Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy of agomelatine (25 to 50 mg/day) given orally on quality of remission in elderly depressed patients, after a 12-week treatment period. A randomised, double-blind, flexible-dose international multicentre study with parallel groups versus paroxetine (20 to 30 mg/day). Twelve-week treatment plus optional continuation for 12 weeks.**
Study drug	**Agomelatine (S 20098)**
Indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-048**
Study initiation date	**30 November 2005**
Study completion date	**21 January 2008**
Scientific Advisor	[redacted] **- France**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Laboratorios Servier, S.A.** **Avenida de los Madronos, 33** **28043 Madrid - Spain**
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 4 May 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 quality of remission in elderly depressed patients, after a 12-week treatment period. A randomised, double-blind, flexible-dose international multicentre study with parallel groups *versus* paroxetine (20 to 30 mg/day). Twelve-week treatment plus optional continuation for 12 weeks.
Protocol No.: CL3-20098-048

Coordinators:
Scientific advisor: [redacted], France)
National coordinators: [redacted], Australia), [redacted], Belgium), [redacted], Denmark), [redacted], France), [redacted] Hungary), [redacted], Italy), [redacted], Netherlands), [redacted], Norway), [redacted], Poland), [redacted] Portugal), [redacted], Spain).

Study centres:
In all, 65 centres located in 10 countries included at least one patient: Australia (4 centres – 29 included patients), Belgium (4 centres - 27 included patients), Denmark (6 centres - 80 included patients), France, added by Amendment No. 1 (18 centres - 108 included patients), Hungary (4 centres – 35 included patients), Italy (10 centres - 47 included patients), Norway (1 centre - 1 included patient), Poland (4 centres - 25 included patients), Portugal (4 centres - 17 included patients), Spain (10 centres – 43 included patients). In addition, centres in Netherlands did not select any patients.

Publication (reference): Not applicable

Studied period: Initiation date: 30 November 2005 Completion date: 21 January 2008	**Phase of development of the study:** III

Objectives: to assess the efficacy of agomelatine *versus* paroxetine on quality of the remission in elderly depressed out-patients remitted after a 12-week treatment period.
Primary objective: to show that the elderly patients with remitted depression after a 12-week agomelatine treatment period had a better subjective sleep quality than those remitted after a 12-week treatment period with paroxetine.
Secondary objective: to study agomelatine and paroxetine effect on daytime drowsiness, on residual symptoms, on quality of life and on emotional responsiveness in remitters, and to provide additional safety data in this population. The anti-depressant efficacy of agomelatine as compared to paroxetine was also assessed.

Methodology:
Multicentre, multinational, double-blind, randomised, comparative study in 2 parallel groups using a flexible dosage: agomelatine 25 mg/day and paroxetine 20 mg/day. These initial doses could be increased to 50 mg/day and 30 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), in a blinded condition manner for patients and investigators. At the end of the 12-week double-blind period, the patients could either continue in the optional double-blind extension period or stop the study according to investigator's and patient's decision.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 400 patients, 200 patients by group.
Included: 412 patients (213 patients in the agomelatine group, and 199 patients in the paroxetine group).

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Diagnosis and main criteria for inclusion:

Male or female out-patients, aged ≥ 60 years, fulfilling DSM-IV criteria for MDD of moderate or severe intensity.

The patients were included with a recurrent episode which lasted from at least 4 weeks, and for at more 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. At inclusion, the sum of items 1 + 2 + 5 + 6 + 7 + 8 + 10 + 13 of HAM-D 17-item had to be ≥ 55% of HAM-D 17-item total score, and the CGI severity of illness score was to be ≥ 4.

Study drug:

Agomelatine 25 mg tablets, 1 or 2 tablets once a day in 1 yellow capsule, p.o., around 8 p.m.

Patients received 25 mg/day (1 placebo red capsule in the morning + 1 agomelatine tablet in 1 yellow capsule in the evening) from W0, with possible increase in double-blind conditions to 50 mg/day (1 placebo red capsule + 2 agomelatine tablets in 1 yellow capsule) at W2, in case of insufficient improvement. Once adjusted, the dose was maintained throughout the study. Batch Nos. L0006198, L0007594, L0016042, L0006488, L0007685, L0016044.

Reference product:

Paroxetine: one half or one 20 mg tablet or one 30 mg tablet of paroxetine (10 mg, 20 mg or 30 mg) in one red capsule, p.o. daily in the morning with breakfast.

Patients received 20 mg/day (1 paroxetine tablet in red capsule in the morning + 1 placebo yellow capsule in the evening) from W0, with possible increase in double-blind conditions to 30 mg/day (1 paroxetine tablet in 1 red capsule + 1 placebo yellow capsule) at W2, in case of insufficient improvement. Between W22 and W24, a 2-week tapering period (10 mg for patients receiving 20 mg, and 20 mg then 10 mg for patients receiving 30 mg) was used to avoid emergence of discontinuation syndrome. For patients stopping the study at W12 or having discontinued prematurely the study after W2, the 2-week tapering was recommended, according to the investigator's opinion and reasons of withdrawal.

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 optional extension double-blind treatment period (from W12 to W24).
- 2-week follow-up period (at maximum) at the end of the mandatory double blind period or at the end of the optional double blind period, or in case of premature withdrawal. For patients stopping the study at W12 or discontinuing prematurely the study, the 2-week tapering was recommended, according to the investigator's opinion and reasons for withdrawal and was between W12 or withdrawal visit and follow-up visit.

Criteria for evaluation:

EFFICACY MEASUREMENTS:

SLEEP:

Self-rating questionnaires:

- Leeds sleep evaluation questionnaire (LSEQ) completed at each visit from W2 to W22 visits, or in case of premature withdrawal. The main efficacy criterion was the LSEQ quality of sleep score.
- Visual analogue scales (VAS) daytime sleepiness completed at inclusion, W2, W12, and W22 visits, or in case of premature withdrawal.
- Epworth Sleepiness Scale (ESS) completed at inclusion, W6, W12 and W22 visits, or in case of premature withdrawal.

Assessment by the investigator:

- Sleep disturbances 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).

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Criteria for evaluation (Cont'd):

EFFICACY MEASUREMENTS (Cont'd):

DEPRESSION: All the scales were rated by the investigator.

- HAM-D 17-item rated at each visit from selection to W24 visits, or in case of premature withdrawal.
- Clinical Global Impression (CGI) severity of illness score and global improvement score rated at each visit from W0 or W2 to W24 visits, respectively, or in case of premature withdrawal.

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, and at the follow-up visit in case of premature withdrawal.
- Vital signs: Blood pressure and heart rate (sitting position after 5 min rest), and weight were measured at selection, inclusion, W12 and W24 visits, or in case of premature withdrawal.
- 12-lead electrocardiogram (ECG): results available at inclusion and W24 visit, and at the follow-up visit in case of premature withdrawal or for patients not entering the extension period.

OTHER MEASUREMENTS:

All the rating instruments were self-rating questionnaires.

- Quality of Life Enjoyment and Satisfaction Questionnaire, Short-form (Q-LES-Q) completed at W0, W6, W12, and W22 visits, or in case of premature withdrawal.
- Positive and Negative Emotionality Questionnaire – 24 items (PNE) completed at W0, W12, and W22 visits, or in case of premature withdrawal in 4 countries (Australia, Italy, Spain, and France which was added by Amendment No. 1).

Statistical methods:

EFFICACY ANALYSES

The main analysis set was the Remitted Set. It was defined as all included and randomised patients having taken at least one dose of study medication, remitted at W12 and having a value for the primary criterion at W12. The patients were considered as remitted at W12 if they were responders at W10 (decrease in HAM-D total score of at least 50% from baseline), and in remission at W12 (HAM-D total score ≤ 10).

Primary criterion

Main analysis

Comparison of the LSEQ quality of sleep score at W12 between the agomelatine group and paroxetine group in the Remitted Set using a two-way analysis of variance on factors treatment and centre (random effect) without interaction. A two-sided Student's t test for independent samples was performed as sensitivity analysis.

Secondary analyses

Descriptive statistics of the LSEQ quality of sleep score at each visit and at last value over the W0-W12, and W0-W22 periods in the Remitted Set and FAS.

Secondary criteria

In addition to descriptive statistics by treatment group on W0-W12 and W0-W22 in the Remitted Set and FAS for all criteria, and also for criteria relative to depression on W0-W24, the following analyses were performed:

- LSEQ getting off to sleep score: same analysis as the primary criterion
- HAM-D total score: the between-group difference was assessed on the change from baseline at W12 in the Remitted Set, and to last post-baseline value over the W0-W12 period in the FAS using a 95% confidence interval, based on a two-way analysis of covariance with factors treatment and centre (random effect) and baseline as covariate (and with no interaction).

SAFETY ANALYSES

Descriptive analyses were performed by treatment group and dose subgroup in the Safety Set over the W0-W12 and W0-W24 periods.

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SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

	Agomelatine	**Paroxetine**	**All**
W0-W12			
Included (randomised)	**213**	**199**	**412**
Lost to Follow-up	-	-	-
Withdrawn due to	**52 (24.4%)**	**50 (25.1%)**	**102 (24.8%)**
Adverse event	16 (7.5%)	22 (11.1%)	38 (9.2%)
Lack of efficacy	15 (7.0%)	15 (7.5%)	30 (7.3%)
Non-medical reason	12 (5.6%)	7 (3.5%)	19 (4.6%)
Protocol deviation	6 (2.8%)	5 (2.5%)	11 (2.7%)
Remission or marked improvement	3 (1.4%)	1 (0.5%)	4 (1.0%)
Completed the W0-W12 period	**161 (75.6%)**	**149 (74.9%)**	**310 (75.2%)**
Performed the follow-up visit	14 (6.6%)	14 (7.0%)	28 (6.8%)
Entered the W12-W24 extension period	**146 (68.5%)**	**135 (67.8%)**	**281 (68.2%)**
W12-W24			
Lost to Follow-up	-	-	-
Withdrawn due to	**16 (7.5%)**	**4 (2.0%)**	**20 (4.9%)**
Non-medical reason	7 (3.3%)	1 (0.5%)	8 (1.9%)
Protocol deviation	5 (2.3%)	-	5 (1.2%)
Lack of efficacy	1 (0.5%)	3 (1.5%)	4 (1.0%)
Adverse event	3 (1.4%)	-	3 (0.7%)
Completed the W12-W24 period	**130 (61.0%)**	**131 (65.8%)**	**261 (63.4%)**
Performed the follow-up visit	121 (56.8%)	123 (61.8%)	244 (59.2%)
Analysis sets			
Randomised Set	213 (100%)	199 (100%)	412 (100%)
Full Analysis Set (FAS)	209 (98.1%)	194 (97.5%)	403 (97.8%)
Remitted Set	83 (39.0%)	91 (45.7%)	174 (42.2%)
Safety Set	212 (99.5%)	197 (99.0%)	409 (99.3%)

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

Overall, 412 patients were randomised to the agomelatine group (213 patients) or the paroxetine group (199 patients). At W2, 140 patients had a dose increase: 81/197 patients received agomelatine 50 mg (41.1%) and 59/174 patients received paroxetine 30 mg (33.9%). Over the W0-W12 period, the rate of withdrawal was similar in the agomelatine and paroxetine groups (24.4% and 25.1%, respectively). In both groups, the main reasons for withdrawals were adverse events with a lower frequency in the agomelatine group (7.5% in the agomelatine group *versus* 11.1% in the paroxetine group) and lack of efficacy, equally distributed between groups (7.0% in the agomelatine group and 7.5% in the paroxetine group).

The percentage of randomised patients who entered the W12-W24 extension double-blind period showed no relevant difference between groups (68.5%, 146 patients in the agomelatine group and 67.8%, 135 patients in the paroxetine group). Over the W12-W24 extension period, the rate of withdrawals was low in both groups with a higher rate in the agomelatine group (7.5%, 16 patients) than in the paroxetine group (2.0%, 4 patients) mainly due to withdrawals for non-medical reasons (3.3%, 7 patients in the agomelatine group *versus* 0.5%, 1 patient in the paroxetine group), and protocol deviations (2.3%, 5 patients in the agomelatine group *versus* none in the paroxetine group). In the agomelatine group, 3 patients (1.4%) withdrew for adverse events *versus* none in the paroxetine group. Finally, 61.0% of randomised patients in the agomelatine group and 65.8% in the paroxetine group completed the study at W24. As regards dose subgroups, the percentage of completers showed no relevant difference: 85/132 patients (64.4%) in the agomelatine 25 mg subgroup, 45/81 patients (55.6%) in the agomelatine 25-50 mg subgroup, 93/140 patients (66.4%) in the paroxetine 20 mg subgroup, and 38/59 patients (64.4%) in the 20-30 mg paroxetine group.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Randomised patients were 68.5 ± 6.2 years old on average, and 70.1% of the patients were at least 65 years old. Most of these patients were female (73.1%). All patients had a recurrent MDD according to the DSM-IV-TR criteria, mostly moderate DSM-IV severity (83.5% of the patients). In all, 16.5% of patients had a severe intensity without psychotic feature. Melancholic features were reported in 282 patients (68.4%). There were no clinically relevant differences between groups for these characteristics. The number of depressive episodes including the current one ranged from 2 to 40 with a mean ± SD of 4.1 ± 3.3 episodes. The current MDE lasted on average for 2.7 ± 1.2 months. At inclusion, the percentage of patients who received at least one psycholeptic or psychoanaleptic treatment was lower in the agomelatine group (20.7%) than in the paroxetine group (25.1%), and the patients received mainly benzodiazepine derivatives (19.2% in the agomelatine group and 23.6% in the paroxetine group).

Considering sleep and depression efficacy criteria in the Randomised Set, no relevant between-group difference was observed at inclusion. In all, the mean HAM-D sleep sub-score was 4.8 ± 1.2, the mean HAM-D total score was 26.3 ± 2.5, with 73.5% of the patients having a HAM-D total score of at least 25, and the mean CGI severity of illness score was 4.6 ± 0.6, corresponding to "moderately to markedly ill" patients on average.

Regarding Q-LES-Q general activities score, the mean before inclusion was 36.0 ± 13.0. Overall life satisfaction was most frequently very poor or poor (80.3% patients). As regards PNE questionnaires, the mean negative emotion score over the last week before inclusion was 58.9 ± 18.9, and the mean positive emotion score was 27.1 ± 18.1. All these parameters did not show any relevant between-group differences.

Baseline characteristics in the Remitted Set were similar to those observed in the Randomised Set but the proportion of female patients, which was not different between groups in the Randomised Set (71.4% in the agomelatine group and 74.9% in the paroxetine group), was lower in the agomelatine group than in the paroxetine group in the Remitted Set: 69.9% and 80.2%, respectively.

In the Randomised Set, treatment duration was similar in both groups with a mean duration of treatment over W0-W12 of 73.0 ± 26.6 days and a median of 85.0 days, and of 127.8 ± 60.6 days and a median of 168.0 days over W0-W24.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY ON SLEEP AND DAY-TIME SLEEPINESS

- **Primary criterion: LSEQ quality of sleep score (see Table below)**

Over the W0-W12 period, in the Remitted Set, there was an improvement of the quality of sleep showed by the progressive decrease in the mean score up to W12 in both treatment groups. At W12, there was no statistically significant between-group difference after adjustment for centre (main analysis, p = 0.613), and without adjustment (sensitivity analysis, p = 0.875).

LSEQ quality of sleep score (mm) at W12, and comparison between the agomelatine and paroxetine groups in the Remitted Set

		Agomelatine (N = 83)	Paroxetine (N = 91)
W12	n	83	91
	Mean ± SD	23.7 ± 16.6	23.3 ± 20.6
Main analysis	E (SE) (1)	-1.33 (2.62)	
	95% CI (2)	[-6.50 ; 3.85]	
	p-value (3)	0.613	
Sensitivity analysis	E (SE) (4)	-0.44 (2.86)	
	95% CI (2)	[-6.08 ; 5.19]	
	p-value (5)	0.875	

(1) Estimate (Standard Error) of the difference between adjusted treatment group means: paroxetine minus agomelatine
(2) 95% Confidence interval of the estimate
(3) Centre adjusted treatment effect: General linear model with centre as random effect
(4) Estimate (Standard Error) of the difference between treatment group means: paroxetine minus agomelatine
(5) Treatment effect: Two-sided Student's T-test for independent samples

Over the W0-W22 period in the Remitted Set, the mean LSEQ quality of sleep score at last assessment was 21.8 ± 16.0 mm in the agomelatine group, and 17.6 ± 12.4 mm in the paroxetine group.

- **Secondary criteria**

Over the W0-W12 period

- LSEQ getting off to sleep score, sleep awakening score, and integrity of behaviour score

Over the W0-W12 period, in the Remitted Set, the 3 mean scores progressively decreased up to W12 in both treatment groups. At W12, there was no statistically significant difference in the mean LSEQ getting off to sleep score between the agomelatine and paroxetine groups (p = 0.833 after adjustment for centre).

The other 2 mean LSEQ scores (sleep awakening, and integrity of behaviour) showed no relevant differences between groups at last assessment (sleep awakening score: 28.0 ± 18.1 mm in the agomelatine group, and 30.1 ± 21.2 mm in the paroxetine group, and integrity of behaviour score: 26.6 ± 15.8 mm in the agomelatine group, and 26.0 ± 14.9 mm in the paroxetine group).

All LSEQ results in the FAS were in the same line as in the Remitted Set. Considering that the patients in the FAS were not all remitters, results were less marked than in the Remitted Set in both groups.

- ESS

In the Remitted Set, the ESS total score showed an improvement of patients' vigilance over the W0-W12 in both treatment groups (mean decrease of -3.1 ± 4.2 in the agomelatine, and -2.8 ± 4.3 in the paroxetine group between W0 and last post-baseline value).

In the FAS, the mean decrease was larger in the agomelatine group than in the paroxetine group at last post-baseline assessment of both periods (-2.2 ± 4.1 in the agomelatine group *versus* -1.7 ± 4.4 in the paroxetine group over the W0-W12 period).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY ON SLEEP AND DAY-TIME SLEEPINESS (Cont'd)

- VAS daytime sleepiness

In the Remitted Set, the mean daytime sleepiness score decreased over the W0-W12 in both treatment groups, with no relevant difference between groups at the last post-baseline assessment (-22.2 ± 30.3 mm in the agomelatine group, and -20.5 ± 35.3 mm in the paroxetine group).

The mean feeling good score increased over the W0-W12 in both treatment groups. At the last post-baseline assessment, the mean increase was smaller in the agomelatine group (33.7 ± 34.2 mm) than in the paroxetine group (45.8 ± 34.9 mm).

- HAM-D sleep subscore

In the Remitted Set, the mean HAM-D sleep subscore decreased over the W0-W12 in both treatment groups, with no relevant difference between groups at the last post-baseline assessment (-4.1 ± 1.3 in the agomelatine group, and -4.0 ± 1.5 in the paroxetine group).

Over the W0-W22 period

For all sleep criteria, an improvement was observed all along the W0-W22 period in the Remitted Set and FAS. As during the W0-W12 period, results in the FAS were less marked than in the Remitted Set in both groups.

EFFICACY ON DEPRESSION

Over the W0-W12 period

- HAM-D

In the FAS, the mean HAM-D total score decreased over the W0-W12 period in both treatment groups, with no relevant difference between treatment groups, at the last post-baseline assessment (-14.0 ± 8.4 in the agomelatine group, -14.5 ± 8.3 in the paroxetine group, E (SE) = -0.55 (0.76), 95% CI = [-2.04 ; 0.94]).

In the Remitted Set, at W12, the mean decrease from baseline showed similar effect of both treatments (-21.1 ± 3.6 in the agomelatine, -21.0 ± 4.1 in the paroxetine group, E (SE) = 0.14 (0.42), 95% CI = [-0.69 ; 0.96]). As expected, the treatment effect was more marked in the Remitted Set than in the FAS in both groups.

In both patient sets, the percentage of responders and the percentage of remitters showed no relevant difference between the agomelatine and paroxetine groups at the last post-baseline assessment or at W12. In the FAS, 60.8% of patients in each treatment group were responders at the last post-baseline assessment over the W0-W12 period, and 46.9% in the agomelatine group and 52.1% in the paroxetine group were remitters.

A HAM-D residual symptom was defined as an item with a score > 1. In the Remitted Set, 6 symptoms were not residual at W12 in the agomelatine group (feeling of guilt, suicide, insomnia early hours of the morning, retardation, somatic symptoms gastro-intestinal, and insight). Among these symptoms, 3 were residual in the paroxetine group (insomnia early hours of the morning, 3.3% of patients, and retardation, and insight, 1.1% each). The other 11 symptoms were residual at W12 in both groups. There was a relevant difference in favour of agomelatine for 3 symptoms, particularly for genital symptoms (13.3% of patients in the agomelatine group *versus* 24.2% in the paroxetine group).

- CGI

In the FAS, the mean CGI severity of illness score decreased from baseline to the last post-baseline value over the W0-W12 period in both treatment groups. At the last post-baseline assessment, there were no relevant differences between groups (from 4.6 ± 0.6 in each treatment group at baseline to 2.7 ± 1.3 and 2.6 ± 1.3 in the agomelatine and paroxetine groups, respectively).

The mean CGI global improvement score decreased up to the last value over the W0-W12 period in both treatment groups. At the last assessment, there were no relevant differences between groups (2.2 ± 1.3 and 2.1 ± 1.2 in the agomelatine and paroxetine groups, respectively).

In the Remitted Set, as expected, the mean CGI severity of illness score and global improvement score were lower than in the FAS at the last assessment.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY ON DEPRESSION (Cont'd)

Over the W0-W22 or W24 periods

For all depression criteria, a mean score decrease was observed all along the W0-W22 or W24 periods in the FAS in both treatment groups without relevant differences between them. Results in the Remitted Set were in the same line as in the FAS.

QUALITY OF LIFE

Q-LES-Q

In the Remitted Set, the mean Q-LES-Q general activities score increased over the W0-W12 period in both treatment groups. At last post-baseline assessment, the mean increase from baseline showed no relevant difference between groups (29.5 ± 16.0 in the agomelatine group, and 30.8 ± 17.5 in the paroxetine group).

At last post-baseline assessment, the percentage of patients with a good or very good overall life satisfaction score showed no relevant difference between groups (74.7% in the agomelatine group, and 78.0% in the paroxetine group).

At last assessment over the W0-W12 period, the percentage of patients with a good or very good satisfaction with medication score showed no relevant difference between groups (79.3% in the agomelatine group, and 73.6% in the paroxetine group).

Over the W0-W22 period, the mean increases in the 3 Q-LES-Q scores were similar to those reported over the W0-W12 period.

For the 3 Q-LES-Q scores, the results in the FAS were similar to those in the Remitted Set apart from the percentage of patients with a good or very good overall life satisfaction score at last post-baseline assessment over the W0-W12 period in the FAS which was lower in the agomelatine than in the paroxetine group (47.2% *versus* 53.8%). However, results in the FAS were less marked than in the Remitted Set in both groups.

EMOTIONAL RESPONSIVENESS

PNE questionaire

In the Remitted Set, there was an improvement in the emotional responsiveness: the mean positive emotion score increased over the W0-W12 period in both treatment groups, and the mean negative emotion score decreased. At last post-baseline assessment, the mean increase from baseline in the positive emotion score was lower in the agomelatine group than in the paroxetine group (25.8 ± 21.8 (n = 36) *versus* 31.2 ± 19.7 (n = 37)).

The mean decrease from baseline in the negative emotion score showed no relevant difference between groups (-38.3 ± 23.5 (n = 31) and -40.5 ± 22.9 (n = 39). Similar results were observed over the W0-W22 period.

Similar results were observed in the FAS. However, mean changes were less marked than in the Remitted Set in both groups.

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SAFETY RESULTS

Main safety results

		Agomelatine 25 mg (N = 131)	***Agomelatine 25 - 50 mg (N = 81)***	**Agomelatine All (N = 212)**	***Paroxetine 20 mg (N = 138)***	***Paroxetine 20 - 30 mg (N = 59)***	**Paroxetine All (N = 197)**
W0-W12/Wend							
at least one EAE	n (%)	*54 (41.2)*	*34 (42.0)*	88 (41.5)	*69 (50.0)*	*30 (50.8)*	99 (50.3)
at least one treatment-related EAE	n (%)	*32 (24.4)*	*25 (30.9)*	57 (26.9)	*46 (33.3)*	*28 (47.5)*	74 (37.6)
W0-W24/Wend							
at least one EAE	n (%)	*68 (51.9)*	*39 (48.1)*	107 (50.5)	*75 (54.3)*	*33 (55.9)*	108 (54.8)
at least one treatment-related EAE	n (%)	*35 (26.7)*	*25 (30.9)*	60 (28.3)	*49 (35.5)*	*29 (49.2)*	78 (39.6)
During the study							
at least one serious AE (including death)	n (%)	*6 (4.6)*	*6 (7.4)*	12 (5.7)	*5 (3.6)*	-	5 (2.5)
at least one serious EAE (including death)	n (%)	*6 (4.6)*	*4 (4.9)*	10 (4.7)	*4 (2.9)*	-	4 (2.0)
at least one treatment-related serious EAE	n (%)	-	-	-	-	-	-
Treatment discontinuation due to EAE	n (%)	*11 (8.4)*	*7 (8.6)*	18 (8.5)	*16 (11.6)*	*6 (10.2)*	22 (11.2)
Patients who died of EAE[d]	n (%)	*1 (0.8)*[a]	*1 (1.2)*[b]	2 (0.9)	*1 (0.7)*[c]	-	1 (0.5)
Treatment-related death	n (%)	-	-	-	-	-	-

AE: adverse event ; EAE: emergent adverse event ; n: number of patients concerned
[a] Pulmonary embolism ; [b] Malignant neoplasm (neck tumor) ; [c] Colorectal cancer of stage IV ; [d] In addition, 1 patient died of a cerebrovascular accident about 8 weeks after the last intake of agomelatine 25-50 mg. None of these deaths was considered as not related to the study treatment by the investigator.

Over 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 (41.5%) than in the paroxetine group (50.3%). As regards dose subgroups, the incidence showed no relevant difference between both doses for each treatment.

The most frequently affected system organ classes were gastrointestinal disorders and nervous system disorders in both treatment groups with a lower percentage in the agomelatine group than in the paroxetine group for both types of disorders (17.9% *versus* 24.4% for gastrointestinal disorders, respectively, and 13.7% *versus* 18.3% for nervous system disorders). These system organ classes were similarly affected regarding agomelatine dose subgroups.

In the agomelatine group, the most frequent emergent adverse events (at least 3%) were headache, dizziness, nausea, and dry mouth with a lower incidence than in the paroxetine group for nausea (4.2% *versus* 7.1%, respectively), higher for dizziness (4.7% *versus* 3.6%), and similar to for headache (7.1% *versus* 7.6%) and dry mouth (3.8% *versus* 4.1%). As regards agomelatine dose subgroups, the most common emergent adverse event was headache on the agomelatine 25 mg dose (9.2% of patients), and dizziness (6.2%) on the agomelatine 25-50 mg dose, with a higher incidence than in the other agomelatine dose subgroup (headache 3.7% in the agomelatine 25-50 mg subgroup, and dizziness 3.8% in the agomelatine 25 mg subgroup).
In the paroxetine group, in addition to headache, nausea, dry mouth, and dizziness (see above), the other most frequent emergent adverse events (at least 3%) were diarrhoea (6.1%), somnolence (3.6%), and constipation (3.0%). All were less frequent in the agomelatine group than in the paroxetine group, mainly diarrhoea (0.5% *versus* 6.1%).

In the agomelatine group, patients mostly had emergent adverse events of mild (24.5%) or moderate (21.2%) intensity. Similar results were observed in the paroxetine group (26.4% and 29.4%, respectively). The percentage of patients who experienced at least one emergent adverse event rated as severe was lower in the agomelatine group (4.7%) than in the paroxetine group (7.6%). Regarding agomelatine doses, the frequency of severe emergent adverse events was higher with the low dose (5.3%) than with the high dose (3.7%) conversely to paroxetine (7.2% and 8.5% with the 20 and 20-30 mg doses, respectively).

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SAFETY RESULTS (Cont'd)

Most of these emergent adverse events recovered: 90.4% in the agomelatine group and 85.7% in the paroxetine group.

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 (26.9%) than in the paroxetine group (37.6%). This difference was found in the most frequently affected system organ classes: gastrointestinal disorders: 13.2% of patients in the agomelatine group *versus* 21.8%, in the paroxetine group (the difference being mainly attributable to nausea: 3.8% *versus* 7.1%, respectively, and diarrhoea: none *versus* 5.1%), nervous system disorders: 10.8% of patients in the agomelatine group *versus* 16.2% in the paroxetine group (mainly attributable to lower frequency in all adverse events reported in the agomelatine group as compared to the paroxetine group, except dizziness: 3.8% *versus* 3.6%, respectively).

As regards dose subgroups, treatment-related emergent adverse events were less frequent in low dose subgroups than in high dose subgroups for both treatment: 24.4% and 30.9% in the agomelatine 25 mg and 25-50 mg subgroups, respectively, and 33.3% and 47.5% in the paroxetine 20 mg and 20-30 mg subgroups, respectively.

Over the **W0-W24/Wend period**, in the Safety Set, patients were affected by emergent adverse events with a higher frequency than over W0-W12: 50.5% in the agomelatine group *versus* 54.8% in the paroxetine group, respectively. Results obtained over W0-W24 were in the same line as those over W0-W12.

Over the W0-W24 period, **3 patients died** of emergent serious adverse event: one patient of pulmonary embolism and one patient of malignant neoplasm in the agomelatine group, and one patient of colorectal cancer in the paroxetine group. In addition, 1 patient, who had a medical history of hypertension, and an abnormal neurological examination and vascular cerebral perfusion defects detected in the SPECT about one month after the last study drug intake, died of a cerebrovascular accident which occurred about 8 weeks after the last intake of agomelatine. None of these deaths was considered as related to the study treatment according to the investigator.

Emergent non-fatal serious adverse events during the treatment period were reported in 8 patients (3.8%) in the agomelatine group (female breast cancer, fall, gastric stapling and medical device complication in one patient, angina pectoris, acute myocardial infarction, depression, cystitis and ovarian cyst in one patient, coronary artery stenosis), and 3 patients (1.5%) in the paroxetine group (cystocele, fall, breast cancer in situ). None of them was considered as related to the study treatment by the investigator. Emergent non-fatal serious adverse events led to premature study treatment discontinuation in 3 patients (1.4%) in the agomelatine group (fall, acute myocardial infarction, and coronary artery stenosis), and 1 patient (0.5%) in the paroxetine group (breast cancer in situ).

In addition, 18 patients in the agomelatine group (8.5%) had at least one **emergent non-serious adverse event leading to premature study treatment discontinuation** with a lower frequency than in the paroxetine group (22 patients, 11.2%). As regards agomelatine doses, there was no relevant difference in the percentage of patients concerned.

Concerning **biochemical (other than liver parameters) or haematological parameters**, no relevant clinical differences over time nor between groups or dose subgroups were detected. In both treatment groups, emergent PCSA (potentially clinically significant abnormal) values during the W0-W24/Wend period were mainly detected for triglycerides with a lower frequency in the agomelatine group (4.7% *versus* 8.0% in the paroxetine group), and urea, similarly distributed in both groups (2.9% in the agomelatine group and 2.5% in the paroxetine group).

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SAFETY RESULTS (Cont'd)

Over the W0-W24/Wend period, the incidence of patients with at least one emergent liver parameter ≥ 3 ULN was 1.4% (3 patients) in the agomelatine group compared with 2.5% (5 patients) in the paroxetine group.

- In the agomelatine group, the 3 patients had emergent PCSA values for both ASAT and ALAT (including 1 patient who had an ALAT value exceeding 10 ULN associated with borderline high out-of-reference-range values for GGT (1.2 ULN) and alkaline phosphatases (1.1 ULN)). These PCSA values were reported as non-serious adverse events, recovered in 2 cases about 2 months after treatment discontinuation. The patient with ALAT exceeding 10 ULN was recovering at the end of the study, and post-study sampling performed 7 months after treatment discontinuation showed all liver parameters within the normal range.
- In the paroxetine group, 1 patient had one emergent PCSA ALAT (with abnormal ASAT and GGT). Four patients had emergent PCSA GGT, including a patient with GGT exceeding 10 ULN associated with abnormal transaminases and abnormal total and conjugated bilirubin. Among the other 3 patients with PCSA GGT, 2 also had abnormal transaminases. These PCSA values were reported as non-serious adverse events. Two patients recovered (including the patient with GGT > 10 ULN), 2 were recovering, and one did not recover at the end of the study due to alcohol intake according to the investigator.

None of these liver PCSA values were associated with clinical signs, except one patient in the paroxetine group with hepatic steatosis considered as related to medical history (GGT increased).

Vital signs did not show any clinically relevant changes over time nor between-group difference.

Among patients with no ECG abnormality at baseline, the percentage of patients with **emergent ECG abnormalities** was higher in the agomelatine group (8.2%) than in the paroxetine group (2.5%). They were mainly sinus bradycardia (4 in the agomelatine group *versus* none in the paroxetine), and BBB (1 complete right and 1 incomplete right BBB *versus* 1 incomplete left BBB, respectively). None of these ECG abnormalities were considered as clinically relevant by the investigator.

Among patients with at least one ECG abnormality at baseline, 10 patients in the agomelatine group and 7 patients in the paroxetine group presented at least one new ECG abnormality throughout the study. They were mainly sinus bradycardia (1 in each group), incomplete right BBB and 1st degree AV block (1 of each one in the agomelatine group *versus* none in the paroxetine group), repolarisation disturbance (1 in each group), left anterior hemiblock (none *versus* 1, respectively), and ischemia (none *versus* 1, respectively). All these abnormalities were considered as **not clinically relevant** by the investigator but 3 in the paroxetine group (ischaemia reported as adverse event, not considered as treatment-related, and not serious, and which resolved, prolonged QT interval reported as a possibly related adverse event, not serious, and which resolved, and left anterior hemiblock with no corresponding adverse event).

CONCLUSION

This multicentre, double-blind, randomised study conducted in elderly patients with MDD showed that after 12 weeks of treatment, the beneficial effect of agomelatine 25-50 mg/d on the quality of sleep self-assessed by LSEQ in remitted patients was not significantly different from the one observed on paroxetine 20-30 mg/d. Likewise, agomelatine improved all other sleep and vigilance scores assessed by LSEQ, ESS, and VAS in a similar way to paroxetine. Anti-depressive effect of agomelatine on MDD was confirmed, and showed no difference with paroxetine in the whole patients. Self-assessment of quality of life (Q-LES-Q) showed an improvement on agomelatine comparable to the one on paroxetine.
All beneficial effects of agomelatine were maintained over the long-term treatment.
In elderly patients, both doses of agomelatine were well tolerated. No unexpected adverse event was reported. Moreover, agomelatine was better tolerated than paroxetine, specifically for adverse events related to gastrointestinal and nervous system disorders.

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