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Supplementary Material

Article Title: Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder and Anxious Distress: Post Hoc Analysis of a Phase 3, Randomized, Double-Blind Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Methods. Institutional Review Boards/Independent Ethics Committees by Country

- Bulgaria: Ethics Committee for Clinical Trials, Sofia
- Czech Republic: Etická komise Fakultní nemocnice Královské Vinohrady (Ethics Committee of the Královské Vinohrady University Hospital), Prague; Etická komise (Ethics Committee) NZZ Research Site, s.r.o, Pilsen, and NZZ CLINTRIAL, s.r.o., Prague
- Hungary: Medical Research Council Ethics Committee For Clinical Pharmacology, Budapest
- India: Central Drugs Standard Control Organization, FDA Bhavan, ITO, Kotla Road, Ministry of Health and Family Welfare, New Delhi; Institutional Human Ethics Committee, GMERS Medical College and Hospital, Gotri; Hatkesh Healthcare Foundation Ethics Committee, Junagadh; Institutional Ethics Committee King Georges Medical University, Lucknow; Sangini Hospital Ethics Committee Sangini Hospital, Ahmedabad; Ethics Committee Vinaya Hospital, Vinaya Hospital and Research Centre, Mangaluru; Central Ethics Committee Nitte Deemed to be University, University Enclave Medical Sciences Complex Deralakatte, Mangalore; IEC Sardarmal Khandaka Memorial Hospital, Hatoj; Chethana Centre for Neuropsychiatry, Malaparamba; Magna-care Ethics Committee, Chopda Medicare and Research Centre Pvt. Ltd, Nashik; IEC Rughwani Child Care Centre and Hospital, Jaripatka; Institutional Ethics Committee Swagat, Swagat Hospital Pvt Ltd, Guwahati; Drug Trial Ethics Committee, Dayanand Medical College and Hospital, Ludhiana; MAHE Ethics Committee, Manipal; Institutional Ethics Committee TNMC NAIR HOSPITAL, Mumbai City; DMHC Ethics Committee, Varanasi; IEC-MMC and RI and Associated Hospital, Mysuru; Ethics Committee, Shanti Nursing Home Kanchanwadi, Aurangabad; Vivekananda Institutional Ethics Committee, Jaipur; YashSocietysSujata Birla Hospital Ethics Committee, Nashik
- Slovakia: Etická komisia samosprávneho kraja (Ethics Committee of the Self-Governing Region) for: Bratislava; Prešov; Banská Bystrica; Nitra; and Košice
- South Korea: Ministry of Food and Drug Safety (MFDS), Cheongju-si; IRB of Samsung Medical Center, Gangnam-gu, Seoul
- United States: WCG IRB, Princeton

Supplementary Table 1. Change in Efficacy Parameters (mITT Population)

Parameter	Patients With Anxious Distress				Patients Without Anxious Distress			
	Lumateperone 42 mg + ADT (n=109)	Placebo + ADT (n=98)	Comparison With Placebo		Lumateperone 42 mg + ADT (n=130)	Placebo + ADT (n=144)	Comparison With Placebo	
	LS Mean (SE) Change From Baseline to Day 43	LS Mean (SE) Change From Baseline to Day 43	LSMD (95% CI)	Effect Size; *P* Value	LS Mean (SE) Change From Baseline to Day 43	LS Mean (SE) Change From Baseline to Day 43	LSMD (95% CI)	Effect Size; *P* Value
MADRS Total score[a]	−15.6 (0.83)	−8.9 (0.86)	−6.8 (−9.00, −4.51)	0.85; *P*<.0001	−13.9 (0.74)	−10.4 (0.69)	−3.5 (−5.47, −1.58)	0.44; *P*<.001
MADRS inner tension item score[a]	−1.2 (0.12)	−0.5 (0.12)	−0.6 (−0.94, −0.32)	0.59; *P*<.001	−1.3 (0.10)	−0.8 (0.10)	−0.5 (−0.81, −0.28)	0.51; *P*<.001
CGI-S score[a]	−1.7 (0.10)	−0.8 (0.11)	−0.9 (−1.19, −0.62)	0.91; *P*<.0001	−1.5 (0.09)	−1.0 (0.09)	−0.5 (−0.74, −0.25)	0.50; *P*<.0001
QIDS-SR-16 Total score[b]	−9.3 (0.53)	−5.6 (0.54)	−3.7 (−5.01, −2.40)	0.80; *P*<.0001	−6.9 (0.46)	−5.7 (0.43)	−1.3 (−2.42, −0.14)	0.28; *P*<.05
GAD-7 Total score[c]	−5.5 (0.42)	−2.3 (0.43)	−3.2 (−4.29, −2.19)	0.88; *P*<.0001	−4.0 (0.37)	−3.6 (0.34)	−0.4 (−1.31, 0.50)	0.11; *P*=.379
	n (%)	n (%)	Odds Ratio (95% CI)	NNT; *P* Value	n (%)	n (%)	Odds Ratio (95% CI)	NNT; *P* Value
MADRS Total score response at Day 43[d,e]	57 (52.3)	17 (17.3)	5.1 (2.67, 9.62)	3; *P*<.0001	52 (40.0)	41 (28.5)	1.7 (1.00, 2.75)	9; *P*<.05
MADRS Total score remission at Day 43[d,f]	29 (26.6)	11 (11.2)	2.8 (1.34, 5.98)	7; *P*<.01	33 (25.4)	22 (15.3)	1.9 (1.04, 3.44)	10; *P*<.05

[a]Analyzed using an MMRM. [b]Analyzed using an ANCOVA in the ITT population (patients with anxious distress: lumateperone, n=110; placebo, n=99; patients without anxious distress: lumateperone, n=131; placebo, n=144). [c]Analyzed using an MMRM in the ITT population (patients with anxious distress: lumateperone, n=109; placebo, n=99; patients without anxious distress: lumateperone, n=131; placebo, n=144). [d]Analyzed using logistic regression. [e]Response defined as ≥50% decrease in MADRS Total score from baseline. [f]Remission defined as MADRS Total score ≤10.

Abbreviations: ADT, antidepressant therapy; ANCOVA, analysis of covariance; CGI-S, Clinical Global Impression–Severity; GAD-7, Generalized Anxiety Disorder-7 item; ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; NNT, number needed to treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Supplementary Table 2. Overview of TEAEs and Changes in Clinical Laboratory Parameters (Safety Population)

	Patients With Anxious Distress		Patients Without Anxious Distress	
	Lumateperone 42 mg + ADT (n=110) n (%)	**Placebo + ADT (n=99) n (%)**	**Lumateperone 42 mg + ADT (n=131) n (%)**	**Placebo + ADT (n=144) n (%)**
≥1 TEAE	69 (62.7)	43 (43.4)	71 (54.2)	70 (48.6)
Discontinued treatment due to AE	5 (4.5)	0	9 (6.9)	2 (1.4)
≥1 SAE	0	0	1 (0.8)	1 (0.7)
Death	0	0	0	0
TEAEs occurring in ≥5% of the lumateperone + ADT group and at least twice that of placebo + ADT,[a] n (%)				
Dry mouth	17 (15.5)	2 (2.0)	9 (6.9)	3 (2.1)
Fatigue	14 (12.7)	2 (2.0)	9 (6.9)	3 (2.1)
Tremor	8 (7.3)	1 (1.0)	4 (3.1)	0
EPS-related TEAEs per broad SMQ				
≥1 EPS-related TEAE	10 (9.1)	2 (2.0)	5 (3.8)	5 (3.5)
Tremor	8 (7.3)	1 (1.0)	4 (3.1)	0
Akathisia	3 (2.7)	0	0	1 (0.7)
Bradykinesia	0	0	1 (0.8)	0
Tongue spasm	1 (0.9)	0	0	0
Muscle tightness	0	2 (2.0)	0	0
Restlessness	0	0	0	2 (1.4)
Dyskinesia	0	0	0	1 (0.7)
Muscle spasms	0	0	0	1 (0.7)

	Patients With Anxious Distress						Patients Without Anxious Distress					
	Lumateperone 42 mg + ADT (n=110)			Placebo + ADT (n=99)			Lumateperone 42 mg + ADT (n=131)			Placebo + ADT (n=144)		
	n	Baseline mean (SD)	Mean (SD) change at EOT	n	Baseline mean (SD)	Mean (SD) change at EOT	n	Baseline mean (SD)	Mean (SD) change at EOT	n	Baseline mean (SD)	Mean (SD) change at EOT
Clinical laboratory parameters[b]												
Cholesterol, mg/dL												
Total	90	203.1 (47.43)	−12.9 (33.06)	80	202.7 (50.43)	−1.1 (34.97)	103	193.7 (37.77)	−9.7 (30.31)	117	197.8 (44.89)	−2.4 (27.06)
HDL	90	57.4 (19.00)	0.3 (13.62)	80	59.0 (16.36)	−1.0 (11.28)	103	53.0 (16.55)	−1.0 (10.04)	117	56.5 (16.81)	0.1 (9.08)
LDL	90	140.3 (42.40)	−10.9 (29.40)	80	137.9 (52.86)	1.1 (36.14)	103	135.1 (38.18)	−10.0 (29.71)	117	137.9 (42.96)	−3.0 (26.84)
Triglycerides, mg/dL	90	131.7 (75.41)	−7.4 (60.10)	80	138.8 (84.08)	0.2 (66.65)	103	129.6 (74.71)	−0.8 (67.56)	117	122.0 (69.40)	−0.2 (51.95)
Glucose, mg/dL	90	93.5 (13.53)	1.8 (13.24)	79	96.4 (19.05)	1.5 (22.67)	103	87.7 (10.91)	2.8 (11.94)	115	93.2 (14.62)	−0.4 (11.52)
Insulin, mIU/L	89	12.5 (13.38)	1.7 (18.53)	81	13.4 (13.99)	1.7 (23.15)	101	11.6 (9.12)	0.8 (9.20)	115	11.2 (7.52)	2.3 (12.75)
Prolactin, ng/mL	90	9.4 (8.42)	1.5 (8.10)	80	8.8 (5.66)	0.9 (4.60)	103	11.4 (9.85)	0.1 (9.21)	116	9.2 (8.18)	1.2 (5.07)

[a]Based on the overall safety population. [b]Change from baseline to last on-treatment value, under fasted conditions. Baseline was defined as the last non-missing measurement before the first dose of double-blind study treatment. The last on-treatment value was defined as the last non-missing value after the date of the first dose of double-blind study treatment and on/or before the last dose of treatment plus 1 day.

Abbreviations: ADT, antidepressant therapy; AE, adverse event; EOT, end of treatment; EPS, extrapyramidal symptom; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.