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

Title of study: Efficacy and safety of agomelatine with flexible dose (25 mg/day with potential adjustment at 50 mg) given orally for 8 weeks in out-patients with Major Depressive Disorder.
A randomised flexible dose double-blind international multicentric study with parallel groups, versus fluoxetine (20 mg/day with potential adjustment at 40 mg). "Eight weeks mandatory treatment period + 16 weeks extension treatment period" (according to Amendment No. 1, in Malaysia and Singapore).
Protocol No.: CL3-20098-052

National coordinators: [redacted]

Study centres:
Overall, 39 centres located in 5 countries were opened (number of centres were increased following Amendment No. 4) and 38 centres included at least one patient: China, 13 centres in Mainland and 1 in Hong-Kong (245 included patients), Singapore, 2 centres (4 included patients), Malaysia, 3 centres (87 included patients), Taiwan, 6 centres (86 included patients) and Korea, 13 centres (206 included patients).

Publication (reference): NA

Studied period:	**Phase of development of the study:**
Initiation date: 16 August 2006 Completion date: 21 July 2008	III

Objectives: The primary objective of this study was to assess the agomelatine superiority to fluoxetine, using the Hamilton Depression Rating Scale 17 items, after an 8-week treatment period in Asian out-patients suffering from moderate to severe Major Depressive Disorder (MDD).
The secondary objective was to provide additional safety data on agomelatine in the Asian population.

Methodology:
This was an international, multicentre, randomised double-blind phase III study with 2 parallel groups, comparative *versus* fluoxetine using flexible dosages of agomelatine and fluoxetine. This study was to be performed in Asian patients suffering from moderate to severe Major Depressive Disorder.
A double-blind treatment period of 8 weeks (from W0 to W8) was preceeded by a **selection period** between selection and inclusion (W0) visits. At W0, patients were randomised in one of the two treatment groups: agomelatine or fluoxetine. From W0 to W2, patients received agomelatine 25 mg/day or fluoxetine 20 mg/day. At W2, if the improvement of the patient's depressive condition was considered insufficient, the dosage of agomelatine was to be increased to 50 mg daily, in double-blind conditions. Patients of the agomelatine group with a sufficient improvement remained on 25 mg/day and patients of the fluoxetine treatment group remained on 20 mg/day, whatever their improvement at W2. At W4, if the improvement of the patient's depressive condition was considered insufficient, the dosage of fluoxetine was increased to 40 mg/day in double-blind conditions, patients of the fluoxetine treatment group with a sufficient improvement remained on 20 mg/day and patients of the agomelatine treatment group remained on the same dosage than W2.
Then a **double-blind extension treatment period of 16 weeks** (from W8 to W24) was added according to the Amendment No. 1 in Malaysia and Singapore (this period was not mandatory and was proposed to the patient if the investigator considered the patient as a responder to the study treatment, defined as a decrease of the initial HAM-D-17 total score of 50%): patients of the agomelatine treatment group remained on the same dosage than W2 and patients of the fluoxetine treatment group remained on the same dosage than W4.
Treatment period was followed by **a follow-up period** of 1 week (from last visit to Wend visit) after study completion or after treatment discontinuation whatever its time of occurrence.
The criteria for adaptation of the dose at W2 and W4 was defined by the sponsor prior to the study start. The randomisation of treatments was balanced (non-adaptive) with stratification on the centre. Centralised randomisation at W0 and centralised therapeutic units allocation at W0, W2, W4 (and W8, according to the Amendment No. 1) were managed by an Interactive Voice Response System.

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:**	

Number of patients:
Planned: total 600 patients/ 300 patients by treatment group
Included: total 628 patients/ 314 by treatment group

Diagnosis and main criteria for inclusion:
Ambulatory male or female Asian patients aged from 18 to 65 years (both inclusive), fulfilling DSM-IV-TR criteria for MDD of moderate to severe intensity (HAM-D-17 total score greater than or equal to 22 at selection and inclusion without a decrease from selection visit more than 20%), single or recurrent episode (duration ≥ 4 weeks), requiring an antidepressant treatment, with or without melancholic features, without seasonal pattern, without psychotic features and without post partum onset for the current episode. All other concomitant psychiatric disorders were not allowed and were to be documented using the brief structured interview M.I.N.I.
Patients should be included if CGI item 1 "severity of illness" was ≥ 4, if HAD was completed and if washout periods for prohibited treatments during the study were respected.

Study drug:
Agomelatine 25 mg tablets, 1 or 2 tablets masked in a yellow capsule, 1 capsule p.o. once a day around 8 p.m (+ 2 red placebo capsules around 8 a.m).
Batch No. L0008796, L0017923, L0008798, L0018091

Reference product:
Fluoxetine 20 mg capsule, 1 capsule masked in a red capsule, 1 or 2 capsules p.o. once a day around 8 a.m.
[+ 1 placebo capsule twice a day around 8 a.m (red capsule) and 8 p.m (yellow capsule) or one yellow placebo capsule once a day around 8 p.m].

Duration of treatment:
Period from selection (ASSE) to inclusion (W0) without study treatment (between 7 +/- 3 days)
Double-blind mandatory treatment period of 8 weeks (from W0 to W8)
Double-blind extension period of 16 weeks (from W8 to W24) (Amendment No. 1, in Malaysia and Singapore)
Follow-up period of 1 week after study completion or after treatment discontinuation.

Criteria for evaluation:
EFFICACY MEASUREMENTS:
Primary efficacy criterion: Hamilton Depression Rating Scale 17 items (HAM-D-17 items) total score was assessed at each visit from ASSE to W24 (Amendment No. 1, in Malaysia and Singapore).
Secondary efficacy criteria:

- *Clinical Global Impression* (CGI) was rated at each visit from ASSE (for severity of illness score) or W1 (for global improvement score) to W8 visit (or W24 according to the Amendment No. 1, in Malaysia and Singapore).
- *Leeds Sleep Evaluation Questionnaire* (LSEQ) is a self-rating questionnaire to be completed by the patient at W1, W2, W4, W6 and W8 visits to further characterize patient sleeping improvement (getting off to sleep, quality of sleep, sleep awakening and integrity of behaviour).
- *Hamilton Anxiety Rating Scale* (HAM-A) total score, psychic anxiety score and somatic anxiety score were assessed at W0, W1 and W8 or at anytime if the patient withdrew from the study, for the purpose of checking the anxiety improvement.

SAFETY MEASUREMENTS:
Adverse events at each visit from selection to follow-up visit.
Laboratory tests: biological samplings were prescribed at selection and W6 visits (results available in the centre for the inclusion and W8 visits, respectively). According to the Amendment No. 1 (in Malaysia and Singapore), blood samples were added at W20 (results available for the W24 visit). In case of withdrawal of the patient for any reason between W0 and W8 or between W8 and W24 (Amendment No. 1, in Malaysia and Singapore), blood sampling was to be prescribed as soon as possible after the end of study treatment (results available for the follow up visit).

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:**	

SAFETY MEASUREMENTS (Cont'd):

Physical examination at selection, inclusion and W8 visits, W24 visit (Amendment No. 1, in Malaysia and Singapore) and at anytime if the patient withdrew from the study.

ECG prescribed at selection, W6 and W20 (Amendment No. 1, in Malaysia and Singapore) visits: interpretation and traces available in the centre for the inclusion, W8 and W24 visits, respectively. In case of withdrawal of the patient for any reason between W0 and W8 or between W8 and W24 (Amendment No. 1, in Malaysia and Singapore), ECG was to be prescribed as soon as possible after the end of study treatment and results had to be available for the follow up visit.

Liver B ultrasound detection (see Amendment No. 3 applicable only in China Mainland) at selection and W6 visits: interpretations had to be available in the centre for inclusion and W8 visits, respectively. In case of withdrawal between W0 and W8, liver B ultra sound was to be prescribed as soon as possible after the end of study treatment (results available for the follow up visit).

Statistical methods:

EFFICACY ANALYSIS:

Primary criterion

In addition to descriptive statistics over the W0-W8 period in the FAS and the SUB-FAS with W0 HAM-D total score ≥ 25 and over the W0-W24 period in the SUB-FAS in extension period, the following analyses were performed:

Main analysis

A stepwise strategy was set-up concerning the main analysis: First the non-inferiority of agomelatine relative to fluoxetine was investigated taking into account the fixed pre-defined non-inferiority margin of -1.5. Then in case of a significant non-inferiority test, the superiority of agomelatine versus fluoxetine was studied.

These two analyses were carried out in the FAS on the change from baseline to last post-baseline value over the W0-W8 period, using a two-way analysis of covariance on factors treatment as fixed effect and centre as random effect, with baseline as covariate and no interaction.

Sensitivity analysis

An unadjusted analysis based on a two-sided Student's t-test for independent samples was performed in the FAS for the last post-baseline value until W8, and the same stepwise strategy was used.

Secondary analyses

The previous analyses were also performed in the SUB-FAS with W0 HAM-D total score ≥ 25.

The difference between agomelatine and fluoxetine was also studied in the FAS and in the SUB-FAS with W0 HAM-D total score ≥ 25 on the response to treatment taking into account the last post-baseline value until W8, using a Chi-Square test.

Secondary criteria

For each analytical approach of secondary criteria, descriptive statistics were provided:

- Over the W0-W8 period in the FAS and over the W0-W24 period in the SUB-FAS in extension period for CGI scores.
- Over the W0-W8 period in the FAS for LSEQ scores and HAM-A total score and subscores.

For CGI scale, the difference between agomelatine and fluoxetine was also studied in the FAS:

- On the last value for Global improvement score and the last post-baseline value for Severity of illness score until W8, using a two-sided Student's t-test for independent samples and a Mann-Whitney test.
- On the response to treatment, derived from CGI Global improvement score and considering the last value until W8, using a Chi-Square test.

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:**	

Statistical methods (Cont'd):

SAFETY ANALYSIS:

A descriptive analysis was provided for emergent adverse events, biochemistry, haematology, physical examination, BMI and ECG in the Safety Set over the W0-W8/Wend period and in the SUB-SS in extension period over the W0-W24/Wend period (restricted to the period post-W8 for emergent adverse events). The whole AE occurred during the whole study over ASSE-W24/Wend period were also described. In addition in patients from China Mainland, descriptive analysis was provided for liver B ultrasound over the W0-W8/Wend period in the Safety Set.

SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

		Agomelatine	Fluoxetine	All
W0-W8/Wend period				
Included (randomised)	n	**314**	**314**	**628**
Lost to follow-up	n (%)	**-**	**5 (1.6)**	**5 (0.8)**
Withdrawn	n (%)	**70 (22.3)**	**70 (22.3)**	**140 (22.3)**
Adverse event	n (%)	27 (8.6)	35 (11.1)	62 (9.9)
Non-medical reason	n (%)	24 (7.6)	22 (7.0)	46 (7.3)
Lack of efficacy	n (%)	10 (3.2)	10 (3.2)	20 (3.2)
Protocol deviation	n (%)	5 (1.6)	3 (1.0)	8 (1.3)
Recovery	n (%)	4 (1.3)	-	4 (0.6)
Completed the W0-W8 period	n (%)	**244 (77.7)**	**239 (76.1)**	**483 (76.9)**
Performed the follow-up visit	n (%)	228 (72.6)	225 (71.7)	453 (72.1)
W8-W24/Wend period				
Entering the extension period* **	n	**37**	**35**	**72**
Lost to follow-up *	n (%)	**-**	**1 (2.9)**	**1 (1.4)**
Withdrawn*	n (%)	**1 (2.7)**	**6 (17.1)**	**7 (9.7)**
Adverse event *	n (%)	-	2 (5.7)	2 (2.8)
Non-medical reason *	n (%)	1 (2.7)	4 (11.4)	5 (6.9)
Completed the W8-W24 period *	n (%)	**36 (97.3)**	**28 (80.0)**	**64 (88.9)**
Performed the follow-up visit *	n (%)	35 (94.6)	28 (80.0)	63 (87.5)
Analysis sets				
Randomised Set	n	314	314	628
SUB-RS in the extension period	n (%)	37 (11.8)	35 (11.1)	72 (11.5)
Efficacy Sets				
Full Analysis Set (FAS)	n (%)	301 (95.9)	308 (98.1)	609 (97.0)
SUB-FAS with W0 HAM-D total score ≥ 25	n (%)	221 (70.4)	218 (69.4)	439 (69.9)
SUB-FAS in extension period **	n (%)	37 (100.0)	33 (94.3)	70 (97.2)
Safety Sets				
Safety Set (SS)	n (%)	310 (98.7)	310 (98.7)	620 (98.7)
SUB-SS in extension period **	n (%)	37 (100.0)	33 (94.3)	70 (97.2)

n: number of patients

*%: Calculated as percentage of included patients except *: expressed as percentage of patients entering the extension period and **: expressed as percentage of the SUB-RS in extension period; ***: extension period was possible only for Malaysian and Singaporean patients (91 randomised patients: 46 and 45 patients in agomelatine and fluoxetine groups, respectively).*

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:**	

STUDY POPULATION AND OUTCOME (Cont'd)

Over the W0-W8 period, 628 patients were included (314 patients in each agomelatine and fluoxetine groups). Among them, 140 patients *i.e*. 22.3% of the included patients (70 patients in each treatment group) withdrew from the study mainly due to adverse events (62 patients, 9.9%) and non-medical reasons (46 patients, 7.3%). The rate of withdrawals for adverse event was lower in the agomelatine group (8.6%) than in the fluoxetine group (11.1%). The global rate of withdrawals at the beginning of the treatment was lower in the agomelatine group than in the fluoxetine group (10.8% *versus* 14.0%, respectively over the W0-W2 period) mainly due to withdrawals for adverse events (3.8% *versus* 8.3%, respectively). It is to note that 4 patients (all in the agomelatine group) withdrew from the study due to recovery. In addition, 5 patients were lost to follow-up over the W0-W8 period: all in the fluoxetine group. Overall, 483 patients *i.e*. 76.9% of the RS completed the W0-W8 period without relevant difference between groups.

Among the patients continuing the study after the dose adaptation visits, the percentage of patients who had a dose increase was higher in the agomelatine group at W2 (40/280 patients had a dose increase from 25 mg to 50 mg *i.e.* 14.3%) than in the fluoxetine group at W4 (15/247 patients had a dose increase from 20 mg to 40 mg *i.e.* 6.1%).

Regarding the W8-W24 period and according to the Amendment No. 1, among the 91 Malaysian and Singaporean patients of the RS, 72 patients entered the extension period (37 patients in the agomelatine group and 35 patients in the fluoxetine group). The rate of withdrawals during the W8-W24 period was lower in the agomelatine group (1 patient *i.e.* 2.7%) than in the fluoxetine group (6 patients *i.e.* 17.1%). One patient (in the fluoxetine group) was lost to follow-up at W20. Overall, 64 patients (88.9%) completed the W8-W24 period with a higher rate in the agomelatine group (36 patients *i.e.* 97.3%) than in the fluoxetine group (28 patients *i.e.* 80.0%).

Main baseline characteristics

In the Randomised Set, patients were on average (± SD) 39.0 ± 12.7 years, and most of them were female (69.4% of the patients) without relevant difference between groups.

All patients had a Major Depressive Disorder according to DSM-IV criteria mainly of moderate intensity (57.3%) and mainly with recurrent episode (54.0%). The duration of MDD was on average of 4.25 ± 6.44 years (median 1.5 years) and the current MDE lasted for 5.02 ± 4.11 months (median 3.4 months). Overall, 2.9% of the patients received previous antipsychotic treatments. No relevant difference between groups was observed regarding the diagnosis at inclusion and previous psychiatric history.

The mean HAD depression score at selection was 14.3 ± 3.7, without relevant difference between groups. Regarding classes of HAD depression score, the rate of patients with score ≥ 11 (suggesting depression) was 88.5% in the agomelatine group and 82.8% in the fluoxetine group. Overall, 42.8% of the patients had received previous psychotropic treatments within one year prior to the selection in the study, mainly antidepressants (31.4% of patients), mainly selective serotonin reuptake inhibitor (20.1%), without relevant difference between groups.

Regarding liver B ultrasound (performed only in China Mainland) at inclusion, steatosis was less reported in the agomelatine group (6/119 patients *i.e.* 5.0% of the randomised patients with interpretable LBU at inclusion) than in the fluoxetine group (13/122 patients *i.e.* 10.7%) and was mild for all of the patients.

No clinically relevant difference between groups was observed regarding physical examination, ECG and other baseline characteristics.

No relevant difference was observed in both groups regarding efficacy parameters at inclusion: the mean HAM-D rating total score was at 26.8 ± 3.2, the severity of illness score according to CGI was on average at 4.7 ± 0.7 and the mean HAM-A total score was 24.6 ± 6.9.

The demographic data and other baseline characteristics in the FAS were similar to those described in the Randomised Set.

Treatment duration was on average of 49.3 ± 17.4 days, over the W0-W8 period, in the Randomised Set, and 166.8 ± 12.1 days, over the W0-W24 period, in the SUB-RS in extension period without relevant difference between groups. The overall compliance was satisfactory as 90.1% of the patients in the RS had overall compliance between 70% and 130% over the W0-W8 period, without relevant difference between treatment groups.

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:**	

EFFICACY RESULTS

Primary efficacy criterion: HAM-D total score

Main analytical approach of HAM-D total score: change from baseline to last post-baseline value. The main analysis was performed in the FAS.

HAM-D total score over the W0-W8 period in the FAS (N = 609)

HAM-D total score		**Agomelatine (N = 301)**	**Fluoxetine (N = 308)**
Descriptive statistics			
	n	301	308
Baseline (W0)	Mean ± SD	26.8 ± 3.2	26.8 ± 3.3
	Min - Max	22 - 36	22 - 39
Last post-baseline value	Mean ± SD	12.0 ± 7.4	11.8 ± 8.0
	Min - Max	0 - 37	0 -35
Change from baseline to last post-baseline value	Mean ± SD	-14.8 ± 7.3	-15.0 ± 8.1
	Min - Max	- 29 - 4	-30 - 5
Statistical analysis			
Change from baseline to last post-baseline value	E (SE) (1)	-0.25 (0.58)	
	95% CI (2)	[-1.38 ; 0.89]	
Non-inferiority test	p-value (3)	0.015	
Superiority test	p-value (4)	0.669	

General linear model with baseline as covariate and centre as random effect; (1) Estimate (Standard Error) of the difference between adjusted treatment group means: fluoxetine minus agomelatine; (2) Two-sided 95% Confidence Interval of the estimate; (3) Non-inferiority test centred on a non-inferiority margin of -1.5: one-sided p-value to be compared to 0.025. Non-inferiority test followed by a superiority test in case of a significant test of non-inferiority; (4) Superiority test: two-sided p-value to be compared to 0.05.

Mean changes from baseline to last post-baseline value over the W0-W8 period were clinically relevant and similar in both groups (-14.8 ± 7.3 and -15.0 ± 8.1 in agomelatine and fluoxetine groups, respectively), with an estimated between-group difference (SE) of -0.25 (0.58) (fluoxetine minus agomelatine) and 95% CI = [-1.38 ; 0.89]. Regarding the non-inferiority test, the result was significant with a p-value of 0.015 (to be compared to 0.025), the lower limit of 95% CI (-1.38) being greater than the fixed non-inferiority margin of -1.5 planned in the Statistical Analysis Plan. However, the superiority of agomelatine was not demonstrated (p = 0.669).

Those results were confirmed by the unadjusted sensitivity analysis on the last post-baseline value over the W0-W8 period in the FAS: E(SE) = -0.14 (0.63) with 95% CI = [-1.37 ; 1.09], p-values = 0.015 (non-inferiority test) and 0.825 (superiority test).

Regarding the subset of more severely depressed patients (SUB-FAS with W0 HAM-D total score ≥ 25), mean changes (± SD) from baseline to last post-baseline value over the W0-W8 period were -15.2 ± 7.6 and -16.4 ± 8.1, in the agomelatine and fluoxetine groups, respectively. The estimated between-group difference (SE) was -0.98 (0.71), 95% CI = [-2.37 ; 0.41], the non-inferiority of agomelatine to fluoxetine being not showed (p = 0.232). This result was confirmed by the unadjusted analysis on the last post-baseline value over the W0 - W8 period: E(SE) = -0.86 (0.77); 95% CI = [-2.37 ; 0.64] with p-value = 0.204.

In the SUB-FAS in the extension period (37 patients in the agomelatine group and 33 in the fluoxetine group), over the W0-W24 period, mean changes (± SD) from baseline to last post-baseline value were similar in both groups: -23.4 ± 3.6 and -23.2 ± 3.6 in the agomelatine and fluoxetine groups, respectively.

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:**	

EFFICACY RESULTS (Cont'd)

Secondary analytical approaches of the HAM-D total score

Response to treatment (decrease from baseline ≥ 50%)

Over the W0-W8 period, the rate of responders at the last post-baseline assessment according to the HAM-D total score was similar in both groups in the FAS (68.1% and 67.9%, in the agomelatine and fluoxetine groups, respectively) with an estimated between-group difference (SE) of -0.25 (3.78), 95% CI = [-7.66 ; 7.16] and p = 0.947 (superiority test, p-value to be compared to 0.05). In the SUB-FAS with W0 HAM-D total score ≥ 25, the rate of responders was 66.5% in the agomelatine group and 69.7% in the fluoxetine groups without statistically significant difference: E(SE) = 3.21 (4.45), 95% CI = [-5.50 ; 11.92], p = 0.471. In the SUB-FAS in extension period, over the W0-W24 period, at last post-baseline value, the rate of responders was 100.0% in both groups.

Remission (total score ≤ 6)

In the SUB-FAS in extension period, over the W0-W24 period, the rate of remitters was similar in both groups at last post-baseline value: 30 patients (81.1%) *versus* 26 patients (78.8%) in agomelatine and fluoxetine groups, respectively.

Secondary efficacy criteria

CGI scale: regarding both Severity of Illness score and Global Improvement score as well as rate of responders (defined as CGI Global Improvement score equal to 1 or 2), results were clinically relevant and similar in both groups at last post-baseline value over the W0-W8 period in the FAS without statistically significant difference:

Mean Severity of Illness score was 2.6 ± 1.2 and 2.6 ± 1.3 in agomelatine and fluoxetine groups, respectively: E(SE) = -0.02 (0.10), 95%CI = [-0.22 ; 0.18], p = 0.843. Mean Global Improvement score was 2.0 ± 1.0 in the agomelatine group and 1.9 ± 1.1 in the fluoxetine group: E(SE) = -0.08 (0.09), 95%CI = [-0.25 ; 0.09], p = 0.352. Rate of responders was 74.8% and 75.6% in the agomelatine and fluoxetine groups, respectively: E(SE) = 0.90 (3.50), 95%CI = [-5.96 ; 7.76], p = 0.797.

Over the W0-W24 period, in the SUB-FAS in extension period, no relevant between-groups differences were detected regarding CGI at last assessment: Severity of Illnes score was on average 1.3 ± 0.6 *versus* 1.5 ± 0.6 in the agomelatine and fluoxetine groups, respectively and Global Improvement score was 1.0 ± 0.2 *versus* 1.2 ± 0.4 in the agomelatine and fluoxetine groups, respectively. Overall at the last evaluation, 100% of patients were responders. Percentage of patients in remission (defined as CGI Global improvement score equal to 1) was higher in the agomelatine group (97.3%) than in the fluoxetine group (78.8%) at the last assessment.

LSEQ**:** over the W0-W8 period in the FAS, clinically relevant sleep improvement was observed on agomelatine according to the LSEQ scores: the four scores studied decreased on average regularly from W1 to W8 in both groups. Mean last values over the W0-W8 period were similar in agomelatine and fluoxetine groups for all of the scores.

HAM-A scale: over the W0-W8 period in the FAS, clinically relevant improvement of anxiety was observed on agomelatine according to the HAM-A scores: the mean HAM-A total, psychic and somatic anxiety scores decreased from baseline to W8 in both groups. The mean decrease from baseline to last post-baseline value were similar in both groups of treatment for all the 3 scores (more than 50% for each).

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:**	

SAFETY RESULTS

Adverse events

During the W0-W8/Wend period, in the Safety Set, 46.8% of the patients reported at least one emergent adverse event without relevant difference between groups: 46.1% of the patients in the agomelatine group *versus* 47.4% in the fluoxetine group.

In the agomelatine group, the most frequently affected system organ class (in more than 5% of the patients) were nervous system disorders (18.4%), gastrointestinal disorders (17.4%), psychiatric disorders (9.0%) and infections and infestations (6.1%). Incidences of those SOC were similar in both groups except for gastrointestinal disorders less frequently reported in the agomelatine group than in the fluoxetine group (17.4% *versus* 21.0%, respectively).

The most frequently reported emergent adverse events in the agomelatine group (more than 2% of the patients) were dizziness (7.7%), nausea (7.1%), headache (6.1%), insomnia (2.9%), upper respiratory tract infection (2.9%) and dry mouth (2.6%) with similar incidences in the fluoxetine group except for dizziness and nausea. Dizziness was more frequently reported in the agomelatine group than in the fluoxetine group (7.7% *versus* 5.8%). Conversely, nausea was less frequently reported in the agomelatine group than in the fluoxetine group (7.1% *versus* 11.0%).

The percentage of patients who experienced at least one emergent adverse event rated as severe was the same in agomelatine and fluoxetine group (3.2% in both groups). The most frequent SOC in the agomelatine group (> 1%) affected by severe emergent adverse event was psychiatric disorders without relevant difference between groups: 6 patients (1.9%) and 5 patients (1.6%) in agomelatine and fluoxetine groups, respectively.

The percentage of patients who experienced at least one emergent adverse event considered to be related to the study drug was lower in the agomelatine group than in the fluoxetine group (30.0% *versus* 37.4%). The most frequent SOC affected in the agomelatine group were nervous system disorders and gastrointestinal disorders without relevant difference between agomelatine and fluoxetine groups (respectively 15.2% *versus* 17.1% and 14.5% *versus* 16.1%).

The incidence of patients with at least one emergent AE leading to treatment discontinuation was lower in the agomelatine group than in the fluoxetine group (8.7% *versus* 11.0%): the most frequent SOC affected in the agomelatine group were psychiatric disorders (similar incidence in both groups: 4.5%), gastrointestinal disorders (less frequent in the agomelatine group than in the fluoxetine group: 1.3% *versus* 2.6%, respectively) and nervous system disorders (less frequent in the agomelatine group than in the fluoxetine group: 1.6% *versus* 2.3%, respectively).

Recovery was observed for most of the emergent AE in both groups (92.8% and 92.0%) in agomelatine and fluoxetine groups, respectively.

During the W8-W24/Wend period, in the SUB-SS in extension period, 12 patients (17.1%) reported at least one emergent adverse event without relevant difference between groups: 16.2% of the patients in the agomelatine group *versus* 18.2% in the fluoxetine group. The most frequently reported emergent adverse events in the agomelatine group were upper respiratory tract infection (4 patients) and headache (2 patients) which were not reported in the fluoxetine group. No severe emergent adverse event was recorded during the W8-W24/Wend period.

After the treatment period, in the Safety Set, the percentage of patients who experienced at least one adverse event was lower in the agomelatine group than in the fluoxetine group (15.8% *versus* 23.2%). The main SOC recorded were psychiatric disorders less frequent in the agomelatine group than in the fluoxetine group (4.8% *versus* 6.5%) and nervous system disorders similarly reported in both groups (3.5% *versus* 3.9%).

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:**	

SAFETY RESULTS (Cont'd)

One death occurred in the fluoxetine group: a male 27 years old, committed suicide at W2, 2 days after the last study drug intake. The event was considered as not related to the study drug according to the investigator.

During the 8-week treatment period, the percentage of patients with at least one serious emergent AE was higher in the agomelatine group than in the fluoxetine group (3.9% *versus* 2.6%, respectively). Most of serious EAE were related to psychiatric disorders in both groups (1.6% in the agomelatine group *versus* 1.3% in the fluoxetine group), mainly due to suicide attempt without relevant difference between groups (1.3%, in the agomelatine group *versus* 1.0% in the fluoxetine group).

Most of serious emergent AE led to treatment withdrawal: 8/13 in the agomelatine group and 6/8 in the fluoxetine group. Overall, 2 patients (0.6%) in each group reported at least one treatment-related serious EAE: one vertigo and one hepatic enzymes increased in the agomelatine group and 2 suicide attempts in the fluoxetine group (all of these led to treatment discontinuation except hepatic enzymes increased). In addition, 2 non-emergent serious AE were considered as treatment-related: one "bipolar disorder" (occurrence of mixed episode in one patient for whom the diagnosis was initially MDD) and one "mania", both reported after treatment period in the fluoxetine group.

All serious emergent adverse events recovered except intervertebral disc protrusion in the agomelatine group and road traffic accident (recovering) in the fluoxetine group.

Biochemistry and haematology

Neither clinically relevant changes nor differences between groups over time were detected for all parameters during the study.

Liver acceptability

Neither clinically relevant changes nor differences between groups over time were detected for all mean liver parameters values during the study. In the Safety Set, during the W0-W8/Wend period in the agomelatine group, emergent out-of-reference ranges values were mainly reported for elevated ASAT and ALAT with a higher incidence in the agomelatine group (4.9% and 6.4%, respectively) than in the fluoxetine group (2.2% for both parameters). Similar results were observed in the SUB-SS in extension period for ALAT (6 patients, 16.2% *versus* 2 patients, 6.1%).

Overall, 2 patients in the agomelatine 25 mg group reported 4 emergent PCSA values of transaminases and 1 patient in the fluoxetine 20 mg group reported 2 emergent PCSA values of transaminases (all during the W0-W8/Wend period in the SS). There was no case of transaminases increase > 3ULN associated with emergent total bilirubin or ALP ≥ 2ULN.

In the agomelatine group, 2 patients reported both emergent PCSA values of ALAT (11 ULN and 6 ULN, respectively), associated with emergent PCSA values of ASAT (4 ULN and 5 ULN, respectively) and elevated GGT (2 ULN). Hepatic enzymes increase did not lead to drug withdrawal and was reported as probably related to the study drug. Both patients completed the study and recovered after the end of treatment. One patient was obese, carrier of hepatitis B and presented an emergent elevated glucose value.

In the fluoxetine group one patient reported both emergent PCSA values of ASAT (4 ULN) and ALAT (3 ULN). Transaminases increase did not lead to drug withdrawal and was reported as not related to the study drug. The patient completed the study and recovered 7 days after last intake.

Physical examination

In the Safety Set, over the W0-W8 period, neither relevant change over time nor difference between treatment groups were observed regarding physical examination including vital signs. Regarding BMI, the number of patients switching from a normal baseline value to an overweight was higher in the agomelatine than in the fluoxetine group (9 patients *versus* 3 patients) at last post baseline assessment: however, regarding the range of changes in these 12 patients, lower changes were observed in the agomelatine group [from 0.4 to 1.6] than in the fluoxetine group [from 1 to 3].

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:**	

SAFETY RESULTS (Cont'd)

ECG

Among patients without ECG abnormality at baseline, the rate of patients who presented at least one ECG abnormality after W0 was higher in the agomelatine group than in the fluoxetine group (14.7% *versus* 8.1%, respectively) in the Safety Set over the W0-W8/Wend period. This difference was mainly due to T wave abnormal (8 patients *versus* 1 patient) and sinus arrhythmia (6 patients *versus* 1 patient).

Liver B ultrasounds

No relevant between-group difference was observed regarding presence of LBU steatosis after W0 among patients without steatosis at W0: 1.9% (2 patients) *versus* 2.1% (2 patients) in agomelatine and fluoxetine groups, respectively. Similarly, no relevant between-group difference was observed regarding presence of LBU abnormality other than steatosis after W0 among patients without abnormalities other than steatosis at W0: 5.2% (5 patients) and 4.0% (4 patients) in agomelatine and fluoxetine groups, respectively.

CONCLUSION

This double-blind, international, multicentric randomised study conducted in 628 Asian patients, showed an anti depressant efficacy of agomelatine 25-50 mg/d similar to fluoxetine 20-40 mg/d on moderate to severe MDD after an 8-week treatment period, those results being confirmed over an extension period of 16 weeks. The non-inferiority of agomelatine to fluoxetine treatment was demonstrated. Regarding all secondary efficacy criteria (clinical global impression, sleep and anxiety), patients showed a clinically relevant improvement on agomelatine, without difference between groups.

This study showed that agomelatine 25-50 mg/d was well tolerated over 8-week treatment period and 24-week treatment period. The overall incidence of emergent adverse events was similar in both groups except gastrointestinal adverse events less frequently reported in the agomelatine group.

Date of the report: 2 June 2009