Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of agomelatine (25 mg/day with potential blinded adjustment to 50 mg/day) for 12 weeks in non-depressed out-patients with Generalized Anxiety Disorder.** **A 12-week randomised, double-blind, placebo-controlled, with escitalopram (10 mg/day with potential blinded adjustment to 20 mg/day) as validator, 3-arm parallel groups, international multicenter study.**
Study drug	**S 20098**
Studied indication	**Generalized Anxiety Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-071**
Study initiation date	**27 April 2010**
Study completion date	**20 July 2011**
Scientific advisor	[redacted] **- South Africa**
National coordinator	[redacted] **- Finland**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the final report	**Final version of 5 July 2012**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex – France**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: Efficacy and safety of agomelatine (25 mg/day with potential blinded adjustment to 50 mg/day) for 12 weeks in non-depressed out-patients with Generalized Anxiety Disorder.
A 12-week randomised, double-blind, placebo-controlled, with escitalopram (10 mg/day with potential blinded adjustment to 20 mg/day) as validator, 3-arm parallel groups, international multicenter study.
Protocol No. CL3-20098-071.

National coordinators: [redacted], Argentina), [redacted], Czech Republic), [redacted] Finland), [redacted], Korea), [redacted] Poland), [redacted] Russia), [redacted], Slovakia).
Scientific advisor: [redacted], South Africa).

Study centres:
In all, 45 centres located in 7 countries included at least one patient: Argentina (6 centres – 37 patients), Czech Republic (5 centres – 52 patients), Finland (7 centres – 93 patients), Korea (5 centres – 23 patients), Poland (9 centres – 82 patients), Russia (8 centres – 82 patients), Slovakia (5 centres – 43 patients).

Publication (reference): Not applicable.

Studied period: Initiation date: 27 April 2010 Completion date: 20 July 2011	**Phase of development of the study:** III

Objectives:
Primary objective: to confirm the superiority of agomelatine (25-50 mg/day p.o.) compared to placebo on anxiety after a 12-week treatment in non-depressed out-patients suffering from Generalized Anxiety Disorder (GAD). The assay sensitivity was evaluated comparing escitalopram (10-20 mg/day p.o.) with placebo.
Secondary objectives:
- To further describe the global clinical benefit of agomelatine.
- To further describe the effect on anxiety symptoms, sleep patterns and social functioning.
- To provide additional safety and tolerability data on agomelatine.

A pharmacogenetic sub-study (Amendment No.4) was also conducted in order to evaluate associations between polymorphisms in candidate genes and the efficacy and safety of agomelatine. Detailed information regarding this sub-study was available in the specific technical document provided to centres participating in this project. Korea (added by Amendment No. 2) was not involved in this sub-study.

Methodology:
Phase III, international, multicentre study, placebo-controlled, active-reference as validator, double-blind, randomised in 3 parallel groups using agomelatine 25 mg/day with a potential dose adjustement to 50 mg/day, and escitalopram 10 mg/day with a potential dose adjustement to 20 mg/day. Adjustment was done in case of insufficient improvement at W4. The criteria for increasing the dose were defined by the sponsor, based on clinical considerations, before the study beginning, and kept blinded to the investigator and to the patient. The randomisation was balanced (non adaptive), with stratification on the centre. The randomisation, the treatment allocation and the dose increase were done centrally using an Interactive Response System (IRS). This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 390 patients included, *i.e.* 130 patients by treatment group
Included: 412 patients (139 patients in the agomelatine group, 131 patients in the placebo group, 142 patients in the escitalopram group).

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Diagnosis and main criteria for inclusion:
Male or female out-patients, aged between 18 (or legal age of majority in the country) and 65 years (inclusive), fulfilling DSM-IV-TR criteria for Generalized Anxiety Disorder diagnosis. At selection, HAM-A total score was to be ≥ 22, HAM-A item 1 (anxious mood) ≥ 2 and item 2 (tension) ≥ 2, HAM-A item 1 + item 2 ≥ 5, HAD anxiety subscore ≥ HAD depression subscore, and MADRS total score was to be ≤ 16. At inclusion HAM-A total score was still to be ≥ 22 and no more than a 20% of decrease in HAM-A total score between selection and inclusion, and the MADRS total score was still to be ≤ 16.

Study drug:
Agomelatine: capsules of 25 mg or 50 mg, 1 capsule per day, p.o., at bedtime.
Patients received 25 mg/day from W0 with possible increase to 50 mg/day in double-blind conditions from W4, in case of insufficient improvement. Once adjusted (or not) at W4, the dose was maintained up to W12. At W12, or in case of premature withdrawal from W4, patients received the dose received from W4 for additional 7 days (corresponded to the tapering period for escitalopram recommended to avoid possible withdrawal reactions).
Batch Nos. L0031712, L0034409 (25mg) - L0031714, L0034427 (50mg).

Reference product:
Placebo: 1 capsule per day, p.o., at bedtime.
Escitalopram: capsules of 5 mg, 10 mg and 20 mg, 1 capsule per day, p.o., at bedtime.

Patients received 10 mg/day from W0, with possible increase in double-blind conditions to 20 mg/day at W4, in case of insufficient improvement. Once adjusted, the dose was maintained up to W12. At W12, or in case of premature withdrawal from W4, patients having previously received escitalopram 10 mg received 5 mg for 7 days, and patients having received 20 mg until W12 received 10 mg for the first 3 days, then 5 mg for the 4 following days (tapering period recommended to avoid possible withdrawal reactions).

Duration of treatment:
- A 1-to-2-week run-in period without study treatment (from selection to W0).
- A 12-week double-blind treatment period (from W0 to W12).
- A 7-day double-blind treatment tapering period (recommended from W12 to W13 and at withdrawal visit in case of premature discontinuation).
- A 7-day maximum follow-up period without study treatment after W13 or after premature withdrawal (with or without tapering).

Criteria for evaluation:
Efficacy measurements
- Hamilton Anxiety Rating Scale (HAM-A) was rated by the investigator at each visit from the selection visit to W12. The primary efficacy criterion was the HAM-A total score. The main analytical approach was the change from baseline to last post-baseline value over the W0-W12 period.
- Clinical Global Impressions scale (CGI) was rated by the investigator at each visit from the selection visit (at selection and inclusion visits, only severity of illness score (CGI-S)) to W13.
- Hospital Anxiety and Depression scale (HAD) was rated by the patient at selection, inclusion, W8, and W12, or in case of premature withdrawal.
- Leeds Sleep Evaluation Questionnaire (LSEQ) was rated by the patient at W2, W4, W8, and W12.
- Sheehan Disability Scale (SDS) was rated by the patient at inclusion, W8, and W12, or in case of premature withdrawal.

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Criteria for evaluation (Cont'd):

Safety measurements

- Adverse events reported at each visit.
- Laboratory tests (haematology, biochemistry): blood samplings were prescribed at selection, at W4, and W12 in order to have the results at W0, W8, and W13, respectively, or in case of withdrawal in order to have the results at Wend.
- Physical examination: vital signs, *i.e.* sitting blood pressure (DBP, SBP) and heart rate (HR) were measured at selection, inclusion, W12, and Wend, or in case of premature withdrawal. Body weight was measured at selection, inclusion, W4, and W12, or in case of premature withdrawal. Height was measured at selection.
- 12-lead ECGs: one ECG was prescribed at selection in order to have the result for inclusion, and at W12 in order to have the result at W13, or in case of withdrawal in order to have the result for Wend.

Statistical methods:

Efficacy analysis:

Analyses were 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 study medication and having a baseline value and at least one post-baseline value for the primary efficacy criterion on the W0-W12 period. Analyses were also performed on two subsets of patients of the FAS with more severe anxious symptoms (SFAS1, *i.e.* W0 HAM-A total score ≥ 25, and SFAS2, *i.e.* W0 HAM-A total score ≥ 25 and CGI-S ≥ 5)

- **Primary criterion: HAM-A total score**

In addition to descriptive statistics for all analytical approaches on the W0-W12 period in the FAS and in the two subsets of patients of the FAS with more severe anxious symptoms, the following analyses were performed:

Main and assay sensitivity analyses

The superiority of agomelatine as compared to the placebo on anxiety symptoms after 12-week treatment period was assessed from the HAM-A total score expressed in term of change from baseline to last post-baseline value, in the FAS using a single (*i.e.*, including the three treatment groups) two-way analysis of covariance (ANCOVA) model with adjustment for centre (random effect) and baseline (main analysis). Assay sensitivity was studied with the same analysis but for comparison of escitalopram to placebo.

Sensitivity analyses

To assess the robustness of the results of the main and assay sensitivity analyses, the following sensitivity analyses were performed in the FAS:

- A sensitivity analysis to adjustment factors, on the last post-baseline value on the W0-W12 period, using a single one-way analysis of variance model,
- The following sensitivity analyses to the method of handling missing data on the change from baseline to value at W12:
  - Using a single two-way analysis of covariance model with adjustment for center (random effect) and baseline (observed cases analysis).
  - Using mixed-effects model for repeated measures (MMRM) (unplanned analysis).

Secondary analyses

The same analysis strategy as for the main and assay sensitivity analyses was implemented for the two subsets of patients of the FAS with more severe anxious symptoms.

Moreover, the comparison of the efficacy of agomelatine and of escitalopram to placebo on anxiety symptoms was implemented on the response to treatment (defined as a decrease from baseline ≥ 50% in HAM-A total score) as well as on the remission (HAM-A total score ≤ 7) (unplanned analysis) taking into account the last post-baseline value on the W0-W12 period, in patients of the FAS, and for the response to treatment in the two FAS subsets with more severe anxious symptoms (unplanned analyses) using a Chi-square test.

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Statistical methods (Cont'd):
Efficacy analysis (Cont'd):

- **Secondary criteria**

HAM-A

- *Subscores*: for each analytical approach, descriptive statistics were performed over the W0-W12 period in the FAS and two subsets of patients of the FAS with more severe anxious symptoms. The last post-baseline HAM-A psychic and somatic anxiety scores over the W0-W12 period were compared between groups (agomelatine and escitalopram *versus* placebo) in the FAS using a two sided Student's t-test for independent samples and a Mann-Whitney test (unplanned analyses).
- *Item 1 and 2*: for each analytical approach, descriptive statistics were performed over the W0-W12 period in the FAS.

CGI

- CGI scores, expressed in terms of last (post-baseline) value on the W0-W12 period: between-group (agomelatine and escitalopram *versus* placebo) difference studied, using a two sided Student's t-test for independent samples and a Mann-Whitney test in the FAS, as well as in the two FAS subsets with more severe anxious symptoms (unplanned analyses).
- CGI Global improvement score expressed in terms of response to treatment taking into account the last value on the W0-W12 period: between-group (agomelatine and escitalopram *versus* placebo) difference studied using a Chi-square test in the FAS, as well as in the two FAS subsets with more severe anxious symptoms (unplanned analyses).

Descriptive statistics were provided for each analytical approach over the W0-W12 period for all patients in the FAS and the two subsets of patients of the FAS with more severe anxious symptoms, and also at W13 in patients of the FAS with a W12 visit.

HAD, SDS, LSEQ:
Descriptive statistics were provided for each analytical approach over the W0-W12 period in the FAS, as well as in the two FAS subsets with more severe anxious symptoms for the LSEQ scores (unplanned analyses).
Between-group differences (agomelatine and escitalopram *versus* placebo) were assessed for the 4 LSEQ scores, expressed in terms of last value over the W0-W12 period, in patients of the FAS, SFAS1 and SFAS2, using a two sided Student's t-test for independent samples (unplanned analyses).

Safety analysis:
Descriptive statistics were provided in the Safety Set by treatment group and dose subgroup for emergent adverse events, and by treatment group for laboratory tests, and ECG over the W0-W13/Wend period, and for vital signs (blood pressures, heart rate, weight and BMI) over the W0-W12/Wend period.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Status		**Agomelatine**	**Placebo**	**Escitalopram**	**All**
Included and randomised	**n**	**139**	**131**	**142**	**412**
Lost to follow-up	**n (%)**	**-**	**-**	**1 (0.7)**	**1 (0.2)**
Withdrawn over W0-W12 due to	**n (%)**	**23 (16.5)**	**35 (26.7)**	**25 (17.6)**	**83 (20.1)**
Adverse event	n (%)	3 (2.2)	4 (3.1)	11 (7.7)	18 (4.4)
Protocol deviation	n (%)	1 (0.7)	1 (0.8)	1 (0.7)	3 (0.7)
Lack of efficacy	n (%)	14 (10.1)	22 (16.8)	6 (4.2)	42 (10.2)
Non-medical reason	n (%)	4 (2.9)	7 (5.3)	7 (4.9)	18 (4.4)
Cure remission or improvement	n (%)	1 (0.7)	1 (0.8)	-	2 (0.5)
Completed the W0-W12 period	**n (%)**	**116 (83.5)**	**96 (73.3)**	**116 (81.7)**	**328 (79.6)**
Entered the W12-W13 period	**n (%)**	**116 (83.5)**	**95 (72.5)**	**115 (81.0)**	**326 (79.1)**
Withdrawn over W12-W13 due to	**n (%)**	**1 (0.7)**	**-**	**1 (0.7)**	**2 (0.5)**
Lack of efficacy	n (%)	-	-	1 (0.7)	1 (0.2)
Cure remission or improvement	n (%)	1 (0.7)	-	-	1 (0.2)
Completed the W12-W13 period	**n (%)**	**115 (82.7)**	**95 (72.5)**	**114 (80.3)**	**324 (78.6)**
Performed the follow-up visit	***n (%)***	***132 (95.0)***	***124 (94.7)***	***131 (92.3)***	***387 (93.9)***
Analysis sets					
Randomised Set	**n**	**139**	**131**	**142**	**412**
Efficacy Sets					
Full Analysis Set (FAS)	n (%)	139 (100.0)	131 (100.0)	139 (97.9)	409 (99.3)
Sub-FAS with W0 HAM-A total score ≥ 25 (SFAS1)	n (%)	121 (87.1)	112 (85.5)	122 (85.9)	355 (86.2)
Sub-FAS with W0 HAM-A total score ≥ 25 and W0 CGI-S ≥ to 5 (SFAS2)	n (%)	77 (55.4)	74 (56.5)	74 (52.1)	225 (54.6)
Safety Set	**n (%)**	**139 (100.0)**	**131 (100.0)**	**141 (99.3)**	**411 (99.8)**

% according to randomised patients.

A total of 510 patients were selected for the study, and 412 were included and randomly assigned to one of the 3 treatment groups according to IRS procedure: 139 patients in the agomelatine group, 131 patients in the placebo group and 142 in the escitalopram group.

In the Randomised Set, among patients continuing the study at W4, 20 patients (15.5%) in the agomelatine group and 10 patients (8.2%) in the escitalopram had a dose increase due to insufficient improvement. In the placebo group, 33 patients (29.5%) fulfilled the criteria for a dose increase.

One patient in the escitalopram group was lost to follow-up from the W8 visit. In addition, over the W0-W13 period, 85 patients (20.6%) of the Randomised Set were withdrawn from the study. The most frequent reasons for withdrawal were lack of efficacy (10.4%), adverse event or non-medical reason (4.4%, each). The rate of withdrawal was similar in the agomelatine group (17.3%) and the escitalopram group (18.3%) and higher in the placebo group (26.7%). This difference was mainly due to a lower withdrawal rate for lack of efficacy in both active treatment groups (10.1% in the agomelatine group, and 4.9% in the escitalopram group *versus* 16.8% in the placebo group).

In the Randomised Set, patients were aged from 18 to 65 years with a mean ± SD of 42.6 ± 12.4 years. Most patients were female (71.6%).

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

All patients fulfilled DSM-IV diagnostic criteria for GAD. The time since GAD diagnosis covered a wide range from 0 to 445 months (0 – 37.1 years) with a median duration of one month and at least 25% of patients with a GAD diagnosis made within the month before selection. In the same way, the duration since the first anxious symptoms with a functional impact ranged within 5 to 573 months (0 – 47.8 years) with a median duration of 37 months (3.1 years).

About half patients (54.4%) had not taken any previous psychotropic treatments, *i.e.* anxiolytics (including or not benzodiazepines) and/or antidepressants within the last 12 months before the selection. At inclusion, all patients had negative test at the urinary screening of benzodiazepines and tricyclic antidepressants after a period of wash-out.

At inclusion, the mean ± SD MADRS total score was 12.2 ± 2.5 and as required in the selection/inclusion criteria all MADRS total scores were ≤ 16. The mean HAD depression subscore was 6.7 ± 3.4.

At inclusion, the mean HAM-A total score was 28.4 ± 3.8 and as required in the selection/inclusion criteria all HAM-A total scores were ≥ 22. The mean HAM-A psychic anxiety score was higher than the mean somatic anxiety score (15.2 ± 2.2 and 13.3 ± 3.1, respectively). The mean HAD anxiety subscore was 14.8 ± 2.4. The mean CGI severity of illness score was 4.7 ± 0.6.

According to SDS, at baseline (inclusion visit), the patients felt clearly disrupted by symptoms for work, social life, and family life and home responsibilities (mean ± SD: 6.3 ± 1.9, 6.5 ± 1.9, 6.2 ± 1.8, respectively).

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

Baseline characteristics in the FAS were similar to those observed in the Randomised Set. In the different FAS subsets, excluding the criteria of the sets definition, baseline characteristics showed no relevant differences to those observed in the Randomised Set except the duration since the GAD diagnosis, and the duration since the first anxious symptoms with a functional impact which were both longer in the SFAS2 than in the RS and in the SFAS1.

In the Randomised Set, the mean ± SD treatment duration over the W0-W12 period was 74.2 ± 22.8 days with a median of 84 days. There were no clinically relevant differences between the treatment groups.

The mean ± SD overall compliance over the W0-W12 period was good (95.8 ± 14.3%) with no relevant difference between the treatment groups.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Primary assessment criterion: HAM-A Total score
Change from baseline in the FAS

Agomelatine versus placebo

In the FAS, the mean decrease in HAM-A total score from baseline to the last post-baseline assessment over the W0-W12 period was statistically significantly superior in the agomelatine group than in the placebo group (main analysis: $p < 0.0001$, see results in Table below).

This result was confirmed by:

- The sensitivity analysis to adjustment factors on value at the last post-baseline assessment: E (SE) = 4.61 (1.11), 95% CI = [2.42 ; 6.79], $p < 0.0001$, without any adjustment.
- The 2 following sensitivity analyses to the method of handling missing data on the change from baseline to W12:
  - E (SE) = 3.77 (0.90), 95% CI = [2.00 ; 5.55], $p < 0.0001$, after adjustment for center and baseline (observed cases analysis).
  - E (SE) = 4.75 (0.97), 95% CI = [2.84 ; 6.66], $p < 0.0001$ using MMRM (unplanned analysis).

Escitalopram versus placebo

In the FAS, the mean decrease in HAM-A total score from baseline to the last post-baseline assessment over the W0-W12 period was statistically significantly superior in the escitalopram group than in the placebo group (assay sensitivity: $p < 0.0001$, see results in Table below).

This result was confirmed by:

- The sensitivity analysis to adjustment factors, on value at the last post-baseline assessment: E (SE) = 4.67 (1.11), 95% CI = [2.48 ; 6.85], $p < 0.0001$, without any adjustment.
- The 2 following sensitivity analyses to the method of handling missing data on the change from baseline to W12:
  - E (SE) = 4.01 (0.91), 95% CI = [2.22 ; 5.80], $p < 0.0001$, after adjustment for center and baseline (observed cases analysis).
  - E (SE) = 5.19 (0.98), 95% CI = [3.26 ; 7.12], $p < 0.0001$ using MMRM (unplanned analysis).

Summary of statistical results of HAM-A total score at last post-baseline assessment over the W0-W12 period in the FAS

		Agomelatine (N = 139)	Placebo (N = 131)	Escitalopram (N = 139)
Change from baseline to last post-baseline assessment	Mean ± SD	-15.6 ± 9.4	-10.6 ± 9.5	-15.6 ± 8.2
Statistical analysis				
Main analysis [a]	E (SE) [1]	4.71 (1.03)		4.77 (1.03)
	95% CI [2]	[2.69 ; 6.73]		[2.74 ; 6.79]
	p-value[3]	**< 0.0001**		**< 0.0001**
Response at last post-baseline assessment	Yes n (%)	89 (64.03)	48 (36.64)	92 (66.19)
Statistical analysis	E (SE) [1 bis]	-27.39 (5.86)		-29.55 (5.82)
	95% CI [2]	[-38.86 ; -15.91]		[-40.94 ; -18.15]
	p-value[3 b]	**< 0.0001**		**< 0.0001**

(a) Analysis of covariance model on factors treatment (fixed effect) and centre (random effect) and with baseline HAM-A total score as covariate
(b) Chi-square test
(1) Estimate (Standard Error) of the difference between adjusted treatment group means: placebo minus agomelatine or escitalopram.
(1 bis) Estimate (Standard Error) of the difference between treatment group percentages: placebo minus agomelatine or escitalopram.
(2) Two-sided 95% Confidence Interval of the estimate.
(3) p-value of treatment effect.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Change from baseline in the SFAS1 and SFAS2

In both FAS subsets, the mean decrease in HAM-A total score from baseline to the last post-baseline assessment over W0-W12 was statistically significantly superior in the two active treatment groups than in the placebo group as follows:

Agomelatine results

- In the SFAS1: E (SE) = 5.05 (1.12), 95% CI = [2.85 ; 7.25], p <0.0001, after adjustment for center and baseline.
- In the SFAS2: E (SE) = 5.61 (1.49), 95% CI = [2.68 ; 8.55], p <0.001, after adjustment for center and baseline.

Escitalopram results

- In the SFAS1: E (SE) = 4.95 (1.12), 95% CI = [2.75 ; 7.14], p < 0.0001 after adjustment for center and baseline.
- In the SFAS2: E (SE) = 4.08 (1.50), 95% CI = [1.11 ; 7.04], p = 0.007 after adjustment for center and baseline.

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

In the FAS, the percentage of responders at the last post-baseline assessment over the W0-W12 period was statistically significantly greater in the two active treatment groups than in the placebo group as follows:

Agomelatine results

- 64.0% *versus* 36.6%, respectively, p < 0.0001 (see results in Table above).

Escitalopram results

- 66.2% *versus* 36.6%, respectively, p < 0.0001 (see results in Table above).

Response to treatment according to HAM-A total score in the SFAS1 and SFAS2

In both FAS subsets, the percentage of responders was greater in the two active treatment groups than in the placebo group at last post-baseline assessment over the W0-W12 period. These differences in favour of both active treatment groups were statistically significant as follows (unplanned analyses):

Agomelatine results

- In the SFAS1: 64.5% in the agomelatine group *versus* 36.6% in the placebo group: E (SE) = -27.9% (6.3%), 95%CI = [-40.2 ; -15.5]%, p < 0.0001).
- In the SFAS2: 64.9% *versus* 35.1%, respectively: E (SE) = -29.8% (7.8%), 95%CI = [-45.0 ; -14.6]%, p < 0.001).

Escitalopram results

- In the SFAS1: 65.6% in the escitalopram group *versus* 36.6% in the placebo group: E (SE) = -29.0% (6.3%), 95%CI = [-41.2 ; -16.7]%, p < 0.0001.
- In the SFAS2: 59.5% *versus* 35.1%, respectively: E (SE) = -24.3% (8.0%), 95%CI = [-39.9 ; -8.7]%, p = 0.003.

Remission according to HAM-A total score in the FAS (unplanned analyses)

In the FAS, the percentage of remitters at the last post-baseline assessment over the W0-W12 period was statistically significantly greater in the two active treatment groups than in the placebo group as follows:

Agomelatine results

- 36.7% *versus* 19.9%, respectively: E (SE) = -16.8% (5.4%), 95%CI = [-27.4; -6.3]%, p = 0.002.

Escitalopram results

- 31.7% *versus* 19.9%, respectively: E (SE) = -11.8% (5.3%), 95%CI = [-22.1; -1.5]%, p = 0.027.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Secondary assessment criteria

- **HAM-A**

HAM-A psychic and somatic anxiety scores

Agomelatine results

In the FAS, the mean decrease in both HAM-A anxiety scores from baseline to the last post-baseline assessment over the W0-W12 period was higher in the agomelatine group than in the placebo group as follows:

- Psychic anxiety score: –8.1 ± 5.3 *versus* –5.7 ± 5.1, respectively.
- Somatic anxiety score: –7.5 ± 4.8 *versus* –4.9 ± 4.8, respectively.

At the last post-baseline assessment, both mean HAM-A anxiety scores were statistically significantly lower in the agomelatine group than in the placebo group as follows (unplanned analyses):

- Psychic anxiety score: 6.9 ± 5.5 *versus* 9.5 ± 5.1, respectively, E (SE) = 2.55 (0.64), 95%CI = [1.28 ; 3.81], p < 0.0001.
- Somatic anxiety score: 6.0 ± 4.4 *versus* 8.1 ± 4.9, respectively, E (SE) = 2.06 (0.57), 95%CI = [0.94 ; 3.19], p < 0.001.

Escitalopram results

Similar results were observed in the escitalopram group compared to the placebo in the FAS (unplanned analyses):

- Psychic anxiety score: E (SE) = 2.64 (0.59), 95%CI = [1.47 ; 3.81], p < 0.0001.
- Somatic anxiety score: E (SE) = 2.03 (0.57), 95%CI = [0.90 ; 3.16], p < 0.001.

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

HAM-A item 1 (anxious mood) and item 2 (tension)

In the FAS, both mean anxious mood and tension scores at the last post-baseline assessment over the W0-W12 period were lower in the agomelatine group than in the placebo group, as follows:

- Anxious mood score: 1.6 ± 1.0 in the agomelatine group *versus* 2.0 ± 1.0 in the placebo group.
- Tension score: 1.4 ± 1.0 *versus* 1.9 ± 1.1, respectively.

Similar results were observed in the escitalopram group in the FAS.

- **CGI**

Severity of illness score and global improvement score

In the FAS, both mean CGI scores at the last (post-baseline) assessment over the W0-W12 period were statistically significantly lower in the two active treatment groups than in the placebo group (see results in Table below).

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

Summary of statistical results of CGI at last (post-baseline) assessment over the W0-W12 period in the FAS

		Agomelatine (N = 139)	Placebo (N = 131)	Escitalopram (N = 139)
CGI severity of illness score				
Last post-baseline assessment	Mean ± SD	2.7 ± 1.3	3.3 ± 1.3	2.7 ± 1.3
	Median	3.0	4.0	3.0
Statistical analysis	E (SE) (1)	0.60 (0.16)		0.65 (0.16)
	95% CI (2)	[0.28 ; 0.91]		[0.33 ; 0.96]
	p-value(3 a)	**< 0.001**		**< 0.0001**
	p-value(3 b)	**< 0.0001**		**< 0.0001**
CGI global improvement score				
Last assessment	Mean ± SD	2.1 ± 1.3	2.7 ± 1.4	2.1 ± 1.2
	Median	2.0	3.0	2.0
Statistical analysis	E (SE) (1)	0.60 (0.16)		0.65 (0.15)
	95% CI (2)	[0.29 ; 0.92]		[0.35 ; 0.96]
	p-value(3 a)	**< 0.001**		**< 0.0001**
	p-value(3 b)	**< 0.001**		**< 0.0001**
Response at last assessment	Yes n (%)	101 (72.66)	63 (48.09)	103 (74.10)
Statistical analysis	E (SE) (1 bis)	-24.57 (5.77)		-26.01 (5.73)
	95% CI (2)	[-35.89 ; -13.25]		[-37.24 ; -14.77]
	p-value(3 c)	**< 0.0001**		**< 0.0001**

(a) Two sided Student's t test for independent samples
(b) Mann-Whitney test
(c) Chi-square test
(1) Estimate (Standard Error) of the difference between treatment group means: placebo minus agomelatine or escitalopram.
(1 bis) Estimate (Standard Error) of the difference between treatment group percentages: placebo minus agomelatine or escitalopram.
(2) Two-sided 95% Confidence Interval of the estimate
(3) p-value of treatment effect

In the two FAS subsets of more severely anxious patients, results were similar to those observed in the FAS for the two active treatment groups as follows:

Agomelatine results

- Severity of illness score
  - In the SFAS1: 2.8 ± 1.3 (median 3.0) in the agomelatine group *versus* 3.4 ± 1.4 (median 4.0) in the placebo group: E (SE) = 0.62 (0.18), 95% CI = [0.27 ; 0.96], p < 0.001, with Student's t-test, and p < 0.001 with Mann-Whitney test (unplanned analysis).
  - In the SFAS2: 2.9 ± 1.5 (median 3.0) *versus* 3.6 ± 1.5 (median 4.0), respectively: E (SE) = 0.70 (0.24), 95% CI = [0.22 ; 1.17], p = 0.004, with Student's t-test, and p = 0.002 with Mann-Whitney test (unplanned analysis).
- Global improvement score
  - In the SFAS1: 2.1 ± 1.3 (median 2.0) in the agomelatine group *versus* 2.7 ± 1.4 (median 3.0) in the placebo group: E (SE) = 0.61 (0.17), 95% CI = [0.27 ; 0.95], p < 0.001 with Student's t-test and with Mann-Whitney test (unplanned analysis).
  - In the SFAS2: 2.1 ± 1.4 (median 2.0) *versus* 2.7 ± 1.4 (median 3.0), respectively: E (SE) = 0.63 (0.22), 95% CI = [0.19 ; 1.06], p = 0.005 with Student's t-test and p = 0.002 with Mann-Whitney test (unplanned analysis).

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Escitalopram results

- Severity of illness score
  - In the SFAS1: 2.7 ± 1.3 (median 3.0) in the escitalopram *versus* 3.4 ± 1.4 (median 4.0) in the placebo group: E (SE) = 0.65 (0.18), 95% CI = [0.31 ; 1.00], p < 0.001 with Student's t-test and, p < 0.001 with Mann-Whitney test (unplanned analysis).
  - In the SFAS2: 3.1 ± 1.4 (median 3.0) *versus* 3.6 ± 1.5 (median 4.0), respectively: E (SE) = 0.49 (0.23), 95% CI = [0.03 ; 0.94], p = 0.037 with Student's t-test and, p = 0.024 with Mann-Whitney test (unplanned analysis).
- Global improvement score
  - In the SFAS1: 2.0 ± 1.1 (median 2.0) in the escitalopram versus 2.7 ± 1.4 (median 3.0) in the placebo group: E (SE) = 0.66 (0.16), 95% CI = [0.34 ; 0.98], p < 0.0001 with Student's t-test and p < 0.001 with Mann-Whitney test (unplanned analysis).
  - In the SFAS2: 2.2 ± 1.2 (median 2.0) versus 2.7 ± 1.4 (median 3.0), respectively: E (SE) = 0.51 (0.21), 95% CI = [0.10 ; 0.93], p = 0.015 with Student's t-test and p = 0.020 with Mann-Whitney test (unplanned analysis).

Response to treatment (global improvement score = 1 or 2)
In the FAS, the percentage of responders was statistically significantly higher in the two active treatment groups than in the placebo group at the last assessment over the W0-W12 period in the FAS (see results in Table above).
In the two FAS subsets of more severely anxious patients, results were similar to those observed in the FAS:

Agomelatine results

- In the SFAS1: 73.6% in the agomelatine group *versus* 48.2% in the placebo group: E (SE) = -25.3% (6.2%), 95% CI = [-37.5 ; -13.2]%, p < 0.0001 (unplanned analysis).
- In the SFAS2: 74.0% *versus* 44.6%, respectively: E (SE) = -29.4% (7.6%), 95% CI = [-44.4 ; -14.5]%, p < 0.001 (unplanned analysis).

Escitalopram results

- In the SFAS1: 74.6% in the escitalopram group *versus* 48.2% in the placebo group: E (SE) = -26.4% (6.2%), 95% CI = [-38.4 ; -14.3]%, p < 0.0001 (unplanned analysis).
- In the SFAS2: 67.6% *versus* 44.6%, respectively: E (SE) = -23.0% (7.9%), 95% CI = [-38.5 ; -7.4]%, p = 0.005 (unplanned analysis).

- **HAD scale**

Anxiety subscore
In the FAS, the mean decrease in anxiety subscore from baseline to the last post-baseline assessment over the W0-W12 period was higher in the agomelatine group (-7.1 ± 4.7) than in the placebo group (-4.5 ± 5.1).
Similar results were observed in the escitalopram group (-7.5 ± 4.7).

- **SDS**

In the FAS, the 3 mean SDS scores at the last post-baseline assessment over the W0-W12 period were lower in the agomelatine group than in the placebo group as follows:

- Work: 2.7 ± 2.4 (median 2.0) in the agomelatine group *versus* 4.4 ± 2.8 (median 5.0) in the placebo group.
- Social life: 2.8 ± 2.4 (median 2.0) *versus* 4.4 ± 2.8 (median 5.0), respectively.
- Family life and home responsibilities: 2.9 ± 2.5 (median 2.0) *versus* 4.2 ± 2.7 (median 5.0), respectively.

Similar results were observed in the escitalopram group (2.8 ± 2.5, 3.1 ± 2.6, and 2.9 ± 2.6, respectively; median 2.0, 3.0, and 2.0, respectively).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **LSEQ**

In the FAS, the 4 mean LSEQ scores ± SD were lower in the agomelatine group than in the placebo group at the last assessment over the W0-W12 period as follows:

- LSEQ getting off to sleep score: 35.1 ± 15.9 mm on agomelatine *versus* 41.8 ± 19.6 mm on placebo.
- LSEQ quality of sleep score: 30.7 ± 18.9 mm *versus* 40.1 ± 23.6 mm, respectively.
- LSEQ sleep awakening score: 38.8 ± 19.7 mm *versus* 43.7 ± 21.6 mm, respectively.
- LSEQ integrity of behaviour score: 38.4 ± 20.3 mm *versus* 43.5 ± 22.5 mm, respectively.

These results in favour of agomelatine were statistically significant for the getting off to sleep score ($p = 0.002$), the quality of sleep score ($p < 0.001$), and the integrity of behaviour score ($p = 0.049$), and close to statistical significance for the sleep awakening score ($p = 0.052$) (unplanned analyses).

In the escitalopram group, the mean ± SD scores at the last assessment over the W0-W12 period were as follows:

- Getting off to sleep score: 39.6 ± 20.0 mm.
- Quality of sleep score: 37.5 ± 23.6 mm.
- Sleep awakening score: 42.5 ± 21.5 mm.
- Integrity of behaviour score: 40.1 ± 22.2 mm.

No statistically significant differences were observed compared to the placebo for the 4 LSEQ scores (unplanned analyses).

SAFETY RESULTS

Overall summary of safety results in the Safety Set

		Agomelatine (N = 139)	**Placebo (N = 131)**	**Escitalopram (N = 141)**
Patients having reported				
at least one emergent adverse event	n (%)	66 (47.5)	58 (44.3)	68 (48.2)
at least one treatment-related emergent adverse event	n (%)	29 (20.9)	25 (19.1)	42 (29.8)
Patients having experienced				
at least one serious emergent adverse event	n (%)	1 (0.7)	2* (1.5)	1 (0.7)
at least one treatment-related serious adverse event	n (%)	-	-	-
Patients withdrawn				
due to an adverse event	n (%)	3 (2.2)	5** (3.8)	12** (8.5)
due to a serious adverse event	n (%)	-	-	1 (0.7)
due a treatment-related adverse event	n (%)	3 (2.2)	4 (3.1)	10 (7.1)
Patients who died	n (%)	-	-	-

** Including one surgery planned before the study that should not have been considered as serious according to the protocol*
******* For 1 patient, the reason for study withdrawal was lack of efficacy*

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Emergent adverse events

In the Safety Set, the percentage of patients who reported at least one emergent adverse event showed no relevant difference between the three treatment groups: 47.5% in the agomelatine group, 44.3% in the placebo group and 48.2% in the escitalopram group.

The most frequently affected system organ classes in the agomelatine group were gastrointestinal disorders (15.8% of patients), infections and infestations (13.7%), and nervous system disorders (12.2%). In the placebo group, the frequency of these system organ classes was 10.7%, 9.9% and 15.3%, respectively. In the escitalopram group, the percentage of patients with gastrointestinal disorders and nervous system disorders was higher than in the agomelatine group (18.4% and 20.6% respectively).

The emergent adverse event most frequently reported in the agomelatine group was headache, similarly reported on placebo (7.2% of patients *versus* 7.6%, respectively). In the escitalopram group, the percentage of patients with headache was higher (12.8%). In the agomelatine group, other most common emergent adverse events, more frequent than in the placebo group, were diarrhoea (4.3% of patients *versus* 1.5%), nausea (3.6% *versus* 0.8%) and somnolence (3.6% *versus* 2.3%). In the escitalopram group, those frequencies were higher than in the agomelatine group for diarrhoea (6.4% of patients), and nausea (7.8%) and similar for somnolence (3.5%).

Most emergent adverse events were graded as mild or moderate (at least 95% of events in any group). Severe emergent adverse events were less reported in the agomelatine group (1.6%) than in the placebo (4.9%) and escitalopram (5.5%) groups.

As regard to emergent treatment-related adverse events, the percentage of patients concerned was similar in the agomelatine (20.9%) and placebo (19.1%) groups, and both lower than in the escitalopram group (29.8%). The percentage of patients with treatment-related emergent events in nervous system disorders was higher in the agomelatine group than in the placebo group (10.1% *versus* 7.6%, respectively) and similar between the agomelatine and placebo groups for gastrointestinal disorders (8.6% and 7.6%, respectively). In the escitalopram group, the percentage of patients with treatment-related emergent events in both system organ classes was higher (16.3% and 12.1%, respectively) than in the agomelatine and placebo groups.

No death occurred during the study. Non-fatal serious emergent adverse events were reported in 1 patient in each active treatment group (pregnancy in each group), and 2 patients in the placebo group (vertigo and vomiting in one patient, and bunion operation that should not have been considered as serious according to the protocol in the other patient). Pregnancy in the agomelatine-treated patient was diagnosed during the follow-up period, and intrauterine death occurred in the context of first pregnancy at approximately nine weeks of gestations. The other one in the escitalopram group led to treatment withdrawal, and baby was in good health. None of serious emergent adverse events were considered treatment-related by the investigator.

The percentage of patients with non-serious emergent events leading to treatment withdrawal was lower in the agomelatine group (2.2%) than in the placebo group (3.8%), both frequencies being lower than in the escitalopram group (7.8%).

Laboratory tests

- In the Safety Set, no clinically relevant mean changes from baseline to last post-baseline value on treatment in the biochemical and haematological parameters were observed over the W0-W13/Wend period in the agomelatine group, as observed in the placebo and escitalopram groups. Few emergent PCSA values were observed in all treatment groups for biochemical parameters (8, 8 and 9 values, respectively in each group, mainly for triglycerides 6, 6 and 8, respectively) and haematological parameters (2, 2 and 1 values, respectively in each group).

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SUMMARY – CONCLUSIONS (cont'd)

SAFETY RESULTS (Cont'd)

- Liver acceptability

  Emergent PCSA values of ALT were reported in 2 patients each in the agomelatine 25 mg dose subgroup, and escitalopram 10 mg dose subgroup. In the agomelatine group, the emergent PCSA values of ALT were 4.1 ULN in one patient, and 3.4 ULN in the other patient, and were associated with emergent abnormal AST without reaching PCSA limit in both patients. These values were associated with emergent PCSA value of GGT (5.5 ULN, worsening of abnormal value at baseline) in the former patient, and emergent abnormal GGT without reaching PCSA limit in the latter patient. Total bilirubin and alkaline phosphatase were normal in both patients. Both patients recovered after treatment withdrawal.

  In the escitalopram group, the emergent PCSA values of ALT were 4.8 ULN in one patient, and 3.2 ULN in the other patient, and were associated with emergent PCSA AST (3.3 ULN), emergent PCSA GGT (8.9 ULN, worsening of abnormal value at baseline), and emergent abnormal value of ALP without reaching PCSA limit in the former patient, and associated with emergent abnormal value of AST without reaching PCSA limit in the latter patient. Both patients recovered, the former after treatment withdrawal, and the latter on treatment.

Physical examination

In the Safety Set, there were no clinically relevant mean changes from baseline to last post-baseline value for sitting blood pressures and heart rate, and weight during the W0-W12 period in all treatment groups.

Analysis of BMI by class showed that BMI class increases were little frequent in all treatment groups (2.2% of patients in the agomelatine group, 3.1% in the placebo group, and 3.5% in the escitalopram group).

ECG

Over the W0-W13/Wend period, among patients with at least one interpretable ECG at Wend, 22/132 (16.7%) in the agomelatine group, 17/120 (14.2%) in the placebo group, and 19/134 (14.2%) in the escitalopram group presented at least one emergent ECG abnormality at Wend. None of these emergent ECG abnormalities were considered as clinically significant by the investigator.

CONCLUSION

This international, multicentre, placebo-controlled, double-blind, randomised study with escitalopram 10-20 mg/day as active control, confirmed the statistically and clinically significant efficacy of a 12-week treatment period with agomelatine 25-50 mg/day compared to the placebo in GAD patients on the HAM-A total score (primary criterion). The assay sensitivity was stated by the superiority of escitalopram *versus* placebo on the primary efficacy criterion.

The superiority of agomelatine was confirmed in the two FAS subsets of more severely anxious patients.

The statistically significant beneficial effect of agomelatine was also demonstrated on the CGI severity of illness score and global improvement score.

The clinical relevance of the agomelatine effect on GAD was demonstrated by the statistically and clinically significant differences in HAM-A and CGI responder rates compared to the placebo.

The benefit of agomelatine was also confirmed on both psychic and somatic symptoms of GAD assessed by the HAM-A scale, on the functional impairment assessed by the self-rated SDS, and on the subjective sleep assessed by the self-rated LSEQ.

The safety profile of agomelatine 25-50 mg/day over the 13-week treatment period was satisfactory and did not reveal any unexpected adverse events.

Date of the report: 05 July 2012