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| *Document title* | **Clinical Study Report Synopsis** |
| *Study title* | **A study to determine the maintenance of efficacy of agomelatine (25 to 50 mg) in order to prevent relapses in out-patients with Major Depressive Disorder.**<br>**A 8 or 10 weeks open period treatment with agomelatine (25 to 50 mg), followed by 24 weeks randomised double-blind period, placebo-controlled, parallel groups and 20 weeks of optional double-blind treatment period.**<br>***Second report: 44-week double-blind treatment period.*** |
| *Study drug* | **Agomelatine (S 20098)** |
| *Indication* | **Major Depressive Disorder** |
| *Development phase* | **Phase III** |
| *Protocol code* | **CL3-20098-041** |
| *Study initiation date* | **03 February 2005** |
| *Study completion date* | **11 July 2007** |
| *Main coordinator* | [redacted]<br>[redacted] **Paris** [redacted] **- France** |
| *Company / Sponsor* | **Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**50 rue Carnot**<br>**92284 Suresnes Cedex – France**<br><br>**Servier Research and Development Limited (S.R.D.L.)**<br>**Gallions, Wexham Springs**<br>**Framewood Road - Wexham**<br>**SL3 6RJ Slough - United Kingdom** |
| *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 03 March 2008** |

**~~CONFIDENTIAL~~**

## 2. SYNOPSIS

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***Second report: 44-week double-blind treatment period***

**Title of study:** A study to determine the maintenance of efficacy of agomelatine (25 to 50 mg) in order to prevent relapses in out-patients with Major Depressive Disorder.
A 8 or 10 weeks open period treatment with agomelatine (25 to 50 mg), followed by 24 weeks randomised double-blind period, placebo-controlled, parallel groups and 20 weeks of optional double-blind treatment period.
Protocol No.: CL3-20098-041

**Main Coordinator:** [redacted] ([redacted], France).
**National coordinators:** [redacted] ([redacted], Finland), [redacted] ([redacted], South Africa), [redacted] ([redacted], United Kingdom), [redacted] ([redacted], Australia).

**Study centres:**
57 centres located in 5 countries were opened and 56 included at least one patient: Australia (added by Amendment No. 2) - 7 centres (39 included patients), Finland - 11 centres (174 included patients), France – 20 centres (125 included patients), South Africa - 6 centres (75 included patients), United Kingdom – 12 centres (79 included patients).

**Publication (reference):** Not applicable.

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| **Studied period:**<br>Initiation date: 03 February 2005 *(date of first visit)*<br>Completion date: 11 July 2007 *(date of last visit)* | **Phase of development of the study:** III |

**Objectives:**
**Primary objective:** to assess the efficacy of agomelatine (25mg/50 mg), in the prevention of depressive relapse, in ambulatory patients suffering from recurrent Major Depressive Disorder (MDD), during 24 weeks of treatment after an initial response to agomelatine 25 mg or 50 mg.
The response to this objective is displayed in a previous report. The present report showed the efficacy of agomelatine in the prevention of depressive relapse over 44 weeks of treatment.
**Secondary objective:** to provide additional safety data on long term administration of agomelatine.

**Methodology:**
Multinational, multicentric, randomised, double-blind, placebo-controlled study in two parallel groups for efficacy evaluation of agomelatine 25 mg/50 mg in prevention of depressive relapse. The double-blind period was preceded by an open period of 8 to 10 weeks of agomelatine treatment. All patients started on a 25 mg dose, and the dose could be increased to 50 mg in case of insufficient improvement after 2 weeks of treatment. Then, patients could be randomised in the double-blind treatment period at W8 or W10 if they fulfilled pre-defined randomisation criteria, *i.e.* HAM-D total score ≤ 10 and CGI global improvement score = 1 or 2. If not, the patient was withdrawn for lack of efficacy. Patients randomised in the agomelatine group continued on the same dose as that received since W2. The criteria for increasing the dose, and randomisation were defined by the sponsor based on clinical considerations before the study beginning, and kept blinded. The dose increase and the treatment allocation were done centrally using an Interactive Voice Response System (IVRS), in a double-blind manner (so that both patients and investigators were blind with respect to this procedure). At the end of the 24-week double-blind period, the patients could either continue in the optional double-blind extension period or stop the study according to investigator's and patient's decision.
This study was performed in strict accordance with Good Clinical Practice.

**Number of patients:**
Planned: 500 patients included / 316 patients randomised (158 by group).
Included: 492 patients / Randomised: 339 patients (165 in the agomelatine group and 174 in the placebo group).
Entered the optional double-blind extension period: 190 patients (106 in the agomelatine group and 84 in the placebo group).

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**Diagnosis and main criteria for inclusion:**

Ambulatory men and women, aged between 18 and 65 years inclusive, fulfilling DSM IV-TR criteria for MDD of moderate or severe intensity.

The patients were included with a recurrent episode of at least 8 weeks, and at the beginning of the index episode, patients were to be free of any signs or symptoms of their previous episode for at least 6 months.

The HAM-D 17-item total score was to be ≥ 22 at selection and inclusion and a decrease between selection and inclusion (if any) ≤ 20% was permitted. The sum of items H1 + H2 + H5 + H6 + H7 + H8 + H10 + H13 of HAM-D 17-item had to be ≥ 55% of HAM-D 17-item total score at inclusion, CGI severity of illness score ≥ 4 at selection and inclusion, and the depression sub-score (HAD-D) of Hospital Anxiety Depression Scale was to be ≥ 11 (according to Amendment No. 3).

**Study drug:**

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

Patients received 25 mg/day (1 agomelatine tablet + 1 placebo tablet) from W0, with possible increase to 50 mg/day (2 agomelatine tablets) at W2, in case of insufficient improvement. Once adjusted, the dose was maintained throughout the study. Batch No.: L0003634, L0005266, L0005363.

**Reference product:** Placebo, 2 tablets once a day, p.o., around 8 p.m.

**Duration of treatment:**

- Run-in period without study treatment of maximum 1 week.
- 8 to 10-week open treatment period with agomelatine, depending on eligibility for randomisation at W8 or W10 according to IVRS.
- 24-week double-blind randomised treatment period (BW0 to BW24).
- 20-week optional double-blind extension treatment period (BW24 to BW44).
- 2-week follow-up period without study treatment, after treatment discontinuation, regardless of the time of occurrence.

**Criteria for evaluation:**

**Efficacy measurements**

HAM-D 17-item total score and Clinical Global Impression (CGI) scales were assessed by the investigator at each visit from selection to BW44.

**Primary criterion: Depressive relapse**

It was assessed by the investigator at each visit from randomisation and defined as the occurrence of one of the following events:

- HAM-D 17-item total score ≥ 16.
- Any withdrawal for lack of efficacy during the 44-week double-blind period, according to the clinical opinion of the investigator.
- Any suicide or suicide attempt.

All cases listed above (pre-specified events) reported during the 24-week double-blind period had been reviewed in blind condition by an independent Expert Committee at the end of this period, in order to confirm or invalidate the diagnosis of relapse, and to confirm the date of relapse. The Expert Committee meeting took place on 7 February 2007, before the blind was broken (16 March 2007). The results are described in a previous report. The further pre-specified events that occurred during the 20-week double-blind extension period were also reviewed in blind condition despite the blind had been broken for the first analysis (treatment was disclosed to nobody but people involved in the analyses process). The second adjudication meeting was held after the last visit of the last patient on 4 October 2007. Only expert's adjudications were taken into account for analyses.

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**Safety measurements**

- Adverse events at each visit.
- Vital signs (body weight, heart rate, blood pressure) at selection, W8, W10, BW24, and BW44 visits, and at the end of study treatment in case of premature withdrawal.
- 12-lead electrocardiogram (ECG): at selection, BW18 or at visit of premature withdrawal with results available for inclusion, BW24, and follow-up visits, respectively.
- Laboratory tests: between selection and inclusion (results available at W0), within the 2 days following randomisation, within the 7 days following BW24 visit for patients not entering the optional double-blind extension period, or between BW36 and BW44 visits (results available at BW44) for patients entered this period, and at follow-up visit in case of premature withdrawal.

**Statistical methods:**
**Efficacy analyses**

- **Primary criterion**

*Main analysis*:
Incidence over time of patients with a relapse was estimated using Kaplan-Meier method. The time to relapse over BW0-BW44 was compared between agomelatine and placebo groups using a log-rank test stratified for centre type (centres managed by psychiatrists or by GPs) and randomisation visit (W8 or W10) in the FAS. The hazard ratio of relapse on agomelatine as compared to placebo, was estimated with a Cox model associated with the likelihood ratio test, with adjustment for centre type and randomisation visit in the Full Analysis Set.
*Sensitivity analyses*:
The hazard ratio of relapse was estimated using a Cox model with adjustment for HAM-D 17-item total score at inclusion in addition to centre type and randomisation visit. A non-stratified log-rank test and an unadjusted Cox model were also carried out.

*Secondary analyses*:
The same analyses were applied to the two subsets of the FAS (Sub-FAS of patient enrolled by psychiatrists and Sub-FAS of patients with W0 HAM-D total score ≥ 25).

- **Secondary criteria**

HAM-D 17-item total score and CGI scores were described by treatment group in the FAS during the 44-week double-blind treatment period.

**Safety analyses**
During the 44-week double-blind treatment period, all safety parameters were described by treatment group in the Double-Blind Safety Set (DBSS).

**SUMMARY - CONCLUSIONS**

**The results described hereafter are those of the BW0-BW44 double-blind period. Those of the open period and of the BW0-BW24 double-blind period are included in a previous report.**

STUDY POPULATION AND OUTCOME

In all, 492 patients were included in the open period, and 491 received agomelatine 25 mg. Among them, 339 patients (68.9%) were randomly assigned to one of the two treatment groups according to IVRS procedure: 165 continued on agomelatine, and 174 switched to placebo. The distribution of the treatment groups was well-balanced. Among the 206 patients who completed the 24-week double-blind period, 190 (92.2%) continued in the optional double-blind extension period without difference between groups: 106 (92.2%) in the agomelatine group and 84 (92.3%) in the placebo group.

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STUDY POPULATION AND OUTCOME (Cont'd)

During the 44-week double-blind period, 164 patients (48.4%) were prematurely withdrawn, mainly for lack of efficacy (36.9%). The rate of withdrawals was lower in the agomelatine group (37.0%) than in the placebo group (59.2%), mostly related to a lower rate of withdrawals due to lack of efficacy in the agomelatine group (42 patients, 25.5% in the agomelatine group *versus* 83, 47.7% in the placebo group). These withdrawals corresponded to depressive relapses according to investigators' judgement as defined in the protocol, and were reviewed by an independent Expert Committee in order to be confirmed or invalidated.

No patient was lost to follow-up during the study.

Among the patients entered the extension period, excluding patients with depressive relapse, 95 patients (89.6%) in the agomelatine group, and 64 (76.2%) in the placebo group were completers at BW44.

**Disposition of patients**

| **Status** | | **Agomelatine** | **Placebo** | **All** |
|---|---|---|---|---|
| **Included in the open period (W0-W8/W10)** | **n** | **492** | **-** | **492** |
| **Randomised in the 24-week double-blind period (BW0-BW24)** | **n** | **165** | **174** | **339** |
| ***Withdrawn due to*** | ***n (%)*** | ***50 (30.3)*** | ***83 (47.7)*** | ***133 (39.2)*** |
| Adverse event | n (%) | 4 (2.4) | 1 (0.6) | 5 (1.5) |
| Lack of efficacy (relapse*, as requested by the protocol) | n (%) | 37 (22.4) | 71 (40.8) | 108 (31.9) |
| Remission, or marked improvement | n (%) | 4 (2.4) | 3 (1.7) | 7 (2.1) |
| Non-medical reason | n (%) | 4 (2.4) | 8 (4.6) | 12 (3.5) |
| Protocol deviation | n (%) | 1 (0.6) | - | 1 (0.3) |
| **Completed the 24-week double-blind period** (excluding patients with depressive relapse) | **n (%)** | **115 (69.7)** | **91** (52.3)** | **206** (60.8)** |
| **Performed the follow-up visit** | **n** | **53** | **88** | **134** |
| **Entered the double-blind extension period (BW24-BW44)** | **n (%)** | **106 (64.2)** | **84** (48.3)** | **190** (56.0)** |
| ***Withdrawn due to*** | ***n (%)*** | ***11 (10.4)*** | ***20 (23.8)*** | ***31 (16.3)*** |
| Adverse event | n (%) | - | 2 (2.4) | 2 (1.1) |
| Lack of efficacy (relapse*, as requested by the protocol) | n (%) | 5 (4.7) | 12** (14.3) | 17 (8.9)** |
| Remission, or marked improvement | n (%) | 2 (1.9) | 3 (3.6) | 5 (2.6) |
| Non-medical reason | n (%) | 4 (3.8) | 2 (2.4) | 6 (3.2) |
| Protocol deviation | n (%) | - | 1 (1.2) | 1 (0.5) |
| **Completed the double-blind extension period** (excluding patients with depressive relapse) | **n (%)** | **95 (89.6)** | **64 (76.2)** | **159 (83.7)** |
| In conformity with the protocol | n | 51 | 32 | 83 |
| With protocol deviation after BW24 | n | 44 | 32 | 76 |
| **Performed the follow-up visit** | **n** | **102** | **78** | **180** |
| **Analysis sets** | | | | |
| Randomised Set = Full Analysis Set | n (%) | 165 (100.0) | 174 (100.0) | 339 (100.0) |
| Sub-FAS psychiatrists | n (%) | 110 (66.7) | 117 (67.2) | 227 (67.0) |
| Sub-FAS with W0 HAM-D total score ≥ 25 | n (%) | 128 (77.6) | 142 (81.6) | 270 (79.6) |
| Double-Blind Safety Set (DBSS) | n (%) | 165 (100.0) | 174 (100.0) | 339 (100.0) |

*%: % of randomised patients or of patients entered the extension period according to period considered.*

**: All cases of depressive relapse judged by investigators were reviewed in blind condition by an independent Expert Committee in order to confirm or invalidate the diagnosis of relapse. They were reviewed at the end of the 24-week double-blind period for cases occurred during this period, and at the end of the double-blind extension period (after the last visit of the last patient), still in blind condition despite the blind had been broken for the first analysis (treatment was disclosed to nobody but people involved in the analyses process).*

*** Including patient No. 041 826 0411 16163, withdrawn at BW30, and adjudicated as having a relapse at BW24.*

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STUDY POPULATION AND OUTCOME (Cont'd)

Baseline characteristics in the Randomised Set are described in the BW0-BW24 report.

In the Randomised Set, the mean treatment duration was 60.0 ± 6.4 days (median 56 days) during the open period. During the 44-week double-blind period, the mean treatment duration was longer in the agomelatine group than in the placebo group: 221.6 ± 116.2 days (median of 304 days), and 180.4 ± 116.8 days (median of 169 days). This result was in agreement with the lower rate of withdrawals in the agomelatine group.

The mean global compliance during the 44-week double-blind period was satisfactory in both groups (96.0 ± 8.7% in the agomelatine group, and 94.6 ± 13.1% in the placebo group).

EFFICACY RESULTS

- **Primary efficacy criterion: Relapse (see Table and Figure, next page)**

During the 44-week double-blind period, there were 125 withdrawals for lack of efficacy (114 based on HAM-D ≥ 16 and 11 based on investigator's clinical opinion). All were reviewed in blind condition by an independent Expert Committee, in order to confirm or invalidate the diagnosis of relapse, and to confirm the date of relapse. For the pre-specified events that had occurred during the 24-week double-blind period, the Expert Committee meeting took place at the end of this period, before the blind was broken. The further pre-specified events that occurred during the 20-week double-blind extension period were also reviewed in blind condition despite the blind had been broken for the first analysis (treatment was disclosed to nobody but people involved in the analyses process). The second adjudication meeting was held after the last visit of the last patient. Among the relapses judged by investigators, 3 were not adjudicated as relapses because of low HAM-D scores estimated inconsistent with diagnostic of relapse. As result, 122 relapses were adjudicated and taken into account for the main analysis, as described in the table below.

**Relapses according to the investigator's opinion, and adjudicated by the Expert Committee - FAS**

| Criterion for relapse | | According to the investigator | Expert Committee adjudication |
|---|---|---|---|
| HAM-D total score* ≥ 16 | n | 114 | 114 |
| Investigator's opinion | n | 11 | 8 |
| Suicide/suicide attempt | n | - | - |
| **All** | **n** | **125** | **122** |

** CRF value*

In the FAS, the overall percentage of patients with a relapse during the 44-week double-blind period was more than two times lower in the agomelatine group than in the placebo group (23.6% of patients in the agomelatine group versus 47.7% in the placebo group). The incidences over time of patients having a relapse were statistically and clinically significantly lower with agomelatine ($p < 0.0001$, log-rank test stratified for centre type and randomisation visit). The risk of relapse over time was statistically significantly reduced by 56.3% (HR = 0.437) on agomelatine compared to placebo ($p < 0.0001$, Cox model adjusted for centre type and randomisation visit).

These results were supported after additional adjustment for HAM-D total score at W0 ($p < 0.0001$), and with unadjusted analyses ($p < 0.0001$).

The between-group difference in the incidences of relapse progressively rose throughout the treatment up to about 36 weeks, then it was maintained up to the end of treatment. Low and closed incidences between agomelatine and placebo over the first treatment-weeks may be related to the absence of discontinuation symptoms on agomelatine treatment, as demonstrated in specific study (CL3-20098-030, NP15915).

In the Sub-FAS with W0 HAM-D total score ≥ 25, similar results were observed, as the risk of relapse over time was statistically significantly reduced by 58.6% on agomelatine as compared to placebo ($p < 0.0001$, Cox model adjusted for centre type and randomisation visit). In the Sub-FAS psychiatrists, the risk reduction in relapse was more marked. The risk of relapse over time was statistically significantly reduced by 66.6% on agomelatine as compared to placebo ($p < 0.0001$, Cox model adjusted for randomisation visit). All these results were supported after the additional adjustment for HAM-D total score at W0 ($p < 0.0001$), and with unadjusted analyses ($p < 0.0001$).

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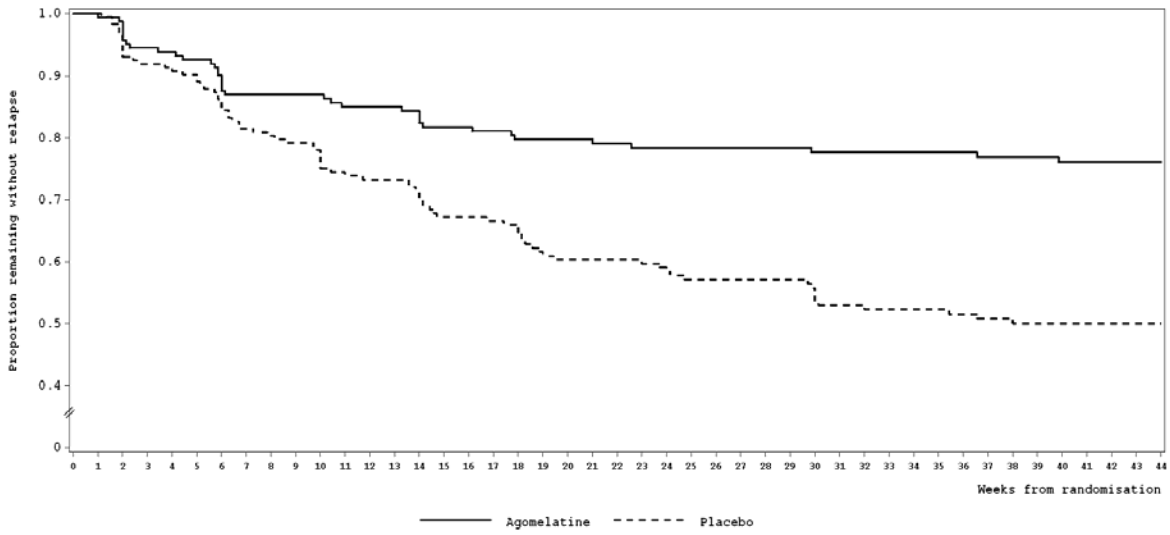
EFFICACY RESULTS (Cont'd)

**Number of patients with a depressive relapse during the 44-week double-blind period, incidence over time, and risk of relapse in the FAS and Sub-FAS**

| | | **Agomelatine** | **Placebo** |
|---|---|---|---|
| **FAS** | | N = 165 | N = 174 |
| **Total Events *** | **n (%)** | **39 (23.6%)** | **83 (47.7%)** |
| ***Main analysis*** | | | |
| Incidence after 308 days | E (SE) [1] | 23.9% (3.5%) | 50.0% (4.0%) |
| Stratified log-rank test [(a)] | p value | **< 0.0001** | |
| Adjusted Cox model [(a)] | E (SE) [2] | 0.437 (0.085) | |
| | 95% CI [3] | [0.298 ; 0.640] | |
| **Sub-FAS psychiatrists** | | N = 110 | N = 117 |
| **Total Events *** | **n (%)** | **24 (21.8%)** | **65 (55.6%)** |
| Incidence after 308 days | E (SE) [1] | 23.7% (4.3%) | 59.6% (4.8%) |
| Stratified log-rank test [(b)] | p value | **< 0.0001** | |
| Adjusted Cox model [(b)] | E (SE) [2] | 0.334 (0.080) | |
| | 95% CI [3] | [0.209 ; 0.534] | |
| **Sub-FAS with W0 HAM-D total score ≥ 25** | | N = 128 | N = 142 |
| **Total Events *** | **n (%)** | **32 (25.0%)** | **73 (51.4%)** |
| Incidence after 308 days | E (SE) [1] | 24.7% (3.9%) | 53.5% (4.4%) |
| Stratified log-rank test [(a)] | p value | **< 0.0001** | |
| Adjusted Cox model [(a)] | E (SE) [2] | 0.414 (0.088) | |
| | 95% CI [3] | [0.273 ; 0.628] | |

**: Total number of patients having a relapse during the 44-week double-blind period ; 1: Estimate (Standard Error) of the percentage of patients with a relapse after 308 days of treatment (Kaplan-Meier's method) ; 2: Estimate (Standard Error) of the adjusted Hazard Ratio of relapse between treatment groups: agomelatine versus placebo ; 3: 95% confidence interval of the estimate ; [(a)]: Stratified or adjusted for centre type, and randomisation visit ; [(b)]: Stratified or adjusted for randomisation visit.*

**Time to relapse over the 44-week double-blind period in the FAS (Kaplan-Meier estimation)**




N = 165 N = 174

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EFFICACY RESULTS (Cont'd)

- **HAM-D total score**

During the 44-week double-blind period, in the FAS, the mean HAM-D total score remained stable between BW0 and the last post-randomisation assessment in the agomelatine group (mean change of 1.7 ± 7.4), whereas it increased in the placebo group (mean change of 5.5 ± 8.5).

- **CGI**

During the 44-week double-blind period, in the FAS, both mean scores were smaller in the agomelatine group than in the placebo group at the last post-randomisation assessment (2.1 ± 1.3 for severity and 3.7 ± 1.7 for global improvement according to randomisation in the agomelatine group *versus* 2.7 ± 1.5, and 4.5 ± 1.8 in the placebo group, respectively). These results showed that in the agomelatine group, the severity of illness and the global improvement remained stable during the extension period whereas both worsened in the placebo group.

SAFETY RESULTS

**Main safety results during the 44-week double-blind treatment period in the DBSS**

| | | **Agomelatine (N = 165)** | **Placebo (N = 174)** |
|---|---|---|---|
| Patients having reported | | | |
| At least one emergent adverse event | n (%) | 98 (59.4%) | 99 (56.9%) |
| At least one treatment-related emergent adverse event | n (%) | 18 (10.9%) | 22 (12.6%) |
| At least one serious adverse event | n (%) | 6 (3.6%) | 6 (3.4%) |
| Patients with treatment discontinuation due to a non serious adverse event | n (%) | 2 (1.2%) | 3 (1.7%) |

During the 44-week double-blind treatment period, in the DBSS, the percentage of patients with at least one emergent adverse event was similar in both treatment groups: 59.4% in the agomelatine group, and 56.9% patients in the placebo group.

The most frequently affected system organ class (in at least 10% of the patients in any group) was Infections and infestations in both groups (34.5% in the agomelatine group, and 31.0% in the placebo group). It was followed by Musculoskeletal and connective tissue disorders (14.5% *versus* 12.1%, respectively), Gastrointestinal disorders (12.7% and 11.5%, respectively), and Nervous system disorders (11.5% and 9.8%, respectively). There were no relevant differences between groups for these system organ classes.
The most frequent emergent adverse events (in more than 5% of patients) were headache, and nasopharyngitis in both groups, then back pain in the agomelatine group, and influenza in the placebo group. The incidence of headache was higher in the agomelatine group (9.7%) than in the placebo group (6.3%), as well as the one of back pain (6.7% in the agomelatine group *versus* 4.0% in the placebo group).

During the 44-week double-blind period, severe emergent adverse events were less frequent in the agomelatine group (7.9%) than in the placebo group (10.3%). Incidence of severe events did not increase with the long-term duration of treatment (1 severe event during the 20-week double-blind extension period in the agomelatine group versus 4 in the placebo group).

No death was reported during the treatment period. During the 44-week double-blind treatment period, the frequency of patients with at least one emergent serious adverse event was similar in the agomelatine and placebo groups (6 patients in each group, 3.6% and 3.4%, respectively). Considering the long duration of treatment, the incidence was low, and showed no increase with time (3.0% over the 24-week double-blind period and 0.6% over the extension period in the agomelatine group).

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SAFETY RESULTS (Cont'd)

In the agomelatine group, the serious emergent adverse events were sparse in different system organ classes (back pain, rectal prolapse, and chronic lymphocytic leukaemia) to the exclusion of transaminase increases (≥ 3 ULN) which were notified as serious adverse events as required by the protocol (see description in liver acceptability below). The 3 events were considered to be not related to the study treatment by the investigator. In the placebo group, there were 2 emergent serious adverse events related to neoplasms (uterine leiomyoma, and stage III breast cancer). Both were diagnosed during the double-blind extension period. Both were considered to be not related to the study treatment by the investigator.

Very few patients were prematurely withdrawn due to non serious emergent adverse event during the 44-week double-blind period (1.2% in the agomelatine group, and 1.7% in the placebo group). In the agomelatine group, no treatment withdrawal was reported during the 20-week double-blind extension period.

**Clinical laboratory evaluation**

- No clinically relevant mean changes nor differences between groups were observed on biochemical and haematological parameters during the 44-week double-blind period in the DBSS.
- Liver acceptability
  During the 44-week double-blind treatment period, 3 patients (2 in the agomelatine group, and 1 in the placebo group) had emergent PCSA values of hepatic enzyme compared with value at randomisation. All patients had an ALAT increase ≥ 3 ULN which was notified as serious adverse event as required by the protocol. All associated ASAT values were abnormal without reaching 3 ULN. The 2 patients (1.2%) in the agomelatine group had emergent ALAT increase during the 24-week double-blind period. One of them corresponded to a worsening of already abnormal value at inclusion. The patient in the placebo group had emergent PCSA value of ALAT, and a worsening of GGT value at Wend after about 8 months on placebo. All patients recovered.

**Vital signs**

Regarding supine blood pressure, heart rate, weight and BMI, there were no clinically relevant mean changes between the baseline and the last assessment during the 44-week double-blind period in both groups in the DBSS.

**CONCLUSION**

**The results over the 44-week double-blind treatment period confirmed the efficacy of agomelatine 25-50 mg to prevent depressive relapse in MDD patients, previously demonstrated over 24 weeks of treatment, and showed the maintenance of efficacy throughout a 1-year agomelatine treatment. The incidences over time of patients having a depressive relapse were statistically and clinically significantly lower with agomelatine 25-50 mg than with placebo. The risk of a relapse was statistically significantly reduced by 56% with agomelatine.**

**Long-term treatment of agomelatine was as well tolerated as placebo. No unexpected safety concern was identified. The most frequent emergent adverse event reported on agomelatine was headache.**

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