Agomelatine Prevents Relapse in Patients With Major Depressive Disorder Without Evidence of a Discontinuation Syndrome: A 24-Week Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: This study evaluates the efficacy of agomelatine, the first antidepressant that is an agonist at MT_1/MT_2 receptors and an antagonist at $5\text{-}HT_{2C}$ receptor, in the prevention of relapse of depression following successful response.

Method: Patients with *DSM-IV-TR* major depressive disorder who responded to an 8- or 10-week course of agomelatine 25- or 50-mg daily treatment were randomly assigned to receive continuation treatment with agomelatine (n = 165) or placebo (n = 174) during a 24-week, randomized, double-blind treatment period. The main outcome measure was time to relapse during the double-blind treatment period. The cumulative probability of relapse was calculated using the Kaplan-Meier method of survival analysis. The study was conducted from February 2005 to February 2007.

Results: During the 6-month evaluation period, the incidence of relapse was significantly lower in patients who continued treatment than in those switched to placebo ($P = .0001$). The cumulative relapse rate at 6 months for agomelatine-treated patients was 21.7%; that for placebo-treated patients was 46.6%. Agomelatine was also superior to placebo in preventing relapse in the subset of patients with baseline 17-item Hamilton Depression Rating Scale total score ≥ 25. Measures of tolerability and safety of both doses of agomelatine were similar to placebo. No pattern of early relapse or adverse events suggestive of withdrawal symptoms was obtained after abrupt cessation of agomelatine.

Conclusions: The findings are important in 2 respects. First, agomelatine is an effective and safe antidepressant continuation therapy, which confirms efficacy seen in short-term studies. Second, few early relapses were observed in the patient group switched to placebo: the survival curve for placebo separated gradually from that of patients taking agomelatine. We suggest this reflects solely the underlying properties of the illness, which is only possible due to the lack of discontinuation syndrome after agomelatine withdrawal. It underlines the novel clinical profile of agomelatine, which quite likely reflects its innovative pharmacology.

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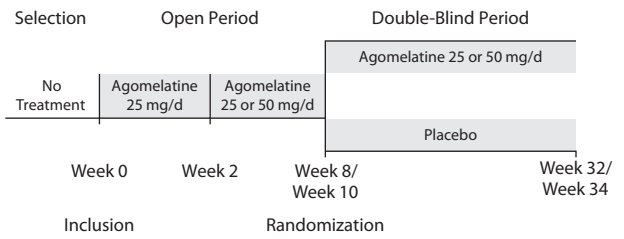
Short-term treatment of major depressive episodes carries an early subsequent risk of relapse.[1] Continuing pharmacotherapy remains the most widely accepted method for preventing relapse, and there is compelling evidence that antidepressant treatment for an inadequate period of time significantly increases the risk of relapse and the associated impairment, morbidity, and mortality. Discontinuation of antidepressant medication within the first few months of a response is associated with a 40% to 60% risk of relapse in controlled studies,[2] while continued antidepressant treatment approximately halves the odds of this outcome.[3] Therefore, various consensus groups have recommended that all depressed patients should continue treatment with an antidepressant for at least 4 months after a treatment response has been achieved.[4,5]

The study drug here, agomelatine, is the first melatonergic antidepressant, being an agonist at MT_1/MT_2 receptors and an antagonist at $5\text{-}HT_{2C}$ receptor. Agomelatine is thought to alleviate the symptoms of depression by reestablishment of normal circadian rhythms[6] and by stimulating dopamine and norepinephrine release in the prefrontal cortex through $5\text{-}HT_{2C}$ receptor antagonism.[7] This represents a novel pharmacology among antidepressants,[7–10] as agomelatine does not affect 5-HT release.[7]

A dose-ranging study conducted in more than 700 patients with major depressive disorder (MDD) demonstrated the clinical efficacy of agomelatine, with a daily 25-mg dose showing significant superiority over placebo.[11] Subsequently, the antidepressant efficacy of agomelatine 25 or 50 mg has been confirmed in 2 additional multinational trials of identical design: double-blind, randomized, parallel groups with a 6-week placebo-controlled treatment period.[9,12] An analysis of the efficacy of agomelatine versus placebo showed efficacy in both moderately and severely

Figure 1. Study Design



depressed populations; the largest treatment effect relative to placebo was seen in more severely depressed patients.[13]

While the overall efficacy of agomelatine in the treatment of depression is comparable to that of available antidepressants, the adverse-event profile is superior. There are some side effects associated with serotonin reuptake inhibition, such as nausea, diarrhea, and sexual dysfunction. The excellent tolerability profile of agomelatine includes a lack of weight gain,[9] a low risk of sexual dysfunction,[14] and the absence of discontinuation symptoms upon withdrawal.[15]

The present placebo-controlled, double-blind, 6-month study was performed in patients with MDD to evaluate, after an initial response to agomelatine (25 mg or 50 mg) during an 8- or 10-week open period, the prevention of relapse by continuation treatment with agomelatine compared with abrupt placebo substitution. A secondary objective of the study aimed at providing additional safety data on long-term use of agomelatine. We were also aware that a relapse prevention study with an antidepressant lacking a marked potential for withdrawal symptoms would have added interest and potential value for long-term treatment research in general.

METHOD

This was an international, double-blind, randomized, placebo-controlled, parallel group study, conducted in 57 centers in 5 countries (Australia, Finland, France, South Africa, and United Kingdom) from February 2005 to February 2007. The study was run in accordance with the principles of Good Clinical Practice E6 of the International Conference on Harmonisation[16] and the Declaration of Helsinki, Finland. The study was approved by the relevant local ethics committees and included only patients who gave written informed consent.

Study Design

This relapse prevention study started with an 8- or 10-week open-label treatment period and was followed by a 24-week, randomized, double-blind treatment period (Figure 1). During the open-label period, patients received agomelatine 25 mg/d during the first 2 weeks. At week 2, the agomelatine dose was either maintained at 25 mg/d or increased to 50 mg/d in patients with insufficient improvement based on blinded criteria. Subsequently, the agomelatine dose was maintained to the end of the open period (week 8 or week 10). The dose modification was blind for both the investigator and the patient. During the duration of the study, all patients took 2 tablets orally once a day in the evening, irrespective of the treatment and daily dosage allocated. The dosage schedule (2 tablets once a day), the appearance of study treatment, and the taste of tablet were the same from inclusion to the end of the treatment period for all patients. Tablets were packaged in identical blisters with identical labeling.

Patients eligible to enter the randomization phase had to meet the following criteria: 17-item-Hamilton Depression Rating Scale (HDRS-17)[17] total score ≤ 10 and Clinical Global Impressions-Improvement scale (CGI-I)[18] score ≤ 2 at week 8 or week 10 at the latest. These criteria were blind for the investigator and the patient and were applied centrally using an Interactive Voice Response System, the latter system being used only for managing treatment allocation.

At week 8, if the patients were eligible for randomization, they entered the double-blind treatment period. Those patients not yet eligible at week 8 could continue the open treatment period until week 10. At that time point, the patients either entered the double-blind treatment period if they fulfilled the randomization criteria or were withdrawn from the study and entered the follow-up period.

Patients eligible for randomization entered the double-blind treatment period and received either agomelatine (at a dose of 25 or 50 mg/d, which was fixed in the acute response phase) or placebo in a 1:1 ratio.

Throughout the 24-week double-blind period, the investigators evaluated relapse symptoms. *Relapse* was thereby defined as a HDRS-17 total score ≥ 16, any withdrawal for lack of efficacy according to the clinical opinion of the investigator (based on the evolution of both HDRS-17 and Clinical Global Impressions scores), or any suicide or suicide attempt. All cases of relapse were reviewed in blind conditions by an independent expert committee at the end of this period (February 2007) in order to confirm or invalidate the diagnosis of relapse and to confirm the date of relapse. Only these expert-validated end points were included for analyses.

Allocation to Treatment

After the open-label period, eligible patients were assigned to agomelatine or placebo treatment according to a balanced (nonadaptive) randomization with stratification on the clinical center and on the randomization visit (week 8 or week 10). The computer-generated randomization list was drawn up blind by the Biometry Department of the Institut de Recherches Internationales Servier, France. All study personnel and participants were blinded to treatment assignment for the duration of the study.

Rater Training

The investigators were trained before and during the study on the diagnosis of depression and the assessment of the main efficacy evaluation of the study (training on HDRS-17 rating used video recording of patients' interviews).

All clinicians were experienced and had met for training in procedures and to establish interrater consistency prior to the start of the trial.

Patients

Patients eligible for this study were male or female outpatients with a primary diagnosis of MDD and a current major depressive episode assessed as moderate or severe, according to *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*) criteria. All patients included gave written informed consent to participate. The recurrent MDD episode was required to have started at least 8 weeks before selection, and patients were to have been previously free of significant symptoms for at least 6 months. The MDD episode could be with or without melancholic features according to *DSM-IV-TR* criteria, but without a seasonal pattern or psychotic features and without postpartum onset.

Patients aged 18 to 65 years were eligible if they had an HDRS-17 total score ≥ 22, a sum of items 1 (depressed mood) + 2 (feelings of guilt) + 5 (insomnia: middle in the night) + 6 (insomnia: early hours of the morning) + 7 (work and activities) + 8 (retardation) + 10 (psychic anxiety) + 13 (general somatic symptoms) of HDRS-17 ≥ 55% of HDRS-17 total score, a Clinical Global Impression-Severity of Illness scale (CGI-S) score ≥ 4, and a Hospital Anxiety Depression Scale[19] depression subscore ≥ 11. The Sheehan Disability Scale,[20] a questionnaire that assesses 3 items (work, social life, and family life/home responsibilities) for how much the symptoms of depression have been disruptive, had to be filled in by patients at selection.

The patients were required to be physically healthy or to have stabilized significant illnesses on the basis of medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory tests (biochemistry and hematology).

Patients with any of the following disorders from *DSM-IV-TR*, identified with the Mini-International Neuropsychiatric Interview,[21] were excluded: (1) chronic depression (> 2 years of a depressive episode); bipolar disorder I and II; major depressive disorder superimposed on dysthymic disorder according to *DSM-IV-TR* (double depression); current panic disorder; obsessive-compulsive disorder; posttraumatic stress disorder; acute stress disorder; schizoaffective disorder of depressive type; or any other psychotic disorder, including major depression with psychotic features; or (2) alcohol or drug abuse or dependence within the past 12 months and any personality disorder that might compromise the study. Patients were also excluded if they were at risk for suicide according to the investigator or had a rating of 4 points on item 3 of HDRS-17.

Patients were also excluded if they had received any of the following recent/concomitant therapies: insight-oriented and structured psychotherapy (interpersonal therapy, psychoanalysis, cognitive-behavioral therapy) started within 3 months of inclusion; light therapy started within 2 weeks; oral antipsychotic drugs within 4 weeks; depot neuroleptics within 6 months; electroconvulsive therapy (ECT) within the last 3 months, requiring ECT at the moment (according to investigator's clinical judgment); or lithium/anticonvulsants within 4 weeks. Washout times required for other medications were usually 1 week for antidepressants (3 weeks for fluoxetine, 2 weeks for nonselective monoamine oxidase inhibitors). All benzodiazepines had to be stopped at the time of selection (at the latest). Only zolpidem could be taken until week 2 (1 tablet per night) in case of insomnia not tolerated by the patient. In addition, patients with a current depressive episode resistant to 2 different previous antidepressant treatments of at least 4 weeks' duration at appropriate dose and patients who had demonstrated a lack of response to previous treatment with agomelatine (including current episode) were excluded.

Assessments

Efficacy and tolerability parameters were assessed by the investigator after 2, 4, 6, and 8 weeks of open-label treatment. For patients randomly assigned to double-blind treatment, efficacy and tolerability parameters were assessed 2 weeks after randomization and then every 4 weeks (6 weeks for the 2 last visits) until their last dose of double-blind treatment (week 32 or 34). Efficacy assessments at each study visit included the HDRS-17, the CGI-S, and the CGI-I.

Patients were evaluated with *DSM-IV-TR* criteria for a major depressive episode during the double-blind period if they met the criteria for relapse (HDRS-17 total score ≥ 16, any withdrawal for lack of efficacy [clinical judgment based on HDRS and CGI], suicide, or suicide attempt).

The prospectively defined primary analysis of efficacy was relapse occurring within 6 months from response (as defined in the protocol). The main measure was, accordingly, the time to relapse during the double-blind treatment period, defined as the time between the date of the first randomized treatment administration and the date of the relapse (or date of censoring).

Secondary efficacy parameters included change in HDRS-17 total score from baseline value to each postbaseline visit and to last postbaseline value and response to treatment (defined as a decrease from baseline ≥ 50%) over the week 0 to week 8/10 period, and change in HDRS-17 total score from randomization value to each postrandomization visit and to last postrandomization value over the week 8/10 to week 32/34 period, also named BW0 to BW24 period. Other secondary efficacy parameters were the CGI-I and CGI-S scores over the week 0 to week 8/10 period (value at each visit and last postbaseline value and, for the global improvement score, response to treatment, defined as a score equal

Table 1. Baseline Characteristics of the 492 Patients Entered Into the Initial Open-Label Agomelatine Treatment Period

Characteristic	Value
Age, mean ± SD, y	43.2 ± 10.8
Gender, %	
Male	29.3
Female	70.7
DSM-IV-TR MDD diagnosis, recurrent episode, %	100
DSM-IV-TR MDD severity, %	
Moderate	51.8
Severe without psychotic feature	48.2
Melancholic features, %	53.7
Duration of MDD, mean ± SD, y	11.4 ± 8.7
No. of depressive episodes, mean ± SD	3.7 ± 2.1
Duration of current MDE, mean ± SD, mo	5.1 ± 4.0
Previous psychotropic treatments, %	72.6
HDRS-17 total score, mean ± SD	27.0 ± 2.7
CGI Severity of Illness score, mean ± SD	4.9 ± 0.7

Abbreviations: CGI = Clinical Global Impressions, HDRS-17 = 17-item Hamilton Depression Rating Scale, MDD = major depressive disorder, MDE = major depressive episode.

to 1 or 2) and over the week 8/10 to week 32/34 period (value at each visit and last postrandomization value).

The tolerability and safety evaluations were based on emergent adverse events spontaneously reported by the patient or elicited by the investigator (from week 0 to follow-up), vital signs (supine systolic blood pressure and diastolic blood pressure, supine heart rate, and weight, which were assessed at selection, week 8, week 10, week 24), biochemistry and hematology parameters (assessed between selection and week 0, at randomization, and during the follow-up period), and ECG abnormalities (assessed at selection and 18 weeks after randomization).

When premature discontinuation of treatment was due to an adverse event, at least 1 visit was organized to collect the information related to the outcome of the event.

For body weight, the number of patients in each body mass index (BMI) class (underweight: < 18.5 kg/m^2; normal range: 18.5–25.0 kg/m^2; overweight: 25.0–30.0 kg/m^2; obese: ≥ 30.0 kg/m^2) at the last postrandomization visit was compared with BMI at the randomization visit. The number of patients changing BMI class during this period was estimated.

Compliance was assessed by counting returned tablets. It was analyzed at each visit, and global compliance was calculated over each period.

Statistical Analysis

The time to relapse over blind visits BW0 to BW24 was compared for agomelatine and placebo groups using a log rank test stratified for center type and randomization visit. To estimate the hazard ratio of relapse on agomelatine compared with placebo, a Cox model associated with the likelihood ratio test was performed with adjustment for center type and randomization visit. As sensitivity analysis, the hazard ratio of relapse on agomelatine compared with placebo was estimated using a Cox model, with adjustment for HDRS-17 total score at inclusion (in addition to center type and randomization visit). A nonstratified log rank test and an unadjusted Cox model were carried out.

In order to determine from what time point the probability of relapse becomes significantly different between agomelatine and placebo, the difference seen at various time points between treatments was analyzed by comparing the ratio of the difference of the estimated proportions relapse-free divided by the standard error of that difference to a standard normal distribution.

Statistical analysis was performed on SAS software, version 8.2 (SAS Institute Inc, Cary, North Carolina). The type I error was set at 5%. Descriptive statistics were provided for secondary efficacy parameters and for emergent adverse events during the double-blind treatment period.

RESULTS

Patient Characteristics

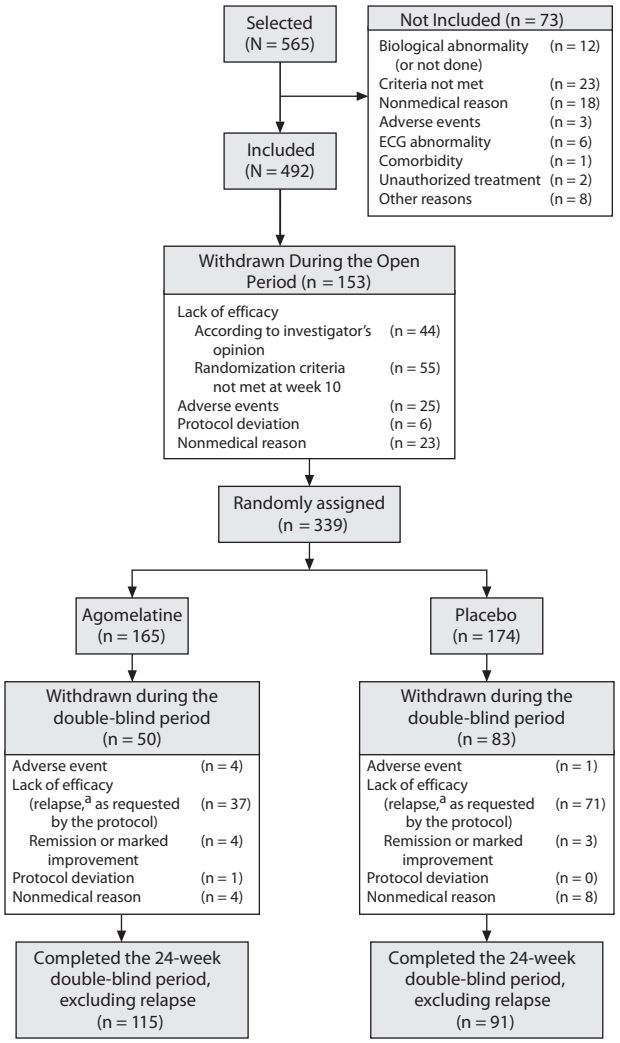
Of the 492 patients entering the open-label period (Table 1), 339 patients (68.9%) were randomly assigned to double-blind treatment: 165 patients to agomelatine and 174 patients to placebo (Figure 2). For demographic characteristics, there were no significant differences between patients treated with agomelatine and those treated with placebo (Table 2). The mean ± SD age of the randomly assigned patients was 43.3 ± 10.6 years (range, 19–65), and 74.3% were female; 32.1% were overweight (25.0–30.0 kg/m^2), and 22.4% were obese (> 30 kg/m^2).

Severity of MDD was well matched between the treatment groups at baseline. Severe intensity without psychotic features was seen in 47.3% of the patients in the agomelatine group and 47.1% in the placebo group. At selection, patients were markedly disrupted by their MDD symptoms but comparable in the treatment groups for work group score, social life score, and family life score on the Sheehan Disability Scale.

The median duration of the current episode was 3.5 months (mean ± SD, 4.85 ± 3.81). The patients had a mean number of 3.6 major depressive episodes (median, 3.0; range, 2–23), including the current one. The mean ± SD HDRS-17 total score was 27.0 ± 2.7 at inclusion. At week 2, 109 patients (corresponding to 22.1% of included patients) showed poor improvement at 25 mg/d and, thus, had their agomelatine dose increased to 50 mg/d. During the open-label period, the mean ± SD HDRS-17 total score decreased over time from 27.0 ± 2.7 at inclusion to 9.9 ± 7.3 at the last postbaseline assessment, at which point 78.6% of patients were rated as responders to treatment.

In the open-treatment phase, the mean ± SD CGI-S score (4.9 ± 0.7 at week 0) dropped to 2.4 ± 1.3 at the last postbaseline assessment before randomization. At the same time, the percentage of responders defined according to the CGI-I score (score of 1 or 2) was 80.3% at the last assessment. There were no clinically relevant differences in

Figure 2. Disposition of Included and Randomly Assigned Patients



[a]All cases of depressive relapse judged by investigators were reviewed in blind condition by an independent expert committee at the end of the double-blind period in order to confirm or invalidate the diagnosis of relapse.
Abbreviation: ECG = electrocardiogram.

Table 2. Baseline Demographic and Clinical Characteristics of the Patients Randomly Assigned to the 6-Month, Double-Blind, Treatment Arm

Characteristic	Agomelatine (N = 165)	Placebo (N = 174)
Age, mean ± SD, y	43.4 ± 10.9	43.1 ± 10.3
Gender, %		
Male	27.9	23.6
Female	72.1	76.4
DSM-IV-TR MDD diagnosis, recurrent episode, %	100.0	100.0
DSM-IV-TR MDD severity, %		
Moderate	52.7	52.9
Severe without psychotic feature	47.3	47.1
Melancholic features, %	49.7	51.1
Duration of MDD, mean ± SD, y	10.5 ± 8.6	12.4 ± 9.0
No. of depressive episodes, mean ± SD	3.5 ± 2.0	3.7 ± 2.2
Duration of current MDE, mean ± SD, mo	4.4 ± 3.7	5.3 ± 3.9
Previous psychotropic treatments, %	72.7	71.3
HDRS-17 total score, mean ± SD		
Wk 8	7.6 ± 4.2	7.5 ± 4.7
Wk 10	7.3 ± 2.1	7.5 ± 1.7
CGI-S score, mean ± SD		
Wk 8	2.1 ± 1.0	2.1 ± 1.0
Wk 10	2.1 ± 0.7	2.0 ± 0.7

Abbreviations: CGI = Clinical Global Impressions-Severity of Illness, HDRS-17 = 17-item Hamilton Depression Rating Scale, MDD = major depressive disorder, MDE = major depressive episode.

the severity of depression as measured by CGI-S between patients randomly assigned to agomelatine (1.8 ± 0.8) or placebo (1.8 ± 0.7) at the start of the double-blind period.

The mean ± SD global compliance was 98.7% ± 3.3%, without significant difference between agomelatine and placebo groups.

The mean ± SD HDRS-17 total score at randomization (week 8/week 10) was 6.1 ± 2.6 in the agomelatine group and 6.0 ± 2.7 in patients switched to placebo.

Efficacy

Ninety-three percent of relapses were defined by an increase in the HDRS-17 total score to 16 or more during the 24-week double-blind period. For 4 patients with an HDRS-17 total score = 15, the clinical diagnosis of relapse was confirmed by the independent expert committee. The relapse was not confirmed by the experts for 3 patients because HDRS-17 total scores remained low (12 or 13).

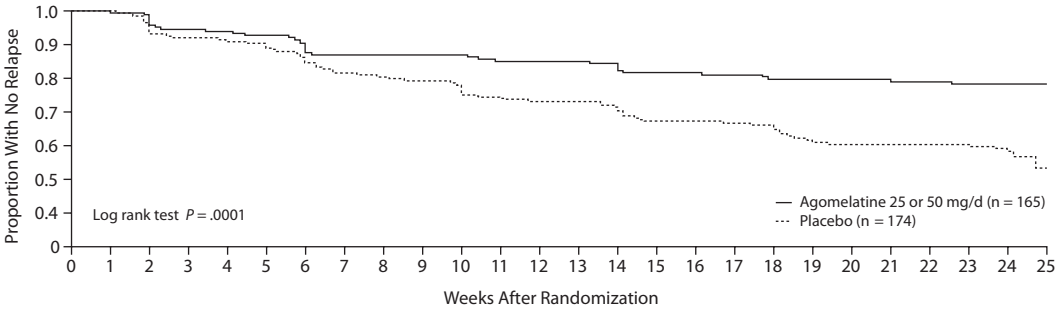
The results of the primary analysis showed a beneficial effect of agomelatine relative to placebo in the prevention of depressive relapse. Note that numbers shown as relapse (Table 3) are not identical with numbers given as withdrawn (Figure 2). Thus, in the agomelatine group, 37 patients were withdrawn for a lack of efficacy by the investigators, but the relapse was not confirmed by the blinded independent expert committee in 3 cases, which gave 34 relapses for analysis. In the placebo group, 1 patient completed the week 24 visit (last visit of the randomization period) with an HDRS-17 total score of 17. This case was validated by the expert committee in blind conditions as a relapse (HDRS-17 ≥ 16) and was considered as such in the analysis of relapse at 24 weeks. This patient does not appear as withdrawn because the 24-week double-blind period had been completed. In the intention-to-treat population, the proportion of patients who relapsed during the double-blind period in the agomelatine group (20.6%, 34 patients) was less than half that in the placebo group (41.4%, 72 patients). The incidence of relapse over 6 months was significantly lower with agomelatine compared to placebo (stratified log rank test, $P = .0001$), and the adjusted Cox proportional hazard model showed that the risk of relapse over time was reduced by 54% for agomelatine-treated patients (Cox model hazard ratio, 0.458; 95% CI, 0.305–0.690) (Table 3). Sensitivity analyses confirmed these results.

Table 3. Overview of Time-to-Relapse Analyses During the 6-Month Double-Blind Period

Group	No. of Patients	Relapses n	Relapses %	Cumulative Incidence of Relapse at 175 Days, Estimate (SE), %	Cox Model Hazard Ratio Estimate	Cox Model Hazard Ratio 95% CI	Log Rank Test *P* Value
Total population							
Agomelatine, 25–50 mg/d	165	34	20.6	21.7 (3.3)	0.458	0.305–0.690	.0001
Placebo	174	72	41.4	46.6 (5.0)			
Patients with baseline HDRS-17 total score ≥ 25							
Agomelatine, 25–50 mg/d	128	28	21.9	22.7 (3.8)	0.432	0.277–0.673	.0001
Placebo	142	64	45.1	50.4 (5.3)			

Abbreviation: HDRS-17 = 17-item Hamilton Depression Rating Scale.

Figure 3. Primary Efficacy Result: Time to Relapse for the Patients Treated With Agomelatine (n = 165) and Those Treated With Placebo (n = 174) Over the 6-Month Double-Blind Treatment Period (Kaplan-Meier survival estimation)



It is clear from the observed Kaplan-Meier curves results for time to relapse that differences between agomelatine and placebo in terms of the probability of relapse began from the point of randomization and gradually increased as time moved on (Figure 3). The *P* values at the individual time points show statistical significance at the 5% level from week 10 onward, at which point the magnitude of the difference in the probability of relapse differed in absolute terms by 11.88% (95% CI, 3.57–20.20).

A post hoc analysis showed, first, that dose and dose adjustment in the open phase and, second, that the visit of randomization (week 8 or week 10) made no difference to the observed effect. Agomelatine was significantly superior to placebo in preventing relapse in the subset of severe patients with baseline HDRS-17 total score ≥ 25 (79.6% of the 339 patients: agomelatine, n = 128; placebo, n = 142). In this subset of patients, the relapse rate in the agomelatine group was 21.9% (28 patients), whereas the relapse rate in the placebo group was 45.1% (64 patients) over 6 months. The survival analysis showed a statistically significant difference in favor of agomelatine (log rank test, $P = .0001$). The risk of relapse over time was significantly reduced by 57% in patients taking agomelatine compared to those taking placebo (Table 3).

During the double-blind period, the effect of long-term treatment as measured by the HDRS-17 total score was stable over time for the agomelatine group and showed a slight deterioration in the placebo group. Thus, the mean ± SD HDRS-17 total scores at randomization and last evaluations were 6.1 ± 2.6 and 7.5 ± 7.0, respectively, for patients receiving agomelatine and 6.0 ± 2.7 and 10.6 ± 8.4, respectively, for patients receiving placebo, giving a mean ± SD change over this period of 1.4 ± 6.9 in the agomelatine group and 4.7 ± 8.4 in the placebo group.

A similar pattern was observed for CGI scores. At the last postrandomization value, in the intention-to-treat population, both mean ± SD scores were lower in the agomelatine group (2.1 ± 1.2 for severity and 3.8 ± 1.6 for global improvement) than in the placebo group (2.6 ± 1.5 and 4.4 ± 1.7, respectively). In the agomelatine group, the therapeutic benefit, acquired during the open period, was maintained during the double-blind period with regard to the severity of illness, whereas worsening had become apparent in the placebo group.

The mean ± SD global compliance was 95.6% ± 11.1%, without significant difference between agomelatine and placebo groups.

More than half of the included patients were either overweight (154 patients, 31.3%) or obese (109 patients, 22.1%), but response to agomelatine at the end of the open period was unaffected by this variable (overweight patients: mean ± SD HDRS-17 score change was −17.6 ± 7.4, and 79.2% were responders; obese patients: mean ± SD HDRS-17 score change was −17.4 ± 6.9, and 84.4% were responders). In patients within the normal weight range, mean ± SD HDRS-17 score change was −16.5 ± 7.7, and 75.2% were responders.

Body weight had also no major influence on the proportion of relapsing patients during the double-blind period:

Table 4. Most Frequently Reported Adverse Events Expressed as a Percentage of the Number of Affected Patients to the Number of Patients in the Agomelatine and Placebo Groups During the Double-Blind Treatment Period (at least 3 patients in agomelatine group)

Adverse Event, %	Agomelatine (n = 165)	Placebo (n = 174)
Headache	7.9	6.3
Nasopharyngitis	6.7	9.8
Back pain	5.5	3.4
Influenza	3.6	5.2
Upper respiratory tract infection	2.4	2.3
Gastroenteritis	1.8	2.9
Sinusitis	1.8	2.3
Neck pain	1.8	…
Constipation	1.8	…
Dyspepsia	1.8	…
Initial insomnia	1.8	…

Symbol: … = None.

Table 5. Adverse Events Suggestive of Withdrawal Symptoms Within the First Month After Randomization, Expressed as a Percentage of the Number of Affected Patients to the Number of Patients in the Agomelatine and Placebo Groups

Adverse Event, %	Agomelatine (n = 165)	Placebo (n = 174)
Asthenia	0.6	…
Depression aggravated	…	0.6
Diarrhea	…	…
Headache	3.6	3.4
Insomnia	0.6	…
Irritability	…	0.6
Muscle spasms	0.6	…
Musculoskeletal pain	3.6	2.3
Nausea/vomiting	1.8	…
Palpitations	…	0.6

Symbol: … = None.

this proportion was constantly around half that in the respective placebo group (proportion of relapse for patients with normal BMI: agomelatine, 16.2% vs placebo, 37.2%; overweight patients: agomelatine, 25.9% vs placebo, 46.4%; obese patients: agomelatine, 20.9% vs placebo, 41%).

The proportion of completers among patients with normal BMI was 70.6%. In the 2 subgroups of overweight or obese patients, the proportions of completers were 66.7% and 72.1%, respectively.

Withdrawals

During the 8- or 10-week open-label treatment period, 153 patients (31.1%) withdrew from the study, among them 44 (8.9%) as a result of lack of efficacy according to the investigator's opinion, 55 (11.1%) because they did not respond sufficiently to meet the eligibility criteria for the randomization phase, and 25 (5.1%) due to adverse events (Figure 2).

Of the 339 patients continuing into the double-blind period of the study (165 patients in the agomelatine group and 174 in the placebo group), 115 agomelatine-treated (69.7%) (of whom 17 on treatment with agomelatine, 50 mg) and 91 placebo-treated patients (52.3%) completed the 24-week study.

During the double-blind period, 133 of 339 patients (39.2%) were prematurely withdrawn, mainly due to lack of efficacy (31.9%). The rate of withdrawal was lower in the agomelatine group (30.3%) than in the placebo group (47.7%), mostly related to a lower rate of withdrawals due to lack of efficacy in the agomelatine group (37 patients [22.4%] in the agomelatine group versus 71 [40.8%] in the placebo group).

During this period, the overall withdrawal rate unrelated to lack of efficacy was comparable for both treatments: 7.8% for patients treated with agomelatine (13 patients) and 6.9% for patients treated with placebo (12 patients).

Tolerability

Four patients (2.4%) in the agomelatine group and 1 patient (0.6%) in the placebo group withdrew as a result of adverse events during the double-blind period. In both groups, the majority of the adverse events reported during the double-blind period were mild to moderate, and the percentage of patients with at least 1 emergent adverse event was similar (n = 85 [51.5%] in the agomelatine group and n = 91 [52.3%] in the placebo group). The 27 patients (8.0%) reporting at least 1 severe emergent adverse event were comparably distributed between the agomelatine (n = 12 [7.3%]) and the placebo group (n = 15 [8.6%]). The most common emergent adverse events reported in the agomelatine group were effectively the same as for placebo: headache (7.9% of patients versus 6.3% in the placebo group), nasopharyngitis (6.7% of patients versus 9.8% in the placebo group), and back pain (5.5% of patients versus 3.4% in the placebo group) (Table 4). No death occurred during the treatment period.

When considering the pattern of adverse events appearing within the first month after randomization, there were no observations suggestive of withdrawal symptoms caused by the abrupt cessation of the 8- or 10-week agomelatine treatment (Table 5).

There were no clinically relevant mean changes from baseline to the end of the study or differences between treatment groups in laboratory parameters and vital signs. The weight of patients remained stable during the agomelatine treatment period, irrespective of the dose of agomelatine given or the patient's initial class of BMI at randomization.

DISCUSSION

This study provides convincing and consistent evidence that patients who are maintained on a regimen of agomelatine 25 or 50 mg/d over a 6-month treatment period have a substantially reduced risk of relapse compared with those who are switched to placebo under double-blind conditions. Agomelatine has a novel pharmacology, and this study offers

2 critical advances. First, the clinically relevant reduction of relapse risk confirms the clinical benefit of acute treatment with agomelatine: the active drug must have been especially effective in the open-label phase.[22] Second, the pattern of relapse indicates that agomelatine does not precipitate early relapse following sudden withdrawal.

The efficacy of agomelatine 25 or 50 mg/d in severe depression has been demonstrated in 3 placebo-controlled studies and in a pooled analysis of the data from the 3 studies.[13] It is established that the level of pretreatment severity of depression has a marked effect on the risk of relapse after completion of initial treatment.[3] The present study provides evidence of the significant long-term efficacy of agomelatine in preventing relapses compared to placebo, even in more severely depressed patients. Prevention of relapse in a population with an increased hazard for relapse, therefore, confirms the robustness of the antidepressant effect.

The rate of relapse on agomelatine therapy is apparently consistent with the findings of similar studies with other antidepressants, including duloxetine,[23] fluoxetine,[24] venlafaxine,[25] mirtazapine,[26] and escitalopram.[27,28] Indeed, a systematic review of the literature previously found a homogeneous effect, without different relapse rates for any particular class of antidepressant despite variable definitions of the outcome.[3] In all these studies, patients who had responded to open-label antidepressant treatment and were switched to placebo had an approximately 40% likelihood of relapse, whereas approximately 20% of patients who continued treatment with antidepressants experienced a relapse.

However, in the present study, no separation of agomelatine from placebo occurred before 6 weeks of randomized treatment. Instead, a gradual accumulation of excess relapses over the whole observation interval was the pattern for patients switched to placebo compared with those patients continuing on treatment with agomelatine. The contrast with the abrupt appearance of relapse reported with other antidepressants is striking.[23–26,28] Indeed, the previous classical pattern showed the active treatment and placebo curves separating as soon as the first month following randomization so that most of the final placebo-active treatment difference is achieved at that time.[23–26,28]

A skeptical observer could attribute this finding to the confounding effects of withdrawal phenomena prominent with some other antidepressants.[23,29,30] All currently available antidepressant agents, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors, and atypical agents, such as venlafaxine, mirtazapine, trazodone, and duloxetine, have had case reports or warnings from their manufacturers of reactions occurring in response to either abrupt discontinuation or medication tapering.[31] These discontinuation symptoms appear rapidly, typically within 3 days of stopping antidepressant medication, and what may appear to be a depressive relapse could actually be a discontinuation syndrome.[31] In relapse prevention studies of escitalopram and duloxetine, the placebo group and the active treatment group separated as early as 1 month after randomization, at a time when a great number of adverse events were reported.[23,25,28] Adverse events could increase the risk of a true relapse or subvert the blind and inflate the true relapse rate.

Tapering may lower the incidence of discontinuation symptoms,[32] but, again, most of the final placebo-active treatment difference appears to be achieved at 6 to 8 weeks. Thus, the pharmacology of these compounds may lead to a transient depletion of key neurotransmitters, analogous to the effects of experimental monoamine depletion. For example, there is speculation concerning the possibility of a temporary deficiency of synaptic serotonin with abrupt withdrawal of an SSRI.[33] This is believed to result in antidepressant discontinuation syndrome directly or indirectly via downstream effects on other neurotransmitter systems implicated in depressive disorders (eg, norepinephrine, dopamine, and γ-aminobutyric acid). With such a remodelling of neurotransmitter systems, the medication tapering would not help so much. Such depletion effects may be seen as provoking a true relapse, obviously to the disadvantage of the patient. The existence of such effects with the commonly used antidepressants is not encouraging for a field already beset by controversy.

Just as our relapse prevention study showed a different pattern of early relapse, agomelatine has been shown to provoke no increase in symptoms after its abrupt cessation in a study specifically designed to assess the onset of discontinuation symptoms.[15] In the present study, the low number of early relapses (up to 6–8 weeks after randomization) reported by patients switched to placebo parallels a low rate of adverse events appearing in the first month after randomization. We conclude that, for agomelatine, the absence of discontinuation effects means that the risk of relapse cannot be increased by a direct quasi-pharmacologic response to the withdrawal of the medication per se and, accordingly, the effectiveness of continuation therapy will not be overestimated: the observed relapses in patients assigned to placebo are solely due to the reemerging underlying disorder.

Interestingly, the relapse prevention studies of bupropion and fluoxetine also documented a later-emerging drug-placebo difference,[34,35] but it is difficult to compare those results with the present study because there are major differences in study designs and definitions of end points. Moreover, the necessary study to establish the absence of a discontinuation syndrome with bupropion has not been reported, while the absence of a discontinuation syndrome with fluoxetine is a pharmacokinetic phenomenon due to the long elimination half-life of its principal active metabolite, norfluoxetine.

Further observations relate to dose of agomelatine and BMI of patients. First, the proportion of patients with relapse during the double-blind period was reduced equally for patients treated with 25 mg/d and 50 mg/d. The increase

in dose to 50 mg occurred, under double-blind conditions, in patients without an early response to 25 mg and so will directly inform clinical practice. Secondly, more than half of the patients included were either overweight or obese. For those patients, agomelatine was as efficacious at the end of the open period (HDRS-17 score change: –17.6, and more than 80% were responders) as in patients with normal weight, with a good adherence to treatment (proportion of completers: 70.6% for patients with normal BMI and 66.7% and 72.1% in overweight and obese patients, respectively). This is in striking contrast to SSRIs,[36] with which overweight or obese, depressed patients do not experience the same therapeutic benefit compared with the normal weight, depressed patients. Overweight and obesity may characterize a subgroup of MDD patients with unfavorable treatment outcome.[37] These findings could have important clinical implications, so they merit further clinical confirmation in a larger cohort of patients.

It is broadly accepted that tolerability is necessarily linked to patient compliance in both acute and long-term treatment and ultimately to overall success of treatment.[38,39] The present study confirms good adherence of patients to agomelatine treatment as reflected by a high, 70% completion rate among those agomelatine-treated patients who entered the double-blind period. The overall retention rate of 42% observed in the present study is comparable to what has been typically reported with other antidepressants studied in a similar design.[23–25,40] This is in good agreement with earlier studies[9,11] in which the tolerability and safety of both doses of agomelatine were very similar to placebo.

In summary, the results of this prospective study demonstrate that continuation treatment with agomelatine is effective in preventing relapse during 6 months of double-blind treatment in MDD patients who had been successfully treated with agomelatine over an 8- or 10-week acute treatment period. The design of the study and the pharmacology of agomelatine give the results unusual interest. Thus, the effectiveness of continuation therapy with this new antidepressant is reliably estimated because it is not driven by a discontinuation syndrome. Instead, relapse rates after switch to placebo are likely due solely to the underlying disorder.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), venlafaxine (Effexor and others), zolpidem (Ambien, Edluar, and others).

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