Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy of agomelatine (25 to 50 mg/day) given orally on improvement of subjective sleep in patients with Major Depressive Disorder. A randomised, double-blind, flexible-dose international multicentre study with parallel groups *versus* escitalopram (10 to 20 mg/day). Twelve week treatment plus double-blind extension for 12 weeks**
Study drug	**Agomelatine (S20098)**
Studied indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-063**
Study initiation date	**6 July 2007**
Study completion date	**6 September 2008**
Main coordinator	[redacted] **Le Kremlin Bicetre - France**
Sponsors	**Institut de Recherche Internationales Servier (I.R.I.S.) 50 rue Carnot 92284 Suresnes Cedex - France** **Servier Canada Inc 235, Armand-Frappier Blvd Laval, Québec - Canada H7V 4A7** **Servier Research And Development Gallions, Wexhams Springs, Framewood Road - Wexham Slough SL3 6RJ - UK**
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 18 December 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 of agomelatine (25 to 50 mg/day) given orally on improvement of subjective sleep in patients with Major Depressive Disorder.
A randomised, double-blind, flexible-dose international multicentre study with parallel groups *versus* escitalopram (10 to 20 mg/day). Twelve week treatment plus double-blind extension for 12 weeks.
Protocol No.: CL3-20098-063

Scientific advisor: [redacted] (France)
National coordinators: [redacted] (Australia), [redacted] (Brazil), [redacted] (Canada), [redacted] (France), [redacted] (South Africa), [redacted] (Russia), [redacted] (United Kingdom).

Study centres:
In all, 51/53 centres located in 7 countries included at least one patient: Australia (5 centres – 22 included patients), Brazil (3 centres - 16 included patients), Canada (7 centres - 60 included patients), France (14 centres - 100 included patients), Russia (9 centres - 51 included patients), South Africa (5 centres - 40 included patients), United Kingdom (8 centres - 35 included patients).

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 6 July 2007 Completion date: 6 September 2008	III

Objectives: to assess the efficacy of agomelatine compared to escitalopram on early improvement of subjective sleep in depressed outpatients.
Primary objective: to show that patients treated with agomelatine have an earlier improvement of subjective sleep than patients treated with escitalopram, within 3 weeks after the start of treatment.
Secondary objectives: to study the effects of agomelatine and escitalopram on depression, other sleep patterns, daytime sleepiness, quality of life and to provide additional safety and acceptability data in this population with a particular attention to sexual function and discontinuation symptoms.

Methodology:
Multicentre, multinational, double-blind, randomised, comparative study in 2 parallel groups using a flexible dosage: agomelatine 25 mg/day and escitalopram 10 mg/day. These initial doses could be increased to 50 mg/day and 20 mg/day, respectively, in case of insufficient improvement after 2 weeks of treatment. The criteria for increasing the dose were defined by the sponsor, based on clinical considerations, before the study beginning, and kept blinded. 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), and an Interactive Web Response System (IWRS), in a blinded condition manner for patients and investigators. At the end of the 12-week double-blind period, the patients could continue in the optional double-blind extension period if they had a CGI improvement score = 1 or 2.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 300 patients (150 by group)
Included: 324 patients (164 in the agomelatine group and 160 in the escitalopram group)

Diagnosis and main criteria for inclusion:
Male or female out-patients, aged between 18 and 70 years, fulfilling DSM-IV criteria for MDD of moderate or severe intensity, with a single or recurrent episode which lasted from at least 4 weeks. The HAM-D 17-item total score was to be ≥ 22, Hospital Anxiety Depression Scale (HAD) Depression score ≥ 11. In addition, HAM-D 17-item total score between selection and inclusion had not to decrease by more than 20%, and the CGI severity of illness score was to be ≥ 4 at inclusion.

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Study drug:
Agomelatine 25 mg tablets, 1 or 2 tablets once a day in 1 capsule, po, around 8 p.m.
Patients received 25 mg/day from W0, with possible increase in double-blind conditions to 50 mg/day at W2, in case of insufficient improvement. Once adjusted, the dose was maintained up to W24. Between W24 and W25, the patients received 1 placebo capsule in order to blind the tapering period recommended for escitalopram.
Batch Nos: 25 mg: L0018220, L0018507, L0020880 ; 50 mg: L0017735, L0019077, L0020882

Reference product:
Escitalopram 5, 10, 20 mg tablets, 1 tablet once a day in 1 capsule, po, around 8 p.m.
Patients received 10 mg/day from W0, with possible increase in double-blind conditions to 20 mg/day at W2, in case of insufficient improvement. Once adjusted, the dose was maintained up to W24. Between W24 and W25, patients having previously received escitalopram 10 mg received 5 mg for 7 days, and patients having received 20 mg until W24 received 10 mg for the first 3 days, then 5 mg for the 4 following days.

Duration of treatment:
- 3 to 7-day run-in period without study treatment from selection to inclusion (W0) visits.
- 12-week mandatory double-blind treatment period (from W0 to W12).
- 12-week extension double-blind treatment period (from W12 to W24).
- 1-week placebo or tapering period (W24-W25) for patients in the agomelatine and escitalopram groups, respectively.
- 7-day follow-up period (at maximum) without treatment at the end of the mandatory double blind period or at the end of the extension double blind period, or in case of premature withdrawal. For patients stopping the study at W12 or having prematurely discontinued the study, the follow-up period took place either one week after the tapering period (if tapering treatment dispensed), or one week after the discontinuation visit (if tapering treatment not dispensed), according to investigator's opinion and reason for withdrawal.

Criteria for evaluation:
EFFICACY MEASUREMENTS:

SLEEP:
Self-rating questionnaires:
- Sleep visual analogue scales (VAS): 6 items rated at each visit between inclusion and W24. The main efficacy criterion was the "Global satisfaction on sleep score". The other items were "Getting off to sleep", "Quality of sleep", "Early awakening", "Feeling on waking", and "Sense of balance and coordination".
- Pittsburg Sleep Quality Index (PSQI): rated at inclusion, and W2, W6, W12 and W24 visits, or in case of premature withdrawal.
- Daytime sleepiness visual analogue scales: 2 items ("Daytime sleepiness", and "Feeling good") rated at inclusion, at each visit of the mandatory period, and at W24 visit or in case of premature withdrawal.

Assessment by the investigator:
Sleep sub-score from the HAM-D 17-item scale (see below "Efficacy on depression"): sum of items 4 (insomnia: early in the night), 5 (insomnia: middle of the night) and 6 (insomnia: early hours in the morning).

DEPRESSION: both scales were rated by the investigator.
- Hamilton Depression scale 17 items (HAM-D 17-item): rated at each visit from selection to W25 visits.
- Clinical Global Impression (CGI): severity of illness score and global improvement score rated at each visit from W0 or W1 to W25 visits, respectively.

QUALITY OF LIFE
Global Assessment of Functioning scale (GAF scale): rated by the investigator at inclusion, W12 and W24 or in case of premature withdrawal.

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SAFETY MEASUREMENTS:

- Adverse events recording at each visit from selection to the follow-up visit.
- Laboratory tests: results available at inclusion, W12 and W24 visits, or at the follow-up visit (Wend) in case of premature withdrawal. In addition, according to Amendment No. 1, further blood samples were taken at W4, W8, W16, and W20 in Canadian patients to assess liver enzymes.
- Vital signs: Blood pressure and heart rate (sitting position after 5 min rest), and weight were measured at selection, inclusion, W12, W24, and W25 visits (except weight at W25), or in case of premature withdrawal.
- 12-lead electrocardiogram (ECG): results available at inclusion and W24 visit, or at the follow-up visit for patients not entered the extension period or in case of premature withdrawal.
- Arizona Sexual Experience Scale (ASEX): filled in by the patients at inclusion, and W2, W4, W12 and W24 visits or in case of premature withdrawal.
- Discontinuation-emergent signs and symptoms (DESS) checklist: rated by the investigators at W25.

ANCILLARY STUDY:

An ancillary study was added (Amendment No. 2) in 4 countries (Australia, Canada, South Africa, and the United Kingdom). It was conducted to assess the performance of the first version of the Oxford Questionnaire on Emotional Side-effects of Antidepressants (OQESA-1) in patients with Major Depressive Disorder, and to investigate emotional side-effects of antidepressants in these patients. The questionnaire was filled in by the patients at selection, inclusion, W2, W12 and W24, or at the withdrawal visit in case of premature withdrawal. The results of the ancillary study are the subject for a separate report.

Statistical methods:

EFFICACY ANALYSES:

The main efficacy analysis set was the FAS. It was defined as all patients of the RS having taken at least one dose of study medication and, having a value at W0 and at least one value at W1, W2 or W3 for the primary criterion, or having a value at W0 and at least one post-baseline value over the W0-W12 period for the HAM-D total score.

Primary criterion

In addition to descriptive statistics (for each analytical approach of the primary criterion) for the two treatment groups over the W0-W12 and W0-W24 periods in the FAS, SUB-FAS with W0 HAM-D total score ≥ 25 and patients of the FAS with W0 PSQI total score ≥ 13, analyses described hereafter were performed.

Main analysis

The difference between agomelatine and escitalopram was studied in the FAS on the change from baseline at W1, W2 and W3 visits using a two-way analysis of covariance on factors treatment and centre (random effect) with baseline as covariate. The Hochberg's procedure was used for the comparison between treatment groups at each visit, in order to take into account the multiplicity issue.

Sensitivity analysis

An unadjusted analysis based on a two-sided Student's t-test for independent samples was performed in the FAS on values at W1, W2 and W3, and the Hochberg's procedure was also used.

Secondary analysis

Difference between agomelatine and escitalopram was assessed in the FAS on the change from baseline to last post-baseline value until W12, using a 95% confidence interval based on a two-way analysis of covariance with factors treatment and centre (random effect) with baseline as covariate.

All these analyses were also performed in patients of the SUB-FAS with W0 HAM-D total score ≥ 25, as secondary analyses.

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EFFICACY ANALYSES (Cont'd)

Secondary criteria

For each analytical approach of secondary criteria, descriptive statistics were provided by treatment group over the W0-W12 and W0-W24 periods in the FAS (and SUB-FAS with W0 HAM-D total score ≥ 25 for HAM-D total score, as raw value and change from baseline).

For getting off to sleep score, quality of sleep score and early awakening score (obtained from the Sleep VAS), difference between agomelatine and escitalopram was studied in the FAS, using the same adjusted and unadjusted analyses as those used for the primary criterion.

For HAM-D total score, the difference between treatment groups was estimated over the W0-W12 and W0-W24 periods using:

- A two-way analysis of covariance with factors treatment and centre (random effect) and W0 HAM-D total score as covariate, for the change from baseline to last post-baseline value in the FAS and SUB-FAS with W0 HAM-D total score ≥ 25. Non-inferiority was tested using a predefined non-inferiority margin fixed at –1.5
- A 95% confidence interval for the response to treatment taking into account last post-baseline value in the FAS.

For CGI global improvement score, the difference between agomelatine and escitalopram was estimated in the FAS over the W0-W12 and W0-W24 periods using:

- A 95% confidence interval on the last value.
- A 95% confidence interval on the response to treatment, considering the last value.

SAFETY ANALYSIS:

Descriptive statistics were provided in the Safety Set for the two treatment groups over the W0-W12 and W0-W24 periods. For DESS, descriptive analysis was performed by dose subgroup at W25 in the DESS Set.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

		Agomelatine	Escitalopram	Whole population
W0-W12				
Included (randomised)	**n**	**164**	**160**	**324**
Lost to Follow-up	**n (%)**	**1 (0.6)**	**1 (0.6)**	**2 (0.6)**
Withdrawn	**n (%)**	**19 (11.6)**	**22 (13.8)**	**41 (12.7)**
Adverse event	n (%)	4 (2.4)	13 (8.1)	17 (5.3)
Lack of efficacy	n (%)	5 (3.1)	3 (1.9)	8 (2.5)
Non-medical reason	n (%)	8 (4.9)	4 (2.5)	12 (3.7)
Protocol deviation	n (%)	2 (1.2)	1 (0.6)	3 (0.9)
Cure, remission or marked improvement	n (%)	-	1 (0.6)	1 (0.3)
Completed the W0-W12 period	**n (%)**	**144 (87.8)**	**137 (85.6)**	**281 (86.7)**
W12-W25				
Entered the W12-W25 period	**n**	**137**	**130**	**267**
Withdrawn*	**n (%)**	**13 (9.5)**	**15 (11.5)**	**28 (10.5)**
Adverse event	n (%)	3 (2.2)	4 (3.1)	7 (2.6)
Lack of efficacy	n (%)	3 (2.2)	1 (0.8)	4 (1.5)
Non-medical reason	n (%)	4 (2.9)	4 (3.1)	8 (3.0)
Protocol deviation	n (%)	1 (0.7)	4 (3.1)	5 (1.9)
Cure, remission or marked improvement	n (%)	2 (1.5)	2 (1.5)	4 (1.5)
Completed the W12-W25 period*	**n (%)**	**124 (90.5)**	**115 (88.5)**	**239 (89.5)**
Main analysis Sets				
Randomised Set	n	164	160	324
Full Analysis Set (FAS)	n (%)	162 (98.8)	160 (100.0)	322 (99.4)
Safety Set	n (%)	163 (99.4)	160 (100.0)	323 (99.7)

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

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STUDY POPULATION AND OUTCOME (Cont'd)

Overall, 324 patients were randomized: 164 patients to the agomelatine group and 160 patients to the escitalopram group. In all, 83 patients had a dose increase: 41 (26.1%) of 157 agomelatine-treated patients continuing at W2 received the 50 mg dose, and 42 (27.5%) of 153 escitalopram-treated patients received the 20 mg dose. During the study, one patient in each treatment group was lost to follow-up. They were reported at W2 in the agomelatine group, and at W12 in the escitalopram group. Over the W0-W12 and W12-W25 extension periods, the rate of withdrawals was lower in the agomelatine group than in the escitalopram group (11.6% *versus* 13.8%, and 9.5% *versus* 11.5%, respectively, percentages excluding lost to follow-up patients). The difference was mainly due to withdrawals for adverse events which were less frequent in the agomelatine group than in the escitalopram group during both periods, particularly during the W0-W12 period (2.4% *versus* 8.1%, and 2.2% *versus* 3.1% during the extension period), and due to withdrawals for protocol deviations during the extension period (0.7% *versus* 3.1%). Finally, the percentage of randomised patients who completed the study at W25 was 75.6% in the agomelatine group and 71.9% in the escitalopram group.

Randomised patients were 43.2 ± 12.4 years old on average (± SD), ranging from 18 to 79 years. Most of them were female (71.0%). According to the DSM-IV-TR criteria, 74.1% of patients were diagnosed as recurrent MDD, and the other ones had single episode (25.9%). Three quarters of patients (75.0%) had a moderate MDD, and 25.0% a severe MDD without psychotic feature. Melancholic features were observed in 76.2% of patients. Mean number of depressive episodes was 2.8 ± 2.3 including the current one, ranging from 1 to 25. Mean duration of the current MDE was 5.1 ± 8.2 months (median 3.3 months). Previous psychotropic drug treatment was reported in 51.9% of patients, mainly SSRIs (21.6%) and benzodiazepine derivatives (17.6%).
No clinically relevant differences between groups were observed for demographic and disease characteristics at baseline.
As regards sleep criteria, the mean VAS sleep satisfaction score was 20.7 ± 14.4 mm, and the other sleep VAS items had a mean score included between 20 and 30 mm. The mean VAS daytime sleepiness score was 65.9 ± 24.1 mm, and the mean VAS feeling good score was 20.5 ± 15.0 mm. The mean PSQI total score was 13.1 ± 3.0. As regards depression criteria, the mean HAM-D total score was 26.7 ± 2.8. The mean CGI severity of illness score was 4.7 ± 0.6.
Considering efficacy criteria for sleep and depression in the Randomised Set, no relevant between-group difference was observed at inclusion.
Baseline characteristics in the FAS were similar to those observed in the Randomised Set.
In the Randomised Set, mean treatment duration was 78.5 ± 18.9 days (median 84.0 days) over the W0-W12 period, and 146.3 ± 48.2 days (median 168.0 days) over the W0-W24 period. Global compliance was 96.6 ± 10.7% over W0-W12 and 96.0 ± 10.9% over W0-W24. Treatment duration and global compliance showed no relevant difference in both groups over both periods.

EFFICACY RESULTS

- **PRIMARY ASSESSMENT CRITERION: Global satisfaction on sleep score of sleep visual analogue scale (VAS)**

Over the W0-W3 period, in the FAS, the mean global satisfaction on sleep score progressively increased in both treatment groups. The mean increase from baseline at W1, W2, and W3 showed no statistically significant difference between groups (main analysis, see Table below). Sensitivity analysis showed the same results.

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EFFICACY RESULTS (Cont'd)

Global satisfaction on sleep score (mm): Mean change from baseline by visit over W0-W3, and comparison between the agomelatine and escitalopram groups at each visit in the FAS

		Agomelatine (N = 162)	**Escitalopram (N = 160)**
W0	n	160	160
	Mean ± SD	19.7 ± 13.1	21.5 ± 15.4
Change from baseline at W1	n	156	157
	Mean ± SD	16.0 ± 23.9	14.2 ± 22.2
	E (SE) (1)	-0.74 (2.42)	
	95% CI (2)	[-5.50 ; 4.02]	
	p-value (3)	0.760	
Change from baseline at W2	n	157	157
	Mean ± SD	20.8 ± 26.8	22.8 ± 25.8
	E (SE) (1)	3.26 (2.72)	
	95% CI (2)	[-2.10 ; 8.62]	
	p-value (3)	0.233	
Change from baseline at W3	n	152	149
	Mean ± SD	29.3 ± 26.2	28.7 ± 26.0
	E (SE) (1)	0.21 (2.77)	
	95% CI (2)	[-5.24 ; 5.67]	
	p-value (3)	0.939	

General linear model with baseline as covariate, and centre as random effect.
(1) Estimate (Standard Error) of the difference between adjusted treatment group means: escitalopram minus agomelatine
(2) 95% Confidence interval of the estimate
(3) Centre and baseline adjusted treatment effect: Adjustment for multiplicity using Hochberg procedure

Over the W0-W12 period, in the FAS, the mean increase from baseline at the last post-baseline assessment in both groups showed no significant difference between groups: 43.5 ± 29.1 mm in the agomelatine group, and 42.7 ± 30.6 mm in the escitalopram group, E(SE) = 0.86 (2.85) mm, 95% CI [-4.75 ; 6.46].
Over the W0-W24 period, in the FAS, the mean increase from baseline at the last post-baseline assessment was higher in the agomelatine group (47.7 ± 30.2 mm) than in the escitalopram group (43.5 ± 32.0 mm).
Response to treatment
In the FAS, the percentage of responders similarly increased over the W0-W12 period in both groups (61.3% in the agomelatine group and 60.6% in the escitalopram group at the last post-baseline assessment). Over the W0-W24 period, the percentage of responders was higher in the agomelatine group than in the escitalopram group at the last post-baseline assessment (66.3% versus 59.4%, respectively).
Similar results were observed in the Sub-FAS with HAM-D total score ≥ 25, and the Sub-FAS with PSQI total score ≥ 13 over both periods. In the latter subset, complementary analysis unplanned showed that the difference in favour of agomelatine at the last post-baseline assessment over W0-W24 had a statistical trend to significance (E(SE) = -11.88 (6.92) mm, 95% CI [-25.44 ; 1.69], p=0.087).

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- **SECONDARY ASSESSMENT CRITERIA**

  Efficacy on sleep

  - ***Other scores of the sleep VAS***

    - *Getting off to sleep score, Quality of sleep score, Early awakening score*

      Over the W0-W3 period, in the FAS, the 3 mean scores increased between baseline and W1, W2, and W3 in both groups without statistically significant difference between them at each visit. Results of the mean increase from baseline at W3 in the agomelatine group and escitalopram group were as follows:

      - Getting off to sleep score: 29.2 ± 32.9 mm, and 26.0 ± 32.3 mm, respectively, E(SE) = -0.54 (3.02) mm, 95% CI [-6.48 ; 5.41], p = 0.859.
      - Quality of sleep score: 26.6 ± 25.6 mm, and 25.4 ± 25.2 mm, respectively, E(SE) = -0.69 (2.65) mm, 95% CI [-5.90 ; 4.52], p = 0.796).
      - Early awakening score: 22.3 ± 34.0 mm, and 25.2 ± 32.5 mm, respectively, E(SE) = 4.73 (3.14) mm, 95% CI [-1.46 ; 10.91], p = 0.134).

      Sensitivity analysis showed the same results for the 3 scores.

      Over the W0-W12, and W0-W24 periods, for the 3 scores, the mean increase from baseline at the last post-baseline assessment was as follows:

      - Getting off to sleep score: higher in the agomelatine group than in the escitalopram group over both periods:
        - W0-W12: 41.7 ± 32.9 mm *versus* 34.6 ± 36.4 mm, respectively.
        - W0-W24: 43.8 ± 33.3 mm *versus* 39.1 ± 36.9 mm, respectively.
      - Quality of sleep score:
        - W0-W12: no relevant difference between groups (38.3 ± 27.2 mm and 39.1 ± 26.9 mm, respectively).
        - W0-W24: higher in the agomelatine group than in the escitalopram group (44.2 ± 28.8 mm *versus* 40.4 ± 28.2 mm, respectively).
      - Early awakening score: no relevant difference between groups over both periods:
        - W0-W12: 35.6 ± 37.3 mm and 38.2 ± 32.4 mm, respectively.
        - W0-W24: 38.9 ± 37.1 mm and 40.6 ± 32.8 mm, respectively.

    - *Feeling on waking score, Sense of coordination score:*

      Over the W0-W12, and W0-W24 periods, in the FAS, for the 2 scores, the mean increase from baseline at the last post-baseline assessment was as follows:

      - Feeling on waking score: higher in the agomelatine group than in the escitalopram group over both periods:
        - W0-W12: 38.4 ± 29.1 mm *versus* 32.7 ± 31.4 mm, respectively.
        - W0-W24: 42.3 ± 29.2 mm *versus* 34.7 ± 34.9 mm, respectively.
      - Sense of coordination score: no relevant difference between groups over both periods:
        - W0-W12: 27.5 ± 28.4 mm and 25.1 ± 31.5 mm, respectively
        - W0-W24: 28.6 ± 28.6 mm and 25.0 ± 33.3 mm, respectively.

      Over the W0-W24 period, for 3 scores (getting off to sleep score, quality of sleep score and feeling on waking score), the mean increase from baseline at the last post-baseline assessment was higher in the agomelatine group than in the escitalopram group in the FAS. In the Sub-FAS with PSQI total score ≥ 13 over the W0-W24 period, complementary analysis unplanned showed that the difference in favour of agomelatine was statistically significant for the quality of sleep score (E(SE) = -8.72 (3.60) mm, 95% CI [-15.82 ; -1.62], p = 0.016), and the feeling on waking score (E(SE) = -10.77 (4.05) mm, 95% CI [-18.76 ; -2.78], p = 0.009).

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EFFICACY RESULTS (Cont'd)

- ***Pittsburgh Sleep Quality Index (PSQI)***
  Over the W0-W12, and the W0-W24 periods, in the FAS, the mean decrease in PSQI total score between the baseline and the last post-baseline assessment showed no relevant difference between groups:
  - W0-W12: -6.5 ± 4.5 in the agomelatine group and -6.3 ± 4.4 in the escitalopram group.
  - W0-W24: -6.8 ± 4.9 and -6.4 ± 4.7, respectively.

- ***Visual analogue scale (VAS) daytime sleepiness***
  Over the W0-W12, and the W0-W24 periods, in the FAS, the mean decrease in daytime sleepiness score between the baseline and the last post-baseline assessment, as well as the mean increase in feeling good score showed no relevant difference between groups over both periods:
  - Daytime sleepiness score:
    - W0-W12: -28.9 ± 31.5 mm in the agomelatine group, and -26.1 ± 33.6 mm in the escitalopram group.
    - W0-W24: -32.3 ± 32.5 mm, and -29.5 ± 34.2 mm, respectively.
  - Feeling good score:
    - W0-W12: 35.5 ± 31.1 mm, and 37.2 ± 30.1 mm, respectively.
    - W0-W24: 40.7 ± 31.9 mm, and 38.0 ± 34.0 mm, respectively.

In the Sub-FAS with PSQI total score ≥ 13 over the W0-W24 period (complementary analysis unplanned), the mean daytime sleepiness at the last post-baseline assessment showed no statistically significant difference between groups whereas the mean feeling good score was statistically significantly higher in the agomelatine group (64.0 ± 28.1 mm) than in the escitalopram group (55.0 ± 28.9 mm, E(SE) = -9.06 (4.17) mm, 95% CI [-17.28 ; -0.83], p = 0.031).

Efficacy on depression

- ***Hamilton Depression Rating Scale-17 items (HAM-D)***
  Over the W0-W12, and the W0-W24 periods, in the FAS, the mean decrease in HAM-D total score between the baseline and the last post-baseline assessment in the agomelatine group was significantly non-inferior to escitalopram group as per the predefined non-inferiority margin fixed at –1.5.
  - W0-W12: -18.7 ± 6.9 in the agomelatine group, and -18.3 ± 6.8 in the escitalopram group, E(SE) = 0.36 (0.67), 95% CI = [-0.96 ; 1.68], p=0.003.
  - W0-W24: -19.9 ± 7.6 in the agomelatine group, and -19.2 ± 7.2 in the escitalopram group, E(SE) = 0.69 (0.76), 95% CI = [-0.81 ; 2.19], p=0.002.

  The percentage of responders (decrease in HAM-D total score of at least 50% from baseline) showed no relevant difference between groups at the last post-baseline assessment over both periods:
  - W0-W12: 83.2%, and 80.0% in the agomelatine and escitalopram groups, respectively; E (SE) = -3.23% (4.32), 95% CI of [-11.70 ; 5.24].
  - W0-W24: 82.6%, and 81.3%, respectively; E (SE) = -1.36% (4.29), 95% CI of [-9.78 ; 7.06].

  The percentage of remitters (HAM-D total score ≤ 7) was higher in the agomelatine group than in the escitalopram group at the last post-baseline assessment over both periods:
  - W0-W12: 60.9% *versus* 54.4%.
  - W0-W24: 69.6% *versus* 63.1%.

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- ***Clinical Global Impression (CGI)***
  Over the W0-W12, and the W0-W24 periods, in the FAS, the mean scores of severity of illness and global improvement decreased along time in both groups. There were no relevant differences between groups at the last (post-baseline) assessment for both scores as follows:
  - *CGI severity of illness score*: from 4.7 ± 0.6 (median 5) in both treatment groups at baseline to:
    - W0-W12: 2.1 ± 1.1 (median 2) in both treatment groups.
    - W0-W24: 1.8 ± 1.2 and 1.9 ± 1.2 (median 1 in each group) in the agomelatine and escitalopram groups, respectively.
  - *CGI global improvement score*:
    - W0-W12: 1.5 ± 0.9 (median 1) in both treatment groups, E (SE) = -0.01 (0.10), 95% CI [-0.20 ; 0.18].
    - W0-W24: 1.5 ± 1.0 and 1.6 ± 1.1 in the agomelatine and escitalopram groups, respectively (median 1 in each group), E (SE) = 0.09 (0.12), 95% CI [-0.14 ; 0.32].

  Similar results were observed for the percentage of responders (global improvement score = 1 or 2) at the last assessment over both periods:
  - W0-W12: 90.7% and 90.0%, respectively: E (SE) = -0.68% (3.30), 95% CI [-7.15 ; 5.78].
  - W0-W24: 86.3% and 85.0%, respectively, E (SE) = -1.34% (3.91), 95% CI [-9.00 ; 6.33].

  Similar results were observed for the percentage of remitters (global improvement score = 1) at the last assessment over both periods:
  - W0-W12: 67.1% and 67.5% in the agomelatine and escitalopram groups, respectively.
  - W0-W24: 75.8% and 70.6%, respectively.

- ***Global Assessment of Functioning (GAF)***
  In the FAS, the mean increase in functional assessment (GAF) score between the baseline and the last post-baseline value over the W0-W12 and W0-W24 periods showed no relevant differences between groups as follows:
  - W0-W12: 23.7 ± 13.1 and 24.7 ± 12.4 in the agomelatine and escitalopram groups, respectively.
  - W0-W24: 27.0 ± 15.6 and 27.0 ± 15.0 at W24, respectively.

SAFETY RESULTS

- Emergent adverse events

During the W0-W12/Wend period in the Safety Set, the percentage of patients who reported at least one emergent adverse event was lower in the agomelatine group than in the escitalopram group (63.8% *versus* 70.0%).

The most frequently affected system organ classes (in more than 10% of patients) in the agomelatine group were gastrointestinal disorders (32.5% of patients) and nervous system disorders (25.2%), similarly reported in the escitalopram group (31.9% and 26.3%), respectively, and infections and infestations (22.7%), less common than in the escitalopram group (30.6%). In addition, in the escitalopram group, there were psychiatric disorders, less common in the agomelatine group (8.0% *versus* 15.0%).

The most frequent emergent adverse events (at least 5% of patients) in the agomelatine group were headache (10.4%), nausea (8.6%), diarrhoea (7.4%), dizziness (5.5%), and dry mouth (5.5%). Compared to escitalopram, the incidences were lower in the agomelatine group for headache (10.4% *versus* 14.4%), and nausea (8.6% *versus* 13.8%), and similar to for diarrhoea (6.9%), dizziness (6.3%), and dry mouth (6.3%).

In the escitalopram group, in addition to the adverse events described above, the other most frequent emergent adverse events (at least 5%) were nasopharyngitis and gastroenteritis (5.0% each), both less frequent in the agomelatine group (3.7% and 1.8%, respectively).

In the agomelatine group, patients had mostly emergent adverse events of mild (43.6%) or moderate intensity (41.1%). Similar results were observed in the escitalopram group (49.4% and 45.0% of the patients, respectively).

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SAFETY RESULTS (Cont'd)

The percentage of patients who experienced at least one emergent adverse event rated as severe was higher in the agomelatine group than in the escitalopram group (11.0% *versus* 7.5%, respectively). In both groups, severe emergent adverse events were more specifically related to gastrointestinal disorders (8/18 patients in the agomelatine group, and 5/12 patients in the escitalopram group), mainly nausea (3/18 and 3/12 patients, respectively) and diarrhoea in the agomelatine group (3/18 patients), and related to infections and infestations (5/18 in the agomelatine group, and 5/12 in the escitalopram group). Most emergent adverse events resolved without difference between groups (88.7% and 88.9% in the agomelatine and escitalopram groups, respectively).

The percentage of patients with at least one emergent adverse event considered to be related to the study treatment by the investigator was lower in the agomelatine group (38.7%) than in the escitalopram group (48.8%). In both treatment groups, the system organ classes most commonly affected were the same with lower percentages in the agomelatine group: gastrointestinal disorders (18.4% *versus* 24.4%), nervous system disorders (16.0% *versus* 21.3%), and psychiatric disorders (6.7% *versus* 11.9%).

During the W0-W24/Wend period in the Safety Set, as during the W0-W12/Wend period, the percentage of patients with at least one emergent adverse event was lower in the agomelatine group (70.6%) than in the escitalopram group (76.3%). Results obtained over W0-W24 were in the same line as those over W0-W12.

No death was reported during the study. The incidence of non fatal emergent serious adverse event was similar in both groups (3.7%, and 3.8%, i.e. 6 patients in each group, in the agomelatine and escitalopram groups, respectively). In addition, 2 patients (1.3%) in the escitalopram group had one serious adverse event during the follow-up period.

In both groups, serious adverse events were mainly related to psychiatric disorders (4 patients in each group, i.e. 2.5% in each group). In the agomelatine group, there were 4 suicide attempts, all on 25 mg, distributed all over the treatment period (between 31 and 165 days of treatment). One was considered as related to the study treatment by the investigator. The four events led to study treatment discontinuation.

In the escitalopram group, psychiatric events included one suicide attempt after 34 days on 10 mg, and one episode of mania after 119 days on 10 mg. This latter episode was considered as related to the study treatment by the investigator. Both events led to study treatment discontinuation. In addition, one depression suicidal reported after the last intake was considered to be related to the withdrawal of escitalopram by the investigator. The fourth psychiatric event was one alcoholism reported 4 days after the last intake.

For the other serious adverse events not related to psychiatric disorder, none were considered as related to the study treatment by the investigator, except one in the escitalopram group (chest pain).

All patients with serious adverse events recovered at the end of the study in both groups (one with sequelae in each group) except one patient in the agomelatine group (gastric cancer in a patient with a medical history of chronic gastritis with recurrent dyspepsia).

The percentage of patients who had treatment withdrawal due to non serious emergent adverse events was lower in the agomelatine group (3.1%, 5 patients) than in the escitalopram group (8.8%, 14 patients). In both groups, these events were most commonly related to nervous system disorders (2 events in the agomelatine group, i.e., one treatment-related sedation, and epilepsy in a patient with a medical history of epilepsy, and 4 events in the escitalopram group), and to psychiatric disorders (one depression in the agomelatine group, and 3 events in the escitalopram group). In addition, in the escitalopram group, 2 nausea led to treatment withdrawal.

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SAFETY RESULTS (Cont'd)

- **Laboratory parameters**
  - Biochemical and haematological parameters did not show any relevant change of the mean parameters throughout the study in both treatment groups.
  - Liver acceptability
    During the W0-W24/Wend period, the percentage of patients with at least one emergent PCSA value of liver parameter showed no relevant difference between the agomelatine (1.8%, 3 patients) and escitalopram groups (2.5%, 4 patients). In both groups, emergent PCSA values were related to transaminases and GGT as follows:
    - In the agomelatine group:
      - 2 patients on 50 mg had emergent PCSA transaminases. PCSA transaminases were reported as adverse event in one patient (ALAT = 16 ULN, and ASAT = 6 ULN), and led to treatment withdrawal. They were considered as possibly related to the study treatment by the investigator. In the second patient, PCSA transaminases (ALAT = 4 ULN, and ASAT = 4 ULN) were considered as clinically significant by the investigator, and reported as probable gastroenteritis not related to the study treatment. Study treatment was stopped.
      - 1 patient on 25 mg had emergent PCSA transaminases (ALAT = 4 ULN, and ASAT = 3 ULN), associated with emergent PCSA GGT (4 ULN). For this patient who had GGT elevated at baseline (2 ULN) and an alcohol consumption of 14 units/week since 21 years, the transaminase increase was a possible effect of alcohol according to investigator.

      For these 3 patients, PCSA transaminases were never associated with emergent abnormal total bilirubin or ALP ≥ 2 ULN. All patients recovered, one on treatment.

    - In the escitalopram group:
      - 1 patient on 10 mg had emergent PCSA transaminases (ASAT = 7 ULN, and ALAT = 12 ULN), associated with emergent PCSA GGT (5 ULN). These enzyme increases were considered as clinically significant by the investigator, and were associated with a dengue fever, not related to the study treatment.
      - 3 patients (2 on 10 mg and 1 on 20 mg) had emergent PCSA GGT (3 - 4 ULN) associated with both transaminases above the upper normal limit without reaching PCSA limit in 2 patients, and associated with abnormal ALAT in one patient. In one of them, the high GGT was already associated with abnormal transaminases at selection, and considered as clinically significant by the investigator and not related to the study treatment.

      Among the 4 patients, one recovered, one was recovering, and 2 still had PCSA GGT at the last test.

- **Vital signs and Body Mass Index (BMI)**

There were no relevant mean changes in sitting blood pressures and heart rate as well as in weight between baseline and last post-baseline value over the W0-W12 and W0-W24 periods in the Safety Set in both treatment groups. As regards BMI, most patients remained in the same BMI class as baseline in both groups over both periods (85.9% in the agomelatine group and 86.9% in the escitalopram group over the W0-W12 period).

- **Electrocardiogram (ECG)**

Two abnormalities in 2 agomelatine-treated patients were considered as clinically relevant by the investigator. One emergent atrial fibrillation was reported at W12, and was considered as related to medical history by the investigator. Cardiac failure was not resolved at the last visit. The other abnormality (septal myocardial infarction with clinically significant T wave abnormality) was reported 11 days after the last treatment intake, and considered as related to possible anterior ischemia, and right bundle branch block already reported at inclusion.

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SAFETY RESULTS (Cont'd)

- **Discontinuation Emergent Signs and Symptoms (DESS) check-list**

In the DESS Set, the mean number of emergent symptoms at W25 showed no relevant difference after one week of agomelatine discontinuation and after one week of escitalopram down-tapering (2.5 ± 4.6 and 2.6 ± 4.1, respectively, median 0 in each group).

- **Arizona Sexual Experience Scale (ASEX)**

In the Safety Set, the percentage of patients with an emergent dysfunction at the last post-baseline assessment was lower in the agomelatine group (5.1%) than in the escitalopram group (8.8%) over the W0-W12 period. ASEX total score was calculated in few patients in the Safety Set (at baseline: n = 34 in the agomelatine group, and n = 46 in the escitalopram group) considering that it could be calculated only if patients had sexual activity in the past week. Over the W0-W24 period, the mean decrease in ASEX total score was higher in the agomelatine group (-4.6 ± 4.3, median -4.0) than in the escitalopram group (-4.0 ± 5.6, median = -3.0).
ASEX results were consistent with the fact that emergent adverse events related to sexual dysfunction were reported on escitalopram only (libido decreased, ejaculation delayed, ejaculation disorder, and erectile dysfunction (2 patients each, 1.3%), abnormal orgasm and ejaculation failure (1 patient each, 0.6%)).

CONCLUSION

This multicentre, double-blind, randomised study conducted in patients with MDD confirmed that agomelatine 25-50 mg/d improved the subjective sleep of depressed patients during the first 3 weeks of treatment and after 12 weeks of treatment. This beneficial effect showed no significant difference from the one observed on escitalopram 10-20 mg/d. Likewise, agomelatine improved all other subjective sleep scores in a similar way to escitalopram. Anti-depressive effect of agomelatine on MDD after 12 weeks was confirmed, and a non-inferiority was demonstrated *versus* escitalopram.

Beneficial effects of agomelatine on sleep and remission of depression were maintained over the long-term treatment (24 weeks). Interestingly, in patients with a more pronounced sleep disturbances pattern at baseline (defined by a PSQI score at least 13), a better sleep and daytime functioning was observed on long-term treatment in the agomelatine group than in the escitalopram group with statistically significant differences in Quality of sleep, Feeling on waking and Feeling good scores (post-hoc analyses).

Agomelatine 25-50 mg was well tolerated. No unexpected adverse event was reported. The absence of discontinuation symptoms with agomelatine was confirmed. Moreover, agomelatine was better tolerated than escitalopram for sexual acceptability.

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