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Lumateperone for the Treatment of Major Depressive Disorder With Mixed Features or Bipolar Depression With Mixed Features

A Randomized Placebo-Controlled Trial

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Abstract:

Background: This randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov identifer NCT04285515) evaluated efficacy and safety of lumateperone to treat major depressive episodes (MDEs) associated with major depressive disorder (MDD) or bipolar depression with mixed features.

Procedures: Patients (18–75 years) with Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)–defined MDD with mixed features (n = 185) or bipolar disorder with mixed features (n = 200) and experiencing an MDE were randomized 1:1 to 6-week placebo (n = 195) or lumateperone 42 mg (n = 193). Primary and key secondary endpoints were change from baseline to day 43 in Montgomery-Åsberg Depression Rating Scale Total and Clinical Global Impression Scale-Severity (CGI-S) scores in 3 populations with combined MDD/bipolar depression, individual MDD, and individual bipolar depression. Safety included adverse events (AEs), extrapyramidal symptoms, and laboratory parameters.

Results: Lumateperone met the primary endpoint, significantly improving Montgomery-Åsberg Depression Rating Scale total score at day 43 in populations with combined MDD/bipolar depression (least squares mean difference vs placebo [LSMD], −5.7; 95% confidence interval [CI], −7.60, −3.84; effect size [ES], −0.64; $P < 0.0001$), MDD (LSMD, −5.9; 95% CI, −8.61,−3.29; ES, −0.67; $P < 0.0001$), and bipolar depression (LSMD, −5.7; 95% CI, −8.29,−3.05; ES, −0.64; $P < 0.0001$). Lumateperone significantly improved CGI-S and Young Mania Rating Scale total scores at day 43 in these populations. Lumateperone was well-tolerated. Treatment-emergent AEs (≥5%, twice placebo) in the combined population were somnolence (placebo, 1.6%; lumateperone, 12.5%), dizziness (placebo, 2.1%; lumateperone, 12.0%), and nausea (placebo, 1.6%; lumateperone, 9.9%). There were no mania/hypomania treatment-emergent AEs with lumateperone and minimal extrapyramidal symptoms or metabolic risk.

Conclusions: Lumateperone 42 mg significantly improved depression symptoms and disease severity and was generally safe and well-tolerated in patients with MDD or bipolar depression with mixed features.

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Major depressive disorder (MDD) and bipolar disorder are serious mental illnesses associated with debilitating depressive episodes that reduce quality of life.[1,2] Approximately 25%–35% of patients with MDD or bipolar depression experience major depressive episodes (MDEs) with complex clinical presentations meeting mixed features criteria.[3] The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and DSM-5 Text Revision define the mixed features specifier in MDD or bipolar depression as ≥3 of 7 manic/hypomanic symptoms (elevated mood, inflated self-esteem, hypertalkative, racing thoughts, increased energy/goal-directed activity, increased activity with potential painful consequences, and decreased need for sleep) during the majority of days of the current or most recent MDE.[4,5] Patients with mixed features are challenging to treat and have greater symptom severity, increased comorbidities, and heightened risk of suicide compared with patients without mixed features.[3,6,7] Previously, a post hoc analysis of a placebo-controlled trial (ClinicalTrials.gov identifer NCT03249376) demonstrated efficacy of lumateperone in patients with bipolar depression with or without mixed features using Young Mania Rating Scale (YMRS) total score as a proxy for mixed features.[8,9]

Lumateperone (lumateperone tosylate, ITI-007), a mechanistically novel antipsychotic, is US Food and Drug Administration approved for the treatment of schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate.[10,11] Lumateperone simultaneously modulates key neurotransmitters implicated in serious mental illness[11,12] as 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 AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartate) currents, and a serotonin reuptake inhibitor.[11,12] Lumateperone exerts negligible binding (K_i > 100 nM) to H_1 histaminergic, 5-HT_{2C}, and muscarinic receptors, which minimizes the potential for adverse cognitive effects and metabolic disturbances including weight gain.[11] Additionally, lumateperone has a unique ~60-fold separation between affinities for 5-HT_{2A} (K_i 0.5 nM) and D_2 (K_i 32 nM), and a lower striatal D_2 receptor occupancy compared with other antipsychotics (39% vs 65%–80%) at clinically relevant doses, along with D_2 presynaptic partial agonist activity, which is thought to limit the risk of extrapyramidal symptoms (EPS).[11,13] While several antipsychotics are approved to treat bipolar I depression (lumateperone,[10] cariprazine,[14] quetiapine,[15,16] lurasidone[17]), only quetiapine[15,16] and lumateperone[10] are approved to treat both bipolar I and bipolar II depression.[18]

Here, we report the first randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of lumateperone 42 mg to treat MDEs associated with MDD or bipolar disorder in patients with DSM-5–defined mixed features.

MATERIALS AND METHODS

Patients

A protocol amendment (2.0) in November 2020 was implemented to investigate monotherapy in patients with MDEs associated with MDD with mixed features or bipolar depression with mixed features. Additional information on the protocol amendment and rationale is in the Supplemental Digital Content, http://links.lww.com/JCP/A941 (overall study population results). Patients with mixed features are the focus of this report; thus, patients randomized before the protocol amendment and not evaluated for mixed features criteria were not included in the modified intent-to-treat (mITT) population. Analyses in the overall population, including all patients randomized before and after the protocol amendment, and analyses in only patients randomized before the amendment are in the Supplemental Digital Content (overall study population results, change in efficacy parameters).

After protocol amendment 2.0, eligible males and females aged 18–75 years had MDD with mixed features or bipolar I or bipolar II disorder with mixed features meeting DSM-5 criteria, confirmed using the Mini International Neuropsychiatric Interview. A depressive episode with mixed features was defined as ≥3 manic/hypomanic symptoms during the majority of days of the current or most recent MDE without meeting full mania/hypomania criteria, according to the DSM-5.[4] Patients needed to experience an MDE beginning ≥2 weeks and ≤6 months before screening and causing clinically significant distress or functional impairment. At screening and baseline, patients' depression symptoms needed to be at least moderate severity (Montgomery-Åsberg Depression Rating Scale [MADRS][19] total score ≥24 and Clinical Global Impression Scale-Severity [CGI-S] score ≥4) with YMRS total score 4–16, inclusive.

Patients were excluded if there was a ≥25% MADRS total score decrease between screening and baseline (to minimize the placebo response), a significant risk for suicidal behavior, or any confirmed psychiatric illness other than MDD or bipolar disorder within 12 months of screening. Patients experiencing hallucinations, delusions, or any other psychotic symptomatology in the current MDE were excluded if those symptoms were attributable to a primary DSM-5 diagnosis other than MDD or bipolar disorder. Full criteria can be found in the Supplemental Digital Content, http://links.lww.com/JCP/A941 (Inclusion and Exclusion Criteria).

Study Design

This randomized, double-blind, placebo-controlled, multicenter study (NCT04285515) conducted globally at 49 sites included a 2-week screening period, 6-week double-blind treatment period, and 2-week safety follow-up period. Patients were stratified by MDD or bipolar disorder diagnosis; those with bipolar disorder were further stratified by bipolar I or bipolar II diagnosis. At baseline, patients were randomized 1:1 using an interactive voice response system/interactive web response system to 6-week lumateperone 42 mg or placebo. Independent external biostatistics personnel not participating in any study conduct generated a permuted block randomization schedule for the system using sequential patient randomization numbers. All study drugs were administered orally via capsule once daily; treatments were identical in appearance (eg, color, size, shape, taste) and supplied in identical treatment cards and packaging. The study team remained blinded from the treatment assignment throughout the study. Efficacy and safety assessments occurred at baseline and weekly clinic visits (Days 8, 15, 22, 29, 36, and 43; all visits ±1 day), and safety follow-up was on day 57. The study was approved by the appropriate institutional review board/independent ethics committee and performed in accordance with the Declaration of Helsinki, in compliance with Good Clinical Practice guidelines. Written informed consent was obtained from each patient before entering the study.

Assessments

The primary and key secondary efficacy measures were MADRS total score and CGI-S score, respectively. Additional efficacy measures were YMRS total score, response (≥50% MADRS total score decrease from baseline), and remission (MADRS total score ≤10 or ≤12). Safety was assessed by adverse events (AEs) coded with Medical Dictionary for Regulatory Activities (MedDRA) version 22.1, clinical laboratory measurements, vital signs, and electrocardiogram results. Treatment-emergent AEs (TEAEs) were AEs that occurred or worsened in severity after the first study medication dose and on/before the date of last study medication dose +1 day. Mania was evaluated using YMRS total score and AEs. Suicidality was monitored by the Columbia-Suicide Severity Rating Scale (C-SSRS) and AEs. EPS were measured with the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale (SAS), and by AEs. Treatment compliance was measured as the total number of capsules taken multiplied by 100, out of the total number of capsules prescribed.

Statistical Analyses

Primary and key secondary endpoints were analyzed in the mITT population, defined as all randomized patients who received ≥1 dose of study drug, had a valid predose assessment, had ≥1 valid postbaseline MADRS assessment, and were randomized after protocol amendment 2.0. The primary and key secondary efficacy endpoints were mean change from baseline to day 43 in MADRS total score and CGI-S score, respectively, analyzed in 3 patient populations with mixed features: combined MDD/bipolar depression population, individual MDD population, and individual bipolar depression population. Additional endpoints included mean change from baseline in MADRS total score, CGI-S score, and YMRS total score by-visit. Primary and key secondary endpoints were analyzed using a mixed-effect model for repeated measures (MMRM) and a fixed-sequence strategy combined with Hochberg procedure (0.05 level). An unstructured covariance matrix was used to estimate the covariance among repeated measurements within a patient. Response and remission were analyzed with a logistic regression model. YMRS total score was analyzed as a post hoc efficacy measure using an MMRM similar to the primary and secondary endpoints. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Safety parameters were summarized descriptively in all patients who were randomized and received ≥1 dose of study drug.

In each treatment group, ~175 patients were expected to have evaluable data. The study was designed to have 90% power to detect a 0.37 effect size in the combined MDD/bipolar depression population, corresponding to a 3.3-point difference in change from baseline to day 43 in MADRS total score between lumateperone and placebo (2-sided significance level 0.05). Additional statistical methods are reported in the Supplemental Digital Content (Supplementary Methods), http://links.lww.com/JCP/A941.

RESULTS

Patient Population

Of the 558 patients with MDD with mixed features or bipolar depression with mixed features screened for eligibility after protocol amendment 2.0, 388 were randomized (placebo, 195; lumateperone, 193), and 385 received ≥1 dose of study treatment and were included in the safety population (Fig. 1). The proportion of patients with MDD or bipolar depression was similar. The mITT population comprised 383 patients with either MDD with mixed features (placebo, 92; lumateperone, 92) or bipolar depression with mixed features (placebo, 99; lumateperone, 100).

The majority of patients with MDD (placebo, 81 [87%]; lumateperone, 85 [92%]) or bipolar depression (placebo, 93 [93%]; lumateperone, 85 [85%]) completed the double-blind treatment period (Fig. 1). The most common reasons for treatment discontinuation were withdrawal of consent and AEs in patients with MDD or bipolar depression, respectively. The patient disposition in the overall population, including patients randomized before and after the protocol amendment, is in Supplemental Digital Content Table S1, http://links.lww.com/JCP/A941.

Baseline demographics and characteristics were similar between treatment groups and between patients with MDD or bipolar depression with mixed features (Table 1). Most patients in the safety population were White (324 [84.2%]) and female (238 [61.8%]), and the mean age was 43 years. Mean MADRS total score of 31.2 and mean CGI-S score of 4.5 at baseline indicate moderate-to-severe depressive symptoms before receiving treatment for the combined population.[20] Baseline mean CGI-S score (range 4.4–4.6) and YMRS total scores (range 8.7–9.3) were similar between groups. Mean treatment compliance was 100% in the placebo group and 99% in the lumateperone group.

Efficacy

In the combined MDD/bipolar depression population with mixed features, lumateperone 42 mg significantly reduced MADRS total score from baseline to day 43 compared with placebo (least squares [LS] mean change = −18.1; LS mean difference vs placebo [LSMD] = −5.7; 95% CI = −7.60, −3.84; effect size [ES] = −0.64; $P < 0.0001$; Figure 2A, Supplemental Digital Content Table S2, http://links.lww.com/JCP/A941). There were also significant improvements with lumateperone in MADRS total score at day 43 in the individual MDD population (LS mean change = −18.2; LSMD = −5.9; 95% CI = −8.61, −3.29; ES = −0.67; $P < 0.0001$; Fig. 2B, Supplemental Digital Content Table S2) and individual bipolar depression population (LS mean change = −17.7; LSMD = −5.7; 95% CI = −8.29, −3.05; ES = −0.64; $P < 0.0001$; Fig. 2C, Supplemental Digital Content Table S2). These 3 primary comparisons were statistically significant with overall control for multiplicity (0.05 level).

MADRS response (≥50% decrease from baseline) rate at day 43 was significantly greater with lumateperone vs placebo in the combined MDD/bipolar depression population (placebo, 78 [40.8%]; lumateperone, 114 [59.4%]; $P = 0.0003$) and in the MDD population (placebo, 36 [39.1%]; lumateperone, 58 [63.0%]; $P = 0.0011$), with numerical improvement in the bipolar depression population (placebo, 42 [42.4%]; lumateperone, 56 [56.0%]; $P = 0.0518$). Remission (MADRS total score ≤10) rate at day 43 was significantly higher with lumateperone vs placebo in the combined MDD/bipolar depression population (placebo, 38 [19.9%]; lumateperone, 74 [38.5%]; $P < 0.0001$), MDD population (placebo, 19 [20.7%]; lumateperone, 37 [40.2%]; $P = 0.0046$), and bipolar depression population (placebo, 19 [19.2%]; lumateperone, 37 [37.0%]; $P = 0.0036$).

Lumateperone significantly improved CGI-S score from baseline to day 43 vs placebo in the combined MDD/bipolar depression population (LS mean change = −1.8; LSMD = −0.6; 95% CI = −0.81, −0.39; ES = −0.59; $P < 0.0001$; Fig. 2D, Supplemental Digital Content Table S2, http://links.lww.com/JCP/A941). Similarly, lumateperone significantly reduced CGI-S score at day 43 from baseline vs placebo in the MDD population (LS mean change = −1.7; LSMD = −0.6; 95% CI = −0.89, −0.27; ES = −0.57; $P = 0.0003$; Fig. 2E, Supplemental Digital Content Table S2) and bipolar depression population (LS mean change = −1.8; LSMD = −0.6; 95% CI = −0.91, −0.31; ES = −0.61; $P < 0.0001$; Fig. 2F, Supplemental Digital Content Table S2). These 3 key secondary comparisons were statistically significant with overall control for multiplicity (0.05 level).

The significant reductions in MADRS total score and CGI-S score occurred by day 15 and persisted throughout the study in all 3 populations (Fig. 2).

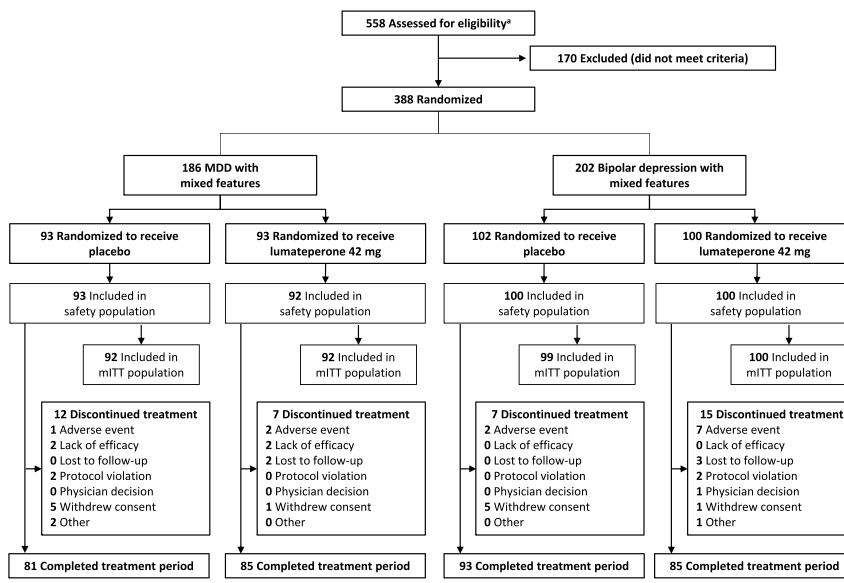

FIGURE 1. Patient disposition. [a] Patients enrolled after protocol amendment 2.0.

TABLE 1. Descriptive Baseline Demographics and Disease Characteristics

	Combined MDD/Bipolar Depression Population		MDD Population		Bipolar Depression Population	
	Placebo	Lumateperone 42 mg	Placebo	Lumateperone 42 mg	Placebo	Lumateperone 42 mg
Demographic parameters, safety population	**(n = 193)**	**(n = 192)**	**(n = 93)**	**(n = 92)**	**(n = 100)**	**(n = 100)**
Age, mean (SD), years	43 (14.0)	43 (14.7)	45 (14.8)	44 (15.0)	41 (12.9)	42 (14.3)
Sex, n (%)						
Female	119 (61.7)	119 (62.0)	55 (59.1)	55 (59.8)	64 (64.0)	64 (64.0)
Male	74 (38.3)	73 (38.0)	38 (40.9)	37 (40.2)	36 (36.0)	36 (36.0)
Race, n (%)						
White	156 (80.8)	168 (87.5)	76 (81.7)	82 (89.1)	80 (80.0)	86 (86.0)
Black	33 (17.1)	22 (11.5)	14 (15.1)	8 (8.7)	19 (19.0)	14 (14.0)
Other*	4 (2.1)	2 (1.0)	3 (3.2)	2 (2.2)	1 (1.0)	0
Hispanic or Latino ethnicity, n (%)	18 (9.3)	18 (9.4)	14 (15.1)	11 (12.0)	4 (4.0)	7 (7.0)
Diagnosis, n (%)						
Bipolar I disorder	79 (40.9)	78 (40.6)	0	0	79 (79.0)	78 (78.0)
Bipolar II disorder	21 (10.9)	22 (11.5)	0	0	21 (21.0)	22 (22.0)
MDD	93 (48.2)	92 (47.9)	93 (100.0)	92 (100.0)	0	0
Age at first diagnosis, mean (SD), years	NA	NA	33 (13.2)	34 (12.7)	30 (10.0)	30 (12.0)
No. lifetime depressive episodes, n (%)						
1–9	NA	NA	87 (93.5)	81 (88.0)	85 (85.0)	86 (86.0)
10–20	NA	NA	4 (4.3)	10 (10.9)	13 (13.0)	9 (9.0)
>20	NA	NA	2 (2.2)	1 (1.1)	1 (1.0)	4 (4.0)
Baseline efficacy parameters, mITT population	**(n = 191)**	**(n = 192)**	**(n = 92)**	**(n = 92)**	**(n = 99)**	**(n = 100)**
MADRS total score, mean (SD)	31.1 (4.07)	31.3 (4.05)	31.2 (4.16)	30.8 (3.59)	31.1 (4.01)	31.8 (4.40)
CGI-S score, mean (SD)	4.5 (0.52)	4.5 (0.54)	4.4 (0.48)	4.4 (0.52)	4.6 (0.54)	4.6 (0.55)
YMRS total score, mean (SD)	9.2 (2.46)	9.0 (2.40)	9.3 (2.09)	9.3 (2.24)	9.1 (2.76)	8.7 (2.52)

*Other includes Asian, other, or multiple.

In the combined MDD/bipolar depression population with mixed features, lumateperone significantly improved YMRS total score from baseline to day 43 compared with placebo (LS mean change = −6.0; LSMD = −1.9; 95% CI = −2.49, −1.22; ES = −0.62; $P < 0.0001$; Fig. 3A, Supplemental Digital Content Table S2, http://links.lww.com/JCP/A941). Similarly, lumateperone significantly reduced YMRS total score in the individual MDD population (LS mean change = −6.3; LSMD = −2.1; 95% CI = −2.90, −1.20; ES = −0.74; $P < 0.0001$; Fig. 3B, Supplemental Digital Content Table S2) and in the individual bipolar depression population (LS mean change = −5.6; LSMD = −1.6; 95% CI = −2.52, −0.64; ES = −0.51; $P = 0.0011$; Fig. 3C, Supplemental Digital Content Table S2) at day 43 vs placebo. YMRS total score was significantly reduced by day 8 in the combined MDD/bipolar depression and individual MDD populations and by day 15 in the individual bipolar depression population, with significant improvements persisting throughout the study (Fig. 3).

Safety

Rates of TEAEs were higher with lumateperone vs placebo in the combined MDD/bipolar depression population (placebo, 72 [37.3%]; lumateperone, 104 [54.2%]), and the individual populations with MDD or bipolar depression (Table 2). The most common TEAEs of somnolence, dizziness, and nausea occurred at similar frequencies among the MDD and bipolar depression populations (Table 2). For the bipolar depression population only, dry mouth and fatigue were also common TEAEs. Most TEAEs (≥99%) reported were of mild or moderate severity in the combined MDD/bipolar depression population, MDD population, and bipolar depression population. One patient (lumateperone group) reported a severe nausea TEAE and a severe vomiting TEAE that led to discontinuation. Nine patients (4.7%) in the lumateperone group and 3 patients (1.6%) in the placebo group discontinued treatment because of AEs. No AEs leading to treatment discontinuation occurred in >1 patient except 2 patients who discontinued because of insomnia (placebo group). No patients died during the study.

According to the C-SSRS, suicidal behavior did not occur during treatment in any group and emergence of suicidal ideation was similar between treatment groups (combined MDD/bipolar depression population: placebo, 8 [4.2%]; lumateperone, 6 [3.1%]). In the combined MDD/bipolar depression population, 2 patients (1.0%) in each treatment group experienced TEAEs of suicidal ideation.

No meaningful changes in EPS-related measurements occurred, including AIMS, BARS, and SAS total scores (Supplemental Digital Content Table S3, http://links.lww.com/JCP/A941). Incidence of akathisia based on a shift from baseline BARS score from ≤2 to >2 at any point during the treatment period was rare (0.5% both groups), as was incidence of Parkinsonism based on a shift in AIMS score (0 to >0; placebo, 1.6%; lumateperone, 0.5%) or SAS score (≤3 to >3; 0.5% both groups) (Supplemental Digital Content Table S3).

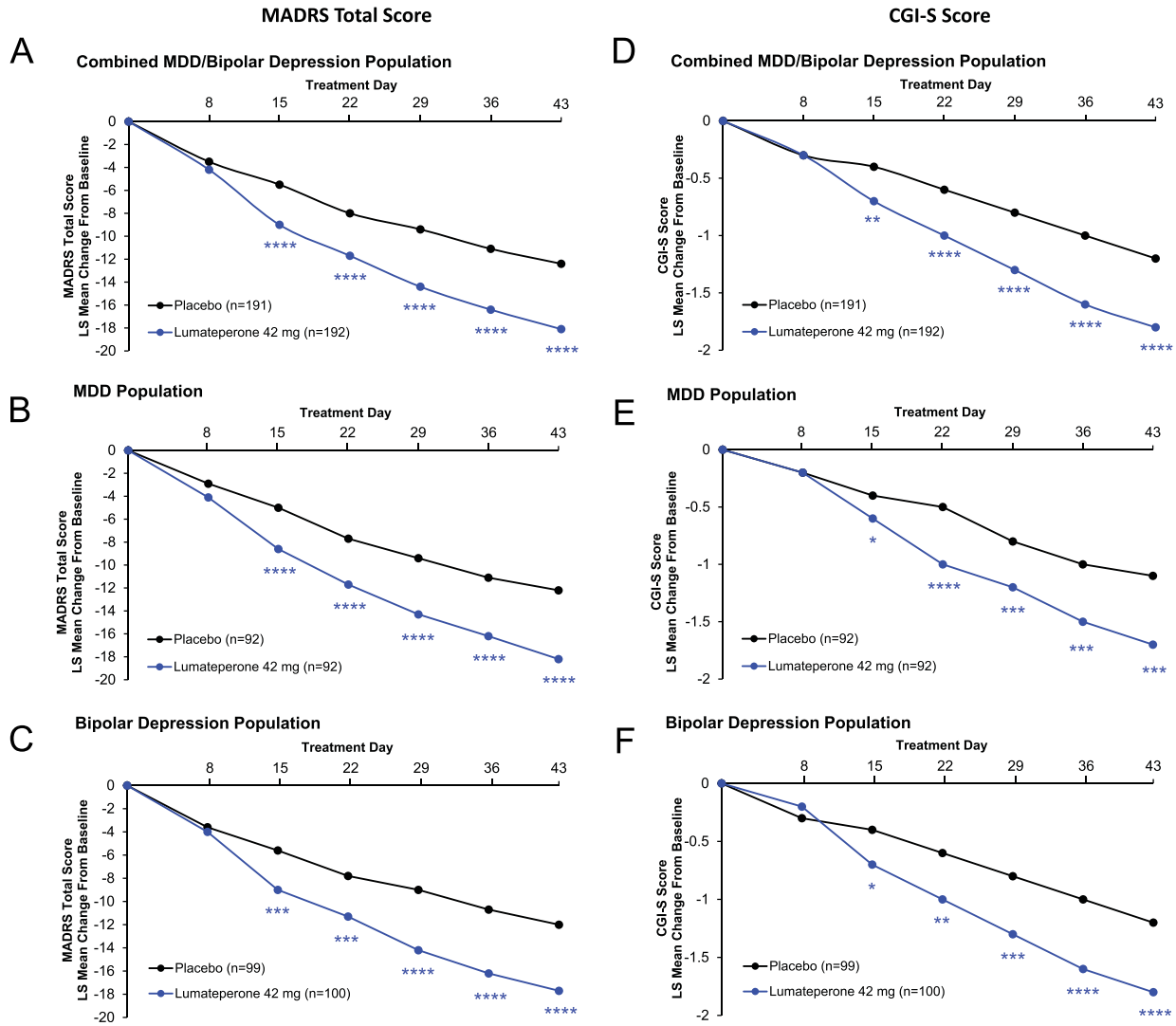

FIGURE 2. LS mean change from baseline in MADRS total score (A–C) and CGI-S score (D–F) in populations with mixed features (mITT population). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. LSMD versus placebo. MMRM.

The only EPS-related TEAE per narrow standard MedDRA query was mild akathisia in 1 patient (MDD, lumateperone group). The incidence of EPS-related TEAEs was also low according to broad standard MedDRA query in the combined MDD/bipolar depression population (placebo, 2 [1.0%]; lumateperone, 8 [4.2%]).

There were no TEAEs of mania/hypomania reported in the combined MDD/bipolar depression population. With lumateperone, there were no meaningful changes in weight, body morphology, total cholesterol, glucose, insulin, or prolactin (Supplemental Digital Content Table S4). Potentially clinically significant weight increase (≥7% from baseline) occurred in 1 patient each in the placebo and lumateperone groups (Supplemental Digital Content Table S4, http://links.lww.com/JCP/A941). One patient with bipolar depression had elevated triglyceride levels at day 43 (2284 mg/dL [1 mg/dL = 0.113 mmol/L]) because of recent diet changes; with counseling, the levels resolved by the follow-up visit (96 mg/dL). Upon exclusion of this patient, there were no clinically meaningful changes in triglyceride levels (Supplemental Digital Content Table S4). No patients had a QT Fridericia-corrected interval ≥480 ms or an increase of >60 ms from baseline, and no patients met criteria for Hy's Law.

DISCUSSION

In this 6-week, randomized, double-blind, placebo-controlled, multicenter trial, lumateperone 42-mg treatment significantly improved symptoms of depression and disease severity compared with placebo in patients with MDD with mixed features or bipolar depression with mixed features. This is the first study investigating lumateperone in patients with MDD or bipolar depression with mixed features meeting DSM-5 criteria. The efficacy of lumateperone observed in this trial is clinically meaningful and consistent with that reported in other short-term trials of lumateperone in bipolar depression.[8,21] The safety profile was favorable, and lumateperone was generally well tolerated.

The definition of mixed features has varied over time, and an accurate diagnosis is important because MDEs with mixed features correspond to a more severe illness compared with that of purely depressive episodes.[22–24] A meta-analysis across 5 second-generation antipsychotics demonstrated significant improvements in depression symptoms and manic/hypomanic symptoms of mixed bipolar depression (defined by either YMRS proxy or DSM-based criteria), highlighting favorable outcomes with

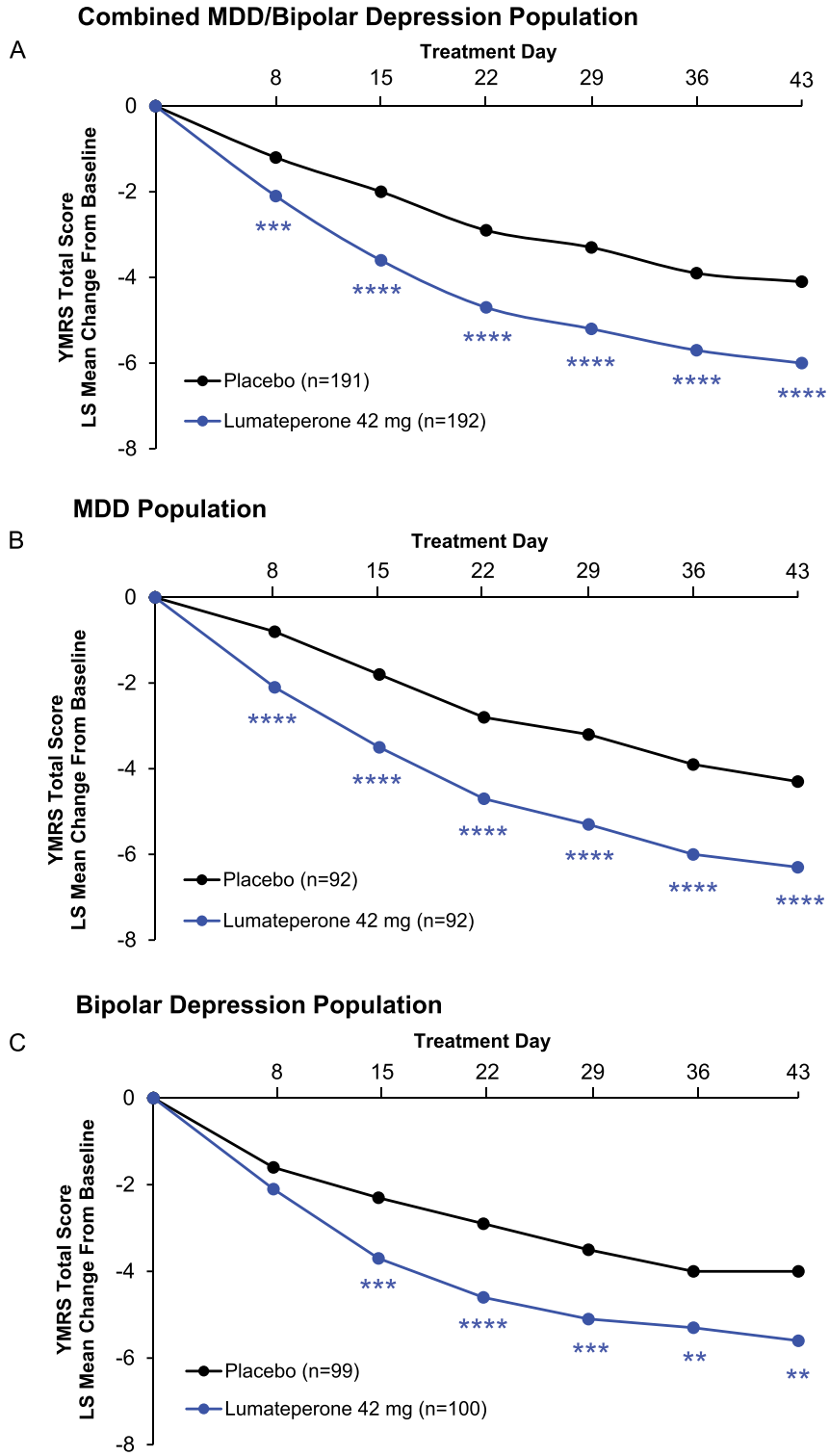

FIGURE 3. LS mean change from baseline in YMRS total score in (A) combined MDD/bipolar depression, (B) MDD, and (C) bipolar depression populations with mixed features (mITT population). $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. LSMD versus placebo. MMRM.

second-generation antipsychotics vs placebo in this population.[25] Previously, the efficacy of lumateperone was demonstrated in a post hoc analysis of patients with bipolar depression with mixed features categorized by baseline YMRS total score.[9] Lumateperone treatment was generally well tolerated and resulted in similar TEAE rates between patients with and without mixed features defined by baseline YMRS total score.[8,9] In other post hoc analyses of patients with bipolar depression and mixed features defined by baseline YMRS total score, lurasidone[26] and cariprazine[27] significantly improved MADRS total score. In analyses defining mixed features

TABLE 2. Summary of Adverse Events (Safety Population)

	Combined MDD/Bipolar Depression Population		MDD Population		Bipolar Depression Population	
	Placebo (n = 193)	Lumateperone 42 mg (n = 192)	Placebo (n = 93)	Lumateperone 42 mg (n = 92)	Placebo (n = 100)	Lumateperone 42 mg (n = 100)
≥1 TEAE	72 (37.3)	104 (54.2)	30 (32.3)	47 (51.1)	42 (42.0)	57 (57.0)
Drug-related TEAE	38 (19.7)	81 (42.2)	16 (17.2)	38 (41.3)	22 (22.0)	43 (43.0)
Discontinued due to AE	3 (1.6)	9 (4.7)	1 (1.1)	2 (2.2)	2 (2.0)	7 (7.0)
SAE	1 (0.5)	0	1 (1.1)	0	0	0
Patients who died	0	0	0	0	0	0
TEAEs occurring in ≥ 5% of the lumateperone group and more than twice that of placebo*						
Somnolence	3 (1.6)	24 (12.5)	1 (1.1)	11 (12.0)	2 (2.0)	13 (13.0)
Dizziness	4 (2.1)	23 (12.0)	4 (4.3)	11 (12.0)	0	12 (12.0)
Nausea	3 (1.6)	19 (9.9)	1 (1.1)	10 (10.9)	2 (2.0)	9 (9.0)

Data are presented as n (%). *For the bipolar depression population only, dry mouth (placebo, 2 [2.0%]; lumateperone, 5 [5.0%]) and fatigue (placebo, 1 [1.0%]; lumateperone, 5 [5.0%]) also met the criteria.

AE, adverse event; TEAE, treatment-emergent AE.

by the number of baseline manic symptoms, significant improvements in MADRS total score were reported with lurasidone in MDD with mixed features[28] and olanzapine in bipolar I depression with mixed features,[29] with no statistically significant difference between olanzapine + fluoxetine combination versus olanzapine.[30] In a 6-week acute depressive mixed state study (defined by DSM-IV criteria) in patients with MDD and bipolar II depression, ziprasidone demonstrated efficacy vs placebo for change in MADRS total score.[31] The interpretation of the results across these studies in patients with MDD or bipolar depression with mixed features is limited because of differences in proxy used to define mixed features, which vary between baseline YMRS total score (YMRS ≥4), number of manic symptoms, and DSM criteria.[22]

In this study, which used DSM-5–defined mixed features, lumateperone significantly improved symptoms of depression and disease severity by day 15 with continued significant improvement throughout the study. In addition to significant improvements in the combined MDD/bipolar depression population, lumateperone 42 mg significantly improved MADRS total score and CGI-S score in the individual populations of MDD and bipolar depression with mixed features. MADRS response and remission rates were significantly greater with lumateperone vs placebo in the combined MDD/bipolar depression population, further highlighting the efficacy of lumateperone in these patients.

Identifying an optimal treatment strategy in patients with mixed depression can be challenging because of the risk of treatment-induced mood switching.[7,32] In this study, lumateperone significantly reduced YMRS total score in patients with MDD or bipolar depression with mixed features, with significant improvements beginning by day 8 in the combined MDD/bipolar depression and individual MDD populations and by day 15 in the individual bipolar depression population, and persisting throughout the study. Additionally, no TEAEs of mania/hypomania were reported with lumateperone.

The favorable safety of lumateperone observed in this trial is consistent with that reported in other short-term lumateperone trials in bipolar depression[8,21] and schizophrenia,[33–35] including similar TEAEs among trials. Here, the most common TEAEs in the combined MDD/bipolar depression population were somnolence (placebo, 1.6%; lumateperone, 12.5%), dizziness (placebo, 2.1%; lumateperone, 12.0%), and nausea (placebo, 1.6%; lumateperone, 9.9%). This trial is the first report of lumateperone in patients with MDD or bipolar depression with mixed features, and no new safety signals were identified. Emergence of suicidal ideation was low and similar to that of placebo, and suicidal behavior did not occur in any group.

Many approved antipsychotics have adverse side effects, including weight gain, metabolic disturbances, and EPS.[36] These side effects can be exacerbated in patients with mixed features, who have a heightened risk of comorbidities compared with those without mixed features.[3] Additionally, preliminary evidence suggests that mixed features is associated with obesity.[37,38] In this study, there were no meaningful changes in EPS scales or metabolic parameters with lumateperone in patients with MDD or bipolar depression with mixed features.

A limitation of the study is excluding patients with treatment-resistant illness, imminent suicidal risk, or some comorbid psychiatric illnesses other than bipolar disorder or MDD, which may limit the generalizability of the findings. An additional limitation is the short-term duration of the study, which may not capture safety risks associated with long-term use. Although functional unblinding may occur during clinical trials because of differing AE profiles, sensitivity analyses that excluded mITT patients who experienced most common TEAEs with lumateperone still demonstrated significant and robust MADRS total score improvement with lumateperone vs placebo at day 43, indicating no functional unblinding.

CONCLUSIONS

Lumateperone 42 mg demonstrated clinically meaningful and statistically significant improvements in symptoms of depression, disease severity, and subsyndromal manic symptoms in patients with MDD with mixed features or bipolar depression with mixed features. Lumateperone was generally well tolerated with a favorable safety profile and did not induce mania. These results support lumateperone 42 mg as a promising treatment for MDEs in MDD with mixed features or bipolar disorder with mixed features.

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AUTHOR DISCLOSURE INFORMATION

S.D, S.G.K., W.R.E., C.C., J.H., and H.L. are full-time employees of Intra-Cellular Therapies, Inc, and may hold equity in the company.

S.S. has served as a consultant to Acadia, Alkermes, Allergan, AbbVie, Arbor Pharmaceuticals, Axovant, Axsome, Celgene, Concert, Clearview, EMD Serono, Eisai Pharmaceuticals, Ferring, Impel NeuroPharma, Intra-Cellular Therapies Inc., Ironshore Pharmaceuticals, Janssen, Karuna, Lilly, Lundbeck, Merck, Otsuka, Pfizer, Relmada, Sage Therapeutics, Servier, Shire, Sunovion, Takeda, Taliaz, Teva, Tonix, Tris Pharma, and Viforpharma; he is a board member of Genomind; he has served on speakers bureaus for Acadia, Lundbeck, Otsuka, Perrigo, Servier, Sunovion, Takeda, Teva, and Vertex; and he has received research and/or grant support from Acadia, Avanir, Braeburn Pharmaceuticals, Eli Lilly, Intra-Cellular Therapies Inc., Ironshore, ISSWSH, Neurocrine, Otsuka, Shire, Sunovion, and TMS NeuroHealth Centers.

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Authors' contributions: S.D., S.G.K., C.C., J.H., and H.L. participated in study design and study conduct. All authors participated in data analysis/interpretation and writing/critical review.

DATA AVAILABILITY STATEMENT

Data will be made available on reasonable request, subject to review and meeting criteria.

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