REVIEW ARTICLE

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A Benefit-Risk Assessment of Agomelatine in the Treatment of Major Depression

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Contents

Abstract

Agomelatine is an antidepressant drug that is a synthetic analogue of the hormone melatonin. It stimulates the activity of melatonin MT_1 and MT_2 receptors and inhibits the activity of serotonin $5HT_{2C}$ receptor subtypes.

The objective of this article is to critically review and evaluate the benefits and risks of agomelatine for the treatment of major depression. The published literature through April 2011 for articles relating to agomelatine, together with unpublished data on agomelatine available from the European

Medicines Agency, the US FDA, US ClinicalTrials.gov and the Novartis Clinical Trial Results Database are reviewed.

The antidepressant efficacy of agomelatine has been systematically assessed in ten short-term, placebo-controlled studies and three longer-term, placebo-controlled, relapse prevention studies. Five short-term trials demonstrated clinically modest, but statistically significant, benefits over placebo, although two of these studies reported opposite effects for 25 mg versus 50 mg doses. The other five short-term trials did not find agomelatine more effective than placebo, but in two of these studies the active control drug was more effective than placebo.

A meta-analysis of six European trials demonstrated a small, statistically significant, marginally clinically relevant difference in efficacy favouring agomelatine over placebo. The only placebo-controlled study in elderly patients did not demonstrate a significant benefit for agomelatine. Agomelatine was shown to be more effective than placebo in one of three relapse prevention studies.

Agomelatine was generally well tolerated compared with placebo. Its adverse effect profile is different to that of other antidepressant drugs, but its overall tolerability in studies with other antidepressants as active control drugs did not appear to be substantially better than the controls. Agomelatine is contraindicated in patients with impaired liver function and in patients taking drugs that potently inhibit cytochrome P450 1A2 metabolic enzymes. Because elevated liver enzymes are common, and there is a rare risk of more serious liver reactions, routine laboratory monitoring of liver function is recommended periodically throughout treatment. Based on this comprehensive review, agomelatine does not have clinically significant advantages compared with other antidepressant drugs, and it has certain limitations and disadvantages. Because of the unique pharmacology of agomelatine and its reported tolerability profile, it should only be considered as an alternative drug for patients who do not respond to or cannot tolerate other antidepressant drugs.

The lifetime prevalence of major depression in various countries around the world ranges from 1.5% to 19%.[1] Major depression is associated with significant social, educational, and vocational impairment, high utilization of social and healthcare services, and increased medical morbidity and mortality. Other forms of depression include dysthymia and minor depression, which are characterized in part by their milder symptom severity, and their prevalence ranges from 3% to 10%.[2,3] Despite having 'milder' depressive symptoms, patients with dysthymia or minor depression have significant levels of impairment, are high utilizers of healthcare services, and have an increased risk of developing major depression.[4,5]

The goal of antidepressant drug therapy for depressive disorders should be to achieve full remission, as demonstrated by the absence of significant depressive symptoms along with a complete recovery of social and vocational function.[6] With any first-choice antidepressant medication, about 50–70% of patients will have a significant treatment response (usually defined as a 50% or greater decrease in depressive symptoms).[6] Of these treatment responders, however, fewer than half attain a full remission.[6] A significant proportion of patients with depression are therefore left with residual or persistent symptoms despite apparently adequate antidepressant therapy. The failure to achieve remission with antidepressant

therapy is associated with an increased risk of relapse or recurrence, higher levels of impaired social and vocational function, and a worse long-term prognosis. Symptomatic improvement of depression can facilitate the process of functional recovery, thereby reducing disability, and this can help prevent possible complications related to the illness such as substance abuse and suicide.[7] Depression also worsens the health outcome and functioning of patients when occurring concomitantly with a variety of other medical disorders.[8] Ineffectively or inadequately treating depression may therefore contribute to the substantial morbidity and mortality associated with many medical conditions as well as with depression itself.

A broad spectrum of various classes of antidepressant drugs, as well as other types of antidepressant therapies (including multiple psychotropic augmentation agents, several depression-focused psychotherapies, electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, exercise and other therapies), are available for treating depression, but their absolute effectiveness is limited.[6,9] Many patients do not respond to available drugs, or they have residual symptoms despite adequate treatment. Some patients respond to medication, but they develop intolerable side effects and stop treatment. For these reasons, new drug therapies are always needed. Even though a new drug may not necessarily be more effective on average compared with available drugs, it might be relatively more efficacious or better tolerated for certain patients.

Agomelatine has been characterized as an antidepressant compound with a novel mechanism of action, which has been extensively investigated in preclinical studies.[10] It has also been investigated in clinical trials in Europe, South America and the US for the treatment of major depression. It was first recommended for approval by the European Medicines Agency (EMA) in November 2008.[11-13] Agomelatine is not yet approved for marketing by the US FDA.[14]

This article critically reviews the efficacy, tolerability and safety of agomelatine for the treatment of major depression in adults. The efficacy of this agent in children and adolescents (younger than 18 years) with major depression has not been investigated. The published literature on MEDLINE, PsychINFO and Google Scholar through April 2011 was searched for articles relating to agomelatine, using the search terms 'agomelatine' or 'S-20098'. Additional literature potentially related to agomelatine was searched for using the terms 'melatonin', 'ramelteon' or 'TAK-375'. Unpublished data on agomelatine was also sourced from the EMA, FDA, US ClinicalTrials.gov and the Novartis Clinical Trial Results Database.[11,14,15]

1. Brief Overview of the Pharmacology of Agomelatine

Agomelatine is a synthetic analogue of the hormone melatonin, which is secreted by the pineal gland and normally serves to regulate various circadian (24-hour) rhythms, including sleep-wake cycles.[16] Agomelatine is a potent melatonin-receptor agonist drug that strongly binds to and stimulates the activity of melatonin MT_1 and MT_2 receptors, which are localized within the suprachiasmatic nucleus of the hypothalamus.[17] Stimulation of MT_1 and MT_2 receptors has a normalizing effect on disturbed circadian rhythms and disrupted sleep-wake cycles. Agomelatine has also been characterized as a serotonin-receptor antagonist that binds to and inhibits the activity of serotonin $5HT_{2C}$ receptor subtypes, but it does not bind to other serotonin receptor subtypes.[10] Antagonism at the $5HT_{2C}$ receptor is associated with antidepressant and anti-anxiety activity and also increases slow-wave sleep (which is abnormally diminished in depression).[18] Agomelatine does not directly affect the uptake of serotonin, noradrenaline (norepinephrine) or dopamine. By inhibiting $5HT_{2C}$ receptors, however, it secondarily increases noradrenaline and dopamine in the frontal cortex of the brain.[19] This effect might contribute to its antidepressant activity. Agomelatine does not bind to adrenergic, cholinergic or histamine receptors.

The pharmacology of agomelatine, with its combined effects at MT_1, MT_2 and $5HT_{2C}$ receptors, is therefore unique and distinct compared with other antidepressant drugs. Sleep EEG studies demonstrate the benefits of agomelatine on sleep in patients with depression (i.e. increases slow-wave sleep and sleep efficiency).[20] Increases in slow-wave

sleep (the deepest stage of sleep) typically correlate with subjective daytime reports of having had a good night's sleep and feeling well rested.[21] Agomelatine has also been shown to influence circadian rhythms in animals and humans.[22-24] These effects are all consistent with what would be expected based on MT_1, MT_2 and $5HT_{2C}$ receptor pharmacology. However, the degree to which $5HT_{2C}$ receptor antagonism explains or contributes to the antidepressant or sleep effects of agomelatine has been questioned.[25]

2. Short-Term Clinical Studies of Agomelatine for Major Depression

The short-term effectiveness of agomelatine in the treatment of major depression has been investigated through separate clinical research programmes conducted in Europe and the US. In addition, one short-term multinational study has been conducted at sites in Europe and South America.[26]

2.1 European Clinical Trials

In Europe, the efficacy of agomelatine for major depression has been investigated in three published[27-29] and three unpublished,[11] randomized, double-blind, placebo-controlled pivotal studies (see table I). Data from the unpublished studies are available from the EMA Committee for Medicinal Products for Human Use (CHMP) Assessment Report for Valdoxan.[11] Paroxetine or fluoxetine was included in some of these trials as an active control drug according to European regulatory guidelines. For each of the pivotal studies, the 17-item Hamilton Rating Scale for Depression (HAM-D) was the primary outcome measure.[34] The primary outcome efficacy variable was the HAM-D score for agomelatine versus placebo at endpoint. Response and remission rates based on the HAM-D were considered secondary outcome variables. Response was defined as a 50% decrease in the HAM-D score from baseline to endpoint, and remission was defined as a HAM-D score of ≤6 at endpoint.

In an 8-week, dose-finding study involving 711 patients (18–65 years of age), Loo and colleagues[27] compared three doses of agomelatine (1, 5 and 25 mg/day), placebo and paroxetine 20 mg/day (as an active control drug). Agomelatine 25 mg (but not the two lower doses) and paroxetine were significantly more effective than placebo. The mean difference in HAM-D was 2.57 for agomelatine (25 mg) versus placebo ($p = 0.034$) and 2.25 for paroxetine versus placebo ($p = 0.030$). Response rates for agomelatine 1 mg (62.5% [$p = 0.021$]) and 25 mg (61.5% [$p = 0.036$]) were significantly better than for placebo (46.3%), but agomelatine 5 mg (51.4%) and paroxetine (56.3%) were not significantly higher than placebo. Remission rates for agomelatine 25 mg (30.4% [$p < 0.01$]) and paroxetine (25.7% [$p < 0.05$]) were significantly greater than for placebo (15.4%), but the rates for agomelatine 1 mg (21.3%) and 5 mg (17.8%) were not significantly better than placebo. The overall rate of treatment-emergent adverse events (TEAEs) was similar for agomelatine (51.1%) and placebo (54.7%), but slightly higher for paroxetine (66.0%). Most adverse events were experienced as mild to moderate in severity. There was no significant difference in dropout rates due to TEAEs between agomelatine, placebo and paroxetine. Reported adverse events of headache, anxiety, abdominal pain, diarrhoea, nausea, somnolence, insomnia, rhinitis and dry mouth were no different between agomelatine and placebo, but nausea was significantly more common with paroxetine ($p = 0.001$) compared with placebo and agomelatine. There were no significant differences among the groups with respect to bodyweight changes, cardiovascular effects or laboratory studies.

In a 6-week study involving 212 patients (18–65 years of age), Kennedy and Emsley[28] compared agomelatine 25–50 mg/day and placebo. After an initial 2-week treatment with agomelatine 25 mg/day or placebo, the study medication dosage of patients with poor response was increased under double-blind conditions to agomelatine 50 mg/day or matching placebo. Among the 106 patients taking agomelatine, 69 patients stayed at 25 mg/day and 36 patients increased to 50 mg/day. Agomelatine (both doses pooled) was significantly more effective than placebo. The mean difference in HAM-D was 2.30 for agomelatine versus placebo ($p = 0.026$). Response rates

Table I. Randomized controlled clinical efficacy studies of agomelatine for major depression

Study	Location	No. of subjects	Duration (wk)	Design	Comparison (mg)	Study outcome
Loo et al.[27]	Europe	711	8	Efficacy and safety	AGO 1 AGO 5 AGO 25 PBO PAR 20	AGO 1 mg = PBO AGO 5 mg = PBO AGO 25 mg >> PBO PAR >> PBO
Kennedy and Emsley[28]	Europe	212	6	Efficacy and safety	AGO 25–50 PBO	AGO >> PBO
Olie and Kasper[29]	Europe	238	6	Efficacy and safety	AGO 25–50 PBO	AGO >> PBO
CL3-022[11]	Europe	419	6	Efficacy and safety	AGO 25 PBO FLX 20	AGO = PBO FLX >> PBO
CL3-023[11]	Europe	418	6	Efficacy and safety	AGO 25 PBO PAR 20	AGO = PBO PAR = PBO
CL3-024[11]	Europe	607	6	Efficacy and safety	AGO 25 AGO 50 PBO FLX 20	AGO = PBO FLX = PBO
CL3-026[11]	Europe	218	6	Efficacy and safety in the elderly	AGO 25 PBO	AGO = PBO
Zajecka et al.[30]	USA	511	8	Efficacy and safety	AGO 25 AGO 50 PBO	AGO 25 mg = PBO AGO 50 mg >> PBO
Stahl et al.[31]	USA	503	8	Efficacy and safety	AGO 25 AGO 50 PBO	AGO 25 mg >> PBO AGO 50 mg = PBO
CAGO178A2303[32]	USA	503	8	Efficacy and safety	AGO 25–50 PBO PAR 20–40	AGO = PBO PAR >> PBO
Hale et al.[26]	Multinational	515	8	Efficacy and safety	AGO 25–50 FLX 20–40	AGO >> FLX
Goodwin et al.[33]	Multinational	339	34	Relapse prevention	AGO 25–50 PBO	AGO >> PBO
CL3-021[11]	Europe	367	34	Relapse prevention	AGO 25 PBO	AGO = PBO
CAGO178A2304[32]	USA	633	52	Relapse prevention	AGO 25–50 PBO	AGO = PBO

AGO = agomelatine; **FLX** = fluoxetine; **PAR** = paroxetine; **PBO** = placebo; **>>** indicates significantly better than; **=** indicates no significant difference.

for agomelatine (49.1%) and placebo (34.3%) were significantly different ($p = 0.03$), but remission rates for agomelatine (20.8%) and placebo (13.3%) were not significantly different ($p = 0.152$). The overall rate of TEAEs was similar for agomelatine (30.2%) and placebo (36.2%). Most TEAEs were mild to moderate in severity. Dropout rates due to TEAEs were similar for placebo (4.8%) and agomelatine (4.7%). Dizziness and rhinitis were more common with agomelatine compared with placebo, whereas headache, nausea, fatigue, dry mouth and diarrhoea were more common with placebo compared with agomelatine. There were no differences between agomelatine and placebo with respect to bodyweight changes, cardiovascular effects or laboratory studies.

In a second 6-week study involving 238 patients (18–65 years of age), Olie and Kasper[29] compared agomelatine 25–50 mg/day and placebo. If patients did not respond adequately after 2 weeks of agomelatine 25 mg/day or placebo, the dosage was increased under double-blind conditions to 50 mg/day or matching placebo. Among the 118 patients taking agomelatine, 82 stayed at a dosage of 25 mg/day and 29 increased to 50 mg/day. Agomelatine (both doses pooled) was significantly more effective than placebo. The mean difference in HAM-D was 3.18 for agomelatine versus placebo ($p = 0.002$). Response rates for agomelatine (54.3%) and placebo (35.3%) were significantly different ($p = 0.003$), but remission rates for agomelatine (17.2%) and placebo (11.8%) were not significantly different. The overall rate of TEAEs was similar for agomelatine (42.4%) and placebo (42.5%). Most TEAEs were of mild to moderate severity. Dropout rates due to TEAEs were slightly higher for placebo (5.8%) compared with agomelatine (3.4%). Fatigue, nausea, dizziness, rhinitis and dry mouth were no different between agomelatine and placebo, but headache was significantly more common for placebo compared with agomelatine ($p = 0.027$). Sexual functioning, bodyweight changes, cardiovascular effects and laboratory studies did not differ between groups.

In a 6-week unpublished study (CL3-022)[11] involving 419 patients (18–60 years of age), investigators compared agomelatine 25 mg/day, placebo and the selective serotonin reuptake inhibitor (SSRI) drug fluoxetine 20 mg/day (as an active control drug). Agomelatine was not significantly more effective than placebo (the mean difference in HAM-D was 1.4 for agomelatine vs placebo). Response rates for agomelatine (53%) and placebo (47%) were not significantly different. Remission rates for agomelatine and placebo also were not significantly different (actual rates were not reported). By contrast, fluoxetine was significantly more effective than placebo (the mean difference in HAM-D was 2.59 for fluoxetine vs placebo [$p = 0.008$]). Response and remission rates for fluoxetine were not reported. There was no significant difference in dropout rates due to TEAEs during the 6-week trial between agomelatine, placebo and fluoxetine. At the end of 6 weeks, subjects responding to agomelatine or fluoxetine were eligible for an 18-week, double-blind, placebo-controlled extension phase. Among these subjects, the depression score at the end of the extension phase was lower in the agomelatine group than in the placebo group, but the difference was not statistically significant. Nine subjects in the agomelatine group (14.3%), 20 in the placebo group (33.3%) and 13 in the fluoxetine group (17.8%) relapsed during the extension phase. The survival curve time to relapse analysis showed a statistically significant difference favouring the active drug (agomelatine [$p = 0.017$] or fluoxetine [$p = 0.045$]) compared with placebo.

In another 6-week unpublished study (CL3-023),[11] involving 418 patients (18–60 years of age), investigators compared agomelatine 25 mg/day, placebo and paroxetine 20 mg/day (as an active control drug). Agomelatine was not significantly more effective than placebo (the mean difference in HAM-D was 0.8 for agomelatine vs placebo). Response and remission rates for agomelatine and placebo were not significantly different (actual rates were not reported). Paroxetine was not significantly more effective than placebo (the mean difference in HAM-D was 1.6 for paroxetine vs placebo). Response and remission rates for paroxetine were not reported. During the 6-week trial, there was no significant difference in dropout rates due to TEAEs between agomelatine, placebo and paroxetine. At the end of 6 weeks, subjects responding to agomelatine or paroxetine were eligible for an 18-week, double-blind, placebo-controlled extension phase. There were no significant differences in outcome between active drugs and placebo in the extension phase. Dropout rates due to TEAEs during the extension phase were similar for agomelatine (3.3%) and placebo (3.4%), but higher for paroxetine (8.6%).

In the last 6-week unpublished study (study CL3-024)[11] involving 607 patients (18–65 years of age), investigators compared two doses of agomelatine (25 and 50 mg/day), placebo and fluoxetine 20 mg/day (as an active control drug). Agomelatine 25 mg was not significantly more effective than placebo (the mean difference in

HAM-D was 1.4 for agomelatine vs placebo). Agomelatine 50 mg was also not significantly more effective than placebo (HAM-D data were not reported). Similarly, fluoxetine was not significantly more effective than placebo (the mean difference in HAM-D was 0.53 for fluoxetine vs placebo). Response and remission rates for agomelatine and fluoxetine were not reported. At the end of 6 weeks, subjects responding to agomelatine or fluoxetine were eligible for an 18-week, double-blind, placebo-controlled extension phase. In this phase, there were no significant differences in outcome between active drugs and placebo. Throughout the acute and extension phases of the study, there was no significant difference in dropout rates due to TEAEs between agomelatine, placebo and fluoxetine.

In addition to the six pivotal studies, a 6-week unpublished study (study CL3-026)[11] involving 218 elderly patients (60 years of age and older) was conducted comparing agomelatine 25 mg/day and placebo (see table I). For this study, the Montgomery Åsberg Depression Rating Scale (MADRS)[35] was the primary outcome measure and the primary outcome efficacy variable was the MADRS score for agomelatine versus placebo at endpoint. The response rate based on the MADRS was considered a secondary outcome variable. Response was defined as a 50% decrease in the MADRS score from baseline to endpoint. Remission rates were not reported in this study. Agomelatine was not significantly more effective than placebo (the mean difference in MADRS was 0.19 for agomelatine vs placebo). Response rates for agomelatine (46%) and placebo (52%) were not significantly different. At the end of 6 weeks, subjects responding to acute treatment were eligible for an 18-week, double-blind, placebo-controlled extension phase. There were no significant differences in outcome between active drugs and placebo during the extension phase. In an unplanned *post hoc* subgroup analysis of data from this study, agomelatine was significantly more effective than placebo among the subgroup of 86 patients with more severe levels of depression.[11] In an unpublished *post hoc* pooled analysis of data from the three published short-term pivotal studies,[27-29] which included subjects over 60 years of age, a significant antidepressant effect was observed in the subgroup of 53 patients who were 60–66 years of age.[11]

2.2 US Clinical Trials

Phase III clinical trials of agomelatine for major depression (three placebo-controlled, short-term efficacy and safety trials and one placebo-controlled, longer-term relapse prevention trial)[30-32] have been conducted and completed in the US. All of these trials are listed on ClinicalTrials.gov.[36-39] The findings from two of the short-term studies have been published (reviewed in the paragraphs that follow).[30,31] Results from the unpublished short-term and longer-term relapse prevention studies are available on the Novartis Clinical Trial Results Database website.[32] A rapidly dissolvable sublingual tablet formulation of agomelatine is also currently being evaluated in phase III efficacy and safety clinical trials (two short-term, placebo-controlled trials[40,41] and one open-label, longer-term trial[42]) for major depression in the US, but these trials have not yet been completed.

The US trials were 8-week, randomized, double-blind, placebo-controlled, phase III studies (see table I). In one unpublished study, paroxetine was included as an active control drug. For each of the studies, the 17-item HAM-D was the primary outcome measure and the primary outcome efficacy variable was the change in HAM-D score from baseline to week 8 for agomelatine versus placebo. Response and remission rates based on the HAM-D were considered secondary outcome variables. Response was defined as a 50% decrease in the HAM-D score from baseline to endpoint. Remission was defined as a HAM-D score of ≤7 at endpoint.

In the first published US study[30] involving 511 patients (18–70 years of age), investigators compared two doses of agomelatine (25 mg/day and 50 mg/day) with placebo. Agomelatine 25 mg was not significantly more effective than placebo (the mean difference in HAM-D was 0.6 for agomelatine vs placebo [$p = 0.505$]). Agomelatine 50 mg was significantly more effective than placebo (the mean difference in HAM-D was 2.5 for agomelatine vs placebo [$p = 0.004$]). Response

rates for agomelatine 25 mg (42.3%) and placebo (37.7%) were not significantly different (p = 0.421), but were for agomelatine 50 mg (49.7%) versus placebo (p = 0.029). Remission rates for agomelatine 25 mg (16.7% [p = 0.983]) and agomelatine 50 mg (22.4% [p = 0.202]) were not significantly different compared with placebo (16.8%). The overall rate of TEAEs was similar for agomelatine 25 mg (75.9%), agomelatine 50 mg (74.2%) and placebo (74.6%). Most adverse events were experienced as mild to moderate in severity. There was no significant difference in dropout rates due to TEAEs for agomelatine 25 mg (4.3%), agomelatine 50 mg (6.1%) and placebo (6.5%). Psychiatric adverse events (e.g. worsening depression or suicidal ideation) was the primary reason for placebo patients dropping out of the study, whereas a variety of psychiatric and medical adverse events were the reasons for dropouts among agomelatine-treated patients. For patients taking agomelatine (both dose groups pooled) versus placebo, the most common adverse events were headache (16.3% vs 14.2%), nausea (12.0% vs 5.9%), diarrhoea (10.5% vs 7.1%), dizziness (8.6% vs 4.7%), dry mouth (7.1% vs 7.7%), somnolence (7.1% vs 5.9%), sedation (6.8% vs 5.3%), fatigue (5.2% vs 4.1%), insomnia (5.2% vs 10.7%), constipation (3.4% vs 2.4%) and abnormal dreams (2.8% vs 0.6%). There were no significant differences among the three study groups with respect to bodyweight changes or cardiovascular effects. With the exception of liver function tests, there were no significant differences among the three study groups on any laboratory tests. Significant liver enzyme elevations occurred more often in the agomelatine 50 mg group (reviewed in more detail in section 7).

In the second published US study[31] involving 503 patients (18–70 years of age), investigators compared two doses of agomelatine (25 mg/day and 50 mg/day) with placebo. Agomelatine 25 mg was significantly more effective than placebo (the mean difference in HAM-D was 2.2 for agomelatine vs placebo [p = 0.01]). Agomelatine 50 mg was not significantly more effective than placebo (the mean difference in HAM-D was 1.2 for agomelatine vs placebo [p = 0.144]). Response rates for agomelatine 25 mg (46.8%) and placebo (33.1%) were significantly different (p = 0.013), but agomelatine 50 mg (41.6%) was not significantly different to placebo (p = 0.116). Remission rates for agomelatine 25 mg (22.2% [p = 0.070]) and agomelatine 50 mg (17.4% [p = 0.457]) were not significantly different compared with placebo (14.7%). The overall rate of TEAEs was similar for agomelatine 25 mg (69.9%), agomelatine 50 mg (70.7%) and placebo (65.5%). Most adverse events were experienced as mild to moderate in severity. There was no significant difference in dropout rates due to TEAEs for agomelatine 25 mg (4.3%), agomelatine 50 mg (6.0%) and placebo (4.8%). The reasons for dropping out did not differ substantially among the three study groups. For patients taking agomelatine (both dose groups pooled) versus placebo, the most common adverse events were headache (13.3% vs 17.0%), somnolence (9.1% vs 4.2%), dizziness (7.3% vs 3.0%), diarrhoea (7.3% vs 6.7%), nausea (6.1% vs 4.8%), fatigue (5.8% vs 2.4%), sedation (5.2% vs 4.2%), dry mouth (4.8% vs 8.5%), insomnia (3.3% vs 6.1%), anxiety (2.4% vs 3.0%), constipation (2.7% vs 1.8%) and abnormal dreams (2.1% vs 1.8%). There were no significant differences among the three study groups with respect to bodyweight changes or cardiovascular effects. With the exception of liver function tests, there were no significant differences among the three study groups on any laboratory tests. Significant liver enzyme elevations occurred only in the agomelatine 50 mg group (reviewed in more detail in section 7).

In the unpublished US study (CAGO178A2 303)[32] involving 503 patients (18–70 years of age), investigators compared agomelatine (25–50 mg/day) and paroxetine (20–40 mg/day) with placebo. Patients were started on agomelatine 25 mg/day, paroxetine 20 mg/day or placebo. Those patients who did not show the minimum required response at the end of week 4 had their doses increased to 50 mg/day, 40 mg/day or matching placebo, respectively. Agomelatine 25–50 mg was not significantly more effective than placebo (the mean difference in HAM-D was 0.5 for agomelatine vs placebo [p = 0.539]). Paroxetine 20–40 mg was significantly more effective than placebo (the mean difference in HAM-D was 3.4 for paroxetine

vs placebo [p < 0.001]). Response rates according to HAM-D criteria were not reported, although clinical improvement based on the Clinical Global Impression-Improvement Scale[43] showed a statistically significant benefit for paroxetine versus placebo (p = 0.002), but no significant benefit for agomelatine versus placebo (p = 0.389). Remission rates for agomelatine 25–50 mg (5.6% [p = 0.018]) and paroxetine 20–40 mg (22.7% [p = 0.040]) were each significantly different from placebo (13.9%). The overall rate of TEAEs was similar for agomelatine 25–50 mg (71.9%), paroxetine 20–40 mg (81.3%) and placebo (79.8%). There was no significant difference in dropout rates due to TEAEs for agomelatine 25–50 mg (2.4%), paroxetine 20–40 mg (4.8%) and placebo (5.5%). For patients taking agomelatine versus paroxetine versus placebo, the most common adverse events were headache (13.2%, 18.7%, 18.4%, respectively), dry mouth (9.6%, 9.6%, 8.0%), somnolence (7.8%, 9.0%, 9.2%), nausea (6.0%, 16.3%, 9.2%), fatigue (5.4%, 10.2%, 4.3%), sedation (5.4%, 4.2%, 3.1%), dizziness (4.8%, 6.0%, 3.7%) and stomach discomfort (4.2%, 1.8%, 0.0%). There were no significant differences among the three study groups with respect to adverse effects on sexual function or cardiovascular tests. With the exception of liver function testing, there were no significant differences among the three study groups on any laboratory tests. Significant liver enzyme elevations occurred in three agomelatine-treated patients, one paroxetine-treated patient and no placebo-treated patients (reviewed in more detail in section 7).

2.3 Summary and Critique of Short-Term, Placebo-Controlled Studies of Agomelatine

The antidepressant efficacy of agomelatine has been systematically assessed in ten short-term, placebo-controlled studies conducted in Europe and the US. Five trials demonstrated only clinically modest, but statistically significant, benefits for agomelatine over placebo, although two of these studies found opposite effects for the two doses of agomelatine. The opposite efficacy findings for agomelatine 25 mg and 50 mg from the two US studies is confusing and not readily interpretable. Five trials demonstrated no difference between agomelatine and placebo. Unfortunately, not all studies have been published. Based on the unpublished data reviewed in this article, it is clear that publication bias is present, such that favourable studies have generally been published and unfavourable studies have generally not been published. Of particular concern, fluoxetine and paroxetine (but not agomelatine) were each more effective than placebo in two of the unpublished trials. In two other unpublished studies, agomelatine, fluoxetine and paroxetine were each found to be not more effective than placebo, perhaps due to low drug dosing or possibly high placebo responder rates. Agomelatine was generally well tolerated compared with placebo in all studies, but the overall tolerability of agomelatine did not appear to be substantially better than the active drug controls.

2.4 Multinational Clinical Trial

In addition to the European and US studies, the short-term effectiveness of agomelatine versus fluoxetine for the treatment of major depression has been investigated in an 8-week, randomized, double-blind, multinational study conducted at sites in Europe and South America (see table I).[26] The 17-item HAM-D was the primary outcome measure and the primary outcome efficacy variable was the change in HAM-D score from baseline to week 8 for agomelatine versus fluoxetine. Response and remission rates based on the HAM-D were considered secondary outcome variables. Response was defined as a 50% decrease in the HAM-D score from baseline to endpoint. Remission was defined as a HAM-D score of ≤6 at endpoint.

In this study, 515 patients (18–65 years of age) received agomelatine 25–50 mg/day or fluoxetine 20–40 mg/day. Patients initially took agomelatine 25 mg/day, but the dose could be increased to 50 mg/day after 2 weeks for an insufficient response. Similarly, patients initially took fluoxetine 20 mg/day, but the dose could be increased to 40 mg/day after 4 weeks for an insufficient response. Ultimately, 29.0% of agomelatine-treated patients took 50 mg/day and 23.0% of fluoxetine-treated patients took 40 mg/day. Agomelatine

was significantly more effective than fluoxetine (the mean difference in HAM-D was 1.49 for agomelatine vs fluoxetine [p = 0.024]). Response rates for agomelatine (71.7%) and fluoxetine (63.8%) were not significantly different (p = 0.060). Remission rates for agomelatine (32.0%) and fluoxetine (28.4%) were also not significantly different (p = 0.381). The overall rate of TEAEs was similar for agomelatine (57.2%) and fluoxetine (56.3%). Most adverse events were experienced as mild to moderate in severity. There was no significant difference in dropout rates due to TEAEs for agomelatine (4.0%) and fluoxetine (6.5%). The reasons for dropping out did not differ substantially between the two study groups. For patients taking agomelatine versus fluoxetine, the most common adverse events were headache (16.0% vs 11.4%), nausea (8.0% vs 11.4%), somnolence (6.0% vs 3.4%), abdominal pain (4.4% vs 2.7%), dry mouth (3.2% vs 3.0%), constipation (3.2% vs 1.1%), dizziness (2.8% vs 3.4%) and diarrhoea (2.8% vs 2.7%). There were no significant differences between the two study groups with respect to bodyweight changes or cardiovascular effects. With the exception of liver function tests, there were no significant differences between groups on any laboratory tests. Significant liver enzyme elevations occurred in five agomelatine-treated patients and in one fluoxetine-treated patient (reviewed in more detail in section 7).

3. Longer-Term Relapse Prevention Studies of Agomelatine for Major Depression

The effectiveness of agomelatine has been investigated in one published[33] and two unpublished[11,32] longer-term, randomized, double-blind, placebo-controlled, relapse prevention studies in patients with recurrent major depression (see table I). In two studies,[11,33] subjects were eligible for the randomized phase if they had a response (50% reduction in HAM-D) or a remission (HAM-D <7) after open-label treatment with agomelatine in the acute phase. In these two studies, relapse was defined as one of the following: a HAM-D score >15, withdrawal for lack of efficacy, suicide or suicide attempt. In the third study,[32] subjects were eligible for the randomized phase if they were in remission after open-label treatment in the acute phase with agomelatine. In this study, relapse was defined as one of the following: a HAM-D score >15, withdrawal for lack of efficacy, suicide or suicide attempt, or hospitalization due to depression.

In a multinational trial reported by Goodwin and colleagues,[33] 492 patients (19–65 years of age) were initially treated openly with agomelatine 25–50 mg/day for up to 10 weeks. After 2 weeks of agomelatine 25 mg/day, the dosage for poor responders was increased to 50 mg/day. The 339 patients who were responders or remitters were then randomized to receive double-blind treatment with agomelatine (at their current dose) or placebo for up to 24 weeks until they suffered a relapse. At the time of randomization, 22% of subjects were taking 50 mg/day and the remaining patients were taking 25 mg/day. Among all patients, 70% taking agomelatine completed the 24-week study compared with only 52% taking placebo. Overall, agomelatine patients had a significantly lower cumulative relapse rate (21.7%) compared with placebo patients (46.6%) [p = 0.0001]. In a *post hoc* data analysis, the cumulative relapse rate for agomelatine-treated patients (22.7%) was significantly lower than the rate for placebo-treated patients (50.4%) among the subgroup of patients with more severe levels of depression (p = 0.0001). The overall rate of TEAEs was similar for agomelatine (51.5%) and placebo (52.3%). The most common TEAEs were headache (agomelatine 7.9%, placebo 6.3 %), rhinitis (agomelatine 6.7%, placebo 9.8%) and back pain (agomelatine 5.5%, placebo 3.4%). Agomelatine was not associated with significant effects on sexual functioning, bodyweight, cardiovascular effects or laboratory studies.

In an unpublished trial (study CL3-021),[11] 551 patients (19–67 years of age) initially received agomelatine 25 mg/day open-label for up to 8 weeks. The 367 patients who were responders or remitters were then randomized to receive double-blind treatment with agomelatine or placebo for up to 34 weeks until they suffered a relapse. Overall, agomelatine-treated patients had a similar

cumulative relapse rate (25.9%) compared with placebo-treated patients (23.5%). In a *post hoc* data analysis, the cumulative relapse rate for agomelatine-treated patients (21.3%) was significantly lower than the rate for placebo-treated patients (31.3%) among the subgroup of patients with more severe levels of depression ($p = 0.046$).

One unpublished phase III, placebo-controlled, longer-term, relapse prevention trial has been conducted and completed in the US (CAGO178A2 304).[32] In this study, 633 patients (18–70 years of age) were initially treated openly with agomelatine 25–50 mg/day for 4–12 weeks. After 4 weeks of agomelatine 25 mg/day the dosage for poor responders was increased to 50 mg/day. After this initial phase, 406 patients in remission were then entered into a 12-week stabilization phase where they continued to take the same dose. After the stabilization phase, the 281 patients who were still in remission were then randomized to receive double-blind treatment with agomelatine (at their current dose) or placebo for up to 52 weeks until they suffered a relapse. At the time of randomization, 154 subjects were taking 50 mg/day and 127 were taking 25 mg/day. Among all patients, 44.3% taking agomelatine completed the 52-week study compared with only 51.8% taking placebo. There was no significant difference in the time to relapse for agomelatine versus placebo ($p = 0.6668$). Agomelatine patients had a relapse rate (23.0%) that was not significantly different from placebo patients (26.2% [$p = 0.5319$]). The proportion of patients who were in remission at week 52 was not significantly different for agomelatine (51.4%) versus placebo (56.4% [$p = 0.4050$]).

A rapidly dissolvable sublingual tablet formulation of agomelatine is also currently being evaluated in a phase III, open-label, long-term safety and tolerability trial for major depression in the US, but it has not yet been completed.[42]

4. Tolerability and Safety of Agomelatine in Placebo-Controlled Trials

4.1 Adverse Event Profile in Short-Term Trials

The tolerability and safety of agomelatine has been assessed extensively in the six short-term pivotal studies conducted as part of the European research programme.[11,27-29] Safety data from these studies were pooled and analysed (analysis available from the EMA CHMP report) and included 1120 patients taking agomelatine 25–50 mg/day, 998 patients taking placebo, 284 patients taking fluoxetine 20 mg/day and 283 patients taking paroxetine 20 mg/day.[11] The overall rate of TEAEs was similar for agomelatine (52.8%), placebo (51.7%) and fluoxetine (49.3%), but slightly higher for paroxetine (67.5%). The most commonly reported adverse events for agomelatine (in descending order of their incidence) were headache, nausea, dizziness, dry mouth, diarrhoea, somnolence, fatigue, upper abdominal pain and anxiety. Each of these adverse events was reported in <15% of patients. The incidence of adverse events was slightly higher for the 50 mg dose compared with the 25 mg dose. Most agomelatine adverse events were mild to moderate in severity. The only adverse events with a significantly higher incidence for agomelatine compared with placebo were dizziness, paresthesias and blurred vision. For the two SSRI drugs pooled together, the most commonly reported adverse events (in descending order of their incidence) were nausea, headache, dry mouth, diarrhoea, somnolence, fatigue, insomnia, dizziness and anxiety. Each of these was reported in <16% of patients. The largest difference between agomelatine and the SSRI drugs in the incidence of any adverse event was for nausea, which favoured agomelatine.

Although findings from all of the clinical studies conducted in the US have not been comprehensively reported, the tolerability and safety data of agomelatine described in the two published reports by Zajecka et al.[30] and Stahl et al.,[31] the unpublished study (CAGO178A2 303)[32] and the findings from the multinational study by Hale et al.,[26] do not appear to differ substantially from the European experience.

4.2 Adverse Event Profile in Long-Term Trials

In addition to the three relapse prevention studies (described in section 3 above),[11,32,33] many of the short-term pivotal studies conducted in Europe had optional extension phases. Based

on data collected from the relapse prevention and extension phase studies altogether, longer-term tolerability and safety of agomelatine has been assessed for up to 52 weeks.[11]

In an analysis of pooled data from these studies in patients taking agomelatine for up to 34 weeks, there were 511 patients taking agomelatine 25–50 mg/day, 406 patients taking placebo, 222 patients taking fluoxetine 20 mg/day and 105 patients taking paroxetine 20 mg/day.[11] The overall rate of TEAEs was similar for agomelatine (38.8%) and placebo (38.4%), but slightly lower for fluoxetine (32.0%) and slightly higher for paroxetine (44.8%). The rate of TEAEs was higher for agomelatine 50 mg/day (48.3%) than for 25 mg/day (35.8%). The most commonly reported adverse events for agomelatine (in descending order of their incidence) were headache, back pain and insomnia, each of which was reported in <10% of patients. The only adverse event that was significantly higher for agomelatine compared with placebo was insomnia (p-value not reported). For the two SSRI drugs pooled together, the most commonly reported adverse events (in descending order of their incidence) were headache, diarrhoea, insomnia and anxiety. Each of these was reported in <9% of patients. There were no major differences in long-term tolerability between the SSRI drugs and agomelatine.

A limited number of patients (n = 400) in the European studies took agomelatine for 1 year.[11] There were few TEAEs during this extended time (each occurring in fewer than 3% of patients), and none were different from what was seen in the short- and long-term studies. No comparisons were available with placebo or SSRI drugs.

The short-term, phase III clinical trials conducted in the US all had open-label extension phases lasting up to 52 weeks, but tolerability and safety data are not available from these studies. In the unpublished 52-week relapse prevention study conducted in the US (CAGO178A2304),[32] the overall rate of TEAEs was similar for agomelatine 25 mg (75.0%), agomelatine 50 mg (68.0%) and placebo (72.1%). Dropout rates due to TEAEs were 4.3% for agomelatine 25–50 mg versus 2.1% for placebo. The most common TEAEs for agomelatine 25–50 mg versus placebo were headache (11.5%, 17.1 %, respectively), rhinitis (10.8%, 9.3%), diarrhoea (7.9%, 5.0%), insomnia (5.8%, 5.7%), anxiety (5.0%, 5.0%), nausea (4.3%, 1.4%), vomiting (4.3%, 0.7%) and back pain (3.6%, 7.9%). Effects on sexual functioning or bodyweight were not reported. Overall, 29 patients taking agomelatine during the open-label phase developed newly occurring liver function test elevations, and during the double-blind phase three patients taking placebo developed newly occurring liver function test elevations.

4.3 Severe or Serious Adverse Event Profile

Among all patients enrolled in the European clinical studies (pooled analysis reported in EMA CHMP report),[11] there was no significant difference in the overall rate of serious adverse events for agomelatine 25 mg/day (125 of 3052 patients [4.1%]) and 50 mg/day (26 of 588 patients [4.4%]) compared with placebo (34 of 826 patients [4.1%]). The most common serious adverse events were suicide attempts (agomelatine 0.6% vs placebo 0.4%), depression (agomelatine 0.5% vs placebo 0.8%) and falls (agomelatine 0.3% vs placebo 0.3%). In this analysis, deaths (all but one due to suicide) were reported in 4 of 3956 patients taking agomelatine (0.1%), 1 of 826 patients taking placebo (0.1%) and 3 of 449 patients taking paroxetine (0.7%). In the published studies by Zajecka et al.,[30] Stahl et al.,[31] and Hale et al.,[26] there were no reported suicide attempts or patient deaths. In clinical trials in patients with conditions (unspecified) other than depression, the percentage of deaths among patients taking agomelatine (16 of 782 patients [2.0%]) was higher than for patients taking placebo (1 of 327 patients [0.3%]).[11] Fifteen of the 16 deaths in agomelatine-treated patients occurred in a study of 356 elderly patients who had Alzheimer's dementia (a mortality rate of 4.2%).

5. Tolerability and Safety of Agomelatine in Other Clinical Trials

In addition to the randomized, placebo-controlled studies of agomelatine for major depression, data on the use of the drug are available

from other clinical trials. These studies were not designed primarily to definitively test the efficacy of agomelatine for major depression, but they do provide additional data on its tolerability and safety.

In an early, 4-week, phase II, safety and efficacy pilot study, 28 hospitalized patients with major depression (18–65 years of age) were randomized to receive double-blind treatment at one of two doses of agomelatine (5 mg/day vs 100 mg/day).[11,44] There was no placebo-control and the MADRS was the primary outcome measure. MADRS scores decreased significantly in both groups and there was no significant difference between groups. One subject in each group dropped out because of adverse events and two dropped out in each group because of lack of efficacy. Acceptability of both doses was reported to be good, but there were slightly more TEAEs and severe TEAEs in the 100 mg group. There were no observed adverse cardiovascular effects or abnormal laboratory studies in either group.

5.1 Studies on Sexual Function

In a 12-week, randomized, double-blind study involving 276 male and female patients with major depression (18–60 years of age), Kennedy and colleagues[45] compared agomelatine (50 mg/day) and the serotonin-noradrenaline (norepinephrine) reuptake inhibitor (SNRI) antidepressant venlafaxine (titrated from 75 mg/day to 150 mg/day after 2 weeks). The primary objective of this study was to compare the effects of these two drugs on sexual function using data taken from the Sex Effects Scale. On the primary outcome measure of sexual function, there was a numerical advantage favouring agomelatine over venlafaxine, but these results were not statistically significant. Only several of the secondary outcome measures of sexual function showed statistically significant differences in favour of agomelatine. The overall rate of TEAEs for agomelatine (20.4%) was lower than for venlafaxine (38.1%). The most commonly reported adverse events were nausea (agomelatine 11.7% vs venlafaxine 17.3%) and headache (agomelatine 10.2% vs venlafaxine 7.9%). Dropout rates due to TEAEs were 2.2% for agomelatine and 8.6% for venlafaxine. There was no difference in antidepressant efficacy between the two drugs.

The objective of another study was to compare the effects of agomelatine and paroxetine on sexual function in healthy non-depressed male subjects.[46] In this 8-week, double-blind study, 92 subjects (18–30 years of age) were randomized to one of two doses of agomelatine (25 or 50 mg/day), placebo or paroxetine (20 mg/day). On the primary and secondary outcome measures of sexual function (using data taken from the Psychotropic-Related Sexual Dysfunction Questionnaire), agomelatine (at both doses) and placebo were not significantly different. These three groups were significantly less impaired than the paroxetine-treated group.

5.2 Studies on Sleep

In a 6-week, randomized, double-blind study involving 332 male and female patients with major depression (18–65 years of age), Lemoine and colleagues[47] compared agomelatine (25–50 mg/day) and venlafaxine (75–150 mg/day). The primary objective of this study was to compare the effect of these two drugs on sleep using the Leeds Sleep Evaluation Questionnaire (LSEQ). On the primary outcome measure of sleep, and on most of the secondary outcome measures, there was a clinically modest, but statistically significant advantage favouring agomelatine over venlafaxine. The overall rate of TEAEs was slightly lower for agomelatine (52%) compared with venlafaxine (57%). The most commonly reported adverse events (agomelatine vs venlafaxine) were nausea (6.0% vs 22.6%), headache (9.6% vs 11.9%), dizziness (1.8% vs 9.5%), vomiting (1.2% vs 4.8%), diarrhoea (4.8% vs 1.8%) and somnolence (3.6% vs 4.8%). Rates of discontinuation due to TEAEs were 4.2% for agomelatine and 13.2% for venlafaxine. There was no difference in antidepressant efficacy between the two drugs.

A 6-week, randomized, double-blind study involving 313 male and female patients with major depression (18–60 years of age) compared agomelatine (25–50 mg/day) and the SSRI drug sertraline (50–100 mg/day).[48] The primary study objective was to compare the effects of agomelatine and

sertraline on changes of the relative amplitude of the individual rest-activity cycles, collected from continuous records using wrist actigraphy and sleep logs, from baseline to week 6. Secondary objectives of this study were to compare the effect of these two drugs on objective measures of sleep (sleep efficiency and sleep latency) using actigraphy-derived recordings, and on subjective measures of sleep (getting to sleep and sleep quality) using the LSEQ. The 17-item HAM-D was used as a secondary outcome efficacy measure (assessing the change in HAM-D score from baseline to week 6 for agomelatine vs sertraline). Response and remission rates based on the HAM-D were also considered secondary outcome variables. Response was defined as a 50% decrease from baseline in the HAM-D score at endpoint. Remission was defined as a HAM-D score of ≤6 at endpoint. In this study, patients initially took agomelatine 25 mg/day, but the dose could be increased to 50 mg/day after 2 weeks for an insufficient response. Similarly, patients initially took sertraline 50 mg/day, but the dose could be increased to 100 mg/day after 2 weeks for an insufficient response. Ultimately, 25.3% of agomelatine-treated patients took 50 mg/day and 24.5% of sertraline-treated patients took 100 mg/day. On the primary outcome measure (changes in amplitude of the rest-activity cycle), agomelatine was significantly better than sertraline by week 1, but there was no difference between drugs from week 2 to week 6. On the secondary measure of actigraphy-derived sleep efficiency and sleep latency, agomelatine was significantly superior to sertraline throughout the 6 weeks. On the secondary measures of getting to sleep and quality of sleep, derived from the LSEQ, agomelatine was superior to sertraline at week 2, but the drugs were similar at weeks 4 and 6. On the secondary outcome measures (depression), agomelatine was significantly more effective than sertraline (the mean difference in HAM-D was 1.68 for agomelatine vs sertraline). Response rates for agomelatine (70.0%) and sertraline (61.5%) were not significantly different. Remission rates for agomelatine (32.7%) and sertraline (28.8%) were also not significantly different. The overall rate of TEAEs was similar for agomelatine (48.0%) and sertraline (49.1%). Most adverse events were experienced as mild to moderate in severity. Dropout rates due to TEAEs for agomelatine (3.2%) were lower than for sertraline (8.8%). For patients taking agomelatine versus sertraline, the most common adverse events were headache (8.6% vs 10.1%), fatigue (5.9% vs 1.3%), dry mouth (5.3% vs 5.0%), diarrhoea (3.9% vs 5.7%) and sweating (0.0% vs 5.0%). There were no significant differences between the two study groups with respect to bodyweight changes or cardiovascular effects. With the exception of liver function testing, there were no significant differences between groups on any laboratory tests. Significant liver enzyme elevations occurred in one agomelatine-treated patient and in none of the sertraline-treated patients (reviewed in more detail in section 7).

5.3 Studies on Discontinuation Symptoms

The effects of abruptly discontinuing agomelatine and paroxetine have been compared in a randomized, double-blind, placebo-controlled study.[49] After 12 weeks of double-blind treatment with agomelatine 25 mg/day or paroxetine 20 mg/day, 192 patients with major depression who were in sustained remission were randomized to continue taking their current drug or to switch to placebo for 2 weeks. Discontinuation symptoms (rated on the Discontinuation Emergent Signs and Symptoms checklist) were significantly higher in the paroxetine-discontinuation group during the first week of placebo, but not during the second week. Discontinuation symptoms were not observed in the agomelatine-discontinuation group during the first or second week of taking placebo.

5.4 Studies in Various Other Psychiatric Indications

Calabrese et al.[50] conducted an open-label study of agomelatine 25 mg/day for 21 male and female patients (19–76 years of age) with bipolar disorder (type I, currently depressed). Subjects were also taking mood-stabilizer medication (either lithium or valpromide). They were treated for 6 weeks, and were then able to continue open-label treatment during a 46-week extension phase

(total of 1 year of treatment). On the primary outcome measure of efficacy (50% improvement on the 17-item HAM-D), 17 of 21 subjects (81%) were considered treatment responders after 6 weeks. Eight of 21 subjects (38.1%) achieved remission (a HAM-D score of ≤6) after 6 weeks. Of the 19 subjects who continued agomelatine beyond 6 weeks, 16 (84%) were considered treatment responders at some point during the extension phase. Eleven subjects took agomelatine for the entire year. The overall rate of TEAEs was 71.%. Specific side effects were not reported. There were no dropouts related to TEAEs during the 6-week acute phase. Three patients discontinued treatment due to TEAEs during the extension phase. Three cases of mania or hypomania and two cases of agitation were reported as serious adverse events among the 21 subjects. There were no reported adverse effects on bodyweight, cardiovascular function or laboratory studies.

Pjrek et al.[51] described the results of an open-label study of agomelatine 25 mg/day for patients with depression and seasonal affective disorder. The 37 male and female subjects (20–60 years of age) were treated for 14 weeks. The primary outcome measure was the seasonal affective disorder (SAD) version of the HAM-D (SAD-HAM-D).[52] After 14 weeks, 75.7% of subjects were considered treatment responders (50% improvement on the SAD-HAM-D) and 70.3% were in remission (SAD-HAM-D score of ≤7). Reported side effects were minimal. One patient experienced daytime fatigue and 12 patients reported mild sleepiness. There were no dropouts due to TEAEs.

In a 12-week, randomized, double-blind, placebo-controlled study involving 121 male and female patients with generalized anxiety disorder (18–65 years of age), Stein and colleagues[53] compared agomelatine (25–50 mg/day) and placebo. If patients did not respond adequately after 2 weeks of agomelatine 25 mg/day or placebo, the dosage was increased under double-blind conditions to 50 mg/day or matching placebo. Agomelatine was significantly more effective than placebo on the primary outcome measure of anxiety (total score on the Hamilton Anxiety Rating Scale.[54] The overall rate of TEAEs was similar for agomelatine 25 mg (36.1%), 50 mg (38.5%) and placebo (34.5%). The most common TEAEs that were reported more frequently in the agomelatine group than in the placebo group were dizziness (7.9% vs 3.4%) and nausea (4.8% vs 1.7%). Most TEAEs were of mild to moderate severity. Dropout rates due to TEAEs were slightly lower for placebo (none) compared with agomelatine (1.6%). Cardiovascular effects and laboratory studies did not differ between groups.

6. Tolerability and Safety of Agomelatine in Overdose, Pregnancy and Paediatric Populations

There is limited clinical experience with agomelatine overdose in humans.[11] Reported overdoses with agomelatine (up to 525 mg) have not resulted in significant or serious sequelae. It should also be noted that in the earliest clinical studies, healthy subjects took agomelatine doses as high as 1200 mg and the maximum tolerated dose was 800 mg. In animals, the LD_{50} dose (i.e. the dose that kills 50% of the experimental animals) is at least 100-fold greater than the comparable human dose. Hence, agomelatine has a relatively favourable safety profile with regards to acute toxic effects

There are no specific data on the safety of agomelatine during pregnancy or with breast-feeding. Two phase I studies (one in men, one in women) did not demonstrate any adverse effect of agomelatine on various gonadotrophic hormones, spermogram or menstrual cycle.[11] Reproduction toxicity studies in animals did not reveal any adverse effect of agomelatine on fertility or on embryonic or fetal development.

A small, open-label sleep study in nine paediatric patients (6–17 years of age) with Smith-Magenis syndrome reported that agomelatine was well tolerated.[55] The tolerability and safety of agomelatine has not otherwise been studied in children and adolescents.

7. Hepatic Function and Agomelatine

Agomelatine is almost entirely metabolized through the liver and undergoes extensive first-pass hepatic metabolism. One specific study investigated

the influence of liver insufficiency in patients with hepatic cirrhosis on plasma levels of agomelatine.[11] In patients with mild hepatic impairment, the increase in agomelatine exposure was more than 50-fold higher compared with healthy subjects, and for patients with moderate hepatic impairment the exposure was more than 100-fold higher compared with healthy subjects. In addition, because of decreases in plasma proteins, the unbound free fraction of agomelatine was increased in subjects with hepatic insufficiency. The free fraction was approximately twice as great in patients with moderate hepatic impairment. Liver insufficiency therefore results in a significant increase in the exposure to agomelatine. Because the safety of such large concentrations of agomelatine is unknown, it should not be used in patients with hepatic insufficiency, such as cirrhosis or other active liver disease.

The major cytochrome P450 (CYP) enzyme involved in the metabolism of agomelatine is CYP1A2 (accounting for about 90% of its metabolism), with minor metabolic contributions by CYP2C9 and CYP2C19.[10] Agomelatine has at least four main metabolites. The pharmacological activity of the metabolites at the $5HT_{2C}$, MT_1 and MT_2 receptors is not clearly established. None of the metabolites have any known toxic effects. Agomelatine does not appear to inhibit or induce the activity of any CYP enzymes in humans, but enzyme induction has been demonstrated in animal studies.[11]

In humans, the oral bioavailability of agomelatine at doses of 25 and 50 mg is very low. The bioavailability may increase at higher doses, perhaps due to saturation of first-pass hepatic metabolism or non-linear pharmacokinetics. The oral bioavailability of agomelatine is estimated to be relatively higher in women compared with men, and to be relatively higher in elderly versus younger individuals, perhaps due to sex and age effects on hepatic blood flow and metabolic enzyme activity.[11] However, because of significant intra- and inter-individual pharmacokinetic variability, dose changes based on age or sex are not considered to be routinely necessary.

In an analysis of data pooled from European clinical trials (available in the EMA CHMP report), significant elevations of liver enzymes (i.e. increases >3 × the upper limit of normal [ULN]) occurred in 1.39% of patients taking agomelatine 50 mg/day, 1.04% taking 25 mg/day and 0.72% taking placebo.[11] For this analysis, the total number of subjects taking agomelatine 25/50 mg/day was 4068; the number of subjects taking placebo was not clearly indicated. These liver reactions occurred at various times throughout the 6-month observation period of these studies. They were detected in patients only through laboratory monitoring, because they did not have obvious clinical signs or symptoms indicating liver injury. Some reactions recovered during continued treatment and some recovered after treatment discontinuation. Serious liver reactions, including hepatitis and enzyme elevations >10 × the ULN, were reported less frequently. One patient developed hepatitis that did not recover at follow-up (2.5 years after discontinuation of agomelatine). These reactions in humans are not inconsistent with the findings from animal studies. Repeated dose toxicity studies in rats and monkeys have indicated that the liver is the target organ of toxicity. Agomelatine causes hepatic enzyme induction in these animals, and they consequently showed enlarged livers or hepatocellular hypertrophy.[11]

In the short-term US study by Zajecka et al.,[30] significant liver enzyme elevations (i.e. increases >3 × the ULN) occurred in seven subjects (4.5%) taking agomelatine 50 mg, but in none of the agomelatine 25 mg or placebo subjects. The liver enzyme elevations were noted between weeks 6 and 8. One subject stopped the drug and their liver function tests normalized. Six patients continued to take agomelatine (including five during an extension phase) and their liver function tests all normalized. The investigators noted at baseline that the prevalence of pre-existing hepatobiliary disorders was 3.1% in the agomelatine 50 mg group, 0.6% in the 25 mg group and 0.6% in the placebo, but they did not report whether pre-existing hepatobiliary disease was associated with the later development of significant liver enzyme elevations.

In the short-term US study by Stahl et al.,[31] significant liver enzyme elevations (i.e. increases >3 × the ULN) occurred in five subjects (3.0%)

taking agomelatine 50 mg, in one subject (0.6%) taking 25 mg and in one subject taking placebo (1.3%). The liver enzyme elevations were noted between weeks 6 and 8. Two agomelatine 50 mg subjects stopped the drug and their liver function tests normalized. Four patients continued to take agomelatine during an extension phase and their liver function tests normalized. One subject with liver enzyme elevations was lost to follow-up.

In the unpublished short-term US study (CAGO178A2 303),[32] significant liver enzyme elevations (i.e. increases >3 × the ULN) occurred in two subjects (1.3%) taking agomelatine 25 mg, in one subject (0.6%) taking 50 mg and in one subject (0.6%) taking paroxetine 20 mg. One patient taking agomelatine stopped the drug and their liver function tests normalized, while two patients continued to take agomelatine and their liver function tests normalized. One subject with liver enzyme elevations taking paroxetine was switched to agomelatine during an open-label extension phase and liver function tests normalized.

In the unpublished longer-term US relapse prevention study,[32] 29 of 633 patients (4.6%) taking agomelatine during the open-label phase developed newly occurring liver function test elevations. The outcome of these cases was not described.

In the multinational study by Hale et al.,[26] significant liver enzyme elevations (i.e. increases >3 × the ULN) occurred in five agomelatine-treated patients and in one fluoxetine-treated patient. All these subjects continued to take their medication and apparently (according to the study authors) their liver function tests normalized, but no additional information about these subjects was reported.

In the study by Kasper et al.,[48] significant liver enzyme elevations occurred in one agomelatine-treated patient and in none of the sertraline-treated patients. The patient who developed elevated liver enzymes was described as an 'alcoholic', but no further details were given in the report.

8. Renal Function and Agomelatine

Agomelatine and its metabolites are mainly excreted through the kidneys. The elimination half-life of agomelatine is very short (about 2–3 hours). The effects of renal function on agomelatine pharmacokinetics were investigated in a study of healthy subjects and subjects with severe impairment of renal function.[11] In the subjects with severe renal impairment, exposure to agomelatine increased more than 25% compared with healthy subjects.[11]

Agomelatine does not significantly affect renal function. In patients with normal hepatic function, impaired renal function would be expected to result in greater exposure to agomelatine metabolites rather than to the parent drug. Available safety data from the clinical trials in patients with major depression did not demonstrate any significant tolerability or safety issues with the use of agomelatine compared with placebo among patients with mildly to moderately impaired renal function;[11] however, experience in patients with more severe renal impairment is unknown. Although agomelatine can be used in patients with renal impairment, such patients should be monitored more closely.

9. Bodyweight, Metabolic and Cardiovascular Safety of Agomelatine

Agomelatine has not been associated with significant bodyweight gain or adverse metabolic effects. In the European studies, only 4 of 400 patients taking agomelatine for 1 year gained bodyweight.[11] Data presented in section 4 from the European and US studies have also not demonstrated that agomelatine is associated with adverse cardiac effects (e.g. ECG or blood pressure changes). A single published case report described a 58-year-old depressed woman who developed a corrected QT interval prolongation during treatment with agomelatine, which fully reversed when the drug was stopped.[56] A proposed study comparing the effect of agomelatine and fluoxetine on heart rate variability in patients with major depression has been withdrawn before enrolment.[57] The reason for withdrawing the study is not known. With the exception of potential adverse liver effects, animal and human studies have not identified any other significant toxicities, even with excessively high doses.

10. Safety of Agomelatine in Older Patients

Among patients older than 65 years, safety data are available from the European studies on 109 patients taking agomelatine and 76 taking placebo.[11] Rates of TEAEs were similar for agomelatine (63.3%) and placebo (59.2%). Discontinuation rates due to TEAEs were 12.8% for agomelatine and 9.2% for placebo. Serious adverse events occurred in 4.6% of patients taking agomelatine and 5.2% taking placebo. The two published US studies included subjects up to age 70 years, but findings from these studies on the safety and tolerability of agomelatine among those older than 65 years have not been specifically reported.[30,31]

11. Drug Interactions and Agomelatine

Similar to most other psychotropic drugs, agomelatine is highly protein bound (its plasma protein binding is >95%).[58] Taking multiple drugs that bind to the same plasma protein can sometimes cause displacement of the protein-bound fraction of a drug, resulting in higher concentrations of the free fraction. Based on *in vitro* studies, agomelatine does not modify free concentrations of drugs highly bound to plasma proteins, nor do other drugs affect its protein binding;[11] however, this has not been studied *in vivo* in humans.

Agomelatine does not appear to inhibit or induce the activity of any CYP enzymes in humans, suggesting a low likelihood that it will affect the hepatic metabolism of other drugs, but enzyme induction has been demonstrated in animal studies.[11] Although the oral bioavailability of agomelatine at doses of 25 and 50 mg is very low, it is relatively higher in non-smokers versus smokers and in women taking oestrogen-containing drugs compared with women who do not. These findings are explained by the metabolic enzyme-inducing effects of smoking and the enzyme-inhibiting effects of oestrogens. Agomelatine does not affect the pharmacokinetics of the bronchodilator drug theophylline, which is a substrate for CYP1A2. The SSRI drug fluvoxamine is a potent inhibitor of CYP1A2 and a moderate inhibitor of CYP2C9, and it can significantly increase serum concentrations of agomelatine. By contrast, the SSRI paroxetine is a moderate inhibitor of CYP1A2 and does not significantly increase the concentration of agomelatine. The antifungal drug fluconazole is a potent inhibitor of CYP2C9, but it has not been shown to significantly influence the pharmacokinetics of agomelatine. Specific drug-drug interaction studies involving lithium, lorazepam, alcohol and valproic acid have not demonstrated any significant effects of these drugs on the pharmacokinetics of agomelatine.[11]

12. Discussion

The antidepressant efficacy of agomelatine has been systematically assessed in ten short-term, placebo-controlled acute studies and three longer-term, placebo-controlled, relapse prevention studies. Five short-term trials demonstrated clinically modest but statistically significant benefits over placebo, although two of these studies found opposite effects for the agomelatine 25 and 50 mg doses. Five short-term trials did not find agomelatine to be more effective than placebo. Fluoxetine 20 mg/day was more effective than placebo in one of these negative trials. Paroxetine 20–40 mg/day also was more effective than placebo in another negative trial. Low-dose fluoxetine and low-dose paroxetine were not more effective than placebo in the other two negative trials. The lack of efficacy of the active control drugs in these two trials were believed mainly to be due to an insufficient dose and possibly to unusually high placebo responder rates.[11]

The only controlled study conducted in elderly patients did not demonstrate a significant benefit for agomelatine compared with placebo. Agomelatine was more effective than placebo in only one of the three relapse prevention studies. Unlike many other antidepressant drugs, agomelatine has not been systematically studied beyond continuation-phase treatment. A meta-analysis of the six short-term trials submitted to the EMA demonstrated a small, statistically significant treatment effect of about 1.5 on the HAM-D in favour of agomelatine over placebo.[11] The results from these studies suggest that agomelatine

25 mg/day is probably less effective than other antidepressant drugs. In their summary in approving agomelatine, the EMA concluded that some positive treatment effect of agomelatine in major depression was demonstrated, but that the magnitude of effect was considered to be of marginal clinical relevance.[11] The two published US studies also demonstrated small positive treatment effects for agomelatine, but the positive outcomes were opposite for 25 mg/day versus 50 mg/day in the two studies. Neither dose was consistently effective in both studies. That there might be an unusual nonlinear or differential dose-response pharmacological effect of agomelatine on CNS processes is consistent with a recent study conducted in non-depressed subjects.[59] In this 7-day study, agomelatine 25 mg/day (but not 50 mg/day) significantly facilitated positive versus negative affective memory recall and reduced the perception of sadness. Hence, more work is needed to better understand the dose-response characteristics of agomelatine in a wider range of populations of patients with depression.

In these clinical trials, agomelatine was generally well tolerated compared with placebo. The most common side effects associated with agomelatine are headache, nausea, dizziness, dry mouth, diarrhoea, somnolence, fatigue, upper abdominal pain and anxiety. The relatively benign side effect profile of agomelatine (especially the lack of clinically significant bodyweight gain, the low risk of sexual dysfunction, the low incidence of gastrointestinal symptoms and the absence of discontinuation symptoms) is different from and compares favourably with SSRI and SNRI drugs. However, the overall tolerability of agomelatine was not substantially better than active drug controls, as evidenced by the approximately similar rates of TEAEs and similar dropout rates due to TEAEs.

Liver function appears to be of particular concern with the use of agomelatine. Significant elevations of liver enzymes were common in the European studies and were also noted in the US and multinational clinical trials. In the European trials, these hepatic changes were sometimes very serious and included rare cases of hepatitis, but serious liver injury was not described in the more recently published studies by Zajecka et al.,[30] Stahl et al.[31] and Hale et al.[26] Some of the data reviewed previously suggest that liver enzyme elevations might be dose-related and might be more likely with agomelatine compared with other antidepressant drugs. Because these hepatic reactions were not predictable based on clinical symptoms or the duration of treatment, monitoring of liver enzyme levels of all patients has been recommended (by the EMA)[11] before starting treatment, after 6, 12 and 24 weeks of treatment, and then thereafter when clinically indicated based on the judgement of the treating physician. 'Real-world' patients in general practice are likely to be quite different from patients enrolled in clinical trials.[60] As a result, the relative safety of agomelatine is unknown when used in patients who might have undetected liver impairment or liver disease, or in patients who are at risk for developing liver disease. This would include, for example, depressed patients at risk for developing viral hepatitis, and patients who use alcohol, paracetamol (acetaminophen) or other prescription and non-prescription drugs that affect the liver. Also, pharmacokinetic studies indicate that even mild hepatic insufficiency results in very elevated concentrations of agomelatine. For this reason, agomelatine is contraindicated in patients with any degree of liver impairment, such as cirrhosis or other active liver disease.[11] All of these issues regarding the liver are of obvious concern for the routine use of agomelatine. Liver precautions and the need for laboratory monitoring are a distinct disadvantage for the use of agomelatine compared with virtually all other antidepressant drugs.

Agomelatine is metabolized primarily by CYP1A2 enzyme in the liver, with lesser metabolic contributions from CYP2C9/2C19. Based on this, the use of agomelatine is contraindicated in patients taking drugs strongly inhibiting this enzyme (e.g. fluvoxamine). Moderate inhibitors of CYP1A2, such as oestrogen-containing oral contraceptives and paroxetine, increase agomelatine concentrations to a lesser degree. Patients taking any drugs having moderate inhibitory effects on CYP1A2 or drugs having inhibitory effects on CYP2C9/2C19 should simply be monitored for increased adverse effects. It is possible

that patients taking one or more drugs that have moderate metabolic enzyme inhibiting effects would benefit from taking and staying on lower agomelatine doses (i.e. 25 mg/day or lower). By contrast, patients who smoke, and those taking drugs that induce CYP1A2 enzyme activity (e.g. the proton pump inhibitor drug omeprazole), may be more likely to require doses of 50 mg/day or possibly even higher doses (although this has not been evaluated clinically).

In patients with normal hepatic function, impaired renal function may result in higher concentrations of agomelatine metabolites rather than the parent drug. Patients with renal impairment do not require any special laboratory monitoring with the use of agomelatine, but they should still be monitored for increased adverse effects.

Because the oral bioavailability of agomelatine is very low at recommended doses, its pharmacokinetics, efficacy, tolerability and safety in patients taking doses higher than 50 mg/day deserves further study. In clinical practice, it is likely that some prescribers will use agomelatine in the 50–100 mg/day dose range.

The efficacy, tolerability and safety of agomelatine for depression should be further investigated in 'real-world' patient populations, paediatric and geriatric patients, maintenance therapy studies extending for more than 6 months, bipolar disorder and seasonal affective disorder. Information is also needed about the effects of agomelatine during pregnancy and breastfeeding.[61,62]

The relative effectiveness of agomelatine should be further evaluated in comparison with SSRI drugs, SNRI drugs and other antidepressant drugs using their full dose range, rather than minimally effective doses.[9,63] Because of agomelatine's unique pharmacology and putatively favourable clinical profile (e.g. putative claims that it has a low risk of adverse effects on sexual function and the gastrointestinal system, low risk of bodyweight gain and a positive effect on sleep), comparing it with the antidepressant drugs bupropion, nefazodone and mirtazapine in particular would be of interest. Bupropion is a non-serotonergic drug that has relatively benign effects on sexual function, the gastrointestinal system and bodyweight. Nefazodone is a $5HT_{2A}$ receptor antagonist, with favourable effects on sleep, anxiety, sexual function, the gastrointestinal system and bodyweight. Mirtazapine has a complicated pharmacology that includes $5HT_{2A}$, $5HT_{2C}$, and $5HT_3$ receptor antagonism, and it has favourable effects on anxiety, sleep, gastrointestinal function and sexual function, but is prone to sedation and bodyweight gain. Trazodone also has $5HT_{2A}$ and $5HT_{2C}$ receptor antagonist effects; however, it is most commonly used in low doses as a hypnotic and is rarely used as an antidepressant because of sedation and the risk in men of developing priapism when used at higher antidepressant therapeutic doses.

SSRI and SNRI drugs have been extensively investigated, approved and marketed for the treatment of different anxiety disorders. Except for a single published study in generalized anxiety disorder, the effectiveness of agomelatine for the treatment of various anxiety disorders is not known.[53] A 16-week, placebo-controlled, phase II clinical trial with agomelatine for obsessive-compulsive disorder is currently being conducted, but findings have not yet been reported.[64] A recent randomized, placebo-controlled, 8-week study (published only in abstract form) found no benefit for agomelatine over placebo in obsessive-compulsive disorder.[65] The authors also reported that clinically notable aminotransferase elevations were observed transiently in the agomelatine 50 mg dose group.

For patients not responding adequately to an initial antidepressant medication, or for patients who cannot tolerate the medication, the two main treatment approaches are switching or augmentation.[9] The unique pharmacology of agomelatine suggests a potential role not only as an appropriate switch agent for medication intolerance or non-response, but also as an augmentation agent that could be used in combination with other antidepressant drugs. Combining antidepressant drugs for treatment non-responders is commonly done in clinical practice. Combining agomelatine and other antidepressant drugs, especially SSRI and SNRI drugs, could be tried to achieve a synergistic antidepressant effect. Similarly, the $5HT_{2C}$ receptor antagonist effects of agomelatine might justify its use in combination with SSRI or

SNRI drugs as a way to counter serotonin-related adverse effects, such as sexual dysfunction, gastrointestinal complaints or insomnia. Controlled studies investigating the use of agomelatine as a switch agent or in combination with other antidepressant drugs for these clinical purposes are warranted.

13. Conclusions

Given the wide variety of potentially effective antidepressant therapies, the initial selection of an antidepressant medication should be governed by an overall assessment of such factors as cost and availability, patient preference, past treatment history, family treatment history, clinical symptoms, expected side effect profile and safety, and the need for medical/laboratory monitoring.[66] Comparative data on the relative efficacy, tolerability, safety and acceptability of antidepressant drugs would be helpful but are often lacking.[67,68] As a relatively newer product, less is known about many of these issues with agomelatine vis-à-vis other antidepressant drugs. The choice of drug treatment for an individual patient should be based as much as possible on the best unbiased clinical and scientific information available. Agomelatine does not have clinically significant advantages compared with other antidepressant drugs, and it has certain limitations and disadvantages. Controlled studies have demonstrated that agomelatine has a small, statistically significant, but marginally clinically relevant, antidepressant effect compared with placebo. Based on the entire published and unpublished data reviewed in this article, it is clear that publication bias is present, such that more favourable agomelatine studies have been published. For example, fluoxetine and paroxetine (but not agomelatine) were each shown to be more effective than placebo in two of the unpublished trials. The adverse effect profile of agomelatine is different from other antidepressant drugs, but the overall tolerability of agomelatine was not substantially better than active drugs included as controls. Agomelatine is contraindicated in patients with impaired liver function and in patients taking drugs that potently inhibit CYP1A2 metabolic enzymes. Because elevated liver enzymes are common, and there is a rare risk of more serious liver reactions, routine laboratory monitoring of liver function is recommended periodically throughout treatment. Because of the unique pharmacology of agomelatine and its reported tolerability profile, it should be considered only as an alternative drug for patients who do not respond to or cannot tolerate other antidepressant drugs.

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