Efficacy of agomelatine, a MT<sub>1</sub>/MT<sub>2</sub> receptor agonist with 5-HT<sub>2C</sub> antagonistic properties, in major depressive disorder

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Abstract

Current antidepressants used in major depressive disorder (MDD) are still not efficacious enough for many patients due to high levels of treatment resistance and bothersome side-effects. Using a novel blinding method (interactive voice response system), this flexible-dosing study examined the effects of therapeutic doses of agomelatine, a new approach to depressive therapy offering potent melatonergic MT<sub>1</sub>/MT<sub>2</sub> receptor agonism with 5-HT<sub>2C</sub> receptor antagonist properties, in patients with moderate-to-severe MDD. This 6-wk, double-blind, parallel-group study randomized 238 patients to 25 mg/d agomelatine (with dose adjustment at 2 wk to 50 mg/d in patients with insufficient improvement) or placebo. Depression severity was assessed using the Hamilton Depression Rating Scale (HAMD) and the Clinical Global Impression (CGI) scale. Agomelatine was significantly more efficacious than placebo, with an agomelatine–placebo difference of 3.44 (p < 0.001) using the HAMD final total score. Compared with placebo, agomelatine also had a significant positive impact on CGI – Improvement (treatment difference = 0.45) and CGI – Severity (treatment difference = 0.50) (both p < 0.006), response rate (54.3% vs. 35.5% with placebo, p < 0.05) and time to first response (p = 0.008). Similar results were seen in patients with the most severe MDD. Depressed mood and sleep items of the HAMD were also significantly improved with agomelatine, which was well tolerated with a safety profile similar to placebo at both doses. This study confirms that agomelatine is effective in treating major depression, including the most severely depressed patients, with a good safety and tolerability profile, therefore providing physicians with an effective pharmacological approach to antidepressant therapy.

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Introduction

Depression is an extremely debilitating disease. It has severe consequences for patients and their families in terms of excess mortality, disability and secondary morbidity. The latest epidemiological estimate of the lifetime prevalence of major depressive disorder (MDD) in Western Europe is 12.8%, with a 12-month prevalence of 3.9% (Alonso et al., 2004). Similar values have been reported from studies in the USA (Kessler et al., 2003), with the additional observation that only 21.7% of cases of 12-month MDD receive adequate treatment. These figures are of great concern, since the incidence of depression is set to rise due to social and demographic changes and increased life expectancy in those suffering from chronic disease.

There are many pharmacological treatments available for MDD with vastly differing mechanisms of action. Despite the plethora of options available, many patients fail to respond to treatment, with reported non-response rates of 30–40% (Kennedy et al., 2001). Moreover, only around 30% of treated patients with MDD achieve satisfactory remission, despite receiving medications with different mechanisms of action and subsequently different treatment strategies (Rush et al., 2006; Trivedi et al., 2006). The introduction of selective serotonin reuptake inhibitors (SSRIs), which have
a superior safety profile compared with older tricyclic antidepressants (TCAs), improved the treatment of depression enormously, especially in terms of the tolerance of side-effects (Gruenberg and Goldstein, 2003). However, SSRIs have adverse effects of their own, including gastrointestinal disturbances, weight gain, daytime sleepiness, sexual dysfunction and discontinuation symptoms (Masand and Gupta, 1999). Moreover, their efficacy in more severe depression has been questioned (Anderson, 2000; Danish University Antidepressant Group, 1986, 1990; Sonawalla and Fava, 2001; Vestergaard et al., 1993). Clearly, there is room for further improvement in the pharmacological treatment of depression and much research is currently directed towards more efficacious and better tolerated new agents that are effective in both newly diagnosed patients and in those who fail to respond to prior treatments.

Agomelatine (Valdoxan®), is a new treatment for depression, acting as a potent melatonergic MT<sub>1</sub>/MT<sub>2</sub> receptor agonist with 5-HT<sub>2C</sub> receptor antagonist properties (Millan et al., 2003; Yous et al., 1992). The rationale for the development of agomelatine was based on the observations that: (i) alterations in circadian rhythms accompany endogenous depression in humans (Brown et al., 1985; Claustrat et al., 1984; Souetre et al., 1989; Thompson et al., 1988); (ii) disturbances in circadian rhythms are observed in animal models of depression (Cheeta et al., 1997; Gorka et al., 1996); and (iii) unavoidable disruptions in normal circadian rhythms can trigger depressive episodes in patients with affective disorders (Wehr and Wirz-Justice, 1982; Wirz-Justice, 1995). Developing a drug to improve the synchronization of biological rhythms therefore appeared to be a reasonable and new approach to antidepressive therapy. In addition to targeting MT<sub>1</sub>/MT<sub>2</sub> receptors, agomelatine also acts as an antagonist of 5-HT<sub>2C</sub> receptors, another therapeutic target in depression (Gurevich et al., 2002; Yamada and Sugimoto, 2001). Both properties appear to contribute towards agomelatine’s antidepressant activity (Papp et al., 2003).

Agomelatine has demonstrated antidepressant properties in animal models of depression (Barden et al., 2005; Bertaina-Anglade et al., 2002; Bourin et al., 2004; Papp et al., 2003), including learned helplessness, despair test and chronic mild stress, and has been shown to mimic the actions of melatonin in the synchronization of circadian rhythm patterns in rodents (Pitrosky et al., 1999) and tree shrews (Simon et al., 2004). Furthermore, agomelatine has shown efficacy in several animal models of anxiety (Millan et al., 2005).

Clinically, the efficacy of agomelatine was demonstrated in an extensive international dose-ranging study involving 711 depressed patients meeting the DSM-IV criteria for MDD or bipolar II disorders. Agomelatine (25 mg/d) demonstrated efficacy that was significantly superior to placebo and comparable with 20 mg/d paroxetine (Loo et al., 2002). Furthermore, agomelatine produced a significant improvement compared with placebo at week 2. In contrast, paroxetine did not differ significantly from placebo until week 4. In a subgroup of severely depressed patients [Hamilton Depression Rating Scale (HAMD; Hamilton, 1960) ≥25 at inclusion] there was also a significant difference compared with placebo (p < 0.05) favourable to agomelatine, which was not the case for paroxetine. Additional clinical advantages of agomelatine include weight neutrality and, unlike many current antidepressant agents (Hindmarch et al., 2000; Judge et al., 2002; Michelson et al., 2000; Rosenbaum et al., 1998), agomelatine is not associated with discontinuation symptoms such as dizziness, fatigue, insomnia, gastrointestinal disorders and influenza symptoms (Montgomery et al., 2004).

It is common in everyday clinical practice to titrate the dose of an antidepressant according to tolerability and efficacy. In compliance with this approach, this 6-wk, placebo-controlled, flexible-dosing study aimed to investigate the efficacy and tolerability of therapeutic doses of agomelatine (25–50 mg/d) in patients with moderate-to-severe MDD using a novel blinding protocol. This protocol was designed to extend the observations reported in a previous study by minimizing the placebo response and enabling assessment of the contribution of the 50-mg dose in patients with an insufficient improvement with 25 mg/d agomelatine (Kennedy and Emsley, 2006).

Methods

Study design

This was a prospective, double-blind, randomized, parallel-group study performed in France and Finland comprising a ≤7-d selection period (no medication) and a 6-wk placebo-controlled treatment period. Thirty-two centres (24 in France and 8 in Finland) actively recruited patients into the study. Patients meeting inclusion criteria at screening were randomized at week 0 to 25 mg/d agomelatine or placebo. Following 2-wk treatment, patients with an insufficient response, based on a predetermined cut-off on the 17-item HAMD total score and global improvement score of the Clinical Global Impression (CGI-I) scale, had their
agomelatine dose adjusted to 50 mg/d for the remaining 4 wk (Figure 1). Placebo patients with an insufficient response continued on placebo but were followed separately in a ‘control-adjusted group’. Study visits took place at selection, week 0 (randomization), and weeks 2, 4 and 6.

Blinding was achieved through a double-dummy technique (Figure 1) and the use of an interactive voice response system (IVRS) for initial randomization and allocation of patients to the ‘insufficient response’ groups (meaning neither patients nor investigators were aware of the criteria for, or designation of, ‘insufficient responders’ and subsequent dose adjustment). IVRS (S-Clinica, Brussels, Belgium) is a software application that accepts data via a combination of voice telephone input and touch-tone keypad selection, and provides pre-recorded voice responses for different situations, keypad signal logic, access to relevant data and the ability to record voice input for later data handling. At week 0, a therapeutic unit number was assigned to each patient using the IVRS according to baseline HAMD total score. At week 2, patients were assigned a new therapeutic unit number based on insufficient or sufficient improvement (as described above) that was used by the IVRS to determine whether a dose adjustment was required. Patients and investigators were not encouraged to guess which treatment patients were receiving at any time during the study so as not to compromise blinding. Placebo tablets contained the same non-active constituents as agomelatine tablets and were identical in colour and appearance. From the beginning of the treatment, all patients were instructed to take two tablets in the evening: one 25-mg agomelatine and one placebo tablet (agomelatine group) or two placebo tablets (placebo group); after the first 2 wk, patients requiring dose adjustment received two 25-mg agomelatine tablets (agomelatine group only) or continued to receive the two placebo tablets.

The protocol was approved by independent ethics committees in each centre and the study was conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent prior to entry into the study.

**Patient population**

Male and female in- and outpatients aged 18–65 yr fulfilling DSM-IV criteria for MDD (APA, 2004) with a current depressive episode, a HAMD score ≥22 and requiring antidepressant treatment were included in the study. Patients were excluded if they had depression with seasonal pattern, psychotic features or postpartum onset, previous resistance to antidepressants (defined as the failure to respond to two different prior antidepressant medications prescribed for ≥4 wk during the current depressive episode), marked suicidal intent or known suicidal tendencies, treatment with electroconvulsive therapy (ECT) or insight-orientated/structured psychotherapy within the last 3 months, history of alcohol or drug abuse (according to DSM-IV criteria) within the last 12 months, phototherapy within the last 2 wk, worked shifts, or had any condition thought by the investigator to interfere with the evaluation of the study (including antisocial, borderline, histrionic or other severe personality disorders and other severe/untreated organic diseases). Patients receiving psychoactive agents either currently or within 1–4 wk of selection were excluded, as were patients receiving any other treatments likely to interfere with study evaluations. An exception was that chronic treatment...
with a benzodiazepine (other than alprazolam) was permitted if started at least 4 wk before week 0. The dosage was to be progressively decreased down to a maximum of 5 mg/d diazepam equivalent at week 0.

**Efficacy assessments**

Symptom severity was assessed at selection, weeks 0, 2, 4 and 6 using the 17-item HAMD. The CGI improvement (CGI-I) and CGI severity of illness (CGI-S) scales were assessed at weeks 0, 2, 4 and 6. The primary efficacy variable was the HAMD total score, assessed in the intention-to-treat (ITT) population using the last observation carried forward (LOCF) approach over weeks 0–6. The secondary efficacy variables were the response to treatment (defined as \( \geq 50\% \) reduction from baseline in HAMD score), time to first response, CGI-S and CGI-I scores. A post-hoc exploratory analysis was performed on item 1 (relating to depressed mood, one of the core variables for depression assessment) and on items 4, 5 and 6 (relating to sleep variables: early, middle and late insomnia, respectively) of the HAMD.

**Safety assessments**

Adverse events (AEs) expressed spontaneously by the patient or elicited retrospectively during discussion with the investigator were recorded at each clinic visit. Investigators graded AEs as mild, moderate or severe using their own clinical judgement. Serious AEs were predefined using standard criteria and the judgement of the investigator. Blood samples were collected at weeks 0 and 6 (or upon withdrawal). Blood pressure and heart rate were measured at selection, weeks 0 and 6, and bodyweight at weeks 0 and 6. An ECG was performed at week 0 and at the last visit.

**Statistical analysis**

Efficacy analyses were performed on the ITT population (all patients having taken at least one dose of the study medication and with at least one post-baseline efficacy assessment for HAMD total score). Analyses were also performed on one subset of the ITT group representing the severely depressed patients (patients with a HAMD total score \( \geq 25 \) and CGI-S \( \geq 5 \) at week 0), and one subset of the ITT group who were not receiving concomitant benzodiazepines and all randomized patients. All analyses were conducted using the LOCF approach. For all efficacy variables, the two-sided Student’s \( t \) test for independent samples was used to analyse the differences between agomelatine and placebo-treated groups. The difference in HAMD total score was also studied, with adjustment for centre and baseline, using a one-way analysis of covariance (ANCOVA) on the factors group and centre (random effect) with baseline as a covariate and without interaction. The differences in HAMD total score at each visit were studied using an analysis of variance (ANOVA) with repeated measures taking into account the following factors: treatment, time and treatment×time interaction. The effect size adjusted for baseline and centre was calculated for the primary efficacy variable as the between-treatment difference in mean HAMD total score at week 6 divided by the corresponding pooled standard deviation. Significance was determined using the same two-tailed type I error (5%). Response to treatment (defined as \( \geq 50\% \) reduction from baseline in HAMD score) was analysed using a \( \chi^2 \) test. Time to first response was determined using Kaplan–Meier event-free survival curves and tested for significance between groups using the log-rank test. Safety analyses (safety set) included all patients having taken at least one dose of study medication and were performed using descriptive statistics. Differences between the two treatment groups in the incidence of the most common AEs (defined as events occurring in \( > 2\% \) of patients in either group) were analysed using Fisher’s exact test. All statistical analyses were performed using SAS® software, version 8.2 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Patient population, baseline characteristics**

In total, 260 patients were selected for the study and entered the run-in phase. Two hundred and thirty-eight patients [mean ± standard deviation (s.d.) age 45.0 ± 11.3 yr; 73.5% female] were included in the study and randomized to agomelatine (\( n = 118 \)) or placebo (\( n = 120 \)). Eight patients who received agomelatine and four patients who received placebo were in-patients at the start of the study. The demographic data, disease history and other baseline characteristics were similar between treatment groups (Table 1). In total, 46.6% (\( n = 55 / 118 \)) of agomelatine-treated patients had received previous antidepressant treatment prior to the study compared with 34.2% (\( n = 41 / 120 \)) of placebo-treated patients.

Seventy-two percent of ITT patients (\( n = 165 \)) represented the subpopulation of severely depressed patients. Demographic and baseline characteristics, including depression history, in the severely depressed population were similar to those observed in
the ITT population, with the exception of HAMD total score (mean ± S.D.: 28.3 ± 2.4 vs. 27.3 ± 2.8 respectively) and CGI-S score (5.2 ± 0.4 vs. 4.9 ± 0.7 respectively) at baseline. Unless stated otherwise, results are presented for the pre-specified pooled agomelatine groups (25 mg/d and 25 mg/d dose-adjusted) and the pooled placebo groups (control and ‘control-adjusted’). The ITT population consisted of 235 patients (two randomized to agomelatine and one to placebo were excluded due to lack of post-baseline efficacy evaluation).

**Patient disposition**

The patient disposition is shown in Figure 2. A total of 35 patients discontinued during weeks 0–6, 17 (14.4%) in the agomelatine group and 18 (15.0%) in the placebo group. The most common reason for discontinuation was lack of efficacy. Overall, 85.3% of patients completed weeks 0–6. Of the patients continuing at week 2, 28/111 (25.2%) patients in the agomelatine group were classified as having insufficient improvement compared with 55/113 (48.6%) patients in the placebo group (p < 0.001).

**Efficacy**

**Primary efficacy variable**

Agomelatine (25–50 mg/d) was significantly more efficacious than placebo in the overall population (Table 2) and this efficacy separated significantly from placebo after only 2 wk of treatment (Figure 3). The differences in HAMD total score between placebo and agomelatine in the ITT population at visits in weeks 2, 4 and 6 were 1.59 (p = 0.042), 2.29 (p = 0.003) and 3.18 (p < 0.001) respectively. The mean effect size at week 6 was 0.4076 after adjustment for baseline and centre. The mean LOCF of HAMD total score in the ITT group was significantly lower in the agomelatine group than in the placebo group (p < 0.001), resulting in a difference [standard error (s.e.)] of 3.44 (0.92) after adjustment for baseline and centre. Similar results were seen in the ITT group [difference (s.e.) 2.99 (1.02), 95% confidence interval (CI) 0.97–5.01, p = 0.004] and in the subset of patients (n = 169) not receiving concomitant benzodiazepines [difference (s.e.) 2.50 (1.18), 95% CI 0.17–4.84, p = 0.036].

The efficacy of agomelatine was demonstrated in the patients who received a dose-adjustment of agomelatine, their HAMD total score (mean ± S.D.) being lower than in the placebo patients acting as the control

**Figure 2.** Patient disposition. * From the 55 and 28 patients assigned to the ‘control-adjusted’ and agomelatine dose-adjusted groups respectively, one patient was incorrectly not adjusted and one patient incorrectly dose-adjusted. AE, Adverse event.
dose-adjusted group [LOCF: 15.9 ± 8.0 vs. 18.9 ± 7.3] respectively, resulting in a difference (s.e.) of 3.71 (1.53) after adjustment for baseline and centre; 95% CI 0.65–6.77, p = 0.018]. The differences in HAMD total score between placebo and agomelatine at visits in weeks 2, 4 and 6 were 2.11 (p = 0.084), 1.32 (p = 0.277) and 2.97 (p = 0.015) respectively (Figure 4).

Clinical Global Impression scores

The mean LOCF for CGI-S in the ITT group was significantly lower in the agomelatine group than the placebo group (p = 0.006) (Table 2). Over the course of the study, CGI-S scores (mean ± S.D.) in the agomelatine group decreased from 4.9 ± 0.7 at baseline to 4.2 ± 1.0 at week 2, 3.6 ± 1.1 at week 4 and 3.1 ± 1.4 at end of study (LOCF). In the placebo group, scores decreased from 4.9 ± 0.7 at baseline to 4.4 ± 0.9 at week 2, 4.0 ± 1.1 at week 4 and 3.6 ± 1.4 at end of study. For CGI-I, patients receiving agomelatine had a lower mean LOCF than those receiving placebo (p = 0.006) (Table 2). CGI-I scores (mean ± S.D.) in agomelatine-treated patients were 3.0 ± 1.0 at week 2, 2.5 ± 0.9 at week 4 and 2.2 ± 1.2 at end of study (LOCF). In placebo-treated

Table 2. Primary and secondary efficacy variables (LOCF) in the ITT population: HAMD total score, proportion of responders and CGI-I/CGI-S scores

<table>
<thead>
<tr>
<th></th>
<th>Agomelatine (n = 116)</th>
<th>Placebo (n = 119)</th>
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<tr>
<td><strong>HAMD total score (mean ± S.D.)</strong></td>
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<tr>
<td>Baseline</td>
<td>27.4 ± 2.7</td>
<td>27.2 ± 2.7</td>
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<tr>
<td>LOCF/week 6</td>
<td>13.9 ± 7.7</td>
<td>17.0 ± 7.9</td>
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<tr>
<td>Between treatment difference (s.e.)</td>
<td>3.18 (1.02)</td>
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<td>95% CI</td>
<td>1.18 to 5.18</td>
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<td>p value</td>
<td>p = 0.02</td>
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<td><strong>HAMD total score, adjustedb (mean ± S.D.)</strong></td>
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<tr>
<td>LOCF/week 6</td>
<td>13.7 ± 0.8</td>
<td>17.1 ± 0.8</td>
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<tr>
<td>Between treatment difference (s.e.)</td>
<td>3.44 (0.92)</td>
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<td>95% CI</td>
<td>1.63 to 5.26</td>
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<tr>
<td>p value</td>
<td>p &lt; 0.001</td>
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<td><strong>Responders, %</strong></td>
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<tr>
<td>LOCF/week 6</td>
<td>54.3</td>
<td>35.3</td>
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<tr>
<td>Between treatment difference (s.e.)</td>
<td>−19.02 (6.37)</td>
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<tr>
<td>95% CI</td>
<td>−31.50 to −6.53</td>
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<td>p value</td>
<td>p = 0.003</td>
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<td><strong>CGI-I (mean ± S.D.)</strong></td>
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<tr>
<td>LOCF/week 6</td>
<td>2.2 ± 1.2</td>
<td>2.7 ± 1.2</td>
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<tr>
<td>Between treatment difference (s.e.)</td>
<td>0.45 (0.16)</td>
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<tr>
<td>95% CI</td>
<td>0.13 to 0.76</td>
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<td>p value</td>
<td>p = 0.006</td>
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<td><strong>CGI-S (mean ± S.D.)</strong></td>
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<tr>
<td>LOCF/week 6</td>
<td>3.1 ± 1.4</td>
<td>3.6 ± 1.4</td>
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<tr>
<td>Between treatment difference (s.e.)</td>
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<tr>
<td>95% CI</td>
<td>0.15 to 0.86</td>
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<td>p value</td>
<td>p = 0.006</td>
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LOCF, Last observation carried forward; ITT, intention to treat; HAMD, Hamilton Depression Rating Scale; S.D., standard deviation; S.E., standard error; CI, confidence interval; CGI-I, Clinical Global Impression scale (global improvement); CGI-S, Clinical Global Impression scale (severity).

a Two-sided Student’s t test for independent samples; b Least Squares means (adjusted for centre and baseline); c Linear mixed effects model with baseline as covariate and centre as random effect; d χ² test; e Two-sided Student’s t test for independent samples (results were confirmed by Mann–Whitney tests).
patients, scores were 3.3 ± 0.9 at week 2, 2.8 ± 0.9 at week 4 and 2.7 ± 1.2 at end of study.

In patients who received a dose adjustment, the LOCF for CGI-S (mean ± S.D.) was lower in the agomelatine group than the control dose-adjusted placebo group, although the difference between the groups did not reach statistical significance [3.3 ± 1.3 vs. 3.8 ± 1.4 respectively; difference (S.E.) 0.47 (0.32), 95% CI −0.16 to 1.10, p = 0.141]. For CGI-I, dose-adjusted patients receiving agomelatine showed a trend for lower LOCF (mean ± S.D.) compared with those receiving control dose-adjusted placebo [2.4 ± 1.3 vs. 2.9 ± 1.3, difference (S.E.) 0.49 (0.29), 95% CI 0.09 to 1.07, p = 0.094].

Response to treatment

Response rates are shown in Table 2. In total, 54.3% and 35.3% of agomelatine and placebo patients respectively in the ITT group were responders (p = 0.003). The proportion of responders in the agomelatine dose-adjusted group was 48.3% compared with 25.9% in the placebo patients acting as control [difference (S.E.) −22.40% (11.03), 95% CI −43.97 to −0.73, p < 0.05].

Time to first response to treatment

In the ITT group, survival analysis showed a difference between groups for the time to first response (p = 0.008) in favour of agomelatine. From 14 d onwards, the incidence of patients with a first response to treatment was significantly higher in the agomelatine group than in the placebo group (Figure 5).

Efficacy variables in the severe subpopulation

In the subpopulation of severely depressed patients, for the primary efficacy variable, the difference (S.E.) in mean LOCF of HAMD total score (adjusted for centre and baseline) was 3.60 (1.12) (95% CI 1.39–5.81, p = 0.002) between agomelatine and placebo (mean ± S.D. scores: 14.6 ± 7.4 vs. 18.1 ± 8.4 respectively), which was similar to that seen in the ITT group. The benefit seen in the ITT group for CGI-S and CGI-I was also observed in the severely depressed subpopulation: mean ± S.D. scores for agomelatine and placebo, respectively, of 3.3 ± 1.4 vs. 3.7 ± 1.5 [difference (S.E.) 0.45 (0.22), 95% CI 0.02–0.89, p = 0.042] for CGI-S and 2.3 ± 1.1 vs. 2.8 ± 1.2 [difference (S.E.) 0.48 (0.18), 95% CI 0.11–0.84, p = 0.010] for CGI-I. The response rates for the severely depressed patients were 49.4% vs. 34.1% for agomelatine-treated and placebo groups respectively (difference −15.25%, 95% CI −30.12 to −0.38, p = 0.047). Survival analysis showed a difference between groups for time to first response (p = 0.032) in favour of agomelatine.

Depressed mood (item 1) on the HAMD (exploratory analysis)

In the ITT population, a significant difference between agomelatine and placebo groups in favour of agomelatine was observed for the response to item 1 on the HAMD [mean difference (S.E.) LOCF 0.32 (0.13), 95% CI 0.06–0.58, p = 0.015].
Sleep items (4, 5 and 6) on the HAMD (exploratory analysis)

Significant improvements for agomelatine vs. placebo were seen for the HAMD item insomnia early in the night [mean difference (S.E.) LOCF 0.23 (0.10), 95% CI 0.03–0.43, \( p = 0.023 \)] and insomnia in the middle of the night [mean difference (S.E.) LOCF 0.29 (0.10), 95% CI 0.09–0.48, \( p = 0.004 \)]. In addition, there was a trend towards improvement in insomnia in the early hours of the morning [mean difference (S.E.) LOCF 0.19 (0.10), 95% CI −0.02 to 0.39, \( p = 0.075 \)]. A pooled analysis of items 4, 5 and 6 also showed a significant improvement for agomelatine vs. placebo [mean difference (S.E.) LOCF 0.71 (0.23), 95% CI 0.25–1.16, \( p = 0.002 \)].

Safety

The percentage of patients reporting AEs was similar in both the agomelatine (42.4%) and the placebo (42.5%) groups during the 6-wk treatment period. AEs occurring in \( \geq 2 \)% of patients in any treatment group are shown in Table 3. The majority of AEs were mild to moderate in severity in all treatment groups. The proportion of patients who discontinued due to AEs was 3.4% in the agomelatine group and 5.8% in the placebo group.

Six patients experienced serious emergent AEs. Four of these were in the agomelatine group (two suicide attempts, one radius fracture and one carpal tunnel syndrome) and two in the placebo group (one suicide attempt and one completed suicide). None of these events were considered by the investigator to be related to study treatment. No relevant differences between treatment groups were observed in any of the biochemical or physical examination variables during treatment.

There were no relevant differences in the proportion of patients reporting AEs in the 25-mg agomelatine and 25–50 mg agomelatine (dose-adjusted) groups, except for infections, which were reported in 10.3% of patients in the dose-adjusted group and 6.1% of patients in the 25-mg group. The incidence of infections in the corresponding placebo groups was 14.8% and 11.9% respectively. Regarding sexual side-effects, emergent reproductive system and breast disorder AEs reported during the study included dysmenorrhoea (one patient in each group), menometrorrhagia (one patient in the placebo group) and breast tenderness (one patient in the agomelatine group). Treatment with agomelatine was not found to be associated with any other sexual side-effects, such as impotence, ejaculation difficulties and decreased libido.

Discussion

Using a novel technique to maintain study blinding, this flexible-dosing study confirms that agomelatine, a \( \text{MT}_1/\text{MT}_2 \) receptor agonist with 5-HT\( \text{\textsubscript{2C}} \) antagonistic
In the meta-analysis, 46% of 4314 TCA-treated patients with major depression reported a $\geq 50\%$ improvement in total HAMD score. This compares with a 54% response rate observed with agomelatine treatment in the present study and is in concordance with the observed effect size of approximately 0.407. Response rates with placebo in the meta-analysis were similar to those reported in this study (31% vs. 35.3% respectively) (95% CI for drug–placebo difference in the meta-analysis: 11.5–17.1) (Storosum et al., 2001). The agomelatine–placebo difference of 3.44 points in HAMD total score reported here also compares favourably with efficacy data reported for SSRIs. In an analysis of data (4- to 8-wk, registrational, placebo-controlled trials with completion rate $\geq 70\%$, typically involving patients with moderate-to-severe depression) submitted to the U.S. Food and Drug Administration (FDA) for the six most widely prescribed antidepressants approved between 1987 and 1999, a difference of around 2–3 points in mean 17-item HAMD total score (weighted for sample size) was reported for sertraline (2.0), citalopram (2.0) and paroxetine (3.2) vs. placebo (Kirsch et al., 2002). Similarly, for the most recently licensed antidepressant, duloxetine, the drug–placebo difference in HAMD total score was found to be 2.7 points in two positive, placebo-controlled studies that used this drug at its licensed dose (EMEA, 2005). The present study would also be considered ‘successful’ according to the methods applied in a recent exploration of FDA approval reports, which found (from a total of 52 trials evaluated) a mean treatment difference (drug–placebo) in HAMD score improvement (from baseline to study end) of 3.07 (Khan et al., 2004).

At baseline, the mean HAMD total score in the ITT group was $27.3 \pm 2.8$, indicative of the severity of depression in the population included in this study. Correspondingly, a high proportion of patients (72%) comprised the severely depressed patient subgroup. Agomelatine offered severely depressed patients similar advantages as seen in the ITT population; an important finding, given that these patients are difficult to treat and frequently fail to recover or suffer recurrent episodes of depression because of inadequate symptom relief with some treatments, including SSRIs (Anderson, 2000; Clerc, 2001; Danish University Antidepressant Group, 1986, 1990; Sonawalla and Fava, 2001; Vestergaard et al., 1993). These encouraging preliminary data suggest that agomelatine may serve as a useful alternative to SSRIs in the treatment of severe depression.

Sleep patterns are thought to be important in the aetiology of depression and are disturbed in depressed patients (Nofzinger et al., 1999). In the exploratory

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients (%)</th>
<th>p value for the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Agomelatine (n=118)</td>
<td>Placebo (n=120)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (5.1)</td>
<td>17 (14.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (5.1)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (4.2)</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (4.2)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (3.4)</td>
<td>7 (5.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>3 (2.5)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (2.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Nightmare</td>
<td>0 (0.0)</td>
<td>4 (3.3)</td>
</tr>
</tbody>
</table>

$^a$ Fisher’s exact test.
subanalysis of HAMD sleep scores in the present study, agomelatine improved the three types of insomnia symptoms. This improvement in sleep was expected given the pharmacological profile of the product. Circadian rhythms are disturbed in depressed patients (Wehr and Wirz-Justice, 1982; Wirz-Justice, 1995). Some biological parameters (i.e., certain hormones, body temperature, and cardiac rhythm) present advanced or delayed phases, and in general their amplitude is flattened (Souetre et al., 1989; Thompson et al., 1988). Preclinical studies have shown that agomelatine resynchronizes circadian rhythms in various experimental models of rhythm disturbance designed to simulate jet lag (phase shift of the light–dark cycle), delayed sleep-phase syndrome and blindness (free-running rodent model) (Armstrong et al., 1993; Martinet et al., 1996; Redman et al., 1995). Resynchronization of circadian rhythms in animals appears to occur following brief exposure to agomelatine, an effect that is consistent with its short half-life (1–2 h), while prolonged exposure is much less effective (Pitrosky et al., 1999). The effect of agomelatine on circadian rhythms has also been observed in healthy volunteers (Krauchi et al., 1997; Leproult et al., 2005). Furthermore, the correction of circadian disturbances by agomelatine was detected in a preliminary study in depressed patients using polysomnography (Quera Salva et al., 2005). In this study, treatment with agomelatine induced increases in slow-wave sleep and resynchronization of slow-wave sleep normalization throughout the night.

The antidepressant-like activity of agomelatine is superior to that of melatonin in animal models of depression (Bertaina-Anglade et al., 2002; Bourin et al., 2004; Papp et al., 2003). Apart from the differences in half-life (in both rodents and humans, the half-life of melatonin is shorter than that of agomelatine) (Mallo et al., 1990; Yeleswaram et al., 1997) one of the possible reasons for this may be due to the antagonism of the 5-HT2C receptor by agomelatine. This receptor has been reported to be involved in circadian rhythm resynchronization (Kennaway and Moyer, 1998; Varcoe et al., 2003) in addition to its role in mood regulation (Gurevich et al., 2002; Yamada and Sugimoto, 2001).

One limitation of the current study is that no circadian marker was analysed to investigate the contribution of the regulation of circadian rhythms to the mode of action of agomelatine. Studies are presently ongoing to confirm this hypothetical mode of action. The morningness–eveningness has not been explored in this study. It is assessed in an ongoing study where actigraphy and other circadian parameters are measured after treatment with agomelatine.

The study design followed the recommendations of the Committee for Proprietary Medicinal Products (CPMP, 2002) including a limit of 6 wk duration for placebo-controlled trials. This study differed from the standard double-blind, flexible-dose study in that the criteria for insufficient response were defined centrally using a novel IVRS protocol and not disclosed to physicians, meaning they were unaware of whether their patients had received a dose-adjustment or not, further reducing the confounding effect of physician expectation on treatment outcomes. In addition, the allocation of placebo patients to a ‘mock’ dose-adjusted arm allowed comparisons between agomelatine and placebo to be made in patients not exhibiting a pronounced placebo response. Placebo-treated patients were twice as likely to meet the criteria for non-response at week 2 than patients treated with agomelatine ($p < 0.001$). Dose adjustment of agomelatine from 25 mg/d to 50 mg/d after 2 wk treatment was associated with a significant improvement in HAMD score in comparison with placebo at week six ($p = 0.015$). The safety and tolerability were comparable between patients remaining on 25 mg agomelatine and in patients dose-adjusted, showing that dose-adjustment does not affect tolerability. This implies, therefore, that patients with suboptimal symptom improvement at the lower dose may undergo dose escalation to achieve satisfactory clinical effect without compromising safety. Interestingly, dose-adjusted patients (i.e., those who did not exhibit sufficient improvement at week 2), had a slightly higher mean HAMD total score – indicating more severe depression – at baseline (28.4), which suggests that severe patients are more difficult to treat.

The excellent tolerability of agomelatine was reflected by the low rate of discontinuations due to AEs in the agomelatine group (3.4%), which was similar to that observed in the placebo group (5.8%) and in agreement with the good tolerability profile shown in a previous study (Lőo et al., 2002). Indeed, with the exception of headache, which was reported more frequently in the placebo group, agomelatine was associated with a similar safety profile to placebo. In contrast to SSRIs (Ferguson, 2001), few sexual side-effects, with no reports of impotence, ejaculation difficulties and decreased libido. This low incidence of side-effects on sexual function could be due to the melatonergic effect (Brotto and Gorzalka, 2000), and/or the antagonism of the 5-HT2C receptor (Clayton et al., 2003; Ferguson et al., 2001). It is probable that the novel mode of action of agomelatine (selective binding profile, not inducing serotonin release or increasing serotonin extracellular levels and no 5-HT1A activity)
Efficacy of agomelatine in MDD

(Hanoun et al., 2004; Millan et al., 2003) may be responsible for its favourable safety profile.

High discontinuation rates in clinical trials of antidepressant agents are a considerable issue (Fava et al., 2003) with up to 40% of patients discontinuing treatment (Khan et al., 2003). Discontinuation rates in this study were just 14% and 15% for agomelatine and placebo respectively, which supports the robustness of the findings presented here and suggests that agomelatine is an acceptable treatment for patients.

In conclusion, this study confirms that agomelatine is effective in the treatment of depression, including the most severely depressed patients, and has a good safety and tolerability profile. Head-to-head studies comparing the relative efficacy and safety of agomelatine with present ‘standard of care’ antidepressants are ongoing in patients with varying severities of illness. The results of these studies are awaited and should substantiate the role of agomelatine in the treatment of MDD.

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Statement of Interest

The sponsor (IRIS) planned and conducted the study and analysed the data. The authors had full access to all the data from the study, were involved in data interpretation, produced and directed the manuscript in collaboration with the sponsor and had final responsibility for the decision to submit for publication.

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