

SUPPLEMENTAL DIGITAL CONTENT

Supplemental Table 1

Description of the Short-Form MEI, SDS, and SF-36

Instrument	Overview	Examples of Items	Scoring
Motivation and Energy Inventory (MEI-Short Form)	<ul style="list-style-type: none"> ▪ Patient-rated instrument ▪ 18 items measuring the impact of reduced motivation and fatigue on daily activities over the past week ▪ 2 subscales measuring cognitive/mental energy (6 items) and social motivation (5 items) 	<ul style="list-style-type: none"> ▪ “During the past 7 days, how often did you feel enthusiastic when you began your day?” Rating: 0 (never) to 6 (every day) ▪ “During the past 7 days, how much of the time did you feel energetic?” Rating: 0 (none of the time) to 6 (all of the time) ▪ “During the past 7 days, to what extent were you interested in social activities like visiting friends, going out to dinner, or parties?” Rating: 0 (not at all interested) to 6 (extremely interested) 	<ul style="list-style-type: none"> ▪ Item scores: range, 0 to 6 ▪ Cognitive subscale score: range, 0 to 36 ▪ Social subscale score: range, 0 to 20 ▪ Total score: range, 0 to 108
Sheehan Disability Scale (SDS)	<ul style="list-style-type: none"> ▪ Patient-rated instrument ▪ 3 items, or subscales, measuring the impact of symptoms on ability to function ▪ Each subscale represents a different area of impact 	<ul style="list-style-type: none"> ▪ “The symptoms have disrupted your work/school work:” Rating: 0 (not at all) to 10 (extremely) ▪ “The symptoms have disrupted your social life/leisure activities:” Rating: 0 (not at all) to 10 (extremely) ▪ “The symptoms have disrupted your family life/home responsibilities:” Rating: 0 (not at all) to 10 (extremely) 	<ul style="list-style-type: none"> ▪ Subscale scores: range, 0 to 10 ▪ Total score: range, 0 to 30
Medical Outcomes Study Short Form-36 Health Survey (SF-36)	<ul style="list-style-type: none"> ▪ Patient-rated instrument ▪ 36 items measuring general health and ability to participate in usual activities ▪ Items allocated into 8 domains, all of which contribute to a summary score but are weighted more heavily as follows: <ul style="list-style-type: none"> ○ Physical Component Summary (PCS): physical functioning, role limitations-physical, bodily pain, general health ○ Mental Component Summary (MCS): mental health, role limitations-emotional, social functioning, vitality 	<ul style="list-style-type: none"> ▪ “Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?” Rating: 1 (limited a lot) to 3 (not limited at all) ▪ “During the past week, how much of the time have you had the following problems with work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious): <i>cut down on the amount of time you spent on work or other activities</i>” Rating: 1 (all of the time) to 5 (none of the time) ▪ “During the past week, to what extent has your physical health or emotional problems interfered with family, friends, neighbors, or groups?” Rating: 1 (not at all) to 5 (extremely) 	<ul style="list-style-type: none"> ▪ All raw scores (item, domain, and summary scores) are transformed into normalized scores ranging from 0 (worst functional health) to 100 (best functional health), with 50 representing the general population norm

Supplemental Table 2

Effects of treatment on SF-36 domain score changes from baseline (ITT Population and MEI subgroups, LOCF)

	ITT Population		High Motivation/Energy ^a		Low Motivation/Energy ^b	
	Placebo, n=214 Levomilnacipran ER, n=215		Placebo, n=111 Levomilnacipran ER, n=103		Placebo, n=102 Levomilnacipran ER, n=112	
	LSMD (95% CI) ^c	Effect Size	LSMD (95% CI) ^c	Effect Size	LSMD (95% CI) ^c	Effect Size
SF-36 mental health domains						
Mental health	2.28 (-0.28, 4.84)	0.32	-0.16 (-3.91, 3.59)	0.25	4.54 (0.94, 8.14) ^d	0.34
Role emotional	2.94 (0.36, 5.53) ^d	0.24	0.12 (-3.64, 3.88)	0.04	5.88 (2.20, 9.57) ^d	0.41
Social functioning	3.31 (0.93, 5.69) ^d	0.37	2.97 (-0.52, 6.45)	0.43	3.70 (0.31, 7.09) ^d	0.26
Vitality	2.01 (-0.28, 4.30)	0.25	-0.34 (-3.68, 3.01)	0.16	4.27 (1.02, 7.53) ^d	0.30
SF-36 physical health domains						
Physical functioning	1.40 (-0.08, 2.89)	0.26	-0.24 (-2.40, 1.92)	0.07	2.99 (0.88, 5.11) ^d	0.38
Role physical	1.88 (-0.10, 3.87)	0.23	0.28 (-2.61, 3.18)	0.11	3.50 (0.67, 6.34) ^d	0.34
Bodily pain	1.86 (-0.03, 3.75)	0.21	1.44 (-1.32, 4.21)	0.15	2.15 (-0.56, 4.86)	0.23
General health	1.57 (0.05, 3.10) ^d	0.28	0.38 (-1.84, 2.60)	0.16	2.73 (0.55, 4.91) ^d	0.37

^aPatients with MEI total score >28 at baseline.

^bPatients with MEI total score ≤28 at baseline.

^cBased on ANCOVA model with treatment, pooled study center, MEI category and treatment-by-MEI category interaction, and corresponding baseline as covariates. Positive LSMD value indicates greater improvement with levomilnacipran ER versus placebo. Analyses conducted in patients with nonmissing values at baseline and at end of treatment.

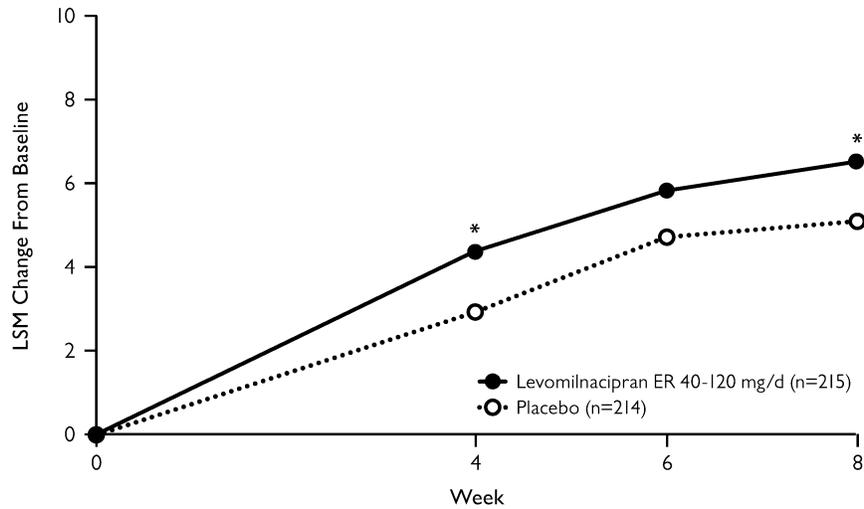
^d*P*<.05 for levomilnacipran ER versus placebo.

ANCOVA, analysis of covariance; CI, confidence interval; ER, extended release; ITT, intent to treat; LOCF, last observation carried forward; LSMD, least squares mean difference between levomilnacipran ER and placebo; MEI, Motivation and Energy Inventory-Short Form; SF-36, Short Form-36 Health Survey.

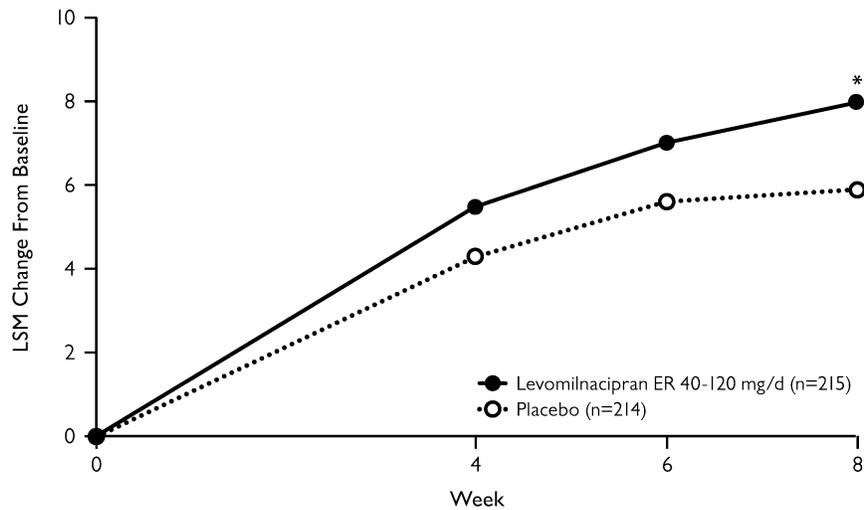
Supplemental Figure 1

Change from baseline in MEI subscale scores by study visit (ITT Population, MMRM)

A. MEI Social



B. MEI Cognitive



***P<.05 versus placebo. *P<.05 versus placebo.**

Analysis includes all study visits at which MEI was evaluated.

ER, extended release; ITT, intent to treat; LSM, least squares mean; MEI, Motivation and Energy Inventory-Short Form; MMRM, mixed-effects model for repeated measure.