Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**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.**
Test drug code	**S 01574**
Indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-01574-237**
Study initiation date	**28 October 2013**
Study completion date	**13 January 2016**
International coordinator	[redacted]
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**30 June 2016**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product: STABLON** **Name of Active Ingredient: TIANEPTINE**		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: 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.

Protocol No.: CL3-01574-237

EudraCT No.: 2012-005612-26

The description of the study protocol given hereafter includes the modifications of the two substantial amendments to the protocol.

National coordinators:

[redacted]

Study centres:

Forty-four centres located in 10 countries included 311 patients: 6 centres in Bulgaria (26 patients included), 6 centres in Estonia (29 patients included), 4 centres in Finland (89 patients included), 3 centres in France (12 patients included), 4 centres in Republic of Korea (23 patients included), 1 centre in Malaysia (3 patients included), 5 centres in Mexico (43 patients included), 4 centres in Poland (10 patients included), 8 centres in Romania (39 patients included) and 3 centres in Slovakia (37 patients included).

Publication (reference): Not Applicable

Studied period:	**Phase of development of the study:**
Initiation date: 28 October 2013 (date of first visit first patient) Completion date: 13 January 2016 (date of last visit last patient)	Phase III

Objectives:

Primary objective:

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

Secondary objectives:

- To study tianeptine acceptability in this population after 8 weeks of treatment
- To study tianeptine effects on patient's social functioning after 8 weeks of treatment
- To obtain additional efficacy data in this population after 6 months of treatment
- To obtain additional acceptability data in this population after 6 months of treatment

Methodology:
Target population:

- Elderly (≥ 65-years of age) out-patients, diagnosed with a recurrent Major Depressive Disorder (DSM-IV-TR) and a moderate to severe current episode.

Study design:

- International multicentre, development Phase III study.
- 8-week, double-blind, randomised, placebo and escitalopram controlled, parallel-group study (flexible dose of tianeptine: 25 or 50 mg/day from W2, depending on a blind pre-determined clinical improvement criterion).
- Followed by an optional 16-week, double-blind extension period (only for patients considered as responders to treatment at W8 and W12).

Stratification: On centre.

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned:
Total planned: 300 patients randomised to 3 parallel groups according to a balanced ratio (100 patients by treatment group).
Included: 311 patients:

- 105 patients in the tianeptine group
- 99 patients in the escitalopram group
- 107 patients in the placebo group

Diagnosis and main criteria for inclusion:
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.

Test drug:
Tianeptine (S 01574): 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.
Batch No: L0047920, L0048789, L0050030, L0052945, L0052974, L0052991, L0056172, L0056246, L0056248, L0056507, L0056800, L0056855, L0057962, L0057990, L0057992.

Comparator (Reference product and/or placebo):

- Placebo: capsules taken orally twice daily (one capsule in the morning and one capsule in the evening before meals).
- Escitalopram: 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.

Duration of treatment:
Run-in period: 3 to 7 days between selection visit (ASSE) and W0.
Double-blind treatment period: 8 weeks (from W0 to W8 visit).
Optional extension double-blind treatment period: 16 weeks (from W8 to W24 visit), only for patients considered by investigators as responders to treatment at W8. At W12, only patients presenting with a clinical CGI global improvement score ≤ 2 were allowed to continue further in the extension period.
Tapering treatment period: 1 week, starting either after the 8-week double-blind treatment period for patients not continuing in the extension period or after the extension double-blind period for patients continuing in this optional part or in case of premature withdrawal occurred after W2, ending at WDOT visit.
Wash-out / follow-up period: 1 week after the last treatment intake.

Criteria for evaluation:

Efficacy measurements:

Primary efficacy criterion:

Hamilton depression rating scale 17 items (HAM-D): rated by the investigators at ASSE, W0, W2, W4, W6, W8 or in case of study withdrawal on the W0-W8 period.

The main analytical approach was the HAM-D total score expressed in terms of change from baseline to W8.

Response to treatment was defined as a decrease from baseline in the HAM-D total score of at least 50%.

Secondary efficacy criteria:

- Clinical global impression (CGI) scale: severity of illness, global improvement or efficacy index scores: rated by the investigators at ASSE and W0 (severity of illness only), then at W2, W4, W6, W8, W12, W16, W20, W24 or in case of study withdrawal.
- Hospital anxiety and depression (HAD) scale: filled in by the patient at ASSE, W2, W8 or in case of study withdrawal on the W0-W8 period.
- Social functioning: Sheehan disability scale (SDS): filled in by the patient at ASSE, W2, W8 or in case of study withdrawal on the W0-W8 period.

Safety measurements:

- Adverse events: at each visit from ASSE or in case of premature withdrawal.
- Laboratory parameters: at ASSE, W8 and W24 or in case of premature withdrawal for all parameters except for thyroid hormones, and serology for hepatitis A, B and C at selection only.
- Vital signs (sitting systolic and diastolic blood pressure, heart rate): at each visit from ASSE or in case of premature withdrawal.
- Body weight and body mass index: at ASSE, W0, W4, W8, W24 or in case of premature withdrawal (height at ASSE only).

Statistical methods:

Analysis Sets:

- Randomised Set (RS): all included and randomised (according to IRS procedure) patients.
- Full Analysis Set (FAS): all patients of the RS having taken at least one dose of IMP and having a value at baseline and at least one post-baseline value for the primary efficacy criterion on the W0-W8 period.
- Safety Set (SS): all included patients having taken at least one dose of IMP.

Efficacy analysis:

Primary criterion:

Primary analysis:

Superiority of tianeptine compared with placebo after an 8-week treatment period was assessed in patients of the FAS on the change from baseline to W8 of HAM-D total score, using a two-way analysis of covariance (ANCOVA) model according to last observation carried forward (LOCF) method. Analysis included 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. Sensitivity analyses regarding the method of handling missing data and the adjustment of covariates included mixed-effects model for repeated measures (MMRM) and one-way analysis of variance (ANOVA) model. Escitalopram was compared with placebo (as an assay sensitivity analysis) using strictly the same strategy.

Secondary analysis:

Response to treatment was derived from HAM-D total score at W8 according to LOCF approach. Comparison between treatment groups and placebo were analysed with a Chi-Square test on response to treatment results.

Secondary criteria:

CGI: comparison between treatment groups and placebo was assessed with a two-sided Student's t-test for independent samples and a Mann-Whitney test with normal approximation and correction for continuity on CGI severity of illness and CGI global improvement values at W8 according to LOCF approach. Comparison between treatment groups and placebo was also assessed with a Chi-Square test on the response to treatment (CGI global improvement score = 1 or 2) values at W8, according to LOCF approach.

HAD scale and SDS scale: descriptive statistics were provided by treatment group in the FAS on the W0-W8 using the LOCF approach.

Safety analysis: Descriptive statistics were provided in the Safety Set on the W0-W9/WEND period and W0-W25/WEND period.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Summary of patient disposition

	Tianeptine (N = 105)	Placebo (N = 107)	Escitalopram (N = 99)	All (N = 311)
Included / randomized	**105**	**107**	**99**	**311**
Withdrawn on W0-W8 due to	**8 (7.6%)**	**16 (15.0%)**	**11 (11.1%)**	**35 (11.3%)**
- adverse event	3	6	6	15
- non-medical reason	3	5	2	10
- lack of efficacy	2	5	2	9
- protocol deviation	-	-	1	1
Withdrawn on W8-W24 due to	**6 (5.7%)**	**9 (8.4%)**	**6 (6.1%)**	**21 (6.8%)**
- lack of efficacy	4	5	1	10
- adverse event	1	2	2	5
- non-medical reason	-	2	3	5
- protocol deviation	1	-	-	1
Withdrawn on tapering period	**-**	**1 (0.9%)**	**-**	**1 (0.3%)**
- lack of efficacy	-	1	-	1
Completed the W0-W8 period	**97 (92.4%)**	**91 (85.0%)**	**88 (88.9%)**	**276 (88.7%)**
Ongoing in the extension period	**77 (73.3%)**	**57 (53.3%)**	**75 (75.8%)**	**209 (67.2%)**
Completed the W8-W24 period	**71 (67.6%)**	**48 (44.9%)**	**69 (69.7%)**	**188 (60.5%)**
Full Analysis Set (FAS)	**105 (100%)**	**106 (99.1%)**	**98 (99.0%)**	**309 (99.4%)**
Safety Set (SS)	**105 (100%)**	**107 (100%)**	**98 (99.0%)**	**310 (99.7%)**

A total of 311 patients was included and randomised in the study: 105 in the tianeptine group, 99 in the escitalopram group and 107 in the placebo group. Among the randomised patients, 276 (88.7%) completed the W0-W8 period, 275 (88.4%) completed the W0-W9 period, and 188 (60.5%) completed the W0-W24 period.

Premature withdrawals occurred in 36 patients (11.6%) during the W0-W9 period (15 due to adverse events, 10 due to lack of efficacy, 10 for non-medical reason and 1 due to protocol deviation) and in 57 patients (18.3%) during the W0-W25 period (20 due to adverse events, 20 due to lack of efficacy, 15 for non-medical reason and 2 due to protocol deviation). For both periods, W0-W9 and W0-W25, the rate of study withdrawals was lower in the tianeptine group (7.6% and 13.3%, respectively) than in the placebo group (15.9% and 24.3%, respectively), mainly related to lack of efficacy (1.9% and 5.7% respectively with tianeptine *versus* 5.6% and 10.3% with placebo). In the same way, for both periods, the rate of study withdrawals was lower in the escitalopram group (11.1% and 17.2%, respectively) than in the placebo group (15.9% and 24.3%, respectively), mainly related to lack of efficacy (2.0% and 3.0% respectively with escitalopram *versus* 5.6% and 10.3% with placebo).

Protocol deviations were reported in 57 patients (18.3%) before or at W0, in 56 patients (18.0%) during the W0-W8 period and in 72 patients (23.2%) during the W0-W24 period. The most frequent reason for protocol deviation at each period concerned laboratory parameters assessments (36 patients [11.6%] at W0, 37 patients [11.9%] during W0-W8 and 48 patients [15.4%] during W0-W24). Rate of protocol deviations was comparable between treatment groups.

BASELINE CHARACTERISTICS

Demographic and baseline characteristics in the RS were in line with inclusion criteria defined for the study and were comparable between treatment groups. All patients were at least 65 years old. Mean (± SD) age was 70.4 (± 4.8) years old and most patients were between 65 and 74 years old (80.4%). Patients were female for 72.4% of them.

All patients had a recurrent Major Depressive Disorder (MDD) according to DSM-IV-TR with a current major depressive episode (MDE). Patients had depressive disease for 19.2 (± 13.0) years on average (median 15.2 years) and had 2.6 (± 1.9) previous depressive episodes at ASSE. The last episode occurred 84.0 (± 102.5) months ago on average (median 51.9 months) with a shorter time interval in the tianeptine group (73.0 (± 87.3) months, median: 36.5 months) than in the other 2 treatment groups. The current MDE lasted for 4.5 (± 3.0) months on average (median 3.7 months).

Patients were previously treated with at least one psychotropic treatment (40.5% of patients) including antidepressants (34.7%) and anxiolytics (9.6%).

At inclusion, patients were taken anxiolytics (benzodiazepine derivatives) for 13.2% of them or hypnotics and sedatives for 6.4% of them.

Main frequent previous medical histories other than MDD included hypertension in 48.9% of patients, hypercholesterolemia in 19.0% of patients and type 2 diabetes mellitus in 14.1% of patients.

SUMMARY – CONCLUSIONS (Cont'd)

EXTENT OF EXPOSURE

In the RS, mean (± SD) treatment duration was 54.5 (± 9.9) days during the W0-W8 period, 126.2 (± 57.1) days during the W0-W24 period and 7.7 (± 0.7) days during the tapering period. Treatment durations were comparable between treatment groups for each period.

Global compliance was good during the study: mean (± SD) was 97.5% (±10.0%) during the W0-W8 period, 97.4% (± 10.0%) during the W0-W24 period and 97.0% (± 7.4%) during the tapering period. In all, 97.8% of patients had a global compliance between 70% and 130% during the W0-W8 and W0-W24 periods and 99.3% during the tapering period. Comparable global compliance was reported between treatment groups for each period.

EFFICACY RESULTS

- **Primary assessment criterion: HAM-D total score**

Primary analysis: change in HAM-D total score from baseline to W8 period (see Table below).

A two-way analysis of covariance (including treatment, centre and value at baseline as covariates or factors) showed that the decrease in the tianeptine group was statistically higher than in the placebo group (E[SE] = 3.84 [0.85], p < 0.001).

A sensitivity analysis was performed with a MMRM analysis. It showed that the HAM-D total score decrease from baseline to W8 was statistically higher in the tianeptine group than in the placebo group (E[SE] = 3.65 [0.92], p < 0.001) in the FAS.

A second sensitivity analysis performed with a one-way ANOVA model showed that HAM-D total score at W8 according to LOCF approach was statistically lower in the tianeptine group than in the placebo group (E[SE] = 3.82 [0.94], p < 0.001) in the FAS.

In the escitalopram group, comparable results were observed *versus* the placebo group in the primary analysis and the two sensitivity analyses.

Primary criterion: Change in HAM-D total score from baseline to W8 according to LOCF approach in the FAS (N = 309)

		Tianeptine (N = 105)	Placebo (N = 106)	Escitalopram (N = 98)
Descriptive Statistics				
Baseline	n	105	106	98
	Mean ± SD	26.7 ± 3.2	26.6 ± 3.6	26.7 ± 3.2
W8 (LOCF)	n	105	106	98
	Mean ± SD	13.3 ± 7.0	17.1 ± 6.9	13.1 ± 6.6
W8 (LOCF) - Baseline	n	105	106	98
	Mean ± SD	-13.4 ± 7.4	-9.5 ± 6.9	-13.6 ± 7.2
Statistical analysis				
W8 (LOCF) - Baseline	E (SE) (1)	3.84 (0.85)		4.09 (0.86)
	95% CI (2)	[2.17 ; 5.51]		[2.39 ; 5.79]
	p-value (3)	< 0.001		< 0.001

Analysis of covariance model on factors treatment and centre (random effect) with baseline HAM-D total score as covariate. (1) Estimate (standard error [SE]) of the difference between adjusted treatment group means: placebo minus tianeptine or escitalopram. (2) Two-sided 95% CI of the estimate. (3) Two-sided p-value, n = number of patients, N = number of patients in a given treatment group

- **Secondary analyses: response to treatment (HAM-D total score)**.

In the FAS, the percentage of responder at W8 (LOCF) was higher in the tianeptine group than in the placebo group (46.7% *versus* 34.0%) with a trend (E[SE] = 12.70 [6.70], p = 0.06). In the escitalopram group, the difference *versus* placebo was statistically significant (55.1% *versus* 34.0%, E[SE] = 21.14 [6.81], p = 0.002).

- **Secondary assessment criteria**

CGI

In the FAS, the mean CGI severity of illness and global improvement scores at W8 (LOCF) were statistically significantly lower in the tianeptine group than in the placebo group (see Table below). Comparable results were observed with escitalopram.

In the tianeptine group, regarding CGI global improvement, the percentage of responders at W8 (LOCF) was higher than in the placebo group (71.4% *versus* 51.9%, p = 0.004). Comparable results were observed in the escitalopram group (77.6% *versus* 51.9%, p < 0.001).

EFFICACY RESULTS (Cont'd)

Change in CGI severity of illness and CGI global improvement scores from baseline to W8 according to LOCF approach in the FAS (N = 309)

		Tianeptine	Placebo	Escitalopram
CGI severity of illness				
Descriptive Statistics				
W8 (LOCF)	n	105	106	98
	Mean ± SD	2.8 ± 1.0	3.5 ± 1.2	2.9 ± 1.0
	Median	3.0	3.0	3.0
Statistical analysis				
W8 (LOCF)	E (SE) (1)	0.66 (0.15)		0.61 (0.15)
	95% CI (2)	[0.37 ; 0.96]		[0.31 ; 0.92]
	p-value (3)	< 0.001		< 0.001
	p-value (4)	< 0.001		< 0.001
CGI global improvement score				
Descriptive Statistics				
W8 (LOCF)	n	105	106	98
	Mean ± SD	2.0 ± 0.9	2.6 ± 1.1	2.1 ± 1.0
	Median	2.0	2.0	2.0
Statistical analysis				
W8 (LOCF)	E (SE) (1)	0.57 (0.14)		0.48 (0.14)
	95% CI (2)	[0.30 ; 0.83]		[0.20 ; 0.76]
	p-value (3)	< 0.001		< 0.001
	p-value (4)	< 0.001		< 0.001

(1) Estimate (SE) of the difference between treatment group means: placebo minus tianeptine or escitalopram. (2) Two-sided 95% CI of the estimate, (3) Two-sided p-value of Student's t-test, (4) Two-sided p-value of Mann-Whitney test, n = number of patients, N= number of patients in a given treatment group

HAD

Mean decreases (± SD) in HAD total score and depression score were higher in the tianeptine group than in the placebo group: -10.5 (± 7.8) *versus* -7.8 (± 7.1) for the HAD total score and -7.1 (± 5.1) *versus* -4.8 (± 4.5) for the HAD depression score. The decrease in the HAD anxiety score was comparable in the tianeptine group (-3.4 [± 3.8]) and the placebo group (-3.0 [± 3.7]).

The percentage of patients who had improved their depressive symptoms based on the HAD depression score was higher in the tianeptine group than in the placebo group: 44.8% *versus* 30.2% of patients had a HAD depression score [0 ; 7] at W8 (LOCF). The rate of patients who reached HAD anxiety score [0 ; 7] at W8 (LOCF) was comparable in the tianeptine group (61.0%) and in the placebo group (59.4%).

Comparable results were observed in the escitalopram group: mean decreases (± SD) were -12.8 (± 7.9) for the HAD total score, -8.1 (± 5.0) HAD depression score, -4.7 (± 3.8) HAD anxiety score and rate of patients with HAD depression score [0 ; 7] at W8 (LOCF) was 53.1%. The rate of patients with a HAD anxiety score [0 ; 7] at W8 (LOCF) was higher in the escitalopram group (71.4%) than in the placebo group (59.4%).

SDS

Mean decrease (± SD) in SDS total score at W8 (LOCF) was comparable in the tianeptine group and in the placebo group: -6.9 (± 5.8) and -6.7 (± 6.4) respectively.

Mean decreases (± SD) in SDS social life and family life/home responsibilities scores at W8 (LOCF) were higher in the tianeptine group than in the placebo group: -3.0 (± 2.6) *versus* -2.2 (± 2.4) and -3.2 (± 2.8) *versus* -2.3 (± 2.4) respectively.

Mean decrease (± SD) in SDS work score at W8 (LOCF) was comparable in the tianeptine group and in the placebo group: -2.3 (± 2.1) and -2.2 (± 2.6) respectively.

Comparable results were observed in the escitalopram group at W8 (LOCF): mean decreases (± SD) in SDS total score was -7.2 (± 7.2), in SDS social life score was -3.2 (± 2.6), in SDS family life/home responsibilities score was -3.2 (± 2.7) and in SDS work score was -2.6 (± 2.7).

SAFETY RESULTS

- **Emergent adverse events**

The proportion of patients who have reported at least one EAE was comparable in the tianeptine group and the placebo group during the W0-W9 period (42.9% and 41.1% respectively) or the W0-W25 period (49.5% and 50.5% respectively). The proportion of patients who have reported at least one EAE was higher in the escitalopram group than in the placebo group during the W0-W9 period (54.1% and 41.1% respectively) and during the W0-W25 period (65.3% and 50.5% respectively).

Most of the patients who have reported at least one EAE during the whole study have reported it during the W0-W9 period whatever the treatment group.

Overall summary for adverse events in the Safety Set

		Tianeptine (N = 105)	Placebo (N = 107)	Escitalopram (N = 98)
W0-W9 period				
Patients having reported				
at least one emergent adverse event	n (%)	45 (42.9)	44 (41.1)	53 (54.1)
at least one treatment-related emergent adverse event	n (%)	24 (22.9)	22 (20.6)	40 (40.8)
Patients having experienced				
at least one serious emergent event (including death)	n (%)	2 (1.9)	2 (1.9)	2 (2.0)
at least one treatment-related serious adverse event	n (%)	-	-	-
Patients with treatment withdrawal				
due to an emergent adverse event	n (%)	4 (3.8)	6 (5.6)	6 (6.1)
due to an emergent serious adverse event	n (%)	1 (1.0)	-	2 (2.0)
due a treatment-related emergent adverse event	n (%)	2 (1.9)	6 (5.6)	4 (4.1)
due a treatment-related emergent serious adverse event	n (%)	-	-	-
Patients who died	n (%)	-	-	-
W0-W25 period				
Patients having reported				
at least one emergent adverse event	n (%)	52 (49.5)	54 (50.5)	64 (65.3)
at least one treatment-related emergent adverse event	n (%)	24 (22.9)	25 (23.4)	43 (43.9)
Patients having experienced				
at least one serious emergent event (including death)	n (%)	2 (1.9)	3 (2.8)	2 (2.0)
at least one treatment-related serious adverse event	n (%)	-	-	-
Patients with treatment withdrawal				
due to an emergent adverse event	n (%)	4 (3.8)	8 (7.5)	8 (8.2)
due to an emergent serious adverse event	n (%)	1 (1.0)	1 (0.9)	2 (2.0)
due a treatment-related emergent adverse event	n (%)	2 (1.9)	6 (5.6)	4 (4.1)
due a treatment-related emergent serious adverse event	n (%)	-	-	-
Patients who died	n (%)	-	-	-

*n: Number of patients with at least one EAE, N: Number of patients in a given treatment group, %: (n/N)*100*

Most frequently reported EAEs

In the tianeptine group, the most frequently reported EAEs (≥ 3% of patients) were headache (10.5%), nausea (8.6%), flatulence (3.8%) and fatigue (3.8%) during the W0-W9 period and headache (12.4%), nausea (9.5%), flatulence (3.8%), fatigue (3.8%) and nasopharyngitis (3.8%) during the W0-W25 period.

In the placebo group, the most frequently reported EAEs (≥ 3% of patients) were dizziness (9.3%), nausea (5.6%), headache (3.7%), dry mouth (3.7%), and arthralgia (3.7%) during the W0-W9 period and dizziness (11.2%), nausea (5.6%), headache (5.6%), dry mouth (4.7%), abdominal pain upper (4.7%) and arthralgia (3.7%) during the W0-W25 period.

SAFETY RESULTS (Cont'd)

As regards tianeptine group, the incidence of its most frequent EAEs was higher than in the placebo group except for dizziness and abdominal pain upper.

Except for fatigue and nasopharyngitis, the most frequent emergent adverse events reported during the W0-W9 and W0-W25 periods were in accordance with expected AEs described in the reference safety information (RSI) of tianeptine (approved on 02 March 2015).

In the escitalopram group, the most frequently reported EAEs (≥3% of patients) were headache (13.3%), nausea (11.2%), dry mouth (7.1%), dizziness (5.1%), flatulence (4.1%), diarrhoea (4.1%), tremor (4.1%), fatigue (3.1%), hyperhidrosis (3.1%), insomnia (3.1%) and decreased appetite (3.1%) during the W0-W9 period and headache (17.3%), nausea (12.2%), dizziness (9.2%), dry mouth (8.2%), hyperhidrosis (5.1%), fall (5.1%), tremor (5.1%), flatulence (4.1%), fatigue (4.1%), anxiety (4.1%), diarrhoea (4.1%), insomnia (4.1%), back pain (4.1%), somnolence (4.1%), gastroenteritis (3.1%), decreased appetite (3.1%), hypertension (3.1%) and upper respiratory tract infection (3.1%) during the W0-W25 period.

As regards escitalopram, the incidence of its most frequent EAEs was higher than in the placebo group except for dizziness.

Except for flatulence and hyperhidrosis (period W0-W9 and W0-W25), fall, fatigue and back pain (period W0-W25), the most frequent emergent adverse events were in accordance with expected AEs described in the SmPC of escitalopram.

Severe EAEs were rare and described with a comparable proportion between treatment groups during the W0-W9 period: 4.8% of patients in the tianeptine group, 4.7% in the placebo group, and 5.1% in the escitalopram group. During the W0-W25 period, patients who had reported severe EAEs were 5.7% in the tianeptine group, 7.5% in the placebo group, and 9.2% in the escitalopram group.

Treatment-related EAEs were reported with a comparable proportion in patients in the tianeptine group and patients in the placebo group (22.9% and 20.6% respectively during the W0-W9 period and 22.9% and 23.4% respectively during the W0-W25 period). In the escitalopram group, the proportion of patients with treatment-related EAEs was two times higher than that in the placebo group for both periods: 40.8% *versus* 20.6% during the W0-W9 period and 43.9% *versus* 23.4% during the W0-W25 period.
In all treatment groups, the most frequent treatment-related EAEs were headache and nausea in the tianeptine and escitalopram groups, and dizziness in the placebo group during both periods.

Percentage of patients having at least one **EAE leading to treatment withdrawal** was lower in the tianeptine than that in the placebo group (3.8% *versus* 5.6% during the W0-W9 period and 3.8% *versus* 7.5% during the W0-W25 period). In the escitalopram group, 6.1% of patients had at least one EAE leading to treatment withdrawal during the W0-W9 period and 8.2% during the W0-W25 period.

Serious EAEs were rare and described with a comparable proportion between treatment groups during the W0-W9 period (1.9% of patients in the tianeptine group, 1.9% in the placebo group and 2.0% in the escitalopram group) or during the W0-W25 period (only one patient more in the placebo group, 2.8%). None of the serious EAEs were considered as treatment related.
No patient died during the study.

Laboratory parameters
In the Safety Set, neither clinically relevant changes from baseline to post-baseline value on treatment nor difference between groups were detected in biochemical or haematological parameters during the W0-W9 period or the W0-W25 period.
Emergent PCSA values for biochemical or haematological parameters were sparse in all groups and for each parameter during the W0-W9 period or the W0-W25 period.

Vital signs and clinical examination
Clinically relevant changes from baseline to last post-baseline value on treatment for sitting SBP, DBP or HR were not detected in the tianeptine and the placebo groups during both periods. In the escitalopram group, small decreases in sitting SBP during both periods did not reach clinical relevance (-2.2 ± 9.3 mmHg during the W0-W9 period and -2.3 ± 9.1 mmHg during the W0-W25 period).

CONCLUSION

This was an international, multicentre, randomised, double-blind, placebo-controlled, phase III study conducted in elderly patients suffering from Major Depressive Disorder with escitalopram 10 mg/day to evaluate assay sensitivity. Tianeptine (25 or 50 mg/day) showed the superiority of its antidepressant efficacy compared to placebo on a 8-week treatment period in elderly depressed patients. The therapeutic effect of escitalopram observed in the same conditions was as expected and validated the study results.

Safety profile of the tianeptine 25-50 mg/day on elderly was good during the 25-week treatment period and close to that of placebo regarding adverse events, biochemical or haematological parameters and vital signs. The safety profile of tianeptine in this study was in line with its RSI. In the same way, the safety profile of escitalopram is in line with its SmPC.

Date of the report: 30 June 2016

Version of the report: Final version