patients had to be responder to treatment according to HAM-D total score at W8 (decrease from baseline in HAM-D total score of at least 50%). At W12, only patients with a Clinical Global Impression (CGI) global improvement (item 2) ≤ 2 could continue in the optional extension period up to W24.

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

Dosage and administration details:

One capsule taken orally twice daily (one capsule in the morning and one capsule in the evening before meals).

Number of subjects in period 2[1]	Tianeptine	Escitalopram	Placebo
Started	77	75	57
Completed	71	69	48
Not completed	6	6	9
Adverse event, non-fatal	1	2	2
Lack of efficacy	4	1	5
Protocol deviation	1	-	-
Non medical reasons	-	3	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: To continue in the optional extension period, patients had to be responder to treatment according to HAM-D total score at W8 (decrease from baseline in HAM-D total score of at least 50%). At W12, only patients with a Clinical Global Impression (CGI) global improvement (item 2) ≤ 2 could continue in the optional extension period up to W24. 20 patients in the tianeptine group, 13 patients in the escitalopram group and 34 patients in the
placebo group did not enter the optional extension period.

Period 3

Period 3 title	Tapering period of 1 week
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Tianeptine

Arm description:

During tapering period, dose of tianeptine was unchanged. The tapering period was planned after W2 to avoid discontinuation symptoms of escitalopram as recommended in the SmPC of escitalopram.

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

Dosage and administration details:

Capsules of 12.5 or 25 mg of tianeptine, taken orally twice daily (one capsule in the morning and one capsule in the evening before meals).
The tianeptine dose fixed in blind condition at W2 according to clinical improvement (25 mg/day or 50 mg/day) remained unchanged during the tapering period (end of the study or in case of premature study discontinuation).

Arm title	Escitalopram

Arm description:

The tapering period was planned after W2 to avoid discontinuation symptoms of escitalopram as recommended in the SmPC of escitalopram. Only escitalopram dose was decreased during this period.

Arm type	Active control to assay sensitivity

Investigational medicinal product name	Escitalopram
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsule of 5 mg or 10 mg of escitalopram or placebo, taken orally twice daily (one escitalopram capsule in the morning and one placebo capsule in the evening before meals).
From W2, all patients received 10 mg/day. After W2, a one-week tapering period at 5 mg/day was planned to avoid possible withdrawal reactions.

Arm title	Placebo

Arm description:

The tapering period planned to follow the SmPC of escitalopram was in blind condition.

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

Dosage and administration details:

One capsule taken orally twice daily (one capsule in the morning and one capsule in the evening before meals).

Number of subjects in period 3	Tianeptine	Escitalopram	Placebo
Started	71	69	48
Completed	71	69	47
Not completed	0	0	1
Lack of efficacy	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Tianeptine
Reporting group description:	
All patients received 25 mg/day of tianeptine during the first 2 weeks of treatment. At W2, patients with insufficient clinical improvement according to a blind pre-determined clinical improvement criterion received 50 mg/day. After W2, the 25 mg or 50 mg dose was maintained up to W8.	
Reporting group title	Escitalopram
Reporting group description:	
All patients received a starting dosage of 5 mg/day during the first 2 weeks of treatment. At W2, all patients increased to 10 mg/day (mandatory adjustment). At the end of the study or in case of premature study withdrawal after W2, all patients received 5 mg/day for the last week (tapering period).	
Reporting group title	Placebo
Reporting group description:	
Potential or mandatory dose increase (tianeptine and escitalopram groups, respectively) and dose decrease (escitalopram group) were in blind condition.	

Reporting group values	Tianeptine	Escitalopram	Placebo
Number of subjects	105	99	107
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)	0	0	0
From 65-84 years	105	98	107
85 years and over	0	1	0
Age continuous Units: years			
arithmetic mean	70.2	70.3	70.8
standard deviation	± 4.3	± 4.9	± 5.1
Gender categorical Units: Subjects			
Female	71	74	80
Male	34	25	27

Reporting group values	Total		
Number of subjects	311		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	310		
85 years and over	1		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	225		
Male	86		

End points

End points reporting groups

Reporting group title	Tianeptine

Reporting group description:

All patients received 25 mg/day of tianeptine during the first 2 weeks of treatment. At W2, patients with insufficient clinical improvement according to a blind pre-determined clinical improvement criterion received 50 mg/day. After W2, the 25 mg or 50 mg dose was maintained up to W8.

Reporting group title	Escitalopram

Reporting group description:

All patients received a starting dosage of 5 mg/day during the first 2 weeks of treatment. At W2, all patients increased to 10 mg/day (mandatory adjustment). At the end of the study or in case of premature study withdrawal after W2, all patients received 5 mg/day for the last week (tapering period).

Reporting group title	Placebo

Reporting group description:

Potential or mandatory dose increase (tianeptine and escitalopram groups, respectively) and dose decrease (escitalopram group) were in blind condition.

Reporting group title	Tianeptine

Reporting group description:

To continue in the optional extension period, patients had to be responder to treatment according to HAM-D total score at W8 (decrease from baseline in HAM-D total score of at least 50%). At W12, only patients with a Clinical Global Impression (CGI) global improvement (item 2) ≤ 2 could continue in the optional extension period up to W24.

Reporting group title	Escitalopram

Reporting group description:

To continue in the optional extension period, patients had to be responder to treatment according to HAM-D total score at W8 (decrease from baseline in HAM-D total score of at least 50%). At W12, only patients with a Clinical Global Impression (CGI) global improvement (item 2) ≤ 2 could continue in the optional extension period up to W24.

Reporting group title	Placebo

Reporting group description:

To continue in the optional extension period, patients had to be responder to treatment according to HAM-D total score at W8 (decrease from baseline in HAM-D total score of at least 50%). At W12, only patients with a Clinical Global Impression (CGI) global improvement (item 2) ≤ 2 could continue in the optional extension period up to W24.

Reporting group title	Tianeptine

Reporting group description:

During tapering period, dose of tianeptine was unchanged. The tapering period was planned after W2 to avoid discontinuation symptoms of escitalopram as recommended in the SmPC of escitalopram.

Reporting group title	Escitalopram

Reporting group description:

The tapering period was planned after W2 to avoid discontinuation symptoms of escitalopram as recommended in the SmPC of escitalopram. Only escitalopram dose was decreased during this period.

Reporting group title	Placebo

Reporting group description:

The tapering period planned to follow the SmPC of escitalopram was in blind condition.

Primary: HAM-D total score (main analysis)

End point title	HAM-D total score (main analysis)

End point description:

The treatment difference between tianeptine and placebo was studied in the FAS from the HAM-D total score expressed in terms of change from baseline to W8, using a two-way analysis of covariance (ANCOVA) model (including the three treatment groups).

Analysis include the fixed, categorical effects of treatment, the random categorical effect of centre as well as the continuous, fixed covariate of baseline HAM-D total score.
Missing data at W8 were imputed using LOCF approach.

End point type	Primary

End point timeframe:

The primary efficacy criterion was the HAM-D 17 total score expressed mainly in term of change from baseline to W8.

End point values	Tianeptine	Escitalopram	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105[1]	98[2]	106[3]	
Units: score				
arithmetic mean (standard deviation)	-13.4 (± 7.4)	-13.6 (± 7.2)	-9.5 (± 6.9)	

Notes:

[1] - Full analysis Set
Missing data at W8 were imputed using the Last Observation Carried Forward (LOCF)
[2] - Full Analysis Set
Missing data at W8 were imputed using the Last Observation Carried Forward (LOCF)
[3] - Full Analysis Set
Missing data at W8 were imputed using the Last Observation Carried Forward (LOCF)

Statistical analyses

Statistical analysis title	Main analysis (Tianeptine versus placebo)

Statistical analysis description:

Analysis of covariance model on factors treatment and centre (random effect) with baseline HAM-D total score as covariate.

Comparison groups	Tianeptine v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.17
upper limit	5.51
Variability estimate	Standard error of the mean
Dispersion value	0.85

Statistical analysis title	Assay sensitivity (escitalopram vs placebo)

Statistical analysis description:

Escitalopram was compared to placebo using strictly the same strategy as for the comparison between tianeptine and placebo

Comparison groups	Escitalopram v Placebo

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.39
upper limit	5.79
Variability estimate	Standard error of the mean
Dispersion value	0.86

Notes:

[4] - Analysis of covariance model on factors treatment and centre (random effect) with baseline HAM-D total score as covariate.

Primary: HAM-D total score (sensitivity analysis)

End point title	HAM-D total score (sensitivity analysis)

End point description:

Sensitivity analysis to the method of handling missing data: MMRM analysis in all patients of the FAS. Tianeptine and escitalopram were compared to placebo in the FAS on the change from baseline to W8 of HAM-D total score, using a restricted maximum likelihood (REML)-based, mixed-effects repeated measures approach (MMRM) using all the longitudinal observations at each post-baseline visit (W2, W4, W6 and W8) expressed as change from baseline. Analysis included the fixed, categorical effects of treatment, visit and treatment-by-visit interaction, the random categorical effect of centre as well as the continuous, fixed covariate of baseline.

End point type	Primary

End point timeframe:

The primary efficacy criterion was the HAM-D 17 total score expressed mainly in term of change from baseline to W8.

End point values	Tianeptine	Escitalopram	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	99[5]	90[6]	96[7]	
Units: score				
arithmetic mean (standard deviation)	-13.9 (± 7.4)	-14.5 (± 6.4)	-10.4 (± 6.4)	

Notes:

[5] - FAS patients with HAM-D total score both at baseline and W8

[6] - FAS patients with HAM-D total score both at baseline and W8

[7] - FAS patients with HAM-D total score both at baseline and W8

Statistical analyses

Statistical analysis title	Sensitivity analysis (Tianeptine vs placebo)

Statistical analysis description:

Maximum likelihood (REML)-based, mixed-effects repeated measures approach (MMRM) using all the longitudinal observations at each post-baseline visit (W2, W4, W6 and W8) expressed as change from baseline.
Analysis included the fixed, categorical effects of treatment, visit and treatment-by-visit interaction, the random categorical effect of centre as well as the continuous, fixed covariate of baseline.

Comparison groups	Tianeptine v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.84
upper limit	5.47
Variability estimate	Standard error of the mean
Dispersion value	0.92

Statistical analysis title	Sensitivity analysis (escitalopram vs placebo)
Comparison groups	Escitalopram v Placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.67
upper limit	6.4
Variability estimate	Standard error of the mean
Dispersion value	0.95

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported at each visit over the whole duration of the study. Adverse events presented here are those reported during the W0-W25 treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Tianeptine
Reporting group description: -	
Reporting group title	Escitalopram
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Tianeptine	Escitalopram	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 105 (1.90%)	2 / 98 (2.04%)	3 / 107 (2.80%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 105 (0.00%)	1 / 98 (1.02%)	0 / 107 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 105 (0.00%)	1 / 98 (1.02%)	0 / 107 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 105 (0.95%)	0 / 98 (0.00%)	0 / 107 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Paraesthesia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 98 (0.00%)	1 / 107 (0.93%)
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			
Abdominal pain upper			
subjects affected / exposed	0 / 105 (0.00%)	1 / 98 (1.02%)	0 / 107 (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			
Agitation			
subjects affected / exposed	0 / 105 (0.00%)	1 / 98 (1.02%)	0 / 107 (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
Panic attack			
subjects affected / exposed	0 / 105 (0.00%)	0 / 98 (0.00%)	1 / 107 (0.93%)
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	0 / 105 (0.00%)	1 / 98 (1.02%)	0 / 107 (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
Bradyphrenia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 98 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 105 (0.00%)	0 / 98 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			

subjects affected / exposed	0 / 105 (0.00%)	0 / 98 (0.00%)	1 / 107 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 98 (0.00%)	0 / 107 (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: 3.5 %

Non-serious adverse events	Tianeptine	Escitalopram	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 105 (48.57%)	63 / 98 (64.29%)	53 / 107 (49.53%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 105 (0.00%)	5 / 98 (5.10%)	2 / 107 (1.87%)
occurrences (all)	0	5	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 105 (2.86%)	9 / 98 (9.18%)	12 / 107 (11.21%)
occurrences (all)	3	9	14
Headache			
subjects affected / exposed	13 / 105 (12.38%)	17 / 98 (17.35%)	6 / 107 (5.61%)
occurrences (all)	17	18	10
Somnolence			
subjects affected / exposed	1 / 105 (0.95%)	4 / 98 (4.08%)	0 / 107 (0.00%)
occurrences (all)	1	4	0
Tremor			
subjects affected / exposed	0 / 105 (0.00%)	5 / 98 (5.10%)	2 / 107 (1.87%)
occurrences (all)	0	5	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 105 (3.81%)	4 / 98 (4.08%)	1 / 107 (0.93%)
occurrences (all)	4	4	1

Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 105 (2.86%)	1 / 98 (1.02%)	5 / 107 (4.67%)
occurrences (all)	4	1	5
Diarrhoea			
subjects affected / exposed	0 / 105 (0.00%)	4 / 98 (4.08%)	3 / 107 (2.80%)
occurrences (all)	0	4	3
Dry mouth			
subjects affected / exposed	3 / 105 (2.86%)	8 / 98 (8.16%)	5 / 107 (4.67%)
occurrences (all)	3	8	5
Flatulence			
subjects affected / exposed	4 / 105 (3.81%)	4 / 98 (4.08%)	2 / 107 (1.87%)
occurrences (all)	4	4	2
Nausea			
subjects affected / exposed	10 / 105 (9.52%)	12 / 98 (12.24%)	6 / 107 (5.61%)
occurrences (all)	10	13	6
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 105 (0.95%)	5 / 98 (5.10%)	1 / 107 (0.93%)
occurrences (all)	1	5	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 105 (2.86%)	4 / 98 (4.08%)	1 / 107 (0.93%)
occurrences (all)	3	4	1
Insomnia			
subjects affected / exposed	1 / 105 (0.95%)	4 / 98 (4.08%)	2 / 107 (1.87%)
occurrences (all)	1	4	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 105 (2.86%)	1 / 98 (1.02%)	4 / 107 (3.74%)
occurrences (all)	3	1	5
Back pain			
subjects affected / exposed	1 / 105 (0.95%)	4 / 98 (4.08%)	0 / 107 (0.00%)
occurrences (all)	1	4	0
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 105 (3.81%) 4	1 / 98 (1.02%) 1	2 / 107 (1.87%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2013	Applicable to all countries. It mainly concerned the implementation of the changes related to the revision (dated 02 October 2013) of escitalopram SmPC. According to this revision, one non selection or non-inclusion criterion was added for patients with angle-close glaucoma or history of glaucoma and a caution was warranted for concomitant use of medicinal products inducing hypokalaemia/hypomagnesaemia as these conditions increased the risk of malignant arrhythmias with study drugs. One other change implemented with this amendment was the update of the Declaration of Helsinki to be in accordance with the revised version of Fortaleza, October 2013. Secondary objectives of this amendment were to complete or correct the following information: - Conditions of storage of the treatments. - Antihistamines with central effects in the list of forbidden treatments due to their possible action on the central nervous system. - Doses of the benzodiazepines authorized as concomitant medications (equivalent to 10 mg of diazepam). - Collected blood volumes and interpretation of hepatitis B serology status. - Use of the computerized medical file. - MINI and CGI scales according to the final e-CRF format.
22 October 2014	Three countries participating to the study were added (Bulgaria, Poland and South Africa) and one country was removed (Argentina).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported