Document title	**Clinical Study Report Synopsis**
Study title	**Efficacy and safety of agomelatine (25mg/day with potential adjustment at 50mg/day) given orally compared to placebo, in addition to a mood stabilizer in Bipolar I patients with a current major depressive episode.** **An 8-week randomised, double-blind, controlled, parallel groups study followed by a double-blind extension treatment period up to 1 year.**
Study drug	**Agomelatine (S 20098)**
Indication	**Major depressive episode in the framework of bipolar disorder**
Development phase	**Phase III**
Protocol code	**CL3-20098-047**
Study initiation date	**18 July 2006**
Study completion date	**22 December 2008**
Signatory coordinator	[redacted] [redacted] **Nantes - 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** **Servier Canada Inc.** **235 Armand Frappier Blvd** **Laval H7V 4A7 - Canada**
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 6 September 2011**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

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Title of study: Efficacy and safety of agomelatine (25 mg/day with potential adjustment at 50 mg/day) given orally compared to placebo, in addition to a mood stabilizer in Bipolar I patients with a current major depressive episode.
An 8-week randomised, double-blind, controlled, parallel groups study followed by a double-blind extension treatment period up to 1 year.
Protocol No. CL3-20098-047

Coordinators:
Scientific advisors: [redacted] ([redacted] USA), [redacted] ([redacted] UK)
National coordinators: [redacted] ([redacted] Argentina), [redacted] ([redacted] Australia), [redacted] ([redacted] Austria), [redacted] ([redacted] Brazil), [redacted] ([redacted] Canada), [redacted] ([redacted] Denmark), [redacted] ([redacted] Finland), [redacted] ([redacted] France), [redacted] ([redacted] Germany), [redacted] ([redacted] India), [redacted] ([redacted] Korea), [redacted] ([redacted] The Netherlands), [redacted] ([redacted] Poland), [redacted] ([redacted] South Africa), [redacted] ([redacted] Spain).

Study centres:
In all, 67/75 centres located in 15 countries included at least one patient: Argentina (6 centres - 27 patients), Australia (6 centres - 28 patients), Austria (3 centres - 28 patients), Brazil (4 centres - 46 patients), Canada (8 centres - 26 patients), Denmark (2 centres - 16 patients), Finland (4 centres - 15 patients), France (6 centres - 39 patients), Germany (4 centres - 27 patients), India (5 centres - 21 patients), Korea (4 centres - 8 patients), Netherlands (2 centres - 4 patients), Poland (7 centres - 20 patients), South Africa (5 centres - 36 patients), Spain (1 centre - 4 patients).

Publication (reference): Not applicable

Studied period: Initiation date: 18 July 2006 Completion date: 22 December 2008 (last visit, last patient)	**Phase of development of the study:** III

Objectives: to assess the efficacy and safety of agomelatine *versus* placebo in addition to a mood stabilizer in bipolar I patients with a current major depressive episode.
Primary objective: to assess the antidepressant efficacy of agomelatine compared to placebo in addition to a mood stabilizer in these patients after 8 weeks of treatment.
Secondary objectives: to assess the safety of agomelatine in addition to a mood stabilizer, and to obtain preliminary data on agomelatine maintenance of efficacy in the extension treatment period.

Methodology:
Multicentre, international, double-blind, randomised, controlled, study in 2 parallel groups using placebo and a flexible dosage of agomelatine, in combination with a mood stabilizer (lithium or valproic acid). The initial dose of 25 mg/day of agomelatine could be increased to 50 mg/day in case of insufficient improvement after 2 weeks of treatment. The criteria for increasing the dose were defined by the sponsor, based on clinical considerations, before the study beginning, and kept blinded to the investigator and the patient as well as whether or not the adaptation has taken place. The mood stabilizer treatment had to remain stable during all the study period. The randomisation (at W0) was balanced (non-adaptive) with stratification on centre and ongoing mood stabilizer. The randomisation, the treatment allocation and the dose increase were done centrally using an Interactive Voice Response System (IVRS). At the end of the 8-week acute double-blind treatment period, the patients could continue in the double-blind extension treatment period according to the investigator's clinical judgement.
This study was performed in strict accordance with Good Clinical Practice.

Number of patients:
Planned: 300 patients (150 patients by group)
Included and randomised: 344 patients (172 patients in each group)

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Diagnosis and main criteria for inclusion:

Male or female out-patients or in-patients, at least 18 years old (at least 21 years old in Argentina according to Amendment No. 1), suffering from a bipolar I disorder currently in a Major Depressive Episode according to DSM-IV-TR criteria (diagnosis confirmed with the MINI) with a current Major Depressive Episode lasting between at least 4 weeks and at more 12 months. At selection and inclusion, HAM-D 17 items total score had to be ≥ 18, and YMRS total score ≤ 8. Patients had to be either on lithium or valproic acid treatment for a minimum of 6 weeks before selection visit with a documented blood level of lithium between 0.5 and 1.0 mEq/L or valproic acid between 50 and 100 µg/mL.

Study drug:

Agomelatine 25 mg tablets, 1 or 2 tablets once a day, po, around 8 p.m.

Patients received 25 mg/day (1 tablet of 25 mg + 1 placebo tablet) from W0, with possible increase in double-blind conditions to 50 mg/day (2 tablets of 25 mg) at W2, in case of insufficient improvement. The dose was maintained up to M12.

Batch Nos. L0009699, L0014110, L0016005, L0020763.

Reference product:

Placebo, 2 tablets once a day, po, around 8 p.m.

Duration of treatment:

- 2 to 10-day selection period without study treatment.
- 8-week acute double-blind treatment period (W0 to W8).
- 10-month double-blind extension treatment period (W8 to M12).
- 1-week follow-up period without study treatment which took place after study treatment discontinuation regardless of its time of occurrence.

Criteria for evaluation:

Efficacy measurements

On depression

- Montgomery and Åsberg Depression Rating Scale (MADRS) was rated by the investigator at selection, inclusion, and each visit up to M12. The primary efficacy criterion was the MADRS total score.
- Hamilton Depression Rating Scale 25 items (HAM-D-17 items + 8 items of Reversed Vegetative Symptom Scale) was rated by the investigator at selection, inclusion, and W8, or in case of withdrawal over the W0-W8 period.
- Clinical Global Impressions scale for bipolar disorder - Modified (CGI-BP-M) was rated by the investigator at selection, inclusion, and each visit up to M12.

On anxiety

Hamilton Rating Scale for Anxiety (HAM-A) was rated by the investigator at inclusion and W8, or in case of withdrawal over the W0-W8 period.

On sleep

Leeds Sleep Evaluation Questionnaire (LSEQ) was self-assessed by the patients at W2, W4, W6 and W8.

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Criteria for evaluation (Cont'd)
Safety measurements

- Young Mania Rating Scale (YMRS) was rated by the investigator at selection, inclusion and each visit up to M12.
- Adverse events reported at each visit including switch to mania or hypomania defined as a significant mood elevation according to the investigator's clinical judgement.
- Laboratory tests: Blood samplings were prescribed at selection, and W6, M5 and M10 visits, or in case of withdrawal in order to get the results for inclusion, and W8, M6 and M12 or follow-up visits, respectively.
  Blood samples were added at W4, M3, M4, M5, M8 and M10 visits to assess ASAT, ALAT, total bilirubin, and alkaline phosphatases in Canadian patients only (Amendment No. 6).
  In addition, urinary porphyrins were assayed at inclusion, W8 and M12, or in case of withdrawal in Canadian patients (Amendment No. 4).
- Vital signs (body weight, supine heart rate, and blood pressure) at selection, W8, M6, and M12 visits, and at the end of study treatment in case of premature withdrawal. Height was measured at selection.
- 12-lead electrocardiogram (ECG): prescribed at selection and M12 visit, or in case of withdrawal to have results available for the inclusion and the follow-up visit.

Quality of life measurements
Quality of Life Enjoyment and Satisfaction Questionnaire, Short-form (Q-LES-Q) was filled by the patients at inclusion, W8, M6 and M12 visits, or in case of withdrawal.

Statistical methods
The blind was broken once all data of the selection-M6 period were available and validated, in order to perform the analysis of this period and, in particular, the main analysis. However, although the blind was broken before the end of the study, neither investigators, nor patients, nor monitors were informed of the study treatment taken during the treatment period. Moreover, the analysis strategy associated to the whole study period (ASSE-M12) was finalised before study unblinding.

Efficacy analysis
In addition to descriptive statistics by treatment group on the W0-W8 period in patients of the FAS and the OCW8S (except for secondary criteria but remission based on the CGI-BP-M scale depression and mania scores) and on the W0-M12 period in patients of the FAS, the SUB-FAS in extension period, and, for some analytical approaches, the SUB-FAS in extension period of responders at W8, the following analyses were performed.

Primary criterion

- Main analysis:

The superiority of agomelatine as compared to placebo was studied on the change from baseline to last post-baseline value on the W0-W8 period, in patients of the FAS, using a three-way analysis of covariance on factors treatment and type of mood stabiliser (MS) as fixed effects, centre as random effect, with baseline as covariate and without interaction.
Sensitivity analyses: the previous analysis was performed in patients of the RS, substituting the baseline value for last post-baseline value in case of missing value. Moreover an unadjusted analysis, based on the two-sided Student's t-test for independent samples, was performed on the last post-baseline value on the W0-W8 period, in patients of the FAS and the RS (substituting the baseline value for last post-baseline value in case of missing value).

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Efficacy analysis (Cont'd)

- Secondary analyses:

The adjusted and unadjusted analyses described above were performed in patients of the OCW8S considering the change from baseline to value at W8 and the value at W8, respectively.
The difference between agomelatine and placebo was studied on the response to treatment taking into account the last post-baseline value on the W0-W8 period, in patients of the FAS, using a Chi-Square test.
The difference between agomelatine and placebo was also studied on the maintenance of efficacy from the time to first loss of response to treatment on the W8-M12 period, considering two definitions of loss of response to treatment, in patients of the SUB-FAS in extension period of responders at W8. The incidence of loss of response on the W8-M12 period was compared between the two treatment groups using a log-rank test. In order to estimate the hazard ratio of loss of response on agomelatine as compared to placebo, a Cox model associated with the likelihood ratio test was performed. A Cox model with adjustment for the type of MS and the W0 MADRS total score (as continuous variable) was also used as sensitivity analysis.
Secondary criteria
The difference between agomelatine and placebo was studied, in patients of the FAS :

- For the HAM-D 17-item total score, on the change from baseline to last post-baseline value on the W0-W8 period, using a three-way analysis of covariance on factors treatment and type of MS as fixed effects, centre as random effect, with baseline as covariate and without interaction.
- For the CGI-BP-M scale depression score, on the last post-baseline value on the W0-W8 period, using the two-sided Student's t-test for independent samples and the Mann-Whitney test.
- For the HAM-A total score, on the change from baseline to last post-baseline value on the W0-W8 period, using a one-way analysis of covariance on factor treatment as fixed effect, with baseline as covariate and without interaction.

Complementary analyses unplanned:
The mean change from baseline in MADRS total score and HAM-D total score at the last post-baseline assessment over the W0-W8 period was compared between treatment groups in the FAS in more severely ill patients, defined as pronounced, serious or very serious according to general score of the CGI-BP-M at inclusion using a three-way analysis of covariance on factors treatment and type of mood stabiliser (MS) as fixed effects, centre as random effect, with baseline as covariate and without interaction.

Safety analysis
Descriptive statistics were provided in the Safety Set for the two treatment groups and the 3 dose subgroups (agomelatine 25 mg, agomelatine 25-50 mg, placebo) over the W0-W8/Mend and W0-M12/Mend periods.
A complementary analysis was performed on (hypo)manic symptoms. The difference between agomelatine and placebo was studied on the time to onset of (hypo)manic symptoms over the W0-M12/Mend period. The incidence of (hypo)manic symptoms over the W0-M12 period was compared between the two treatment groups using a log-rank test. In order to estimate the hazard ratio of (hypo)manic symptoms on agomelatine as compared to placebo, a Cox model associated with the likelihood ratio test was performed. A Cox model with adjustment for the type of MS and the duration of current MDE was also used as sensitivity analysis.

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SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

Disposition of included patients

Status		Agomelatine	Placebo	All
W0-W8				
Included	n	**172**	**173****	**345**
Randomised	n	**172**	**172 *****	**344**
Lost to follow-up	n (%)	**1 (0.6)**	**-**	**1 (0.3)**
Withdrawn due to	n (%)	**44 (25.6)**	**41 (23.8)**	**85 (24.7)**
Adverse event	n (%)	11 (6.4)	8 (4.7)	19 (5.5)
Lack of efficacy	n (%)	22 (12.8)	25 (14.5)	47 (13.7)
Non-medical reason	n (%)	6 (3.5)	5 (2.9)	11 (3.2)
Protocol deviation	n (%)	4 (2.3)	3 (1.7)	7 (2.0)
Remission or marked improvement	n (%)	1 (0.6)	-	1 (0.3)
Completed the W0-W8 period	n (%)	**127 (73.8)**	**131 (76.2)**	**258 (75.0)**
W8-M12				
Entered the W8-M12 extension period	n (%)	**125 (72.7)**	**122 (70.9)**	**247 (71.8)**
Lost to follow-up*	n (%)	**1 (0.8)**	**1 (0.8)**	**2 (0.8)**
Withdrawn due to*	n (%)	**50 (40.0)**	**47 (38.5)**	**97 (39.3)**
Adverse event	n (%)	17 (13.6)	14 (11.5)	31 (12.6)
Lack of efficacy	n (%)	19 (15.2)	18 (14.8)	37 (15.0)
Non-medical reason	n (%)	8 (6.4)	9 (7.4)	17 (6.9)
Protocol deviation	n (%)	5 (4.0)	4 (3.3)	9 (3.6)
Remission or marked improvement	n (%)	1 (0.8)	2 (1.6)	3 (1.2)
Completed the W8-M12 extension period	n (%)	**74 (43.0)**	**74 (43.0)**	**148 (43.0)**
Performed the follow-up visit (W0-M12)	n (%)	150 (87.2)	152 (88.4)	302 (87.8)
Analysis sets				
Randomised Set	n (%)	172 (100.0)	172 (100.0)	344 (100.0)
Full Analysis Set (FAS)	n (%)	168 (97.7)	171 (99.4)	339 (98.5)
Observed Cases W8 Set (OCW8S)	n (%)	134 (77.9)	143 (83.1)	277 (80.5)
Sub-FAS in extension period	n (%)	124 (72.1)	120 (69.8)	244 (70.9)
Sub-FAS in extension period of responders at W8 (Sub-FAS-R)	n (%)	93 (54.1)	94 (54.7)	187 (54.4)
Safety Set#	n (%)	171 (99.4)	173 (100.0)	344 (99.7)

*%: Expressed as percentage of the patients from the Randomised Set except *: expressed as percentage of patients entered the W8-M12 extension period and # expressed as percentage of patients included ; ** Patient No. 047 040 0202 21825 received placebo but was not randomised by IVRS ; ***2 randomised patients (No. 047 076 0305 21480 and 047 250 0702 21008) received placebo instead of agomelatine due to lack of treatment pack*

Overall, 344 included patients were randomly assigned, according to the IVRS procedure, to one of the two treatment groups. Among them, 172 patients received agomelatine and 172 received placebo. A perfectly balanced distribution was reached. One patient included but not randomised via IVRS received a treatment pack of placebo. This patient continued the study up to M12. The patient was only included in the Safety Set.
In the agomelatine group, 87 patients among the 157 agomelatine-treated patients continuing at W2 (55.4%) had a dose increase.
Two patients in the agomelatine group and 1 patient in the placebo group were lost to follow-up during the study. The rate of withdrawals showed no relevant difference between the agomelatine and placebo groups during both periods. A total of 74 patients (43.0%) in each of the agomelatine and placebo groups completed at M12.

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Patients of the Randomised Set were 45.2 ± 12.6 years old on average (± SD), ranging from 19 to 76 years. Most of the patients were female (61.1% in both treatment groups).

The bipolar I disorder has lasted for 16.7 ± 11.2 years (median 14.6). The first episode was more frequently a depressive episode (62.5% of patients). 32.0% had first a manic episode, and 4.7% of patients had first a mixed episode. Within the previous 10 years, the mean number of episodes was 2.6 ± 2.7 (median 2.0) for manic episodes, 0.8 ± 1.6 (median 0.0) for mixed episodes, and 4.9 ± 4.9 (median 4.0) for previous depressive episodes. During the last 12 months, the mean number of mood episodes was 1.7 ± 0.9 (median 2.0).

There was a family history of mood disorder in 59.9% of patients. It was mainly depressive disorder (33.6% of patients), then bipolar disorder (bipolar I or not specified: 13.2% and 15.8% of patients, respectively).

According to DSM-IV-TR criteria, 198 patients (57.6%) had a moderate MDE, 141 (41.0%) had a severe MDE without psychotic feature, and 5 patients (1.5%) had a mild episode. Melancholic features were observed in 240 patients (69.8%). The current MDE has lasted for 3.2 ± 2.3 months on average (median 2.4 months). In all, one quarter of patients (25.0%, 86 patients) previously had 2.3 ± 1.9 suicide attempts on average (median 1.0).

In all, 294 patients of the Randomised Set (85.5%) had received psychotropic treatments other than lithium or valproic acid within the year prior to the selection in the study. The treatments were mainly anti-depressant (58.7% of patients), then antipsychotic (49.1%), and anxiolytics (37.2%).

No relevant differences between treatment groups were observed for demography and the characteristics of bipolar I disorder. Similar results were observed for the FAS and OCW8S.

Regarding efficacy criteria at inclusion, the mean score (± SD) were:

- MADRS total score = 30.0 ± 5.4.
- HAM-D 17-item total score = 25.0 ± 3.7.
- RVSS total score = 5 .0 ± 3.0. Of the 8 items, the highest score was observed for psychic retardation (1.3 ± 0.8, median 1).
- CGI-BP-M: depression score = 4.6 ± 0.8, mania score = 1.1 ± 0.3 (corresponding to normal on average), and general score = 4.5 ± 0.9.
- HAM-A total score = 20.3 ± 6.7.

Regarding Q-LES-Q at inclusion, the mean general activities score over the last week before inclusion was 37.2 ± 14.5 corresponding to dissatisfied patients on average. Nearly three quarters of patients (74.2% patients) found their overall life satisfaction very poor or poor.

Regarding the YMRS, the mean total score was 2.8 ± 1.8 at inclusion.

There were no relevant differences between treatment groups for all criteria of efficacy, and for Q-LES-Q, and YMRS at baseline. Similar results were observed for the FAS and OCW8S.

In the Randomised Set, treatment duration ranged between 0 and 64 days with a mean ± SD of 50 ± 14 days and a median of 56 days during the W0-W8 period, and it ranged between 0 and 436 days with a mean ± SD of 211 ± 145 days and a median of 226 days during the W0-M12 period. No relevant difference between treatment groups was observed. Global compliance was good over both periods on average, and showed no relevant difference between treatment groups (96.4 ± 13.0% over W0-W8 and 95.0 ± 13.1% over W0-M12).

All patients received either lithium (54.7%) or valproic acid (45.4%) over the whole study. At inclusion, the mean blood level of both mood stabilizers were within the therapeutic range in both treatment groups (lithium 0.75 ± 0.17 and 0.77 ± 0.15 mmol/L in the agomelatine and placebo groups, respectively, and valproic acid 75.3 ± 16.2 and 79.5 ± 14.5 µg/mL, respectively).

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EFFICACY RESULTS

- **Primary efficacy criterion: Montgomery and Asberg rating scale (MADRS) total score**
  - *Change from baseline to last post-baseline value (main analytical approach)*
    In the FAS, the mean MADRS total score progressively decreased over the W0-W8 period in both treatment groups. At the last post-baseline assessment, the mean decrease from baseline showed no statistically significant between-group difference after adjustment on mood stabilizer, baseline and centre (main analysis, see Table below).
    Sensitivity analyses and analyses in the OCW8S led the same conclusion.

MADRS total score: between-group comparison in the FAS over the W0-W8 period

		Agomelatine (N = 168)	**Placebo (N = 171)**
Baseline (W0)	n	168	171
	Mean ± SD	29.5 ± 5.4	30.6 ± 5.2
Last post-baseline value	n	168	171
	Mean ± SD	14.1 ± 10.2	15.4 ± 12.1
Change from baseline to last post-baseline value	n	168	171
	Mean ± SD	-15.4 ± 10.3	-15.2 ± 11.8
Statistical analysis			
*Main analysis**	E (SE) (1)	-0.65 (1.13)	
	95% CI (2)	[-2.87 ; 1.57]	
	p-value(3)	0.565	
*Sensitivity analysis***	E (SE) (4)	-1.30 (1.22)	
	95% CI (2)	[-3.69 ; 1.10]	
	p-value(3)	0.286	

** General linear model with type of mood stabilizer as fixed effect, centre as random effect and with baseline as covariate*
*** Two-sided Student's t-test for independent samples*
(1) Estimate (Standard Error) of the difference between adjusted treatment group means: agomelatine minus placebo
(2) Two-sided 95% Confidence Interval of the estimate
(3) p-value of treatment effect
(4) Estimate (Standard Error) of the difference between treatment group means: agomelatine minus placebo

Complementary analysis unplanned in more severely ill patients (defined as pronounced, serious or very serious according to general score of the CGI-BP-M at inclusion, i.e. longitudinal severity of bipolar disorder during the previous year, n = 76 in the agomelatine group and n = 81 in the placebo group), showed that the mean decrease from baseline in MADRS total score at the last post-baseline assessment was higher in the agomelatine group (-16.8 ± 10.6) than in the placebo group (-13.9 ± 13.9). The difference in favour of agomelatine was clinically relevant without reaching the statistical significance (E(SE) = -2.92 (1.93), 95% CI = [-6.74 ; 0.90], p = 0.132).

Over the W0-M12 period, the mean decrease in MADRS total score at the last post-baseline assessment was -15.4 ± 12.7 in the agomelatine group, and -14.9 ± 13.6 in the placebo group in the FAS.

  - *Response to treatment (defined as a decrease from baseline in MADRS total score of at least 50%)*
    Over the W0-W8 period, in the FAS, the percentage of responders showed no statistically significant difference in the agomelatine and placebo groups at the last post-baseline assessment (61.9%, and 60.8%, respectively; E (SE) = 1.09% (5.29%), 95% CI of [-9.28% ; 11.45%], p = 0.837).
    Over the W0-M12 period, the percentage of responders at the last post-baseline assessment was 61.9% in the agomelatine group and 55.0% in the placebo group in the FAS.

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EFFICACY RESULTS (Cont'd)

- **Primary efficacy criterion: Montgomery and Asberg rating scale (MADRS) total score (Cont'd)**
  - *Loss of response (defined as the occurrence over the W8-M12 period of a non response, or a withdrawal due to lack of efficacy or suicide attempt)*
    In patients of the Sub-FAS in extension period of responders at W8 (Sub-FAS-R), the overall percentage of patients who had a loss of response during the W8-M12 period was 33.3% (31 patients) in the agomelatine group and 37.2% (35 patients) in the placebo group. The incidences over time of patients having a loss of response were not statistically significantly different between treatment groups (p = 0.559, log-rank test). On agomelatine, the risk of loss of response overtime was reduced by 13.1% compared to placebo without statistical significance (HR (SE) = 0.869 (0.21 4) and 95% CI = [0.536 ; 1.409], p = 0.567, Cox model). Similar results were observed after adjustment for type of mood stabilizer and W0 MADRS total score (HR (SE) = 0.901 (0.225) and 95% CI = [0.552 ; 1.471], p = 0.677, adjusted Cox model) as well as considering a loss of response defined as the occurrence at the last visit on the W8-M12 period of a non response or a withdrawal due to lack of efficacy or suicide attempt.
  - *Remission (defined as a MADRS total score ≤ 12)*
    Over the W0-W8 period, in the FAS, the percentage of remitters at the last post-baseline assessment was similar in both treatment groups (53.0% and 53.2% in the agomelatine and placebo groups, respectively).
    Over the W0-M12 period, the percentage of remitters at the last post-baseline assessment was higher in the agomelatine group (57.7%) than in the placebo group (52.6%) in the FAS.
- **Secondary efficacy criteria**
  - *Hamilton Depression Rating Scale - 17 items (HAM-D)*
    In the FAS, the mean HAM-D total score decreased between the baseline and the last post-baseline assessment over the W0-W8 period in both treatment groups. The mean decrease from baseline at last post-baseline assessment was -13.2 ± 8.0 in the agomelatine group and -12.3 ± 9.1 in the placebo group without statistically significant difference (E(SE) = -1.13 (0.85), 95% CI = [-2.81 ; 0.54], p = 0.184).
    Complementary analysis unplanned in more severely ill patients showed that the mean decrease from baseline at last post-baseline assessment was in favour of agomelatine over placebo. This between-group difference reached a clinical significance and was very close to the statistical significance (n = 155, -14.0 ± 8.5 in the agomelatine group *versus* -10.8 ± 10.1 in the placebo group, E(SE) = -2.76 (1.44), 95% CI = [-5.61 ; 0.10], p = 0.058).
  - *Reversed Vegetative Symptom Scale (RVSS)*
    In the FAS, the mean RVSS total score decreased between the baseline and the last post-baseline assessment over the W0-W8 period in both treatment groups without relevant difference between them as follows:
    - In the agomelatine group: from 4.9 ± 3.0 (median 5.0) to 2.4 ± 2.7 (median 2.0).
    - In the placebo group: from 5.1 ± 3.1 (median 5.0) to 2.3 ± 2.4 (median 2.0).
  - *Clinical Global Impression - Bipolar version (CGI-BP-M)*
    In the FAS, the mean depression score and general score decreased between the baseline and the last-post-baseline assessment over the W0-W8 period in both treatment groups without relevant difference between them as follows:
    - Depression score:
      - In the agomelatine group: from 4.6 ± 0.8 (median 5.0) to 2.9 ± 1.4 (median 3.0).
      - In the placebo group: from 4.7 ± 0.8 (median 5.0) to 2.9 ± 1.6 (median 3.0).

    At the last post-baseline assessment, the mean depression score showed no statistically significant between-group difference (E(SE) = -0.07 (0.16), 95% CI = [-0.39 ; 0.25]), p = 0.681 with two-sided Student's t-test, p = 0.955 with Mann-Whitney test).

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EFFICACY RESULTS (Cont'd)

- **Secondary efficacy criteria (Cont'd)**
  - *Clinical Global Impression - Bipolar version (CGI-BP-M) (Cont'd)*
    - General score:
      - In the agomelatine group: from 4.4 ± 0.9 (median 4.0) to 2.9 ± 1.4 (median 3.0).
      - In the placebo group: from 4.5 ± 0.9 (median 4.0) to 3.0 ± 1.6 (median 3.0).

      On the other hand, the mean mania score was stable over the W0-W8 period in both treatment groups:
      - In the agomelatine group: from 1.1 ± 0.3 (median 1.0) to 1.2 ± 0.5 (median 1.0).
      - In the placebo group: from 1.1 ± 0.3 (median 1.0) to 1.1 ± 0.5 (median 1.0).

      Over the W0-M12 period, similar results were observed in the FAS.

    Remission (defined as depression and mania scores = 1)

    In the FAS, at the last post-baseline assessment over the W0-W8 period, the percentage of remitters showed no relevant difference between treatment groups (16.7% in the agomelatine group and 19.9% in the placebo group).
  - *Hamilton Anxiety Rating Scale (HAM-A)*

    In the FAS, the mean HAM-A total score decreased between the baseline and the last post-baseline assessment over the W0-W8 period in both treatment groups. The mean decrease from baseline at last post-baseline assessment was -9.9 ± 8.5 in the agomelatine group and -9.3 ± 8.8 in the placebo group without statistically significant difference (E(SE) = - 0.54 (0.85), 95% CI = [-2.20 ; 1.12]), p = 0.523).
  - *Leeds sleep evaluation questionnaire (LSEQ)*

    In the FAS, over the W0-W8 period, mean scores at last assessment in the agomelatine and placebo groups, showed no relevant difference between treatment groups as follows:
    - Getting off to sleep score: 38.6 ± 17.6 mm and 40.4 ± 21.2 mm, respectively.
    - Quality of sleep score: 39.2 ± 23.6 mm and 38.2 ± 24.6 mm.
    - Sleep awakening score: 41.2 ± 22.1 mm and 40.4 ± 24.2 mm.
    - Integrity of behaviour score: 40.7 ± 21.7 mm and 41.6 ± 23.7 mm.
  - *Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)*
    - General activities score

      In the FAS, the mean Q-LES-Q general activities score increased between the baseline and the last post-baseline assessment over the W0-W8 period in both treatment groups without relevant difference between treatment groups (+14.7 ± 19.8 in the agomelatine group, and +13.9 ± 19.6 in the placebo group).
    - Overall life satisfaction score

      In the FAS, the percentage of patients with a score improvement between the baseline and the last post-baseline assessment was 61.3% in the agomelatine group, and 60.4% in the placebo group.
    - Satisfaction with medication score

      In the FAS, the percentage of patients with a good or very good satisfaction with medication score at the last assessment over the W0-W8 period was 59.6% in the agomelatine group and 55.3% in the placebo group.

    Over the W0-M12 period, similar results were observed for the 3 scores.

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SAFETY RESULTS

- **Emergent adverse events**

Overall summary of safety results

		Agomelatine (N = 171)	**Placebo (N = 173)**
W0-W8/Mend			
at least one EAE	n (%)	93 (54.4)	80 (46.2)
at least one treatment-related EAE	n (%)	50 (29.2)	49 (28.3)
W0-M12/Mend			
at least one EAE	n (%)	119 (69.6)	112 (64.7)
at least one treatment-related EAE	n (%)	64 (37.4)	65 (37.6)
During the study			
at least one non-fatal serious AE	n (%)	14 (8.2)	12 (6.9)
at least one non-fatal serious EAE	n (%)	12 (7.0)	10 (5.8)
at least one treatment-related non-fatal serious EAE	n (%)	7 (4.1)	1 (0.6)
Treatment discontinuation due to EAE	n (%)	37 (21.6)	33 (19.1)
Patients who died of EAE	n (%)	-	1 (0.6)

AE: adverse event; EAE: emergent adverse event; n: number of patients concerned; %: n/N x 100

Over the W0-W8/Mend period in the Safety Set, the percentage of patients who reported at least one emergent adverse event showed no relevant difference between treatment groups (54.4% in the agomelatine group and 46.2% in the placebo group).

The most frequent system organ classes affected (in more than 5% of patients) were the same in the agomelatine and placebo groups without relevant difference in incidence as follows:

- Gastrointestinal disorders: 16.4% of patients and 17.9%, respectively.
- Nervous system disorders: 15.2% and 16.8%, respectively.
- Psychiatric disorders: 12.3% and 12.1%, respectively.
- Infections and infestations: 8.2% and 9.8%, respectively.

During the W0-W8/Mend period, the most frequent emergent adverse events (reported in at least 3% of patients) in the agomelatine group were headache and somnolence (5.8% each), nausea (4.7%) and nasopharyngitis (3.5%). In the placebo group, they were headache (7.5%), nausea (5.8%), dizziness and constipation (4.0% each), and insomnia (3.5%).

Among these most frequent emergent adverse events, somnolence and nasopharyngitis were more frequent in the agomelatine group than in the placebo group (5.8% *versus* 2.9%, and 3.5% *versus* 1.7%, respectively), the other ones being less or similarly reported.

In the agomelatine group, patients had mostly emergent adverse events of mild (31.6%) or moderate (22.8%) intensity. Similar results were observed in the placebo group (31.2% and 22.0% of the patients respectively). The percentage of patients who experienced at least one emergent adverse event rated as severe showed no relevant difference between treatment groups (5.8% in the agomelatine group and 4.0% in the placebo group).

During the W0-W8/Mend period, a total recovery was observed in most of the emergent adverse events reported in both treatment groups: 134/147 emergent adverse events i.e. 91.2% in the agomelatine group and 141/156, 90.4% in the placebo group.

During the W0-W8/Mend period, the percentage of patients with at least one emergent adverse event considered to be related to the study treatment by the investigator showed no relevant difference between treatment groups (29.2% in the agomelatine group, and 28.3% in the placebo group).

During the W0-M12/Mend period in the Safety Set, as during the W0-W8/Mend period, the percentage of patients with at least one emergent adverse event showed no relevant difference between treatment groups (69.6% in the agomelatine group and 64.7% in the placebo group). Results obtained over W0-M12/Mend were in the same line as those over W0-W8/Mend.

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SAFETY RESULTS (Cont'd)

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

  During the study, the percentage of patients who experienced manic or hypomanic symptoms was 12.9% (22 patients) in the agomelatine group and 7.5% (13 patients) in the placebo group. A complementary analysis showed no statistically significant difference between the treatment groups.

  During the W0-W8 period, the percentage of patients who experienced emergent manic or hypomanic symptoms showed no relevant difference between treatment groups (7 patients, 4.1% in the agomelatine group and 6 patients, 3.5% in the placebo group). In the agomelatine group, the emergent (hypo)manic symptoms over the W0-W8 period were considered to be treatment related in all patients, and in 4/6 patients in the placebo group. All patients recovered. In the agomelatine group, these emergent (hypo)manic symptoms led to treatment discontinuation in all patients, and in half patients (3/6) in the placebo group. For 3 patients (1.8%) in the agomelatine group, these events were notified as serious (1 mixed episode, 1 mania, and 1 elevated mood). In the placebo group, 2 patients (1.2%) had emergent events notified as serious (2 mania). During the W8-M12 period, 13 additional patients (7.6%) in the agomelatine group and 7 (4.1%) in the placebo group experienced emergent manic or hypomanic symptoms. Among these symptoms, emergent hypomania were more frequent in the agomelatine group (7/13) than in the placebo group (2/7).

  During the study, in the placebo group, one patient died of an upper respiratory tract infection, after 35 days of treatment. This death was considered as not related to the study treatment by the investigator. The percentage of patients who reported at least one non fatal emergent serious adverse event showed no relevant difference between treatment groups (7.0%, 12 patients, in the agomelatine group, and 5.8%, 10 patients, in the placebo group). In both treatment groups, emergent non-fatal serious adverse events were mainly related to psychiatric disorders (including (hypo)manic symptoms described above: 10/12 in the agomelatine group, and 9/10 in the placebo group). Among these events, suicide attempts were less frequent event in the agomelatine group (2 patients, 1.2%) than in the placebo group (5 patients, 2.9%). Emergent non-fatal serious adverse events led to treatment withdrawal in 9 patients (5.3%) in the agomelatine group, and 8 patients (4.6%) in the placebo group. Emergent non-fatal serious adverse events were considered as treatment related by the investigator in 7 patients (4.1%) in the agomelatine group, and 1 patient (0.6%) in the placebo group. All patients recovered in both treatment groups.

  As regards non serious emergent adverse events leading to treatment withdrawal during the W0-M12 period, the percentage of patients concerned showed no relevant difference between treatment groups (16.4%, 28 patients, in the agomelatine group, and 14.5%, 25 patients, in the placebo group). In both treatment groups, treatment withdrawals were mainly related to psychiatric disorders (23/28 patients and 17/25 in the agomelatine and placebo groups, respectively).

- **Laboratory parameters**
  - In the Safety Set, over both periods, biochemical and haematological parameters did not show any clinically relevant change over time on average in both treatment groups nor relevant difference between them. For biochemical parameters, emergent PCSA values were reported in 27 patients (15.8%) in the agomelatine group, and 14 patients (8.1%) in the placebo group over the W0-M12/Mend period. They concerned mainly triglycerides in both treatment groups (20/26 in the agomelatine group, and 8/14 in the placebo group). For haematological parameters, emergent PCSA values were reported in 12 patients (7.0%) in the agomelatine group, and 7 patients (4.0%) in the placebo group. These PCSA values concerned low and high values of WBC, neutrophils and platelets in both treatment groups without relevant differences between them, and one high value of eosinophils, and one low value of haematocrit in the placebo group.

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SAFETY RESULTS (Cont'd)

- **Laboratory parameters (Cont'd)**
  - Liver acceptability: in the Safety Set, during the W0-M12/Mend period, emergent PCSA liver values concerned transaminases in both treatment groups (one patient in each group). In the agomelatine group (25 mg), the patient had emergent PCSA ALAT at W8 associated with emergent PCSA ASAT at M6 (4 ULN then 7.1 ULN, and 6.5 ULN, respectively). These emergent PCSA values were both reported as adverse event and led to treatment withdrawal at M6. Both events were considered as related to the study drug by the investigator. The patient recovered. In the placebo group, the patient had emergent PCSA ASAT at W8 (8.0 ULN). At the last sampling (not on treatment), value was still abnormal without reaching PCSA limit.
- **Young Mania Rating Scale (YMRS)**
  In the Safety Set, the mean YMRS total score was stable between the baseline and the last post-baseline assessment over the W0-W8 period in both treatment groups (-0.38 ± 3.67, median -1.00 in the agomelatine group, and -0.51 ± 3.77, median -1.00 in the placebo group).
  Over the W0-M12 period, the change from baseline to the last post-baseline assessment was 0.49 ± 5.07, median -1.00 in the agomelatine group, and 0.25 ± 4.80, median 0.00 in the placebo group.
- **Vital signs and Body Mass Index (BMI)**
  There were no relevant mean changes in supine blood pressures and heart rate as well as in weight between baseline and last post-baseline assessment over the selection-W8 period and selection-M12 periods in the Safety Set in both treatment groups. As regards BMI, most patients remained in the same BMI class as baseline in both treatment groups over the selection-M12 period (80.1% in the agomelatine group and 85.4% in the placebo group). In addition, 15 patients (9.0%) normalised in the agomelatine group and 6 (3.5%) in the placebo group.
- **Electrocardiogram (ECG)**
  During the study, no clinically significant ECG abnormality was reported in both treatment groups.

CONCLUSION

This multicentre, double-blind, randomised, placebo-controlled study in patients suffering from Bipolar I Disorder with current major depressive episode did not show any beneficial effect of agomelatine in combination with lithium or valproic acid as compared to placebo on MADRS total score reduction over an 8-week treatment period in the FAS (primary efficacy criterion). The high rate of responders (61%) in the placebo group receiving also mood stabilizers may have contributed to the failure to demonstrate a statistically or clinically significant difference. Results of secondary criteria on depression, anxiety, sleep and quality of life were in the same line. Besides, in the subgroup of more severe patients, a clinically relevant difference in favour of agomelatine was observed, very close to statistical significance with HAM-D (post-hoc analyses).

The safety of agomelatine was satisfactory, including liver acceptability, and similar to placebo. Regarding emergence of (hypo)manic symptoms during the study, there was no statistically significant difference between the agomelatine and placebo groups. Nevertheless, hypomania was more frequent on agomelatine over the long-term period (W8-M12).

Date of the report: 6 September 2011