

# The efficacy of extended-release levomilnacipran in moderate to severe major depressive disorder: secondary and post-hoc analyses from a randomized, double-blind, placebo-controlled study

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Levomilnacipran (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor that is Food and Drug Administration approved for once-daily treatment of major depressive disorder in adults. Secondary and post-hoc analyses were carried out on data from a positive 10-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, proof-of-concept trial (EudraCT Number: 2006-002404-34) on 75 or 100 mg/day levomilnacipran extended release (ER). Included outpatients (18–70 years) met the criteria for a major depressive episode. There was a statistically significant difference in favor of levomilnacipran ER versus placebo in change from baseline to week 10 on every Montgomery Åsberg Depression Rating Scale (MADRS) single item (mixed-effects model for repeated measures;  $P < 0.05$ ) and most Hamilton Depression Rating Scale (HAM-D<sub>17</sub>) single items. Significantly more levomilnacipran ER versus placebo patients ( $P < 0.05$ ) achieved 'complete' (MADRS  $\leq 5$ ; 24 vs. 10%) and 'sustained' (MADRS  $\leq 10$  in Weeks 4–10; 16 vs. 10%) remission, Sheehan Disability Scale (SDS) response (total score  $\leq 12$  and each item score  $\leq 4$ ; 52 vs. 35%) and remission (total score  $\leq 6$  and each item score  $\leq 2$ ; 26 vs. 17%), and combined

symptomatic (MADRS) and functional (SDS) remission (19 vs. 8%). Treatment effects of similar magnitude were observed in the severe depression subgroup (MADRS  $\geq 30$ ). These results demonstrate the benefit of levomilnacipran ER over placebo for patients with symptomatic and functional impairment associated with major depressive disorder. *Int Clin Psychopharmacol* 29:26–35 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

Major depressive disorder (MDD) is a heterogeneous disorder that usually follows a chronic course, with disability characterized by both symptomatic and functional impairment. Remission, or the return to normal functioning, is the goal of depression treatment for all patients. Ideally, remission should be determined by a reduction in the number and severity of depression symptoms, in addition to improved work, social, and family functioning (Israel, 2006). The broad spectrum of symptoms associated with MDD, different levels of depression severity, and lack of comprehensive efficacy with available treatments predicate the need for new treatments that offer advantages in efficacy, as well as good safety and tolerability.

Levomilnacipran (1*S*, 2*R*-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor that is Food and Drug Administration approved for the treatment of MDD in adults; an extended-release (ER) formulation was developed to allow for once-daily dosing. In-vitro studies have shown that levomilnacipran has two-fold greater potency for norepinephrine reuptake inhibition relative to serotonin reuptake inhibition (Auclair *et al.*, 2013). Levomilnacipran has 10-fold higher selectivity for inhibiting norepinephrine reuptake versus serotonin reuptake compared with duloxetine and an even higher selectivity for norepinephrine reuptake inhibition compared with desvenlafaxine or venlafaxine (Deecker *et al.*, 2006; Auclair *et al.*, 2013).

The safety and efficacy of levomilnacipran ER in the treatment of MDD have been established in four positive randomized, double-blind, placebo-controlled studies of fixed-dose or flexible-dose design (Sambunaris *et al.*, 2012; Asnis *et al.*, 2013; Bakish *et al.*, 2013; Montgomery

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*et al.*, 2013). An additional flexible-dose trial demonstrated consistent improvement in depressive symptoms with 40–120 mg/day levomilnacipran ER relative to placebo, but the overall difference between treatments was not statistically significant (Gommoll *et al.*, 2011). A relapse prevention study comparing levomilnacipran ER and placebo has also been conducted (Shiovitz *et al.*, 2012); although time to relapse was slower in the levomilnacipran ER group versus placebo, the treatment difference did not reach statistical significance because of the limited number of patients who relapsed. Levomilnacipran ER was generally well tolerated in all studies.

The first positive trial of levomilnacipran ER was a 10-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, proof-of-concept trial (EudraCT Number: 2006-002404-34; Montgomery *et al.*, 2013) in which 75 or 100 mg/day levomilnacipran ER demonstrated efficacy versus placebo. To fully assess the results from this trial, multiple secondary and post-hoc analyses were carried out to evaluate the efficacy across the range of depression symptoms, improvement in functional impairment, and a severe depression patient subgroup; the clinical relevance of the effects of levomilnacipran ER treatment was evaluated using remission and number needed to treat (NNT) analyses.

## Methods

This prospective randomized controlled trial was conducted between 13 December 2006 and 22 October 2007 at 68 international sites in France, Finland, Latvia, Lithuania, Sweden, Germany, Estonia, Czech Republic, Bulgaria, India, and South Africa. The study was performed in accordance with the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines, and the final study protocol was approved by appropriate ethics committees and authorities. All patients provided written informed consent.

Detailed study design, inclusion and exclusion criteria, and statistical methods have been reported in a prior publication (Montgomery *et al.*, 2013). In brief, the study consisted of a 3-day to 21-day drug wash-out, followed by a 2-week progressive titration period, an 8-week double-blind treatment period, and a 1-week down-titration period. Patients randomized to levomilnacipran ER received 25 mg on Days 1–3, 50 mg on Days 4–7, and 75 mg on Days 8–11; the 100-mg levomilnacipran ER target dose was reached on Day 12 if good tolerance was demonstrated. If tolerability issues arose, down-titration to 75 mg was allowed and this dose was fixed for the remainder of the trial.

### Inclusion/exclusion criteria

Outpatients between the ages of 18 and 70 years who met the criteria for a major depressive episode (moderate or severe, without psychotic features) according to the

*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. – text revision (APA, 2000) were included. Depressive episode duration was 1 month or more and patients had a Hamilton Depression Rating Scale (HAM-D<sub>17</sub>; Hamilton, 1960) score of greater than 22 and a Sheehan Disability Scale (SDS; Sheehan *et al.*, 1996) score of 10 or higher, with at least one subscale (work, social life, or family life) score of 6 or higher. Standard exclusion criteria were applied including the presence of clinically relevant laboratory and ECG abnormalities, history of some psychiatric disorders, use of certain concomitant medications, and specified physical conditions or disorders.

### Efficacy assessments

Efficacy assessments in the primary study included the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), HAM-D<sub>17</sub>, and SDS total score and subscales. Retrospective analyses evaluated the single items of MADRS and HAM-D<sub>17</sub>, MADRS ‘complete’ and ‘sustained’ remission, SDS response and remission, combined SDS and MADRS remission, and NNTs for MADRS and SDS response and remission. In addition, post-hoc analyses evaluated the subset of patients with severe depression at baseline.

### Statistical analyses

Efficacy analyses were carried out on the full analysis set (FAS), which consisted of all randomized patients who had received at least one dose of study drug (safety population) and had undergone at least one postbaseline MADRS total score assessment. The prospective primary outcome parameter was a change in the MADRS total score from baseline to Week 10 analyzed using a likelihood-based mixed-effects model for repeated measures (MMRM) on the FAS and analysis of covariance.

### Post-hoc analyses

Post-hoc and secondary analyses were retrospectively carried out to more completely evaluate the primary results. Change from baseline to Week 10 in MADRS and HAM-D<sub>17</sub> single items was analyzed using MMRM analysis, which is similar to the primary analysis on the FAS; *P*-values were not adjusted for multiple comparisons. The rate of ‘complete remission’ at Week 10, defined in this analysis as a MADRS total score of 5 or lower (Zimmerman *et al.*, 2004; Wade *et al.*, 2009; Favre, 2012), was calculated using a logistic regression model with treatment and baseline MADRS score as explanatory variables analyzed with a last observation carried forward (LOCF) approach on the FAS. ‘Sustained remission’ was defined in these analyses as a MADRS total score of 10 or lower persisting from Week 4 through to Week 10 and was analyzed using the same model with an observed cases approach.

Functional improvement was evaluated as the proportion of patients achieving SDS response (total score  $\leq 12$  and all item scores  $\leq 4$ ) and remission (total score  $\leq 6$  and all item scores  $\leq 2$ ; Sheehan and Sheehan, 2008; Sheehan *et al.*, 2011). Analyses were carried out on the basis of a logistic regression model with treatment group and corresponding baseline SDS total score as explanatory variables using an LOCF approach. To determine the proportion of patients who achieved combined symptomatic and functional improvement, an analysis was carried out to determine the proportion of patients who achieved both SDS and MADRS remission (SDS total score  $\leq 6$  and all item scores  $\leq 2$ , and MADRS total score  $\leq 10$ ). Analysis was carried out on the basis of a logistic regression model with treatment group and corresponding baseline SDS and MADRS total scores as explanatory variables using an LOCF approach.

NNTs to achieve MADRS response (total score reduction  $\geq 50\%$ ), remission (total score  $\leq 10$ ; Montgomery *et al.*, 2013), and 'complete remission' were calculated for the overall population and the subgroup of patients with severe depression; the NNT for SDS response and remission were also determined. The NNT was calculated as the reciprocal of the difference of the event proportions between the levomilnacipran ER group and the placebo group (Altman, 1998).

Post-hoc analyses of the subgroup of patients with severe baseline depression (MADRS  $\geq 30$ ) were carried out using MMRM analysis on the FAS. MADRS change from baseline to Week 10, MADRS single-item analyses, and response and remission rates were determined.

## Results

A total of 557 patients were included in the Safety Population; the FAS consisted of 553 patients (placebo = 277; levomilnacipran ER = 276). After the titration period, 72% of levomilnacipran ER patients were taking a 100 mg/day target dosage; 10% subsequently down-titrated to 75 mg/day during the study. Demographic and disease characteristics were similar between groups in the FAS, as detailed in the prior publication (Montgomery *et al.*, 2013). No statistically significant differences in premature discontinuation for any reason, including adverse events (AEs), worsening of MDD, or insufficient therapeutic response, were observed between the levomilnacipran ER-treatment and placebo-treatment groups (safety population).

The study was completed by 75% of placebo patients and 80% of levomilnacipran ER patients. Mean MADRS baseline scores (placebo = 30.5; levomilnacipran ER = 30.9) indicated a moderate to severe level of depression in both treatment groups on average; 161 placebo patients and 173 levomilnacipran ER patients were included in the severe depression subgroup (MADRS  $\geq 30$ ) for post-hoc analyses.

## Summary of prospective efficacy outcomes (Montgomery *et al.*, 2013)

On the prospectively defined primary efficacy parameter, MADRS total score change from baseline to Week 10, the least squares mean difference (LSMD) with 95% confidence interval (95% CI) was significantly superior for levomilnacipran ER-treated patients compared with placebo-treated patients [LSMD = -4.2 (95% CI, -5.7 to -2.6);  $P < 0.0001$ ; MMRM]. Functional improvement was demonstrated by a significantly different change from baseline to Week 10 in favor of levomilnacipran ER versus placebo in SDS total score [LSMD = -3.4 (-4.6 to -2.2);  $P < 0.0001$ ] and in each subscale: work [LSMD = -1.1 (95% CI, -1.5 to -0.7);  $P < 0.0001$ ], social life [LSMD = -1.0 (95% CI, -1.5 to -0.6);  $P < 0.0001$ ], and family life [LSMD = -1.2 (95% CI, -1.6 to -0.8);  $P < 0.0001$ ]. Levomilnacipran ER-treated patients versus placebo-treated patients achieved significantly higher rates of MADRS response (MADRS total score reduction  $\geq 50\%$ ; 59 vs. 42%;  $P < 0.0001$ ) and remission (total score  $\leq 10$ ; 46 vs. 26%;  $P < 0.0001$ ). The NNTs for MADRS response and remission for levomilnacipran ER compared with placebo were 6 and 5, respectively.

## Post-hoc and secondary analyses

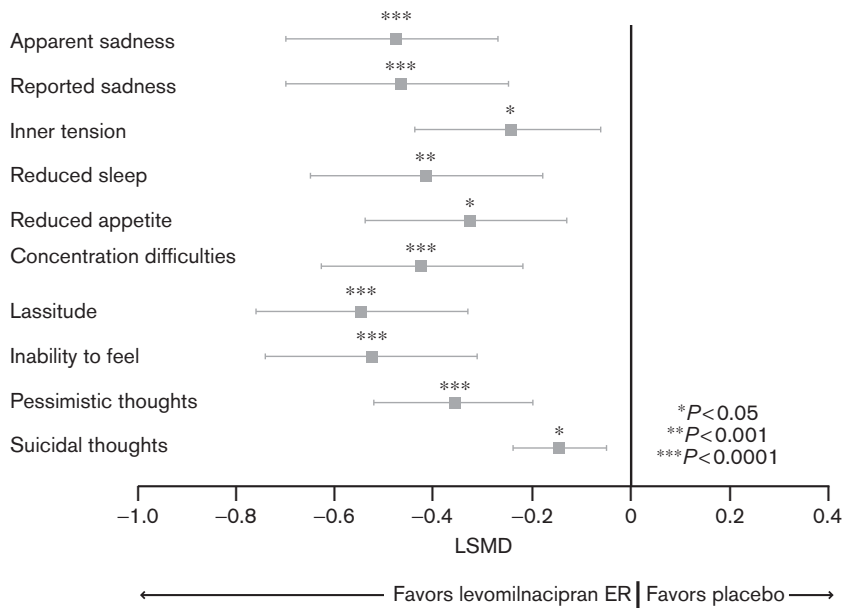
### Single-item analyses

There was a statistically significant difference in favor of levomilnacipran ER versus placebo in change from baseline to Week 10 in every MADRS single item ( $P < 0.05$ ; MMRM; Fig. 1). Supporting evidence of efficacy across a broad range of symptoms was demonstrated by statistically significant differences in change from baseline to Week 10 for levomilnacipran ER relative to placebo in most HAMD<sub>17</sub> single items ( $P < 0.05$ ; MMRM; Fig. 2). Separation from placebo was achieved on all items except suicide, anxiety (somatic), agitation, loss of weight, and insight.

### MADRS remission analyses

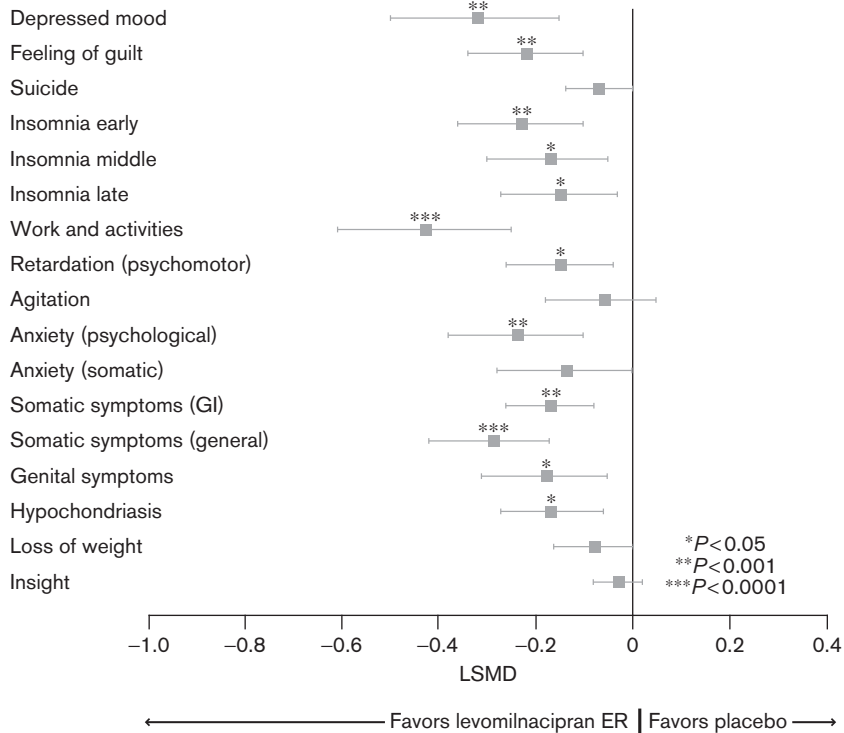
In post-hoc analyses, 'complete remission' (MADRS total score  $\leq 5$ ) and 'sustained remission' (MADRS total  $\leq 10$  that persisted from Week 4 through Week 10; observed cases) were analyzed. Compared with the primary remission analysis that used standardized criteria (MADRS  $\leq 10$  at Week 10; LOCF), the proportion of patients who achieved remission on using the more stringent 'complete' and 'sustained' criteria was statistically greater for levomilnacipran ER versus placebo (Fig. 3). NNT analyses in the overall population demonstrated that six patients would need to be treated with levomilnacipran ER versus placebo for one additional outcome of response (MADRS total score reduction  $\geq 50\%$ ) and five patients would need to be treated for one additional outcome of remission (MADRS total score  $\leq 10$ ; Montgomery *et al.*, 2013); the NNT for 'complete remission' was seven patients.

**Fig. 1**



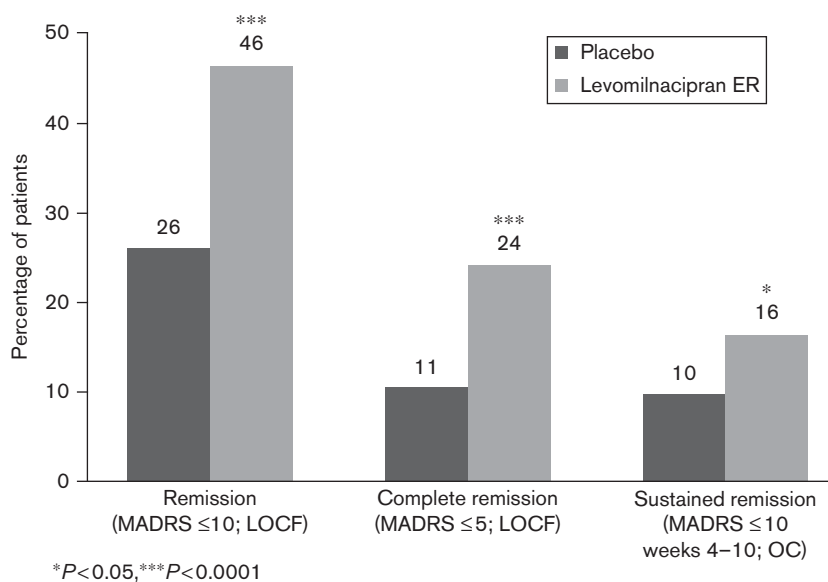
Levomilnacipran ER versus placebo: improvement from baseline to Week 10 on MADRS single items (MMRM). ER, extended release; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures.

**Fig. 2**



Levomilnacipran ER versus placebo: improvement from baseline to Week 10 on HAMD<sub>17</sub> single items (MMRM). ER, extended release; GI, gastrointestinal; HAMD<sub>17</sub>, Hamilton Depression Rating Scale; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures.

Fig. 3



MADRS rates of remission (FAS). ER, extended release; FAS, full analysis set; LOCF, last observation carried forward; OC, observed cases.

### SDS response and remission analysis

Significantly more levomilnacipran ER patients compared with placebo patients achieved SDS response (total score  $\leq 12$  and each item score  $\leq 4$ ) and remission (total score  $\leq 6$  and each item score  $\leq 2$ ; Sheehan and Sheehan, 2008; Sheehan *et al.*, 2011; Fig. 4). Levomilnacipran ER produced clinically meaningful functional improvement as demonstrated by NNTs for SDS response and remission of 6 and 10, respectively.

### Combined MADRS and SDS remission analysis

In a post-hoc analysis evaluating combined symptomatic and functional remission (MADRS total score  $\leq 10$ , and SDS total score  $\leq 6$  and each item score  $\leq 2$ ), a significantly greater proportion of levomilnacipran ER patients (19%) compared with placebo patients (8%) achieved combined remission criteria as shown by an OR of 2.54 (95% CI, 1.51, 4.30;  $P < 0.001$ ). The NNT for combined symptomatic and functional remission was 10.

### Clinical outcomes for patients with severe baseline depression (MADRS $\geq 30$ )

To evaluate whether efficacy in the overall population extended to the subgroup of patients with severe depression (MADRS  $\geq 30$ ), additional post-hoc analyses were carried out. Similar to results from the overall patient population, changes in MADRS and HAMD<sub>17</sub> total scores from baseline to Week 10 were statistically different for levomilnacipran ER compared with placebo in patients with severe depression (Table 1). In addition, broad efficacy across symptoms for patients with severe

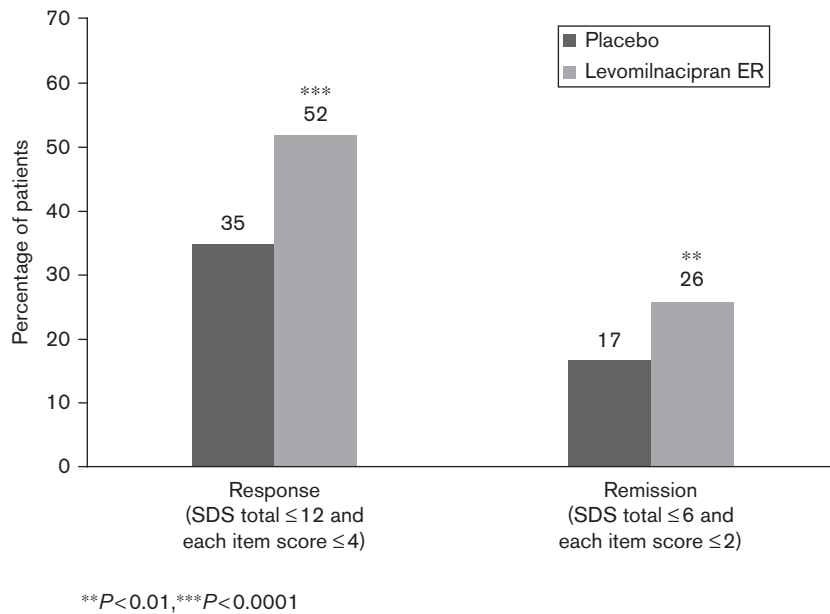
depression was demonstrated by MADRS single-item analysis, which showed a statistically significant baseline to Week 10 change on every MADRS single item in favor of levomilnacipran ER compared with placebo (Fig. 5).

The same measures of clinical relevance (response = MADRS total score reduction  $\geq 50\%$ ; remission = MADRS  $\leq 10$ ) that were used to evaluate the overall population in the primary study were applied to the severe depression patient subgroup in post-hoc analyses. A significantly higher percentage of levomilnacipran ER patients versus placebo patients achieved response (54 vs. 37%;  $P = 0.0035$ ) and remission (40 vs. 22%;  $P = 0.0004$ ; LOCF). Similar to patients in the overall population (Fig. 3), patients with severe depression who were treated with levomilnacipran ER versus placebo had statistically higher rates of 'complete remission' (MADRS  $\leq 5$ ) at Week 10 and 'sustained remission' (MADRS  $\leq 10$  from Weeks 4 to 10; Fig. 6). The absolute difference in 'complete remission' (20 vs. 13%) and 'sustained remission' (9 vs. 6%) for levomilnacipran ER compared with placebo was greater for patients with severe depression versus the overall population; the absolute difference for remission was greater in the overall population (20%) than in the severe depression subgroup (14%). The NNT was 6 for response, remission, or 'complete remission' for patients in the severe depression subgroup.

### Discussion

Post-hoc and secondary analyses were carried out on data from a positive proof-of-concept, randomized, double-

**Fig. 4**



SDS rates of response and remission (LOCF, FAS). ER, extended release; FAS, full analysis set; LOCF, last observation carried forward; SDS, Sheehan Disability Scale.

**Table 1 Change from baseline to Week 10 for patients with severe depression (MADRS ≥ 30; MMRM, FAS)**

Depression rating scale	Placebo	Levomilnacipran ER (75 or 100 mg/day)	P-value
<b>MADRS</b>			
<i>n</i>	161	173	-
Change from baseline, LS [mean (SE)]	-15.27 (0.81)	-19.85 (0.76)	-
LSMD (95% CI)		-4.58 (-6.74, -2.42)	<0.0001
<b>HAMD<sub>17</sub></b>			
<i>n</i>	161	173	-
Change from baseline, LS [mean (SE)]	-11.06 (0.64)	-14.67 (0.60)	-
LSMD (95% CI)		-3.61 (-5.32, -1.90)	<0.0001

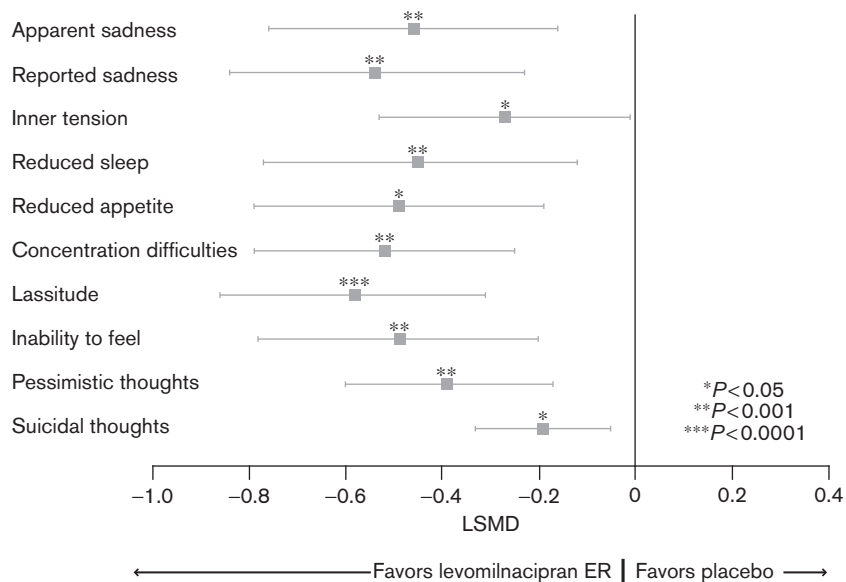
CI, confidence interval; ER, extended release; FAS, full analysis set; HAMD<sub>17</sub>, Hamilton Depression Rating Scale; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures.

blind, placebo-controlled study (Montgomery *et al.*, 2013). Retrospective findings supported the clinically relevant treatment effect of levomilnacipran ER compared with placebo on the primary efficacy measure (MADRS change from baseline to Week 10) in the initial study. Broad efficacy across multiple symptom domains was demonstrated by MADRS and HAMD<sub>17</sub> single-item analyses in both the overall population and the severe depression patient subgroup. Remission rates obtained using more stringent criteria supported the findings based on standard remission criteria (MADRS total score ≤ 10) from the earlier publication (levomilnacipran 46%; placebo 26%; *P* < 0.0001; Montgomery *et al.*, 2013).

The failure of antidepressants to treat the full range of diagnostic and core symptoms of depression is of great concern. The disturbances in monoamine neurotransmission that occur in depression are most likely basic to its pathophysiology (Leonard, 1997; Charney, 1998), although different symptoms of depression may be particularly responsive to increases in the levels of certain neurotransmitters (Nutt, 2008). As such, the strong norepinephrine-related pharmacological profile of levomilnacipran ER may offer potential advantages in treating certain symptoms of depression for which selective serotonin reuptake inhibitors (SSRIs) may be less effective (e.g. decreased concentration, loss of energy, lassitude, tiredness, and reduced self-care; Nutt, 2008). Of interest in the present analyses, efficacy across a full range of depressive symptoms was demonstrated with significant differences in favor of levomilnacipran ER over placebo in all MADRS single-item items, showing broad efficacy against symptoms that may be associated with serotonin and/or norepinephrine.

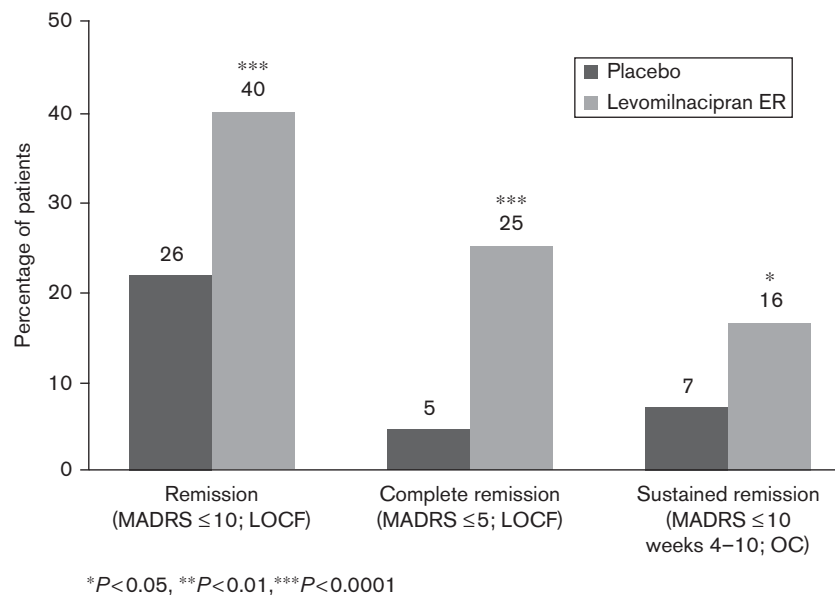
A critical distinction between the MADRS and HAMD<sub>17</sub> is the inclusion of items in HAMD<sub>17</sub> that correspond more closely with the somatic symptoms of MDD. As such, statistically significant differences compared with placebo in most of the single items of this scale support the concept of broad efficacy of levomilnacipran ER across the core symptoms and somatic symptoms of depression. The slightly better drug–placebo difference in MADRS compared with HAMD<sub>17</sub> in the post-hoc

Fig. 5



Change from baseline to Week 10 in MADRS single items in patients with severe depression (MADRS ≥ 30). LSMD, least squares mean difference.

Fig. 6



Rates of remission in patients with severe depression (MADRS ≥ 30; FAS). ER, extended release; FAS, full analysis set; LOCF, last observation carried forward; OC, observed cases.

analyses may have been related to the inclusion of agitation, loss of weight, somatic anxiety, and insight factors in the HAMD<sub>17</sub> scale. Wide-ranging symptomatic improvement is an essential component of stable recovery and the return to wellness as residual symptoms have been identified as a predictor of MDD relapse (Judd *et al.*,

1997; Thase, 2009), whereas remission is associated with a reduced relapse risk (Montgomery *et al.*, 1991).

The goal of antidepressant treatment is to achieve and maintain remission, a state of symptomatic wellness that is compatible with normal life and functioning. The

remission rate achieved by levomilnacipran ER patients in the initial study (46%) was high in comparison with that in the STAR\*D study (37% after acute treatment), a large, naturalistic antidepressant trial that was conducted in primary and specialty care settings (Rush *et al.*, 2006). Remission is an accepted measure of the clinical relevance of treatment; as statistical significance alone may not sufficiently reveal important clinical implications, clinical relevance takes into account both the size and consistency of treatment differences between the active drug and placebo (Thase, 2008).

It is unusual to achieve significantly different remission rates for drug versus placebo in a single acute study. Remission often takes longer to achieve than the treatment duration in an acute study and the numbers of patients achieving remission within a study are normally too low for a meaningful analysis (Montgomery and Moller, 2009). In secondary analyses, remission was evaluated using more stringent criteria than the prospective measure in the primary study. On the measure defined as ‘complete remission’ (MADRS total score  $\leq 5$ ), the difference of 13 percentage points between levomilnacipran ER and placebo met or exceeded the 10–15 point difference in response or remission that is considered clinically relevant (Thase, 2011). Complete remission, which indicates a symptom-free state, has not been examined in relapse prevention studies, but it is reasonable to assume that it could be associated with a lower level of subsequent relapse because the residual symptom burden is very low after complete remission criteria are met (Pintor *et al.*, 2004).

Further exploratory analysis of remission revealed that when remission was achieved at Week 4, it was sustained through to Week 10 by a significant percentage of levomilnacipran ER patients. The six-point difference between levomilnacipran ER and placebo observed at Week 10 for patients who achieved ‘sustained remission’ from Week 4 was statistically significant. In addition, the rate of ‘sustained remission’ achieved by patients with severe depression was significantly greater for levomilnacipran ER compared with placebo despite a lower number of patients and consequent loss of statistical power.

NNT calculation is a standard reflection of clinical significance in the context of evidence-based medicine for categorical outcomes (Kraemer and Kupfer, 2006) such as response and remission. For antidepressants, an NNT of 10 is considered to be the threshold of clinical relevance (Thase, 2008; Montgomery and Moller, 2009), meaning that 10 additional patients would need to be treated with the more effective intervention to achieve one additional response or remission. A significant difference is often judged to be clinically meaningful if the difference in a clinically relevant outcome is equal to or greater than 10%, which is the same as an NNT of 10 or less (Cipriani *et al.*, 2006; Thase, 2011).

The NNT for MADRS response, remission, and ‘complete remission’ was very similar for the entire population (6, 5, and 7, respectively) and for those with severe depression (6, 6, and 6, respectively), indicating that levomilnacipran ER can produce clinically relevant outcomes across a range of depression severity. This is noteworthy as patients with higher symptom severity scores require a greater change in rating scale scores to achieve remission (Thase, 2009), and greater severity of depression predicts longer time to remission (Israel, 2006).

As functional improvement frequently lags behind symptomatic improvement in patients with MDD (Israel, 2006; Sheehan and Sheehan, 2008), it is interesting to find significant concurrent functional and symptomatic improvements in a single acute study. In the primary study, significant differences in favor of levomilnacipran ER versus placebo were demonstrated by a change from baseline in SDS total and subscale scores (Montgomery *et al.*, 2013); post-hoc analyses revealed clinically relevant SDS response (NNT = 6) and remission (NNT = 10) at Week 10, which supports the primary outcome. Of additional interest, significant improvement for levomilnacipran ER versus placebo in a measure of combined symptomatic and functional remission (MADRS total score  $\leq 10$ , and SDS total score  $\leq 6$  and subscale scores  $\leq 2$ ) further indicates that symptomatic and functional improvement took place concomitantly in this study; an NNT of 10 for the combined remission measure demonstrated the clinical relevance of this finding.

Limitations of this study include the retrospective nature of these analyses. In addition, these data have not been subject to statistical adjustment for multiple analyses and are presented using the customary *P* less than 0.05 significance criterion because of the number of exploratory analyses undertaken; the results should therefore be interpreted with caution. Although the significant differences between levomilnacipran ER and placebo that were observed in post-hoc remission analyses should be regarded as a demonstration of clinical relevance, the stringent criteria used are not standard measures and are therefore difficult to generalize. Although the remission rates observed in the primary study and additional analyses raise the possibility that levomilnacipran ER may be unusually effective in achieving remission, it may alternatively indicate that the population studied included patients who were particularly sensitive to treatment. Rising placebo response observed in recent studies may compromise the ability to assess efficacy. The placebo response rate of 37% in the present study is lower than that observed in some other recent studies (Rutherford and Roose, 2013). This may be because great care was taken by the investigators in selecting the study population, by ensuring roughly equal numbers of those with moderate and severe depression, and by achieving good compliance in the 10-week study.



## Conclusion

Significant differences between levomilnacipran ER and placebo in a variety of post-hoc and secondary measures support the primary and secondary efficacy outcomes reported previously in this study. Results from single-item analyses and measures of functional improvement support the broad efficacy across diverse symptoms and domains of depression. Significant differences in rates of remission between levomilnacipran ER and placebo, as well as the NNTs in the overall population and in patients with severe depression, satisfy the criteria frequently used to assess clinically relevant or meaningful treatment differences. The results from these analyses are convincing and demonstrate the benefit of treatment with levomilnacipran ER compared with placebo for patients with symptomatic and functional impairment associated with MDD.

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## Conflicts of interest

Stuart Montgomery acknowledges a potential conflict of interest in the past year as a consultant to Forest, Lundbeck, Pierre Fabre, Richter, Servier, and Takeda and as a speaker or advisory board member for AstraZeneca, Lundbeck, and Pierre Fabre. Carl Gommoll and Dayong Li acknowledge a potential conflict of interest as employees of Forest Research Institute at the time of the study. Lucilla Mansuy acknowledges a potential conflict of interest as an employee of Pierre Fabre Médicament. Adam C. Ruth acknowledges a potential conflict of interest as an employee of Prescott Medical Communications Group, a contractor for Forest Research Institute.

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