I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**Effects of agomelatine (25 to 50 mg/day) on sleep EEG parameters compared to escitalopram in patients with Major Depressive Disorder.** **A 6-week randomised, double-blind parallel groups study *versus* comparator, followed by a double-blind optional treatment extension period up to 6 months.**
Study drug	**Agomelatine (S 20098)**
Studied indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-056**
Study initiation date	**03 May 2007**
Study completion date	**16 October 2008**
Main coordinator	[redacted] **France**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Laboratorios Servier** **33 Avenida de los Madroños** **28043 Madrid - Spain** **Servier Research and Development Limited** **Gallions, Wexham Springs, Framewood Road - Wexham** **Slough SL3 6RJ - United Kingdom**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 18 June 2010**

~~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: Effects of agomelatine (25 to 50 mg/day) on sleep EEG parameters compared to escitalopram in patients with Major Depressive Disorder.
A 6-week randomised, double-blind parallel groups study *versus* comparator, followed by a double-blind optional treatment extension period up to 6 months.
Protocol No.: CL3-20098-056

National Coordinators: [redacted] - Australia), [redacted] – Austria), [redacted] – Brazil), [redacted] – Finland), [redacted] - France), [redacted] – Germany), [redacted] – Spain), [redacted] Taiwan ROC), [redacted] - United Kingdom).

Study centres:
23 centres included at least one patient in 8 countries: Australia – 1 centre (4 included patients), Austria – 3 centres (17 included patients), Brazil - 1 centre (10 included patients), Taiwan - 1 centre (16 included patients), Finland - 3 centres (27 included patients), France - 3 centres (10 included patients), Germany – 8 centres (44 included patients), Spain - 3 centres (10 included patients). In addition, centres in United Kingdom did not select any patients.

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 03 May 2007 Completion date: 16 October 2008	Phase III study

Objectives:
Main objective: to demonstrate that depressed patients treated with agomelatine present a greater improvement in sleep efficiency than patients treated with escitalopram after 2 weeks of treatment.
Secondary objectives: to show that agomelatine improves other objective sleep parameters, improves subjective sleep, restores a more physiological sleep architecture and does not impair daytime performance in depressed patients after short-term, medium-term and long-term treatment.
The effects of both treatments on depressive symptoms were also assessed, as well as their acceptability.
A pharmacogenomics ancillary study was also conducted in order to evaluate associations between polymorphisms in candidate genes and responses to treatment.

Methodology:
International, multicentric, randomised, double-blind, comparative phase III study with parallel groups (agomelatine 25 mg/d *versus* escitalopram 10 mg/d) using a flexible dosage. 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 to the investigator and the patient. The randomisation (at D0) was balanced (non-adaptive) with stratification on centre and patient's age (≤ 40; > 40). The randomisation, the treatment allocation and the dose increase were done centrally using an Interactive Voice Response System (IVRS). At the end of the 6-week double-blind acute treatment period, the improved patients (CGI global improvement score ≤ 3) could continue in the optional double-blind extension treatment period.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 130 patients randomised (65 in each group).
Patients Included: 138, *i.e.* 71 patients in the agomelatine group and 67 patients in the escitalopram group.

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Diagnosis and main criteria for inclusion:
Male or female outpatients, aged between 18 and 60 years inclusive, fulfilling DSM-IV-TR criteria for MDD, with single or recurrent episode, with or without melancholic features, without seasonal pattern, without psychotic or catatonic features, without post-partum onset, and requiring antidepressant treatment.
HAM-D 17-item total score was to be ≥ 22 at selection and inclusion.

Study drug:
Agomelatine, tablets of 25 mg, masked in capsule, 1 or 2 tablets per day, single administration, p.o., in the evening.
Patients received 25 mg/day (1 capsule containing 1 tablet of 25 mg) from D0 with possible increase to 50 mg/day in double-blind conditions (1 capsule containing 2 tablets of 25 mg) from D15, in case of insufficient improvement. During the optional period (D42-W25), patients received the same dose as during D15-D42 period.
Batch No. L0014440, L0019127, L0020880, L001442, L0019077.

Reference product:
Escitalopram, tablets of 5, 10 and 20 mg, masked in capsule, 1 or 2 tablets per day, single administration, p.o., in the evening.
Patients received 10 mg/day from D0, with possible increase in double-blind conditions to 20 mg/day at D15, in case of insufficient improvement. From D15, the dose was maintained up to W24. Between W24 and W25, patients having 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:

- Period from selection to inclusion (D0) without treatment (should not exceed 10 days).
- Double-blind acute treatment period of 6 weeks (from D0 to D42).
- Double-blind optional extension treatment period of 19 weeks (from D42 to W25).
  Including a 1-week tapering period (W24-W25) for patients in the escitalopram group. Patients in the agomelatine group remained at the same dosage as during the D15-W24 period.
  For patients stopping the study at D42 or having prematurely discontinued the study, the follow-up period took place either after the tapering period, or immediately after the discontinuation visit, according to investigator's opinion and reason for withdrawal.
- 7-day follow-up period without treatment after treatment discontinuation whatever its time of occurrence.

Criteria for evaluation:
EFFICACY MEASUREMENTS:

ON SLEEP

- Polysomnography (PSG) (objective evaluation)
  Polysomnography recordings were performed in sleep laboratory, twice in-between selection and inclusion visits with interval period that should not exceed 10 days, once at D14 and D41 visits, and twice, 23 weeks after the first drug intake. PSG 1 and 5 were considered as adaptation nights.
  An urine sample was collected before inclusion and before each PSG recording at the sleep laboratory and sent to the central laboratory for hypnotics screening.
  The primary efficacy criterion was the sleep efficiency index 1 (SE1) calculated as total sleep time/sleep period time x 100.

  Other polysomnographic parameters:
  - Standard parameters: Sleep Latency, Sleep period Time, Wake after Sleep Onset, Total Sleep Time (TST), Time of Sleep Onset, Time of Last Awakening, Sleep efficiency index 2 (SE2) calculated as (Total Sleep Time/Time in Bed) x 100, absolute and relative duration of each sleep stage (stage 1, stage 2, stage 3-4 and REM), Duration of each sleep stage by cycle in the first 4 cycles, REM latency, Number of Awakenings per hour of TST, Number of Sleep cycles, Number of transitions per hour of TST, Number of PLM per hour of TST, REM onset.

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Criteria for evaluation (Cont'd):
EFFICACY MEASUREMENTS (Cont'd):

- Spectral analysis: Absolute and relative delta power (0.5 - 4 Hz) for the night. Delta power ratio calculated as the absolute delta power NREM in cycle 1 divided by the absolute delta power NREM in cycle 2. Relative power of the night was also calculated in the theta (4.0 - 7.75 Hz), alpha (8 - 12 Hz), and beta (≥ 15.25 Hz) frequency bandwidths.

- Self-rating questionnaires (subjective evaluation):
  - Leeds Sleep Evaluation Questionnaire (LSEQ): at D14, D41 and W23.
  - Pittsburgh Sleep Quality Index (PSQI): at selection, D14, D41 and W23.
  - Screening of Sleep and Circadian Rhythms Disorders Questionnaire (CIRSCREEN): at selection, D41 and W23.

ON DAYTIME PERFORMANCE
- Psychomotor Vigilance Task (PVT): at selection, D14, D41 and W23.
- Visual Analogue Scales on Daytime Performance (VAS): at selection, D14, D41 and W23.

ON DEPRESSION:
- Hamilton Depression scale 17 items (HAM-D - 17 items): at selection, inclusion, D15, D28, D42 and at W10, W14, W18, W21, W24.
- Clinical Global Impression (CGI): severity of illness score and global improvement score rated at selection, and inclusion (only for severity of illness score), D15, D28, D42 and at W10, W14, W18, W21, W24.

SAFETY MEASUREMENTS:

- Adverse events reported at each visit during the study (from selection to the follow-up visit).
- Laboratory parameters (biochemistry and haematology): Blood sampling in fasting condition was prescribed at selection visit in order to have the results before inclusion. During the study, it was prescribed at visit D28 and W21 in order to have the results for visit D42 and W24, respectively, or in case of premature withdrawal.
- Vital signs: supine blood pressure and heart rate after a 5-minute rest, weight, and height were measured at selection, then all criteria but height at D42 and W24 or in case of premature withdrawal.
- 12-lead electrocardiogram (ECG) prescribed at selection and W21 (with results made available for inclusion and W24), or in case of premature withdrawal.

Statistical methods:
EFFICACY ANALYSIS:
In addition to descriptive statistics by treatment group for each analytical approach of the primary and secondary criteria over D0-D42 in the FAS and over D0-W24 in the FAS (only for HAM-D and CGI), in the SUB-FAS in extension period, and in the PSG Set (as complementary analyses for most of the PSG criteria only, and considering value at baseline, at each post-baseline visit, and the change from baseline at each post-baseline visit), the following analyses were performed:

Primary criterion
The superiority of agomelatine compared to escitalopram was studied in the FAS on the change from baseline at D14 (main analysis). Considering that the criterion distribution deviates from the normal distribution, a rank-based approach was used (robust general linear model (Wilcoxon norm) with class of age and centre as fixed effects, and with baseline as covariate) instead of the parametric approach initially considered (three-way analysis of covariance on factors treatment, class of age and centre (random effect), and with baseline as covariate). As complementary unplanned analyses, the difference between the 2 treatment groups was studied in the PSG Set on the change from baseline at each post-baseline visit over D0-W24 using unadjusted analyses based on Hodges-Lehmann's estimate and Mann-Whitney test. In addition, SE1 improvement (SE1 change from baseline > 0%) in the FAS, at each post-baseline visit and considering the last post-baseline assessment over the D0-D42 period was compared between treatment groups using a Chi-square test.

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Statistical methods (Cont'd):
EFFICACY ANALYSIS (Cont'd):

Secondary criteria

For PSG secondary criteria (sleep latency, number of sleep cycles, SE2, total sleep time, absolute duration of stage 3+4, relative duration of stage 1, relative duration of REM, and REM latency), unplanned between-group comparisons were added for the change from baseline to each post-baseline visit over D0-W24 in the PSG Set using the Mann-Whitney test. Estimate of the difference between treatment groups and associated 95% confidence interval were provided using Hodges-Lehmann method. For REM onset, unplanned within-group comparison was performed at each post-baseline visit over D0-W24 in the PSG Set using a Sign test. Same analyses were performed for REM onset and time of sleep onset in patients of the PSG Set with a late sleep onset at baseline (time of sleep onset ≥ baseline Q3 all treatment groups pooled).

For HAM-D total score, the difference between treatment groups was estimated over the D0-D42 period using a two-way analysis of covariance on factors treatment and centre (random effect) and with D0 HAM-D total score as covariate for the change from baseline to last post-baseline value, in the FAS. Non-inferiority was tested using the predefined margin of -1.5.
For CGI global improvement score, the difference between agomelatine and escitalopram was estimated in the FAS, using a 95% confidence interval on the last value until D42.

SAFETY ANALYSIS:
Descriptive statistics were provided in the Safety Set for the two treatment groups over the D0-D42/Wend and D0-W24/Wend periods.

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

Disposition of patients

		Agomelatine	**Escitalopram**	**Whole population**
D0-D42				
Included (randomised)	**n**	**71**	**67**	**138**
Withdrawn	**n (%)**	**6 (8.5)**	**8 (11.9)**	**14 (10.1)**
Adverse event	n (%)	2 (2.8)	5 (7.5)	7 (5.1)
Lack of efficacy	n (%)	2 (2.8)	2 (3.0)	4 (2.9)
Protocol deviation	n (%)	2 (2.8)	1 (1.5)	3 (2.2)
Completed the D0-D42 period	**n (%)**	**65 (91.5)**	**59 (88.1)**	**124 (89.9)**
Entered the D42-W24 period	**n (%)**	**58 (81.7)**	**54 (80.6)**	**112 (81.2)**
Lost to follow-up	**n (%)**	**-**	**1 (1.5)**	**1 (0.7)**
Withdrawn	**n (%)**	**10 (14.1)**	**9 (13.4)**	**19 (13.8)**
Adverse event	n (%)	1 (1.4)	-	1 (0.7)
Lack of efficacy	n (%)	5 (7.0)	4 (6.0)	9 (6.5)
Non-medical reason	n (%)	4 (5.6)	5 (7.5)	9 (6.5)
Completed the D0-W24 period	**n (%)**	**48 (67.6)**	**44 (65.7)**	**92 (66.7)**
Analysis Sets				
Randomised Set	n (%)	71 (100.0)	67 (100.0)	138 (100.0)
Full Analysis Set (FAS)	n (%)	68 (95.8)	61 (91.0)	129 (93.5)
Polysomnography set (PSG Set)	n (%)	62 (87.3)	53 (79.1)	115 (83.3)
SUB-FAS in extension period	n (%)	57 (80.3)	50 (74.6)	107 (77.5)
Safety Set	n (%)	71 (100.0)	66 (98.5)	137 (99.3)

%: Expressed as percentage of the patients from the Randomised Set

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Overall, 138 patients were randomised: 71 patients to the agomelatine group and 67 patients to the escitalopram group. In all, 25 patients had a dose increase, similarly distributed between treatment groups (13, *i.e.* 18.8% of 69 agomelatine-treated patients continuing on D15 received the 50 mg dose, and 12, *i.e.* 18.8% of 64 escitalopram-treated patients continuing on D15 received the 20 mg dose). During the study, one patient in the escitalopram 10 mg group was lost to follow-up at W14. Over the D0-D42 period, the rate of withdrawals was lower in the agomelatine group than in the escitalopram group (8.5% *versus* 11.9%). The difference was mainly due to withdrawals for adverse events which were less frequent in the agomelatine group than in the escitalopram group (2.8% *versus* 7.5%). Finally, the percentage of randomised patients who completed the study at W24 showed no relevant difference between treatment groups (67.6% in the agomelatine group and 65.7% in the escitalopram group).

Randomised patients were 41.4 ± 11.5 years old on average (± SD), ranging from 19 to 60 years. More than half of patients (59.4%) were more than 40 years old. Most patients were female (64.5%). According to the DSM-IV criteria, 76.8% of patients were diagnosed as recurrent MDD, and the other ones had single episode (23.2%). Two thirds of patients (66.7%) had a moderate MDD, and 33.3% a severe MDD without psychotic feature with a higher frequency in the agomelatine group (36.6%) than in the escitalopram group (29.9%). Melancholic features were observed in 68.8% of patients with a higher frequency in the agomelatine group (76.1%) than in the escitalopram group (61.2%).

Mean duration of the disease was 8.6 ± 9.3 years (median 5.5 years), ranging from 0.1 to 42.2 years. Mean number of depressive episodes was 2.8 ± 1.9 (median 2.0) including the current one, ranging from 1 to 12. Mean duration of the current MDE was 6.2 ± 5.1 months (median 4.9 months). Previous psychotropic drug treatment was reported in 68.8% of patients, mainly SSRIs (26.8%) and other antidepressants (26.8%) and benzodiazepine derivatives (19.6%) with a lower frequency in the agomelatine group (14.1%) than in the escitalopram group (25.4%).
No clinically relevant differences between treatment groups were observed for demographic and disease characteristics at baseline except more severe episode, more frequent melancholic feature, and less previous treatment by benzodiazepine derivatives in the agomelatine group as described above.

In the FAS, demographic and disease characteristics at baseline were in the same line as in the Randomised Set except the severity of the episode which was similar between groups.
Efficacy criteria for depression, sleep, and daytime performance in the Randomised Set were as follows at inclusion:

- As regards depression criteria, there were no differences between treatment groups. Overall, the mean HAM-D total score was 26.1 ± 2.7. The mean CGI severity of illness score was 4.7 ± 0.6.
- As regards sleep criteria, the mean sleep efficiency index 1 (SE1) was 86.8% ± 9.6% (median 88.6%). The mean PSQI total score was 11.6 ± 3.4. Both criteria showed no relevant difference between groups.
- As regards daytime performance, the psychomotor vigilance task showed no relevant difference between the treatment groups for the mean reaction time (median 270.9 ms in the agomelatine group and 281.1 ms in the escitalopram group) as well as the median number of lapses (0 and 1.0, respectively).
- As regards VAS, the 3 median VAS daytime sleepiness (feeling now) scores were lower in the agomelatine than in the escitalopram group indicating that, in the agomelatine group, patients felt more sleepy (37.0 mm versus 47.0 mm), more confused (57.0 mm versus 75.0 mm), and more clumsy (51.0 mm versus 69.0 mm) at baseline than in the escitalopram group. As regards the VAS daytime sleepiness (over the last week) scores, the median feeling sleepy score and the median feeling good score showed no relevant difference between groups (68.0 mm and 66.0 mm in the agomelatine and escitalopram groups, respectively for the former, and 35.0 mm and 36.0 mm, respectively for the latter).
- Based on subjective parameters, patients in the agomelatine group seemed more impaired as regards their present daytime sleepiness, characteristics which are not confirmed by the objective parameters.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Baseline characteristics of depression and sleep showed no relevant difference between groups in the Randomised Set. In the FAS, baseline characteristics of depression, sleep, and daytime performance criteria were in the same line as in the Randomised Set.

In the Randomised Set, mean treatment duration was 39.6 ± 8.4 days (median 41.0 days) over the D0-D42 period, and 134.1 ± 58.8 days (median 167.0 days) over the D0-W24 period. Treatment duration showed no relevant difference in both treatment groups over both periods.

Global compliance was 95.7 ± 13.4% over D0-D42 and 93.5 ± 15.3% over D0-W24. Global compliance showed no relevant difference in both treatment groups.

- Primary efficacy criterion: Polysomnographic sleep efficiency index 1 (SE1)

In the FAS, the median (Q1 ; Q3) change from baseline of SE1 at D14 was 0.00% (-7.90% ; 3.40%) in the agomelatine group and -2.50% (-6.50% ; 0.40%) in the escitalopram group indicating that unlike the patients on agomelatine, a great majority of patients on escitalopram tended to have an impairement in SE1 (see Table below). In order to test the superiority of agomelatine *versus* escitalopram at D14, a rank-based approach was used instead of the parametric approach initially considered, the former method being more suitable considering that the criterion distribution deviates from the normal distribution.

The analysis showed that the difference between the 2 treatments considering the change from baseline at D14 was in favour of agomelatine as compared to escitalopram without reaching statistical significance (see Table below).

In addition, as observed with the quartiles of the change from baseline at D14 (median of 0.00% in the agomelatine group and third quartile of 0.40% in the escitalopram), 49.3% of the agomelatine-treated patients improved their SE1 at D14 compared to 27.9% of the escitalopram-treated patients (p = 0.013, complementary Chi-square test).

Over the D0-D42 period, the median SE1 change from baseline to D41 was of -0.70% (Q1 ; Q3 = -5.05% ; 4.00%) for agomelatine and -1.25% (Q1 ; Q3 = -9.40% ; 4.60%) for escitalopram. No statistically significant difference was observed between groups (E(SE) = 1.13% (1.50%) with a corresponding 95% CI of [-1.85% ; 4.12%], p = 0.453 based on rank-based approach with adjustment for centre, class of age and baseline). Similar result was observed at last post-baseline assessment.

Similar results were observed in the PSG Set.

Between-group difference in SE1 (%) over the D0-D14 period in the FAS

		Agomelatine (N = 68)	**Escitalopram (N = 61)**
Baseline	n	67	61
	Mean ± SD	86.89 ± 9.54	86.84 ± 9.83
	Median	88.80	88.00
	Q1 ; Q3	84.10 ; 93.90	82.00 ; 94.20
D014	n	67	61
	Mean ± SD	84.11 ± 14.07	83.45 ± 13.08
	Median	88.80	87.70
	Q1 ; Q3	79.60 ; 93.60	76.20 ; 91.60
Change from baseline to D14	n	67	61
	Mean ± SD	-2.77 ± 14.36	-3.39 ± 9.69
	Median	0.00	-2.50
	Q1; Q3	-7.90 ; 3.40	-6.50 ; 0.40
Statistical analysis			
Change from baseline to D14	E (SE) (1)	2.52 (1.61)	
	95% CI (2)	[-0.68 ; 5.71]	
	p-value (3)	0.121	

Rank-based approach: robust general linear model (Wilcoxon norm) with class of age and centre as fixed effects, and with baseline as covariate
(1) Estimate (Standard Error) of the difference between treatment groups: agomelatine minus escitalopram.
(2) Two-sided 95% Confidence Interval of the estimate
(3) p-value of treatment effect

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- Secondary efficacy criteria

EFFICACY ON SLEEP

- ***Other polysomnographic parameters***

  In the PSG Set, the following polysomnographic parameters showed a difference in favour of agomelatine as compared to escitalopram. Similar results were observed in the FAS.

  - *Sleep latency*

    In the PSG Set, over the D0-D42 period, the sleep latency shortened from D14 for the great majority of patients on agomelatine as compared to baseline whereas it lengthened for a majority of patients on escitalopram (see quartiles change from baseline in Table below) leading to a statistically significant difference in favour of agomelatine at each visit (complementary analyses):
    - D14: E = -19.0 min with a corresponding 95% CI of [-30.0; -9.0 min], $p < 0.001$.
    - D41: E = -14.0 min with a corresponding 95% CI of [-24.0 ; -5.0 min], $p = 0.003$.

    Over the D0-W24 period, similar results (descriptive analysis) were observed in the Sub-FAS in extension period.

Change from baseline in sleep latency (min) to D14 and D41 over the D0-D42 period in the PSG Set

		Agomelatine (N = 62)	**Escitalopram (N = 53)**
Baseline	n	62	53
	Median	26.0	24.0
	Q1 ; Q3	13.0 ; 49.0	12.0 ; 42.0
Change from baseline to D14	n	61	52
	Median	-8.0	9.5
	Q1 ; Q3	-22.0 ; 3.0	-5.0 ; 24.5
Change from baseline to D41	n	58	48
	Median	-12.5	3.0
	Q1; Q3	-30.0 ; 1.0	-13.5 ; 14.0

  - *Sleep efficiency index 2 (SE2)*

    In the PSG Set, unlike the patients on agomelatine, an impairement of the SE2 was observed at D14 in most of patients in the escitalopram group (see quartiles change from baseline in Table below) leading to a statistically significant difference in favour of agomelatine (complementary analysis: E = 5.70% with a corresponding 95% CI of [1.30% ; 10.0%], $p = 0.012$). The impairement was still present at D41 to a lesser extent (see quartiles change from baseline in Table below) only leading to a trend to statistical significance in favour of agomelatine (complementary analysis: E = 4.00% with a corresponding 95% CI of [-0.40% ; 9.20%], $p = 0.070$).

    Over the D0-W24 period, similar results (descriptive analysis) were observed in the Sub-FAS in extension period.

Change from baseline in SE2 (%) to D14 and D41 over the D0-D42 period in the PSG Set

		Agomelatine (N = 62)	**Escitalopram (N = 53)**
Baseline	n	62	53
	Median	82.60	82.50
	Q1 ; Q3	70.60 ; 87.60	74.20 ; 87.30
Change from baseline to D14	n	61	53
	Median	0.80	-4.50
	Q1 ; Q3	-5.70 ; 6.50	-15.40 ; 0.60
Change from baseline to D41	n	58	48
	Median	1.55	-1.60
	Q1 ; Q3	-5.00 ; 7.00	-11.00 ; 5.95

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

EFFICACY ON SLEEP (CONT'D)

- *Number of cycles*

  In the PSG Set, over the D0-D42 period, the number of sleep cycles on agomelatine was preserved whereas it decreased (median from 4 to 2 cycles) on escitalopram leading to a statistically significant difference in favour of agomelatine at each visit (E = 2.0, 95%CI = [1.0 ; 2.0], p < 0.0001 for each comparison, complementary analyses).

  Over the D0-W24 period, similar results (descriptive analysis) were observed in the Sub-FAS in extension period.

- *REM latency*

  In the PSG Set, unlike the patients on agomelatine, more than three quarters of patients on escitalopram had a marked lengthening in REM latency at both visits (see quartiles change from baseline in Table below) leading to a statistically significant difference in favour of agomelatine at each visit (complementary analysis at D14: E = -66.0 min with a corresponding 95% CI of [-95.0 ; -38.0 min], p < 0.0001; at D41: E = -53.0 min with a corresponding 95% CI of [-77.0 ; -33.0 min], p < 0.0001).

  Over the D0-W24 period, similar results (descriptive analysis) were observed in the Sub-FAS in extension period.

Change from baseline in REM latency (min) to D14 and D41 over the D0-D42 period in the PSG Set

		Agomelatine (N = 62)	**Escitalopram (N = 53)**
Baseline	n	62	53
	Median	68.0	68.0
	Q1 ; Q3	51.0 ; 101.0	52.0 ; 101.0
Change from baseline to D14	n	61	49
	Median	11.0	68.0
	Q1; Q3	-9.0 ; 40.0	29.0 ; 132.0
Change from baseline to D41	n	58	46
	Median	5.0	52.0
	Q1; Q3	-15.0 ; 19.0	28.0 ; 98.0

- *Relative duration of REM*

  In the PSG Set, the majority of patients had a decrease, smaller in the agomelatine group than in the escitalopram group at D14 and D41 (see quartiles change from baseline in Table below) leading to a statistically significant difference in favour of agomelatine at each visit (complementary analysis at D14: E = 5.20% of SPT with a corresponding 95% CI of [2.80; 7.50% of SPT], p < 0.0001 ; at D41: E = 2.30% of SPT with a corresponding 95% CI of [0.10 ; 4.80% of SPT], p = 0.049).

  Over the D0-W24 period, similar results (descriptive analysis) were observed in the Sub-FAS in extension period.

Change from baseline in relative duration of REM (% of SPT) to D14 and D41 over the D0-D42 period in the PSG Set

		Agomelatine (N = 62)	**Escitalopram (N = 53)**
Baseline	n	62	53
	Median	20.85	19.80
	Q1 ; Q3	17.40 ; 25.10	15.90 ; 24.00
Change from baseline to D14	n	61	53
	Median	-2.10	-6.00
	Q1; Q3	-5.20 ; 2.30	-11.30 ; -2.70
Change from baseline to D41	n	58	48
	Median	-1.75	-3.60
	Q1; Q3	-5.00 ; 3.00	-7.55 ; 0.30

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

EFFICACY ON DAYTIME PERFORMANCE

- ***Psychomotor Vigilance Task (PVT)***

  In the FAS, the median of all PVT parameters remained stable between the baseline and the last post-baseline assessment over the D0-D42 period in both treatment groups as follows. This result indicated that no sedative effect have been observed in both treatment groups.

  - Mean reaction time
    - In the agomelatine group: from 270.9 ms (Q1 ; Q3 = 248.3 ; 307.7 ms) to 271.2 ms (Q1 ; Q3 = 245.1 ; 299.5 ms) ; median change of - 1.1 ms (Q1 ; Q3 = -17.6 ; 20.7 ms).
    - In the escitalopram group: from 281.1 ms (Q1 ; Q3 = 257.5 ; 315.5 ms) to 271.2 ms (Q1 ; Q3 = 246.6 ; 302.8 ms) ; median change of -9.0 ms (Q1 ; Q3 = -33.5 ; 9.3 ms).
  - SD reaction time
    - In the agomelatine group: from 54.7 ms (Q1 ; Q3 = 45.5 ; 85.6 ms) to 59.2 ms (Q1 ; Q3 = 44.2 ; 78.5 ms) ; median change of -0.4 ms (Q1 ; Q3 = -12.7 ; 17.4 ms).
    - In the escitalopram group: from 67.1 ms (Q1 ; Q3 = 51.2 ; 104.9 ms) to 59.2 ms (Q1 ; Q3 = 42.9 ; 92.3 ms) ; median change of -8.5 ms (Q1 ; Q3 = -32.8 ; 12.0 ms).
  - Number of lapses
    - In the agomelatine group: from 0.0 (Q1 ; Q3 = 0.0 ; 2.0) to 1.0 (Q1 ; Q3 = 0.0 ; 2.0) ; median change of 0.0 (Q1 ; Q3 = 0.0 ; 2.0).
    - In the escitalopram group: from 1.0 (Q1 ; Q3 = 0.0 ; 3.0) to 1.0 (Q1 ; Q3 = 0.0 ; 3.0) ; median change of 0.0 (Q1 ; Q3 = -2.0 ; 1.0).

  Over the D0-W24 period, similar results were observed in the Sub-FAS in extension period.

EFFICACY ON DEPRESSION

- ***HAM-D***

  In the FAS, the mean HAM-D total score decreased between the baseline and the last post-baseline assessment over the D0-D42 period in both treatment groups with a greater decrease on agomelatine (-14.6 ± 6.1) than on escitalopram (-13.3 ± 7.0). As per the pre-defined non-inferiority margin fixed at -1.5, agomelatine was statistically significantly non-inferior to escitalopram (p = 0.002, see Table below).

  In the FAS, over the D0-W24 period, the mean decrease from baseline in HAM-D total score at the last post-baseline assessment was -16.9 ± 7.9 on agomelatine and -16.1 ± 7.9 on escitalopram.

Between-group difference in HAM-D total score over the D0-D42 period in the FAS

		Agomelatine (N = 68)	**Escitalopram (N = 61)**
	n	68	61
D0	Mean ± SD	26.1 ± 2.3	26.0 ± 2.9
Last post-baseline value	Mean ± SD	11.4 ± 5.9	12.7 ± 6.7
Change from baseline to last post-baseline value	Mean ± SD	-14.6 ± 6.1	-13.3 ± 7.0
Statistical analysis			
Change from baseline to last post-baseline value	E (SE) (1)	1.461 (1.031)	
	95% CI (2)	[-0.582 ; 3.504]	
	p-value (3)	0.0024	

General linear model with centre as random effect and with baseline (D0) as covariate.
(1) Estimate (Standard Error) of the difference between adjusted treatment group means: Escitalopram minus Agomelatine
Pre-defined non-inferiority margin fixed at -1.5
(2) Two-sided 95% Confidence Interval of the estimate
(3) Non-inferiority test: one-sided p-value to be compared to 0.025

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

EFFICACY ON DEPRESSION (CONT'D)

In the FAS, the HAM-D response to treatment (decrease from baseline ≥ 50%) over the D0-D42 period was higher on agomelatine (64.7%) than on escitalopram (59.0%) at last post-baseline assessment.
In the FAS over the D0-W24 period, similar results were observed (76.5% on agomelatine versus 73.8% on escitalopram).

- ***CGI***
  In the FAS, the mean CGI global improvement and severity of illness scores decreased along time in both treatment groups. There were no relevant differences between groups at the last (post-baseline) assessment for both scores as follows:
  - *CGI global improvement score*: from 2.9 ± 0.9 and 2.8 ± 0.9 at D15 in the agomelatine and escitalopram groups, respectively to 1.9 ± 0.8 and 2.1 ± 1.2, respectively; E (SE) = -0.2 (0.2) and 95% CI [-0.5 ; 0.2].
  - *CGI severity of illness score*: from 4.7 ± 0.6 and 4.7 ± 0.7 at baseline in the agomelatine and escitalopram groups, respectively to 2.8 ± 1.2 and 2.9 ± 1.1, respectively.

For both criteria, similar results were observed in the FAS over the D0-W24 period.

SAFETY RESULTS

- **Emergent adverse events**

Overall summary of emergent adverse events

		Agomelatine 25-50 mg (N = 71)	**Escitalopram 10-20 mg (N = 66)**
D0-D42/Wend			
at least one EAE	n (%)	36 (50.7)	42 (63.6)
at least one treatment-related EAE	n (%)	17 (23.9)	33 (50.0)
D0-W24/Wend			
at least one EAE	n (%)	47 (66.2)	54 (81.8)
at least one treatment-related EAE	n (%)	18 (25.4)	37 (56.1)
During the study			
at least one serious AE	n (%)	1 (1.4)	3 (4.5)
at least one serious EAE	n (%)	1 (1.4)	1 (1.5)
at least one treatment-related serious EAE	n (%)	-	-
Treatment discontinuation due to serious EAE	n (%)	-	1 (1.5)
Treatment discontinuation due to non serious EAE	n (%)	3 (4.2)	5 (7.6)
Patients who died of EAE	n (%)	-	-

AE: adverse event; EAE: emergent adverse event; n: number of patients concerned

During the D0-D42/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 (50.7% *versus* 63.6%).
The most frequently affected system organ classes (in more than 10% of patients) in the agomelatine group were gastrointestinal disorders (19.7% of patients) similarly reported in the escitalopram group (22.7%), nervous system disorders (15.5%), and infections and infestations (12.7%), both more frequently reported in the escitalopram group (31.8% and 16.7%, respectively).
The most frequent emergent adverse events (reported at least once in 5% of patients) in the agomelatine group were headache and nausea (9.9% each), then diarrhoea and nasopharyngitis (5.6% each). Compared to escitalopram, the incidences were lower in the agomelatine group for headache (9.9% *versus* 16.7%), and nausea (9.9% *versus* 15.2%), higher for diarrhoea (5.6% *versus* 3.0%), and similar for nasopharyngitis (5.6% and 6.1%).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

In the escitalopram group, in addition to the adverse events described above, the other most frequent emergent adverse events (at least 5% of patients) were fatigue, hyperhidrosis and somnolence (6.1% each), all less frequent in the agomelatine group (1.4%, 1.4% and none, respectively).

Most emergent adverse events resolved without difference between groups (56/64 events, 87.5% and 90/95 events, 94.7% 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 (23.9%) than in the escitalopram group (50.0%). The system organ classes most commonly affected were the same in both treatment groups with lower percentages in the agomelatine group: nervous system disorders (8.5% *versus* 27.3%), and gastrointestinal disorders (11.3% *versus* 21.2%).

During the D0-W24/Wend period in the Safety Set, as during the D0-D42/Wend period, the percentage of patients with at least one emergent adverse event was lower in the agomelatine group (66.2%) than in the escitalopram group (81.8%). Results obtained over D0-W24/Wend were in the same line as those over D0-D42/Wend.

No death was reported during the study. The incidence of non fatal emergent serious adverse event was similar in both treatment groups: 1 patient, 1.4% (gastritis) in the agomelatine group, and 1 patient, 1.5% (pneumonia) in the escitalopram group. None of these serious adverse events were considered as related to the study treatment by the investigator.

During the study, 3 patients (4.2%) in the agomelatine group, and 5 patients (7.6%) in the escitalopram group had treatment withdrawal due to non serious emergent adverse events. The treatment discontinuation occurred during the D0-D42 period in all patients but one in the agomelatine group. In both treatment groups, treatment withdrawals were mainly due to psychiatric disorders (2/3 patients in the agomelatine group, and 3/5 patients in the escitalopram group).

- **Laboratory parameters**
  - In the Safety Set, mean biochemical and haematological parameters did not show any relevant change throughout the study in both treatment groups. For biochemical parameters, emergent PCSA values were reported for triglycerides only (2 patients, 2.8%, in the agomelatine group and 4 patients, 6.1%, in the escitalopram group). For haematological parameters, emergent PCSA values were reported for one low haematocrit in the escitalopram group.
  - Liver acceptability
    In the Safety Set, during the D0-W24/Wend period, emergent PCSA values were related to GGT only. Two patients, *i.e.* 2.9%, in the agomelatine group had isolated emergent PSCA GGT. In one patient, the emergent value was reported as adverse event and considered as related to patient 's medical history by the investigator. In both patients, GGT was still abnormal without reaching PCSA limit at the last test (on treatment).

- **Vital signs and BMI**

There were no relevant mean changes in supine blood pressures and heart rate as well as in weight between baseline and last post-baseline assessment over the ASS1-D42 and ASS1-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 treatment groups over both periods (85.7% in the agomelatine group and 90.8% in the escitalopram group over the ASS1-W24 period).

- **ECG**

In the Safety Set, one emergent ECG abnormality was reported as adverse event in the agomelatine group: one first degree atrioventricular block reported the day after the last study drug intake at W23, and considered as possibly related to the study treatment by the investigator. Patient recovered.

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CONCLUSION

This multicentre, double-blind, randomised study conducted in patients with MDD showed that effects of agomelatine 25-50 mg/d and escitalopram 10-20 mg/d on sleep parameters measured by polysomnography was in favour of agomelatine. As regards the primary criterion, after 2 weeks of treatment, the change from baseline in the sleep continuity (sleep efficiency index 1) was better on agomelatine than on escitalopram without reaching the statistical significance. Sleep latency shortened from week 2 on agomelatine as compared to baseline whereas it lengthened on escitalopram leading to a statistically significant difference in favour of agomelatine throughout the study. Most patients on escitalopram had an impairment of the sleep efficiency (sleep efficiency index 2) leading to a statistically significant difference in favour of agomelatine after 2 weeks of treatment and a statistical trend after 6 weeks. In addition, agomelatine preserved the number of sleep cycles whereas this parameter was altered on escitalopram as well as the REM sleep over the short- and long-term treatment. Furthermore, agomelatine but not escitalopram showed an improvement on patients' condition at awakening from the first evaluation to the end of the study (alerter and less confused). In the daytime, agomelatine-treated patients felt less sleepy at the beginning and at the end of the treatment than on escitalopram.
Anti-depressive effect of agomelatine on MDD after 6 weeks was confirmed, and a non-inferiority was demonstrated versus escitalopram (effect size of 1.46 on HAM-D, in favour of agomelatine).
Beneficial effects of agomelatine on depression were maintained over the long-term treatment (24 weeks).

Agomelatine 25-50 mg was well tolerated. No unexpected adverse event was reported. Moreover, agomelatine was better tolerated than escitalopram during short-term and long-term treatment, particularly for nervous system disorders. Liver acceptability was good.

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