

<i>Document title</i>	<b>CLINICAL STUDY REPORT SYNOPSIS</b>
<i>Study title</i>	<b>Efficacy and safety of 2 doses of agomelatine (10 mg/day or 25 mg/day) versus placebo given orally for 12 weeks in non-depressed out-patients with Generalized Anxiety Disorder.</b>
	<b>A 12-week randomised, double-blind, placebo-controlled, 3-arm parallel groups, international multicenter study.</b>
<i>Study drug</i>	<b>S 20098</b>
<i>Studied indication</i>	<b>Generalized Anxiety Disorder</b>
<i>Development phase</i>	<b>Phase III</b>
<i>Protocol code</i>	<b>CL3-20098-087</b>
<i>Study initiation date</i>	<b>19 August 2013</b>
<i>Study completion date</i>	<b>21 January 2015</b>
<i>Scientific advisor</i>	
<i>Sponsors</i>	<b>Institut de Recherches Internationales Servier (I.R.I.S.) 50 rue Carnot, 92284 Suresnes Cedex - France</b> <b>Les Laboratoires Servier, ICTR Russia Paveletskaya sq 2, bld 3, Moscow 115054 - Russia</b>
<i>Responsible medical officer</i>	
<i>GCP</i>	<b>This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.</b>
<i>Date of the report</i>	<b>19 August 2015</b>
<i>Version of the report</i>	<b>Final version</b>
	<b><del>CONFIDENTIAL</del></b>

## 2. SYNOPSIS

<b>Name of Sponsor:</b> <b>I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France</b> <b>Les Laboratoires Servier, ICTR Russia, Paveletskaya sq 2, bld 3, Moscow 115054 - Russia</b>		<i>(For National Authority Use only)</i>
<b>Test drug</b> <b>Name of Finished Product:</b> <b>Valdoxan®</b> <b>Name of Active Ingredient:</b> <b>Agomelatine (S 20098)</b>		
<b>Individual Study Table Referring to Part of the Dossier</b>	<b>Volume:</b>	<b>Page:</b>
<b>Title of study:</b> Efficacy and safety of 2 doses of agomelatine (10 mg/day or 25 mg/day) <i>versus</i> placebo given orally for 12 weeks in non-depressed out-patients with Generalized Anxiety Disorder. A 12-week randomised, double-blind, placebo-controlled, 3-arm parallel groups, international multicentre study. Protocol No.: CL3-20098-087 EudraCT No.: 2012-001666-15		
<b>National coordinators:</b>		
<b>Study centres:</b> In all, 35 centres located in 5 countries included a total of 412 patients: Finland (6 centres - 110 patients), Poland (9 centres - 56 patients), Russia (6 centres - 75 patients), Slovakia (6 centres - 71 patients), Ukraine (8 centres - 100 patients).		
<b>Publication (reference):</b> Not applicable.		
<b>Studied period:</b> Initiation date: 19 August 2013 (date of first visit first patient) Completion date: 21 January 2015 (date of last visit last patient)		<b>Phase of development of the study:</b> Phase III
<b>Objectives:</b> <b>The primary objective</b> was to demonstrate the short-term efficacy of at least one of the 2 doses of agomelatine ( <i>versus</i> placebo) using Hamilton Anxiety rating scale (HAM-A) scale after a 12-week treatment period.  <b>The secondary objectives were:</b> <ul style="list-style-type: none"> <li>- To assess the short-term efficacy on anxiety symptoms, global improvement and social functioning using HAM-A sub-scores, Clinical Global Impression Scale (CGI), Hospital Anxiety and Depression scale (HAD) and Sheehan Disability Scale (SDS).</li> <li>- To provide additional safety and tolerability data on agomelatine. Usual safety parameters and liver function parameters were carefully assessed throughout the study.</li> <li>- To evaluate the associations between polymorphisms in candidate genes on efficacy and safety of agomelatine in a pharmacogenetic sub-study. Detailed information is available in the attached sub-study protocol.</li> </ul>		
<b>Methodology:</b> Phase III, international, multicentre study, placebo-controlled, double-blind, randomised in 3 parallel groups (agomelatine 10 mg/day, agomelatine 25 mg/day and placebo) in non depressed out-patients suffering from Generalized Anxiety Disorder (GAD). The randomisation was balanced (non adaptive and non centralized), with stratification on the centre.  This study was performed in strict accordance with Good Clinical Practice (GCP) including the archiving of essential documents.		
<b>Number of patients:</b> <b>Planned:</b> approximately 390 included patients (130 in each treatment group). <b>Included and randomised:</b> 412 patients (131 in the agomelatine 10 mg/day group, 139 in the agomelatine 25 mg/day group and 142 in the placebo group).		

**Diagnosis and main criteria for inclusion:**

Adult (18 years or legal age for majority) out-patients of both genders, fulfilling DSM-IV criteria for GAD (confirmed by M.I.N.I structured interview). At selection, Hamilton Anxiety Rating Scale (HAM-A) total score was to be  $\geq 22$ , HAM-A item 1 (anxious mood)  $\geq 2$  and item 2 (tension)  $\geq 2$ , HAM-A item 1 + item 2  $\geq 5$ , HAD anxious score  $\geq$  HAD depression score, and MADRS total score was to be  $\leq 16$ . At inclusion HAM-A total score was still to be  $\geq 22$  with no more than a 20% of decrease (if any) in HAM-A total score between selection and inclusion.

**Test drug:**

Agomelatine 10 or 25 mg: one capsule once daily taken orally at bedtime.

Batch Nos.: L0044520, L0047630 (10 mg), L0045269, L0047704 (25 mg)

**Comparator (Reference product and/or placebo):**

Matching placebo: 1 capsule once daily taken orally at bedtime.

**Duration of treatment:**

- Run-in period: 1-2 weeks without treatment (from selection (ASSE) to inclusion (W0)).
- Active treatment period in double blind: 12 weeks: agomelatine 10 mg/day or 25 mg/day or placebo (from W0 to W12).
- Follow-up period: 1 week without any study treatment after W12 or after treatment discontinuation.

**Criteria for evaluation:**Efficacy measurements:

- HAM-A rated by the investigator at the selection and inclusion visits, and at each visit during the treatment period (W2, W4, W8, and W12). The primary criterion was the HAM-A total score mainly analysed as change from baseline to W12.
- CGI rated by the investigator. At the selection and inclusion visits, only CGI severity of illness was rated, and at each visit during the treatment period (W2, W4, W8, and W12) both severity and improvement were rated.
- Hospital Anxiety and Depression Scale (HAD); Anxiety and Depression sub-scores were rated by the patient at selection, inclusion, W8, W12 or at withdrawal visit in case of premature withdrawal.
- Sheehan Disability Scale (SDS) score; Work, Social life and Family life scores were rated by the patient at selection, W8, W12 or at withdrawal visit in case of premature withdrawal.

Safety measurements:

- Adverse events reported at each visit.
- Laboratory tests (haematology and biochemistry including liver parameters): blood samplings were prescribed at selection, W4, W8, W12 or at the withdrawal visit in case of premature withdrawal. At W4 and W8 only liver parameters were assessed.
- Clinical examination: Sitting Systolic/Diastolic Blood Pressure (SBP/DBP), heart rate (HR), body weight and body mass index (BMI) were measured at selection, inclusion, W12 or at withdrawal visit in case of premature withdrawal.
- Columbia-Suicide Severity Rating Scale (C-SSRS) was rated by the investigator at inclusion, W2, W4, W8 and W12 visits.
- 12-lead ECG was performed, at selection, W12 or at withdrawal visit in case of premature withdrawal.

Sub-Study

Pharmacogenetic study sample collection was to be performed once at any time between W2 and W12 of treatment. Results will be the subject of a separate report.

**Statistical methods:*****Analysis Set:***

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

**Statistical methods (Cont'd):****Efficacy analysis:****Primary criterion: HAM-A total score****Primary analysis**

The superiority of at least one agomelatine dose as compared to placebo on anxiety symptoms after a 12-week treatment period was assessed in patients of the FAS on the change from baseline to W12 of HAM-A total score, using a single 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 (primary analysis). Missing data were imputed using the LOCF approach and the Hochberg procedure was used to take into account the multiplicity of comparisons.

**Sensitivity analyses**

To assess the robustness of the results of the primary analysis, the following sensitivity analyses to the method of handling missing data were performed in the FAS:

- Mixed-effects Model for Repeated Measures (MMRM): each agomelatine dose was compared to placebo on the change from baseline to W12 of HAM-A total score, 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 analysis: the same ANCOVA as for the primary analysis was performed on the change from baseline to W12 in patients having a value of HAM-A total score at W12.
- For both sensitivity analyses, the Hochberg procedure was used to control the familywise error rate.

In addition, descriptive statistics were provided by treatment group for all expressions of the primary efficacy criterion in the FAS. In particular, descriptive statistics were also given after imputing missing data at W12 using the LOCF approach for the description of the value at this visit and the change from baseline to this visit.

**Secondary analyses**

The same analysis strategy as for the primary analysis, including sensitivity analyses to the method of handling missing data and Hochberg procedure, was implemented for the two subsets of patients of the FAS with more severe anxious symptoms (SFAS1, *i.e.* W0 HAM-A total score  $\geq 25$ , and SFAS2, *i.e.* W0 HAM-A total score  $\geq 25$  and W0 CGI  $\geq 5$ ).

Moreover, each agomelatine dose was compared to placebo in patients of the FAS on the response to treatment derived from HAM-A total score (defined as a decrease from baseline  $\geq 50\%$ ) at W12, imputing missing data with the LOCF approach, using a Chi-Square test.

In addition, descriptive statistics were provided by treatment group for response to treatment at each post-baseline visit and at W12 after imputing missing data using the LOCF approach in the FAS.

Descriptive statistics were also provided by treatment group for all expressions of the primary efficacy criterion, including response to treatment, on the W0-W12 period in the two subgroups of more anxious patients in the FAS.

**Secondary criteria**

The difference between each dose of agomelatine and placebo was studied in patients of the FAS on anxiety symptoms after a 12-week treatment period:

- From CGI scores (Severity of illness score and Global Improvement score) using a two-sided Student's t-test for independent samples and a Mann-Whitney test on the value at W12, imputing missing data with the LOCF approach.
- From response to treatment (derived from CGI Global Improvement score and defined as a score equal to 1 or 2) using a Chi-Square test on the value at W12, imputing missing data with the LOCF approach.

In addition, descriptive statistics were provided by treatment group for all expressions of secondary efficacy criteria (HAM-A Psychic and Somatic anxiety scores, CGI scores and response, HAD Anxiety and Depression sub-scores and SDS scores) on the W0-W12 period in the FAS. Besides, all expressions of secondary criteria derived from HAM-A and CGI scales were described by treatment group in the two subgroups of patients of the FAS with more severe anxious symptoms. In particular, descriptive statistics were also provided after imputing missing data at W12 using the LOCF approach for the description of the value at this visit and the change from baseline to this visit, if applicable.

**Study outcome and safety analyses:** Descriptive statistics were provided in the Safety Set by treatment group over the W0-W12 period.

**SUMMARY - CONCLUSIONS****DISPOSITION OF PATIENTS AND ANALYSIS SETS****Disposition of randomised patients by treatment and overall**

Status	Agomelatine 10 mg	Agomelatine 25 mg	Placebo	All
	n (%)	n (%)	n (%)	n (%)
<b>Included</b>	<b>131</b>	<b>139</b>	<b>142</b>	<b>412</b>
In compliance with the protocol	130	135	139	404
With a protocol deviation before or at inclusion	1	4	3	8
<b>Withdrawn due to</b>	<b>18 (13.7)</b>	<b>13 (9.4)</b>	<b>30 (21.1)</b>	<b>61 (14.8)</b>
Lack of efficacy	8 (6.1)	1 (0.7)	20 (14.1)	29 (7.0)
Non-medical reason	8 (6.1)	8 (5.8)	8 (5.6)	24 (5.8)
Adverse event	1 (0.8)	3 (2.2)	1 (0.7)	5 (1.2)
Protocol deviation	1 (0.8)	1 (0.7)	1 (0.7)	3 (0.7)
<b>Lost to follow-up</b>	-	-	-	-
<b>Study completed</b>	<b>113 (86.3)</b>	<b>126 (90.6)</b>	<b>112 (78.9)</b>	<b>351 (85.2)</b>
In compliance with the protocol	111	123	108	342
With a protocol deviation after inclusion	2	3	4	9
<b>Randomised Set (RS)</b>	<b>131</b>	<b>139</b>	<b>142</b>	<b>412</b>
<b>Efficacy Sets</b>				
Full Analysis Set (FAS)	130 (99.2)	138 (99.3)	140 (98.6)	408 (99.0)
Sub-FAS with W0 HAM-A total score $\geq$ 25 (SFAS1)	115 (87.8)	122 (87.8)	128 (90.1)	365 (88.6)
Sub-FAS with W0 HAM-A total score $\geq$ 25 and W0 CGI-S $\geq$ to 5 (SFAS2)	65 (49.6)	72 (51.8)	65 (45.8)	202 (49.0)
<b>Safety Set (SS)</b>	<b>131 (100)</b>	<b>139 (100)</b>	<b>140 (98.6)</b>	<b>410 (99.5)</b>

*% calculated according to the number of patients included/randomised in each treatment group; n: number of patients affected;*

A total of 412 patients were included and randomly assigned to one of the 3 following treatment groups: 131 patients in the agomelatine 10 mg group, 139 in the agomelatine 25 mg group, and 142 in the placebo group.

During the W0-W12 period, the rate of study withdrawal was lower in both agomelatine groups (13.7% in the agomelatine 10 mg group and 9.4% in the agomelatine 25 mg group) than in the placebo group (21.1%). The most frequent reason of withdrawal was lack of efficacy, with a lower frequency in the 2 agomelatine groups (6.1% in the agomelatine 10 mg group and 0.7% in the agomelatine 25 mg group) than in the placebo group (14.1%).

**BASELINE CHARACTERISTICS**

In the Randomised Set, patients were aged from 18 to 81 years (8.7% of them were aged at least 65 years old), with a mean  $\pm$  SD of  $43.9 \pm 13.9$  years. Most patients were female (67.7%).

The time since GAD diagnosis covered a wide range from 0 to 632 months (0 - 52.7 years) and at least 25% of patients had a GAD diagnosis made within the month before selection. The duration since the first anxiety symptoms with a functional impact ranged within 6 to 716 months (0.5 - 59.7 years) with a median duration of 44 months (3.7 years), without relevant differences between groups.

As regards C-SSRS at inclusion, a total of 5.3% of patients reported suicidal ideations during their lifetime and 1.5% within the last month, without relevant difference between groups. At inclusion, one patient in the placebo group reported a suicidal behaviour during her lifetime (actions or preparations toward an imminent suicidal behaviour as well as one suicide attempt). Non-suicidal self-injurious behaviour was reported, in the past year in one patient in the placebo group, and during lifetime in one patient of the agomelatine 25 mg group.

In all, 39.8% of patients had taken previous psychotropic treatments, *i.e.* antidepressants (24.5% of patients), and/or anxiolytics (17.7%) including benzodiazepines (10.4%), within the last 12 months before the selection. At inclusion, no patient received a specific concomitant treatment.

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

At selection, the mean  $\pm$  SD MADRS total score was  $11.6 \pm 2.5$ ; all patients fulfilled the selection/inclusion criteria (*i.e.* MADRS total score  $\leq 16$  as required by the study protocol).

At baseline, the mean  $\pm$  SD HAM-A total score was  $28.8 \pm 3.6$ , ranging from 22 to 40, *i.e.*  $\geq 22$  as required in the selection/inclusion criteria. The mean  $\pm$  SD HAM-A psychic anxiety score was higher than the mean  $\pm$  SD HAM-A somatic anxiety score ( $16.0 \pm 2.3$  versus  $12.8 \pm 2.6$ , respectively). The mean  $\pm$  SD CGI severity of illness was  $4.5 \pm 0.6$ , and the mean  $\pm$  SD HAD anxiety sub-score and depression sub-score were of  $14.5 \pm 2.5$  and  $6.1 \pm 2.9$  respectively. The mean  $\pm$  SD SDS total score was ( $18.9 \pm 4.2$ ) and item scores *i.e.*, work, social and family life were respectively  $6.4 \pm 1.7$ ,  $6.5 \pm 1.8$  and  $6.3 \pm 1.7$ .

There were no clinically relevant differences between the treatment groups for demographic criteria, GAD characteristics (except time since GAD diagnosis), HAM-A total score, and all anxiety criteria.

Baseline characteristics in the FAS were similar to those observed in the Randomised Set. In the 2 FAS subsets of more severely anxious patients (SFAS1 *i.e.* sub-FAS with W0 HAM-A total score  $\geq 25$ , and SFAS2 *i.e.* with W0 HAM-A total score  $\geq 25$  and CGI S  $\geq 5$ ), apart for the criteria defining the subsets and the median duration since GAD diagnosis in SFAS1 as well as median duration since the first anxiety symptoms with a functional impact in the agomelatine 25 mg and placebo groups in the SFAS2, baseline characteristics were similar to those observed in the Randomised Set.

**EXTENT OF EXPOSURE**

In the Randomised Set, the mean  $\pm$  SD treatment duration over the W0-W12 period was  $78.6 \pm 16.1$  days with a median of 84 days. The mean  $\pm$  SD overall compliance was  $97.9 \pm 9.9\%$  and for 98.3% of patients, the compliance was comprised in the [70 ; 130]% range. There was no relevant difference between the treatment groups regarding duration of treatments and compliance to them during the study.

**EFFICACY RESULTS****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 all treatment groups. At W12 (LOCF), the mean decrease from baseline was statistically significantly superior in the 2 agomelatine groups than in the placebo group as follows (primary analysis: adjustment for baseline HAM-A total score and centre (random effect); Missing data: LOCF approach; see Table below):

- Agomelatine 10 mg group *versus* placebo: E (SE) = 7.16 (1.00), 95% CI = [5.19 ; 9.13],  $p < 0.0001$ .
- Agomelatine 25 mg group *versus* placebo: E (SE) = 11.08 (0.98), 95% CI = [9.14 ; 13.01],  $p < 0.0001$ .

In the agomelatine 25 mg group, the difference *versus* placebo was greater than in the agomelatine 10 mg group.

These results were confirmed by the following sensitivity analyses to the method of handling missing data, using:

- MMRM:
  - Agomelatine 10 mg group *versus* placebo E (SE) = 6.97 (1.02), 95% CI = [4.95 ; 8.98],  $p < 0.0001$ .
  - Agomelatine 25 mg group *versus* placebo: E (SE) = 11.26 (1.01), 95% CI = [9.27 ; 13.24],  $p < 0.0001$ .
- Observed cases analysis:
  - Agomelatine 10 mg group *versus* placebo: E (SE) = 6.14 (1.00), 95% CI = [4.17 ; 8.10],  $p < 0.0001$ .
  - Agomelatine 25 mg group *versus* placebo E (SE) = 9.66 (0.98), 95% CI = [7.72 ; 11.59],  $p < 0.0001$ .

**SUMMARY - CONCLUSIONS (Cont'd)****EFFICACY RESULTS (Cont'd)**

**Summary results of HAM-A total score: Change from baseline to W12 (LOCF),  
response to treatment at W12 (LOCF) and between-group comparisons to the placebo in the FAS**

		<b>Agomelatine 10 mg (N = 130)</b>	<b>Agomelatine 25 mg (N = 138)</b>	<b>Placebo (N = 140)</b>
	n	130	138	140
<b>Change from baseline to W12 (LOCF)</b>	<b>Mean ± SD</b>	<b>-13.7 ± 8.7</b>	<b>-18.0 ± 7.7</b>	<b>-6.9 ± 9.2</b>
<b>Statistical analysis</b>				
<b>Primary analysis<sup>(a)</sup></b> (change from baseline to W12 (LOCF))	E (SE) <sup>(1)</sup>	7.16 (1.00)	11.08 (0.98)	
	95% CI <sup>(2)</sup>	[5.19 ; 9.13]	[9.14 ; 13.01]	
	p-value <sup>(3)</sup>	< <b>0.0001</b> <sup>(4)</sup>	< <b>0.0001</b> <sup>(1)</sup>	
<b>Responders* at W12 (LOCF)</b>	<b>n (%)</b>	<b>67 (51.5)</b>	<b>97 (70.3)</b>	<b>32 (22.9)</b>
<b>Statistical analysis</b>				
	E (SE) <sup>(4)</sup>	28.68 (5.64)	47.43 (5.27)	
	95% CI <sup>(2)</sup>	[17.63 ; 39.74]	[37.11 ; 57.75]	
	p-value <sup>(5)</sup>	< <b>0.0001</b>	< <b>0.0001</b>	

N: Number of patients in each treatment group.

n: Number of patients.

%. (n/N)x100

\* A responder to treatment was defined as a patient with a decrease in HAM-A total score of at least 50% from baseline.

(a) Analysis of covariance model on factor treatment with baseline HAM-A total score and centre (random effect) as covariates.

(1) Estimate (Standard Error) of the difference between adjusted treatment group means: Placebo minus Agomelatine dose.

(2) Two-sided 95% Confidence Interval of the estimate (without Hochberg adjustment).

(3) Two-sided Hochberg-adjusted p-value (to be compared to 0.05) with (I) / (II) corresponding to the ordered unadjusted p-values from the most significant to the least significant one.

(4) Estimate (Standard Error) of the difference between treatment group percentages: Agomelatine dose minus Placebo

(5) Two-sided p-value (Chi-Square test)

**Change from baseline to W12 in the SFAS1 and SFAS2**

In the two FAS subgroups of more severely anxious patients, results were in the same way as in the FAS. In both subsets, the mean change from baseline to W12 was statistically significantly higher in the 2 agomelatine groups than in the placebo group, after adjustment for centre (random effect) and baseline HAM-A total score, and using LOCF approach for missing data at W12, as follows:

- In the SFAS1:
  - Agomelatine 10 mg group *versus* placebo: E (SE) = 7.20 (1.06), 95% CI = [5.11 ; 9.29], p < 0.0001.
  - Agomelatine 25 mg group *versus* placebo: E (SE) = 11.72 (1.05), 95% CI = [9.67 ; 13.78], p < 0.0001.
- In the SFAS2:
  - Agomelatine 10 mg group *versus* placebo: E (SE) = 8.11 (1.39), 95% CI = [5.37 ; 10.84], p < 0.0001.
  - Agomelatine 25 mg group *versus* placebo: E (SE) = 12.86 (1.35), 95% CI = [10.20 ; 15.52], p < 0.0001.

It is noteworthy that in the two SubFAS as in the FAS, the effect size of the agomelatine 25 mg dose was greater than with the 10 mg dose.

Results were confirmed by sensitivity analyses to the method of handling missing data (MMRM and observed case analysis; with p < 0.0001) in SFAS1 and SFAS2.

**Response to treatment according to HAM-A total score in the FAS**

In the FAS, the percentage of responders was statistically significantly greater in the 2 agomelatine groups (with a higher rate of responders in the 25 mg group) than in the placebo group at W12 (LOCF), as follows (see results in the table above):

- Agomelatine 10 mg group: 51.5% *versus* 22.9% responders, respectively, E (SE) = 28.68 (5.64); 95% CI = [17.63 ; 39.74]%, p < 0.0001 (Chi-Square test).
- Agomelatine 25 mg group: 70.3% *versus* 22.9% responders, respectively, E (SE) = 47.43 (5.27); 95% CI = [37.11 ; 57.75]%, p < 0.0001 (Chi-Square test).

**SUMMARY - CONCLUSIONS (Cont'd)****EFFICACY RESULTS (Cont'd)****Response to treatment according to HAM-A total score in the SFAS1 and SFAS2**

Descriptive results observed in each FAS subgroup were in the same line than those observed in the FAS, *i.e.*, a greater rate of responders at W12 (LOCF) in the 2 agomelatine groups (especially in the 25 mg group) than in the placebo group, as follows:

- In the SFAS1: 49.6% and 71.3% *versus* 21.1% responders, respectively for agomelatine 10 mg and 25 mg groups *versus* placebo.
- In the SFAS2: 50.8% and 70.8% *versus* 15.4% responders, respectively.

**Secondary assessment criteria****HAM-A psychic anxiety score**

In the FAS, the HAM-A psychic anxiety mean score decreased from baseline to W12 (LOCF) with a higher decrease in the agomelatine 10 mg and 25 mg groups ( $-7.8 \pm 4.9$  and  $-10.2 \pm 4.7$ , respectively) than in the placebo group ( $-3.9 \pm 5.1$ ).

Similar results were observed in the 2 FAS subsets of more severely anxious patients.

**HAM-A somatic anxiety score**

In the FAS, the HAM-A somatic anxiety mean score decreased from baseline to W12 (LOCF) with a higher decrease in the agomelatine 10 mg and 25 mg groups ( $-5.9 \pm 4.5$  and  $-7.8 \pm 3.9$ , respectively) than in the placebo group ( $-3.0 \pm 4.6$ ).

In the two FAS subsets of more severely anxious patients, similar descriptive results were observed.

**CGI Severity of illness score and global improvement score**

In the FAS, both mean CGI scores at W12 (LOCF) were statistically significantly lower in the 2 agomelatine groups (with a lower score in the 25 mg group) than in the placebo group (see results in Table below).

**Summary of statistical results of CGI at W12 (LOCF) in the FAS**

		Agomelatine 10 mg (N = 130)	Agomelatine 25 mg (N = 138)	Placebo (N = 140)
<b>CGI severity of illness score</b>				
W12 (LOCF)	Mean $\pm$ SD	2.9 $\pm$ 1.3	2.3 $\pm$ 1.0	3.8 $\pm$ 1.3
	Median	3.0	2.0	4.0
<b>Statistical analysis</b>	E (SE) <sup>(1)</sup>	0.82 (0.16)	1.42 (0.14)	
	95% CI <sup>(2)</sup>	[0.51 ; 1.13]	[1.14 ; 1.70]	
	p-value <sup>(3)</sup>	< 0.0001	< 0.0001	
	p-value <sup>(4)</sup>	< 0.0001	< 0.0001	
<b>CGI global improvement score</b>				
W12 (LOCF)	Mean $\pm$ SD	2.2 $\pm$ 1.1	1.7 $\pm$ 0.8	3.2 $\pm$ 1.3
	Median	2.0	1.0	3.0
<b>Statistical analysis</b>	E (SE) <sup>(1)</sup>	1.00 (0.15)	1.56 (0.13)	
	95% CI <sup>(2)</sup>	[0.71 ; 1.30]	[1.30 ; 1.82]	
	p-value <sup>(3)</sup>	< 0.0001	< 0.0001	
	p-value <sup>(4)</sup>	< 0.0001	< 0.0001	
<b>Responders* at W12 (LOCF)</b>	n (%)	87 (66.9)	116 (84.1)	39 (27.9)
<b>Statistical analysis</b>	E (SE) <sup>(5)</sup>	39.07 (5.60)	56.20 (4.91)	
	95% CI <sup>(2)</sup>	[28.09 ; 50.05]	[46.59 ; 65.82]	
	p-value <sup>(6)</sup>	< 0.0001	< 0.0001	

\* The response to treatment according to CGI-I was defined as a score = 1 or 2

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

(1) Estimate (Standard Error) of the difference between treatment group means: Placebo minus Agomelatine dose,

(2) Two-sided 95% Confidence Interval of the estimate,

(3) Two-sided p-value (Student's t-test),

(4) Two-sided p-value (Mann-Whitney test),

(5) Estimate (Standard Error) of the difference between treatment group percentages: Agomelatine dose minus Placebo,

(6) p-value of treatment effect (Chi-Square test)

**SUMMARY - CONCLUSIONS (Cont'd)****EFFICACY RESULTS (Cont'd)**

In the two FAS subsets of more severely anxious patients, descriptive results at W12 (LOCF) were similar to those observed in the FAS as follows:

- CGI Severity of illness score
  - In the SFAS1:  $3.0 \pm 1.2$  (median = 3.0) in the agomelatine 10 mg group and  $2.3 \pm 1.0$  (median = 2.0) in the agomelatine 25 mg group versus  $3.8 \pm 1.3$  (median = 4.0) in the placebo group.
  - In the SFAS2:  $3.1 \pm 1.2$  (median = 3.0) and  $2.3 \pm 1.2$  (median = 2.0) versus  $4.3 \pm 1.2$  (median = 5.0), respectively.
- CGI Global improvement score
  - In the SFAS1:  $2.3 \pm 1.1$  (median = 2.0) and  $1.6 \pm 0.8$  (median = 1.0), versus  $3.3 \pm 1.3$  (median = 3.0), respectively.
  - In the SFAS2:  $2.2 \pm 1.0$  (median = 2.0) and  $1.5 \pm 0.7$  (median = 1.0), versus  $3.3 \pm 1.3$  (median = 3.0), respectively.

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

In the FAS, the percentage of responders was statistically significantly higher in the 2 agomelatine groups than in the placebo group at W12 (LOCF) in the FAS, with a placebo-difference more pronounced in the agomelatine 25 mg group than in the agomelatine 10 mg group (see results in Table above).

In the two FAS subsets of more severely anxious patients, descriptive results at W12 (LOCF) were similar to those observed in the FAS:

- In the SFAS1: 65.2% of responders in the agomelatine 10 mg group and 86.1% in the agomelatine 25 mg group versus 26.6% in the placebo group.
- In the SFAS2: 67.7% and 87.5% versus 23.1%, respectively.

**HAD Anxiety sub-score**

In the FAS, the mean decrease in anxiety sub-score from baseline to W12 (LOCF), over the W0-W12 period, was higher in the 2 agomelatine groups than in the placebo group. It was more pronounced in the 25 mg group ( $-9.3 \pm 4.6$ ) than in the 10 mg group ( $-7.2 \pm 4.7$ ) (versus  $-3.2 \pm 4.6$  in the placebo group).

In addition, the percentage of anxious patients (anxiety sub-score of at least 11) decreased more in the 2 agomelatine groups than in the placebo group from baseline to W12 (LOCF), with a more pronounced decrease in the 25 mg group than in the 10 mg group: from 94.6% (123/130 patients) at baseline to 28.1% (36/128) at W12 (LOCF) in the agomelatine 10 mg group, from 96.4% (133/138) at baseline to 12.5% (17/136) at W12(LOCF) in the agomelatine 25 mg group, and from 92.1% (129/140) at baseline to 60.0% (84/140) at W12 (LOCF) in the placebo group.

**SDS**

In the FAS, self-patient assessment covering disruption of work, social life and family life or home responsibilities showed a better patients's improvement under the 2 agomelatine doses than under placebo in the 3 functional domains. At W12 (LOCF), the mean decreases from baseline in the 3 SDS scores (and total score) were higher in the 2 agomelatine groups than in the placebo group, with a more pronounced decrease in the agomelatine 25 mg group than in the 10 mg group, as follows:

- Work:  $-3.0 \pm 2.6$  (median -3.0) in the agomelatine 10 mg group and  $-3.9 \pm 2.8$  (median -4.0) in the agomelatine 25 mg group versus  $-1.5 \pm 2.5$  (median -1.0) in the placebo group.
- Social life:  $-3.1 \pm 2.8$  (median -3.0) and  $-4.3 \pm 2.5$  (median -5.0) versus  $-1.2 \pm 2.6$  (median -1.0), respectively.
- Family life and home responsibilities:  $-3.1 \pm 2.9$  (median -3.5) and  $-4.2 \pm 2.4$  (median -4.0) versus  $-1.3 \pm 2.4$  (median -1.0), respectively.
- Total score:  $-9.2 \pm 7.8$  (median -9.0) and  $-12.3 \pm 7.2$  (median -13.0) versus  $-4.1 \pm 6.8$  (median -3.0), respectively.

**SUMMARY - CONCLUSIONS (Cont'd)****SAFETY RESULTS****Overall summary of safety results in the Safety Set**

		<b>Agomelatine 10 mg (N = 131)</b>	<b>Agomelatine 25 mg (N = 139)</b>	<b>Placebo (N = 140)</b>
<b>Patients having reported</b>				
at least one emergent adverse event (EAE)	n (%)	39 (29.8)	48 (34.5)	36 (25.7)
at least one treatment-related EAE	n (%)	13 (9.9)	27 (19.4)	14 (10.0)
<b>Patients having experienced</b>				
at least one serious adverse event	n (%)	4 (3.1)	3 (2.2)	3 (2.1)
at least one serious EAE	n (%)	4 (3.1)	3 (2.2)	2 (1.4)
at least one treatment-related serious EAE	n (%)	1 (0.8)	1 (0.7)	-
<b>Patients with treatment withdrawal</b>				
due to an EAE	n (%)	1 (0.8)	3 (2.2)	2 (1.4)
due to an serious EAE	n (%)	1 (0.8)	1 (0.7)	1* (0.7)
due a treatment-related EAE	n (%)	-	2 (1.4)	-
due a treatment-related serious EAE	n (%)	-	-	-
<b>Patients who died</b>	n (%)	-	-	-

*N: Number of patients by treatment group, n: Number of patients in a category, %: n/N x100*

*\* For patient No. 087 804 0606 87235, the reason for study withdrawal was lack of efficacy*

**Emergent adverse events**

During the 12-week treatment period in the Safety Set, the percentage of patients who reported at least one emergent adverse event was higher in the 2 agomelatine groups (29.8% in the 10 mg group and 34.5% in the 25 mg group) than in the placebo group (25.7%).

As regards agomelatine groups, the percentage of patients with at least one emergent adverse event was lower in the agomelatine 10 mg group than in the 25 mg group.

The most frequently affected system organ classes (in more than 10 patients) in any agomelatine group were nervous system disorders, gastrointestinal disorders, and infections and infestations. In the placebo group it was nervous system disorders and infections and infestations. Nervous system disorders and gastrointestinal disorders were more common in the agomelatine 25 mg group (12.9% and 9.4%, respectively) than in the placebo group (8.6% and 4.3%) and similarly reported in the agomelatine 10 mg group (8.4% and 3.8%, respectively) and in the placebo group. The infections and infestations class was more common in the agomelatine 10 mg (11.5%) than in the placebo group (7.9%), and showed no relevant difference between the agomelatine 25 mg group (8.6%) and the placebo group. As regards the 2 agomelatine doses, nervous system disorders and gastrointestinal disorders were more common on 25 mg than on 10 mg, and inversely for infections and infestations.

The most frequent emergent adverse events on agomelatine (reported in at least 5 patients in any agomelatine group) were headache, nasopharyngitis and back pain. The frequency of headache was similar in the agomelatine 25 mg group and placebo group (6.5% and 6.4%, respectively), and lower in the agomelatine 10 mg group (4.6%) than in the placebo group. The frequency of nasopharyngitis was higher in the agomelatine 10 mg group than in the placebo group (5.3% versus 0.7%, respectively) and no relevant difference between the agomelatine 25 mg group (0.7%) and the placebo group was observed.

The frequency of back pain was higher in the agomelatine 25 mg group than in the placebo group (4.3% versus 0.7%, respectively). No patient reported back pain in the agomelatine 10 mg group. As regards the 2 agomelatine doses, headache and back pain were more common on 25 mg than on 10 mg, and inversely for nasopharyngitis.

Most emergent adverse events were graded as mild or moderate (at least 90% of events in any group).

Few patients (2 patients in each group) experienced severe emergent adverse events during the 12-week-treatment period.

During the 12-week treatment period, in the Safety Set, the percentage of patients with at least one emergent adverse event considered to be related to the study treatment by the investigator was higher in the agomelatine 25 mg group (19.4% of patients) than in the placebo (10.0%) and showed no relevant difference between the agomelatine 10 mg group (9.9%) and the placebo group. No serious event was upgraded in terms of causality by the Sponsor.

**SUMMARY - CONCLUSIONS (Cont'd)****SAFETY RESULTS (Cont'd)****Emergent adverse events (Cont'd)**

In the 2 agomelatine groups, the most common system organ class of treatment-related EAEs was nervous system disorders. Similar results were observed in the placebo group. The frequency of nervous system disorders was higher in the agomelatine 25 mg group (9.4%) than in the placebo (5.7%), and it was lower in the agomelatine 10 mg group (3.1%) than in the placebo group.

No death was reported during the study. The percentage of patients having reported at least one serious emergent adverse event (SEAEs) showed no relevant difference between groups: 4 patients, 3 patients and 2 patients respectively in the agomelatine 10 mg group, 25 mg group and placebo group. Among these patients, one patient in each agomelatine group (*versus* none in the placebo group) had SEAEs considered as treatment-related according to the investigator (somnolence in the 10 mg group, AST increased and ALT-increased in the 25 mg group - none of them led to study drug withdrawal). Emergent serious adverse events led to study drug withdrawal in one patient in each treatment group.

In all, 3 patients experienced at least one emergent non-serious adverse event leading to study treatment discontinuation: none in the agomelatine 10 mg group, 2 patients in the agomelatine 25 mg group and one patient in the placebo group.

**Clinically laboratory evaluation**

In the Safety Set, neither clinically relevant changes over time nor differences between groups were detected for biochemical and haematological parameters over both periods.

Few biochemical and haematological emergent PCSA values under treatment were observed in all treatment groups. The percentage of patients concerned was lower in the 2 agomelatine groups than in the placebo group or showed no relevant differences between groups.

As regards liver acceptability, emergent PCSA values of ALT and/or AST (> 3 ULN) were reported in 1 patient in the agomelatine 10 mg group and in 2 patients in the agomelatine 25 mg group (including one particular case in the 25 mg group) *versus* none in the placebo group.

The patient in the agomelatine 10 mg group had one emergent PCSA value of AST (4.1 ULN) reported as a serious adverse event and considered as not related to the study drug. According to the opinion of the committee of 5 independent experts (Liver Safety Committee; LSC) who assessed the case in blind conditions, this PCSA value of AST was considered unlikely related to agomelatine.

One patient in the agomelatine 25 mg group experienced emergent abnormal ALT and AST values at W8 which worsened at W12 and reached PCSA limits. These emergent PCSA values of ALT (11.4 ULN) and AST (8.3 ULN) were reported as serious adverse events and were considered as related to study treatment by the investigator. According to LSC opinion, these PCSA values were probably related to agomelatine.

In addition, a particular case was observed in the agomelatine 25 mg group, for which no laboratory report was available so no data was entered in the database. This patient reported emergent PCSA values for AST (7.0 ULN), ALT (5.7 ULN) and GGT (3.7 ULN) reported as serious adverse events and considered as not related to the study treatment by the investigator. According to the LSC opinion these increases of liver parameters were unlikely related to agomelatine.

**Other safety evaluation****Columbia-Suicide Severity Rating Scale**

In the Safety Set, few patients presented suicidal ideations between the baseline and the last post-baseline assessment over the W2-W12 period in all groups. No patient had suicidal behaviour at baseline and/or during the W2-W12 period. In addition, no patient reported complete suicide, suicide attempt or preparatory actions toward imminent suicidal behaviour at baseline and/or during the W2-W12 period.

However, one patient in the placebo group reported non-suicidal self-injurious behaviour at baseline (during the past year) which was no more observed (at W2) over the W2-W12 period.

**Vital signs and clinical examination**

In the Safety Set, there were no clinically relevant mean changes in weight, in sitting blood pressures and heart rate between baseline and the last post-baseline value under treatment over the W0-W12/Wend period in any group, nor relevant differences between the treatments groups.

Analysis of BMI by class showed that BMI class increases were infrequent in the 3 treatment groups (4.6%, 3.6% and 5.0% of patients in the agomelatine 10 mg, 25 mg and placebo groups, respectively).

**ECG**

Over the W0-W12 period, one patient in the placebo group presented at least one emergent ECG abnormality, considered as clinically significant by the investigator.

**CONCLUSION**

**This international, multicentre, placebo-controlled, double-blind, randomised study conducted in non depressed out-patients with Generalized Anxiety Disorder (GAD) demonstrated the statistically and clinically significant superiority of the two doses of agomelatine, 10 mg and 25 mg, as compared to placebo (with a greater placebo difference with the dose of 25 mg) on anxiety symptoms on the HAM-A total score (primary criterion) after a 12-week treatment period. The benefit of the 2 agomelatine doses was also confirmed on both psychic and somatic symptoms of GAD. The clinical relevance of the 2 agomelatine doses effect on anxiety symptoms was also demonstrated in term of response rate (per the HAM-A) compared to the placebo.**

**The clinically and statistically significant beneficial effect of the 2 agomelatine doses was confirmed on the CGI severity of illness score, CGI global improvement score, CGI responder rates, on HAD anxiety sub-score, and on the functional impairment assessed by the self-rated SDS.**

**In the two FAS subsets of more severely anxious patients, efficacy results were confirmed for both agomelatine groups with a greater effect with the 25 mg dose for all criteria.**

**The safety profile of agomelatine 10 and 25 mg/day over the 12-week treatment period was satisfactory and did not reveal any unexpected adverse events.**

**Date of the report:** 19 August 2015

**Version of the report:** Final version