Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Efficacy and safety of agomelatine (25 mg/day with blinded potential adjustment to 50 mg/day) *versus* escitalopram (10 mg/day with blinded potential adjustment to 20 mg/day) given orally for 12 weeks in non-depressed out-patients with severe Generalized Anxiety Disorder.** **A 12-week randomised, double-blind, *versus* escitalopram, 2-arm parallel groups, international multicenter study with a 9-month extension period**
Study drug	**S 20098 (Agomelatine: Valdoxan®)**
Studied indication	**Generalized Anxiety Disorder**
Development phase	**III**
Protocol code	**CL3-20098-089**
Study initiation date	**23 April 2013**
Study completion date	**11 February 2015**
Scientific advisor	[redacted]
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot - 92284 Suresnes cedex – France** **Servier Canada Inc.** **235 Armand-Frappier Blvd.** **Laval, Quebec H7V 4A7 Canada** **Les Laboratoires Servier (L.L.S.)** **50 rue Carnot - 92284 Suresnes cedex – France** **Paveletskaya sq 2, bld 3, Moscow, 115054 - Russia**
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	**04 December 2015**
Version of the report	**Final version**
	~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex – France **Servier Canada Inc. 235 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4A7** **Les Laboratoires Servier (L.L.S.), 50 rue Carnot - 92284 Suresnes cedex – France/ Paveletskaya sq 2, bld 3, Moscow, 115054 - Russia**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Valdoxan® **Name of Active Ingredient:** Agomelatine (S 20098)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Efficacy and safety of agomelatine (25mg/day with blinded potential adjustment to 50mg/day) *versus* escitalopram (10mg/day with blinded potential adjustment to 20mg/day) given orally for 12 weeks in non-depressed out-patients with severe Generalized Anxiety Disorder.

A 12-week randomised, double-blind, *versus* escitalopram, 2-arm parallel groups, international multicenter study with a 9-month extension period.

Protocol No.: CL3-20098-089 – EudraCT No. 2012-003699-37

The description of the study protocol given hereafter includes the modifications of the 4 substantial amendments to the protocol.

National coordinators: [redacted]

Study centres: In all, 61 centres located in 9 countries included at least one patient: Australia (6 centres – 25 patients), Canada (6 centres – 49 patients), Czech republic (10 centres – 125 patients), Finland (6 centres – 40 patients), Germany (9 centres – 70 patients), Hungary (6 centres – 72 patients), Poland (7 centres – 49 patients), Russia (7 centres – 65 patients), Slovakia (4 centres – 28 patients).

Publication (reference): Not Applicable

Studied period:	**Phase of development of the study:**
Initiation date: 23 April 2013 (date of first visit first patient) Completion date: 11 February 2015 (date of last visit last patient)	III

Objectives:

The purpose of this study was to assess the efficacy and safety of agomelatine (25-50 mg/day p.o.) compared to escitalopram (10-20 mg/day p.o.) after a 12-week treatment in non-depressed out-patients suffering from severe Generalized Anxiety Disorder (GAD) with a HAM-A total score at inclusion ≥ 25.

Primary objective: was to compare the efficacy of agomelatine (25-50 mg/d) *versus* escitalopram (10-20mg /d) using HAM-A scale after a 12-week treatment period.

Secondary objectives were:

- To further describe the effects on anxiety symptoms.
- To differentiate the treatment effects of agomelatine as compared to escitalopram on:
  - Daytime alertness with the Toronto Hospital Alertness Test (THAT).
  - On subjective sleep with the Leeds Sleep Evaluation Questionnaire (LSEQ).
  - On anhedonia using the Snaith-Hamilton Pleasure Scale (SHAPS).
- To provide additional long-term efficacy data of agomelatine.
- To provide additional short-term and long-term safety and tolerability data on agomelatine.

A pharmacogenetic sub-study was to be also conducted in order to evaluate associations between polymorphisms in candidate genes and the efficacy and safety of agomelatine in patients suffering from severe GAD. Detailed information regarding this sub-study is available in the attached sub-study protocol.

Methodology:
This was a 12-week international, multicentre, comparative double-blind, randomised, phase III study with 2 parallel groups having a possible dose adaptation at W4 under blinded conditions (agomelatine 25 mg/day, with a potential increase to 50 mg/day, and escitalopram 10 mg/day with a potentital increased to 20 mg/day), and an optional double-blind extension period of 12 weeks (as added by Amendment No. 4) or 40 weeks.
The criteria for increasing the dose at W4 were defined by I.R.I.S., before the study beginning and kept blinded to the investigator and the patient.
Randomisation was balanced, non adaptive, with stratification on the centre. Treatment randomisation and allocation were centralized with an Interactive Response System (IRS).
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: approximately 510 patients (255 by treatment group).
Included: 523 patients (261 in the agomelatine 25/50 mg group and 262 in the escitalopram 10/20 mg group).

Diagnosis and main criteria for inclusion:
Non-depressed patients suffering from severe Generalized Anxiety Disorder according to DSM-IV-TR, Hamilton Anxiety rating scale (HAM-A) and Montgomery–Åsberg Depression Rating Scale (MADRS). Legal age for majority to 65 years old (inclusive) out-patients of both genders (in daily contact with another adult person for patients in Czech republic only according to Amendment No. 1), fulfilling DSM-IV-TR criteria for GAD confirmed by Mini International Neuropsychiatric Interview (M.I.N.I.) and with HAM-A total score $\geq$ 25 (severe symptoms), HAM-A item 1 (Anxious mood) $\geq$ 2 and item 2 (Tension) $\geq$ 2, HAM-A item 1 + item 2 $\geq$ 5, MADRS total score $\leq$ 16, and HAD anxiety sub-score $\geq$ 11 and $\geq$ HAD depression sub-score.
Patients without other psychiatric disorder prone to interfere with the evaluation of the study, and without any severe or uncontrolled organic disease. Treatments likely to interfere with central nervous system or with study evaluation were forbidden during the study. According to Amendment No. 3, occasional intake of hypnotics limited to zolpidem, zopiclone, eszopiclone was allowed after W12 if needed and according to the investigator's judgment.

Study drug:
Agomelatine, capsules of 25 and 50 mg. One capsule o.d. at bedtime.
For patients receiving agomelatine 25 mg at inclusion (W0), a potential adjustment to 50 mg/day might occur at W4 using pre-determined fixed criteria, under double-blind conditions (neither the investigator nor the patients knew whether the dose had been increased) in case of insufficient improvement of anxiety symptoms. Patients with sufficient improvement remained on agomelatine 25 mg.
Batch No.: Agomelatine 25 mg: L0046722, L0048401, L0048797, L0051969, L0053874, L0048525.
Agomelatine 50 mg: L0046877, L0048799, L0051971, L0053876

Reference product:
Escitalopram capsules of 5 mg, 10 mg and 20 mg. One capsule o.d. at bedtime.
For patients receiving escitalopram 10 mg at inclusion, a potential adjustment to 20 mg/day might occur at W4 using the same pre-determined criteria as those used for agomelatine adjustment in case of insufficient improvement of anxiety symptoms. Patients with sufficient improvement remained on escitalopram 10 mg.
In order to avoid possible withdrawal reactions at the end of the treatment, the dose of escitalopram was gradually reduced during a one week tapering period under double-blind conditions. Patients previously treated with escitalopram 10 mg/day were to receive escitalopram 5 mg/day for 1 week and patients previously treated with escitalopram 20 mg/day were to receive escitalopram 10 mg/day for 3 days followed by 4 days of escitalopram 5 mg.

Duration of treatment:

- Run-in period: 1-2 week(s) without treatment.
- Active treatment period: 12 weeks (agomelatine or escitalopram).
- Optional extension period: 12 weeks (as added Amendment No. 4) or 40 weeks (agomelatine or escitalopram).
- Tapering period: 1 week (agomelatine or escitalopram).
- Follow-up period: 1 week after discontinuation of Investigational Medicinal Product (IMP).

Criteria for evaluation:

Efficacy measurements:

- HAM-A (Psychic/Somatic anxiety sub-scores and total score) rated by the investigator, at each visit from the selection visit to the W52 visit. HAM-A total score over the W0-W12 period was the primary efficacy criterion, expressed mainly in terms of change from baseline to W12.
- Clinical Global Impression Scale (CGI) rated by the investigator; item 1 (severity of illness) and item 2 (global improvement) scores at each visit visit from the selection visit to the W52 visit (except item 2, only from week 2 of treatment and afterwards).
- Toronto Hospital Alertness Test (THAT) total score, rated by the patient, at inclusion (W0), at W2, W4 , W8, W12, W24, and W52 or at the withdrawal visit in case of premature withdrawal from the study.
- Leeds Sleep Evaluation Questionnaire (LSEQ) scores rated by the patient, at W2, W4, W8, and W12 visits.
- Snaith-Hamilton Pleasure Scale (SHAPS) total score, rated by the patient, at inclusion (W0) at W2, W4 , W8, W12, W24, and W52 or at the withdrawal visit in case of premature withdrawal from the study.

Safety measurements

- Adverse events reported at each visit.
- Laboratory tests: biochemical (including liver function parameters) and haematological results were to be obtained at the latest for inclusion visit, at W12, at W24 only for patients stopping the extension period according to Amendment No. 4, at W52 or in case of premature withdrawal.
  Liver function parameters were assessed at W4, W8, W16, W24 (for patient continuing in the extension period until W52, as clarified by Amendment No. 4) and W40 visits. As added by Amendment No. 2, these parameters were also assessed at W32, W48 and WEND, for patients selected in Canada only.
- Clinical examination: Sitting Systolic/ Diastolic Blood pressure (SBP/DBP), Heart rate (HR), body weight, and Body Mass Index (BMI) at selection, at inclusion, at W12, W24 and W52 or at the withdrawal visit in case of premature withdrawal from the study.
- Columbia-Suicide Severity Rating Scale (C-SSRS) was rated by the investigator, at inclusion, at W2, W4, W8, W12, W24 and W52 or at the withdrawal visit in case of premature withdrawal from the study.
- 12-Lead ECG, at selection, at W12, W24, W32 and W52 or at the withdrawal visit in case of premature withdrawal from the study.

Pharmacogenetic measurements:
Study sample collection was to be performed once at any time at W4, W8, W12 or at the withdrawal visit in case of premature discontinuation.

Statistical methods:
Analysis Set:
The primary analysis was performed on the Full Analysis Set (FAS) defined in accordance with the intention-to-treat principle and ICH-E9 guideline, as all patients of the Randomised Set (RS) having taken at least one dose of IMP and having a value at baseline (W0) and at least one post-baseline value for the primary efficacy criterion on the W0-W12 period.

Efficacy analysis
Primary criterion

- Main analysis

To compare the efficacy of agomelatine *versus* escitalopram on anxious symptoms after a 12-week treatment period, the treatment difference between Agomelatine and Escitalopram was studied in patients of the FAS on the change from baseline to W12 of HAM-A total score, using a two-way analysis of covariance (ANCOVA) model including the fixed, categorical effect of treatment, the random categorical effect of centre, as well as the continuous, fixed covariate of baseline HAM-A total score. Missing data at W12 were imputed using the Last Observation Carried Forward (LOCF) approach.
A non-inferiority analysis was carried out taking into account the fixed pre-defined non- inferiority margin of 1.5 points. If the lower end of the two-sided 95% confidence interval of the treatment difference was superior to -1.5, the non-inferiority of agomelatine to escitalopram was established (with, in that case, a p-value from the non-inferiority unilateral test less than or equal to 0.025).
A switching strategy from non-inferiority to superiority analysis of agomelatine to escitalopram could be carried out (primary analysis strategy).

- Sensitivity analyses

The previous analysis was to be performed in the Per Protocol Set (PPS) as a sensitivity analysis, except in case of switching from non-inferiority to superiority in the FAS.
To assess the robustness of the results of the primary analysis, the following sensitivity analyses to the method of handling missing data were performed:

- *Mixed-effects Model Repeated Measures (MMRM)*: Agomelatine was compared to escitalopram on the change from baseline to W12 of HAM-A total score in patients of the FAS (and PPS if applicable), using a MMRM including 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.
- *Observed Cases (OC) analysis*: the same ANCOVA as for the primary analysis was performed on the change from baseline to W12 in patients of the Observed Cases W12 Set (OC).

The same analysis strategy as for the primary analysis was implemented regarding the non-inferiority analysis.

In addition, descriptive statistics were provided by treatment group for the value at baseline and at each post-baseline visit, as well as for the change from baseline to each post-baseline visit, of the primary efficacy criterion on the W0-W12 period in the FAS, the PPS (if applicable) and the OC. In particular, descriptive statistics were also given after imputing missing data at W12 using the LOCF approach for the description of the value at W12 and the change from baseline to W12 in the FAS and in the PPS (if applicable).

- Secondary analyses

The same analysis strategy as for the primary analysis on HAM-A total score, was implemented for the subgroup of patients of the FAS with more severe anxious symptoms (CGI Severity of illness score at W0 greater than or equal to 5).
The response to treatment derived from HAM-A total score was described on the W0-W12 period in the FAS. Moreover, all expressions of the primary efficacy criterion (except for remission) were described on the W0-W12 period in the sub-FAS of more severely anxious patients.
Descriptive statistics for all expressions of the primary efficacy criterion were also provided on the W0-W24 and W0-W52 periods in the FAS and in the sub-FAS of more severely anxious patients.

Statistical methods (Cont'd):
Secondary efficacy criteria:

- HAM-A Psychic and Somatic anxiety scores.
- Obtained from the CGI:
  - Severity of Illness score.
  - Global Improvement score and response to treatment (Global improvement score equal to 1 or 2).
- THAT total score.
- Obtained from the LSEQ: getting off to sleep score, quality of sleep score, sleep awakening score, and integrity of behaviour score.
- The SHAPS total score.

CGI Global improvement score and response to treatment, as well as LSEQ scores were expressed as value at each visit (no baseline for these scores). CGI Severity of illness was expressed as value at baseline and at each post-baseline visit.
Other secondary efficacy criteria were expressed as value at baseline, at each post-baseline visit and change from baseline to each post-baseline visit.
Descriptive statistics were provided for all expressions of the secondary efficacy criteria on the W0-W12, W0-W24 and W0-W52 periods in the FAS and in the sub-FAS of more severely anxious patients.
Moreover, descriptive statistics were also provided on the W0-W12 period in the OC for the THAT, LSEQ and SHAPS scores.
Conditionally to the non-inferiority or the superiority of Agomelatine compared to Escitalopram on HAM-A total score at W12 in the OC, the difference between Agomelatine and Escitalopram was planned to be studied in this set on the value at W12 of THAT, LSEQ and SHAPS scores, using a two sided Student's t-test for independent samples.

The psychometric properties of the THAT scale (quality of completion, internal consistency reliability and construct validity) were assessed at baseline, independently from treatment groups, on the Randomised set.

Study outcome analysis: descriptive statistics were provided in the Randomised Set, FAS, PPS, Sub-FAS, Sub-PPS (and in Safety Set for some parameters).

Safety analysis: descriptive statistics were provided in the Safety Set.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of patients

Status		Agomelatine (N = 261)	Escitalopram (N = 262)	All (N = 523)
Included/randomised				
In compliance with the protocol	n	221	221	442
With a protocol deviation before or at inclusion	n	40	41	81
W0-W13/WEND period	**n**	**261**	**262**	**523**
Withdrawn over W0-W12 period due to	**n (%)**	**49 (18.8)**	**42 (16.0)**	**91 (17.4)**
Adverse event	n (%)	15 (5.7)	19 (7.3)	34 (6.5)
Lack of efficacy	n (%)	13 (5.0)	3 (1.2)	16 (3.1)
Cure, remission, improvement	n (%)	-	1 (0.4)	1 (0.2)
Non-medical reason	n (%)	21 (8.0)	15 (5.7)	36 (6.9)
Protocol deviation	n (%)	-	4 (1.5)	4 (0.8)
Completed the W0-W12 period	**n (%)**	**212 (81.2)**	**220 (84.0)**	**432 (82.6)**
In compliance with the protocol	n	200	211	411
With a protocol deviation after inclusion	n	12	9	21
Performed the tapering period	*n (%)*	*15 (6.8)*	*11 (4.2)*	*26 (49.7)*
Performed the follow-up visit (unplanned analysis)	*n (%)*	*40 (15.3)*	*42 (16.0)*	*82 (15.7)*
Not on-going in the extension period at W12	**n (%)**	**12 (4.6)**	**14 (5.3)**	**26 (5.0)**
On-going in the extension period at W12	**n (%)**	**200 (76.6)**	**206 (78.6)**	**406 (77.6)**
Withdrawn on W16-W24 period* due to	**n (%)**	**19 (9.5)**	**9 (4.4)**	**28 (6.9)**
Lost to follow-up	n (%)	1 (0.5)	-	1 (0.2)
Adverse event	n (%)	3 (1.5)	2 (1.0)	5 (1.2)
Lack of efficacy	n (%)	5 (2.5)	2 (1.0)	7 (1.7)
Non-medical reason	n (%)	8 (4.0)	5 (2.4)	13 (3.2)
Protocol deviation	n (%)	2 (1.0)	-	2 (0.5)
Completed the W16-W24 period*	**n (%)**	**181 (90.5)**	**197 (95.6)**	**378 (93.1)**
In compliance with the protocol	n	165	185	350
With a protocol deviation after inclusion	n	16	12	28
*Performed the tapering period**	*n (%)*	*106 (53.0)*	*115 (55.8)*	*221 (54.4)*
Performed the follow-up visit (unplanned analysis)*	*n (%)*	*105 (52.5)*	*118 (57.3)*	*223 (42.6)*
Stopping the extension period at W24	**n (%)**	**104 (39.8)**	**115 (43.9)**	**219 (41.9)**
On-going in the extension period at W24	**n (%)**	**77 (29.5)**	**82 (31.3)**	**159 (30.4)**
Withdrawn on the period up to W52 due to**	**n (%)**	**10 (13.0)**	**11 (13.4)**	**21 (13.2)**
Adverse event	n (%)	1 (1.3)	1 (1.2)	2 (1.3)
Lack of efficacy	n (%)	3 (3.9)	-	3 (1.9)
Cure, remission, improvement	n (%)	1 (1.3)	1 (1.2)	2 (1.3)
Non-medical reason	n (%)	5 (6.5)	8 (9.8)	13 (1.9)
Protocol deviation	n (%)	-	1 (1.2)	1 (0.6)
Completed the period up to W52**	**n (%)**	**67 (87.0)**	**71 (86.6)**	**138 (86.8)**
In compliance with the protocol	n	61	64	125
With a protocol deviation after inclusion	n	6	7	13
*Performed the tapering period**	*n (%)*	*72 (93.5)*	*72 (87.8)*	*144 (90.6)*
*Performed the follow-up visit** (unplanned analysis)*	*n (%)*	*72 (93.5)*	*67(81.7)*	*139 (87.4)*
Efficacy Sets				
Full Analysis Set (FAS)	n (%)	258 (98.9)	261 (99.6)	519 (99.2)
Observed Cases W12 Set	n (%)	220 (84.3)	229 (87.4)	449 (85.9)
Sub-FAS of more severely anxious patients	n (%)	191 (73.2)	188 (71.8)	379 (72.5)
Per Protocol Set (PPS)	n (%)	222 (85.1)	220 (84.0)	442 (84.5)
Sub-PPS of more severely anxious patients	n (%)	164 (62.8)	162 (61.8)	326 (62.3)
Safety Set	**n (%)**	**260 (99.6)**	**262 (100)**	**522 (99.8)**

*%: Expressed as percentage of the patients from the Included/Randomised Set except for * expressed as percentage of patients entered in the extension period at W12 and ** expressed as percentage of patients on going in the extension period at W24.*

A total of 523 patients were included and randomly assigned to one of the 2 groups: 261 patients in the agomelatine group and 262 in the escitalopram group. The planned balanced distribution was reached. In the Randomised Set, among patients continuing the study after the W4 visit, 38/239 patients (15.9%) in the agomelatine group and 28/237 patients (11.8%) in the escitalopram group had a dose increase at W4 (*unplanned analysis*).

SUMMARY – CONCLUSIONS (Cont'd)
DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

Over the W0-W12 period, in the Randomised Set, no relevant difference between groups was observed regarding the rate of withdrawals (18.8% in the agomelatine group *versus* 16.0% in the escitalopram group); however, the rate of withdrawals for lack of efficacy was higher in the agomelatine group (13 patients, 5.0%) than in the escitalopram group (3 patients, 1.2%).

Among the patients entering the extension period at W12, the rate of withdrawals on the W16-W24 period was higher in the agomelatine group (19 patients, 9.5%) than in the escitalopram group (9 patients, 4.4%). No relevant difference between groups was observed regarding the rate of withdrawals among the patients who continued in the extension period at W24 (10 patients, 13.0% in the agomelatine group *versus* 11 patients, 13.4% in the escitalopram group).

Data on premature withdrawals in the FAS and in the sub-FAS were similar to those observed in the RS.

In the Randomised Set, the rate of patients with protocol deviations was similar between groups at inclusion (15.3% in the agomelatine group *versus* 15.6% in the escitalopram group) and after inclusion until W12 (11.5% *versus* 9.9%, respectively) or until W52 (17.6% *versus* 14.5%, respectively). At inclusion, the most frequent deviations concerned biochemistry/haematology (41 deviations *i.e.* 41.8% of the deviations), less frequently reported in the agomelatine group than in the escitalopram group (17 deviations *versus* 24 deviations, respectively), mainly "at least one clinically significant abnormal value" less frequently reported in the agomelatine group (16 deviations) than in the escitalopram group (24 deviations).
After inclusion, the most frequent deviations concerned biochemistry/haematology: 68 deviations, *i.e.* 54.0% of the deviations until W12 more frequent in the agomelatine group (41 deviations) than in the escitalopram group (27 deviations) and 86 deviations *i.e.* 46.2% until W52 without relevant difference between groups (46 deviations *versus* 40 deviations). No relevant difference between groups was observed regarding the other deviations.

BASELINE CHARACTERISTICS
At selection in the Randomised Set, patients were 41.0 ± 12.1 years old on average (age ranging from 18 to 65 years old). Most of them (69.0%) were female, as usually observed in this pathology.

All patients fulfilled DSM-IV diagnostic criteria for GAD. DSM-IV symptoms associated with anxiety and worry were each reported by more than 90% of the patients. At selection, the time since GAD diagnosis covered a large range from 0 to 516 months (0 to 43 years) with a median duration of 3 months. In the same way, the duration since the first symptoms with social, occupational or functional impairment ranged within 6.0 to 680.0 months (0.5 to 56.7 years) with a median duration of 49 months (4.1 years) without clinically relevant difference between groups (3.4 years and 4.5 years in agomelatine and escitalopram groups, respectively). At selection, no patient had psychiatric disorders other than GAD, diagnosed using the M.I.N.I.; suicidality was reported for 6 patients (3 in each group).

In all, 224 patients (42.8%) had taken previous psychotropic treatments in the last 12 months before selection. The most frequent were antidepressants (30.2% of the patients) and anxiolytics (17.6% of the patients). One patient (in the agomelatine group) had taken a specific concomitant treatment at inclusion (antidepressant: trazodone hydrochloride): the patient had a protocol deviation. All patients had negative test at the urinary psychotropic drug screening at inclusion, except one patient in the escitalopram group who had a positive test for benzodiazepines (a retest performed 3 weeks later was negative).

At selection, the mean MADRS total score was 11.6 ± 2.7, all scores were ≤ 16 as required in the selection/inclusion criteria. This mean total score was in line with the patients' non depressive condition seen by the investigators (confirmed by M.I.N.I) and with patient's judgement according to the HAD depression score at baseline which was on average 6.5 ± 3.6. In all, 13.8% of the patients reported a HAD depression score ≥ 11 with a slightly higher rate of these patients in the agomelatine group than in the escitalopram group (16.5% *versus* 11.1%). HAD anxiety score was on average 15.7 ± 2.5; 98.5% of the patients had a HAD anxiety score ≥ 11 indicating that patients felt anxious, as required in the protocol.
According to self-assessment (on the SDS), the patients felt clearly disrupted by symptoms with a mean ± SD SDS total score at selection of 19.5 ± 4.5 (6.7 ± 2.0 for work, 6.6 ± 1.8 for social life and 6.2 ± 1.8 for family life/home responsibilities).

SUMMARY – CONCLUSIONS (Cont'd)
BASELINE CHARACTERISTICS (Cont'd)

As regards C-SSRS, suicidal ideations were reported by 17 patients (3.3%) during their lifetime and by 5 patients (1.0%) in the month before inclusion. Suicidal behaviour was reported by 7 patients (1.3%) during lifetime. Among them, 6 reported previous suicide attempt (3 in each group). No patient reported suicidal behaviour within the past year before inclusion. No relevant difference between groups was observed, neither for suicidal ideations nor for suicidal behaviour.

Regarding anxiety at baseline, in the Randomised Set, HAM-A total score was on average 30.3 ± 3.4, ranging from 25 to 46, *i.e.* ≥ 25 (severe symptoms) as required in the selection/inclusion criteria; psychic anxiety score was on average 16.1 ± 2.2 and somatic anxiety score was 14.2 ± 2.9. The mean ± SD CGI severity of illness score was 4.9 ± 0.7 (on average markedly ill), ranging between 3 and 7. The mean ± SD THAT total score was 21.7 ± 8.0 (ranging between 4 and 50) *i.e.* showing a low alertness: according to Ionescu *et al,* 2001 (retinitis pigmentosa patients (RP patients) *versus* control group), the mean THAT total score in the control group was 38 ± 7 and the score was lower in RP patients (29 ± 9). The mean ± SD SHAPS total score was 29.4 ± 6.9 (ranging between 14 and 51).

No clinically relevant difference between groups was observed regarding demographic data, HAM-A total score, other efficacy criteria for anxiety, C-SSRS and characteristics of GAD except a slightly higher rate of patients with HAD depression score ≥ 11 in the agomelatine group (43 patients, 16.5%) than in the escitalopram group (29 patients, 11.1%).

Baseline characteristics described in the FAS (99.2% of the RS) and in the PPS (84.5% of the RS) were similar to those in the Randomised Set. In the sub-FAS and sub-PPS of more severely anxious patients, excluding the criteria of the set definition (trend to higher CGI severity of illness score), baseline characteristics showed no clinically relevant difference compared to those observed in the Randomised Set.

Patient's characteristics were in accordance with the target population defined in the study protocol. Demographic data, GAD characteristics and efficacy criteria at baseline were comparable in both treatment groups.

EXTENT OF EXPOSURE

In the Randomised Set over the W0-W12 period, treatment duration ranged between 0 and 106 days with a mean ± SD of 76.6 ± 21.2 days (median of 84.0 days). No relevant difference between groups was observed regarding treatment duration, whatever the study period.

The mean treatment compliance was good over the W0-W12 period (95.7 ± 14.5%): similar results were observed over each treatment period, without relevant difference between groups.

EFFICACY RESULTS

Following Amendment No. 4, only patients who had reached W24 before approval of this amendment could continue the extension period until W52. Consequently, many patients stopped the study at W24 and had no evaluation at W52. Thus, results at W52 (reached by about ¼ of patients), should be interpreted with caution and were only described in the body of this report.

Primary assessment criterion: HAM-A total score

- Change from baseline to W12 in the FAS

In the FAS, the mean **HAM-A total score** decreased over the W0-W12 period in both treatment groups. At W12 (LOCF), the mean ± SD decrease from baseline was -16.0 ± 9.1 in the agomelatine group and -16.9 ± 8.4 in the escitalopram group. Considering the pre-defined non-inferiority margin of 1.5, the non-inferiority of agomelatine compared to escitalopram group was not statistically demonstrated (E (SE) = -0.91 (0.69), 95% CI [-2.26 ; 0.44], one-sided p-value (to be compared to 0.025) = 0.195), after adjustement for centre (random effect) and baseline HAM-A total score, using LOCF approach for missing data at W12 (primary analysis).

This result was confirmed by the 2 sensitivity analyses to the method of handling missing data in the FAS, MMRM analysis and Observed case analysis.

SUMMARY – CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

HAM-A total score: Description at baseline, W12, corresponding change from baseline, and between-group comparisons in the FAS

		Agomelatine (N = 258)	Escitalopram (N = 261)
Baseline	n	258	261
	Mean ± SD	30.3 ± 3.5	30.3 ± 3.3
W12	n	220	229
	Mean ± SD	12.2 ± 8.0	11.7 ± 7.3
W12 (LOCF)	n	258	261
	Mean ± SD	14.4 ± 9.5	13.4 ± 8.6
Change from baseline to W12	n	220	229
	Mean ± SD	-18.1 ± 7.5	-18.7 ± 6.9
Change from baseline to W12 (LOCF)	n	258	261
	Mean ± SD	-16.0 ± 9.1	-16.9 ± 8.4
Statistical analysis			
Primary analysis [a]	E (SE) [1]	-0.91 (0.69)	
(change from baseline to W12 (LOCF))	95% CI [2]	[-2.26 ; 0.44]	
	p-value[3]	0.195	
Sensitivity analyses [b]			
MMRM [c]	E (SE) [1]	-1.00 (0.63)	
(change from baseline to W12)	95% CI [2]	[-2.24 ; 0.23]	
	p-value[3]	0.214	
Observed cases analysis [a]	E (SE) [1]	-0.49 (0.57)	
(change from baseline to W12)	95% CI [2]	[-1.61 ; 0.63]	
	p-value[3]	0.038	

N: Number of patients in each treatment group.
n: Number of patients.
(a) Analysis of covariance model on factors treatment and centre (random effect) with baseline HAM-A total score as covariate.
(b) Sensitivity analysis to the method of handling missing data.
*(c) Mixed-effects Model with Repeated Measures including terms for effects of treatment, baseline HAM-A total score, centre (random effect), visit and an interaction term treatment*visit.*
(1) Estimate (Standard Error) of the difference between adjusted treatment group means: Escitalopram minus Agomelatine.
(2) Two-sided 95% Confidence Interval of the estimate.
(3) Non-inferiority test centred on a non-inferiority margin of 1.5: one-sided p-value to be compared to 0.025.

A similar conclusion could be drawn in the PPS using LOCF approach for missing data at W12 (E (SE) = -1.15 (0.61), 95% CI [-2.36 ; 0.05], one-sided p-value = 0.285) and MMRM analysis (E (SE) = -0.98 (0.63), 95% CI [-2.22 ; 0.25], one-sided p-value = 0.206).
Results observed in the Sub-FAS (and in the Sub-PPS) of more severely anxious patients were comparable to those observed in the FAS (and in the Sub-FAS) using the LOCF approach and the MMRM analyses.

- Change from baseline over the W0- W24 periods
Regarding HAM-A total score over the W0-W24 in the FAS, no relevant difference between agomelatine and escitalopram groups was observed in mean decrease from baseline to W24 (LOCF): -17.7 ± 9.8 *versus* -18.8 ± 9.1, respectively. The non relevant difference between groups was confirmed when regarding observed values* (**without imputation of missing data*): -21.5 ± 6.8 *versus* -21.6 ± 6.7, respectively. Results observed in the Sub-FAS were similar to those observed in the FAS.

SUMMARY – CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

- **Response to treatment according to HAM-A total score**

In the FAS at W12 (LOCF), the rate of responders (patient with a decrease in HAM-A total score of at least 50% from baseline) was slightly lower in the agomelatine group than in the escitalopram group (60.9% *versus* 64.8%). At W24 (LOCF), results showed similar trend (68.2% in the agomelatine group *versus* 72.0% in the escitalopram group). Results regarding observed values at W12 and W24 showed no relevant difference between groups (69.6% *versus* 71.6% and 84.0% *versus* 84.9%, respectively).
Results regarding responders (according to HAM-A) in the Sub-FAS of more severely anxious patients were along the same lines as those in the FAS, with however a higher difference between agomelatine and escitalopram groups regarding observed values at W12 in the sub-FAS (68.1% *versus* 72.7% of responders, respectively) than in the FAS (69.6% *versus* 71.6%, respectively).

- **Remission according to HAM-A total score**

Using the LOCF approach at W24, the rate of remitters (defined as patients with a HAM-A total score ≤ 7) showed no relevant difference between agomelatine and escitalopram groups (38.8% *versus* 40.2%, respectively). When regarding observed values, half of the patients were remitters without relevant difference between agomelatine and escitalopram groups at W24 (50.5% *versus* 49.3%, respectively). Results in the Sub-FAS of more severely anxious patients were along the same lines as those in the FAS.

Secondary assessment criteria

- **HAM-A 14 item scale: psychic and somatic anxiety sub-scores**

Mean **HAM-A psychic and somatic anxiety** sub-scores decreased over the W0-W12 period in both treatment groups. At W12 (LOCF), the mean change from baseline showed no relevant difference between the agomelatine and the escitalopram groups (-8.4 ± 5.1 *versus* -9.0 ± 4.7 for psychic sub-score and -7.6 ± 4.7 *versus* -7.9 ± 4.5 for somatic sub-score, respectively). There was a similar trend regarding observed values at W12 (-9.5 ± 4.3 *versus* -9.9 ± 4.0 for psychic sub-score and -8.5 ± 4.1 *versus* -8.8 ± 3.9, for somatic sub-score, respectively).
Over the W0-W24 period, no relevant difference between groups was observed regarding the mean decrease from baseline to W24, using LOCF approach (-9.3 ± 5.5 *versus* -9.8 ± 5.0 for psychic sub-score and -8.4 ± 5.0 *versus* -9.0 ± 4.9 for somatic sub-score, respectively) or regarding observed values (-11.4 ± 3.8 *versus* -11.3 ± 3.9 for psychic sub-score and -10.2 ± 3.8 *versus* -10.3 ± 3.9 for somatic sub-score, respectively).

- **Clinical Global Impression Scale (CGI)**

Severity of illness score

The mean CGI severity of illness score decreased from baseline to W12 (LOCF) in both treatment groups in the FAS. At W12 (LOCF), the mean score showed no relevant difference between agomelatine and escitalopram groups (3.0 ± 1.4 *versus* 2.8 ± 1.3, respectively). There was a similar trend when regarding observed values at W12 (2.7 ± 1.2 *versus* 2.6 ± 1.2, respectively).
No relevant difference between agomelatine group and escitalopram group was observed at W24 using LOCF approach (2.7 ± 1.5 *versus* 2.6 ± 1.4, respectively) which was confirmed when regarding observed values at W24 (2.2 ± 1.1 in both groups).

Global improvement score

In the FAS over the W0-W12 period, the mean CGI global improvement score decreased in both treatment groups indicating that patients improved. At W12 (LOCF), the mean score showed no relevant difference between the agomelatine and the escitalopram groups (2.1 ± 1.2 *versus* 1.9 ± 1.1, respectively) with similar trend when regarding observed values at W12 (1.8 ± 0.9 *versus* 1.7 ± 0.8, respectively). No relevant difference between groups was observed at W24 (LOCF) (1.9 ± 1.3 *versus* 1.8 ± 1.1, respectively), which was confirmed when regarding corresponding observed values at W24 visit (1.4 ± 0.7 *versus* 1.4 ± 0.6, respectively).

Response to treatment (CGI global improvement score = 1 or 2)

As regards to response to treatment in the FAS over the W0-W12 period, the percentage of responders increased in both treatment group with a slightly lower rate of responders in the agomelatine group than in the escitalopram group at W12 (LOCF) (72.9% *versus* 78.2%); a similar trend was seen at W12 when regarding observed values (82.7% *versus* 86.0%, respectively). At W24 (LOCF), the rate of responders showed the same trend *i.e.* a slightly lower rate in the agomelatine group than in the escitalopram group (77.9% *versus* 81.6%, respectively). When regarding observed values at W24 visit, results were similar in both groups (94.7% *versus* 94.0%, respectively).

SUMMARY – CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

- THAT

The mean **THAT** total score increased over the W0-W12 period in the FAS in both treatment groups, indicating that patient felt more alert. At W12 (LOCF), the mean change from baseline was lower in the agomelatine group than in the escitalopram group (7.8 ± 10.3 *versus* 9.6 ± 9.9, respectively): these changes corresponded to mean THAT total scores of 29.4 ± 10.3 (median = 30.0) in the agomelatine group and 31.3 ± 9.7 (median = 33.0) in the escitalopram group. When regarding observed values at W12, there was no relevant difference between groups in mean change from baseline (9.3 ± 10.1 in the agomelatine group *versus* 10.5 ± 9.6 in the escitalopram group, corresponding to mean THAT total scores of 30.9 ± 9.6 (median = 32.0) *versus* 32.3 ± 9.2 (median = 33.0), respectively).
At W24 (LOCF), the mean change from baseline was lower in the agomelatine group than in the escitalopram group (9.1 ± 10.5 *versus* 11.2 ± 10.5, respectively): these changes corresponded to mean THAT total score of respectively 30.6 ± 10.8 (median = 33.0) *versus* 32.9 ± 9.6 (median = 34.5).
Results regarding observed values at W24 showed no relevant difference between agomelatine and escitalopram groups: the mean changes from baseline were 11.7 ± 9.6 *versus* 12.8 ± 10.0, respectively, corresponding to mean THAT total score of 33.2 ± 9.5 (median = 35.0) *versus* 34.6 ± 8.6 (median = 36.0).

- LSEQ

The 4 mean LSEQ scores decreased over the W0-W12 period in the FAS in both treatment groups showing that the patients had a sleep improvement compared to the period without medication. At W12 (LOCF), there were no relevant differences between groups for any score, as follows:

- Getting off to sleep score at W12 (LOCF): 37.8 ± 18.6 mm on agomelatine *versus* 39.5 ± 18.4 mm on escitalopram.
- Quality of sleep score at W12 (LOCF): 36.9 ± 21.3 mm *versus* 37.7 ± 22.2 mm, respectively.
- Sleep awakening score at W12 (LOCF): 43.1 ± 20.2 mm *versus* 43.1 ± 21.5 mm, respectively.
- Integrity of behaviour score at W12 (LOCF): 42.7 ± 21.5 mm *versus* 41.0 ± 21.2 mm, respectively.

It is however noteworthy that the mean getting off to sleep score and quality of sleep score were lower in the agomelatine group than in the escitalopram group at W2 (observed values) (respectively 40.1 ± 17.6 *versus* 44.8 ± 18.3 for getting off to sleep score and 41.2 ± 19.8 *versus* 45.3 ± 21.4 for quality of sleep score) showing an earlier effect of agomelatine on these 2 criteria compared to escitalopram.

- SHAPS

Regarding the SHAPS in the FAS over the W0-W12 period, the total score decreased in both treatment groups indicating that patients improved in their ability to experienced pleasure. At W12 (LOCF), the mean ± SD change from baseline was lower in the agomelatine group than in the escitalopram group (-3.1 ± 7.1 *versus* -4.2 ± 6.5, respectively). There was a similar trend when regarding observed values at W12 (respectively -3.8 ± 7.0 *versus*-4.7 ± 6.2).
Over the W0-W24 period in the FAS, the mean ± SD change from baseline to W24 (LOCF) was lower in the agomelatine group than in the escitalopram group (respectively -3.8 ± 7.6 *versus* -5.1 ± 7.0). This trend was similar when regarding observed values at W24 visit (respectively -5.0 ± 7.5 *versus* -6.1 ± 6.6).

Regarding secondary efficacy criteria in the Sub-FAS of more severely anxious patients (patients with a CGI Severity of illness score at W0 greater than or equal to 5) and in the OC at W12 results were, for most of them, along the same lines as those observed in the FAS.

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Due to the high number of patients who did not continue at W24 (*i.e.* stopped at W24 following Amendment No. 4 or withdrawn on the W0-W24 period: 364/523 *i.e.* 69.6% of the RS), analyses on W0-W53 periods should be interpreted with caution.

- **Emergent adverse events**

Overall summary of emergent adverse events in the Safety Set over the W0-W13 period

		Agomelatine (N = 260)	Escitalopram (N = 262)
Patients having reported			
at least one emergent adverse event	n (%)	122 (46.9)	154 (58.8)
at least one treatment-related emergent adverse event	n (%)	82 (31.5)	114 (43.5)
Patients having experienced			
at least one serious emergent event (including death)	n (%)	7 (2.7)	6 (2.3)
at least one treatment-related emergent serious adverse event	n (%)	6 (2.3)	2 (0.8)
Patients with treatment withdrawal			
due to an emergent adverse event	n (%)	17 (6.5)	22 (8.4)
due to an emergent serious adverse event	n (%)	3 (1.2)	2 (0.8)
due a treatment-related emergent adverse event	n (%)	15 (5.8)	22 (8.4)
due a treatment-related emergent serious adverse event	n (%)	3 (1.2)	2 (0.8)
Patients who died	n (%)	-	-

N: Number of patients in each treatment group, n: Number of patients, %: (n/N)x100

Overall summary for adverse events in the Safety Set over the W0-W25 period

		Agomelatine (N = 260)	Escitalopram (N = 262)
Patients having reported			
at least one emergent adverse event	n (%)	139 (53.5)	171 (65.3)
at least one treatment-related emergent adverse event	n (%)	86 (33.1)	120 (45.8)
Patients having experienced			
at least one serious emergent event (including death)	n (%)	8 (3.1)	12 (4.6)
at least one treatment-related emergent serious adverse event	n (%)	7 (2.7)	2 (0.8)
Patients with treatment withdrawal			
due to an emergent adverse event	n (%)	18 (6.9)	23 (8.8)
due to an emergent serious adverse event	n (%)	3 (1.2)	3 (1.1)
due a treatment-related emergent adverse event	n (%)	15 (5.8)	22 (8.4)
due a treatment-related emergent serious adverse event	n (%)	3 (1.2)	2 (0.8)
Patients who died	n (%)	-	-

N: Number of patients in each treatment group, n: Number of patients, %: (n/N)x100

Overall summary for adverse events in the Safety Set over the W0-W53 period

		Agomelatine (N = 260)	Escitalopram (N = 262)
Patients having reported			
at least one emergent adverse event	n (%)	148 (56.9)	175 (66.8)
at least one treatment-related emergent adverse event	n (%)	91 (35.0)	121 (46.2)
Patients having experienced			
at least one serious adverse event (including death)	n (%)	8 (3.1)	17 (6.5)
at least one serious emergent event (including death)		8 (3.1)	16 (6.1)
at least one treatment-related serious adverse event	n (%)	7 (2.7)	3 (0.8)
Patients with treatment withdrawal			
due to an emergent adverse event	n (%)	19 (7.3)	25 (9.5)
due to an emergent serious adverse event	n (%)	3 (1.2)	3 (1.1)
due a treatment-related emergent adverse event	n (%)	16 (6.2)	22 (8.4)
due a treatment-related emergent serious adverse event	n (%)	3 (1.2)	2 (0.8)
Patients who died	n (%)	-	-

N: Number of patients in each treatment group, n: Number of patients, %: (n/N)x100

SUMMARY – CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

During the W0-W13 period (including the tapering period) in the Safety Set, the incidence of patients who reported at least one emergent adverse event (EAE) was lower in the agomelatine group than in the escitalopram group (46.9% *versus* 58.8%, respectively).

The most frequently affected system organ classes (in more than 10% of patients) in the agomelatine group were nervous system disorders (18.5%), gastrointestinal disorders (18.1%), infections and infestations (11.5%) and psychiatric disorders (10.0%). These SOCs were also the most frequently reported in the escitalopram group. Among them, gastrointestinal disorders and psychiatric disorders were less reported in the agomelatine than in the escitalopram group (18.1% *versus* 23.7% and 10.0% *versus* 16.8%, respectively).
The other system organ classes were less frequently affected in the agomelatine group than in the escitalopram group in particular skin and subcutaneous tissue disorders (2.3% of the patients *versus* 7.3%, respectively) and reproductive system and breast disorders (0.8% of the patients *versus* 4.6%, respectively) or showed no relevant difference between groups.

The most frequent emergent adverse events on agomelatine (> 3% of patients) were headache (10.4%), nausea (6.5%), fatigue (4.6%), nasopharyngitis (4.2%) and dry mouth (3.8%). In the escitalopram group, the most frequent EAEs were nausea (17.9%), headache (12.2%), insomnia (6.1%), hyperhidrosis (5.0%), diarrhoea (4.6%), fatigue (4.2%), nasopharyngitis (3.8%), dizziness (3.8%) and anxiety (3.4%).
Among the most frequent emergent adverse events reported in the agomelatine group, the incidence of dry mouth was higher in the agomelatine group than in the escitalopram group (3.8% *versus* 1.9%) and the incidence of nausea was lower in the agomelatine group than in the escitalopram group (respectively 6.5% *versus* 17.9%).
Regarding other emergent adverse events, the incidence of the following ones was higher in the agomelatine group than in the escitalopram group: tension headache (2.7% *versus* 1.1%, respectively), constipation (2.7% *versus* none, respectively) and irritability (1.5% *versus* none, respectively).
Other emergent adverse events were less frequently reported in the agomelatine group than in the escitalopram group or showed no relevant difference between groups.

Most of emergent adverse events were rated as mild or moderate (at least 90% of the EAEs) in both treatment groups. The percentage of severe EAEs was similar in agomelatine and escitalopram groups (9.0% *versus* 8.6%, respectively).

The percentage of patients with at least one treatment-related EAE was lower in the agomelatine group than in the escitalopram group (31.5% *versus* 43.5%, respectively). Among these EAEs, dry mouth and constipation were more frequently reported in the agomelatine group than in the escitalopram group (3.5% *versus* 1.9% and 2.3% *versus* none, respectively).

No relevant difference between groups was observed regarding the rate of patients having at least one EAE leading to treatment stopped (6.5% of the patients in the agomelatine group *versus* 8.4% in the escitalopram group).

No death was reported during the study.

Over the W0-W13 period, the incidence of patients who experienced serious emergent adverse events (SEAEs) was similar in both groups: 7 patients (2.7%) in the agomelatine group *versus* 6 patients (2.3%) in the escitalopram group. All SEAEs were reported once. SEAEs led to study drug withdrawal in 3 patients (1.2%) in the agomelatine group *versus* 2 patients (0.8%) in the escitalopram group. SEAEs were considered as treatment-related in 6 patients (2.3%) in the agomelatine group *versus* 2 patients (0.8%) in the escitalopram group.
Results regarding emergent adverse events over the W0-W25 and W0-W53 periods showed similar trends between groups compared to those observed over the W0-W13 period. The difference between groups in the rate of patients with at least one serious EAE was more marked over W0-W25 period (3.1% *versus* 4.6%, respectively) and W0-W53 period (3.1% *versus* 6.5%, respectively) than over W0-W12 period (2.7% *versus* 2.3%, respectively).

SUMMARY – CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

- **Laboratory tests**

In the Safety Set, neither clinically relevant changes nor differences between groups over time were detected for biochemical (including liver parameters) and haematological parameters over the W0-W13 period. Similar trends were observed on W0-W25 and W0-W53 periods.

In the Safety Set over the W0-W13 period, emergent biochemical potentially clinically significant abnormal values (PCSA) other than those for liver parameters were sparse in both treatment groups, except for the triglycerides (high PCSA values), which were more frequently reported in the agomelatine group than in the escitalopram group (9 patients, 3.8% *versus* 5 patients, 2.1%). For 2 patients in the agomelatine group and one patient in the escitalopram group, these PCSA values were observed in non-fasting samples.
Regarding emergent haematological PCSA values, the only emergent haematological PCSA values observed in the agomelatine group were low leucocytes reported in 4 patients *versus* none in the escitalopram.
Similar trends were observed over W0-W25 and W0-W53 periods.

Regarding liver acceptability, PCSA values reported during the W0-W13 period were sparse without relevant difference between agomelatine and escitalopram groups, as follows: high aspartate aminotransferase (AST) (one patient *versus* 2 patients, respectively), high alanine aminotransferase (ALT) (2 patients *versus* 4 patients) and high gamma-glutamyl transferase (GGT) (3 patients in both groups).
Over the W0-W25 period, emergent high PCSA values were reported as follows: high AST (one patient *versus* 2 patients, respectively), high ALT (3 patients *versus* 4 patients) and high GGT (3 patients *versus* 4 patients).
Over the W0-W53 period, emergent high PCSA values were reported as follows: high AST (one patient *versus* 3 patients, respectively), high ALT (3 patients *versus* 5 patients) and high GGT (3 patients *versus* 5 patients).
PCSA transaminase elevations (AST or ALT > 3 ULN) reported in the 3 patients of the agomelatine group under treatment over the W0-W53 period were considered as probably related to agomelatine, according to Liver Safety Committee (LSC) opinion.
In the escitalopram group, PCSA transaminases elevations (AST or ALT > 3 ULN) reported in 6 patients under treatment over the W0-W53 period were considered by the LSC as probably related in one patient, possibly related in one patient, unlikely related in 2 patients and not related in 2 patients.

- **C-SSRS**

Over the W2-W12 period, one patient in both agomelatine and escitalopram groups had suicidal ideation at the last post-baseline assessment without suicidal ideation at baseline; it can be noted that in the agomelatine group, 2 patients without suicidal ideations at baseline had missing status for suicidal ideations at last post-baseline assessment.
No suicidal behaviour was reported during the study. Overall, 2 patients in the agomelatine group had a missing status for suicidal behaviour (suicide attempt) at last post-baseline assessment without suicide attempt reported at baseline (within past year).
Similar results were observed over W2-W24 and W2-W52 periods.

- **Other safety evaluation**

There were no clinically relevant mean changes in weight, BMI, sitting blood pressures and heart rate between baseline and the last post-baseline value under treatment over the W0-W13 period in any group, nor relevant differences between the treatment groups. Similar results were observed over the W0-W25 and W0-W52 periods except a lower rate of patients with BMI class increase in the agomelatine group than in the escitalopram group: 1.9% *versus* 6.5% and 3.1% *versus* 8.0%, respectively.

Regarding ECG over the W0-W13 period, 3 patients in both the agomelatine and escitalopram groups reported at least one emergent clinically significant ECG abnormality under treatment. The investigator reported one case of "electrocardiogram QT prolonged" at W12 in the agomelatine group, which was contradicted by the expert cardiologist in charge of the ECG re-reading.
Over the W0-W23 periods and W0-W53 periods, 4 patients *versus* 3 and 7 patients *versus* 5 reported at least one emergent clinically significant ECG abnormality in the agomelatine and escitalopram groups, respectively.

CONCLUSION

This international, multicentre, double-blind, randomised phase III study conducted in non depressed out-patients with severe Generalized Anxiety Disorder (GAD) did not demonstrate the statistically non-inferiority of agomelatine (25-50 mg) as compared to escitalopram (10-20 mg) on anxious symptoms on the HAM-A total score (primary criterion) after a 12-week treatment period. This conclusion was confirmed in the subset of more severely anxious patients.

The safety profile of agomelatine over the 12-week, 24-week and 52-week treatment periods was satisfactory. The rate of emergent adverse events was lower in the agomelatine group than in the escitalopram group, especially for gastrointestinal and psychiatric disorders. No relevant difference between groups was observed regarding the PCSA values of liver function tests.

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