Week 12 – 14 out of 21 (67%) – and declines thereafter. Acute response to antidepressants within the first 12 weeks is consistent with Gijsman et al.'s meta-analysis (2), but again, this does not establish long-term benefit.

In addition, Calabrese et al. report that there were three cases of mania or hypomania and two cases of agitation. The nature of the agitation is not described but could potentially indicate a mixed state or subthreshold hypomania. This is a rate of mood switches between 14.3% and 24% and, again, is likely to increase with time.

Long-term outcome in bipolar disorder is poor, yet long-term stability is the ultimate goal of treatment in order to reduce the high rates of disability and mortality from this illness. From the patients' point of view, an antidepressant response during the first 12 weeks is of limited benefit if not sustained over the long term. In bipolar patients treated with adjunctive antidepressants, rates of mood switches and relapse increase as a function of study length (3). The goal for the patient is long-term stability, not acute antidepressant response. It appears from this albeit preliminary open study that agomelatine, like established antidepressants, is unlikely to contribute to long-term stability and sustained improvement for many patients with bipolar disorder.

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Key words: antidepressants – bipolar – depression

Reply to Dr. Eppel regarding 'Letter to the Editor: Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data'

To the Editor:

We agree with the caution that Dr. Eppel has recommended regarding the interpretation of these open agomelatine data (1). In addition, it is worth noting that compounds that do not cause sedation, increased appetite, and weight gain, such as is the case with agomelatine, tend to have difficulty separating from placebo. 'Clean' drugs, compounds with fewer side effects, seem to be more difficult to develop because our rating scales tend to count side effects (increased appetite, sedation, etc.) as evidence of efficacy. Accordingly, we agree that such preliminary data should only be viewed as 'hypothesis-seeking', and never confirmatory. That being said, the community of mental health providers and the patients we serve are in desperate need of new treatments for bipolar depression.

The design of this pilot study included two different phases, which were used as endpoints for the estimates of efficacy: (i) acute efficacy after six weeks of adjunctive agomelatine, and (ii) longer-term efficacy with ongoing open-label treatment up to one year.

At Week 6, 17 of 21 (81%) subjects treated with agomelatine responded favorably as measured by ≥50% reduction in Hamilton Depression Rating Scale (HAM-D) scores. A similar rate of response (15 of 21, or 71%) was observed in the intent-to-treat population using the Montgomery-Åsberg Depression Rating Scale (MADRS). These open data suggest potential antidepressant efficacy with adjunctive agomelatine over an *acute* six-week course.

Of the 19 subjects who elected to continue treatment with agomelatine beyond the acute six-week period, 11 completed the full year. However, during the course of that year, 16 of the 19 subjects met response criteria based on their depression score at time of last evaluation. Therefore, only 58% (11/19) completed a full year of agomelatine treatment, while 84% (16/19) experienced antidepressant response (≥50% symptomatic reduction) at some point during that year. Indeed, nearly three-quarters (14/19) of agomelatine-treated subjects over that year achieved remission (HAM-D ≤ 6 for at least eight weeks). The duration of sustained remission among these 14 subjects, including the initial eight weeks with HAM-D ≤ 6, was as follows: 10–20 weeks (n = 6), 40–51 weeks (n = 6), with two other subjects in remission during two successive periods of 12–16 and 16–22 weeks, respectively. These extended open data suggest that adjunctive agomelatine may have efficacy in continuation and maintenance treatment of depression associated with bipolar disorder, calling for larger, double-blind, placebo-controlled trials.

Furthermore, although there were three cases of mania or hypomania and two cases of agitation reported as serious adverse events among the 21 subjects exposed to adjunctive agomelatine in this study, only one episode of mania and one episode of hypomania were judged by the treating investigator as related to treatment. No cases of agitation were judged to be related to treatment with agomelatine. If one makes the assumption, as does Dr. Eppel, that all five of these cases were related to agomelatine treatment, this 24% (5/21) rate of treatment-emergent affective switching (TEAS) over one year is lower than the 38% switch rate reported by Post et al. (2) with a traditional antidepressant plus mood stabilizer. Given the facts, as reported in the paper, it would appear that in this small sample there was a very low rate of TEAS (14.3% or lower).

We agree with Dr. Eppel's recommendation that the ultimate goal in the treatment of patients with bipolar disorder goes beyond acute antidepressant response and should focus on extended stability. However, until larger studies are completed it is premature to conclude that adjunctive agomelatine does or does not contribute to desired long-term mood stability. The current study simply provides a signal that should be followed in the pursuit of a more definitive answer to this important clinical question.

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Key words: adjunctive therapy – agomelatine – bipolar depression