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

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BACKGROUND

- Approximately 68% of patients with major depressive disorder (MDD) experience comorbid sexual dysfunction[1]
  - Antidepressant therapy (ADT) can lead to new or worsening sexual dysfunction, including decreased sexual desire, sexual excitement, and orgasmic function, which negatively impacts quality of life and reduces treatment adherence[1,2]
  - Effective, novel treatments with minimal sexual side effects are needed for patients with MDD
- Lumateperone is a mechanistically novel antipsychotic that is US FDA approved to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate[3,4]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[3]
  - Specifically, lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a dopamine D_2 receptor presynaptic partial agonist and postsynaptic antagonist, a D_1 receptor-dependent indirect modulator of glutamatergic AMPA and NMDA currents, and a serotonin reuptake inhibitor[3]
  - This novel mechanism of action with multimodal effects may confer robust efficacy with improved safety and tolerability compared with current treatment options
- In a recent Phase 3, randomised, double-blind, placebo-controlled, multicentre trial (Study 502; NCT05061706), lumateperone 42 mg/day adjunctive to ADT significantly improved depressive symptoms compared with placebo adjunctive to ADT, as measured by both clinician-rated and patient-rated outcomes, in patients with MDD with inadequate ADT response[5]
  - Lumateperone 42 mg/day + ADT had a favourable safety profile, with no notable changes in cardiometabolic parameters or body morphology and a low risk of extrapyramidal symptoms[5]
- This analysis of Study 502 investigated the impact of lumateperone 42 mg/day + ADT on sexual functioning, assessed by the Changes in Sexual Functioning Questionnaire 14-item version (CSFQ-14), in patients with MDD with inadequate ADT response

METHODS

- Eligible adults (18-65 years) met DSM-5 criteria for MDD with inadequate response to 1-2 courses of ADT in the current depressive episode (defined as <50% improvement with ≥6 weeks ADT monotherapy as confirmed by the Antidepressant Treatment Response Questionnaire [ATRQ])
  - Patients were experiencing a major depressive episode (Montgomery-Åsberg Depression Rating Scale [MADRS] total score ≥24 and Clinical Global Impression-Severity [CGI-S] score ≥4), and had Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score ≥14 at screening and baseline
  - Patients were randomised 1:1 to oral lumateperone 42 mg/day + ADT or placebo + ADT for 6 weeks
- The primary endpoint was the change from baseline to Day 43 in MADRS total score, analysed using a mixed-effects model for repeated measures (MMRM)
- Sexual function was assessed by changes in CSFQ-14 total score[6] in the intent-to-treat (ITT) population and in subgroups by baseline sexual dysfunction (CSFQ-14 total score ≤41 in women and ≤47 in men), sex (women and men), and age (<45 and ≥45 years) using an MMRM
  - Changes from baseline to Day 43 in CSFQ-14 domain scores were evaluated using an MMRM
  - Higher CSFQ-14 total scores indicate better sexual functioning[6] and CSFQ-14 total scores ≤41 in women and ≤47 in men denote sexual dysfunction
  - Changes/differences from placebo of 2-3 points on CSFQ-14 total score can be considered clinically meaningful[7]

RESULTS

Patient Population

- All 480 patients who were randomised received adjunctive treatment and were included in the ITT population (lumateperone + ADT, n=242; placebo + ADT, n=238); 89.4% completed treatment
- Demographics and baseline characteristics were similar between groups (**Table 1**)
  - The majority of patients (82.5%) met criteria for sexual dysfunction at baseline (women, 284/334 [85.0%]; men, 112/146 [76.7%])

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

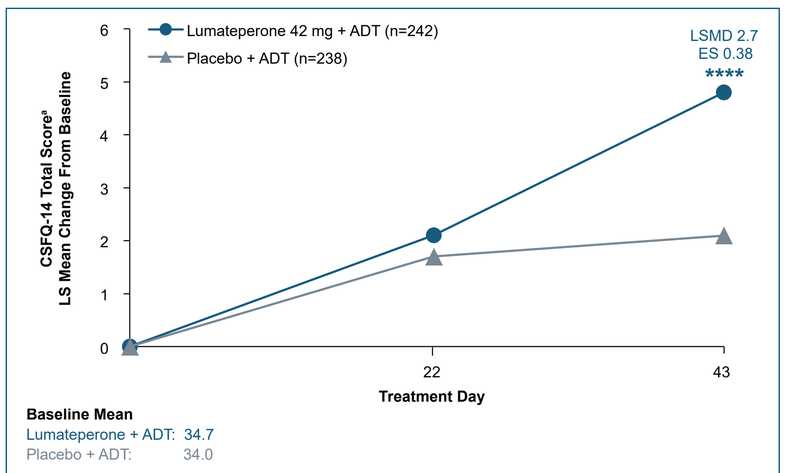
	Lumateperone 42 mg/day + ADT (n=242)	Placebo + ADT (n=238)
Demographic Parameters		
Age, mean (range), years	46 (18-65)	46 (18-65)
Sex, n (%)		
Women	169 (69.8)	165 (69.3)
Men	73 (30.2)	73 (30.7)
Race, n (%)		
White	235 (97.1)	223 (93.7)
Asian	1 (0.4)	3 (1.3)
Black	6 (2.5)	8 (3.4)
Other	0	4 (1.7)
Hispanic 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 (3.87)	31.5 (3.98)
CSFQ-14 total score, mean (SD)	34.7 (10.12)	34.0 (9.94)
Sexual dysfunction, n (%)[a,b]	198 (81.8)	198 (83.2)
Women	142 (58.7)	142 (59.7)
Men	56 (23.1)	56 (23.5)

[a]Sexual dysfunction defined as baseline CSFQ-14 total score ≤41 for women and ≤47 for men. [b]Percentage of patients in the safety population; lumateperone 42 mg + ADT, n=242; placebo + ADT, n=238.
ADT, antidepressant therapy; CSFQ, Changes in Sexual Functioning Questionnaire 14-item version; ITT, intent-to-treat; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Efficacy

- The primary endpoint was met for lumateperone + ADT, with significantly greater MADRS total score improvement from baseline to Day 43 compared with placebo + ADT in the modified ITT population (lumateperone + ADT, n=232; placebo + ADT, n=237; least squares mean difference vs placebo + ADT [LSMD], −4.5; effect size [ES], −0.56; *P*<.0001)
- Lumateperone + ADT significantly improved CSFQ-14 total score at Day 43 compared with placebo + ADT in the ITT population (**Figure 1**)

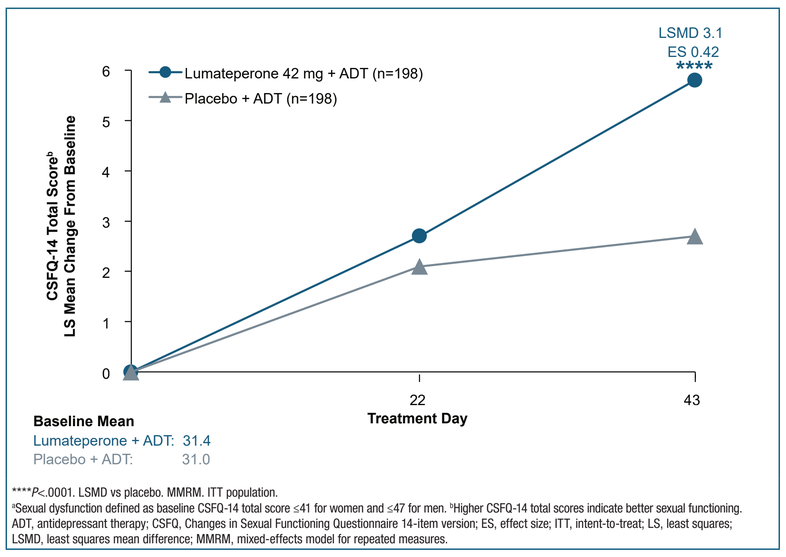
Figure 1. LS Mean Change From Baseline in CSFQ-14 Total Score



****P<.0001. LSMD vs placebo. MMRM. ITT population.
[a]Higher CSFQ-14 total scores indicate better 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.

- In the subgroup of patients with sexual dysfunction at baseline (lumateperone + ADT, n=198; placebo + ADT, n=198), lumateperone + ADT significantly improved CSFQ-14 total score at Day 43 compared with placebo + ADT (**Figure 2**)
  - In women with sexual dysfunction at baseline (n=142 in each treatment group), lumateperone + ADT significantly improved CSFQ-14 total score at Day 43 (baseline mean: lumateperone + ADT, 28.7; placebo + ADT, 28.5; change at Day 43: LSMD, 3.8; ES, 0.50; *P*<.0001)
  - In men with sexual dysfunction at baseline (n=56 in each treatment group), a numerical increase in CSFQ-14 total score occurred at Day 43 (baseline mean: lumateperone + ADT, 38.3; placebo + ADT, 37.2; change at Day 43: LSMD, 2.2; ES, 0.36; *P*=.0975)
- No changes in CSFQ-14 total score occurred at Day 43 in patients without baseline sexual dysfunction (baseline mean: lumateperone + ADT, 50.1; placebo + ADT, 49.1; change at Day 43: LSMD, −0.4; ES, −0.10; *P*=.73)

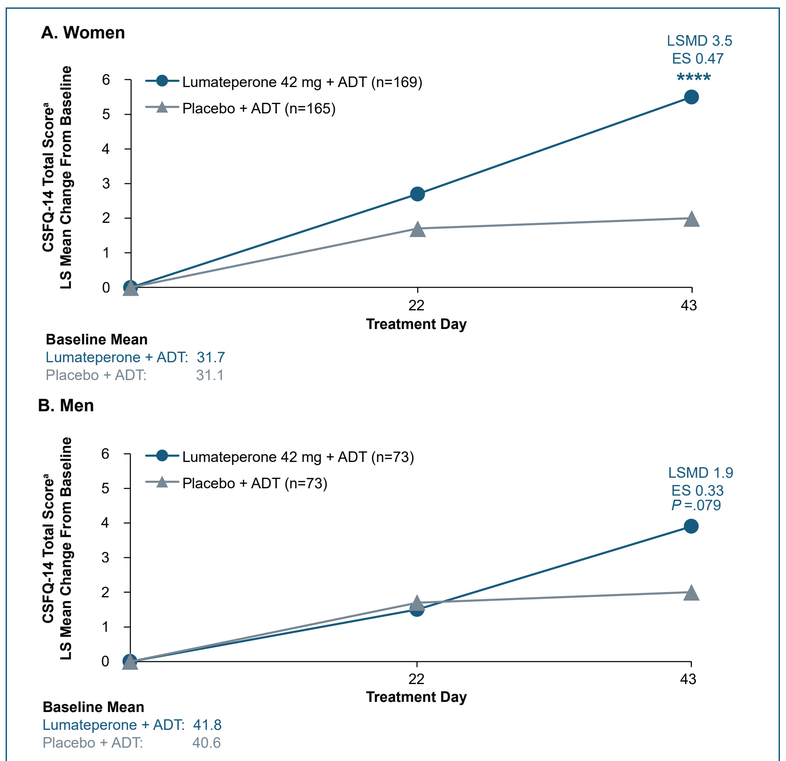
Figure 2. LS Mean Change From Baseline in CSFQ-14 Total Score in Patients With Baseline Sexual Dysfunction[a]



****P<.0001. LSMD vs placebo. MMRM. ITT population.
[a]Sexual dysfunction defined as baseline CSFQ-14 total score ≤41 for women and ≤47 for men. [b]Higher CSFQ-14 total scores indicate better 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.

- CSFQ-14 total score significantly improved with lumateperone + ADT compared with placebo + ADT from baseline to Day 43 for women (**Figure 3**)
  - Numerical improvements in CSFQ-14 total score from baseline to Day 43 were observed for men (*P*=.079)

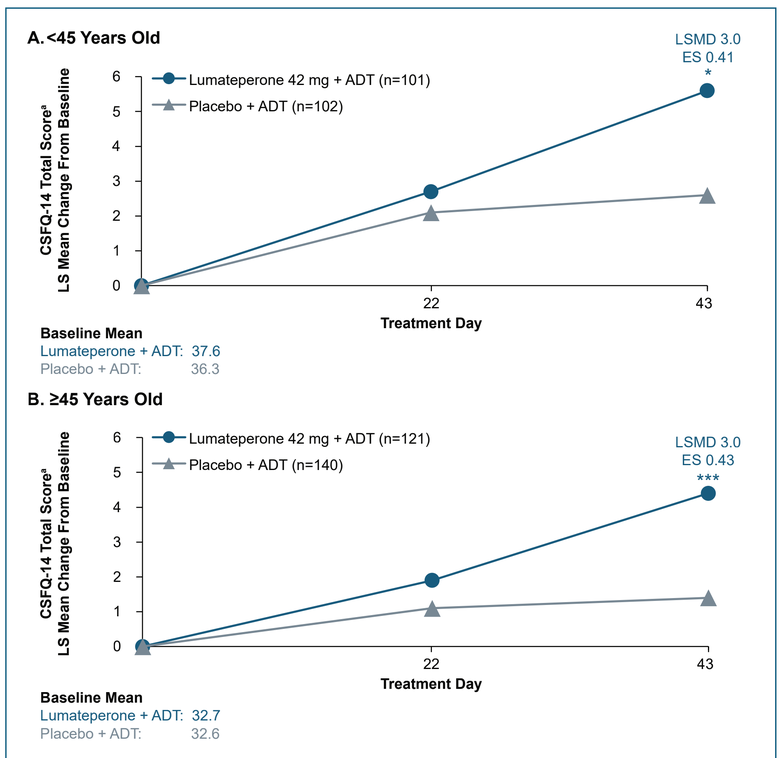
Figure 3. LS Mean Change From Baseline in CSFQ-14 Total Score by Sex



****P<.0001. LSMD vs placebo. MMRM. ITT population.
[a]Higher CSFQ-14 total scores indicate better 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.

- In both younger (<45 years) and older (≥45 years) subgroups of patients, lumateperone + ADT significantly improved CSFQ-14 total score from baseline to Day 43 compared with placebo + ADT (**Figure 4**)

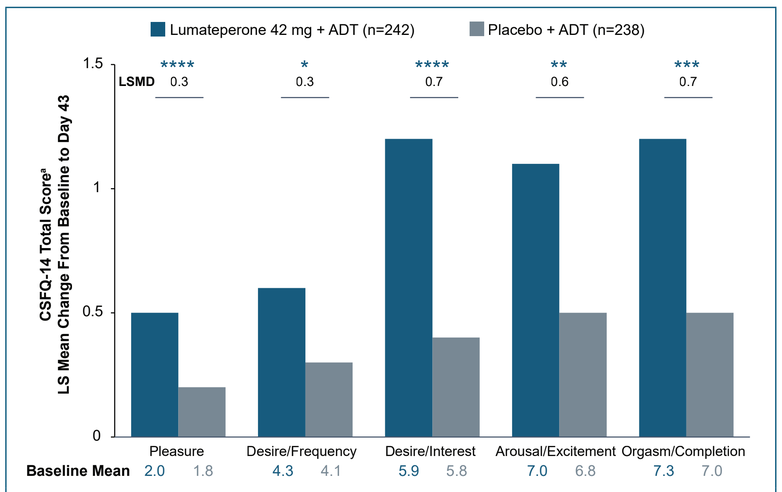
Figure 4. LS Mean Change From Baseline in CSFQ-14 Total Score by Age



*P<.05 ***P<.001. LSMD vs placebo. MMRM. ITT population.
[a]Higher CSFQ-14 total scores indicate better 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.

- Lumateperone + ADT significantly improved all CSFQ-14 domain scores (pleasure, desire/frequency, desire/interest, arousal/excitement, and orgasm/completion) at Day 43 compared with placebo + ADT (**Figure 5**)

Figure 5. LS Mean Change at Day 43 in CSFQ-14 Domain Scores



*P<.05 **P<.01 ***P<.001 ****P<.0001. LSMD vs placebo. MMRM. ITT population.
[a]Higher CSFQ-14 scores indicate better sexual functioning. The domain "Pleasure" consists of CSFQ-14 item 1 score; the domain "Desire/Frequency" is the sum of item 2 and item 3 scores; the domain "Desire/Interest" is the sum of item 4, item 5, and item 6 scores; the domain "Arousal/Excitement" is the sum of item 7, item 8, and item 9 scores; the domain "Orgasm/Completion" is the sum of item 11, item 12, and item 13 scores.
ADT, antidepressant therapy; CSFQ, Changes in Sexual Functioning Questionnaire 14-item version; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures.

CONCLUSIONS

- **Lumateperone 42 mg/day + ADT significantly improved sexual function compared with placebo + ADT, as measured by CFSQ-14 total score, in patients with MDD with inadequate ADT response**
  - **With lumateperone 42 mg/day + ADT, significant improvements in sexual function occurred across patient subgroups, including those with baseline sexual dysfunction, women, younger patients, and older patients**
  - **All CSFQ-14 domain scores significantly improved with lumateperone 42 mg/day + ADT versus placebo + ADT, demonstrating broad efficacy on sexual function**
- **These results indicate that lumateperone 42 mg/day adjunctive to ADT was not associated with treatment-related sexual dysfunction, supporting lumateperone 42 mg/day as a promising adjunctive treatment option in patients with MDD with inadequate ADT response**

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