Journal of Affective Disorders 193 (2016) 137–143

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

The effects of levomilnacipran ER in adult patients with first-episode, highly recurrent, or chronic MDD

Susan G. Kornstein [a,*], Carl Gommoll [b], Changzheng Chen [b], Kenneth Kramer [b]

[a] Department of Psychiatry and Institute for Women's Health, Virginia Commonwealth University School of Medicine, Richmond, VA, United States
[b] Forest Research Institute (an Allergan affiliate), Jersey City, NJ, United States

ARTICLE INFO

Article history:
Received 6 October 2015
Received in revised form
23 December 2015
Accepted 26 December 2015
Available online 30 December 2015

Keywords:
Antidepressant
Depression symptoms
Recurrent depression
Chronic depression
Functional impairment

ABSTRACT

Background: Major depressive disorder (MDD) can be challenging to manage due its variable and episodic nature. Post hoc analyses were conducted on five studies (NCT00969709, NCT01377194, NCT00969150, NCT01034462, EudraCT:2006-002404-34) to evaluate the efficacy of levomilnacipran extended-release (ER) in patients with different MDD episode histories.

Methods: Adults with MDD were randomized to double-blind treatment with levomilnacipran ER (40–120 mg/d) or placebo. Three subgroups were identified: first-episode ($n=494$); highly recurrent (≥ 3 major depressive episodes; $n=1954$); and chronic (current episode duration ≥ 2 years; $n=218$). Mean changes from baseline to end of study (Week 8 [US studies], Week 10 [non-US study]) in Montgomery–Åsberg Depression Rating Scale (MADRS), 17-item Hamilton Depression Rating Scale ($HAMD_{17}$), and Sheehan Disability Scale (SDS) total scores were analyzed in each subgroup. MADRS response, defined as $\geq 50\%$ total score improvement from baseline to Week 8/10, was also analyzed.

Results: Least squares mean differences (LSMDs) between treatment groups indicated significantly greater improvements with levomilnacipran ER versus placebo in MADRS (first-episode, −2.5; highly recurrent, −3.0; chronic, −4.9; all $P<.05$) and $HAMD_{17}$ (first-episode, −2.1; highly recurrent, −1.6; chronic, −2.6; all $P<.05$) total scores. LSMDs for SDS total score were statistically significant in the first-episode and highly recurrent MDD subgroups (both subgroups, −2.3; $P<.01$). MADRS response rate was significantly higher with levomilnacipran ER versus placebo in all three subgroups (first-episode, 44.5% versus 35.0%; highly recurrent, 44.3% versus 33.5%; 36.8% versus 22.0%; all $P<.05$).

Limitations: MDD subgroups were defined post hoc; none of the studies were prospectively designed to evaluate outcomes in these subgroups. Other limitations include lack of active comparators and variability of dose/duration due to data being pooled from multiple clinical trials.

Conclusions: Results suggest that levomilnacipran ER improves depression symptoms and functional impairment in adult patients with different histories of MDD episodes.

1. Introduction

In patients with major depressive disorder (MDD), the primary goals of initial treatment are to achieve symptom remission and restore patient functioning to pre-illness levels (APA, 2013). However, MDD can be challenging to manage due to the variable and episodic nature of this disorder (Jefferson, 2011). Either psychotherapy or pharmacologic treatment can be initiated in patients with mild-to-moderate MDD (APA, 2010). In patients with severe depression, initiation of an approved pharmacotherapy is strongly recommended, with treatment continuing for at least 6 weeks at the maximum tolerated dose (Trivedi and Daly, 2008) and medication selection based on the patient's clinical features and medical history (APA, 2010). Effective management of MDD also requires therapies that can successfully resolve symptoms and improve functional impairment in patients with more chronic or recurrent conditions, especially since previous depressive episodes have been associated with greater disease burden and each successive episode may further increase the risk of relapse or recurrence (Rush et al., 2012; APA, 2013). To reduce risk of relapse, continuation of antidepressant therapy for 4–9 months may be required; maintenance therapy is recommended in patients who have chronic depression and in patients with ≥ 3 prior major depressive episodes (APA, 2010).

Levomilnacipran extended-release (ER) is a serotonin and norepinephrine reuptake inhibitor (SNRI) that is currently approved for the treatment of MDD in adults (Forest, 2013). Five

* Correspondence to: Department of Psychiatry and Institute for Women's Health, P.O. Box 980319, Virginia Commonwealth University, Richmond, VA 23298, United States.
E-mail address: susan.kornstein@vcuhealth.org (S.G. Kornstein).

http://dx.doi.org/10.1016/j.jad.2015.12.058

randomized, double-blind, placebo-controlled trials have been conducted to evaluate the efficacy and safety of levomilnacipran ER in adults with MDD (Asnis et al., 2013; Montgomery et al., 2013; Bakish et al., 2014; Gommoll et al., 2014; Sambunaris et al., 2014a). In all of these studies, the primary and secondary efficacy parameters were defined as change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) and Sheehan Disability Scale (SDS) total score, respectively. Previous post hoc analyses of data from the five studies have shown that in the pooled Intent-to-Treat (ITT) Population, patients who received levomilnacipran ER versus placebo had significantly greater improvements in both of these measures (Sambunaris et al., 2014b; Montgomery et al., 2015).

One of the previous post hoc analyses (Montgomery et al., 2015) also found significantly greater MADRS total score improvements and higher response rates (defined as $\geq$50% improvement in MADRS total score) with levomilnacipran ER relative to placebo in both first-episode and recurrent-episode patients, as well as in patients with varying numbers of previous episodes (1–2, 3–4, $\geq$5). Similarly significant findings were found in patients with shorter current episode durations ($<$6 months, $\geq$6 to $<$12 months) but not in patients with a longer episode duration ($\geq$12 months). Building on these previously reported results, the current post hoc analysis was conducted to further evaluate the effects of levomilnacipran ER in patients with different depressive episode histories. In contrast to the prior post hoc analysis, the current analysis only focuses on three patient subgroups of clinical interest: (1) MDD patients in their first major depressive episode; (2) patients with highly recurrent MDD, defined as 3 or more lifetime major depressive episodes; and (3) patients with chronic MDD, defined as current episode duration $\geq$2 years.

2. Methods

2.1. Studies

The five randomized, double-blind, placebo-controlled, multicenter, clinical trials included in this post hoc analysis comprised four US studies (Asnis et al., 2013; Bakish et al., 2014; Gommoll et al., 2014; Sambunaris et al., 2014a) and one non-US study (Montgomery et al., 2013); methods for all of these trials have been previously published. Two studies evaluated the effects of levomilnacipran ER at fixed doses: 40, 80, or 120 mg/day (Asnis et al., 2013); 40 or 80 mg/day (Bakish et al., 2014); both of these were used for US Food and Drug Administration (FD) approval. Three studies used a flexible-dose design: 40–120 mg/day (Gommoll et al., 2014; Sambunaris et al., 2014a); 75–100 mg/day (Montgomery et al., 2013); one of these studies (Sambunaris et al., 2014a) was also used for FDA approval. The duration of double-blind treatment was 8 weeks in the US studies and 10 weeks in the non-US study.

2.2. Patients

The levomilnacipran ER clinical trials included men and women, $\geq$18 years of age, with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR) diagnosis of MDD who were in a current major depressive episode with a duration of $\geq$4 weeks (Montgomery et al., 2013; Gommoll et al., 2014; Sambunaris et al., 2014a, 2014b), $\geq$8 weeks (Asnis et al., 2013), or $\geq$6 weeks to 12 months (Bakish et al., 2014). Other key eligibility criteria included: MADRS total score $\geq$30 (Asnis et al., 2013; Gommoll et al., 2014; Sambunaris et al., 2014a) or total score $\geq$26 (Bakish et al., 2014); Clinical Global Impressions-Severity (CGI-S) score $\geq$4 (Bakish et al., 2014); 17-Item Hamilton Depression Rating Scale ($HAMD_{17}$) total score $>$22 (Montgomery et al., 2013); and SDS total score $\geq$10, with $\geq$1 subscale score $\geq$6 (Montgomery et al., 2013). Patients with a principal DSM-IV-TR Axis I diagnosis other than MDD were not allowed to participate in the studies. Other key exclusion criteria included history of non-response to $\geq$2 antidepressants (at adequate doses and treatment duration) and significant risk of suicide, as judged by the Investigator and based on patient responses to the Columbia-Suicide Severity Rating Scale or other formal assessment (e.g., score $\geq$5 on MADRS item 10 [suicidal thoughts]).

2.3. Efficacy measures

The 10-item MADRS (total score range, 0–60) and $HAMD_{17}$ (total score range, 0–50) were both used to evaluate overall depression symptom severity (Hamilton, 1960; Montgomery and Asberg, 1979). The SDS (total score range, 0–30) was used to measure functional impairment (Sheehan et al., 1996). In all of these scales, a higher score indicates worse severity. A more detailed description of these assessment tools is presented in Supplementary File 1.

2.4. Post hoc analyses

Analyses were based on the pooled ITT Population, defined as all randomized patients who received $\geq$1 dose of double-blind study treatment and had $\geq$1 postbaseline MADRS assessment. All levomilnacipran ER dosage groups were pooled for the current analyses.

The number of depressive episodes for each patient was recorded in all five studies; the four US studies also collected information about current episode duration. Three subgroups were identified based on these available data: (1) first-episode MDD, defined as all patients (treatment-naïve and previously treated) who entered the study during their first major depressive episode; (2) highly recurrent MDD, defined as all patients with $\geq$3 lifetime depressive episodes; and (3) chronic MDD, defined as all patients with a current episode duration $\geq$2 years, with the cutoff based on diagnostic criteria for persistent depressive disorder (APA, 2013). Although the first-episode and highly recurrent MDD subgroups were mutually exclusive, the chronic MDD subgroup was composed of patients from both of these subgroups. No statistical testing between patient subgroups was conducted.

In order to evaluate the effects of levomilnacipran ER on overall depression symptoms and functional impairment, least squares mean (LSM) changes from baseline to end of study (Week 8 for US studies, Week 10 for non-US study) in MADRS, $HAMD_{17}$, and SDS total scores were analyzed in all three MDD subgroups. The least squares mean differences (LSMDs) between levomilnacipran ER and placebo for these score changes were analyzed using an analysis of covariance (ANCOVA) model that included study, site, treatment, baseline MDD status (i.e., MDD subgroup), treatment-by-baseline status interaction as factors and baseline score as a covariate. Missing values were imputed using the last observation carried forward (LOCF) approach.

The LSM change from baseline in MADRS total score was analyzed at each study visit (Weeks 1, 2, 4, 6, and 8) in all three MDD subgroups to explore the time course of treatment effects. Based on the LSMD at each study visit, analyses were conducted using a mixed-effects model for repeated measures (MMRM) that included study site, treatment, visit, treatment-by-visit interaction, baseline score, and baseline score-by-visit interaction as covariates. Week 10 data from the non-US study were not included in this analysis.

Three different types of response were analyzed based on the following criteria: (1) MADRS response, defined as $\geq$50% total score improvement from baseline at end of treatment (Week 8/10)