Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of 3 dose regimens of agomelatine (10, 25, 25-50 mg) *versus* placebo given once a day for 6 weeks in out-patients suffering from moderate to severe Major Depressive Disorder.** **A 6-week randomised, double-blind, placebo-controlled, parallel groups study followed by a double-blind optional 18-week extension period.**
Study drug	**Agomelatine (S 20098)**
Studied indication	**Major Depressive Disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-069**
Study initiation date	**28 October 2009**
Study completion date	**11 May 2012**
Main coordinator	[redacted] [redacted] **Moscow - Russia**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officer	[redacted] **(I.R.I.S.)**
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 23 November 2012**

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2. SYNOPSIS

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Title of study: Efficacy and safety of 3 dose regimens of agomelatine (10, 25, 25-50 mg) versus placebo given once a day for 6 weeks in out-patients suffering from moderate to severe Major Depressive Disorder.
A 6-week randomised, double-blind, placebo-controlled, parallel groups study followed by a double-blind optional 18-week extension period.
Protocol No. CL3-20098-069 – EudraCT No. 2009-011238-84

National coordinators: [redacted] (, Argentina), [redacted] (, Bulgaria), [redacted] (, Finland), [redacted] (, Russia), [redacted] (, Slovakia), [redacted] (Ukraine).

Study centres: In all, 45 centres located in 6 countries included at least one patient: Argentina (10 centres – 102 included patients), Bulgaria (8 centres – 95 included patients), Finland added by Amendment No. 4 (3 centres – 51 included patients), Russia (10 centres – 156 included patients), Slovakia (5 centres – 61 included patients), Ukraine (9 centres – 84 included patients).

Publication (reference): Not applicable

Studied period: Initiation date: 28 October 2009 Completion date: 11 May 2012	**Phase of development of the study:** III

Objectives: to assess the efficacy and safety of 3 dose regimens of agomelatine (10, 25, 25-50 mg) *versus* placebo in out-patients suffering from moderate to severe Major Depressive Disorder.
Primary objective: to demonstrate the short-term efficacy of at least one of the 3 dose regimens of agomelatine (*versus* placebo) using HAM-D-17 items scale.
Secondary objectives: to assess the short-term efficacy (using CGI, HAD and SDS) and safety of the 3 dose regimens of agomelatine, to compare the flexible dose regimen recommended (50 mg o.d. if no improvement after 2 weeks of 25 mg o.d.) and the fixed dose regimen (25 mg o.d.) on the W0-W6 period, to compare the subgroup of patients insufficiently improved after 2 weeks of treatment in the flexible 25-50 mg arm and the subgroup of patients insufficiently improved after 2 weeks of treatment in the fixed 25 mg arm in a descriptive way on the W0-W6 period, to study the long-term efficacy and safety of the 10 mg dose of agomelatine during the extension period, to provide additional long-term efficacy and safety data of agomelatine 25 mg and 50 mg during the extension period, and to evaluate the influence of genetic factors on efficacy and safety of agomelatine in a pharmacogenetic sub-study.

Methodology: This was a phase III, multicentre, international, randomised, double-blind, placebo-controlled study with therapeutic benefit, with 4 parallel groups, *i.e.*, agomelatine 10 mg o.d., agomelatine 25 mg o.d. (fixed dose regimen), agomelatine 25 mg o.d. increased up to 50 mg o.d. if no improvement after 2 weeks (dose regimen corresponding to agomelatine 25-50 mg group in the results), and placebo o.d. 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 W6, only patients having CGI global improvement score ≤ 3 could enter the 18-week extension double-blind treatment period with the same treatment according to investigator's opinion and patient's agreement. The other patients were considered as having completed the mandatory W0-W6 period. At W10 visit, only the patients having CGI item $2 \leq 2$ were allowed to continue in the extension period. The patients having CGI item $2 > 2$ at W10 visit, had to be withdrawn from the study.
Randomisation was balanced, non-adaptive, with stratification on the centre. Treatment randomisation and allocation were centralised with an Interactive Response System (IRS).
This study was performed in strict accordance with Good Clinical Practice.

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Number of patients:

Planned: 520 patients (130 by treatment group).

Included: 549 patients (133 in the agomelatine 10 mg group, 138 in the agomelatine 25 mg fixed group, 137 in the agomelatine 25-50 mg group, and 141 in the placebo group).

Diagnosis and main criteria for inclusion:

Male or female out-patients, aged between 18 and 65 years (inclusive), fulfilling Diagnosis and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV TR) criteria for a moderate to severe single or recurrent episode of a Major Depressive Disorder. At selection Hamilton Depression Rating Scale 17 items (HAM-D-17) total score was to be ≥ 22, CGI item 1 score ≥ 4, and Hospital Anxiety Depression (HAD) depression sub-score ≥ 11. At inclusion, HAM-D 17 items total score was still to be ≥ 22 and no more than a 20% decrease in HAM-D total score between selection and inclusion, and CGI severity of illness was still to be ≥ 4.

Study drug:

Agomelatine, capsules of 10 mg, 25 mg and 50 mg. One capsule o.d. at bedtime.

For patients receiving agomelatine 10 mg/day, and agomelatine 25 mg/day fixed dose, the same dose was taken throughout the study.

For patients receiving agomelatine 25 mg/day flexible dose, a potential adjustment to 50 mg/day might occur at W2 using pre-determined fixed criteria, in double-blind conditions (neither the investigator, nor the patients knew whether the dose had been increased) for patients with insufficient improvement of depressive symptoms. Patients with sufficient improvement remained at the initial dosage until the end of the study.

Batch No.: Agomelatine 10 mg: L0028872, L0033796; Agomelatine 25 mg: L0029482, L0033399; Agomelatine 50 mg: L0029508, L0033401

Reference product:

Placebo, one capsule o.d. at bedtime.

Duration of treatment:

- 3 to 7-day run-in period without treatment (from selection visit (ASSE) to W0).
- 6-week double-blind treatment period (from W0 to W6).
- 18-week double-blind optional extension treatment period (from W6 to W24).
- 1-week follow-up period without study treatment after W6 for patients not continuing the extension period at W6, or after W24, or in case of premature withdrawal.

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Criteria for evaluation:
Efficacy measurements

- Hamilton Depression Rating Scale 17 items (HAM-D-17): 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-W6 period.
- Clinical Global Impression scale (CGI): 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): rated by the patient at selection, W6, and W24, or in case of premature withdrawal.
- Hospital Anxiety and Depression scale (HAD): rated by the patient at selection and W6, or in case of premature withdrawal between W0 and W6.

Safety measurements

- Adverse events reported at each visit.
- Laboratory tests: biochemical and haematological tests available at inclusion visit, W6, W14 (only liver function tests), and W24 (prescription at the previous visit) or at the follow-up visit (Wend) in case of premature withdrawal.
- Physical examinations:
  - Blood pressure and heart rate were measured at selection, inclusion, W6 and W24, or in case of premature withdrawal.
  - Body weight and Body Mass Index were assessed at selection, inclusion, W6 and W24, or in case of premature withdrawal.
- 12-lead ECG: results available at inclusion visit and W24 (prescription at the previous visit) or at the follow-up visit in case of premature withdrawal (prescription at the withdrawal visit) or patients not continuing in the extension period.

Other measurements

- Pharmacogenetic sub-study: data collected at W6 or in case of premature withdrawal in patients who agreed to take part in the sub-study. Data will be analysed in the 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 on pooled data.

Statistical methods:
Efficacy analysis
Primary criterion

- Main analysis

The superiority of at least one agomelatine dose regimen as compared to placebo on depressive symptoms after a 6-week treatment period was assessed on the last post-baseline value until W6 of the HAM-D 17-item total score in the Full Analysis Set (FAS), using a single two-way analysis of covariance model on factor treatment as fixed effect, with centre (random effect), and baseline HAM-D 17-item total score as covariates, and without interaction. Hochberg procedure was used to control the familywise error rate in the context of multiple comparisons *versus* placebo.

- Sensitivity analyses

To assess the robustness of the main analysis results, sensitivity analyses to the method of handling missing values (Mixed-effects Repeated Measures Model (MMRM)), to the adjustment for covariates (unadjusted analysis) were performed in the FAS.

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Efficacy analysis (Cont'd)
Primary criterion (Cont'd)

- Secondary analyses

The same analysis strategy as the main analysis was implemented on the W0-W6 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).
In addition, the difference between the two agomelatine 25 mg dose regimens was estimated on the HAM-D total score at the last post-baseline assessment over the W0-W6 period in the FAS using a two-way analysis of covariance model similarly as for the main analysis but including only the two agomelatine 25 mg dose regimens. The 2 regimens were also described in the Sub-FAS 25 mg insufficiently improved at W2 (2 groups: agomelatine 25-25 mg fixed and 25-50 mg).
One complementary analysis was added in order to estimate the difference between the agomelatine 10 mg treatment group and the two agomelatine 25 mg dose regimens on the HAM-D total score at the last post-baseline assessment over the W0-W6 period in the FAS using a two-way analysis of covariance model similarly as for the main analysis but including only the three agomelatine dose regimens.
Moreover, each agomelatine dose regimen 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 W6 using a Chi-square test in patients of the FAS and its subsets of more severely depressed patients.

Secondary criteria
For CGI scale, each agomelatine dose regimen was compared to placebo in the FAS after a 6-week treatment period:

- 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 until W6.
- Response to treatment (global improvement score = 1 or 2), using a Chi-square test on the last value until W6.

Over the W0-W24 period, descriptive statistics were provided for all analytical approaches of the primary criterion and secondary criteria in the FAS and the two FAS subsets of more severely depressed patients.

Safety analysis
Descriptive statistics were provided in the Safety Set by treatment group over the ASSE-W6/Wend and ASSE-W24/Wend periods for emergent adverse events, serious adverse events (over the ASSE-W24/Wend period only), and laboratory parameters, over the W0-W6 and W0-W24 periods for physical examination, and over the W0-W24/Wend period for ECG abnormalities.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Status		Agomelatine 10 mg	Agomelatine 25 mg fixed	Agomelatine 25-50 mg	Placebo	All
W0-W6						
Included and randomised	**n**	**133**	**138**	**137**	**141**	**549**
Withdrawn over W0-W6	**n (%)**	**10 (7.5)**	**8 (5.8)**	**11 (8.0)**	**15 (10.6)**	**44 (8.0)**
Adverse event	n (%)	1 (0.8)	1 (0.7)	1 (0.7)	-	3 (0.6)
Protocol deviation	n (%)	2 (1.5)	1 (0.7)	1 (0.7)	-	4 (0.7)
Lack of efficacy	n (%)	5 (3.8)	3 (2.2)	5 (3.7)	9 (6.4)	22 (4.0)
Non-medical reason	n (%)	2 (1.5)	3 (2.2)	4 (2.9)	6 (4.3)	15 (2.7)
Completed the W0-W6 period	**n (%)**	**123 (92.5)**	**130 (94.2)**	**126 (92.0)**	**126 (89.4)**	**505 (92.0)**
Performed the follow-up visit	*n (%)*	*29 (21.8)*	*20 (14.5)*	*16 (11.7)*	*50 (35.5)*	*115 (20.9)*
W6-W24						
Did not enter the extension period	**n (%)**	**23 (17.3)**	**19 (13.8)**	**11 (8.0)**	**41 (29.1)**	**94 (17.1)**
Entered the extension period	**n (%)**	**100 (75.2)**	**111 (80.4)**	**115 (83.9)**	**85 (60.3)**	**411 (74.9)**
Lost to follow-up*	**n (%)**	**-**	**1 (0.9)**	**-**	**-**	**1 (0.2)**
Withdrawn over W6-W24*	**n (%)**	**27 (27.0)**	**11 (9.9)**	**20 (17.4)**	**27 (31.8)**	**85 (20.7)**
Adverse event	n (%)	2 (2.0)	1 (0.9)	5 (4.4)	1 (1.2)	9 (2.2)
Protocol deviation	n (%)	-	-	-	-	-
Lack of efficacy	n (%)	18 (18.0)	6 (5.4)	7 (6.1)	23 (27.1)	54 (13.1)
Non-medical reason	n (%)	7 (7.0)	4 (3.6)	8 (7.0)	2 (2.4)	21 (5.1)
Cure, remission or improvement	n (%)	-	-	-	1 (1.2)	1 (0.2)
Completed the W6-W24 period*	**n (%)**	**73 (73.0)**	**99 (89.2)**	**95 (82.6)**	**58 (68.2)**	**325 (79.1)**
*Performed the follow-up visit**	*n (%)*	*87 (87.0)*	*105 (94.6)*	*105 (91.3)*	*81 (95.3)*	*378 (92.0)*
Analysed Sets						
Randomised Set	**n (%)**	**133**	**138**	**137**	**141**	**549**
Efficacy Sets						
Full Analysis Set (FAS)	n (%)	132 (99.2)	138 (100.0)	136 (99.3)	141 (100.0)	547 (99.6)
Sub-FAS 25 mg insufficiently improved at W2 (FAS W2)	n (%)	-	53 (38.4)	48 (35.0)	-	101 (18.4)
Sub-FAS with baseline HAM-D total score ≥ 25 (FAS Sev1)	n (%)	108 (81.2)	107 (77.5)	105 (76.6)	112 (79.4)	432 (78.7)
Sub-FAS with baseline HAM-D total score ≥ 25 and baseline CGI-S ≥ to 5 (FAS Sev2)	n (%)	73 (54.9)	70 (50.7)	63 (46.0)	68 (48.2)	274 (49.9)
Safety Set	**n (%)**	**132 (99.2)**	**138 (100.0)**	**136 (99.3)**	**141 (100.0)**	**547 (99.6)**

*%: Expressed as percentage of the patients from the Randomised Set except for * expressed as percentage of patients entered the W6-W24 extension period*

A total of 653 patients were selected, and 549 patients were included and randomly assigned to one of the 4 groups according to IRS procedure. Distribution was well balanced (see Table above).

At W2, in the agomelatine 25-50 mg group, 49/134 patients ongoing after W2 (36.6%) with an insufficient improvement (including 1 patient sufficiently improved with dose wrongly increased) had a dose increase from 25 mg/day to 50 mg/day in double-blind conditions.

At W6, among the patients completed, the percentage of patients not entering the extension period was lower in each agomelatine group (18.7% in the agomelatine 10 mg group, 14.6% in the agomelatine 25 mg fixed group, 8.7% in the agomelatine 25-50 mg group) than in the placebo group (32.5%).

During the study, 1 patient in the agomelatine 25 mg fixed group was lost to follow-up at W14.

The rate of withdrawals over the W0-W6 and W6-W24 periods, excluding this patient lost to follow-up, was lower in each agomelatine group than in the placebo group.

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

This difference was mainly due to the withdrawals related to lack of efficacy which were less frequent in each agomelatine group than in the placebo group.

Finally, the percentage of included and randomised patients who completed the study at W24 was higher in each agomelatine group than in the placebo group: 54.9% in the agomelatine 10 mg group, 71.7% in the agomelatine 25 mg fixed group, 69.3% in the agomelatine 25-50 mg group, and 41.1% in the placebo group.

In the Randomised Set, patients were 45.0 ± 12.6 years old on average (± SD) at selection, ranging from 18 to 65 years. Most patients were female (73.0%). According to the DSM-IV-TR criteria, all patients were diagnosed as MDD. In all, 76.0% of patients had a recurrent MDE, and 24.0% had a single MDE. MDE was moderate in 68.1% of patients, and severe without psychotic features in 31.9%. MDE with melancholic features was observed in most patients (87.3%). Mean number of depressive episodes (including the current one) was 2.8 ± 1.9, ranging from 1 to 18. Mean duration of the current MDE was 3.5 ± 3.0 months (median 2.5 months). Previous psychotropic drug treatment within one year prior to selection was reported in 42.6% of patients, mainly SSRIs (20.8%).

At inclusion, the mean HAM-D total score was 26.8 ± 2.8, and the mean CGI severity of illness score was 4.6 ± 0.6 corresponding to "markedly" ill patients.

At selection, the mean HAD depression sub-score was 16.0 ± 2.6. All patients had a depression score ≥ 11 except one patient who had a corresponding protocol deviation. The mean HAD anxiety sub-score was 10.7 ± 3.9. In all, 51.9% of patients felt at least moderately anxious (score ≥ 11).

According to SDS, on average, the patients felt markedly disrupted by symptoms for the 3 domains: work and activity (7.3 ± 1.5), social life (7.4 ± 1.5), and family life and home responsibilities (7.2 ± 1.5). On average in the week prior to selection, 2.6 ± 2.6 days were lost, and 5.0 ± 2.1 days were underproductive.

No clinically relevant differences between the treatment groups were observed for demographic, disease characteristics, and efficacy criteria at baseline.

Baseline characteristics in the FAS were similar to those observed in the Randomised Set. These characteristics were in accordance with the inclusion criteria of the study. In the different FAS subsets, apart from the criteria defining the subsets and related criteria, baseline characteristics were similar to those observed in the Randomised Set.

In the Randomised Set, mean treatment duration was 41.3 ± 5.9 days (median 42.0 days) over the W0-W6 period, and 123.6 ± 58.7 days (median 167.0 days) over the W0-W24 period with a mean treatment duration longer in the 3 agomelatine groups than in the placebo group over the W0-W24 period (from 118.5 ± 59.5 days, median 166 days in the agomelatine 10 mg group to 138.4 ± 54.1 days, median 168 days in the agomelatine 25 mg fixed group *versus* 100.0 ± 60.1, median 74 days in the placebo group). Mean global compliance was 98.6 ± 8.7% over the W0-W6 period, and 98.3 ± 8.9% over the W0-W24 period. Global compliance showed no differences between groups.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Results over the 6-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 3 agomelatine groups than in the placebo group at the last post-baseline assessment over the W0-W6 period (main analysis, see Table below).

It can be emphasised that the lower bound of the 95% CI of the placebo-difference in the agomelatine 25 mg fixed and 25-50 mg groups (3.23 and 3.43, respectively) confirmed the potent treatment effect of these therapeutic doses of agomelatine. In the agomelatine 10 mg group, the placebo difference was less pronounced than in these 2 agomelatine groups.

These results were confirmed by all sensitivity analyses.

In the FAS, the mean HAM-D total score at the last post-baseline assessment over the W0-W6 period showed no significant difference between the agomelatine 25 mg fixed and 25-50 mg groups: E(SE) = 0.21 (0.67), 95% CI = [-1.12 ; 1.54] after adjustment for baseline HAM-D total score, and centre.

The comparison between the agomelatine 10 mg group and the two agomelatine 25 mg dose regimens on the mean HAM-D total score at the last post-baseline assessment over the W0-W6 period showed that between-groups differences were in favour of the two agomelatine 25 mg dose regimens (complementary analysis). The between-group differences (after adjustment for baseline HAM-D total score, and centre) were as follows:

Agomelatine 10 mg *versus*:

- Agomelatine 25 mg fixed : E(SE) = 2.24 (0.72), 95% CI = [0.82 ; 3.65].
- Agomelatine 25-50 mg group: E(SE) = 2.44 (0.72), 95% CI = [1.02 ; 3.86].

The percentage of responders to treatment was statistically significantly higher in the 3 agomelatine groups than in the placebo group at the last post-baseline assessment. The difference in favour of agomelatine compared to placebo was less pronounced in the agomelatine 10 mg group (16%) than in the other 2 dose regimens groups (26% and 27% in the agomelatine 25 mg fixed and 25-50 mg groups, respectively).

Summary of statistical results of HAM-D total score at last post-baseline assessment over the W0-W6 period in the FAS

		Agomelatine 10 mg (N = 132)	Agomelatine 25 mg fixed (N = 138)	Agomelatine 25-50 mg (N = 136)	Placebo (N = 141)
HAM-D					
Total score					
Last post-baseline value	Mean ± SD	16.5 ± 7.0	14.0 ± 6.6	13.9 ± 6.3	18.7 ± 7.3
Statistical analysis (a)			***Main analysis***		
	E (SE) (1)	2.46 (0.76)	4.71 (0.75)	4.92 (0.76)	
	95% CI (2)	[0.96 ; 3.96]	[3.23 ; 6.19]	[3.43 ; 6.40]	
	p-value (3)	**0.001 (III)**	**< 0.0001 (II)**	**< 0.0001 (I)**	
Response to treatment (yes)					
Last post-baseline value	n (%)	54 (40.91)	70 (50.72)	71 (52.21)	35 (24.82)
Statistical analysis (b)					
	E (SE) (1)	-16.09 (5.62)	-25.90 (5.60)	-27.38 (5.62)	
	95% CI (2)	[-27.10 ; -5.08]	[-36.88 ; -14.93]	[-38.40 ; -16.37]	
	p-value (4)	**0.005**	**< 0.0001**	**< 0.0001**	

(a) Analysis of covariance model on factor treatment with baseline HAM-D total score and centre (random effect) as covariates

(b) Chi-Square test

(1) Estimate (Standard Error) of the difference between adjusted (or unadjusted) treatment group means (or percentages): Placebo minus Agomelatine dose regimen

(2) Two-sided 95% Confidence Interval of the estimate

(3) Two-sided Hochberg-adjusted p-value (to be compared to 0.05) with (I) / (II) / (III) corresponding to the ordered unadjusted p-values from the most significant to the least significant one

(4) Two-sided p-value

n: Number of responders to treatment; p-value in bold: statistically significant

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SUMMARY – CONCLUSIONS (cont'd)

EFFICACY RESULTS (Cont'd)

- In the Sub-FAS with baseline HAM-D total score ≥ 25 (FAS Sev1)

The mean HAM-D total score was statistically significantly lower in the 3 agomelatine groups than in the placebo group at the last post-baseline assessment over the W0-W6 period after adjustment for baseline HAM-D total score, and centre as follows and confirmed by all sensitivity analyses:

- Agomelatine 10 mg *versus* placebo: E(SE) = 2.22 (0.87), 95% CI = [0.50 ; 3.93], p = 0.012.
- Agomelatine 25 mg fixed *versus* placebo: E(SE) = 5.12 (0.87), 95% CI = [3.41 ; 6.83], p < 0.0001.
- Agomelatine 25-50 mg *versus* placebo: E(SE) = 5.05 (0.88), 95% CI = [3.32 ; 6.77], p = < 0.0001.

The percentage of responders to treatment was statistically significantly higher in the 3 agomelatine groups than in the placebo group at the last post-baseline assessment over the W0-W6 period:

- Agomelatine 10 mg *versus* placebo: E(SE) = -13.9 (6.2)%, 95% CI = [-26.0 ; -1.8]%, p = 0.026.
- Agomelatine 25 mg fixed *versus* placebo: E(SE) = -25.4 (6.3)%, 95% CI = [-37.8 ; -13.1]%, p < 0.0001.
- Agomelatine 25-50 mg *versus* placebo: E(SE) = -27.3 (6.3)%, 95% CI = [-39.7 ; -14.9]%, p < 0.0001.

- In the Sub-FAS with baseline HAM-D total score ≥ 25 and CGI-S ≥ 5 (FAS Sev2)

The mean HAM-D total score was lower in the 3 agomelatine groups than in the placebo group at the last post-baseline assessment over the W0-W6 period after adjustment for baseline HAM-D total score, and centre. This difference in favour of agomelatine was statistically significant for the agomelatine 25 mg fixed and 25-50 mg groups as follows and confirmed by all sensitivity analyses:

- Agomelatine 10 mg *versus* placebo: E(SE) = 1.57 (1.16), 95% CI = [-0.71 ; 3.85], p = 0.176.
- Agomelatine 25 mg fixed *versus* placebo: E(SE) = 5.38 (1.16), 95% CI = [3.10 ; 7.67], p < 0.0001.
- Agomelatine 25-50 mg *versus* placebo: E(SE) = 5.53 (1.20), 95% CI = [3.18 ; 7.89], p < 0.0001.

The percentage of responders to treatment was higher in the 3 agomelatine groups than in the placebo group at the last post-baseline assessment over the W0-W6 period. This difference in favour of agomelatine was statistically significant for the agomelatine 25 mg fixed and 25-50 mg groups as follows:

- Agomelatine 10 mg *versus* placebo: E(SE) = -10.6 (7.7)%, 95% CI = [-25.7 ; 4.4]%, p = 0.171.
- Agomelatine 25 mg fixed *versus* placebo : E(SE) = -25.0 (8.0)%, 95% CI = [-40.6 ; -9.4]%, p = 0.002.
- Agomelatine 25-50 mg *versus* placebo: E(SE) = -25.8 (8.2)%, 95% CI = [-41.9 ; -9.7]%, p = 0.002.

- In the Sub-FAS 25 mg insufficiently improved at W2 (FAS W2)

At the last post-baseline assessment over the W0-W6 period, the mean HAM-D total score was 15.9 ± 6.6 in the 53 patients insufficiently improved at W2 in the agomelatine 25 mg fixed group and 15.3 ± 4.9 in the 48 patients insufficiently improved at W2 who received the 50 mg dose from W2 in the agomelatine 25-50 mg group.

The percentage of responders to treatment was similar in both groups (37.7%, and 37.5%, respectively) at the last post-baseline assessment over the W0-W6 period.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

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-W6 period were statistically significantly lower in the 3 agomelatine groups than in the placebo group with both tests (Student's T-test and Mann-Whitney test) except a trend to statistical significance for the agomelatine 10 mg group with Student's T-test (see Table below).

The percentage of responders according to CGI global improvement score (score = 1 or 2) was statistically significantly higher in the 3 agomelatine groups than in the placebo group at the last assessment. The difference in favour of agomelatine compared to placebo was less pronounced in the agomelatine 10 mg group (15%) than in the other 2 dose regimens groups (35% and 34% in the agomelatine 25 mg fixed and 25-50 mg groups, respectively).

Summary of statistical results of the 2 CGI scores at last (post-baseline) assessment over the W0-W6 period in the FAS

		Agomelatine 10 mg (N = 132)	Agomelatine 25 mg fixed (N = 138)	Agomelatine 25-50 mg (N = 136)	Placebo (N = 141)
Severity of illness score					
Last post-baseline value	Mean ± SD	3.5 ± 1.1	3.1 ± 1.1	3.1 ± 1.0	3.7 ± 1.1
	Median	3.0	3.0	3.0	4.0
Statistical analysis					
	E (SE) (1)	0.25 (0.14)	0.67 (0.13)	0.65 (0.13)	
	95% CI (2)	[-0.03 ; 0.52]	[0.41 ; 0.92]	[0.39 ; 0.91]	
	p-value (3)	0.076	**< 0.0001**	**< 0.0001**	
	p-value (4)	**0.044**	**< 0.0001**	**< 0.0001**	
Global improvement score					
Last value	Mean ± SD	2.6 ± 1.0	2.2 ± 1.0	2.2 ± 0.9	2.9 ± 1.1
	Median	2.0	2.0	2.0	3.0
Statistical analysis					
	E (SE) (1)	0.33 (0.13)	0.76 (0.13)	0.77 (0.12)	
	95% CI (2)	[0.07 ; 0.59]	[0.51 ; 1.01]	[0.52 ; 1.01]	
	p-value (3)	**0.013**	**< 0.0001**	**< 0.0001**	
	p-value (4)	**0.009**	**< 0.0001**	**< 0.0001**	
Response to treatment (yes)					
Last value	n (%)	69 (52.27)	99 (71.74)	97 (71.32)	52 (36.88)
Statistical analysis					
	E (SE) (1)	-15.39 (5.95)	-34.86 (5.59)	-34.44 (5.62)	
	95% CI (2)	[-27.06 ; -3.73]	[-45.81 ; -23.91]	[-45.45 ; -23.44]	
	p-value (5)	**0.011**	**< 0.0001**	**< 0.0001**	

(1) Estimate (Standard Error) of the difference between treatment group means (or percentages): Placebo minus Agomelatine dose regimen
(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
n: Number of responders to treatment
p-value in bold: statistically significant

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Descriptive results in the two Sub-FAS of more severely depressed patients were in the same line as in the FAS.

In the Sub-FAS 25 mg insufficiently improved at W2, the mean (median) last post-baseline severity of illness scores over the W0-W6 period were 3.4 ± 1.0 (3.0), and 3.3 ± 0.8 (3.0) in the agomelatine 25-25 mg fixed and 25-50 mg groups, respectively, the mean (median) global improvement scores were 2.5 ± 1.0 (2.0) and 2.3 ± 0.8 (2.0), respectively, and the percentages of responders to treatment were 66.0% and 66.7%, respectively.

- Sheehan Disability Scale (SDS)

In the FAS, the mean decreases in the 3 SDS scores at the last post-baseline assessment over the ASSE-W6 period were higher in the 3 agomelatine groups than in the placebo group. They were less pronounced in the agomelatine 10 mg group than in the other 2 agomelatine groups:

- Work and activity: -2.1 ± 2.2, -2.9 ± 2.6, and -2.9 ± 2.2 in the agomelatine 10 mg, 25 mg fixed, and 25-50 mg groups, respectively *versus* -1.6 ± 2.0 in the placebo group.
- Social life: -2.5 ± 2.4, -3.0 ± 2.6, and -3.1 ± 2.5 *versus* -1.7 ± 2.2, respectively.
- Family life and home responsibilities: -2.5 ± 2.4, -3.0 ± 2.6, and -3.1 ± 2.4 *versus* -1.7 ± 2.3, respectively.

Similar results were observed for the number of days lost, and number of underproductive days in the last week except for the decrease in number of days lost similar in the agomelatine 10 mg and 25 mg fixed group:

- Number of days lost: -1.4 ± 2.2, -1.4 ± 2.3, and -1.9 ± 2.6 in the agomelatine 10 mg, 25 mg fixed, and 25-50 mg groups, respectively *versus* -0.9 ± 1.9 in the placebo group.
- Number of days under productive: -1.8 ± 2.8, -2.4 ± 2.5, and -2.8 ± 2.6 *versus* -1.4 ± 2.5.

Results in the two Sub-FAS of more severely depressed patients were in the same line as in the FAS.

- Hospital Anxiety Depression Scale (HAD)

In the FAS, at last post-baseline assessment over the W0-W6 period, the mean decrease in HAD depression and anxiety sub-scores from baseline was higher in the 3 agomelatine groups than in the placebo group, and less pronounced in the agomelatine 10 mg group than in the other 2 agomelatine groups as follows:

- HAD Depression sub-score: -5.8 ± 4.9, -7.2 ± 5.5 and -7.4 ± 5.2 in the agomelatine 10 mg, 25 mg fixed, and 25-50 mg groups, respectively *versus* -4.5 ± 5.0 in the placebo group.
- HAD Anxiety sub-score: -3.3 ± 3.9, -3.7 ± 4.1 and -4.4 ± 3.6 *versus* -2.3 ± 3.6, respectively.

Results in the two Sub-FAS of more severely depressed patients were in the same line as in the FAS.

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 3 agomelatine groups than in the placebo group, and the mean decrease from baseline in the HAM-D total score was higher in the 3 agomelatine groups than in the placebo group. Both results in the agomelatine 10 mg group were less favourable than those in the other 2 agomelatine groups.

- Mean HAM-D total score: 12.0 ± 9.4, 8.6 ± 8.2, and 8.6 ± 8.4 in the agomelatine 10 mg, 25 mg fixed, and 25-50 mg groups, respectively *versus* 16.4 ± 9.8 in the placebo group.
- Mean decrease from baseline in HAM-D total score: -15.3 ± 9.4, -18.1 ± 8.7, and -18.1 ± 8.5 in the agomelatine 10 mg, 25 mg fixed, and 25-50 mg groups, respectively *versus* -10.3 ± 9.8 in the placebo group.

These results were also observed for the percentage of responders at the last post-baseline assessment over the W0-W24 period (63.6%, 78.3%, and 77.2% in the agomelatine 10 mg, 25 mg fixed dose and 25-50 mg groups, respectively *versus* 41.8% in the placebo group).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Emergent adverse events**

Overall summary of emergent adverse events in the Safety Set

		Agomelatine 10 mg (N = 132)	Agomelatine 25 mg fixed (N = 138)	Agomelatine 25-50 mg (N = 136)	Placebo (N = 141)
W0-W6/Wend					
Patients having reported					
at least one emergent adverse event	n (%)	32 (24.2)	38 (27.5)	48 (35.3)	26 (18.4)
*Emergent headache**	*n (%)*	*11 (8.3)*	*6 (4.3)*	*10 (7.4)*	*7 (5.0)*
*Emergent nausea**	*n (%)*	*3 (2.3)*	*7 (5.1)*	*5 (3.7)*	*2 (1.4)*
at least one severe emergent adverse event	n (%)	1 (0.8)	1 (0.7)	-	1 (0.7)
at least one treatment-related emergent adverse event	n (%)	14 (10.6)	19 (13.8)	21 (15.4)	9 (6.4)
W0-W24/Wend					
Patients having reported					
at least one emergent adverse event	n (%)	52 (39.4)	51 (37.0)	64 (47.1)	41 (29.1)
*Emergent headache**	*n (%)*	*14 (10.6)*	*8 (5.8)*	*12 (8.8)*	*12 (8.5)*
*Emergent nasopharyngitis**	*n (%)*	*2 (1.5)*	*2 (1.4)*	*7 (5.1)*	*6 (4.3)*
*Emergent nausea**	*n (%)*	*4 (3.0)*	*8 (5.8)*	*5 (3.7)*	*3 (2.1)*
at least one severe emergent adverse event	n (%)	2 (1.5)	1 (0.7)	-	1 (0.7)
at least one treatment-related emergent adverse event	n (%)	19 (14.4)	20 (14.5)	21 (15.4)	12 (8.5)
During the study					
Patients having experienced					
at least one serious adverse event	n (%)	1 (0.8)	-	1 (0.7)	1 (0.7)
at least one emergent serious adverse event	n (%)	1 (0.8)	-	-	1 (0.7)
at least one emergent treatment-related serious adverse event	n (%)	-	-	-	-
Patients withdrawn					
due to an emergent adverse event	n (%)	5# (3.8)	2 (1.4)	6 (4.4)	2# (1.4)
due to an emergent serious adverse event	n (%)	1# (0.8)	-	-	-
due to an emergent treatment-related adverse event	n (%)	2 (1.5)	2 (1.4)	1 (0.7)	-
due to an emergent treatment-related serious adverse event	n (%)	-	-	-	-
Patients who died	n (%)	-	-	-	-

** Most frequent emergent adverse events reported in at least 5% of patients in any agomelatine groups; # For 2 patients in the agomelatine 10 mg group (1 serious) and 1 patient in the placebo group, the reason for study withdrawal was lack of efficacy*

During the W0-W6/Wend period in the Safety Set, the percentage of patients with at least one emergent adverse event was higher in the 3 agomelatine groups than in the placebo group (see Table above).

As regards agomelatine dose regimens, the percentage of patients with at least one emergent adverse event showed no relevant difference between the agomelatine 10 mg and 25 mg fixed groups, and was lower than in the agomelatine 25-50 mg group.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

The most frequently affected system organ classes on agomelatine (in more than 5% of patients in any agomelatine groups) during the W0-W6/Wend period in the Safety Set were nervous system disorders, gastrointestinal disorders, and infections and infestations. It was also the case in the placebo group. Nervous system disorders (11.4%, 8.7%, and 14.0%, in the agomelatine 10 mg, 25 mg fixed, and 25-50 mg groups, respectively) and gastrointestinal disorders (5.3%, 12.3%, and 9.6%, respectively) were more common in the 3 agomelatine groups than in the placebo group (6.4% and 2.8%, respectively). Incidence of infections and infestations was lower in the agomelatine 10 mg and 25 mg fixed groups (3.0% and 5.1%, respectively) than in the placebo group (8.5%), and showed no relevant differences between the agomelatine 25-50 mg group (7.4%) and the placebo group.

The most frequent emergent adverse events on agomelatine (in at least 5% of patients in any agomelatine groups) were headache and nausea. As compared to placebo, the frequency of headache was higher in the agomelatine 10 mg and 25-50 mg groups (8.3% and 7.4%, respectively) than in the placebo group (5.0%), and was similar in the agomelatine 25 mg fixed group (4.3%) and the placebo group.
The frequency of nausea was higher in the agomelatine 25 mg fixed and 25-50 mg groups (5.1% and 3.7%, respectively) than in the placebo group (1.4%), and was similar in the agomelatine 10 mg group (2.3%) and the placebo group.
The frequency of the most common system organ classes affected and emergent adverse events did not increase with the dose regimen.

Very few patients experienced severe emergent adverse events during the W0-W6/Wend period: 1 patient each in the agomelatine 10 mg and 25 mg fixed groups (hyperhidrosis and dry mouth, respectively), and 1 patient in the placebo group (colitis ulcerative and enterocolitis haemorrhagic).

During the W0-W6/Wend period, in the Safety Set, 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 3 agomelatine groups (10.6%, 13.8%, and 15.4% in the agomelatine 10 mg, 25 mg fixed, and 25-50 mg groups, respectively) than in the placebo group (6.4%).

During the W0-W24/Wend period in the Safety Set as during the W0-W6/Wend period, the percentage of patients with at least one emergent adverse event was higher in the 3 agomelatine groups than in the placebo group without dose regimen dependent increase (39.4%, 37.0%, and 47.1% in the agomelatine 10 mg, 25 mg fixed, and 25-50 mg groups, respectively *versus* 29.1%). Results obtained over W0-W24/Wend were comparable to those observed over W0-W6/Wend.

No death was reported during the study.
During the study, emergent serious adverse events were reported in one patient (0.8%) in the agomelatine 10 mg group (depression, insomnia, anxiety, restlessness, and decreased appetite) and one patient (0.7%) in the placebo group (colitis ulcerative and enterocolitis haemorrhagic). None was considered as treatment related by the investigator. In the agomelatine 10 mg treated patient, the events led to study drug withdrawal.

The percentage of patients who experienced at least one emergent non-serious adverse event leading to study treatment discontinuation was higher in the agomelatine 25-50 mg group (4.4%, 6 patients) than in the placebo group (1.4%, 2 patients). In the agomelatine 10 mg and 25 mg fixed groups, it was 3.0% (4 patients) and 1.4% (2 patients), respectively.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Laboratory tests**
  - In the Safety Set, neither clinically relevant mean changes over time nor differences between groups were detected for biochemical and haematological parameters over both periods.
  - Emergent PCSA biochemical values during the ASSE-W24/Wend period were sparse in all treatment groups except for high PCSA values of triglycerides.
  - Emergent PCSA haematological values during the ASSE-W24/Wend period were similar in all treatment groups.
  - Liver acceptability
    Emergent PCSA values of ALAT and/or ASAT (> 3 ULN) were reported in 1 patient in the agomelatine 10 mg group and 4 patients in the agomelatine 25-50 mg group (2 patients on the 25 mg dose, and 2 on the 50 mg dose). All these PCSA values were reported at W14 visit. All patients recovered after treatment withdrawal (4 patients), and under treatment (1 patient). In 2 patients (1 on 10 mg and 1 on 50 mg) PCSA values were related to concomitant treatment according to investigators (isotretinoin 20 mg/d for around 1 month, and diclofenac 50 mg on request, respectively). PCSA values were as follows:
    - PCSA values of ALAT were associated with PCSA ASAT in 2 patients: one on the 10 mg dose (maximum value 5.2 ULN for ALAT and 3.9 ULN for ASAT), and one on the 25 mg dose (maximum value 5.8 ULN for ALAT and 4.4 ULN for ASAT).
      These PCSA transaminases values were associated with values of GGT and ALP above the upper limit of reference range without reaching the PCSA limit in the 25 mg-treated patient.
    - For the other 3 patients in the agomelatine 25-50 mg group, PCSA values of ALAT (maximum values: 3.9 ULN on 25 mg and 5.3 ULN and 3.6 ULN on 50 mg) were associated with ASAT value above the upper limit of reference range without reaching the PCSA limit.
      These values were associated with free bilirubin above the upper limit of reference range without reaching the PCSA limit in the 25 mg-treated patient, and with bilirubin (total, free and conjugated) above the upper limit of reference range without reaching the PCSA limit in one 50 mg-treated patient.

- **Vital signs and BMI**
  - Blood pressure and heart rate
    In the Safety Set, neither clinically relevant mean changes over both treatment periods nor differences between groups were detected for sitting blood pressures and heart rate.
  - Weight and body mass index (BMI)
    In the Safety Set, neither clinically relevant mean change over both treatment periods nor difference between groups was detected for the weight. Most patients remained in the same BMI class in all treatment groups over both treatment periods. The percentage of patients with a BMI change between the baseline and last post-baseline assessment was similar in the treatment groups over both periods.
    - BMI class increase over the W0-W24 period: 6.1% of patients, 6.5%, 8.8% and 7.1% in the agomelatine 10 mg, 25 mg fixed, 25-50 mg, and placebo groups, respectively.
    - BMI class decrease over the W0-W24 period: 2.3% of patients, 2.9%, 3.7%, and 4.3% in the agomelatine 10 mg, 25 mg fixed, 25-50 mg, and placebo groups, respectively.

- **ECG**

Over the W0-W24/Wend period, among patients with at least one interpretable post-baseline ECG, 13.7% in the agomelatine 10 mg group, 11.5% in the agomelatine 25 mg fixed group, 7.3% in the agomelatine 25-50 mg group, and 7.8% in the placebo group presented at least one emergent ECG abnormality. Emergent ECG abnormalities were considered as clinically significant by the investigator for 1 patient in the agomelatine 25 mg fixed group (ST segment depression) and 2 patients in the placebo group (left bundle branch block, and conduction disorder). None of these ECG abnormalities were judged treatment-related by the investigator.

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CONCLUSION

This international, multicentre, double-blind, placebo-controlled, randomised study conducted in patients with Major Depressive Disorder demonstrated a statistically significant antidepressant efficacy of the three agomelatine dose regimens of 10 mg, 25 mg fixed, and 25-50 mg once daily on the HAM-D total score (primary efficacy criterion), as well as on the CGI scale (severity of illness score, and global improvement score) after 6 weeks of treatment. The clinical benefit of the antidepressant effect was clearly demonstrated for the 3 agomelatine dose regimens by the placebo-differences of 2.5, 4.7, and 4.9 points, respectively for the HAM-D total score. At the therapeutic doses of agomelatine, the lower bound of the 95% confidence interval of the placebo-difference of at least 3.2 points reinforces the strength of the treatment effect observed. The clinical relevance of the antidepressant effect of the 3 agomelatine dose regimens was also demonstrated by the difference in term of HAM-D and CGI responders compared to the placebo. In the most severely depressed subpopulation at baseline, the clinically and statistically significant antidepressant efficacy of agomelatine was maintained with the 25 mg and the 25-50 mg dose regimens only.

This study demonstrated the efficacy of the dose regimen 10 mg and confirmed the efficacy of the dose of 25 mg and the dose regimen 25-50 mg recommended in the current SmPC, both with consistent statistically and clinically relevant differences on the primary HAM-D total score and secondary criteria. The marked efficacy results evidence the effective dosage range.

The 3 dose regimens of agomelatine (10 mg, 25 mg fixed and 25-50 mg once daily) were well tolerated during the 6-week and 24-week treatments. The severity, seriousness and treatment discontinuation showed a similar figure to that observed for the placebo. A higher overall incidence of adverse events and of reversible transaminases increases (> 3 ULN) was reported in the agomelatine 25-50 mg dose regimen. Incidence of transaminases increases was higher in the patients who increased the dose to 50 mg. No unexpected adverse event was reported. The safety profile of agomelatine was confirmed in this study.

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