Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of agomelatine oral administration (25 to 50 mg/day) in elderly patients suffering from Major Depressive Disorder.** **A 8-week, randomised, double-blind, flexible-dose, parallel groups, placebo-controlled, international, multicentre study followed by an extension double-blind treatment period of 16 weeks.**
Study drug	**Agomelatine (S 20098)**
Studied indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-070**
Study initiation date	**4 November 2009**
Study completion date	**7 October 2011**
Main coordinator	[redacted] **- United Kingdom**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50, rue Carnot** **92284 Suresnes Cedex - France** **Servier Research and Development** **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 21 March 2012**

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2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: Efficacy and safety of agomelatine oral administration (25 to 50 mg/day) in elderly patients suffering from Major Depressive Disorder.
A 8-week, randomised, double-blind, flexible-dose, parallel groups, placebo-controlled, international, multicentre study followed by an extension double-blind treatment period of 16 weeks.
Protocol No.: CL3-20098-070

International coordinator: [redacted] United Kingdom)
National coordinators: [redacted] Argentina), [redacted], Finland), [redacted], Mexico), [redacted], Portugal), [redacted], Romania).

Study centres: In all, 27 centres located in 5 countries included at least one patient: Argentina (5 centres, 23 included patients), Finland (7 centres, 104 included patients), Mexico (5 centres, 47 included patients), Portugal (4 centres, 18 included patients) and Romania (6 centres, 30 included patients).

Publication (reference): Not applicable

Studied period: Initiation date: 4 November 2009 Completion date: 7 October 2011	**Phase of development of the study: III**

Objectives: to assess the efficacy and safety of agomelatine compared to placebo in elderly out-patients suffering from Major Depressive Disorder.
Primary objective: to demonstrate the antidepressant efficacy of agomelatine oral administration (25 to 50 mg/day) compared to placebo using the Hamilton Depression Rating Scale (HAM-D-17), after 8 weeks of treatment in elderly out-patients suffering from Major Depressive Disorder.
Secondary objectives: to provide additional efficacy and safety data, to study effects of agomelatine on patient's functioning, to study the subgroup of patients aged 75 years old and older, to provide additional pharmacokinetic data of agomelatine and to evaluate the influence of genetic factors on efficacy and safety of agomelatine in a pharmacogenetic sub-study.

Methodology:
Phase III, international, multicentre, double-blind, placebo-controlled, randomised study with 2 parallel groups comparing a flexible dosage of agomelatine 25 mg/day, increased to 50 mg/day (in case of no improvement at W2) *versus* placebo after 8 weeks of treatments in elderly (aged ≥ 65) out-patients suffering from Major Depressive Disorder. The criteria for increasing the dose at W2 were defined by the Sponsor, based on clinical considerations, before the study beginning and kept blinded to the investigator and the patient. At W8, only patients considered as responders to treatment by investigators and with patient agreement could enter the 16-week extension double-blind treatment period with the same treatment. The other patients were considered as having completed the mandatory period. At W12 visit, only the patients having CGI item 2 ≤ 2 were allowed to continue in the extension period. The patients having CGI item 2 > 2 at W12 visit, had to be withdrawn from the study.
Randomisation was unbalanced with a 2 to 1 ratio, with stratification on the centre and on the age of patients ([65-75[/ ≥ 75). Treatment randomisation and allocation were centralised with an Interactive Response System (IRS).
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:

- Total planned: 210 patients: 140 in the agomelatine group (including at least 50 patients aged ≥ 75) and 70 patients in the placebo group (including at least 25 patients aged ≥ 75).
- Included: 222 patients: 151 in the agomelatine group (including 48 patients aged ≥ 75) and 71 patients in the placebo group (including 21 patients aged ≥ 75).

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Diagnosis and main criteria for inclusion:
Male or female out-patients, aged ≥ 65 years, fulfilling Diagnosis and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV TR) criteria for a moderate to severe episode of a recurrent Major Depressive Disorder, with a Hamilton Depression Rating Scale 17 items (HAM-D-17) total score ≥ 22, a CGI item 1 score ≥ 4, a Hospital Anxiety Depression (HAD) depression sub-score ≥ 11 and a Mini Mental State Examination (MMSE) score ≥ 27.

Study drug:
Agomelatine, 25 mg tablets,
Patients received 25 mg/day (1 tablet of 25 mg and one placebo tablet) at bedtime from W0 with possible increase to 50 mg/day in double-blind conditions (2 tablets of 25 mg) from W2, in case of insufficient improvement. Once adjusted (or not), the dose was maintained up to W8, or W24 if the patient entered the extension period.
Batch No. L0029925

Reference product:
Placebo, tablet, 2 tablets once a day at bedtime.

Duration of treatment:

- 3-to-7-day run-in period without treatment (from selection visit (ASSE) to W0).
- 8-week double-blind treatment period (from W0 to W8).
- 16-week extension double-blind treatment period (from W8 to W24).
- Follow-up period of 1 week maximum without treatment at the end of the 8-week double-blind period, or at the end of the extension double-blind period or in case of premature withdrawal.

Criteria for evaluation:
Efficacy measurements
On depression

- Hamilton Depression Rating Scale 17 items (HAM-D-17) was rated by the investigator at each visit from the selection visit to W24 or in case of premature withdrawal. The primary efficacy criterion was the HAM-D 17 items total score. The main analytical approach was the last post-baseline value on the W0-W8 period.
- Clinical Global Impression scale (CGI) was rated by the investigator at each visit from the selection and inclusion visits to W24 visit for item 1, and from W2 to W24 for item 2, or in case of premature withdrawal.
- Sheehan Disability Scale (SDS) was rated by the patient at selection, W2, W8 and W24, or in case of premature withdrawal.

Safety measurements

- Adverse events reported at each visit.
- Laboratory tests: results available at inclusion visit, W8, W16 and W24 (prescription at the previous visit) or at the follow-up visit (Wend) in case of premature withdrawal.
- Physical examinations:
  - Sitting systolic and diastolic blood pressure and heart rate were measured by the investigator at each visit from the selection to the W24 visit, or in case of premature withdrawal, and at the follow-up visit (Wend).
  - Body weight and Body Mass Index were assessed at selection visit, inclusion visit, W4, W8, W16 and W24, or in case of premature withdrawal.
- 12-lead ECG: results available at inclusion visit, W8 and W24 (prescription at the previous visit) or at the follow-up visit in case of premature withdrawal (prescription at the withdrawal visit).

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Criteria for evaluation (Cont'd)
Other measurement

- Saliva sampling for pharmacokinetic analysis: agomelatine concentration in saliva was measured 1h, 2h, 3h and 12h after the study drug intake of the day before W12 visit.
- Pharmacogenetic sub-study: data collected will be analysed subsequently through an analysis on a pool of agomelatine studies in which a pharmacogenetic sub-study was implemented. The results of the pharmacogenetic analysis will be presented in a separate report.

Statistical methods:
Efficacy analysis
Primary criterion

- Main analysis

The superiority of agomelatine as compared to placebo on depressive symptoms after an 8-week treatment period was assessed from the last post-baseline value until W8 of the HAM-D 17-item total score, in the Full Analysis Set (FAS), using a three-way analysis of covariance model on factor treatment with centre (random effect), class of age ([65-75[/ ≥ 75) (fixed effect) and baseline HAM-D total score as covariates and without interaction.

- Sensitivity analyses

To assess the robustness of the main analysis results, the following sensitivity analyses were performed in the FAS:

- A sensitivity analysis to the method of handling missing values: treatment groups were compared on the value at W8, using a mixed-effects for repeated measures model (MMRM) including terms for effects of treatment, class of age ([65-75[/ ≥ 75) as fixed effects, baseline HAM-D total score, centre as random effect, visit and an interaction term for treatment and visit.
- A sensitivity analysis to the adjustment for covariates, namely an unadjusted analysis using a two-sided Student's t-test for independent samples on the last post-baseline value until W8.

- Secondary analyses

Treatment groups were compared in a descriptive way in the FAS subset of patients ≥ 75 years.
The same analysis strategy as the main analysis was implemented on the W0-W8 period in the two subsets of more severely depressed patients of the FAS (defined as baseline HAM-D total score ≥ 25, and baseline HAM-D total score ≥ 25 and CGI-S ≥ 5).
Moreover, agomelatine was compared to placebo in term of response to treatment (decrease in HAM-D total score of at least 50% from baseline) taking into account the last post-baseline value until W8 using a Chi-square test in patients of the FAS and its subsets of more severely depressed patients.
In addition, descriptive statistics were provided for all analytical approaches of the primary criterion on the W0-W8 and W0-W24 periods in the FAS and its subsets**.**

Secondary criteria
For each analytical approach of secondary criteria, descriptive statistics were provided on the W0-W8 and W0-W24 periods in the FAS and its subsets.
In addition, for CGI scale, agomelatine was compared to placebo in the FAS on psychiatric conditions after an 8-week treatment period:

- From the CGI Severity of Illness and Global Improvement scores, using a two-sided Student's t-test for independent samples and a Mann-Whitney test on the last (post-baseline) value.
- From the response to treatment (global improvement score = 1 or 2), using a Chi-square test on the last value until W8.

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Statistical methods (Cont'd):

Safety analysis

Descriptive statistics were provided in the Safety Set and in the Sub-Safety Set aged ≥ 75 years by treatment group over the ASSE-W8/Wend and ASSE-W24/Wend periods for serious and emergent adverse events, laboratory parameters, physical examination, and ECG abnormalities. In addition, in the Safety Set, descriptive analysis by agomelatine dose subgroup was performed for serious and emergent adverse events.

Pharmacokinetic analysis

A population pharmacokinetic model was developed, pooling the whole PK information available at the time of the analysis. For the CL3-20098-070 study, [redacted]

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Status	Agomelatine	Placebo	All
W0-W8			
Included and randomised	**151**	**71**	**222**
Withdrawn due to	**26 (17.2)**	**21 (29.6)**	**47 (21.2)**
Adverse event	12 (8.0)	5 (7.0)	17 (7.7)
Lack of efficacy	9 (6.0)	7 (9.9)	16 (7.2)
Non-medical reason	4 (2.7)	9 (12.7)	13 (5.9)
Protocol deviation	1 (0.7)	-	1 (0.5)
Completed	**125 (82.8)**	**50 (70.4)**	**175 (78.8)**
Performed the follow-up visit	*39 (25.8)*	*29 (40.8)*	*68 (30.6)*
W8-W24			
Entered the W8-W24 extension period	**109 (72.2)**	**37 (52.1)**	**146 (65.8)**
Lost to follow up*	**1 (0.9)**	-	**1 (0.7)**
Withdrawn due to*	**20 (18.3)**	**9 (24.3)**	**29 (19.9)**
Adverse event	4 (3.7)	-	4 (2.7)
Lack of efficacy	13 (11.9)	5 (13.5)	18 (12.3)
Non-medical reason	3 (2.8)	2 (5.4)	5 (3.4)
Protocol deviation	-	1 (2.7)	1 (0.7)
Cure, remission or marked improvement	-	1 (2.7)	1 (0.7)
Completed the W8-W24 period*	**88 (80.7)**	**28 (75.7)**	**116 (79.5)**
Performed the follow-up visit	*91 (83.5)*	*22 (59.5)*	*113 (77.4)*
Analysis Sets			
Randomised Set	**151**	**71**	**222**
Full Analysis Set (FAS)	148 (98.0)	70 (98.6)	218 (98.2)
Sub-FAS aged ≥ 75 years	48 (31.8)	21 (29.6)	69 (31.1)
Sub-FAS with baseline HAM-D total score ≥ 25	120 (79.5)	53 (74.6)	173 (77.9)
Sub-FAS with baseline HAM-D total score ≥ 25 and CGI-S ≥ 5	97 (64.2)	41 (57.7)	138 (62.2)
Safety Set	**151 (100.0)**	**71 (100.0)**	**222 (100.0)**
Sub-Safety Set aged ≥ 75 years	48 (31.8)	21 (29.6)	69 (31.1)
Pharmacokinetic Set	**99 (65.6)**	-	**99 (44.6)**

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

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

A total of 271 patients were selected, and 222 patients were included and randomly assigned to one of the two treatment groups according to the IRS procedure: 151 patients in the agomelatine group and 71 patients in the placebo group. The distribution of treatment groups was unbalanced as required (ratio 2:1). As regards patients in the older age (≥ 75 years), unbalanced distribution of treatment groups was also respected (48 patients in the agomelatine group and 21 patients in the placebo group).
At W2, among the agomelatine-randomised patients continuing in the study, 21.2% (32 patients) had a dose increase.
During the study, 1 patient in the agomelatine 25-50 mg subgroup was lost to follow-up at W12.

The rate of withdrawals over the W0-W8 and W8-W24 periods, excluding this patient lost to follow-up, was lower in the agomelatine group than in the placebo group (17.2% and 18.3% in the agomelatine group *versus* 29.6% and 24.3% in the placebo group, respectively). This difference between the treatment groups was mainly due to the withdrawals related to a non-medical reason, and to lack of efficacy which were both less frequent in the agomelatine group than in the placebo group, particularly during the W0-W8 period (2.7% *versus* 12.7%, and 6.0% *versus* 9.9%, respectively).

The percentage of randomised patients who completed at W8 visit was 82.8% (125 patients) in the agomelatine group, and 70.4% (50 patients) in the placebo group. Finally, the percentage of randomised patients who completed the study at W24 was higher in the agomelatine group (58.3%) than in the placebo group (39.4%).
At selection, randomised patients were 71.8 ± 5.0 years old on average (± SD), ranging from 65 to 87 years. Among these patients, 31.1% (69 patients) were aged ≥ 75 years. Most patients were female (68.0%). According to the DSM-IV-TR criteria, all patients were diagnosed as recurrent MDD as required in the selection criteria. In all, 47.8% of patients had a moderate MDE, and 52.3% a severe MDE without psychotic features. MDE with melancholic features was observed in 66.7% of patients.

Mean number of depressive episodes was 3.4 ± 2.2 including the current one, ranging from 2 to 20. Mean duration of the current MDE was 5.7 ± 3.3 months (median 5.0 months). Previous psychotropic drug treatment taken within one year prior to selection was reported in 39.2% of patients, mainly SSRIs (15.8%).
At selection, the mean HAD depression sub-score was 14.7 ± 2.5. All patients had a depression score ≥ 11 as required in the selection criteria. The mean HAD anxiety sub-score was 11.0 ± 3.5. About half patients (113, 50.9%) had an anxiety sub-score ≥ 11 indicating that patients felt at least moderately anxious. Then, 34.2% of patients (76) had an anxiety sub-score between 8 and 10, and 14.0% (31 patients) had a sub-score between 0 and 7.
At selection, the mean Geriatric Depression Scale (GDS) total score was 11.3 ± 2.2 (ranging from 4 to 15) indicating that the patients felt depressed on average. All patients had a MMSE score ≥ 27 as required in the selection criteria. The mean MMSE total score was 29.2 ± 0.9 indicating that no patient had relevant cognitive impairment or dementia.
No clinically relevant differences between the treatment groups were observed for demographic and disease characteristics at baseline.

Regarding the severity of depression at inclusion, the mean HAM-D total score was 26.8 ± 2.9, and the mean CGI severity of illness score was 4.9 ± 0.7 corresponding to "markedly" ill patients.
According to SDS, on average, the patients felt markedly disrupted by symptoms for the 3 domains: work and activity (6.9 ± 1.9), social life (7.2 ± 1.7), and family life and home responsibilities (7.1 ± 1.8).
No clinically relevant differences between the treatment groups were observed for all efficacy criteria at baseline.

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Baseline characteristics in the FAS were similar to those observed in the Randomised Set. In the different FAS subsets, apart from the criteria defining the subsets and criteria related, baseline characteristics showed no relevant difference to those observed in the Randomised Set.

In the Randomised Set, mean treatment duration was 50.8 ± 13.7 days (median 56.0 days) over the W0-W8 period, and 115.2 ± 60.9 days (median 164.0 days) over the W0-W24 period with a mean treatment duration longer in the agomelatine group than in the placebo group over the W0-W24 period (123.1 ± 59.5, median 167 days *versus* 98.5 ± 61.0, median 84 days). Mean global compliance was 95.9 ± 12.5% over the W0-W8 period, and 95.5 ± 12.7% over the W0-W24 period. Global compliance to treatment showed no relevant differences between both treatment groups.

EFFICACY RESULTS

Results over the 8-week double-blind treatment period

Primary assessment criterion: HAM-D total score

- In the FAS

The mean HAM-D total score was statistically significantly lower in the agomelatine group than in the placebo group at the last post-baseline assessment over the W0-W8 period (main analysis, p = 0.013, see Table below). This result was confirmed:

- By the sensitivity analysis to the method of handling missing values at W8 (MMRM): E(SE) = 2.76 (1.02), 95% CI = [0.75 ; 4.78], p = 0.007.
- By the unadjusted sensitivity analysis at the last post-baseline assessment: E(SE) = 2.63 (1.10), 95% CI = [0.47 ; 4.79], p = 0.017.

The percentage of responders (decrease in HAM-D total score of at least 50% from baseline) was statistically significantly higher in the agomelatine group (59.5%) than in the placebo group (38.6%) at the last post-baseline assessment (p = 0.004, see Table below) with a difference of 21% in favour of agomelatine.

Summary of statistical results of HAM-D total score at last post-baseline assessment over the W0-W8 period in the FAS

		Agomelatine (N = 148)	Placebo (N = 70)
Total score			
Last post-baseline value	Mean ± SD	13.4 ± 7.5	16.1 ± 7.6
Statistical analysis (a)		***Main analysis***	
	E (SE) [(1)]	2.67 (1.06)	
	95% CI [(2)]	[0.57 ; 4.76]	
	p-value[(3)]	**0.013**	
Response to treatment			
Last post-baseline value	Yes n (%)	88 (59.46)	27 (38.57)
Statistical analysis (b)			
	E (SE) [(4)]	-20.89 (7.08)	
	95% CI [(2)]	[-34.77 ; -7.01]	
	p-value[(3)]	**0.004**	

(a) Analysis of covariance model on factor treatment with baseline HAM-D total score, class of age ([65-75[; ≥ 75) (fixed effect) and centre (random effect) as covariates; (b) Chi-Square test; (1) Estimate (Standard Error) of the difference between adjusted treatment group means placebo minus agomelatine; (2) Two-sided 95% Confidence Interval of the estimate; (3) Two-sided p-value; (4) Estimate (Standard Error) of the difference between treatment group percentages placebo minus agomelatine
p-value in bold statistically significant

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Results over the 8-week double-blind treatment period (Cont'd)

Primary assessment criterion: HAM-D total score (Cont'd)

- In the Sub-FAS aged ≥ 75 years

Due to the small number of the patients in the older age (N = 69) in each treatment group, particularly in the placebo group (N = 21), only descriptive statistics were performed.

In the Sub-FAS aged ≥ 75 years, the mean and median change from baseline to the last post-baseline assessment over the W0-W8 period were respectively, -12.2 ± 7.9 and -13.5 (Q1 ; Q3 = -19.0 ; -8.0) in the agomelatine group, and -11.7 ± 9.0 and -12.0 (Q1 ; Q3 = -15.0 ; -6.0) in the placebo group.

At the last post-baseline assessment, the percentage of responders was 58.3% (28/48) in the agomelatine group, and 47.6% (10/21) in the placebo group. The percentage of responders to agomelatine was maintained compared to the global elderly population (FAS).

- In the Sub-FAS with baseline HAM-D total score ≥ 25

The mean HAM-D total score was statistically significantly lower in the agomelatine group than in the placebo group at the last post-baseline assessment over the W0-W8 period (E(SE) = 3.24 (1.21), 95% CI = [0.85 ; 5.63], p = 0.008). This result was confirmed by the sensitivity analyses.

The percentage of responders was statistically significantly higher in the agomelatine group (64.2%) than in the placebo group (41.5%) at the last post-baseline assessment (E(SE) = -22.7 (8.1), 95% CI = [-38.5 ; -6.9], p = 0.005).

- In the Sub-FAS with baseline HAM-D total score ≥ 25 and CGI-S ≥ 5

The mean HAM-D total score was statistically significantly lower in the agomelatine group than in the placebo group at the last post-baseline assessment over the W0-W8 period (E(SE) = 3.79 (1.37), 95% CI = [1.07 ; 6.51], p = 0.007). This result was confirmed by sensitivity analyses.

The percentage of responders was statistically significantly higher in the agomelatine group (65.0%) than in the placebo group (36.6%) at the last post-baseline assessment (E(SE) = -28.4 (9.0), 95% CI = [-45.9 ; -10.8], p = 0.002).

Secondary assessment criteria

- Clinical Global Impression (CGI)

In the FAS, the mean CGI severity of illness and global improvement scores at the last (post-baseline) assessment over the W0-W8 period were statistically significantly lower in the agomelatine group than in the placebo group (p = 0.010 and p = 0.034, respectively, see Table below). Furthermore, the percentage of responders according to CGI global improvement score (score = 1 or 2) was statistically significantly higher in the agomelatine group (71.0%) than in the placebo group (50.0%) at the last assessment (p = 0.003, see Table below) with a difference of 21% in favour of agomelatine.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Results over the 8-week double-blind treatment period (Cont'd)

Secondary assessment criteria (Cont'd)

Summary of statistical results of CGI at last (post-baseline) assessment over the W0-W8 period in the FAS

			Agomelatine (N = 148)	Placebo (N = 70)
CGI severity of illness score				
Last post-baseline value	Mean ± SD		3.0 ± 1.3	3.5 ± 1.3
	Median		3.0	4.0
Statistical analysis (a)	E (SE) [1]		0.48 (0.19)	
	95% CI [2]		[0.12 ; 0.85]	
	p-value[3]		**0.010**	
	p-value[4]		**0.007**	
CGI global improvement score				
Last value	Mean ± SD		2.2 ± 1.2	2.6 ± 1.2
	Median		2.0	2.5
Statistical analysis (a)	E (SE) [1]		0.36 (0.17)	
	95% CI [2]		[0.03 ; 0.69]	
	p-value[3]		**0.034**	
	p-value[4]		**0.012**	
Response at last value Yes		n (%)	105 (70.95)	35 (50.00)
Statistical analysis (b)				
	E (SE) [1]		-20.95 (7.05)	
	95% CI [2]		[-34.76 ; -7.14]	
	p-value[5]		**0.003**	

(a) Two-sided Student's T-test for independent samples and Mann-Whitney test
(b) Chi-Square test
(1) Estimate (Standard Error) of the difference between treatment group means or percentages Placebo minus Agomelatine.
(2) Two-sided 95% Confidence Interval of the estimate
(3) Student's T-test two-sided p-value
(4) Mann-Whitney test two-sided p-value
(5) Chi-Square test two-sided p-value
p-value in bold statistically significant

In the Sub-FAS aged ≥ 75 years, the mean and median CGI severity of illness scores at last post-baseline assessment over the W0-W8 period showed no relevant difference between the treatment groups: 3.1 ± 1.2 in the agomelatine group (median 3.0) *versus* 3.2 ± 1.3 in the placebo group (median 3.0).

In the Sub-FAS aged ≥ 75 years, the mean CGI global improvement score at the last assessment over the W0-W8 period was 2.3 ± 1.3 in the agomelatine group and 2.6 ± 1.3 in the placebo group. Considering the median score, it was 2.0 in each treatment group with Q1 ; Q3 = 1.5 ; 3.0 in the agomelatine group, and 2.0 ; 3.0 in the placebo group.

The percentage of responders according to CGI global improvement score at the last assessment over the W0-W8 period was 70.8% (34/48) in the agomelatine group, and 52.4% (11/21) in the placebo group. The percentage of responders to agomelatine was maintained compared to that observed in the global elderly population (FAS).

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Secondary assessment criteria (Cont'd)

- Sheehan Disability Scale (SDS)

In the FAS, the mean decreases in the 3 SDS scores were higher in the agomelatine group than in the placebo group at the last post-baseline assessment over the ASSE-W8 period:

- Work and activity: -3.1 ± 2.6 in the agomelatine group *versus* -2.0 ± 2.9 in the placebo group.
- Social life: -3.4 ± 2.8 *versus* -2.6 ± 2.8, respectively.
- Family life and home responsibilities: -3.2 ± 2.9 *versus* -2.1 ± 2.5, respectively.

Results over the 24-week double-blind treatment period

Primary assessment criterion: HAM-D total score

In the FAS, at the last post-baseline assessment over the W0-W24 period, the mean HAM-D total score was lower in the agomelatine group than in the placebo group, and the percentage of responders was higher in the agomelatine group than in the placebo group:

- Mean HAM-D total score : 12.3 ± 8.9 in the agomelatine group *versus* 15.3 ± 8.9 in the placebo group.
- Percentage of responders: 60.8% in the agomelatine group *versus* 42.9% in the placebo group.

In the Sub-FAS aged ≥ 75 years, at the last post-baseline assessment over the W0-W24 period, the mean and median change from baseline in HAM-D total score and the percentage of responders were as follows:

- Mean and median change from baseline in HAM-D total score: -13.0 ± 9.1, and -16.0 (Q1 ; Q3 = -19.5 ; -6.5) in the agomelatine group *versus* -11.0 ± 9.5 and -11.0 (Q1 ; Q3 = -17.0 ; -5.0) in the placebo group.
- Percentage of responders: 56.3% (27/48) in the agomelatine group *versus* 47.6% (10/21) in the placebo group.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Emergent adverse events**

Summary of emergent adverse events in the Safety Set

		Agomelatine 25 mg (N = 119)	Agomelatine 25-50 mg (N = 32)	Agomelatine All (N = 151)	Placebo (N = 71)
W0-W8/Wend					
Patients having reported					
at least one emergent adverse event	n (%)	62 (52.1)	17 (53.1)	79 (52.3)	26 (36.6)
at least one severe emergent adverse event	n (%)	7 (5.9)	-	7 (4.6)	6 (8.5)
at least one treatment-related emergent adverse event	n (%)	32 (26.9)	11 (34.4)	43 (28.5)	14 (19.7)
W0-W24/Wend					
Patients having reported					
at least one emergent adverse event	n (%)	75 (63.0)	20 (62.5)	95 (62.9)	31 (43.7)
at least one severe emergent adverse event	n (%)	8 (8.7)	-	8 (5.3)	6 (8.5)
at least one treatment-related emergent adverse event	n (%)	34 (28.6)	12 (37.5)	46 (30.5)	14 (19.7)
During the study					
Patients having experienced					
at least one serious adverse event	n (%)	4 (3.4)	2 (6.3)	6 (4.0)	4 (5.6)
at least one emergent serious adverse event	n (%)	4 (3.4)	2 (6.3)	6 (4.0)	4 (5.6)
at least one emergent treatment-related serious adverse event	n (%)	1 (0.8)	-	1 (0.7)	-
Patients withdrawn					
due to an emergent adverse event	n (%)	16 (13.4)	-	16 (10.6)	8* (11.3)
due to an emergent serious adverse event	n (%)	3 (2.5)	-	3 (2.0)	2 (2.8)
due an emergent treatment-related adverse event	n (%)	9 (7.6)	-	9 (6.0)	2 (2.8)
due an emergent treatment-related serious adverse event	n (%)	1 (0.8)	-	1 (0.7)	-
Patients who died	n (%)	-	-	-	-

** For 3 patients, the reason for study withdrawal was lack of efficacy*

Over the W0-W8/Wend period in the Safety Set, the percentage of patients with at least one emergent adverse event was higher in the agomelatine group (52.3%) than in the placebo group (36.6%).
As regards agomelatine doses, the percentage of patients with at least one emergent adverse event was 52.1% in the agomelatine 25 mg subgroup, and 53.1% in the agomelatine 25-50 mg subgroup.

The most frequently affected system organ classes (in more than 10% of patients) were the same in the agomelatine and placebo groups (gastrointestinal disorders, nervous system disorders, and infections and infestations). Among these disorders, gastrointestinal disorders, and nervous system disorders were more common in the agomelatine group than in the placebo group (21.9% *versus* 12.7% and 18.5% *versus* 12.7%, respectively). It was also the case for the 2 agomelatine dose subgroups (gastrointestinal disorders: 20.2% and 28.1% and nervous system disorder: 18.5% and 18.8% in the agomelatine 25 mg and 25-50 mg subgroups, respectively).

During the W0-W8/Wend period, the most frequent emergent adverse events (reported in at least 5% of patients) in the agomelatine group were somnolence (6.0%) and headache (5.3%). In the placebo group, they were headache and dizziness (5.6% each). Of these events, only somnolence was more frequent in the agomelatine group than in the placebo group (6.0% *versus* 1.4%).

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SUMMARY - CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

- **Emergent adverse events(Cont'd)**

Among the other most frequent emergent adverse events reported in at least 2 patients in any treatment group, it can be noticed that dry mouth and diarrhoea were more frequent in the agomelatine group than in the placebo group (4.6% *versus* 2.8%, and 4.6% *versus* none, respectively).

As regards agomelatine doses, among the most frequent emergent adverse events, the highest incidences were reported for headache and somnolence in the agomelatine 25 mg subgroup (5.9%, 7 patients, each), and diarrhoea (12.5%, 4 patients) and dry mouth (9.4%, 3 patients) in the agomelatine 25-50 mg subgroup.

The percentage of patients who experienced at least one emergent adverse event rated as severe was lower in the agomelatine group than in the placebo group (4.6% *versus* 8.5%). It concerned mainly headache in the agomelatine group (3 patients, 2.0%), and dizziness in the placebo group (2 patients, 2.8%).
As regards agomelatine doses, all severe emergent adverse events were reported in the agomelatine 25 mg subgroup.

During the W0-W8/Wend period, the percentage of patients with at least one emergent adverse event considered to be related to the study treatment by the investigator was higher in the agomelatine group (28.5%) than in the placebo group (19.7%), and mainly related to nervous system disorders (13.9% *versus* 9.9%), and gastrointestinal disorders (12.6% *versus* 8.5%).

During the W0-W24/Wend period in the Safety Set, as during the W0-W8/Wend period, the percentage of patients with at least one emergent adverse event was higher in the agomelatine group (62.9%) than in the placebo group (43.7%). Results obtained over W0-W24/Wend were comparable to those over W0-W8/Wend.

In patients in the older age (≥ 75 years), the percentage of patients with at least one emergent adverse event was 56.3% in the agomelatine group *versus* 38.1% in the placebo group during the W0-W8/Wend period, and 70.8% *versus* 47.6%, respectively during the W0-W24/Wend period. In this set, description and characteristics of adverse events during both periods were in the same line as those in the Safety Set.

No death was reported during the study.

During the study, the percentage of patients with at least one emergent serious adverse event showed no relevant difference between the treatment groups (6 patients, 4.0%, in the agomelatine group, and 4 patients, 5.6%, in the placebo group).
Four patients (3.4%) in the agomelatine 25 mg dose subgroup, and 2 patients (6.3%) in the agomelatine 25-50 mg dose subgroup had at least one emergent serious adverse event.
In the agomelatine group, 3/6 patients with emergent serious adverse events were aged ≥ 75 (atrial fibrillation, major depression associated to insomnia, and pyelonephritis acute associated to nausea), and 1/4 in the placebo group (myocardial infarction). None of these serious events were considered treatment-related by the investigator.
Gastrointestinal disorders (3 patients, 2.0%) including nausea (2 patients, 1.3%) were the most frequent serious adverse events reported in the agomelatine group. In the placebo group, all emergent serious gastrointestinal disorders were reported in one patient.

The percentage of patients with at least one emergent serious adverse event leading to study drug withdrawals showed no relevant difference between the treatment groups (2.0%, 3 patients, in the agomelatine group, and 2.8%, 2 patients, in the placebo group) as well as the one reported for emergent non-serious adverse events leading to study drug withdrawals (8.6% of patients in the agomelatine group and 8.5% in the placebo group).
All patients in the agomelatine group with emergent adverse events leading to premature treatment discontinuation were receiving the 25 mg dose.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Laboratory tests**
  - In the Safety Set, neither clinically relevant changes over time nor differences between groups were detected for biochemical and haematological parameters over both periods. Similar results were observed in the Sub-SS aged ≥ 75 years.
  - Emergent PCSA biochemical values during the ASSE-W24/Wend period were few in both groups in the Safety Set: 16 values in the agomelatine group, and 8 values in the placebo group. They were sparse except for high urea in the agomelatine group (8 patients, 5.5%) including 5 patients already abnormal at baseline without reaching the PCSA limit. Among these patients, half were in the Sub-SS aged ≥ 75 years.
  - Emergent PCSA haematological values were sparse in both groups (4 PCSA low values in the agomelatine group, and 6 in the placebo group).
  - Liver acceptability

    Emergent PCSA values of ALAT and/or ASAT (> 3 ULN) were reported in 2 patients in the agomelatine group only (one patient in each agomelatine dose subgroup). Both patients were within the normal range at baseline. PCSA values were as follows:
    - In the agomelatine 25-50 mg subgroup: one patient, aged over 75, had emergent PCSA values of both transaminases (ASAT: maximum value 11.2 ULN, and ALAT: maximum value 12.6 ULN) and GGT (maximum value 3.5 ULN) at W8. Alkaline phosphatase was above the reference range without reaching the PCSA limit (maximum value 1.4 ULN).
    - In the agomelatine 25 mg subgroup: one patient had emergent PCSA values of ALAT at W8 (maximum value 3.6 ULN), associated with ASAT above the reference range without reaching the PCSA limit (maximum value 2.6 ULN). Alkaline phosphatase was normal.

    Total, free and conjugated bilirubin were normal in both patients.

    Both patients recovered after treatment withdrawal.

- **Vital signs and BMI**
  - Blood pressure and heart rate

    In the Safety Set, neither clinically relevant changes over both treatment periods nor differences between groups were detected for sitting blood pressures and heart rate.

    Similar results were observed in patients in the older age (≥ 75 years).
  - Weight and body mass index (BMI)

    In the Safety Set, neither clinically relevant change over both treatment periods nor difference between groups were detected for the weight. In both groups, most patients remained in the same BMI class over both treatment periods (87.4% and 88.7% in the agomelatine and placebo groups, respectively over the ASSE-W8/Wend period). The percentage of patients with a BMI change showed no relevant difference between the treatment groups.

    Similar results were observed in patients in the older age (≥ 75 years) except for the percentage of patients with a BMI increase over the ASSE-W8/Wend period which was slightly higher in the agomelatine group than in the placebo group (12.5%, 6/48 patients *versus* 4.8%, 1/21 patients), and the percentage of patients with a BMI decrease which was lower in the agomelatine group than in the placebo group (2.1%, 1/48 patients *versus* 9.5%, 2/21 patients).

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **ECG**

During the study, the percentage of patients with at least one emergent or new ECG abnormality showed no relevant difference between the treatment groups (21.5% and 22.4% in the agomelatine and placebo groups, respectively). Nine QT/QTc prolongations were reviewed by an expert in blind (5 in the agomelatine group and 4 in the placebo group). According to expert's opinion, none of those were of any concern as regards a QT prolongation-dependent proarrhythmic signal with the study drugs administered in these patients.

One emergent ECG abnormality in each treatment group was considered as clinically significant according to the cardiologist associated to investigational centre (ventricular extrasystoles at W8 and W24 in the agomelatine group, and electrocardiogram T wave inversion at Wend in the placebo group).

PHARMACOKINETC RESULTS

Descriptive statistics of the agomelatine pharmacokinetic parameters in plasma per dose and age group

Age	Agomelatine dose (mg)	N	AUC [1] (ng h/mL)	C_{max} [1] (ng/mL)	t_{max} [2] (h)	$t_{1/2\ z}$ [1] (h)
All [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] *mean ± SD (median)* *N number of patients*
[2] *median (min – max)*

At the dose of 25 mg, the median AUC [redacted] compared to median AUC for the patients [redacted]). At the dose of [redacted].

Taking into account the known variability of agomelatine exposure and its wide therapeutic window, no clinical impact of the age is expected. In line with this, within the CL3-20098-070 study, [redacted] Indeed, the observed adverse events [redacted]

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CONCLUSION

This international, multicentre, double-blind, placebo-controlled, randomised study conducted in elderly patients with Major Depressive Disorder demonstrates a statistically significant antidepressant efficacy of agomelatine 25-50 mg once daily on the HAM-D total score (primary efficacy criterion), as well as CGI scale (severity of illness score, and global improvement score) after 8 weeks of treatment. The clinical relevance of the agomelatine antidepressant effect was also demonstrated by the difference in term of HAM-D and CGI responders compared to placebo.

The clinically and statistically significant antidepressant efficacy of agomelatine was also seen in the subgroup of elderly patients with more severe depression at baseline.

In patients in the older age (≥ 75 years), the level of HAM-D and CGI responders was maintained compared to the global elderly population.

Agomelatine 25-50 mg once daily was well tolerated in elderly during treatments of 8 weeks and 24 weeks. No unexpected adverse event was reported. Regarding adverse events reported for agomelatine, severity, seriousness and treatment discontinuation showed a similar figure to that observed for the placebo. In patients in the older age (≥ 75 years), short-term and long-term tolerance was satisfactory.

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