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| *Document title* | **Clinical Study Report Synopsis** |
| *Study title* | **Effects of agomelatine (25 mg) given orally once a day for 7 days on cerebral activity measured by functional MRI during processing of emotional stimuli in patients with Major Depressive Disorder.**<br>**A randomised, double-blind, placebo-controlled study with an open extension period of 6 months with agomelatine (25 mg).**<br>**Comparison to functional MRI profiles of healthy volunteers.** |
| *Study drug* | **Agomelatine (S 20098)** |
| *Studied indication* | **Major Depressive Disorder** |
| *Development phase* | **Phase II** |
| *Protocol code* | **CL2-20098-067** |
| *Study initiation date* | **29 September 2008** |
| *Study completion date* | **19 October 2011** |
| *Main coordinator* | [redacted] **- France** |
| *Sponsor* | **Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**50, rue Carnot**<br>**92284 Suresnes Cedex - France** |
| *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 10 October 2012** |

~~**CONFIDENTIAL**~~

## 2. SYNOPSIS

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**Title of study**: Effect of agomelatine (25 mg) given orally once a day for 7 days on cerebral activity measured by functional MRI during processing of emotional stimuli in patients with Major Depressive Disorder (MDD).
A randomised, double-blind, placebo-controlled study with an open extension period of 6 months with agomelatine (25 mg).
Comparison to functional MRI profiles of healthy volunteers.
Protocol No.: CL2-20098-067

**National Coordinator:** [redacted] - France

**Study centres:**
7 centres in France included at least one participant.

**Publication (reference):** Not applicable

| **Studied period:** | **Phase of development of the study:** |
|---|---|
| Initiation date: 29 September 2008<br>Completion date: 19 October 2011 | Phase II study |

**Objectives:**
**Primary objective**: to assess the effect of 7 days administration of agomelatine (25 mg) compared to placebo, on cerebral activation measured by fMRI during an emotional processing paradigm in MDD patients.
**Secondary objectives**:

- To evaluate the severity of depression in MDD patients by using the Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression (CGI), before treatment, after 7 days administration of agomelatine (25 mg) *versus* placebo, after 7 weeks treatment with agomelatine and at the end of the open extension period (W24).
- To evaluate sleep in MDD patients by using the Leeds Sleep Evaluation Questionnaire (LSEQ) after 7 days administration of agomelatine *versus* placebo and after 7 weeks treatment with agomelatine.
- *To determine metabonomic profiles of MDD patients and Healthy Volunteers (HV) before treatment and after 7 days (and 7 weeks for MDD patients) administration of agomelatine or placebo in order to compare the evolution (if any) of the metabonomic profiles in these two populations.
- To compare fMRI profiles of MDD patients to fMRI profiles of HV before treatment and after 7 days administration of agomelatine or placebo (*i.e.*: MDD *versus* HV before treatment, MDD *versus* HV after placebo treatment and MDD after agomelatine treatment *versus* HV after placebo treatment) and fMRI profiles of MDD patients after 7 weeks treatment with agomelatine *versus* fMRI profiles of patients after 7 days treatment with agomelatine and to HV before treatment and HV after 7 days placebo treatment.
- *To compare structural MRI, Diffusion Tensor Imaging (DTI) and Magnetic Resonance spectroscopy (MRS) data between HV and MDD patients at baseline, W1 (DTI and MRS) and W7 and W7 for MDD and at baseline and W1 for HV (according to Amendment No. 2).

Tentative correlations were performed in MDD patients between:

- *Pharmacodynamic responses (fMRI and metabonomic profiles), depression severity (HAM-D and CGI scores) and sleep evaluation (LSEQ) before treatment, after 7 days treatment with agomelatine or placebo (double blind period) and after 7 weeks treatment with agomelatine (open extension period).
- *Evolution of depression (e.g. rate, amplitude) measured by HAM-D and CGI by the study centre psychiatrist and pharmacodynamic responses.
- *Whole brain structural MRI data, DTI data, MRS data and depression severity at baseline, after 1 week (DTI and MRS) and after 7 weeks treatment with agomelatine (open extension period), according to Amendment No. 2.

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**Objectives: (Cont'd)**
**Secondary objectives: (Cont'd)**

- *Pharmacodynamic responses (fMRI and metabonomic profiles) and genetic variants of 5-HTT, 5-HT2C and MT1/MT2 receptors

*Another objective was to evaluate after 7 weeks treatment with agomelatine if the response to treatment (defined as a total score HAM-D decrease from baseline ≥ 50%) or the remission/non-remission state of MDD patients (remission state cut-off score HAM-D≤7) could be predicted by a pharmacodynamic response (fMRI profile or metabonomic profile) obtained at baseline or after 7 days administration of agomelatine.

*(* These results are presented in a separate report)*

**Methodology:**
Multicentre, Phase II exploratory study.

- For MDD patients, the study was randomised, with parallel groups (agomelatine 25 mg/day versus placebo), with a 7-day double blind period. The double blind period was followed by a one-week single-blind period during which all patients received agomelatine 25 mg/day and an open extension period of 22 weeks with agomelatine 25 mg/day. Study treatments were assigned to MDD patients at inclusion by a balanced randomisation with stratification on centre.
- For HV, the study was a single blind study with placebo during 1 week.

This study was performed in strict accordance with Good Clinical Practice.

**Number of patients:**
Planned: 60 participants:
40 randomised MDD patients (20 patients by treatment group for the double blind period).
20 HV.
Included: 30 MDD patients (15 in each treatment group) and 14 HV.

**Diagnosis and main criteria for inclusion:**
The participants were female outpatients, Caucasian, between 25 and 53 years old (as modified by Amendment No. 4 from the previous condition of "between 25 and 50 years"). MDD outpatients had to fulfil DSM-IV criteria with a HAM-D-17 total score ≥ 22 and a CGI Severity of illness score ≥ 4.

**Study drug:**
Agomelatine, film-coated tablets of 25 mg, one tablet per day, single administration p.o., at around 8 p.m.
**Batch No.** L0018287, L0027378, L0037415.

**Reference product:**
Tablets of matching placebo, one tablet per day, single administration p.o., at around 8 p.m.

**Duration of treatment:**
For MDD patients:

- Period from preselection to inclusion (W0) without treatment (not exceeding 14 days, as modified by Amendment No. 1 from 6 days).
- Double-blind period of 1 week (W0 to W1), agomelatine or placebo treatment.
- Single-blind period of one week (W1 to W2), agomelatine treatment.
- 22-week open extension period (W2 to W24), agomelatine treatment.

For HV:

- Period from selection to W0 without treatment (not exceeding 3 weeks).
- Single-blind period of 1 week (W0 to W1), placebo treatment.

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**Criteria for evaluation:**

***Efficacy and pharmacodynamic measurements:***

*Functional MRI:*

- fMRI exploration of brain activation pattern at rest and for each condition of emotional processing (self-condition, general condition and control condition), based on the Blood Oxygenation Level-Dependent (BOLD) effect, performed at inclusion, W1 and W7 visits (MDD patients).

*Severity of depression (for MDD patients only):*

- At W0, W1, W7 and W24 visits at the Clinical Investigation Centre (CIC) and pre-selection visit, W2, W4, W6, W8, W12, W16, W20, WEND visits with the study centre psychiatrists:
  - Hamilton Depression Rating Scale 17 item (HAM-D-17) total score.
  - CGI scores (severity of illness and global improvement scores).

*Sleep (only for MDD patients):*

- LSEQ sub-scores (getting off to sleep, quality of sleep, sleep awakening, integrity of behaviour) at W1 and W7 visits.

*Other measurements (reported separately):*

- Metabonomic profile in plasma atW0, W1, W7 and W24 visits for MDD patients, at W0 and W1 for HV.
- Genotype 5HT2C, MT1 and MT2 receptors and 5-HTT at W0 for both MDD and HV.
- Whole brain structural MRI (using voxel based morphometry), DTI and MRS, at W0, W1 and W7 for MDD patients and at W0 and W1 for HV. (DTI and MRS were added with Amendment No. 2).

***Safety measurements***

- Adverse events at each study visit (from pre-selection to WEND for MDD and from selection to W1 for HV).
- Physical examination and vital signs: supine blood pressure and heart rate and weight were measured at selection, W0, W1 (MDD and HV); W7 and W24 (MDD patients only).
- 12-lead electrocardiogram (ECG) at selection visit and at W24 (only MDD patients).
- Laboratory parameters (haematology, biochemistry) at selection visit (MDD and HV); at W7 and W24 (MDD patients only).

**Statistical methods:**

The primary criterion was the change (increase or decrease) of BOLD signal during emotional processing compared to control conditions (control task or visual fixation crosshair). As a preliminary step, a group-specific analysis at participant level was done at baseline: agomelatine-treated (only MDD patients) or placebo-treated (MDD patients + HV). Then, a between-group analysis was performed using a multifactorial ANOVA to assess over time the difference of brain activation between MDD patients under agomelatine, MDD patients under placebo and HV under placebo. Analyses were performed on the subjects of the W0-W1 MRI PPS for early effects of agomelatine and W0-W7 MRI PPS for longer term effects of agomelatine treatment. No comparisons were made in the IS.

For the clinical signs of depressive and subjective sleep, the effect of agomelatine *versus* placebo were described on the change in HAM-D-17 total score, CGI and LSEQ over the W0-W1 period in MDD patients in the W0-W1 MRI PPS and in the Included Set. The effect of agomelatine was also described using the same criteria overall and by treatment sequence, on the W0-W7 and W0-W24 periods in MDD patients continuing after W1 in the W0-W7 MRI PPS and in the Included Set (except for LSEQ: last assessment at W7).

Descriptive statistics for safety parameters in the Safety Set were provided over the W0-W1 period (agomelatine *versus* placebo). The safety of agomelatine by treatment sequence, as well as overall was provided on the periods up to W7 and W24.

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**SUMMARY - CONCLUSIONS**

STUDY POPULATION AND OUTCOME

**Disposition of patients**

| | | HV | MDD patients | | | All participants |
|---|---|---|---|---|---|---|
| | | | Ago/Ago | Pbo/Ago | All | |
| **W0-W1** | | | | | | |
| **Included** | **n (%)** | 14 (100) | 15 (100) | 15 (100) | 30 (100) | 44 (100) |
| **Completed the W0-W1 period** | n (%) | 14 (100) | 15 (100) | 15 (100) | 30 (100) | 44 (100) |
| **Entered the W1-W7 period** | **n (%)** | - | 15 (100) | 15 (100) | 30 (100) | - |
| **Withdrawn due to** | **n (%)** | - | 1 (6.7) | 1 (6.7) | 2 (6.7) | - |
| lack of efficacy | n (%) | - | 1 (6.7) | 1 (6.7) | 2 (6.7) | - |
| **Completed the W1-W7 period** | n **(%)** | - | 14 (93.3) | 14 (93.3) | 28 (93.3) | - |
| **Entered the W7-W24 period** | **n (%)** | - | 14 (93.3) | 14 (93.3) | 28 (93.3) | - |
| **Withdrawn due to** | **n (%)** | - | 2 (13.3) | 1 (6.7) | 3 (10.0) | - |
| non-medical reason | n (%) | - | 1 (6.7) | 1 (6.7) | 2 (6.7) | - |
| lack of efficacy | n (%) | - | 1 (6.7) | - | 1 (3.3) | - |
| **Completed the W7-W24 period** | **n (%)** | - | 12 (80.0) | 13 (86.7) | 25 (83.3) | - |
| **Included Set** | **n (%)** | **14 (100)** | **15 (100)** | **15 (100)** | **30 (100)** | **44 (100)** |
| W0-W1 MRI PPS | n (%) | 14 (100) | 13 (86.7) | 12 (80.0) | 25 (83.3) | 39 (88.6) |
| W0-W7 MRI PPS | n (%) | - | 9 (60.0) | 10 (66.7) | 19 (63.3) | 19 (-) |
| **Safety set** | **n (%)** | **14 (100)** | **15 (100)** | **15 (100)** | **30 (100)** | **44 (100)** |

*%: Expressed as percentage of the patients in the Included Set*

A total of 44 participants (14 HV and 30 MDD patients) were selected and included. A well balanced distribution was reached (15 patients in each group). No included participants were lost to follow up.

At baseline in the IS, the participants were aged 41.2 ± 7.2 years overall (median 41.0); all were female, 42 out 44 were Caucasian; 41 were right-handed. The main baseline characteristics are summarised for the W0-W1 MRI PPS in the table below.

| | HV (N = 14) | MDD patients | | | All (N = 39) |
|---|---|---|---|---|---|
| | | Agomelatine (N = 13) | Placebo (N = 12) | All (N = 25) | |
| **Age** (years, median) | 42.0 | 45.0 | 40.5 | 41.0 | 41.0 |
| **Education** (years, median) | 12.0 | 14.0 | 12.0 | 14.0 | 14.0 |
| **MDD** Recurrent (n) | - | 13 | 11 | 24 | - |
| Severity: Moderate (n) | - | 5 | 5 | 10 | - |
| Severe (n) | - | 8 | 7 | 15 | - |
| Duration: of disease (years, median) | - | 16.8 | 9.6 | 11.3 | - |
| of episode (months, median) | - | 5.5 | 2.3 | 2.7 | - |
| No. of episodes (median) | - | 3.0 | 2.0 | 2.0 | - |
| HAM-D-17 total score (median)[§] | - | 23.0 | 25.0 | 24.0 | - |
| HAM-D core depression score (median)[§] | - | 14.0 | 13.0 | 14.0 | - |
| CGI severity score (median)[§] | - | 5.0 | 5.0 | 5.0 | - |

[§] *assessed by CIC psychiatrist at inclusion visit*

All patients had a depression score ≥ 11 at pre-selection (mean HAD depression score = 15.5 ± 2.3, median 16). Previous psychotropic treatment was reported in 12 MDD patients (9 patients in the agomelatine group *versus* 3 in the placebo group), mainly anxiolytics, hypnotics and sedatives and antidepressants.

No clinically relevant differences between the treatment groups were observed for efficacy criteria at baseline. The evaluation by CIC and psychiatrists was similar. Baseline characteristics in the W0-W7 MRI PPS (N = 19) were similar to those observed in the W0-W1 MRI PPS (N = 39)

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**SUMMARY – CONCLUSIONS (Cont'd)**

STUDY POPULATION AND OUTCOME (Cont'd)

The mean overall treatment duration was 7.1 ± 1.1 days (median 7.0 days) over the W0-W1 period, 50.0 ± 2.5 days (median 49.0 days) over the W0-W7 period, and 169.2 ± 3.7 days (median 168 days) over the W0-W24 period. Overall global compliance was satisfactory during the three periods (between 98% and 101%). No relevant differences between groups were observed in treatment duration and compliance.

EFFICACY RESULTS

**Primary assessment criterion**

Consistent with the *a priori* hypothesis, the acutely depressed patients before treatment showed differences in brain activity compared to healthy volunteers during self–referential processing of emotional stimuli, with in particular, hyperactivity of *dorsolateral prefrontal cortex* (DLPFC), *ventrolateral prefrontal cortex* (VLPFC) and *dorsal anterior cingulate regions*.

The activation of the DLPFC and dorsal anterior cingulate regions decreased after one week in both treatment groups, but only in the group of patients who received agomelatine did the hyperactivity of VLPFC normalize after 7 days treatment ((W0>W1: p=0.0006) compared to healthy participants (positive interaction: ago patients > HV x W0 > W1, p=0.0008) and compared to placebo patients group (positive interaction: ago > pbo patients x W0 > W1, p=0.014) and no difference at W1 between the patients group treated with agomelatine and HV)); an interval before which any clinical improvement of depressive symptoms was observed. In the *amygdala* (a region implicated in emotional processing): agomelatine significantly reduced the activity of the amygdala after one week (p=0.038; positive interaction: ago patient>HV x W0>W1, p=0.06).

A decrease of the excessive activation of the DLPFC in self-referential compared to general condition was observed after 6-7 weeks of treatment with agomelatine (p = 0.016; positive interactions: self > general x MDD patient > HV at W0, p = 0.011; self > general x W0 > W7 in MDD patient, p = 0.0002). This change could reflect a normalization of the cognitive control during self-referential processing as observed in HV.

Moreover, there was an increase in the activation of the ventral part of the anterior cingulate cortex after 6-7 weeks of treatment with agomelatine ( p= 0.003, positive interaction: self >general x W7 > W0 in MDD patient p=0.00006; self >general x HV>MDD patient at W0 p = 0.024), which could reflect increased automatic self-relevance processing as observed at baseline in HV.

**Secondary assessment criteria**

Over the W0-W1 period, the mean HAM-D-17 total score decreased in the MDD patients of the W0-W1 MRI PPS, by -3.0 ± 3.2 (median -2.0) in the agomelatine group and by -3.9 ± 3.6 (median -4.5) in the placebo group. The mean CGI-global improvement score was 3.6 ± 0.5 (median 4.0) and 3.3 ± 0.7 (median 3.0), respectively. Results were similar in the MDD patients of the Included Set.

Over the W0-W7 period in the W0-W7 MRI PPS, the mean HAM-D-17 total score decreased similarly in the 2 treatment sequence groups, suggesting that 6 weeks or 7 weeks of active treatment had essentially the same effect on clinical symptoms. The overall mean change as evaluated by the CIC was -11.7 ± 4.3 (median: -13.0) and according to the study centre psychiatrists it was -12.1 ± 6.1 (median: -12.0). The mean CGI global improvement score overall was 2.4 ± 0.8 (median: 2.0) evaluated by the CIC and 2.2 ± 0.9 (median: 2.0) according to the study centre psychiatrists. Thus, a clinically relevant improvement in symptomatic depression was evidenced with no relevant differences between sequence groups.

Over the W0-W24 period, the overall mean change in HAM-D-17 total score in the W0-W7 MRI PPS as evaluated by the CIC was -15.4 ± 5.8 (median: -16.0); the mean CGI-I score was 1.8 ± 0.9 (median: 2.0). Overall response to treatment according to HAM-D scale and CGI-I scores were observed in 15/19 patients and clinical remission was observed in 9/19 patients for both score, respectively.

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**SUMMARY – CONCLUSIONS (Cont'd)**

EFFICACY RESULTS (Cont'd)

Sleep parameters were evaluated after 1 and 7 weeks of treatment. After one week of treatment, there was no relevant difference in LSEQ sub-scores between the 2 treatment groups. Over the W0-W7 period (last value in period), patients felt an improvement of sleep especially for getting off to sleep: declining from 53.1 ± 10.7 (median: 52.3) overall at W1 to 32.4 ± 13.1 (median: 30.3) at W7; and the quality of sleep score: from 48.7 ± 11.9 (median: 49.8) at W1 to 34.5 ± 16.0 (median: 35.5) at W7. The scores for these items were somewhat better in the ago/ago than in the pbo/ago group, suggesting some benefit of 1 week more agomelatine treatment.

SAFETY RESULTS

See table below

**Summary of adverse events in the Safety Set**

| Participants having reported | | Healthy Volunteers | MDD patients | | |
|---|---|---|---|---|---|
| | | Placebo (N = 14) | Agomelatine/ Agomelatine (N = 15) | Placebo/ Agomelatine (N = 15) | All (N = 30) |
| **W0-W1** | | | | | |
| at least one emergent adverse event | n (%) | 2 (14.3) | 4 (26.7) | 4 (26.7) | 8 (26.7) |
| at least one treatment-related emergent adverse event | n (%) | 2 (14.3) | 1 (6.7) | 3 (20.0) | 4 (13.3) |
| **W0-W7 (MDD patients) under agomelatine** | | | | | |
| at least one emergent adverse event | n (%) | - | 9 (60.0) | 7 (46.7) | 16 (53.3) |
| at least one treatment-related emergent adverse event | n (%) | - | 5 (33.3) | 6 (40.0) | 11 (36.7) |
| **W0-W24/Wend (MDD patients) under agomelatine** | | | | | |
| at least one emergent adverse event | n (%) | - | 11 (73.3) | 7 (46.7) | 18 (60.0) |
| at least one treatment-related emergent adverse event | n (%) | - | 6 (40.0) | 6 (40.0) | 12 (40.0) |
| **During the study** | | | | | |
| at least one serious adverse event (including death) | n (%) | - | - | - | - |

In the safety set, during the W0-W1 period, the 2 emergent adverse events reported by HV were asthenia and headache, both considered as treatment-related by the investigator and recovered. In MDD patients, the emergent adverse events reported in the agomelatine group were nausea, rash, dry mouth and insomnia, which are listed in the European SmPC. The EAEs reported in the placebo group were nausea, pruritus, headache and weight increase. These events were all mild, except for insomnia in the agomelatine group and headache in the placebo group that were severe. All events had resolved by the end of the study, except for the insomnia which was reported as improving at the WEND visit.

During the W0-W7 agomelatine treatment period, the most frequent treatment-related emergent adverse events (reported in at least 10% of patients) were dry mouth (2 patients) in the ago/ago group and headache (2 patients) in the pbo/ago group. No additional severe emergent adverse events were reported over this period.
Over the W0-W24/Wend period, as compared to the W0-W7 agomelatine treatment period, 9 new events were reported overall (headache, dizziness, vertigo, migraine, cervical root pain, back pain, myalgia, nephrolithiasis, and benign bone neoplasm). Three of these events were considered by the investigator as being treatment related (headache, dizziness and vertigo); none were severe.

During the study, no death or serious adverse event or any emergent adverse event that led to withdrawal from the study for either of the included populations (HV or MDD patients), were reported.
No event considered to be related to lack of efficacy was observed in MDD patients over the study period, whereas 3 patients were withdrawn for lack of efficacy following the assessment of HAM-D-17.

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**SUMMARY – CONCLUSIONS (Cont'd)**

SAFETY RESULTS (Cont'd)

No clinically relevant changes over time or differences between groups were detected for biochemical and haematological parameters in MDD patients over the Selection-W7 and Selection-W24 periods. There was one emergent PCSA biochemical value (for high triglycerides) was reported in the ago/ago group.

There was no relevant differences in mean changes for supine blood pressures and heart rate over the W0-W1 period in HV or MDD patients, nor between the ago/ago and pbo/ago treatment sequence groups over W0-W7 or W0-W24 periods. There was no relevant change in mean weight, but 4 patients experienced relatively large changes, with 3 patients gaining 5-6 kg in weight and 1 losing 5 kg. Analysis of BMI by class over the Selection-W7 and the Selection-W24 periods in MDD patients showed that all patients remained in the same BMI class between baseline and last post-baseline assessment in both groups.

Among the MDD patients who performed a follow-up ECG at W24 visit (23/27), 3 patients, who had no ECG abnormality at baseline, had an emergent non-clinically relevant ECG abnormality (sinus bradycardia in 2 patients and bradycardia in one patient).

**CONCLUSION**

**This phase II exploratory, multicentre, randomised study conducted in moderate to severe MDD patients and healthy volunteers, investigated the effects of treatment (agomelatine or placebo) on cerebral activation during an emotional stimulus processing paradigm.**

**Agomelatine has an early effect (after 1 week of treatment) on the automatic control of self-referential and emotional processes (translated by decreased activations of ventrolateral prefrontal cortex and the amygdala). This early effect was observed before clinical improvement of symptoms as there was no relevant difference between agomelatine and placebo groups in terms of symptomatic disease. Agomelatine has a later effect (after 7 weeks of treatment) leading to a more balanced allocation between cognitive control and automatic processes of self-referential relevance (translated by decreased activation of dorsolateral prefrontal cortex and an increased activation of ventral anterior cingulate).**

**Over the W0-W1 period there was an improvement of the disease severity (HAM-D-17 total score and CGI) and in sleep parameters (LSEQ). Over the W0-W24 period, further improvements in HAM-D-17 total score and CGI score were observed. A clinical response to treatment was observed in 15 patients and remission in 9 patients.**

**Agomelatine 25 mg was well tolerated in MDD patients. No unexpected adverse event was reported.**

**Overall the fMRI results suggest that brain changes induced by agomelatine target specific regions involved in self-processing and cognitive regulation of emotion. Agomelatine showed different brain effects at W1 and at W7, suggesting a specific time course of brain changes in order to correct depressive symptoms.**

**Date of the report: 10 October 2012**