Document title	**Clinical Study Report Synopsis**
Study title	**Long-term efficacy and safety of agomelatine in non depressed out-patients with Generalized Anxiety Disorder. A 26-week randomised double-blind placebo-controlled parallel group study following an open-label period of 16 weeks with agomelatine (25 mg/day with the possibility for blinded dose-adjustment to 50 mg/day).**
Study drug	**S 20098**
Studied indication	**Generalized Anxiety Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-050**
Study initiation date	**21 November 2007**
Study completion date	**29 September 2009**
Scientific advisors	[redacted] **- SWEDEN** [redacted] **SOUTH AFRICA**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 29 Octobre 2010**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study:
Long-term efficacy and safety of agomelatine in non-depressed out-patients with Generalized Anxiety Disorder. A 26-week randomised double-blind placebo-controlled parallel group study following an open-label period of 16 weeks with agomelatine (25 mg/day with the possibility for blinded dose-adjustment to 50 mg/day).
Protocol No. CL3-20098-050

National coordinators:
[redacted], Canada), [redacted], Denmark) replaced by [redacted], Estonia), [redacted], Finland), [redacted], Hungary), [redacted], Sweden).

Study centres:
In all, 31 centres located in 6 countries included at least one patient: Canada (6 centres - 89 patients), Denmark (5 centres - 86 patients), Estonia (5 centres - 79 patients), Finland (6 centres - 125 patients), Hungary (5 centres - 50 patients), Sweden (4 centres - 48 patients).

Publication (reference): Not applicable

Studied period: Initiation date: 21 November 2007 Completion date: 29 September 2009	**Phase of development of the study:** III

Objectives:
Primary objective: to assess the efficacy of agomelatine (25-50 mg/day p.o.) in the prevention of relapse in non-depressed out-patients with DSM-IV-TR defined Generalized Anxiety Disorder (GAD), during 26 weeks of study treatment after an initial response to agomelatine (25-50 mg).
Secondary objective: to provide additional safety and tolerability data on long-term use of agomelatine and to confirm the absence of discontinuation symptoms, based on the Discontinuation Emergent Signs and Symptoms (DESS) checklist (Rosenbaum *et al*, 1998).

Methodology:
This was an international, multicentre, phase III study, beginning with an open-label treatment period of 16 weeks with agomelatine 25 mg, followed by a 26-week double-blind period comparative phase of agomelatine *versus* placebo in 2 parallel arms. The initial dose of 25 mg/day of agomelatine could be increased to 50 mg/day in case of insufficient improvement after 4 weeks of treatment. 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 the patient as was the decision as to whether or not a dose increase had taken place. At W16, if the response to treatment was sufficient according to investigator opinion, patients continued in the study. Among these patients those fulfilling criteria previously defined to determine who will be randomised were randomised into 2 groups : agomelatine (25 mg or 50 mg depending on their dosage after W4) and placebo. These criteria were not disclosed to investigators. Non-randomised patients continued to be treated with agomelatine at the same dosage and are not included in the primary analysis. At W42, the patients randomised to agomelatine were re-randomised in order to investigate the absence of discontinuation symptoms with agomelatine. Half of the patients on 25 or 50 mg/day agomelatine received placebo during 1 week, whereas the other half continued on active treatment. Patients randomised at W16 to the placebo group remained on placebo until W43. The randomisation (at W16 and W42) was balanced (non-adaptive) with stratification on centre. The 2 randomisations, the treatment allocation at W0 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: 500 patients included (instead of 330 Amendment No. 3) in order to obtain 206 patients randomised in the double-blind period (103 patients by treatment group).
Included: 477 patients, 228 patients randomised (114 in the agomelatine group, and 114 in the placebo group).

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Diagnosis and main criteria for inclusion:

Patients were to be male or female out-patients, aged at least 18 years, fulfilling DSM-IV-TR criteria for Generalized Anxiety Disorder. At inclusion, HAM-A total score was to be ≥ 22 with no more than a 20% decrease in HAM-A total score between selection and inclusion, HAM-A item 1 (Anxious mood) ≥ 2 and item 2 (Tension) ≥ 2, HAM-A item 1 + item 2 ≥ 5, and MADRS total score was to be ≤ 16.

Study drug:

Agomelatine 25 mg tablets, 1 or 2 tablets once a day, po, around 8 p.m.

Patients received 25 mg/day (1 tablet of 25 mg + 1 placebo tablet) from W0, with possible increase under double-blind conditions to 50 mg/day (2 tablets of 25 mg) at W4, in case of insufficient improvement. The dose was maintained up to W42. Between W42 and W43, half patients on agomelatine received placebo (2 tablets), and half remained at the same dose taken since W4.

Batch No. L0018287; L0020763; L0020765; L0022540.

Reference product:

Placebo, 2 tablets once a day, po, around 8 p.m.

Duration of treatment:

- A not more than 7-day selection period.
- A 16-week open-label treatment period (W0 to W16).
- A 26-week double-blind treatment period (W16 to W42).
- A 2-week safety follow-up period (W42 to Wend). This period consisted of:
  - One week for the Discontinuation Emergent Signs and Symptoms Checklist (DESS) evaluation (W42 to W43).
  - One week of follow-up period without treatment after W43 or after treatment discontinuation whatever its time of occurrence.

Criteria for evaluation:

Efficacy measurements:

- Hamilton Rating Scale for Anxiety (HAM-A): rated by the investigator at each visit from selection to W42 or in case of premature withdrawal. The primary efficacy criterion was relapse during the double-blind treatment period defined as a HAM-A 14-item total score ≥ 15, or a lack of efficacy as judged by the investigator among patients who responded to open-label treatment.
- Clinical Global Impressions scale (CGI): rated by the investigator at each visit from selection to W42 or in case of premature withdrawal.
- Hospital Anxiety and Depression scale (HAD); filled in by the patient at the selection visit, at W0, W16 and W42, or in case of premature withdrawal.
- Sheehan Disability Scale (SDS): rated by the patient at W0, W2, W16 and W42, or in case of premature withdrawal.
- Leeds Sleep Evaluation Questionnaire (LSEQ): filled in by the patient at W2, W16 and W42, or in case of premature withdrawal.
- DSM-based GAD Symptom Severity Scale (DGSS): rated by the investigator at W0, W16 and W42, 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 prescribed at the selection visit, at W12 and at W40 or at the withdrawal visit in case of study discontinuation to have results available at inclusion, W16, and W42 or at the follow-up visit. Blood samples were added at W4, W8, W16, W20, W24 and W32 visits by Amendment No. 1 to assess ASAT, ALAT, total bilirubin, and ALP in Canadian patients at the request of the Canadian Therapeutic Products Directorate.
- Clinical examination, body weight, blood pressure and heart rate assessed by the investigator at the selection, at the inclusion, at W16 and W42 or in case of premature withdrawal. Body height measured at the selection visit only.
- A 12-lead ECG prescribed at the selection visit and at W40 or at the withdrawal visit in case of study discontinuation to have results at inclusion and at W42 or at the follow-up visit, respectively.
- Discontinuation Emergent Signs and Symptoms checklist (DESS): rated by the investigator at W42 and W43.

Statistical methods:

Efficacy analyses

- **Primary criterion**

Main analysis:

The main analysis was performed in the Full Analysis Set (FAS) defined, in accordance with the intention-to-treat principle and the section 5.2.1 of ICH-E9 guideline, as all patients of the Randomised Set having taken at least one dose of study randomised treatment and having done at least one post-randomisation visit during the double-blind period.

The difference between agomelatine and placebo was studied in the FAS on time to relapse over the double-blind 26-week period using a log-rank test stratified for country.

An adjusted Cox model (associated with the likelihood ratio test), involving treatment as main factor and country as covariate, was also performed in order to estimate the hazard ratio (and its 95% confidence interval) for relapse on agomelatine as compared to placebo.

Sensitivity analyses:

An adjusted Cox model with treatment as main factor and country and baseline HAM-A total score (known to be an important risk factor of relapse) as covariates, in addition to a non-stratified log-rank test and an unadjusted Cox model, were also carried out in the FAS as sensitivity analyses.

The same analysis strategy was applied to the two FAS subsets of more severe patients (Sub-FAS with W0 HAM-A total score ≥ 25, and Sub-FAS with W0 HAM-A total score ≥ 25 and W0 CGI-S ≥ 5).

- **Secondary criteria**

All criteria were described by treatment group in the Open Set during the open period, in the FAS and its subsets during the double-blind treatment period, and in the Non-Randomised Set over the whole study both doses pooled and for each dose of agomelatine.

Safety analyses

All safety parameters were described by treatment group and dose subgroup for patients in the Double-Blind Safety Set on the W16-W42/W43 period and for patients in the Overall Safety Set for the overall agomelatine period. The adverse events and the discontinuation emergent symptoms were described also for patients in the Discontinuation Safety Set on the W42-W43 period by treatment sequence.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

		Agomelatine	Placebo	All
Open period (W0-W16)				
Included	**n**	**477**	-	
Lost to follow-up	**n (%)**	**1 (0.2)**	-	
Withdrawn due to	**n (%)**	**147 (30.8)**	-	
Adverse event	n (%)	36 (7.5)	-	
Lack of efficacy	n (%)	48 (10.1)	-	
Non-medical reason	n (%)	51 (10.7)	-	
Protocol deviation	n (%)	11 (2.3)	-	
Recovery, improvement	n (%)	1 (0.2)	-	
Completed	**n (%)**	**329 (69.0)**	-	
Double-blind period (W16-W42)				
Randomised	**n**	**114**	**114**	**228**
Lost to follow-up	**n (%)**	-	-	-
Withdrawn due to	n (%)	**29 (25.4)**	**41 (36.0)**	**70 (30.7)**
Adverse event	n (%)	-	2 (1.8)	2 (0.9)
Lack of efficacy (relapse, as requested by the protocol)	n (%)	22 (19.3)	35 (30.7)	57 (25.0)
Non-medical reason	n (%)	5 (4.4)	4 (3.5)	9 (3.9)
Protocol deviation	n (%)	2 (1.8)	-	2 (0.9)
Completed the 26-week double-blind period	**n (%)**	**85 (74.6)**	**73 (64.0)**	**158 (69.3)**
Safety W42-W43 period				
Completed the W42-W43 period	**n (%)**	**85 (74.6)**	**73 (64.0)**	**158 (69.3)**
MAIN ANALYSIS SETS				
Open Set	n (%)	**474** [a] **(99.4)**	-	
Randomised Set	**n (%)**	**114** [b]	**114**	**228 (47.8)**
Efficacy Set				
Full Analysis Set (FAS)	n (%)	113 [c] (99.1)	114 (100.0)	227 (99.6)
Sub-FAS with W0 HAM-A total score ≥ 25	n (%)	94 [d] (82.5)	89 (78.1)	183 (80.3)
Sub-FAS with W0 HAM-A total score ≥ 25 and W0 CGI-S ≥ 5	n (%)	72 [e] (63.2)	63 (55.3)	135 (59.2)
Safety Set				
Double-Blind Safety Set (DBSS)	n (%)	113 [c] (99.1)	114 (100.0)	227 (99.6)
Discontinuation Safety Set (DSS)	n (%)	71 [f] (62.3)	-	71 (31.1)
Overall Safety Set (OSS)	n (%)	476 [g] (99.8)	-	

%: % of the Included Set, or Randomised Set.

[a] *195 patients received agomelatine 50 mg at W4.*

[b] *34 patients received agomelatine 50 mg at randomisation visit.*

[c] *33 patients received agomelatine 50 mg at randomisation visit.*

[d] *28 patients received agomelatine 50 mg at randomisation visit.*

[e] *21 patients received agomelatine 50 mg at randomisation visit.*

[f] *23 patients received agomelatine 50 mg at randomisation visit.*

[g] *179 patients were analysed in the 50 mg subgroup according to the longest treatment dose duration.*

In all, 477 patients were included and 476 took at least one tablet of agomelatine 25 mg. During the open period, 147 patients (30.8%) withdrew from the study, and one patient (0.2%) was lost to follow-up. The most frequent reason of withdrawals were non-medical reasons (10.7%), and lack of efficacy (10.1%). In all, 329 patients (69.0% of the included patients) completed the open period. Among them, 228 patients (47.8% of the included patients) were randomly assigned to one of the two treatment groups according to IRS procedure.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

The distribution of the treatment groups was well-balanced: 114 patients continued to receive agomelatine and 114 patients switched to placebo. In addition, among patients completed at W16, 101 were not randomised (in blinded condition for the investigator) because they did not fulfil the randomisation criteria. On the other hand, according to the investigators' decision, 100 of these not randomised patients even so continued the agomelatine treatment.

As regards agomelatine dose, 195 patients of the 449 continuing at W4 (43.4%) had a dose increase to 50 mg.

During the 26-week double-blind period, 30.7% of the randomised patients withdrew from the study. The rate of withdrawal was lower in the agomelatine group (25.4%) than in the placebo group (36.0%), mostly related to a lower rate of withdrawals due to lack of efficacy in the agomelatine group (19.3% *versus* 30.7%) as defined in the protocol. Finally, 74.6% of patients in the agomelatine group, and 64.0% of patients in the placebo group completed at W42. Among the 85 agomelatine-treated patients who completed at W42, 44 were re-randomised to agomelatine and 41 received placebo. All patients completed at W43.

In the Randomised Set, patients were aged from 18 to 82 years with a mean ± SD of 46.4 ± 14.6 years. They were predominantly female (62.3%). All patients fulfilled DSM-IV diagnostic criteria for GAD. The median duration of anxious symptoms was of 96.5 months (mean ± SD = 178.1 ± 190.7 months). There were no clinically relevant differences between the treatment groups in terms of demographic criteria, disease characteristics and HAM-A severity (see below).

The efficacy parameters progressively improved through the open period, and did not show any relevant differences between the treatment groups, neither at inclusion, nor at randomisation (W16). In all randomised patients, the mean ± SD scores were as follows at inclusion and at W16:

- HAM-A total score: from 27.6 ± 3.6 to 6.0 ± 2.7:
  - HAM-A psychic anxiety score: from 14.5 ± 2.4 to 3.4 ± 1.9.
  - HAM-A somatic anxiety score: from 13.1 ± 3.0 to 2.6 ± 1.7.
- CGI severity of illness score: from 4.7 ± 0.6 to 1.8 ± 0.8.
- CGI global improvement score: 2.9 ± 0.9 (at W2) to 1.3 ± 0.5.
- HAD anxiety score: from 14.0 ± 2.9 to 6.0 ± 3.2.
- HAD depression score: from 7.3 ± 3.4 to 3.2 ± 2.9.
- SDS Work score: from 6.1 ± 1.8 to 2.0 ± 1.6.
- SDS Social life: from 6.2 ± 1.8 to 2.2 ± 1.9.
- SDS Family life and home responsibilities: from 6.1 ± 1.8 to 2.1 ± 1.8.
- LSEQ Getting off to sleep: from 31.6 ± 15.4 (at W2) to 28.5 ± 14.5.
- LSEQ Quality of sleep: from 35.5 ± 18.5 (at W2) to 26.9 ± 18.7.
- LSEQ Sleep awakening score: from 41.2 ± 17.7 (at W2) to 34.5 ± 19.2.
- LSEQ Integrity of behaviour: from 41.3 ± 15.8 (at W2) to 32.3 ± 17.2.
- DGSS total score: from 40.2 ± 5.3 to 10.5 ± 6.8.

Baseline demographic characteristics in the FAS were similar to those observed in the Randomised Set.

In the Randomised Set, the mean treatment duration was 113.1 ± 3.1 days (median 112.0 days) during the open period. During the double-blind period (W16-W42), it was 156.5 ± 53.1 days (median 181.0 days) in the agomelatine group, and 144.3 ± 58.6 days (median 180.0 days) in the placebo group. The distribution of patients showed that 25% of patients in the agomelatine group had a treatment duration shorter than 173.0 days whereas in the placebo group, 25% of patients had a treatment duration shorter than 104.0 days. This result was in agreement with the lower rate of withdrawals in the agomelatine group.

In the OSS, the whole agomelatine mean treatment duration (W0-W43) was 167.3 ± 96.5 days (median 117.0 days). It was shorter in the 25 mg subgroup (156.4 ± 99.4 days, median 114.0 days) than in the 50 mg subgroup (185.0 ± 88.9 days, median 140.0 days).

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Compliance was satisfactory in both periods. In the Randomised Set, the mean global compliance was 98.5 ± 3.7% during the open period, and 97.6 ± 7.5% during the double-blind period, without a relevant difference between the two treatment groups.

EFFICACY RESULTS

- **Primary efficacy criterion: Relapse (see Table and Figure, next page)**

In the FAS, the overall percentage of patients who had a relapse during the double-blind period was lower in the agomelatine group than in the placebo group (19.5%, 22 patients in the agomelatine group *versus* 30.7%, 35 patients in the placebo group). The incidences over time of patients having a relapse were statistically and clinically significantly lower with agomelatine (p = 0.046, log-rank test stratified for country). On agomelatine, the risk of relapse over time was significantly reduced by 41.8% compared to placebo (HR (SE) = 0.582 (0.159) and 95% CI = [0.341 ; 0.995], p = 0.045, adjusted Cox model for country).

With the additional adjustment for HAM-A total score at baseline (W0), the clinically relevant reduction of the risk of relapse in favour of agomelatine (40.0%) was close to statistical significance (p = 0.059). These results were also observed with unadjusted analyses (p = 0.056 with non-stratified log-rank test, and p = 0.054 with unadjusted Cox model).

In more severely anxious patients (Sub-FAS with HAM-A total score at baseline (W0) ≥ 25, a priori defined), the risk of relapse over time was clinically significantly reduced by 42.8% on agomelatine compared to placebo with a statistical trend to significance (p = 0.058, adjusted Cox model for country). In the Sub-FAS with W0 HAM-A total score ≥ 25 and W0 CGI-S ≥ 5, the risk reduction in relapse was more marked as the risk of relapse over time was significantly reduced by 59.3% on agomelatine compared to placebo (p = 0.006, adjusted Cox model for country). Similar results were observed with the additional adjustment for HAM-A total score at W0 (p = 0.013, adjusted Cox model), and confirmed with unadjusted analyses (p = 0.007 with non-stratified log-rank test, and p = 0.007 with unadjusted Cox model).

The between-group difference in the incidences of relapse progressively rose throughout the treatment weeks. Low and closed incidences over the first treatment-weeks showed no evidence of withdrawal symptoms at start of double-blind phase.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Number of patients with relapse during the 26-week double-blind period, incidence over time, and risk of relapse in the FAS (main analysis) and Sub-FAS

		Agomelatine	**Placebo**
FAS		N = 113	N = 114
Total Events *	**n (%)**	**22 (19.5%)**	**35 (30.7%)**
Incidence after 182 days	E (SE) [1]	19.7% (3.8%)	31.7% (4.5%)
Stratified log-rank test	p value [2]	**0.046**	
Adjusted Cox model	E (SE) [3]	0.582 (0.159)	
	95% CI [4]	[0.341 ; 0.995]	
	p value [2]	**0.045**	
Sub-FAS with W0 HAM-A total score ≥ 25		N = 94	N = 89
Total Events *	**n (%)**	**19 (20.2%)**	**29 (32.6%)**
Incidence after 182 days	E (SE) [1]	20.5% (4.2%)	33.5% (5.1%)
Stratified log-rank test	p value [2]	0.063	
Adjusted Cox model	E (SE) [3]	0.572 (0.171)	
	95% CI [4]	[0.319 ; 1.027]	
	p value [2]	0.058	
Sub-FAS with W0 HAM-A total score ≥ 25 and W0 CGI-S ≥ 5		N = 72	N = 63
Total Events *	**n (%)**	**15 (20.8%)**	**27 (42.9%)**
Incidence after 182 days	E (SE) [1]	21.2% (4.9%)	44.0% (6.4%)
Stratified log-rank test	p value [2]	**0.006**	
Adjusted Cox model	E (SE) [3]	0.407 (0.137)	
	95% CI [4]	[0.210 ; 0.788]	
	p value [2]	**0.006**	

**: Total number and percentage of patients having a relapse during the double-blind period.*

1: Estimate (Standard Error) of the percentage of patients with a relapse on the last day of the associated period (Kaplan-Meier's method).

2: Stratified or adjusted for country

3: Estimate (Standard Error) of the Hazard Ratio (adjusted) of relapse between treatment groups: agomelatine versus placebo.

4: 95% confidence interval of the estimate.

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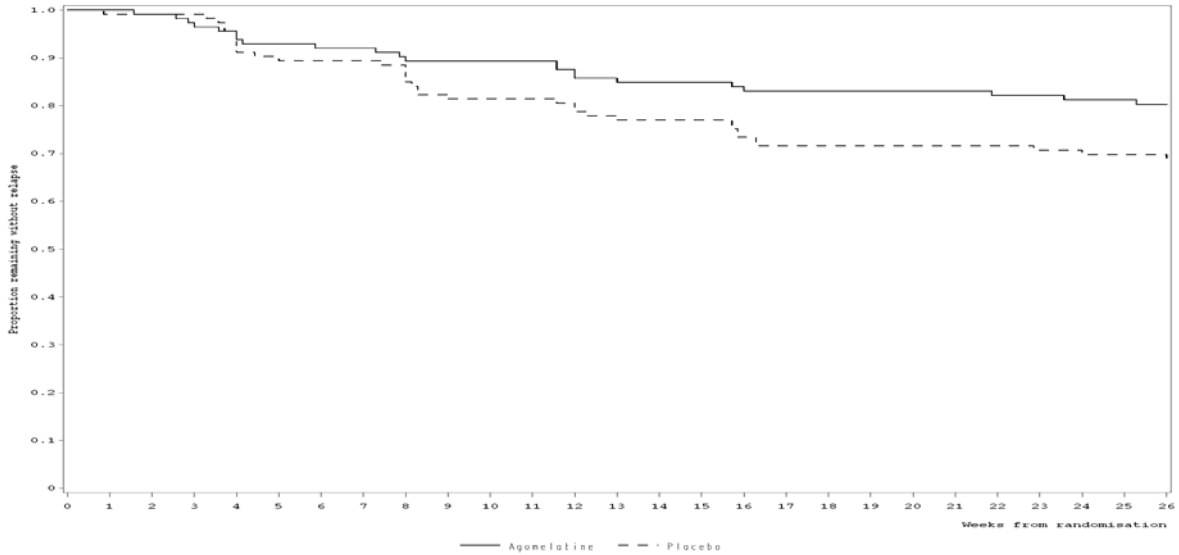
SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Time to relapse over the double-blind period in the FAS (Kaplan-Meier estimation)



- HAM-A

During the open period, the mean HAM-A total score progressively decreased from W0 (mean ± SD = 28.0 ± 3.8) to last post-baseline assessment (11.6 ± 7.6) in the Open Set.

Results were in the same line for the two sub-scores:

- Somatic anxiety score: from 13.2 ± 3.0 to 5.2 ± 3.7.
- Psychic anxiety score: from 14.8 ± 2.4 to 6.5 ± 4.4.

During the double-blind period in the FAS, the mean HAM-A total score remained stable between W16 and the last post-randomisation assessment in the agomelatine group (mean change of 1.6 ± 7.7), whereas it increased in the placebo group (mean change of 3.6 ± 8.4).

Somatic and psychic anxiety scores also remained stable in the agomelatine group (mean change of 0.5 ± 3.8 and 1.2 ± 4.6, respectively). In the placebo group, the somatic anxiety score remained stable (1.2 ± 4.0), and the psychic anxiety score increased (2.4 ± 4.9).

Similar results were observed in both FAS subsets except for the somatic anxiety score which increased in the placebo group in the more severe patients (Sub-FAS with W0 HAM-A total score ≥ 25 and W0 CGI-S ≥ 5).

In the non randomised patients treated after W16 (N = 100), the mean HAM-A total score progressively decreased on agomelatine from baseline (29.2 ± 3.9) to the last post-baseline assessment over the W0-W42 period (13.3 ± 7.5). At the last post-baseline assessment, the mean decrease from baseline was -15.9 ± 8.4.

- CGI

During the open period, the 2 mean scores decreased in the Open Set:

- Severity of illness: from 4.8 ± 0.7 at W0 to 2.7 ± 1.2 at last post-baseline assessment.
- Global improvement: from 3.0 ± 0.9 at W2 to 2.0 ± 1.1 at last assessment.

At last assessment, the percentage of responders (global improvement score = 1 or 2) was 73.0% (complementary analysis unplanned).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

During the double-blind period, in the FAS, in the agomelatine group, the mean severity of illness score remained stable between W16 and the last post-randomisation assessment (1.8 ± 0.7 and 2.0 ± 1.4, respectively), whereas it increased in the placebo group (from 1.8 ± 0.8 to 2.4 ± 1.4). The mean global improvement score according to the patients' condition at randomisation remained stable over the double-blind period in both treatment groups. At the last post-randomisation assessment, the mean global improvement score was lower in the agomelatine group than in the placebo group (3.7 ± 1.6 in the agomelatine group, and 4.2 ± 1.6 in the placebo group).

Similar results were observed in the Sub-FAS with W0 HAM-A total score ≥ 25, and in the Sub-FAS with W0 HAM-A total score ≥ 25 and W0 CGI-S ≥ 5.

- **HAD**

During the open period, the 2 mean scores decreased between the inclusion and the last post-baseline assessment in the Open Set:

- HAD anxiety score: from 14.4 ± 2.8 to 8.4 ± 4.3.
- HAD depression score: from 7.9 ± 3.6 to 5.0 ± 3.8.

During the double-blind period, in the FAS, the 2 mean scores remained stable between W16 and the last post-randomisation assessment in both treatment groups:

- HAD anxiety score: mean change of 0.3 ± 4.1 and 1.2 ± 4.6 in the agomelatine and placebo groups, respectively.
- HAD depression score: mean change of -0.1 ± 3.6 and 0.8 ± 3.4 in the agomelatine and placebo groups, respectively.

Similar results were observed in the Sub-FAS with W0 HAM-A total score ≥ 25, and in the Sub-FAS with W0 HAM-A total score ≥ 25 and W0 CGI-S ≥ 5.

- **SDS**

During the open period, in the Open Set, the 3 mean SDS scores decreased from inclusion to the last post-baseline assessment as follows:

- Work score: from 6.3 ± 1.9 to 3.6 ± 2.5.
- Social life: from 6.3 ± 1.9 to 3.6 ± 2.6.
- Family life and home responsibilities: from 6.0 ± 2.0 to 3.4 ± 2.5.

During the double-blind period, in the FAS, the 3 mean SDS scores in the agomelatine group were stable between W16 and the last post-randomisation assessment as follows:

- Work score: 2.1 ± 1.6 and 2.4 ± 2.5.
- Social life: 2.3 ± 2.0 and 2.5 ± 2.4.
- Family life and home responsibilities: 2.2 ± 1.8 and 2.5 ± 2.5.

In the placebo group, the mean SDS work score and family life and home responsibilities score were stable, and the social life score increased as follows:

- Work score: 2.0 ± 1.7 and 2.7 ± 2.2.
- Family life and home responsibilities: 2.0 ± 1.8 and 2.7 ± 2.5.
- Social life: from 2.1 ± 1.9 to 3.1 ± 2.6.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **LSEQ**

At W2, the 4 mean LSEQ scores indicated that patients tended to feel that they got to sleep easier and quicker than without medication, that they were more restful, with fewer periods of wakefulness than usual, that their awakening was easier and took shorter than usual, and that they felt more alert and less clumsy than usual. Between W2 and the last post-baseline assessment over the open period, the mean score was stable for getting off to sleep and sleep awakening, and decreased for the other 2 items as follows:

- Getting off to sleep: from 33.9 ± 15.5 to 31.8 ± 15.7.
- Sleep awakening score: from 44.1 ± 17.0 to 41.5 ± 20.3.
- Quality of sleep: from 38.4 ± 18.1 to 33.1 ± 19.8.

Integrity of behaviour: from 45.0 ± 16.2 to 40.7 ± 19.7.

During the double-blind period, in the FAS, in the agomelatine group, mean LSEQ scores were stable as above between W16 and the last post-randomisation assessment for all scores except quality of sleep which increased as follows:

- Getting off to sleep: from 28.8 ± 14.8 mm to 32.1 ± 18.3 mm.
- Sleep awakening score: from 35.2 ± 20.1 mm to 36.5 ± 21.2 mm.
- Integrity of behaviour: from 32.2 ± 17.8 mm to 35.0 ± 21.5 mm.
- Quality of sleep: from 27.2 ± 19.2 mm to 32.7 ± 22.5 mm.

In the placebo group, the 4 mean LSEQ scores increased as follows:

- Getting off to sleep: from 28.4 ± 14.4 mm to 40.5 ± 18.7 mm.
- Sleep awakening score: from 33.8 ± 18.4 mm to 39.2 ± 21.5 mm.
- Integrity of behaviour: from 32.2 ± 16.5 mm to 41.1 ± 21.6 mm.
- Quality of sleep: from 26.8 ± 18.3 mm to 37.2 ± 23.9 mm.

- **DGSS**

During the open period, in the Open Set, the mean DGSS total score decreased between the inclusion and the last-post-baseline assessment from 40.3 ± 5.5 to 19.4 ± 12.0.

During the double-blind period, in the FAS, the mean DGSS total score slightly increased between W16 and the last post- randomisation assessment in the agomelatine group and markedly increased in the placebo group.

- Agomelatine group: from 10.6 ± 7.4 (median 10.0) to 14.4 ± 14.3 (median 8.0).
- Placebo group: from 10.4 ± 6.2 (median 10.0) to 17.4 ± 14.6 (median 14.0).

SAFETY RESULTS

- **Emergent adverse events**

Main safety results during the double-blind treatment period in the DBSS

		Agomelatine (N = 113)	**Placebo (N = 114)**
Patients having reported			
at least one emergent adverse event	n (%)	46 (40.7)	31 (27.2)
at least one treatment-related emergent adverse event	n (%)	14 (12.4)	11 (9.6)
at least one serious adverse event	n (%)	-	-
Patients with treatment discontinuation due to a non-serious adverse event	n (%)	-	2 (1.8)

During the double-blind treatment period, in the DBSS, the percentage of patients with at least one emergent adverse event was higher in the agomelatine group (40.7%) than in the placebo group (27.2%).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

The most frequently affected system organ classes (in more than 5% of the patients) were Infections and infestations in both groups (18.6% in the agomelatine group, and 12.3% in the placebo group). In the agomelatine group, it was followed by Nervous system disorders (13.3% *versus* 4.4% in the agomelatine and placebo groups, respectively), and Gastrointestinal disorders (6.2% *versus* 1.8%). The 3 system organ classes were more frequently reported in the agomelatine group than in the placebo group.

The most frequent emergent adverse events (in more than 3% of patients) were headache, nasopharyngitis, nausea, upper respiratory tract infection, and gastroenteritis in the agomelatine group, and nasopharyngitis in the placebo group. The following emergent adverse events, headache, nausea and gastroenteritis were more common in the agomelatine group (10.6%, 4.4%, and 3.5%, respectively) than in the placebo group (2.6%, none, and 1.8%, respectively).

During the overall agomelatine treatment period, in the OSS, 59.3% of patients in the agomelatine 25 mg subgroup and 53.6% in the agomelatine 50 mg subgroup reported at least one emergent adverse event.

The most frequently affected system organ classes with both doses of agomelatine were similar to those in the DBSS: Nervous system disorders (26.8% in the agomelatine 25 mg subgroup and 22.7% in the agomelatine 50 mg subgroup), Gastrointestinal disorders (19.7% and 18.2%, respectively), and Infections and infestations (18.6%, and 18.8%, respectively). The percentage of patients affected was higher in the agomelatine 25 mg subgroup than in the agomelatine 50 mg subgroup for nervous system disorders, and showed no relevant differences between agomelatine doses for gastrointestinal disorders, and infections and infestations.

Headache was the most common emergent adverse event with both doses (12.5% and 9.4% in the agomelatine 25 mg and 50 mg subgroups, respectively), followed by nasopharyngitis (10.8% and 8.3%), dizziness (9.5% and 5.5%), and nausea (7.8% and 4.4%). All these emergent adverse events were more frequent in the agomelatine 25 mg subgroup than in the agomelatine 50 mg subgroup.

No death was reported during the study. In all, 3 patients (0.6%) on agomelatine had one emergent serious adverse event during the open treatment period (anxiety, anal abscess, and atrial fibrillation). No serious adverse event was reported during the double-blind treatment period. None of these events were considered treatment-related by the investigator. One led to premature treatment withdrawal (anxiety). All patients recovered, one with sequelae (anal abscess).

Non-serious emergent adverse events led to treatment discontinuation in 39 patients (8.2%) on agomelatine in the OSS (29 (9.8%) in the agomelatine 25 mg subgroup, and 10 (5.5%) in the agomelatine 50 mg subgroup), and 2 patients (1.8%) on placebo in the DBSS. On agomelatine, treatment withdrawals occurred during the open period in all but 2 patients. Treatment withdrawals were most frequently related to nervous system disorders in the agomelatine group (3.2%) without a difference between dose subgroups (3.1% in the 25 mg subgroup, and 3.3% in the 50 mg subgroup). All patients recovered or were recovering/improving (2 patients).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Clinical laboratory evaluation

- No clinically relevant mean changes nor differences between groups were observed on biochemical and haematological parameters during the double-blind treatment period in the DBSS, nor during the overall agomelatine treatment period in the OSS.
- Liver acceptability

  No clinically relevant mean changes nor differences between groups were observed during the double-blind treatment period in the DBSS, nor differences between dose subgroups during the overall agomelatine treatment period in the OSS.

  Clinically significant transaminase increases (≥ 3ULN) were reported for 8 patients on agomelatine (5 agomelatine 25 mg and 3 agomelatine 50 mg) and 1 patient on placebo. All patients had ALAT increase (max X9.9 ULN) and half of the patients (4/8) on agomelatine and the patient on placebo had concomitant ASAT increase (max X5.9 ULN). Total bilirubin and alkaline phosphatase were within the normal range for all these patients. All ASAT and ALAT values returned to baseline values, on agomelatine (2) or not. As required in the protocol, transaminases increases > 5 ULN led to treatment withdrawal in 3 patients on agomelatine, and the patient on placebo.

  Clinically significant total bilirubin increase (> 34 µmol/L) were reported for 5 patients on agomelatine 25 mg and 4 patients on placebo. All patients but one agomelatine had already abnormal value at baseline. Total bilirubin values returned to baseline values in all patients but 3 on placebo.

Vital signs

Regarding supine blood pressure, heart rate, weight and BMI, there were no clinically relevant mean changes between W16 and the last post-randomisation assessment during the double-blind treatment period in both groups in the DBSS, nor on agomelatine between the baseline and the last post-baseline assessment during the overall agomelatine treatment period in the OSS.

ECG

In the DBSS, 18.9% of patients in the agomelatine group and 24.5% of patients in the placebo group had an emergent ECG abnormality. In the OSS, 10.6% of patients on agomelatine had at least one emergent ECG abnormality, without relevant difference between doses.

ECG abnormalities were considered as clinically significant in 2 patients, 1 on each agomelatine dose (electrocardiogram T wave amplitude increased, abnormal electrocardiogram QRS complex, and left atrial hypertrophy in one patient and sinus tachycardia in the other one). For both patients, they were reported as adverse events and considered to be unrelated to the study treatment by the investigator. One patient recovered, and the other one was recovering at the end of the study.

DESS

In the DSS, at W43, the mean number of discontinuation emergent symptoms according to DESS showed no significant difference between patients maintained on agomelatine, and patients switched to placebo (0.9 ± 1.6 and 0.9 ± 1.9, respectively) nor in the percentage of patients with at least one discontinuation emergent symptom (35.1% in the agomelatine/agomelatine subgroup and 32.4% in the agomelatine/placebo subgroup).

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CONCLUSION

This study demonstrates the efficacy of agomelatine 25-50 mg in preventing relapse in GAD patients. The incidences over time of patients having an anxious relapse were statistically and clinically significantly lower with agomelatine 25-50 mg than with placebo. The risk of a relapse was statistically significantly reduced by 41.8% with agomelatine. This risk reduction was more marked in more severely anxious patients (59.3%).

General and laboratory safety of agomelatine 25-50 mg was satisfactory over the short- and long-term treatment periods. No unexpected safety concern was identified, whatever the dose. Frequent emergent adverse events were those described in the Summary of Product Characteristics of agomelatine. No withdrawal symptoms were observed following discontinuation of agomelatine.

Date of the report: 29 October 2010