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

Anita H. Clayton, MD[1]; Willie R. Earley, MD[2]; Susan G. Kozauer, MD[3]; Yifan Mo, PhD[2]; Betsy Yuan, PharmD, BCPP[2]; John B. Edwards, MD[2]; Suresh Durgam, MD[2]

[1]University of Virginia School of Medicine, Charlottesville, VA, USA; [2]Intra-Cellular Therapies, a Johnson & Johnson company, Bedminster, NJ, USA; [3]Former employee of Intra-Cellular Therapies, a Johnson & Johnson company, Bedminster, NJ, USA

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 an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of MDD in adults as adjunct to ADT[3]
  - Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission[4]
  - 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[4]
  - 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, randomized, double-blind, placebo-controlled, multicenter 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 favorable 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 randomized 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, analyzed 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
  - The ITT population included all randomized patients who received ≥1 dose of study drug and had a baseline MADRS Total score
  - 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 randomized 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**)

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

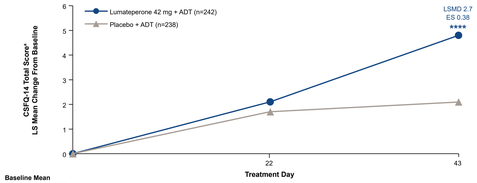
	Lumateperone 42 mg/day + ADT (n=242)	Placebo + ADT (n=238)
Demographic Parameters		
Age, mean (range), years	46 (18-65)	46 (18-65)
Sex, n (%)		
Women	169 (69.8)	165 (69.3)
Men	73 (30.2)	73 (30.7)
Race, n (%)		
White	235 (97.1)	223 (93.7)
Asian	1 (0.4)	3 (1.3)
Black	6 (2.5)	8 (3.4)
Other	0	4 (1.7)
Hispanic 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**)

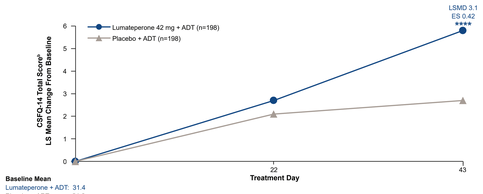
Figure 1. LS Mean Change From Baseline in CSFQ-14 Total Score



****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)

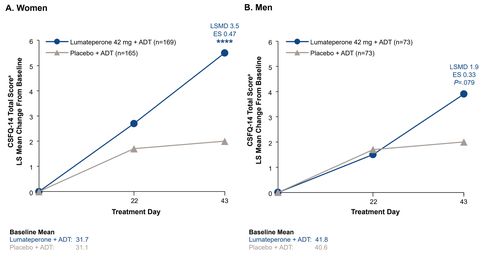
Figure 2. LS Mean Change From Baseline in CSFQ-14 Total Score in Patients With Baseline Sexual Dysfunction[a]



****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)

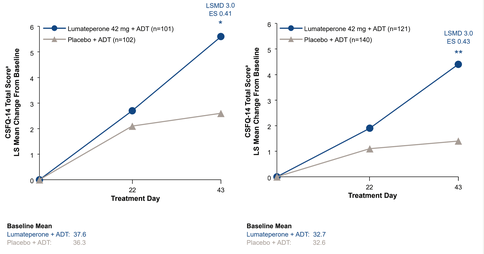
Figure 3. LS Mean Change From Baseline in CSFQ-14 Total Score by Sex



****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**)

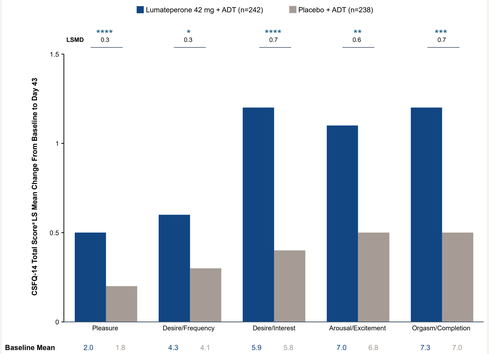
Figure 4. LS Mean Change From Baseline in CSFQ-14 Total Score by Age



*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; items 10 and 14 do not contribute to any domain score but they do impact the total score.
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

Acknowledgments
The authors thank all study investigators, research staff, and patients for their participation. Medical writing support was provided by Kendall Foote, PhD, of Nucleus Global, an Inizio company, funded by Intra-Cellular Therapies, a Johnson & Johnson company.

Disclosures
WR Earley, Y Mo, B Yuan, JB Edwards, and S Durgam are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company. SG Kozauer is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company.

AH Clayton has received grant funding from Janssen, Neumora Therapeutics, Neurocrine Biosciences, Otsuka, Relmada Therapeutics, Reunion Neuroscience, S1 Biopharma; has received consulting fees from AbbVie, Inc., ACCUMIN, Actinogen, AdhereTech, Axsome Therapeutics, Biogen, Inc., Fabre-Kramer, Initiator Pharma, Intra-Cellular Therapies Inc., Janssen Research & Development, LLC, LIVANOVA PLC, MycoMedica Life Sciences, PBC, Neumora Therapeutics, Inc., Neurocrine Biosciences, P/S/L Group Services, Reunion Neuroscience, S1 Biopharma, Seaport Therapeutics, Sertsei Pharmaceuticals, Inc., Vella Bioscience, Inc; has received royalties/copyright from Ballantine Books/Random House, Changes in Sexual Functioning Questionnaire, Guilford Publications; and may hold shares or restricted stock units in Medifilix LLC and S1 Biopharma.

Neuropsychiatry

Scan the QR code
The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Presented at the 29th Annual Meeting of the American Association of Psychiatric Pharmacists (AAPP), April 19-22, 2026, Seattle, WA

References:
1. Jacobsen P, et al. *J Sex Med*. 2019;16(10):1638-1649. 2. Rothmore J. *Med J Aust*. 2020;212(7):329-334. 3. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc;2025; 4. Titulaer J, et al. *Eur Neuropsychopharmacol*. 2022;62:22-35. 5. Durgam S, et al. *Am J Psychiatry*. 2025;182(12):1072-1082. 6. Keller A, et al. *J Sex Marital Ther*. 2006;32(1):43-52. 7. Clayton AH, et al. *Int Clin Psychopharmacol*. 2015;30(4):216-223.

Email questions to
Betsy Yuan at byuan18@its.jnj.com