Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of Agomelatine (25 mg with potential adjustment at 50 mg) given orally once a day for 12 weeks in out-patients with Generalised Anxiety Disorder. A randomised flexible dose double-blind, placebo-controlled, parallel groups, international study.**
Study drug	**S 20098**
Indication	**Generalised Anxiety Disorder**
Development phase	**II**
Protocol code	**CL2-20098-040**
Study initiation date	**12 January 2005**
Study completion date	**9 January 2006**
Coordinators	[redacted] **FINLAND** [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 24 November 2008**

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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: Efficacy and safety of Agomelatine (25 mg with potential adjustment at 50 mg) given orally once a day for 12 weeks in out-patients with Generalised Anxiety Disorder.
A randomised flexible dose double-blind, placebo-controlled, parallel groups, international study.
Protocol No.: CL2-20098-040

Coordinators: [redacted], Finland), and [redacted], South Africa).

Study centres:
Multicentre study involving 11 centres which included at least 1 patient, located in Finland (5 centres - 80 included patients) and South Africa (6 centres - 41 included patients).

Publication (reference): Not applicable

Studied period: Initiation date: 12 January 2005 *(date of first visit)* Completion date: 9 January 2006 *(date of last visit)*	**Phase of development of the study:** II

Objectives:
Primary objective: to assess the efficacy of agomelatine compared to placebo, after a 12-week oral treatment in out-patients suffering from Generalised Anxiety Disorder (GAD) using the Hamilton Anxiety Rating Scale (HAM-A).
Secondary objective: to provide data additional safety and tolerability data on agomelatine.

Methodology:
International, multicentre, randomised (balanced, stratified on centre and previous intake of benzodiazepines and/or anti-depressants, using Interactive Voice Response System (IVRS)), double-blind, in 2 parallel groups, comparative (agomelatine *versus* placebo) 12-week study. Agomelatine was administered at the 25 mg/day dose with a possible increase in the dosage (50 mg/day) after 2 weeks of treatment in case of insufficient improvement. The criteria for dose increase were defined prior to the study start and based on Hamilton Anxiety Rating Scale (HAM-A) total score and Clinical Global Impression (CGI) global improvement score. The dose increase and the treatment allocation were made centrally in a double-blind procedure, so that both patients and investigators were blind to the dose increase.

Number of patients:
Planned: 120 patients (60 per group)
Included: 121 patients (63 in the agomelatine group, and 58 in the placebo group)

Diagnosis and main criteria for selection/inclusion:
Male or female, aged from 18 to 65 years (inclusive), out-patients, fulfilling DSM-IV-TR (American Psychiatric Association, 2000) criteria for GAD as primary diagnosis confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.) questionnaire, willing to have psychotropic treatment, with a HAM-A total score ≥ 22, a score ≥ 2 on both HAM-A item 1 (anxious mood) and item 2 (tension), a Montgomery and Åsberg Depression Rating Scale (MADRS) total score ≤ 16, and a Hospital Anxiety Depression Scale (HAD) Anxiety score ≥ 11, and Anxiety score > Depression score. In addition, HAM-A total score between selection and inclusion must not decrease by more than 20%.

Study drug:
Agomelatine 25 mg tablet, 1 or 2 tablets once a day, orally, around 8 p.m.
Patients received 25 mg/day (1 agomelatine tablet and 1 placebo tablet) from week 0 to week 2, possibly increased to 50 mg/day (2 agomelatine tablets) from week 2 in case of insufficient improvement in double-blind conditions.
Batch No. L0003634

Reference product:
Placebo: 2 tablets once a day, orally, around 8 p.m.

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Duration of treatment:

- A 1-week single-blind placebo run-in period between selection (ASSE: week -1) and inclusion (week 0).
- A 12-week double-blind treatment period (from week 0 to week 12).
- A 1-week follow-up period after treatment discontinuation whatever its time of occurrence (WEND).

Criteria for evaluation:

Efficacy measurements

The following criteria were assessed by the investigators:

- HAM-A rated at the selection and inclusion visits, and at each visit during the treatment period (week 2, week 4, week 6, week 8, and week 12). The primary criterion was the HAM-A total score mainly analysed as change from baseline.
- CGI rated at the selection and inclusion visits for item 1 (severity of illness), and at each visit during the treatment period (week 2, week 4, week 6, week 8, and week 12) for both severity and improvement.
- DSM-based GAD Symptom Severity Scale (DGSS) rated at the inclusion and week 12 visits.

The following criteria were assessed by the patients:

- Sheehan Disability Scale (SDS) covering both disability and perceived stress scales rated at inclusion, week 8, and week 12 visits.
- Leeds Sleep Evaluation Questionnaire (LSEQ) rated at week 2, week 4, week 8, and week 12 visits.

Safety measurements

- Adverse events reported at each visit from selection to the follow-up visit.
- Discontinuation Emergent Symptoms Scale (DESS) rated at the follow-up visit.
- Laboratory tests: results at inclusion, and week 12 or follow-up visit in case of premature withdrawal.
- Vital signs: Blood pressure and heart rate (supine position), and body weight measured at inclusion, and week 12 or follow-up visit in case of premature withdrawal.
- 12-lead electrocardiogram (ECG): results available at inclusion and week 12 or follow-up visit in case of premature withdrawal.

Statistical methods:

In accordance with the intention-to-treat principle and ICH-E9 guideline, the efficacy analyses were performed in the Randomised Set (RS) defined as all randomised patients according to IVRS. For all criteria, the baseline corresponded to the value at inclusion (week 0).

Efficacy analyses

- **Primary criterion**

Main analytical approach

The difference between agomelatine and placebo on the change from baseline to last value of HAM-A total score was studied using a three-way analysis of covariance (main analysis) with factors treatment, centre (random effect) and previous psychotropic treatments intake (fixed effect) with baseline as covariate and no interaction (mixed model). This difference was also studied without adjustment using a two-sided Student's t test for independent samples (sensitivity analysis).

Secondary analytical approaches

The difference between agomelatine and placebo was studied:

- On the change from baseline to value at week 12 of HAM-A total score in the same way as for main analytical approach of HAM-A total score (adjusted and unadjusted analyses).
- On the value of HAM-A total score at each visit using a two way analysis of variance on factors treatment and time with repeated measures on factor time (Bonferroni adjustment on study treatment, complementary analysis, p-value to be compared to 0.01).
- On the response to treatment taking into account last value of HAM-A total score using a Chi-Square test, with response defined as a decrease from baseline in HAM-A total score $\geq 50\%$.
- On the remission taking into account last value of HAM-A total score using a Chi-Square test (complementary analysis), with remission defined as a HAM-A total score ≤ 7.

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- **Secondary criteria**

The difference between treatment groups was studied using a two-sided Student's t test for independent samples:

- On change from baseline to last /week 12 value of HAM-A psychic and somatic anxiety scores.
- On week 12 value of the HAM-A item 1 (anxious mood) and item 2 (tension) (complementary analysis).
- On last value of CGI severity of illness and global improvement scores. In addition, the between-group difference was studied using a Mann Whitney test as sensitivity analysis.

The difference between treatment groups was studied using a Mann Whitney test on week 12 value of each SDS item of the disability scale and of perceived stress item 1 (complementary analysis).

Safety analyses

The Safety Set was defined as all included patients having taken at least one dose of study drug.

Descriptive statistics for adverse events, laboratory tests, vital signs (blood pressure, heart rate, weight and BMI), and ECG were provided by treatment group and by dose subgroup in the Safety Set.

DESS: Number and percentage of patients with at least one emergent discontinuation symptom at the follow-up visit were described in the Safety Set restricted to patients with scale filled in between 6 and 8 days after last treatment administration and without intake of any psychotropic treatment at the time of the evaluation. The total number of discontinuation emergent symptoms was analysed by class by treatment and by dose subgroup.

SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of randomised patients

		Agomelatine	**Placebo**	**Whole population**
Included (randomised)	**n**	**63**	**58**	**121**
Lost to Follow-up	**n**	**-**	**-**	**-**
Withdrawn	**n**	**5**	**4**	**9**
due to adverse event	n	1	-	1
due to non-medical reason	n	1	1	2
due to lack of efficacy	n	3	3	6
Completed	**n**	**58**	**54**	**112**
Corresponding Sets				
Randomised Set (RS)	n	63	58	121
Safety Set	n (%)	63 (100.0)	58 (100.0)	121 (100.0)

%: % of the Randomised Set

Among the 119 patients continuing after week 2, 51 patients (42.9%) had a dose increase due to insufficient improvement: 26/62 patients in the agomelatine group (41.9%) and 25/57 patients in the placebo group (43.9%). Table below shows the number of patients by dose subgroup. It can be noted that the two patients withdrawn at week 2 (one patient in each group) were not taken into account in the analysis by dose subgroup.

Dose subgroups in the randomised patients continuing after week 2

	Agomelatine 25 mg	**Agomelatine 25-50 mg**	**Placebo not increased**	**Placebo increased**	**All**
Number of patients	36	26	32	25	119*

** One patient in each treatment group withdrawn at week 2 before the possible dose increase and thus was not taken into account in the dose subgroups*

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

In the RS, the mean ± SD patients age was 41.7 ± 12.2 years. The proportion of females was greater than males (68.6% *versus* 31.4%). All patients fulfilled DSM-IV diagnostic criteria for GAD. The median duration of GAD was of 5.2 years (mean ± SD = 9.6 ± 10.5 years). The patients attended their primary care doctor twice a year on average (2.3 ± 2.0). More than half patients (54.5%) had never taken previous psychotropic treatments, *i.e*. anxiolytics (including or not benzodiazepines) and/or anti-depressants. At inclusion, all patients had negative test at the urinary benzodiazepines screening after a period of wash-out. At selection, the mean HAD anxiety score was 15.3 ± 2.5 and 14.8 ± 2.5 in the agomelatine and placebo groups, respectively, and the mean HAD depression score was 7.4 ± 2.5 and 6.9 ± 2.4. The mean MADRS total score at inclusion was 11.6 ± 2.9, and 11.7 ± 2.1 in the agomelatine and placebo groups, respectively.

The mean HAM-A total score was 29.0 ± 4.4 and 28.6 ± 3.8 in the agomelatine and placebo groups, respectively, the mean psychic anxiety score was 16.0 ± 2.2 and 15.8 ± 2.3, and the mean somatic anxiety score was 12.9 ± 3.2 and 12.8 ± 3.1. The mean CGI severity of illness score was 4.9 ± 0.7 and 4.7 ± 0.6 in the agomelatine and placebo groups, respectively.

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

In the Randomised Set, treatment duration ranged between 11 and 91 days with a mean ± SD of 80.9 ± 12.6 days. There were no clinically relevant differences between the treatment groups nor the dose subgroups. The overall compliance was on average of 97.8 ± 7.3% and ranged from 36% to 108%, with no relevant difference between the treatment groups.

EFFICACY RESULTS

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

In the RS, the mean HAM-A total score decreased from baseline to week 12 or last value over the week 0-week 12 period in both groups. The mean decreases were higher in the agomelatine group than in the placebo group at each visit from week 4, and at the last value.

The between-group difference of the mean decrease was statistically significant after adjustment for centre, previous psychotropic treatments intake and baseline, at last value (3-way ANCOVA: p = 0.040, main analysis; see Table below), or at week 12 (3-way ANCOVA: p = 0.005; see Table below). Both results were confirmed by the unadjusted analysis (two-sided Student's t test for independent samples: p = 0.040, and p = 0.010, respectively). A complementary analysis of treatment effect over time showed that the mean HAM-A total score was statistically significantly lower in the agomelatine group than in the placebo group at each visit from week 6 (ANOVA with repeated measures on factor time: treatment*time interaction, to be compared to 0.01, Bonferroni adjustment: p = 0.064, week 6: p = 0.009, week 8: p = 0.002, week 12: p= 0.005).

According to previous intake of psychotropic treatment, the mean decrease in HAM-A total score throughout the study showed no clinically relevant difference in previously treated patients compared to psychotropic naïve patients.

Response was analysed at each visit and at last value. In the RS, the percentage of responders was higher in the agomelatine group than in the placebo group at each visit, from week 2 (11.1% *versus* 6.9%) to week 12 (70.7% *versus* 47.3%). Significant superiority in response *versus* placebo was seen at the last value for agomelatine (Chi-Square test: p = 0.026; see Table below).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Remission was analysed for each treatment group at each visit and at last value. Superiority of agomelatine over placebo was seen at the last value (Chi-Square test: p = 0.027; complementary analysis, see Table below).

HAM-A total score – Change from baseline to week 12 and last value over the week 0-week 12 period, response to treatment, and remission at last value in the RS

		Agomelatine (N = 63)	**Placebo (N = 58)**
Baseline	n	63	58
	Mean ± SD	29.0 ± 4.4	28.6 ± 3.8
Change from baseline to last value	n	63	58
	Mean ± SD	-16.6 ± 8.9	-13.2 ± 9.5
Treatment effect			
Adjusted (main analysis)	E (SE) ; 95% CI ; p-value [(1)]	-3.28 (1.58) ; [-6.41 ; -0.15] ; **p = 0.040**	
Non-adjusted	E (SE) ; 95% CI ; p-value [(2)]	-3.48 (1.68) ; [-6.81 ; -0.15] ; **p = 0.040**	
Change from baseline to week 12	n	58	55
	Mean ± SD	-17.7 ± 8.4	-13.2 ± 9.5
Treatment effect			
Adjusted	E (SE) ; 95% CI ; p-value [(1)]	-4.43 (1.53) ; [-7.47 ; -1.39] ; **p = 0.005**	
Non-adjusted	E (SE) ; 95% CI ; p-value [(2)]	-4.44 (1.69) ; [-7.78 ; -1.10] ; **p = 0.010**	
Response to treatment at last value	n (%)	42 (66.7)	27 (46.6)
Treatment effect	E (SE) ; 95% CI ; p-value [(3)]	20.11 (8.84) ; [2.79 ; 37.44] ; **p = 0.026**	
Remission at last value	n (%)	26 (41.3)	13 (22.4)
Treatment effect*	E (SE) ; 95% CI ; p-value [(3)]	18.86 (8.27) ; [2.64 ; 35.07] ; **p = 0.027**	

E (SE): Estimate (standard error) of the difference between treatment groups: agomelatine minus placebo.
95% CI: 95% Confidence interval of the estimate.
(1): Treatment effect adjusted for centre, previous psychotropic treatment intake and baseline: general linear model with baseline as covariate, previous psychotropic treatment intake as fixed effect, and centre as random effect.
(2): Unadjusted treatment effect: two sided Student's t test for independent samples.
(3): Treatment effect: Chi-Square test
** Complementary analysis*

- **Secondary efficacy criteria**
  - **HAM-A**
    - **HAM-A somatic anxiety score**

The mean decrease from baseline in the HAM-A somatic anxiety score was higher in the agomelatine group than in the placebo group at each visit from week 4, and at the last value. At week 12 as well as at the last value, the difference of mean decrease in favour of agomelatine was statistically significant (two-sided Student's t test for independent samples: p = 0.004, and p = 0.015, respectively; see Table below).

    - **HAM-A psychic anxiety score**

The mean decrease from baseline in the HAM-A psychic anxiety score was higher in the agomelatine group than in the placebo group at each visit from week 4, and at the last value. The difference of mean decrease in favour of agomelatine was statistically significant at week 12 (Student's t test: p = 0.048; see Table below).

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

The mean anxious mood and mean tension scores were smaller at week 12 than at baseline in both treatment groups. Both week 12 mean scores were statistically significantly lower in the agomelatine group than in the placebo group with an estimated difference (SE) of -0.39 (0.18), p = 0.034 (Student's t test) for the anxious mood, and of -0.50 (0.18), p = 0.007 (Student's t test) for the tension.

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EFFICACY RESULTS (Cont'd)

- Secondary efficacy criteria (Cont'd)
  - **CGI**
    - **Severity of illness score**

The mean score was smaller in the agomelatine group than in the placebo group at each visit from week 4, and at the last value. This difference in favour of agomelatine was statistically significant at the last value (Student's t test: p = 0.049; see Table below). Sensitivity analysis confirmed this result (Mann-Whitney test: p = 0.041; see Table below).

- **Global improvement score**

The mean score was smaller in the agomelatine group than in the placebo group at all visits from week 2, and at the last value. The mean estimated difference between groups at the last value was in favour of agomelatine without statistically significant difference (E (SE) = -0.33 (0.22), 95% CI = [-0.78 ; 0.11], p = 0.138, Student's t test). Non-parametric analysis showed a statistical trend (Mann-Whitney test: p = 0.066).

- **Efficacy index score**

The combinatory score of therapeutic and side effects showed no clinically relevant differences between the treatment groups.

Summary of statistical results of HAM-A psychic and somatic anxiety scores and CGI severity score in the RS

		Agomelatine (N = 63)	**Placebo (N = 58)**
HAM-A somatic anxiety score			
Baseline	n	63	58
	Mean ± SD	12.9 ± 3.2	12.8 ± 3.1
Change from baseline to last value	n	63	58
	Mean ± SD	-7.7 ± 4.0	-5.8 ± 4.5
Treatment effect	E (SE) ; 95% CI ; p-value [(1)]	-1.90 (0.77) ; [-3.43 ; -0.38] , **p = 0.015**	
Change from baseline to week 12	n	58	55
	Mean ± SD	-8.1 ± 3.8	-5.8 ± 4.5
Treatment effect	E (SE) ; 95% CI ; p-value [(1)]	-2.32 (0.79) ; [-3.88 ; -0.76] ; **p = 0.004**	
HAM-A psychic anxiety score			
Baseline	n	63	58
	Mean ± SD	16.0 ± 2.2	15.8 ± 2.3
Change from baseline to last value	n	63	58
	Mean ± SD	-8.9 ± 5.7	-7.3 ± 6.0
Treatment effect	E (SE) ; 95% CI ; p-value [(1)]	-1.58 (1.06) ; [-3.67 ; 0.52] ; p = 0.138	
Change from baseline to week 12	n	58	55
	Mean ± SD	-9.5 ± 5.4	-7.4 ± 5.9
Treatment effect	E (SE) ; 95% CI ; p-value [(1)]	-2.12 (1.06) ; [-4.22 ; -0.02] ; **p = 0.048**	
CGI Severity of illness score			
Baseline	n	63	58
	Mean ± SD	4.9 ± 0.7	4.7 ± 0.6
Last value	n	63	58
	Mean ± SD	2.7 ± 1.4	3.2 ± 1.4
Treatment effect	E (SE) ; 95% CI ;	-0.51 (0.25) ; [-1.01 ;0.00]	
	p-value [(1)]	**p = 0.049**	
	p-value [(2)]	**p = 0.041**	

E (SE): Estimate (standard error) of the difference between treatment group means: agomelatine minus placebo.
95% CI: 95% Confidence interval of the estimate.
(1): Treatment effect: two sided Student's t test for independent samples.
(2): Treatment effect: Mann-Whitney test.

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EFFICACY RESULTS (Cont'd)

- **Secondary efficacy criteria (Cont'd)**
  - **SDS**

All mean and median SDS scores improved between the baseline and week 12 or last value in the agomelatine group, and were better in the agomelatine group than in the placebo group at both visits of assessment on treatment (week 8 and week 12) and at the last value. Complementary analyses at week 12 showed that the between-group difference in favour of agomelatine was statistically significant for each item of the disability scale:

- Disruption of family life or home responsibilities (median): 2.0 *versus* 4.0 in the agomelatine and placebo groups, respectively, p = 0.042 (Mann-Whitney test).
- Disruption of work (median): 2.0 *versus* 3.0, respectively, p = 0.039 (Mann-Whitney test)
- Disruption of social life (median): 2.0 *versus* 3.0, respectively, p = 0.038 (Mann-Whitney test).

A trend to significance in favour of agomelatine was observed for the Perceived stress for stressful events (1) (median): 4.0 *versus* 5.0, p = 0.073 (Mann-Whitney test).

- **DGSS**

For each of the 8 items, the mean level (sum of frequency and intensity) decreased between the baseline and week 12 in both groups. All mean levels at week 12 were lower in the agomelatine group than in the placebo group. It can be noticed that in all, about one third of week 12 data were missing.

For all items, the percentage of patients with the lowest severity (1) increased between the baseline and week 12 in both groups. At the same time, those with the highest severity (5) decreased. For all items, at week 12, the percentage of patients with a severity of 1 was higher in the agomelatine group than in the placebo group, and that with a severity of 5 was lower.

- **LSEQ**

The patients felt an improvement of sleep which was more marked in the agomelatine group than in the placebo group at each visit from week 2, and at the last value for the mean LSEQ getting off to sleep score (30.3 ± 17.5 mm *versus* 42.3 ± 15.2 mm at the last value), the mean LSEQ quality of sleep score (31.2 ± 21.3 mm *versus* 43.1 ± 18.9 mm at the last value), and the mean LSEQ sleep awakening score (34.8 ± 20.4 mm *versus* 49.1 ± 16.7 mm at the last value), and at each visit from week 4, and at the last value for the mean LSEQ integrity of behaviour score (39.4 ± 19.4 mm *versus* 46.1 ± 18.8 mm at the last value).

SAFETY RESULTS

Safety results by treatment group and by dose subgroup are summarised in Table below.

		Treatment groups		**Agomelatine dose subgroups**	
		Agomelatine (N = 63)	**Placebo (N = 58)**	**25 mg (N = 36)**	**25-50 mg (N = 26)**
Patients having reported					
at least one emergent adverse event	n (%)	37 (58.7)	41 (70.7)	20 (55.6)	16 (61.5)
at least one dizziness*	n (%)	5 (7.9)	2 (3.4)	5 (13.9)	-
at least one nausea*	n (%)	3 (4.8)	1 (1.7)	3 (8.3)	-
at least one treatment-related emergent adverse event	n (%)	24 (38.1)	20 (34.5)	13 (36.1)	10 (38.5)
Patients having experienced					
at least one serious adverse event	n (%)	-	-	-	-
Patients withdrawn					
due to an adverse event	n (%)	1**	-	-	-

** Most common emergent adverse events more frequently reported in the agomelatine group than in the placebo group*

*** Patient withdrawn at week 2 on agomelatine 25 mg before the possible dose increase and thus not taken into account in the dose subgroup*

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Adverse events**

The percentage of patients with at least one emergent adverse event was lower in the agomelatine group (58.7%) than in the placebo group (70.7%).

The most frequently affected system organs (> 10% of patients) were, in both treatment groups, infections and infestations (28.6% of patients *versus* 44.8%), nervous system disorders (27.0% *versus* 20.7%), and gastrointestinal disorder (17.5% and 17.2% in the agomelatine and placebo groups, respectively). Of them, nervous system disorders was the only SOC reported with a higher frequency in the agomelatine group. This difference was mainly due to dizziness, more frequently reported in the agomelatine group than in the placebo group (7.9% *versus* 3.4%), and restless legs syndrome (3.2%) not reported in the placebo group.

Headache, nasopharyngitis and fatigue were the most frequent emergent adverse events reported in the two treatment groups. The percentages of patients concerned were comparable for headache (14.3% and 15.5% in the agomelatine and placebo groups, respectively) and fatigue (9.5% and 8.6% in the agomelatine and placebo groups, respectively) and lower in the agomelatine group for nasopharyngitis (11.1% *versus* 17.2%). In addition to dizziness, nausea was the second most common emergent adverse event more frequently reported in the agomelatine group than in the placebo group (4.8% of patients *versus* 1.7%).

In both treatment groups, most emergent adverse events were moderate (47.6% and 51.7% of the events in the agomelatine and placebo groups, respectively) or mild (36.5% and 34.5% in the agomelatine and placebo groups, respectively). Few severe emergent adverse events were reported, 5 in 5 patients (7.9%) in the agomelatine group and 5 in 3 patients (5.2%) in the placebo group.

The percentage of patients with at least one emergent adverse event considered to be related to the study treatment by the investigator showed no clinically relevant difference between the agomelatine and placebo groups (38.1% and 34.5% in the agomelatine and placebo groups, respectively). The most frequent emergent adverse events considered to be related to the study treatment by the investigator in both groups were headache and fatigue (9.5% of the patients in the agomelatine group for each event, and 12.1% and 8.6%, respectively, in the placebo group).

In all, 1 patient (1.6%) on agomelatine 25 mg had 2 treatment-related emergent adverse events which led to a treatment withdrawal at week 2 (1 severe fatigue associated with 1 moderate upper abdominal pain). No serious adverse events were notified during the study.

As regards agomelatine doses, no dose effect was observed for emergent adverse events in general or for a particular event.

- **Laboratory safety**

There were no clinically relevant between groups difference nor changes from baseline to the last value on treatment in both treatment groups in the biochemical and haematological parameters during the week 0-week 12/WEND period. In all, 2 patients on agomelatine (one in each dose subgroup) had emergent potentially clinically significant abnormal transaminases on treatment (one emergence and one worsening compared to baseline) judged clinically relevant by the investigator (ASAT = 4N, and ALAT = 8N for the patient with emergence, and ALAT = 5N for the patient with worsening). These abnormal values were considered to be not related to the study treatment by the investigator, but related to one concomitant treatment (isotretinoin 5mg/d) or to patient's medical history (hepatitis). For haematological parameters, no emergent abnormal values were judged as clinically significant by the investigator.

- **Vital signs**

There were no clinically relevant between groups difference nor changes from baseline to the last post-baseline value in both groups for the supine blood pressure, heart rate, weight and BMI.

- **ECG**

The percentage of patients with at least one emergent ECG abnormality on treatment was lower in the agomelatine group than in the placebo group (6.3% *versus* 10.3%). None of these ECG abnormalities were considered to be clinically significant by the investigators.

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)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: Agomelatine (S 20098)	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Discontinuation Emergent Symptoms Scale (DESS)**

Of the patients having attended their follow-up visit between 6 and 8 days after the last study drug intake, and taking no psychotropic relay treatment (N = 75), the percentage of patients with at least one emergent DESS symptom was lower in the agomelatine group than in the placebo group (39.5% *versus* 43.8%) as well as the mean number of emergent DESS symptoms (1.8 ± 2.9 *versus* 2.0 ± 3.5 in the agomelatine and placebo groups, respectively).

CONCLUSION

This study demonstrates a clinically and statistically significant effect of a 12-week treatment with agomelatine 25 mg (with possible dose increase to 50 mg after 2 weeks) compared to placebo in patients with GAD assessed by the HAM-A total score (primary efficacy criterion), the response to treatment (defined as at least a 50% decrease in HAM-A), the remission (defined as HAM-A ≤ 7) as well as for the CGI severity of illness score. The broad benefit of agomelatine on both psychic and somatic anxiety symptoms of GAD is noteworthy. In addition to producing a robust effect, agomelatine led to significant global improvement in patient's conditions with a beneficial effect on subjective sleep assessed by the self rated LSEQ.

The incidence of adverse events during the 12-week study period was similar across both treatment groups. There was no significant difference between agomelatine and placebo groups based on DESS total score. This result confirms the absence of discontinuation syndrome of agomelatine (Montgomery *et al*, 2004).

In summary, agomelatine was effective and well-tolerated in the short-term treatment of generalised anxiety disorder as determined by both clinician and patient rated outcome measures.

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