Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of agomelatine (25 mg/day with potential adjustment to 50 mg) given orally for 8 weeks in out-patients with severe Major Depressive Disorder.** **A randomised double-blind, parallel groups, international study *versus* fluoxetine (20 mg/day with potential adjustment to 40 mg) with a double-blind extension period of 16 weeks.**
Study drug	**Agomelatine (S-20098)**
Indication	**Major Depressive disorder**
Development phase	**III**
Protocol code	**CL3-20098-045**
Study initiation date	**06 October 2005**
Study completion date	**14 March 2008**
Main coordinator	[redacted] **UNITED KINGDOM**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France**
Responsible medical officer	[redacted] **(I.R.I.S.)**
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 10 March 2009**
	~~**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:
Efficacy and safety of agomelatine (25 mg/day with potential adjustment to 50 mg) given orally for 8 weeks in out-patients with severe Major Depressive Disorder.
A randomised double-blind, parallel groups, international study *versus* fluoxetine (20 mg/day with potential adjustment to 40 mg) with a double-blind extension period of 16 weeks.
Protocol No.: CL3-20098-045

Coordinator: International coordinator: [redacted] ([redacted], United Kingdom), and national coordinators: [redacted] ([redacted], Argentina), [redacted] ([redacted], Brazil), [redacted] ([redacted], Italy), and [redacted] ([redacted], Spain).

Study centres:
41 centres in 5 countries included at least one patient: Argentina (7 centres, 130 included patients), Brazil (7 centres, 184 included patients), Italy (5 centres, 37 included patients), Spain (11 centres, 51 included patients), United Kingdom (11 centres, 113 included patients)

Publication (reference): not applicable

Studied period:	**Phase of development of the study:**
Initiation date (first visit, first patient): 06 October 2005 Completion date (last visit, last patient): 14 March 2008	III

Objectives:
Primary objective: to assess the agomelatine superiority to fluoxetine, using the Hamilton Depression Rating Scale 17 items, after an 8-week treatment in out-patients suffering from severe Major Depressive Disorder.
Secondary objective: to provide additional sleep, anxiety and safety data on agomelatine in this population.

Methodology:
Double-blind, multicentre, international, randomised, comparative study in two parallel groups using a flexible dosage: agomelatine 25 mg/day and fluoxetine 20 mg/day. These initial doses could be increased to 50 mg/day and 40 mg/day, respectively, in case of insufficient improvement after 2 weeks or 4 weeks of treatment, respectively. The criteria for increasing the dose were defined by the sponsor, based on clinical considerations, before the study beginning, and kept blinded. The randomisation (at W0) was balanced (non-adaptive) with stratification on centre. The treatment allocation and the dose increase were done centrally using an Interactive Voice Response System (IVRS), in a blinded condition manner for patients and investigators. At the end of the 8-week double-blind period, the patients could either continue in the optional double-blind extension period or stop the study according to investigator's and patient's decision.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 500 (250/group).
Included: 515 (252 in the agomelatine group and 263 in the fluoxetine group).

Diagnosis and main criteria for inclusion:
Male or female out-patients, aged between 18 and 65 years, fulfilling DSM-IV-TR criteria for Major Depressive Disorder, of severe intensity (HAM-D-17 total score greater than or equal to 25 and CGI severity of illness score greater than or equal to 4 at selection and inclusion) and seven or more symptoms among A1 to A9 symptoms of the diagnostic criteria for Major Depressive Episode had to be present and markedly interfere with occupational functioning or with usual social activities or relationships with others (Amendment No. 2). Between selection and inclusion, the HAM-D-17 total score had not to decrease of more than 20%. At inclusion, the sum of items 1 + 2 + 5 + 6 + 7 + 8 + 10 + 13 of HAM-D-17 had to be ≥ 55% of HAM-D-17 total score.

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Study drug:
Agomelatine 25 mg tablets, 1 or 2 tablets once a day in 1 yellow capsule, *p.o.*, around 8 p.m.
Patients received 25 mg/day (2 placebo red capsules in the morning + 1 agomelatine tablet in 1 yellow capsule in the evening) from W0, with possible increase in double-blind conditions to 50 mg/day (2 placebo red capsules + 2 agomelatine tablets in 1 yellow capsule) at W2, in case of insufficient improvement. Once adjusted, the dose was maintained throughout the study.
Batches No: L0005189, L0005734, L0006198, L0015446, L0017234, L0016042, L0004584, L0005792, L0006488, L0015448, and L0017236.

Reference product:
Fluoxetine 20 mg capsules - 1 or 2 red capsules once a day, *p.o.*, around 8 a.m.
Patients received 20 mg/day (1 fluoxetine red capsule and 1 placebo red capsule in the morning + 1 placebo yellow capsule in the evening) from W0, with possible increase in double-blind conditions to 40 mg/day (2 fluoxetine red capsules + 1 placebo yellow capsule) at W4, in case of insufficient improvement. Once adjusted, the dose was maintained throughout the study.

Duration of treatment:
- 3 to 7-day run-in period (without study treatment) from selection to inclusion (W0) visits.
- 8-week acute double-blind treatment period (from W0 to W8).
- 16-week optional extension double-blind treatment period (from W8 to W24).
- 1-week follow-up period (without study treatment) at the end of the mandatory double-blind period or at the end of the optional double-blind period, or in case of premature withdrawal.

Criteria for evaluation:
Efficacy measurements:
- HAM-D-17 items rated at selection and at each visit from W0 to W24. The primary assessment criterion was the HAM-D-17 total score.
- CGI item 1 (severity of illness) rated at selection and each visit from W0 to W24, and CGI item 2 (global improvement) rated at each visit from W2 to W24.
- HAM-A (psychic, somatic, and total score) rated at W0 and W8 or before W8 in case of premature withdrawal.
- LSEQ (Leeds Sleep Evaluation Questionnaire) (self questionnaire to be completed by the patient) rated at each visit from W2 to W8.

Safety measurements:
- Physical examination (sitting blood pressure and heart rate, and weight) at selection, W0, W8 and W24 or in case of premature withdrawal.
- Record of adverse events from selection to W24, and follow-up visit.
- Laboratory tests (biochemistry and haematology) results available at W0, W8 and W24, or at the follow-up visit in case of premature withdrawal.
- ECG results available at W0, W8 and W24, or at the follow-up visit in case of premature withdrawal.

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Statistical methods:

Efficacy analysis:

In addition to descriptive statistics for the two treatment groups over the W0-W8 period in the Full Analysis Set (FAS) and over the W0-W24 period in the FAS and SUB-FAS in extension period, the following analyses were performed:

Primary criterion

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 and centre (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, using the same stepwise strategy.

Secondary analysis

The difference between agomelatine and fluoxetine was also studied in the FAS on the response to treatment (decrease from baseline of at least 50 %) taking into account the last post-baseline value until W8, using a Chi-Squared test.

Secondary criteria

For CGI scale, the difference between agomelatine and fluoxetine was also studied on the W0-W8 period in the FAS:

- on the value at W2 (complementary analysis) and the last post-baseline value for Severity of illness score, and on the last post-baseline value for Global improvement score, 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 (score = 1 or 2) and considering the last post-baseline value, using a Chi-Squared test.

Treatment groups were also compared on the W0-W8 period in the FAS on the last post-baseline value of the HAM-D sleep sub-score (sum of the insomnia items 4, 5 and 6 from the HAM-D-17 scale) using a two-sided Student's t-test (complementary analysis).

Safety analysis:

Descriptive statistics were provided in the Safety Set for the two treatment groups and the four dose subgroups (agomelatine 25 mg, agomelatine 25-50 mg, fluoxetine 20 mg, fluoxetine 20-40 mg) over the W0-W8 and W0-W24 periods.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

		Agomelatine	Fluoxetine	Whole population
W0-W8				
Included (randomised)		**252**	**263**	**515**
Lost to Follow-up		**-**	**4 (1.5)**	**4 (0.8)**
Withdrawn	**n (%)**	**30 (11.9)**	**45 (17.1)**	**75 (14.6)**
due to adverse event	n (%)	10 (4.0)	17 (6.5)	27 (5.2)
due to non-medical reason	n (%)	9 (3.6)	13 (4.9)	22 (4.3)
due to recovery	n (%)	1 (0.4)	-	1 (0.2)
due to protocol deviation	n (%)	3 (1.2)	2 (0.8)	5 (1.0)
due to lack of efficacy	n (%)	7 (2.8)	13 (4.9)	20 (3.9)
Completed the W0-W8 period	**n (%)**	**222 (88.1)**	**214 (81.4)**	**436 (84.7)**
Entered the W8-W24 period	**n (%)**	**212 (84.1)**	**197 (74.9)**	**409 (79.4)**
Lost to follow-up*	**n (%)**	**-**	**2 (1.0)**	**2 (0.5)**
Withdrawn*	**n (%)**	**42 (19.8)**	**25 (12.7)**	**67 (16.4)**
due to adverse event	n (%)	9 (4.2)	1 (0.5)	10 (2.4)
due to non-medical reason	n (%)	21 (9.9)	16 (8.1)	37 (9.0)
due to recovery	n (%)	2 (0.9)	1 (0.5)	3 (0.7)
due to protocol deviation	n (%)	-	1 (0.5)	1 (0.2)
due to lack of efficacy	n (%)	10 (4.7)	6 (3.0)	16 (3.9)
Completed the W8-W24 period*	**n (%)**	**170 (80.2)**	**170 (86.3)**	**340 (83.1)**
Completed the study (W0-W24)	**n (%)**	**170 (67.5)**	**170 (64.6)**	**340 (66.0)**
Analysis Sets				
Randomised Set	n (%)	252 (100.0)	263 (100.0)	515 (100.0)
Full Analysis Set (FAS)	n (%)	247 (98.0)	257 (97.7)	504 (97.9)
Safety Set	n (%)	250 (99.2)	263 (100.0)	513 (99.6)

*%: Expressed as percentage of the patients from the Randomised Set except for * expressed as percentage of patients entered the W8-W24 extension period.*

Overall, 515 patients were randomized: 252 patients to the agomelatine group and 263 patients to the fluoxetine group. In all, 123 patients had a dose increase: 70 (29.0%) of 241 agomelatine-treated patients continuing at W2 received the 50 mg dose and 53 (23.0%) of 230 fluoxetine-treated patients continuing at W4 received the 40 mg dose. Over the W0-W8 period, the rate of withdrawals was lower in the agomelatine group (11.9%) than in the fluoxetine group (17.1% and 1.5% lost-to follow-up). The difference was mainly due to withdrawals for adverse events and for lack of efficacy which were less frequent in the agomelatine group (4.0% and 2.8%, respectively) than in the fluoxetine group (6.5% and 4.9%, respectively). Inversely, over the W8-W24 extension period, the rate of withdrawals was higher in the agomelatine group (19.8%) than in the fluoxetine group (12.7%) mainly due to withdrawals for adverse events (4.2% in the agomelatine group *versus* 0.5% in the fluoxetine group). Finally, the percentage of randomised patients who completed the study at W24 showed no relevant difference between treatment groups (67.5% in the agomelatine group and 64.6% in the fluoxetine group). As regards dose subgroups, the percentage of completers showed no relevant difference between both doses of agomelatine: 122/182 patients (67.0%) in the agomelatine 25 mg subgroup, and 48/70 patients (68.6%) in the agomelatine 25-50 mg subgroup. With fluoxetine, the percentage of completers was lower in the 20 mg subgroup (128/210 patients, 61.0%) than in the 20-40 mg subgroup (42/53 patients, 79.2%).

Randomised patients were 42.3 ± 11.6 years old on average ±SD, ranging from 18 to 65 years. Most of them were female (77.7%). According to the DSM-IV-TR code, 94.0% of the patients presented with a severe episode of MDD without any psychotic feature, and 6.0% were rated as moderate. Mean number of depressive episodes was 2.5 ± 2.1 including the current one, ranging from 1 to 20, with a mean duration of the disease of 7.6 ± 9.2 years (median 4.3 years), and a mean duration of the current MDE of 4.9 ± 3.9 months (median 3 months). Previous psychotropic drug treatment was reported in 239 (46.4%) patients, mainly SSRIs (25.2%) and benzodiazepine derivatives (22.9%).

No clinically relevant differences between groups were observed for demographic and disease characteristics at baseline.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Considering efficacy criteria in the Randomised Set, no relevant between-group difference was observed at inclusion. Mean value of HAM-D-17 total score was 28.6 ± 2.6, and ranged from 24 to 39, one patient in the agomelatine group having a HAM-D-17 total score < 25. The mean CGI severity of illness score was 5.0 ± 0.6, corresponding to "markedly ill" patients, and ranged from 4 to 6. The mean HAM-A total score was 26.1 ± 7.0, with a mean psychic anxiety score of 15.7 ± 3.5, and a mean somatic anxiety score of 10.3 ± 4.4.
Baseline characteristics in the FAS were similar to those observed in the Randomised Set.

In the Randomised Set, treatment duration over the W0-W8 period, ranged between 0 and 74 days with a mean of 53.4 ± 13.3 days (median 57.0 days). Treatment duration over the W0-W24 period, ranged between 0 and 218 days with a mean of 139.2 ± 56.9 days, and median of 169 days. Treatment duration showed no relevant difference in both groups over both periods.
Global compliance was 94.5 ± 15.9% over W0-W8 and 96.6 ± 7.7% on average over W0-W24 and was similar in both groups.

EFFICACY RESULTS

Primary assessment criterion: HAM-D-17 total score

Change from baseline in HAM-D-17 total score (main expression, see Table below)

Over the W0-W8 period, the mean decrease in HAM-D-17 total score from W0 to the last post-baseline value was higher in the agomelatine group than in the fluoxetine group in the FAS. The statistical tests showed that agomelatine was statistically significantly superior to fluoxetine (main analysis: non-inferiority test, $p < 0.001$, then superiority test, $p = 0.024$). The sensitivity analysis (unadjusted analysis) confirmed the results with a difference (SE) between treatment in favour of agomelatine at last post-baseline value of 1.54 (0.71); 95% CI [0.14; 2.93] (non-inferiority test, $p < 0.001$ then superiority test, $p = 0.030$).

Comparison of agomelatine and fluoxetine treatments on HAM-D-17 total score decrease between W0 and the last post-baseline value over the W0-W8 period in the FAS

			Agomelatine (N = 247)	Fluoxetine (N = 257)
Descriptive statistics				
	W0	N	247	257
		Mean ± SD	28.5 ± 2.7	28.7 ± 2.5
		Min - Max	24 - 39	25 - 38
	Last post-baseline value	N	247	257
		Mean ± SD	11.1 ± 7.3	12.7 ± 8.5
		Min - Max	0 - 34	0 - 40
	Last post-baseline value – W0	N	247	257
		Mean ± SD	-17.3 ± 7.3	-16.0 ± 8.4
		Min - Max	-31 - 6	-38 - 8
Statistical analysis				
Main analysis	Last post-baseline value – W0	E (SE) (1)	1.49 (0.66)	
		95% CI (2)	[0.20 ; 2.77]	
	Non-inferiority test	p-value (3)	**< 0.001**	
	Superiority test	p-value (4)	**0.024**	

General linear model with baseline as covariate and centre as random effect.
(1) Estimate (Standard Error) of the difference between adjusted 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.
(4) Superiority test: two-sided p-value to be compared to 0.05.

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EFFICACY RESULTS (Cont'd)

Response to treatment and remission

In the FAS, the percentage of responders (decrease from baseline total score ≥ 50%) at the last post-baseline assessment over the W0-W8 period was higher in the agomelatine group (71.7%) than in the fluoxetine group (63.8%) with a trend towards statistical significance (p = 0.060). The percentage of remitters (total score ≤ 6) showed no relevant difference between the agomelatine (32.0%) and fluoxetine (28.4%) groups at the last post-baseline assessment.

Over the W0-W24 period, in the FAS, the mean decrease in HAM-D-17 total score from W0 to the last post-baseline value was higher in the agomelatine group from 28.5± 2.7 to 8.6 ± 8.1 (change of -19.9 ± 8.3) than in the fluoxetine group from 28.7± 2.5 to 9.8 ± 9.6 (change of -18.9 ± 9.6). The percentage of responders, and of remitters showed no relevant difference between the agomelatine and fluoxetine groups (78.9% *versus* 74.3%, and 51.4% *versus* 50.2%, respectively) at the last post-baseline assessment.

Secondary assessment criteria

CGI scale

In the FAS, the mean severity of illness score decreased between W0 and the last post-baseline value over the W0-W8 period in both treatment groups with a lower score in the agomelatine group than in the fluoxetine group (2.6 ± 1.3 *versus* 2.8 ± 1.4). The difference in favour of agomelatine was close to the statistical significance (two-sided Student's t test for independent samples, p = 0.059, and Mann-Whitney test, p = 0.094).

Similarly, the mean global improvement score was lower in the agomelatine group than in the fluoxetine group (1.9 ± 1.0 *versus* 2.1 ± 1.2) approaching statistical significance (two-sided Student's t test for independent samples, p = 0 .063, and Mann-Whitney test, p = 0.238). The percentage of responders to treatment (score=1 or 2) for the last value over the W0-W8 period was statistically significantly higher in the agomelatine group (77.7%) than in the fluoxetine group (68.8%) (p = 0.023). The percentage of remitters (score = 1) showed no relevant difference between the agomelatine (39.3%) and fluoxetine (39.8%) groups at the last assessment.

Over the W0-W24 period, a mean score decrease was observed for both CGI scores in both treatment groups all along the period in the FAS. At the last post-baseline assessment, there were no relevant differences between groups for the mean severity of illness score (2.1 ± 1.3 and 2.2 ± 1.5 in the agomelatine and fluoxetine groups, respectively) and for the mean global improvement score (1.7 ± 1.1 and 1.9 ± 1.3, respectively). The percentage of responders showed no relevant difference between the agomelatine group (79.4%) and the fluoxetine (74.2%) group, and the percentage of remitters was similar for agomelatine and fluoxetine (58.3% and 58.2% respectively).

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EFFICACY RESULTS (Cont'd)

HAM-A

In the FAS, the mean total score, and mean psychic and somatic anxiety scores decreased between W0 and last post-baseline assessment over the W0-W8 period in both treatment groups. At the last post-baseline assessment, the mean total score as well as the 2 sub scores were lower in the agomelatine group than in the fluoxetine group as follows.

Total score: 11.1 ± 8.1 and 12.3 ± 10.0 in the agomelatine and fluoxetine groups, respectively.

Psychic anxiety score: 6.9 ± 4.8 and 7.4 ± 5.5 in the agomelatine and fluoxetine groups, respectively.

Somatic anxiety score: 4.2 ± 3.9 and 4.9± 5.0 in the agomelatine and fluoxetine groups, respectively.

However, the mean decreases showed no relevant difference between treatment groups.

LSEQ

In the FAS, for each score of the LSEQ, a similar improvement was observed in both treatment groups between the mean first assessment at W2 and the mean last assessment over the W0-W8 period. At last assessment, mean scores were as follows:

- Getting of to sleep score: 32.7 ± 20.5 mm and 35.6 ± 22.7 mm in the agomelatine and fluoxetine groups, respectively.
- Quality of sleep score: 31.0 ± 22.7 mm and 34.1 ± 24.3 mm in the agomelatine and fluoxetine groups, respectively.
- Sleep awakening score: 36.6 ± 23.1 mm and 38.1 ± 23.8 mm in the agomelatine and fluoxetine groups, respectively.
- Integrity of behaviour score: 38.6 ± 21.9 mm and 37.8 ± 23.1 mm in the agomelatine and fluoxetine groups, respectively.

HAM-D sleep sub-score

In the FAS, over the W0-W8 period, the mean HAM-D sleep sub-score (sum of the insomnia items 4, 5 and 6 from the HAM-D-17 scale) decreased between baseline and the last post-baseline assessment from 4.9±1.3 to 1.4±1.7 in the agomelatine group and from 4.9±1.3 to 1.8±1.9 in the fluoxetine group with a statistically significant difference of 0.37 in favour of agomelatine on the last post-baseline value (95% CI=[0.06; 0.68], p=0.018, complementary analysis).

SAFETY RESULTS

Adverse events

Main adverse events results in the Safety Set

		Agomelatine (N = 250)	Fluoxetine (N = 263)
W0-W8/WEND			
at least one EAE	n (%)	143 (57.2)	148 (56.3)
at least one treatment-related EAE	n (%)	96 (38.4)	108 (41.1)
W0-W24/WEND			
at least one EAE	n (%)	168 (67.2)	169 (64.3)
at least one treatment-related EAE	n (%)	105 (42.0)	116 (44.1)
During the whole study			
at least one serious AE	n (%)	10 (4.0)	4 (1.5)
at least one serious EAE	n (%)	10 (4.0)	3 (1.1)
at least one treatment-related serious EAE	n (%)	2 (0.8)	-
Treatment discontinuation due to EAE	n (%)	20 (8.0)	19 (7.2)
Death	n (%)	-	-

AE: adverse event ; EAE: emergent adverse event ; n: number of patients concerned ; %: n/N x 100

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During the 8-week treatment period, in the Safety Set, the percentage of patients who reported at least one emergent adverse event showed no relevant difference between groups (57.2% in the agomelatine group, and 56.3% in the fluoxetine group). As regards dose subgroups, the incidence did not increase with the dose for each treatment.
The most frequently affected system organ classes were gastrointestinal disorders and nervous system disorders in both treatment groups. They were equally affected in both groups (26.4%, and 26.6% for gastrointestinal disorders, and 24.0% and 20.2% for nervous system disorders in the agomelatine and fluoxetine groups respectively). As regards agomelatine dose subgroups, these system organ classes were more affected in the 25 mg group (28.9% and 27.2%, respectively) than in the 25-50 mg group (20.0% and 15.7%, respectively).
In the agomelatine group, the most frequent emergent adverse events (at least 5%) were headache, nausea, and somnolence with a lower incidence than in the fluoxetine group for nausea (8.0% *versus* 11.4%, respectively), and a higher incidence for headache (16.0% *versus* 11.4%) and somnolence (6.0% *versus* 3.4%). As regards agomelatine dose subgroups, the most common emergent adverse event was headache on the agomelatine 25 mg dose (20.0% of patients) with a higher incidence than on the 25-50 mg dose (5.7%), and somnolence on the agomelatine 25-50 mg dose (7.1%), with a similar incidence to the 25 mg dose (5.6%).
In the agomelatine group, patients mostly had emergent adverse events of mild (39.6%) or moderate (31.2%) intensity. Similar results were observed in the fluoxetine group (39.5% and 27.8%, respectively).
The percentage of patients who experienced at least one emergent adverse event rated as severe (including somnolence, headache and nausea) showed no relevant difference between treatment groups (4.0% in the agomelatine group, and 5.3% in the fluoxetine group). Regarding agomelatine doses, the frequency of severe emergent adverse events was similar with both doses (3.9% and 4.3% with the 25 and 25-50 mg doses, respectively). In the fluoxetine group, incidence of severe emergent adverse events was similar with the both doses (5.2% and 5.7% with the 20 and 20-40 mg doses respectively).
Most of emergent adverse events recovered without difference in both treatment groups (93.0% and 92.4% in the agomelatine and fluoxetine groups, respectively).
The percentage of patients with at least one emergent adverse event considered to be related to the study treatment by the investigator showed no relevant difference between treatment groups (38.4% and 41.1% in the agomelatine and fluoxetine groups, respectively). In both groups, most frequent treatment-related emergent adverse events were principally found for gastrointestinal disorders class (21.6% and 22.8% in the agomelatine and fluoxetine groups, respectively), and nervous system disorders class (20.0% and 16.7%, respectively).

As regards dose subgroups, treatment-related emergent adverse events were more frequent in low dose subgroups than in high dose subgroups for both treatments: 43.3% and 25.7% in the agomelatine 25 mg and 25-50 mg subgroups, respectively, and 44.3% and 28.3% in the fluoxetine 20 mg and 20-40 mg subgroups, respectively.

During the 24-week treatment period, in the Safety Set, patients were affected by emergent adverse events with a higher frequency than over W0-W8 in line with the longer exposure duration. Incidence of emergent adverse events showed no relevant difference between treatment groups (67.2% in the agomelatine group *versus* 64.3% in the fluoxetine group). Results obtained over W0-W24 were in the same line as those over W0-W8.
No death was reported during the study. During the whole treatment period, 10 patients (4.0%, 5 in each dose subgroup) in the agomelatine group, and 3 patients (1.1%, all on the 20 mg dose) in the fluoxetine group experienced at least one serious emergent adverse event. For two patients in the agomelatine group these SEAE were considered by the investigator to be related to the study treatment: one increase in hepatic enzymes which led to treatment withdrawal, and one myocardial ischemia. Both events resolved, the latter with sequelae.
Serious emergent adverse event led to treatment discontinuation in 3 other patients in the agomelatine group (intentional overdose, congestive cardiomyopathy, and suicidal behaviour). All resolved, congestive cardiomyopathy with sequelae.

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)

During the overall study, non-serious emergent adverse event led to treatment discontinuation in 35 patients without relevant difference between groups (16 patients, 6.4%, in the agomelatine group and 19 patients, 7.2%, in the fluoxetine group). In the agomelatine group, no particular type of events led to treatment withdrawal. In the fluoxetine group, 4 nausea and 3 vomiting led to treatment discontinuation.

Laboratory parameters

- Biochemical parameters other than liver parameters, and haematological parameters did not show any relevant change throughout the study in both treatment groups.
- Liver acceptability

  During the 24-week double-blind treatment period, 6 patients, 2.4%, in the agomelatine group, and 1 patient, 0.4%, in the fluoxetine group had at least one emergent PCSA transaminase value on treatment. No relevant agomelatine dose effect was evidenced (4 patients, 2.2%, with the agomelatine 25 mg dose, and 2 patients, 2.9%, with the agomelatine 50 mg dose).

  - In the agomelatine group, 3 patients had emergent PCSA ALAT (6.1, 15.2 and 19.5 ULN) associated with emergent PCSA ASAT (4.3, 7.9 and 10.9 ULN) and two also had emergent PCSA GGT (3.1 and 4.4 ULN). The other 3 patients had PCSA ALAT (3.4, 4.1 and 5.8 ULN), and ASAT and GGT levels above the upper normal limit without reaching PCSA limit. One of these 3 patients already had ALAT value slightly above the upper normal range at baseline (1.3 ULN). In the 6 cases, PCSA transaminases were never associated with emergent abnormal total bilirubin or emergent ALP ≥ 2 ULN.

  PCSA transaminases were reported as adverse events in 5 patients, led to treatment withdrawal in 3 patients and were considered treatment-related by the investigator in 4 patients. None of these liver PCSA values were associated with clinical signs. All patients recovered, one on treatment.

  - In the fluoxetine group, one patient had an emergent PCSA ASAT (= 3 ULN) reported as adverse event by the investigator and considered treatment-related. Patient recovered on treatment.

Vital signs and BMI

Mean values of vital signs (weight, blood pressure and heart rate) remained stable in both treatment groups and in each dose subgroup over the 8- and 24-weeks treatment periods. Regarding BMI, most of the patients remained in the same class as at baseline during both treatment periods in both treatment groups.

ECG

Among patients without ECG abnormality at inclusion, 6 had emergent ECG abnormalities after inclusion which were considered as clinically significant: 3 had a transient prolonged QT interval (1 in the agomelatine group and 2 in the fluoxetine group), 2 had abnormalities on the T wave (in the agomelatine group) and one had a first degree AV block (in the agomelatine group).

In patients with at least one ECG abnormality at inclusion, 2 (one in each group) emergent clinically significant ECG abnormalities were reported after inclusion: one ST segment abnormal in the agomelatine group, and one repolarisation disturbance in the fluoxetine group.

CONCLUSION

This randomised, double-blind, comparative study demonstrated the therapeutic superiority of agomelatine (25-50 mg) over fluoxetine (20-40 mg), administered for 8 weeks in the treatment of patients with severe episode of Major Depressive Disorder; agomelatine 25 mg and 50 mg was well tolerated over the 8-week and 24-week treatment periods, with no major relevant difference in comparison to fluoxetine.

Date of the report: 10 March 2009