

Supplementary Material

Article Title: Evaluation of Sexual Function With Adjunctive Lumateperone in Patients With Major Depressive Disorder

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Supplementary methods

Statistical analysis

Efficacy and sexual function analyses used a mixed-effects model for repeated measures, including the change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) Total score at each study visit as the response variable; the treatment group, study visit, and site (or pooled sites) as factors; the baseline MADRS Total score as covariate; and interaction terms for baseline MADRS Total score by study visit and treatment group by study visit. An unstructured covariance matrix was used to model the correlation among repeated measurements within patients; the Kenward-Roger method was used to estimate the denominator degrees of freedom. Domain analyses were exploratory and included pleasure, desire/frequency, desire/interest, arousal/excitement, and orgasm/completion. Least-squares mean differences (LSMDs) between treatment groups at Day 43 were estimated. Effect size (ES) was calculated as the LSMD/pooled within-patient error standard deviation of change from baseline at Day 43.

Supplementary results

CSFQ-14 Total score by ADT class

Lumateperone + ADT was associated with statistically significant improvements in Changes in Sexual Functioning Questionnaire (CSFQ-14) Total score compared with placebo at Day 43 regardless of ADT class (selective serotonin reuptake inhibitors [SSRIs] vs serotonin-norepinephrine reuptake inhibitors [SNRIs]/other subgroups); a larger numerical improvement was observed in the SNRI/other subgroup (LSMD, 3.48; ES, 0.49) compared with the SSRI subgroup (LSMD, 2.21; ES, 0.31) (**Supplementary Figure 2**).

Supplementary Table 1. Baseline Demographics and Clinical Characteristics (ITT Population)

	Lumateperone 42 mg/day + ADT (n=242)	Placebo + ADT (n=238)
Demographic Parameters		
Age, mean (range), years	46 (18-65)	46 (18-65)
Sex, n (%)		
Men	73 (30.2)	73 (30.7)
Women	169 (69.8)	165 (69.3)
Race, n (%)		
Asian	1 (0.4)	3 (1.3)
Black	6 (2.5)	8 (3.4)
White	235 (97.1)	223 (93.7)
Other	0	4 (1.7)
Hispanic or Latino ethnicity, n (%)	37 (15.3)	33 (13.9)
Clinical Characteristics		
ADT during double-blind treatment, n (%)^b		
SSRI	160 (66.1)	144 (60.5)
SNRI	67 (27.7)	80 (33.6)
Other (bupropion)	15 (6.2)	14 (5.9)
MADRS Total score, mean (SD)	30.8 (3.9)	31.5 (4.0)
CSFQ-14 Total score, mean (SD)	34.7 (10.1)	34.0 (9.9)
Sexual dysfunction, n (%)^{a,b}	198 (81.8)	198 (83.2)
Men ^c	56 (23.1)	56 (23.5)
Women ^c	142 (58.7)	142 (59.7)

^aSexual dysfunction defined as baseline CSFQ-14 Total score ≤41 for women and ≤47 for men.

^bPercentage of patients in the safety population; lumateperone 42 mg + ADT, n=242; placebo + ADT, n=238.

^cPercentage shown for women and men represents the proportion of patients with sexual dysfunction in each treatment group.

Abbreviations: ADT, antidepressant therapy; CSFQ, Changes in Sexual Functioning Questionnaire 14-item version; ITT, intent-to-treat; MADRS, Montgomery-Asberg Depression Rating Scale; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Supplementary Table 2: Shift in Sexual Function Status From Baseline to End of Double-Blind Treatment

Baseline Category	Lumateperone 42 mg + ADT (n=242) ^a			Placebo + ADT (n=238) ^a		
	N1	End of Double-blind Treatment Category		N1	End of Double-Blind Treatment Category	
		Normal n (%)	Sexual Dysfunction n (%)		Normal n (%)	Sexual Dysfunction n (%)
Normal	43	32 (74.4)	9 (20.9)	39	29 (74.4)	10 (25.6)
Sexual dysfunction ^b	198	52 (26.3)	141 (71.2)	198	30 (15.2)	165 (83.3)

^aN = number of patients in the intent-to-treat Population; N1 = number of the patients with baseline in the specific category and non-missing end of double-blind treatment period value; n = number of the patients (out of N1) with end of double-blind treatment period values in the specific category.

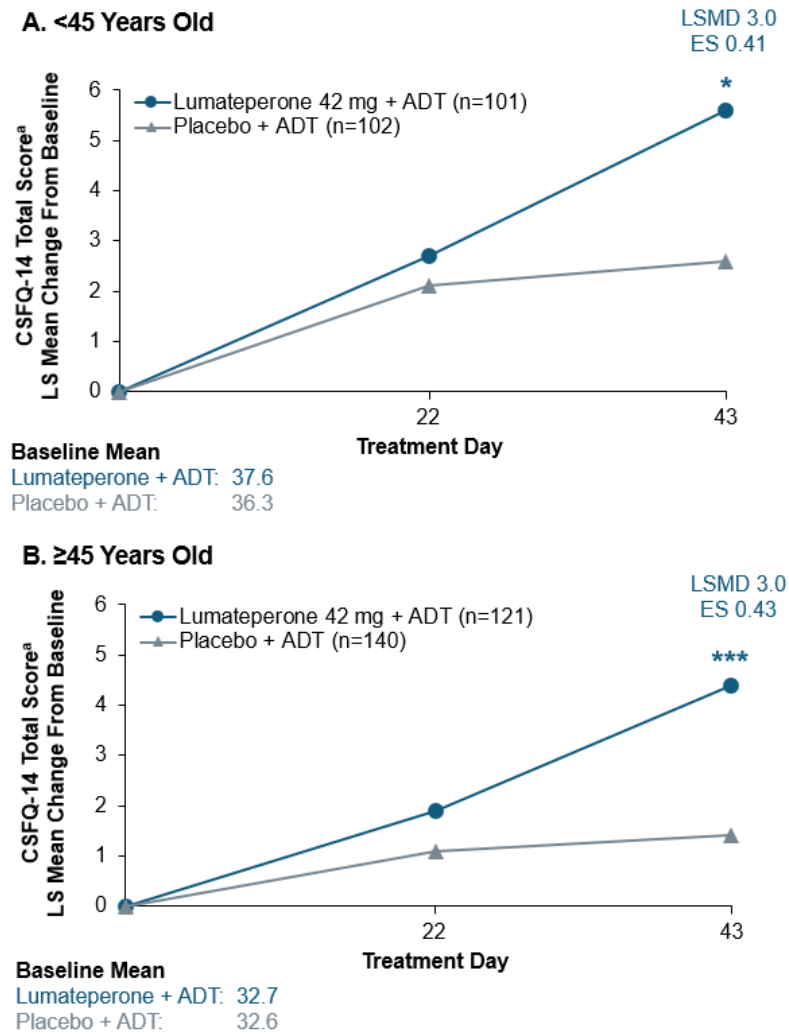
^bSexual dysfunction defined as baseline CSFQ-14 Total score ≤ 41 for women and ≤ 47 for men.
ADT, antidepressant therapy; CSFQ, Changes in Sexual Functioning Questionnaire 14-item version.

Supplementary Table 3: Baseline Distributional Statistics of CSFQ-14 Total and Domain Scores by Sex (ITT Population)

Scale	Female				Male			
	Mean (SD)	Range	Skewness	Kurtosis	Mean (SD)	Range	Skewness	Kurtosis
CSFQ-14 Total score	31.4 (9.0)	42.0	0.6	-0.2	41.2 (8.9)	44.0	0.1	-0.1
Arousal	6.2 (2.5)	10.0	0.4	-0.7	8.5 (2.7)	12.0	-0.1	-0.4
Desire/frequency	3.8 (1.5)	6.0	0.6	-0.1	5.2 (1.8)	8.0	0.6	0.2
Desire/interest	5.3 (2.2)	12.0	1.0	0.8	7.2 (2.3)	10.0	0.2	-0.1
Orgasm	6.5 (3.1)	12.0	0.6	-0.5	8.6 (2.6)	12.0	0.1	-0.3
Pleasure	1.7 (0.9)	4.0	1.1	0.5	2.2 (1.0)	4.0	0.5	-0.1

Abbreviations: CSFQ, Changes in Sexual Functioning Questionnaire14-item version; ITT, intent-to-treat; SD, standard deviation.

Supplementary Figure 1. LS Mean Change From Baseline in CSFQ-14 Total Score by Age



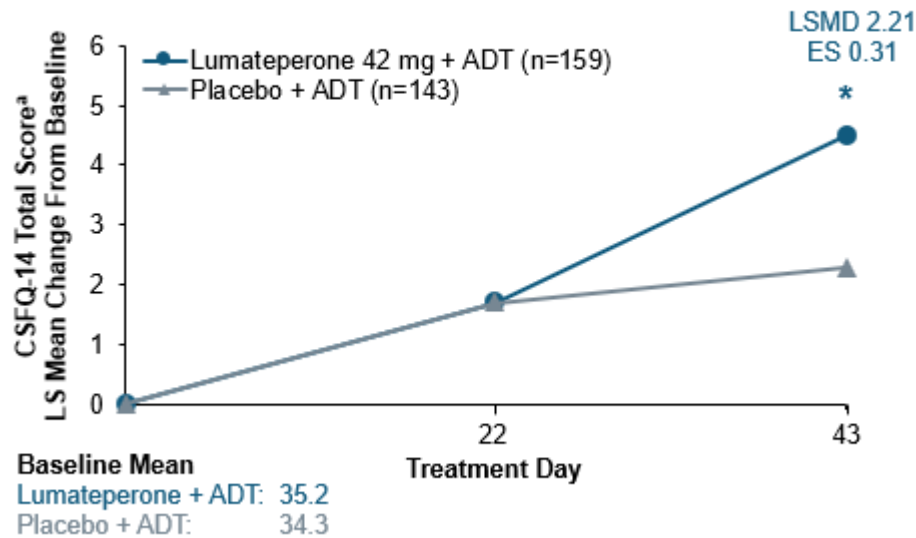
* $P < .05$ *** $P < .001$. LSMD vs placebo. MMRM in ITT population.

^aHigher CSFQ-14 Total scores indicate better sexual functioning.

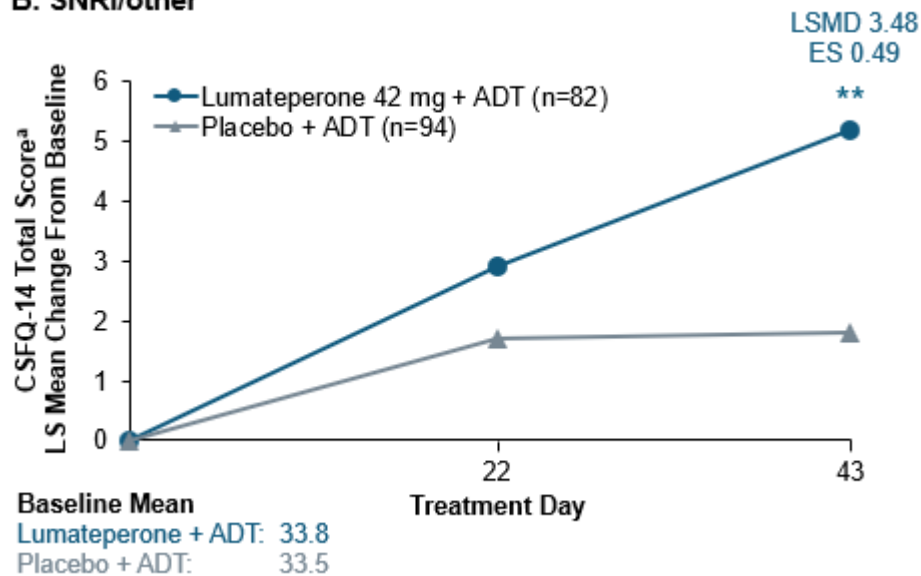
Abbreviations: ADT, antidepressant therapy; CSFQ-14, Changes in Sexual Functioning Questionnaire 14-item version; ES, effect size; ITT, intent-to-treat; LS, least squares; LSMD, least-squares mean difference; MMRM, mixed-effects model for repeated measures.

Supplementary Figure 2: LS Mean Change From Baseline in CSFQ-14 Total by Antidepressant Class

A. SSRI



B. SNRI/other



* $P < .05$ ** $P < .01$ LSMD vs placebo. MMRM. ITT population.

^aHigher CSFQ-14 Total scores indicate higher sexual functioning.

ADT, antidepressant therapy; CSFQ, Changes in Sexual Functioning Questionnaire 14-item version; ES, effect size; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.