Document title	**Clinical Study Report Synopsis**
Study title	**A study to determine the maintenance of efficacy of agomelatine (25 to 50 mg) in order to prevent relapses in out-patients with Major Depressive Disorder.** **A 8 or 10 weeks open period treatment with agomelatine (25 to 50 mg), followed by 24 weeks randomised double-blind period, placebo-controlled, parallel groups and 20 weeks of optional double-blind treatment period.** ***First report: open and 24-week double-blind treatment periods.***
Study drug	**Agomelatine (S 20098)**
Indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-041**
Study initiation date	**03 February 2005**
Study completion date	**07 February 2007 (Last BW24 visit)**
Main coordinator	[redacted] [redacted]**Paris** [redacted] **France**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Servier Research and Development Limited (S.R.D.L.)** **Gallions, Wexham Springs** **SL3 6RJ Wexham - United Kingdom**
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 22 June 2007**

~~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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First report: open and 24-week double-blind treatment periods

Title of study: A study to determine the maintenance of efficacy of agomelatine (25 to 50 mg) in order to prevent relapses in out-patients with Major Depressive Disorder.
A 8 or 10 weeks open period treatment with agomelatine (25 to 50 mg), followed by 24 weeks randomised double-blind period, placebo-controlled, parallel groups and 20 weeks of optional double-blind treatment period.
Protocol No.: CL3-20098-041

Main Coordinator: [redacted] ([redacted] France).
National coordinators: [redacted] (Kuopio, Finland), [redacted] ([redacted] South Africa), [redacted] ([redacted] United Kingdom), [redacted] ([redacted] Australia).

Study centres:
57 centres located in 5 countries were opened and 56 included at least one patient: Australia (added by Amendment No. 2) - 7 centres (39 included patients), Finland - 11 centres (174 included patients), France – 20 centres (125 included patients), South Africa - 6 centres (75 included patients), United Kingdom – 12 centres (79 included patients).

Publication (reference): Not applicable.

Studied period: Initiation date: 03 February 2005 *(date of first visit)* Completion date: 07 February 2007 *(date of last BW24 visit)*	**Phase of development of the study:** III

Objectives:
Primary objective: to assess the efficacy of agomelatine (25mg/50 mg), in the prevention of depressive relapse, in ambulatory patients suffering from recurrent Major Depressive Disorder (MDD), during 24 weeks of treatment after an initial response to agomelatine 25 mg or 50 mg.
Secondary objective: to provide additional safety data on long term administration of agomelatine.

Methodology:
Multinational, multicentric, randomised, double-blind, placebo-controlled study in two parallel groups for efficacy evaluation of agomelatine 25 mg/50 mg in prevention of depressive relapse. The double-blind period was preceded by an open period of 8 to 10 weeks of agomelatine treatment. All patients started on a 25 mg dose, and the dose could be increased to 50 mg in case of insufficient improvement after 2 weeks of treatment. Then, patients could be randomised in the double-blind treatment period at W8 or W10 if they fulfilled pre-defined randomisation criteria, *i.e.* HAM-D total score ≤ 10 and CGI global improvement score = 1 or 2. If not, the patient was withdrawn for lack of efficacy. Patients randomised in the agomelatine group continued on the same dose as that received since W2. The criteria for increasing the dose, and randomisation were defined by the sponsor based on clinical considerations before the study beginning, and kept blinded. The dose increase and the treatment allocation were done centrally using an Interactive Voice Response System (IVRS), in a double-blind manner (so that both patients and investigators were blind with respect to this procedure).
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 500 patients included / 316 patients randomised (158 by group)
Included: 492 patients / Randomised: 339 patients (165 in the agomelatine group and 174 in the placebo group)

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Diagnosis and main criteria for inclusion:
Ambulatory men and women, aged between 18 and 65 years inclusive, fulfilling DSM IV-TR criteria for MDD of moderate or severe intensity.
The patients were included with a recurrent episode of at least 8 weeks, and at the beginning of the index episode, patients were to be free of any signs or symptoms of their previous episode for at least 6 months.
The HAM-D 17-item total score was to be ≥ 22 at selection and inclusion and a decrease between selection and inclusion (if any) ≤ 20% was permitted. The sum of items H1 + H2 + H5 + H6 + H7 + H8 + H10 + H13 of HAM-D 17-item had to be ≥ 55% of HAM-D 17-item total score at inclusion, CGI severity of illness score ≥ 4 at selection and inclusion, and the depression sub-score (HAD-D) of Hospital Anxiety Depression Scale was to be ≥ 11 (according to Amendment No. 3).

Study drug:
Agomelatine 25 mg tablets, 1 or 2 tablets once a day, p.o., around 8 p.m.
Patients received 25 mg/day (1 agomelatine tablet + 1 placebo tablet) from W0, with possible increase to 50 mg/day (2 agomelatine tablets) at W2, in case of insufficient improvement. Once adjusted, the dose was maintained throughout the study. Batch No.: L0003634, L0005266, L0005363.

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

Duration of treatment:
- Run-in period without study treatment of maximum 1 week.
- 8 to 10-week open treatment period with agomelatine, depending on eligibility for randomisation at W8 or W10 according to IVRS.
- 24-week double-blind randomised treatment period (BW0 to BW24).
- *20-week optional double-blind extension treatment period (BW24 to BW44), not the subject of this report.*
- 2-week follow-up period without study treatment, after treatment discontinuation, regardless of the time of occurrence.

Criteria for evaluation during open and 24-week double-blind treatment periods:
Efficacy measurements
HAM-D 17-item total score and Clinical Global Impression (CGI) scales were assessed by the investigator at each visit from selection to BW24.

Primary criterion: Depressive relapse
It was assessed by the investigator at each visit from randomisation and defined as the occurrence of one of the following events:
- HAM-D 17-item total score ≥ 16.
- Any withdrawal for lack of efficacy during the double-blind period, according to the clinical opinion of the investigator. It was to be based on the evolution of both Hamilton and Clinical Global Impression scores.
- Any suicide or suicide attempt.

All cases listed above were reviewed by an independent Expert Committee at the end of the 24-week double-blind period in order to confirm or invalidate the diagnosis of relapse. The Expert Committee meeting took place on 7 February 2007, before the blind was broken (16 March 2007). Only expert's adjudications were taken into account for analyses.

Safety measurements
- Adverse events at each visit.
- Vital signs (body weight, heart rate, blood pressure) at selection, W8, W10, and BW24 visits, and at the end of study treatment in case of premature withdrawal.
- 12-lead electrocardiogram (ECG): at selection, BW18 or at visit of premature withdrawal with results available for inclusion, BW24, and follow-up visits, respectively.
- Laboratory tests: between selection and inclusion (results available at W0), within the 2 days following randomisation, at follow-up visit in case of premature withdrawal, or within the 7 days following BW24 visit for patients not entering the optional double-blind extension period.

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Statistical methods:

Efficacy analyses

- **Primary criterion**

Main analysis:

Incidence over time of patients with a relapse was estimated using Kaplan-Meier method. The time to relapse over BW0-BW24 was compared between agomelatine and placebo groups using a log-rank test stratified for centre type (centres managed by psychiatrists or by GPs) and randomisation visit (W8 or W10) in the FAS. The hazard ratio of relapse on agomelatine as compared to placebo, was estimated with a Cox model associated with the likelihood ratio test, with adjustment for centre type and randomisation visit in the Full Analysis Set.

Sensitivity analyses:

The hazard ratio of relapse was estimated using a Cox model with adjustment for HAM-D 17-item total score at inclusion in addition to centre type and randomisation visit. A non-stratified log-rank test and an unadjusted Cox model were also carried out.

Secondary analyses:

The same analyses were applied to the two subsets of the FAS (Sub-FAS of patient enrolled by psychiatrists and Sub-FAS of patients with W0 HAM-D total score ≥ 25).

- **Secondary criteria**

HAM-D 17-item total score and CGI scores were described in the Open Set during the open period, and by treatment group in the FAS and its subsets during the double-blind treatment period. In addition, during the open period, descriptive statistics were provided regarding response to treatment, defined for HAM-D 17-item total score as a decrease from baseline ≥ 50%, and for CGI global improvement score as a score = 1 or 2.

Safety analyses

During the double-blind treatment period, all safety parameters were described by treatment group and dose subgroup in the Double-Blind Safety Set (DBSS), except biology parameters which were described in the Sub-DBSS not in double-blind extension period.

During the overall agomelatine treatment period, safety parameters were described by agomelatine dose subgroup and overall in the Overall Safety Set.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

In all, 492 patients were included, and 491 received agomelatine 25 mg. During the open period, 153 patients (31.1%) withdrew from the study, mainly due to lack of efficacy: 99 patients, 20.1%, most of them (55) because of randomisation failure at W10. 339 patients (68.9%) completed the open period, and were randomly assigned to one of the two treatment groups according to IVRS procedure. The distribution of the treatment groups was well-balanced: 165 were randomised to agomelatine, and 174 to placebo.

As regards agomelatine dose, 109 patients of the 471 continuing at W2 (23.1%) had a dose increase to 50 mg. Among them, 60 were randomised (23 to agomelatine and 37 to placebo).

During the double-blind period, 133 of 339 patients (39.2%) were prematurely withdrawn mainly due to lack of efficacy (31.9%). The rate of withdrawal was lower in the agomelatine group (30.3%) than in the placebo group (47.7%), mostly related to a lower rate of withdrawals due to lack of efficacy in the agomelatine group (37 patients, 22.4% in the agomelatine group *versus* 71, 40.8% in the placebo group). These withdrawals corresponded to depressive relapses as defined in the protocol, and were reviewed at the end of the period by an independent Expert Committee in order to be confirmed or invalidated.

No patient was lost to follow-up during the study.

Excluding patients with depressive relapse, 115 patients (69.7%) of the agomelatine group (of whom 17 on agomelatine 50 mg), and 91 (52.3%) of the placebo group were completers at BW24.

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Disposition of patients

		Agomelatine	Placebo	All
Open period (W0-W8/W10)				
Included	**n**	**492** [a]	-	
In compliance with the protocol	n	429	-	
With a protocol deviation at inclusion	n	63	-	
Withdrawn	**n (%)**	**153 (31.1)**	-	
Adverse event	n (%)	25 (5.1)	-	
Lack of efficacy	n (%)	99 (20.1)	-	
Mainly due to randomisation criteria not met at W10 visit	*n (%)*	*55 (11.2)*	-	
Non-medical reason	n (%)	23 (4.7)	-	
Protocol deviation	n (%)	6 (1.2)	-	
Completed	**n (%)**	**339 (68.9)**	-	
Double-blind period (BW0-BW24)				
Randomised	**n (%)**	**165**	**174**	**339**
Withdrawn	**n (%)**	**50 (30.3)**	**83 (47.7)**	**133 (39.2)**
Adverse event	n (%)	4 (2.4)	1 (0.6)	5 (1.5)
Lack of efficacy (relapse*, as defined in the protocol)	n (%)	37 (22.4)	71 (40.8)	108 (31.9)
Remission, or marked improvement	n (%)	4 (2.4)	3 (1.7)	7 (2.1)
Non-medical reason	n (%)	4 (2.4)	8 (4.6)	12 (3.5)
Protocol deviation	n (%)	1 (0.6)	-	1 (0.3)
Completed (excluding patients with depressive relapse)	**n (%)**	**115 (69.7)**	**91 (52.3)**	**206 (60.8)**
In compliance with the protocol	n	70	53	123
With a protocol deviation during the study	n	45	38	83
Main analysis sets				
Open period				
Open Set	n	482		
Double-blind period				
Randomised Set = Full Analysis Set	n (%)	165 [b] (100.0)	174 (100.0)	339 (100.0)
Sub-FAS psychiatrists	n (%)	110 [c] (66.7)	117 (67.2)	227 (67.0)
Sub-FAS with W0 HAM-D total score ≥ 25	n (%)	128 [c] (77.6)	142 (81.6)	270 (79.6)
Double-Blind Safety Set (DBSS)	n (%)	165 [b] (100.0)	174 (100.0)	339 (100.0)
Sub-DBSS not in the double-blind extension period	n (%)	59 [d] (35.8)	90 (51.7)	149 (44.0)
Both periods				
Overall Safety Set [e]	n	491 [f]		

*%: % of the Included Set, or Randomised Set; [a]:109 patients received agomelatine 50 mg at W2; [b c d] 24, 20, and 10 patients received agomelatine 50 mg at randomisation visit, respectively; [e]: only information reported until randomisation was taken into account for patients randomised in the placebo group; [f] 102 patients were analysed in the 50 mg group according to the longest treatment dose duration; *: All cases of depressive relapse judged by investigators were reviewed in blind condition by an Expert Committee at the end of the double-blind period in order to confirm or invalidate the diagnosis of relapse.*

In the Randomised Set, patients were aged from 19 to 65 years with a mean ± SD of 43.3 ± 10.6 years. They were mainly female (74.3%). There were no relevant differences between the treatment groups.

All patients had recurrent MDD according to the DSM-IV-TR. The mean number of depressive episodes was 3.6 ± 2.1 without difference between groups. Severity of the MDD according to the DSM-IV-TR criteria was well distributed between the treatment groups. In both groups, about half of patients had moderate MDD (in all, 52.8%) or a severe MDD without psychotic feature (in all, 47.2%). Melancholic feature was observed in 50.4% of patients, similarly distributed in both groups.

The mean MDD duration, and the mean duration of the current MDE were respectively 11.5 ± 8.9 years (median = 9.6), and 4.9 ± 3.8 months (median = 3.5) without clinically relevant difference between the treatment groups.

The efficacy parameters did not show any relevant differences between the treatment groups, neither at inclusion, nor at randomisation (W8 or W10). In all patients, the mean ± SD scores were as follows:

- HAM-D 17- item: 26.8 ± 2.6 at inclusion, and 7.6 ± 4.4 at W8.
- CGI severity of illness score: 4.9 ± 0.6 at inclusion, and 2.1 ± 1.0 at W8.
- CGI global improvement score: 2.8 ± 0.8 at W2, and 1.5 ± 0.6 at W8.

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STUDY POPULATION AND OUTCOME (Cont'd)

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

In the Randomised Set, the mean treatment duration was 60.0 ± 6.4 days (median 56 days) during the open period. During the double-blind period, it was 136.1 ± 56.5 days (median of 168 days) in the agomelatine group, and 122.3 ± 59.5 days (median of 166 days) in the placebo group. The distribution of patients showed that in 25% of patients, the treatment duration was longer in the agomelatine group (Q1 of 113.5 days) than in the placebo group (Q1 of 68.0 days). This result was in agreement with the lower rate of withdrawals in the agomelatine group.

In the OSS, the mean overall agomelatine treatment duration (W0-BW24) was 102.2 ± 75.4 days (median of 69 days): 105.5 ± 77.7 days (median of 70 days) in the agomelatine 25 mg subgroup and 89.7 ± 65.1 days (median of 68 days) in the agomelatine 50 mg subgroup.

Compliance was satisfactory in both periods. In the Randomised Set, the mean global compliance was 98.7 ± 3.3% during the open period, and 95.6 ± 11.1% during the double-blind period, without relevant difference between the two groups.

EFFICACY RESULTS

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

During the double-blind period, there were 108 withdrawals for lack of efficacy (98 based on HAM-D ≥ 16 and 10 based on investigator's clinical opinion). All were reviewed at the end of the period, before the break of the blind, by an independent Expert Committee in order to be confirmed or invalidated as relapses. Among these, 3 were not adjudicated as relapses because of low HAM-D scores judged inconsistent with diagnostic of relapse. For one additional patient who had a HAM-D total score = 17 at BW24 but was not withdrawn at this visit, the experts adjudicated a relapse during the 24-week double-blind period. As result, 106 relapses were adjudicated and taken into account for the main analysis, as described in the table below.

Relapses according to the investigator's opinion, and adjudicated by the Expert Committee - FAS

Criterion for relapse		According to the investigator	Expert Committee adjudication
HAM-D ≥ 16	n	98	99
Investigator's opinion	n	10	7
Suicide/suicide attempt	n	-	-
All	**n**	**108**	**106**

In the FAS, the overall percentage of patients with a relapse during the double-blind period was twice lower in the agomelatine group than in the placebo group (20.6% of patients in the agomelatine group *versus* 41.4% in the placebo group). The incidences over time of patients having a relapse were statistically and clinically significantly lower with agomelatine (p = 0.0001, log-rank test stratified for centre type and randomisation visit). The risk of relapse over time was statistically significantly reduced by 54.2% (HR = 0.458) on agomelatine compared to placebo (p = 0.0001, Cox model adjusted for centre type and randomisation visit).
These results were supported after additional adjustment for HAM-D total score at W0 (p = 0.0002), and with unadjusted analyses (p = 0.0001).

In the Sub-FAS with W0 HAM-D total score ≥ 25, similar results were observed, as the risk of relapse over time was statistically significantly reduced by 56.8% on agomelatine as compared to placebo (p = 0.0001, Cox model adjusted for centre type and randomisation visit). In the Sub-FAS psychiatrists, the risk reduction in relapse was more marked. The risk of relapse over time was statistically significantly reduced by 62.4% on agomelatine as compared to placebo (p < 0.0001, Cox model adjusted for randomisation visit). All these results were supported after the additional adjustment for HAM-D total score at W0 (p ≤ 0.0001), and with unadjusted analyses (p ≤ 0.0001).

The between-group difference in the incidences of relapse progressively rose throughout the treatment weeks. Low and closed incidences over the first treatment-weeks may be related to the absence of discontinuation symptoms, as demonstrated in specific study (CL3-20098-030, NP 15915).

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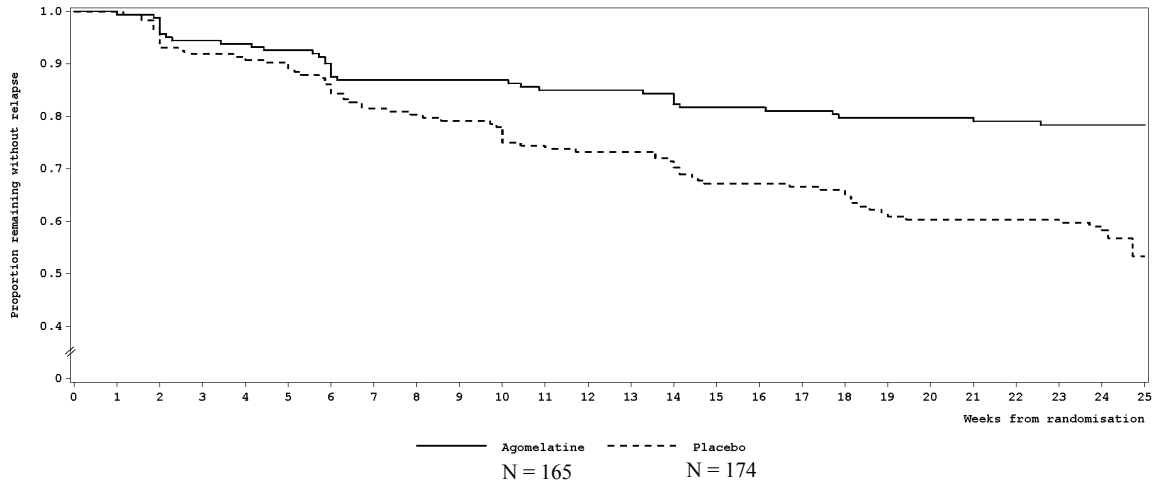
EFFICACY RESULTS (Cont'd)

Number of patients with a depressive relapse during the 24-week double-blind period, incidence over time, and risk of relapse in the FAS and Sub-FAS

		Agomelatine	**Placebo**
FAS		N = 165	N = 174
Total Events *	**n (%)**	**34 (20.6%)**	**72 (41.4%)**
Main analysis			
Incidence after 175 days	E (SE) [1]	21.7% (3.3%)	46.6% (5.0%)
Stratified log-rank test [(a)]	p value	**0.0001**	
Adjusted Cox model [(a)]	E (SE) [2]	0.458 (0.095)	
	95% CI [3]	[0.305 ; 0.690]	
Sub-FAS psychiatrists		N = 110	N = 117
Total Events *	**n (%)**	**22 (20.0%)**	**56 (47.9%)**
Incidence after 175 days	E (SE) [1]	21.3% (4.0%)	56.1% (6.9%)
Stratified log-rank test [(b)]	p value	**< 0.0001**	
Adjusted Cox model [(b)]	E (SE) [2]	0.376 (0.095)	
	95% CI [3]	[0.230 ; 0.617]	
Sub-FAS with W0 HAM-D total score ≥ 25		N = 128	N = 142
Total Events *	**n (%)**	**28 (21.9%)**	**64 (45.1%)**
Incidence after 175 days	E (SE) [1]	22.7% (3.8%)	50.4% (5.3%)
Stratified log-rank test [(a)]	p value	**0.0001**	
Adjusted Cox model [(a)]	E (SE) [2]	0.432 (0.098)	
	95% CI [3]	[0.277 ; 0.673]	

**: Total number of patients having a relapse during the double-blind period.*
1: Estimate (Standard Error) of the percentage of patients with a relapse after 175 days of treatment (Kaplan-Meier's method).
2: Estimate (Standard Error) of the adjusted Hazard Ratio of relapse between treatment groups: agomelatine versus placebo.
3: 95% confidence interval of the estimate.
[(a)]*: Stratified or adjusted for centre type (psychiatrists or GP), and randomisation visit (W8 or W10).*
[(b)]*: Stratified or adjusted for randomisation visit (W8 or W10).*

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



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EFFICACY RESULTS (Cont'd)

- **HAM-D total score**

In the Open Set, the mean HAM-D total score progressively decreased during the open period, from W0 (mean ± SD = 27.0 ± 2.7) up to last post-baseline assessment (9.9 ± 7.3). At the same time, the percentage of responders (defined as patients with a decrease from baseline of at least 50%) progressively increased from 10.4% at W2 to 78.6% at the last assessment.

During the double-blind period, in the FAS, the therapeutic benefit, acquired during the open period was maintained in the agomelatine group (mean change in HAM-D total score of 1.4 ± 6.9 between BW0 and the last post-randomisation assessment). In the placebo group, the mean score increased (mean change of 4.7 ± 8.4). Similar results were observed in both FAS subsets.

- **CGI**

In the Open Set, the mean severity of illness score (mean ± SD = 4.9 ± 0.7 at W0), and the mean global improvement score (3.0 ± 0.8 at W2) decreased up to the last post-baseline assessment during the open period (2.4 ± 1.3, and 1.8 ± 1.1, respectively). At the same time, the percentage of responders according to the global improvement score (score of 1 or 2) increased up to 80.3% at the last assessment.

During the double-blind period, in the FAS, both mean scores were smaller in the agomelatine group than in the placebo group at the last post-randomisation assessment (2.1 ± 1.2 for severity, and 3.8 ± 1.6 for global improvement according to randomisation in the agomelatine group *versus* 2.6 ± 1.5, and 4.4 ± 1.7, respectively). In the agomelatine group, the therapeutic benefit, acquired during the open period was maintained during the double-blind period as regards the severity of illness whereas severity of illness worsened in the placebo group.

Similar results were observed in both FAS subsets.

SAFETY RESULTS

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

		Agomelatine (N = 165)	Placebo (N = 174)
Patients having reported			
at least one emergent adverse event	n (%)	85 (51.5)	91 (52.3)
at least one treatment-related emergent adverse event	n (%)	15 (9.1)	16 (9.2)
at least one serious adverse event	n (%)	5 (3.0)	3 (1.7)
Patients with treatment discontinuation due to a non serious adverse event	n (%)	1 (0.6)	2 (1.1)

During the double-blind treatment period, in the DBSS, the percentage of patients with at least one emergent adverse event was similar in both treatment groups: 51.5% in the agomelatine group, and 52.3% patients in the placebo group.

The most frequently affected system organ class (in more than 5% of the patients in any group) was Infections and infestations in both groups (26.1% in the agomelatine group, and 28.7% in the placebo group). It was followed by Musculoskeletal and connective tissue disorders (11.5% and 9.8%, respectively), Gastrointestinal disorders (10.9% *versus* 7.5%, respectively), and Nervous system disorders (9.1% and 8.6%, respectively). There were no relevant differences between groups except for Gastrointestinal disorders which were more frequently reported in the agomelatine group.

In both groups, the most common emergent adverse events (in more than 3% of the patients in any group) were headache (7.9% in the agomelatine group and 6.3% in the placebo group), nasopharyngitis (6.7% and 9.8%, respectively), back pain (5.5% and 3.4%, respectively), and influenza (3.6% and 5.2%, respectively).

Analysis by time of onset for the most frequent emergent adverse events during the double-blind treatment period showed that they were no relevant differences between the treatment groups in the DBSS. These results are consistent with the absence of withdrawal symptoms at the cessation of agomelatine treatment as previously demonstrated.

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SAFETY RESULTS (Cont'd)

During the overall agomelatine treatment period, 61.7% of the patients under the 25 mg dose and 72.5% under the 50 mg dose reported at least one emergent adverse event.

The most frequently affected system organ classes with both doses (in more than 10.0% of the patients in any group) were similar to those in the DBSS (Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, and Nervous system disorders). In addition, Psychiatric disorders were reported by 9.0% and 10.8% under the 25 mg and the 50 mg doses, respectively. For all these system organ classes, there were no relevant differences between agomelatine doses.

Headache was the most common emergent adverse event with both doses (15.4% and 14.7% under the 25 and 50 mg doses, respectively), followed by nasopharyngitis (9.0% and 6.9%), dizziness (8.5% and 6.9%), and nausea (6.2% and 4.9%), without relevant difference in frequency between doses.

These emergent adverse events occurred mainly within the first 2 weeks of treatment for headache (50.7% of events), dizziness (67.5% of events), and nausea (62.1% of events).

Regarding serious adverse events, one patient was selected and committed suicide before inclusion. No other death was reported during the study. During the study, 21/491 patients (4.3%) had at least one serious adverse event. Among them, 15/491 patients (3.1%) had at least one emergent serious adverse event during the overall agomelatine treatment period, and 3/174 patients (1.7%) under placebo during the double-blind period.

3/491 patients (0.6%) reported suicide attempt during the overall agomelatine treatment period, 2 patients under 25 mg, 11 and 40 days after the beginning of open treatment, and the third one, 3 days after the last intake of agomelatine 50 mg. One additional suicide attempt was reported 36 days after the last agomelatine 25 mg intake despite a relay treatment with citalopram. None were considered treatment-related by the investigator.

Other serious emergent adverse events were sparse in different system organ classes. They were not related to the study treatment according to the investigator except one atrial fibrillation in the placebo group.

During the study, 22/491 patients (4.5%) under agomelatine, and 2/174 patients (1.1%) in the placebo group reported at least one non serious adverse event which led to a premature treatment discontinuation. Under agomelatine, 20 patients had a premature treatment discontinuation related to an emergent adverse event, most frequently nausea (5 patients, 4 under 25 mg, and 1 under 50 mg), headache (2 patients under 25 mg), fatigue (2 patients under 25 mg), and skin disorders (2 patients under 25 mg: allergic dermatitis, and pruritus). All but one (loss of libido) adverse events resolved.

Clinical laboratory evaluation

- No clinically relevant mean changes nor differences between groups were observed on biochemical and haematological parameters during the double-blind period in the Sub DBSS not in double-blind extension period, nor during the overall agomelatine treatment period in the Overall Safety Set.
- Liver acceptability
  Emergent PCSA values of hepatic enzymes were detected in 8 patients in the OSS during the overall agomelatine treatment period: 6 of them for ALAT (4 under 25 mg, including one worsening, and 2 under 50 mg; 2 on each dose had an associated emergent PCSA value of ASAT). All transaminases increases were notified as serious adverse events, as requested by the protocol for transaminases values ≥ 3 ULN. All patients recovered after treatment discontinuation. In addition, 2 patients had emergent PCSA values of GGT, not normalised at the last test. One additional patient under agomelatine 25 mg had emergent high abnormal (not PCSA) values of ASAT and ALAT, considered as clinically significant by the investigator. The patient recovered.

Vital signs

Regarding supine blood pressure, heart rate, weight and BMI, there were no clinically relevant mean changes between the baseline and the last assessment during the double-blind period in both groups, nor under agomelatine during the open period.

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

In the DBSS, 8.8% of the patients in the agomelatine group and 4.9% of the patients in the placebo group had an emergent ECG abnormality. In the OSS, 7.5% of patients under agomelatine had at least one emergent ECG abnormality, without relevant difference between doses.

ECG abnormalities were considered as clinically significant in 2 patients under agomelatine 25 mg: one with ventricular extrasystoles, and one with Q wave abnormal + ST segment elevation + T wave inversion (sequelae of myocardial infarction which occurred 2 weeks before). No QT prolongation was reported on treatment.

CONCLUSION

This study demonstrates the efficacy of agomelatine 25-50 mg to prevent depressive relapse in MDD patients. The incidence over time of patients having a depressive relapse was statistically significantly lower with agomelatine 25-50 mg than with placebo, with a clinically relevant reduction by 54% of relapse risk.

No unexpected safety concern was identified, whatever the dose. The most frequent emergent adverse events reported on agomelatine were headache, dizziness, and nausea as observed in previous studies.

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