The Efficacy of Lumateperone in Patients With Bipolar Depression With Mixed Features

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ABSTRACT

Objective: A post hoc analysis of a phase 3, randomized, double-blind, placebo-controlled outpatient study investigated efficacy of lumateperone 42 mg in patients with bipolar I or bipolar II disorder and experiencing a major depressive episode (MDE) stratified by the presence of mixed features.

Methods: Adults (18–75 years) with bipolar I or bipolar II disorder experiencing an MDE, defined by *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition, criteria, were randomized 1:1 to 6-week oral lumateperone 42 mg/d or placebo (conducted November 2017–March 2019). Montgomery-Asberg Depression Rating Scale (MADRS) total score, Clinical Global Impression Scale-Bipolar Version-Severity (CGI-BP-S) total score, and Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) were analyzed in patients (N = 376) categorized as having mixed features (Young Mania Rating Scale [YMRS] score ≥ 4 and ≤ 12, 41.5%) or not having mixed features (YMRS < 4, 58.5%) at baseline. Treatment-emergent adverse events (TEAEs) including mania/hypomania were assessed.

Results: At day 43, lumateperone significantly improved MADRS and CGI-BP-S total scores change from baseline compared with placebo for patients with mixed features (MADRS least squares mean difference [LSMD] = –4.4, $P < .01$; CGI-BP-S LSMD = –0.7, $P < .05$) and without mixed features (MADRS LSMD = –4.2, $P < .001$, CGI-BP-S LSMD = –1.0, $P < .001$). Q-LES-Q-SF percent score significantly improved at day 43 with lumateperone vs placebo in patients with mixed features (LSMD = 5.9, $P < .05$), with numerical improvements in patients without mixed features (LSMD = 2.6, $P = .27$). TEAEs of mania/hypomania were rare.

Conclusions: Lumateperone 42 mg significantly improved symptoms of depression and disease severity in patients with an MDE associated with bipolar I or bipolar II disorder, with or without mixed features.

Trial Registration: ClinicalTrials.gov identifier: NCT03249376

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Bipolar disorder is a chronic mental illness with disabling symptoms that is characterized by episodes of mania, hypomania, and depression.[1,2] Depressive episodes in patients with bipolar disorder are more frequent compared with mania or hypomania and contribute to the elevated risk of morbidity and mortality in these patients.[2] Symptoms of depression and mania/hypomania can also occur simultaneously in a state referred to as mixed features, which results in a heterogeneous clinical presentation that can increase the risk of misdiagnosis and lead to therapeutic challenges.[3,4]

According to the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition and Text Revision (*DSM-5*, *DSM-5-TR*), a mood episode associated with bipolar disorder must meet the full criteria for either a manic/hypomanic or depressive episode and ≥ 3 symptoms of the opposite mood state to qualify for the mixed features specifier.[4,5] A recent meta-analysis using *DSM-5* criteria determined that the prevalence of mixed features in major depressive and manic/hypomanic episodes is 11.6% and 26.8%, respectively,[6] but rates have been reported from 11% to 70%, depending on the criteria used.[7,8] The clinical implications of mixed features have provided the impetus for dedicated clinical practice guidelines with algorithms to inform treatment selection and sequencing.[9] In 2017, guidelines were published to aid clinicians in diagnosing and treating patients with a major depressive episode (MDE), including those with major depressive disorder or bipolar disorder, with mixed features.[9] However, differences in diagnostic classifications persist, and a lack of consensus regarding how to best diagnose and treat patients with mixed features challenges optimal care.[10–13]

Patients with bipolar disorder with mixed features have increased risks for functional impairment, suicide, and psychiatric comorbidities, including anxiety spectrum disorders, compared with patients without mixed features.[3,13,14] Physical health complications are also common, as cardiovascular disease (CVD) is a frequent cause of death in people with bipolar disorder.[15] Depression and mania/hypomania have been independently associated with increased risk for CVD[16–18]; thus, patients with mixed features of depression and mania/hypomania could experience greater risk for comorbidities compared with those without mixed features.[7,19] In addition, emerging evidence associates mixed features with obesity in people with bipolar disorder.[20,21] Overall, the presence of mixed features is clinically relevant as it increases the morbidity risk by 1.6 times and leads to a poorer prognosis compared with that of patients without mixed features.[22] There are no US Food and Drug Administration (FDA)–approved

Clinical Points

- There are currently no FDA-approved treatments for bipolar depression with mixed features, in which patients experience poorer clinical outcomes compared with patients without mixed features.
- In this post hoc analysis of a phase 3 trial, lumateperone 42-mg treatment significantly improved symptoms of depression and disease severity compared with placebo in patients with bipolar depression, with or without mixed features.
- These results support lumateperone as a treatment for major depressive episodes associated with bipolar I or bipolar II disorder in patients with or without mixed features.

treatments for patients with bipolar depression with mixed features, and few studies have investigated the complexity of treating this patient population.[12,23]

Several antipsychotics, including lumateperone,[24] cariprazine,[25] quetiapine,[26] and lurasidone,[27] are approved to treat depression in bipolar I disorder; however, only quetiapine[26,28] and lumateperone[24] are approved for depressive episodes in bipolar II disorder.[29] A notable limitation of many first- and second-generation antipsychotics is the associated adverse effects of cardiometabolic disturbances and motor impairments, which can reduce treatment adherence and quality of life.[30] The presence of mixed features often indicates poor treatment response, and, to date, no single agent is effective in treating the diverse manifestations that are associated with episodes of mixed features.[14] Consequently, patients with mixed features are often prescribed combinations of atypical antipsychotics and mood stabilizers, which may worsen the side effect burden.[14] Efforts to avoid treatment-emergent switching from symptoms of depression to mania result in additional complexity in treatment decisions[31]; currently, it is unclear whether clinical characteristics can predict treatment response.[11] The lack of safe and effective treatments for patients with bipolar disorder with mixed features, in addition to a historical underdiagnosis of the condition,[3,14] highlights a need for increased understanding and additional treatment options for this patient population.

Lumateperone (lumateperone tosylate, ITI-007), a mechanistically novel antipsychotic, is approved by the FDA to treat adults with schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate.[24,32,33] Lumateperone simultaneously modulates serotonin, dopamine, and glutamate neurotransmission and has negligible binding to receptors such as H_1 histaminergic, 5-HT_{2c}, and muscarinic receptors that have been associated with the adverse metabolic side effects with other antipsychotics.[32,34] 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 AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (*N*-methyl-D-aspartate) currents, and a serotonin reuptake inhibitor.[32,35,36] In a phase 3, randomized, double-blind, placebo-controlled outpatient trial (Study 404; NCT03249376), 6-week lumateperone 42-mg treatment significantly improved Montgomery-Asberg Depression Rating Scale (MADRS) total score[37] from baseline to day 43 compared with placebo in patients with bipolar I or bipolar II disorder who were experiencing an MDE.[38] Lumateperone treatment in Study 404 was also generally well tolerated with minimal changes in metabolic assessments.[38]

This post hoc analysis of Study 404 evaluated the efficacy of lumateperone in patients with bipolar depression stratified by the presence of mixed features.

METHODS

Study Design and Patients

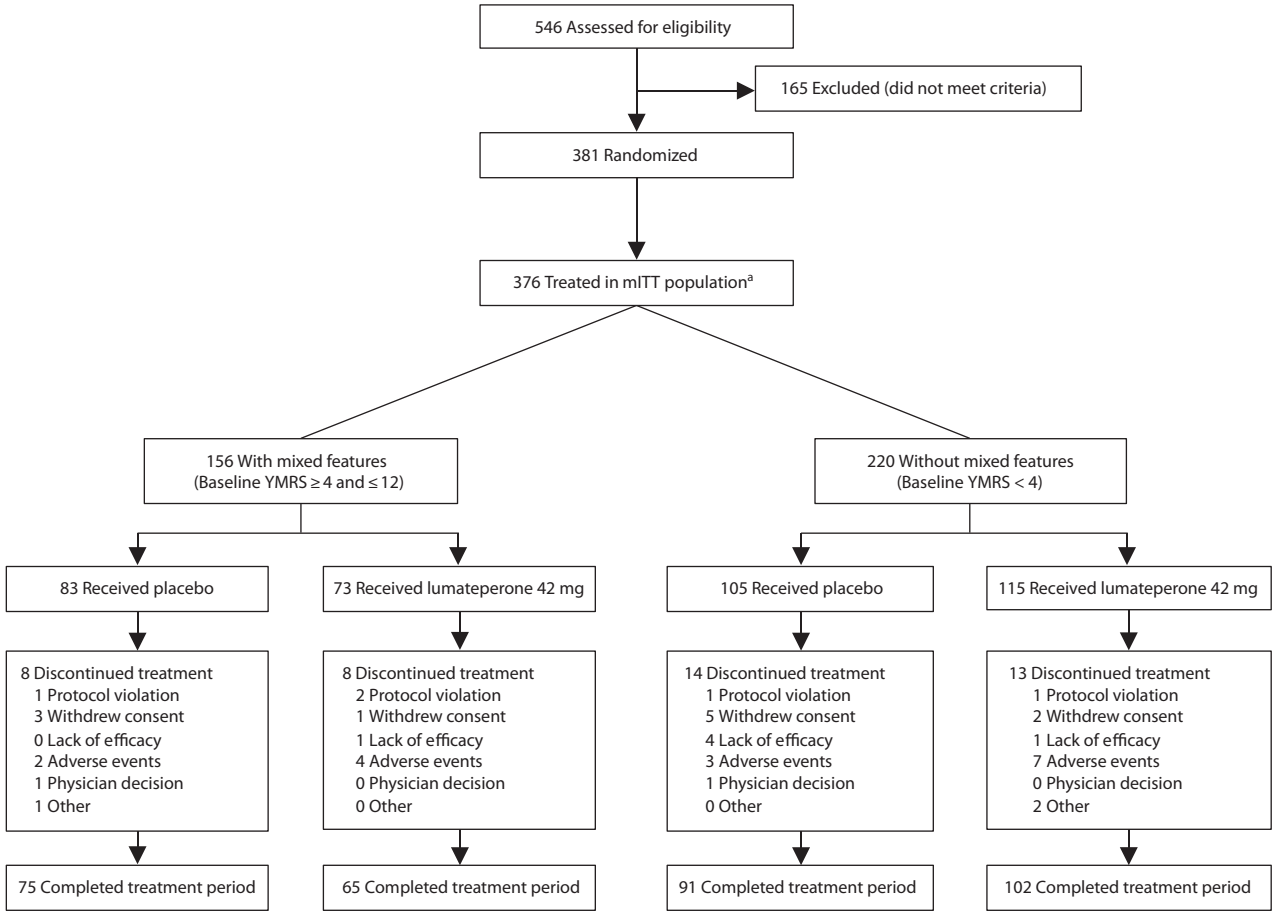
Detailed methods for Study 404 (ClinicalTrials.gov, NCT03249376) have been previously published.[38] Briefly, the study took place from November 2017 to March 2019 and comprised a 2-week screening period, a 6-week double-blind on-treatment period, and a 2-week safety follow-up period. At baseline, patients were randomized 1:1 to lumateperone 42 mg or placebo, administered orally via capsule once daily in the evening for 6 weeks with or without food. Efficacy and safety assessments were conducted at weekly clinic visits (days 8, 15, 22, 29, 36, and 43; all visits ± 1 day); follow-up occurred on day 57 ± 2 days.

Eligible patients were aged 18–75 years, with a confirmed diagnosis of bipolar I or bipolar II disorder according to *DSM-5*, who were experiencing an MDE. Patients had depression of at least moderate severity as determined by a MADRS total score ≥ 20[37] and scores ≥ 4 on the depression and overall bipolar illness subscales of Clinical Global Impression Scale-Bipolar Version-Severity (CGI-BP-S) at screening and baseline.[39] The start of the current MDE must have been ≥ 2 weeks and ≤ 6 months prior to screening and have caused clinically significant distress or functional impairment. Patients were required to have a history of ≥ 1 manic or mixed episode (for bipolar I) or hypomanic episode (for bipolar II) and a Young Mania Rating Scale (YMRS) score ≤ 12 at screening and baseline.[40] Patients were excluded if there was a significant risk for suicidal behavior or if they had been diagnosed with a psychiatric illness other than bipolar disorder within 12 months of screening. All patients were informed of possible side effects and provided written informed consent as approved by the responsible institutional review board/independent ethics committee prior to participating in study-related activities.

Criteria for Mixed Features

Mania in this study was monitored using the YMRS, which is composed of 11 items, with a total score range from 0 to 60.[40,41] According to the *DSM-5* operational definition, in patients with an MDE, a score ≥ 1 on ≥ 3 select YMRS items is consistent with a depressive episode with a mild mixed features specifier.[8] However, patients

Figure 1. Patient Disposition With or Without Mixed Features (CONSORT Diagram)



[a]Received ≥ 1 dose of study medication and had a valid predose baseline assessment and ≥ 1 valid postbaseline assessment of Montgomery-Asberg Depression Rating Scale.
Abbreviations: mITT = modified intent-to-treat, YMRS = Young Mania Rating Scale.

may in fact experience mixed features with fewer manic symptoms than are currently defined in the *DSM-5*.[7,41–43] Prior studies of antipsychotics in bipolar depression have shown an association between baseline YMRS score and treatment response characteristics,[31,44] and analyses of other antipsychotics have utilized a baseline YMRS score of 4 as a proxy to distinguish subgroups of patients with bipolar depression with or without mixed features.[7,41] Similarly, this post hoc analysis categorized patients with a baseline YMRS score ≥ 4 and ≤ 12 as having mixed features and those with a baseline YMRS score < 4 as not having mixed features. This approach to operationalizing mixed features has precedent, and the criteria for mixed features used in this study are consistent with those of prior studies and with the observed baseline mean YMRS score of patients with bipolar depression and concurrent mania.[7,8,31,41]

Statistical Analysis

The primary and key secondary endpoints were mean change from baseline to day 43 in MADRS total score and CGI-BP-S total score, respectively. Additional analyses included change from baseline in MADRS total score, CGI-BP-S total score, CGI-BP-S subscores (Mania, Depression, and Overall Bipolar Illness), Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF),[45] and YMRS, as well as adverse events.

Descriptive statistics were used to analyze baseline demographics and disease characteristics. Treatment effects on primary and key secondary endpoints were evaluated using a mixed-effects model for repeated measures (MMRM) in the prespecified modified intent-to-treat (mITT) population, which was defined as all patients who received ≥ 1 dose of study medication and had a valid predose baseline assessment and ≥ 1 valid postbaseline assessment of MADRS. The model included visit, treatment group, site, and bipolar disorder stratification (bipolar I or bipolar II disorder) as factors; the patient term was included as a random effect and baseline score was included as a covariate with interaction terms for treatment group–by-visit and visit-by–baseline score. An unstructured covariance matrix was used to estimate the correlation of repeated measurements within a patient. Least squares (LS) mean estimates for change from baseline were calculated by treatment group and visit. CGI-BP-S subscores and YMRS were evaluated using an MMRM. Q-LES-Q-SF data were analyzed using an analysis of covariance. Safety parameters were summarized descriptively by treatment

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	With mixed features (baseline YMRS ≥ 4 and ≤ 12)			Without mixed features (baseline YMRS < 4)		
	Placebo (n = 83)	Lumateperone 42 mg (n = 73)	Total (n = 156)	Placebo (n = 105)	Lumateperone 42 mg (n = 115)	Total (n = 220)
Age, mean (SD), y	45.4 (12.5)	46.4 (13.3)	45.9 (12.8)	43.0 (13.2)	45.2 (14.6)	44.2 (14.0)
Sex, n (%)						
Women	56 (67.5)	44 (60.3)	100 (64.1)	63 (60.0)	55 (47.8)	118 (53.6)
Men	27 (32.5)	29 (39.7)	56 (35.9)	42 (40.0)	60 (52.2)	102 (46.4)
Race, n (%)						
White	72 (86.7)	62 (84.9)	134 (85.9)	98 (93.3)	111 (96.5)	209 (95.0)
Black	11 (13.3)	10 (13.7)	21 (13.5)	4 (3.8)	4 (3.5)	8 (3.6)
Other	0	1 (1.4)	1 (0.6)	3 (2.9)	0	3 (1.4)
Hispanic or Latino ethnicity, n (%)	9 (10.8)	9 (12.3)	18 (11.5)	12 (11.4)	9 (7.8)	21 (9.5)
Bipolar disorder diagnosis, n (%)						
Bipolar I	77 (92.8)	66 (90.4)	143 (91.7)	73 (69.5)	84 (73.0)	157 (71.4)
Bipolar II	6 (7.2)	7 (9.6)	13 (8.3)	32 (30.5)	31 (27.0)	63 (28.6)
Age at onset of illness, mean (SD), y	31.6 (12.1)	33.4 (11.7)	32.5 (11.9)	32.3 (11.0)	33.1 (12.2)	32.7 (11.6)
No. of lifetime depressive episodes, n (%)						
≥ 1 to ≤ 9	69 (83.1)	61 (83.6)	130 (83.3)	98 (93.3)	105 (91.3)	203 (92.3)
≥ 10 to ≤ 20	12 (14.5)	12 (16.4)	24 (15.4)	7 (6.7)	9 (7.8)	16 (7.3)
> 20	2 (2.4)	0	2 (1.3)	0	1 (0.9)	1 (0.5)
MADRS total score, mean (SD)	30.5 (4.46)	31.6 (5.08)	31.0 (4.77)	30.1 (4.81)	30.4 (4.79)	30.2 (4.79)
CGI-BP-S total score, mean (SD)	10.3 (1.09)	10.5 (1.12)	10.4 (1.10)	10.0 (1.05)	10.2 (1.11)	10.1 (1.09)
YMRS score, mean (SD)	5.0 (1.25)	5.1 (1.28)	5.0 (1.26)	1.8 (0.94)	1.8 (1.08)	1.8 (1.01)
Q-LES-Q-SF percent score, mean (SD)	40.1 (12.49)	37.4 (10.90)	38.8 (11.82)	37.2 (11.88)	36.8 (13.50)	37.0 (12.73)

Abbreviations: CGI-BP-S = Clinical Global Impression Scale-Bipolar Version-Severity, MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, YMRS = Young Mania Rating Scale.

group. Statistical analyses were performed with SAS software version 9.4 or higher (SAS Institute; Cary, NC).

RESULTS

Patient Population

The study was conducted at 54 sites in 6 countries. Of 546 patients assessed for eligibility, 381 were randomized to receive lumateperone 42 mg (n = 191) or placebo (n = 190); 376 patients were in the mITT population (Figure 1). Of the mITT population, 41.5% had mixed features (placebo, 83; lumateperone, 73), and 58.5% did not have mixed features (placebo, 105; lumateperone, 115) (Table 1). Treatment period completion rates were similar between patients with mixed features (140/156 [89.7%]) and those without mixed features (193/220 [87.7%]). The most frequent reason for treatment discontinuation was adverse events (with mixed features, 3.8%; without mixed features, 4.5%), followed by withdrawal of consent (with mixed features, 2.6%; without mixed features, 3.2%).

Compared with the group without mixed features, the group with mixed features included a higher proportion of women (with mixed features, 64.1%; without mixed features, 53.6%) and Black individuals (with mixed features, 13.5%; without mixed features, 3.6%) (Table 1). The mean baseline MADRS total score and CGI-BP-S total score were similar between groups with or without mixed features and indicated moderate-to-severe symptoms of depression at baseline.[38,46] Quality of life measured by mean baseline Q-LES-Q-SF percent score was also similar between groups with mixed features and those without. Patients with mixed features had a greater baseline mean (SD) YMRS score (5.0 [1.26]) compared with those without mixed features (1.8 [1.01]).

Efficacy

In the overall study population, lumateperone 42-mg treatment significantly reduced MADRS total score from baseline to day 43 compared with placebo (LS mean change, −16.7; LS mean difference vs placebo [LSMD], −4.6; 95% CI, −6.34 to −2.83; effect size, −0.56; $P < .0001$).[38] When stratified by the presence of mixed features, the LS mean change from baseline to day 43 in MADRS total score, the primary outcome, was significantly greater for lumateperone 42 mg compared with placebo for patients with mixed features (LSMD, −4.4; 95% CI, −7.26 to −1.52; effect size, −0.52; $P < .01$) and without mixed features (LSMD, −4.2; 95% CI, −6.46 to −1.92; effect size, −0.53; $P < .001$) (Table 2). For lumateperone compared with placebo, the LS mean change from baseline in MADRS total score was statistically greater at day 22 through 43 in patients with mixed features and at day 8 and day 29 through 43 in patients without mixed features (Figure 2A).

Lumateperone was associated with a significantly greater reduction in CGI-BP-S total score from baseline to day 43, the key secondary outcome, in the overall study population compared with placebo (LS mean change, −3.5; LSMD, −0.9; 95% CI, −1.37 to −0.51; effect size, −0.46; $P < .0001$).[38] In this post hoc analysis, significant reductions from baseline to day 43 were also observed in LS mean CGI-BP-S total score with lumateperone 42-mg treatment compared with placebo for patients with mixed features (LSMD, −0.7; 95% CI, −1.43 to −0.05; effect size, −0.37; $P < .05$) or without mixed features (LSMD, −1.0; 95% CI, −1.62 to −0.47; effect size, −0.52; $P < .001$) (Table 2). In patients without mixed features, significant decreases from baseline in the LS mean CGI-BP-S total score for the lumateperone 42-mg group compared with placebo were observed starting at day 29 and persisted through day 43 (Figure 2B). Additionally,

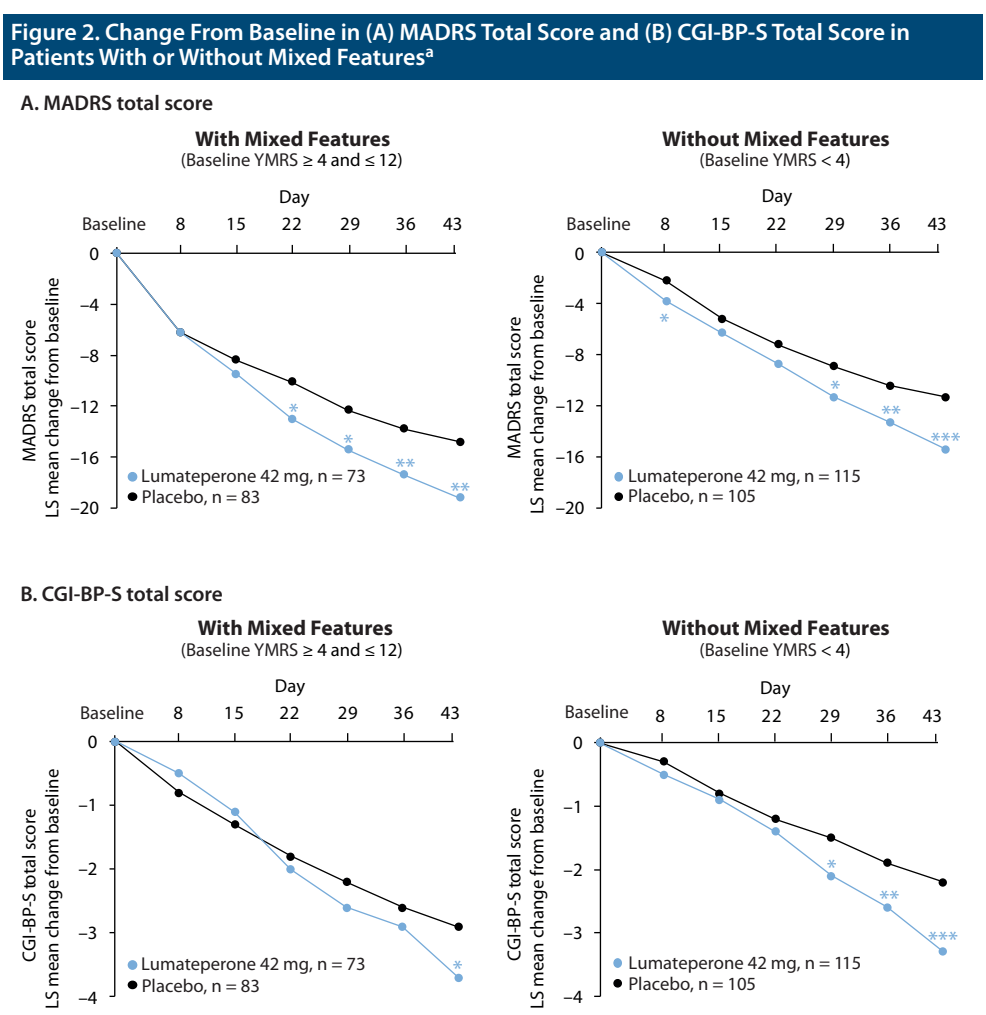
Table 2. Efficacy Outcomes From Baseline to Day 43 in Patients With or Without Mixed Features

	With mixed features (baseline YMRS ≥ 4 and ≤ 12)				Without mixed features (baseline YMRS < 4)			
	Placebo (n = 83)	Lumateperone 42 mg (n = 73)	Comparison with placebo		Placebo (n = 105)	Lumateperone 42 mg (n = 115)	Comparison with placebo	
Outcome	LS mean change at day 43 (MMRM), mean (SE)		LS mean difference (95% CI)	Effect size; *P* value	LS mean change at day 43 (MMRM), mean (SE)		LS mean difference (95% CI)	Effect size; *P* value
MADRS total score	−14.8 (1.20)	−19.2 (1.24)	−4.4 (−7.26 to −1.52)	−0.52; *P* < .01	−11.3 (0.90)	−15.4 (0.87)	−4.2 (−6.46 to −1.92)	−0.53; *P* < .001
CGI-BP-S								
Total score	−2.9 (0.30)	−3.7 (0.31)	−0.7 (−1.43 to −0.05)	−0.37; *P* < .05	−2.2 (0.23)	−3.3 (0.22)	−1.0 (−1.62 to −0.47)	−0.52; *P* < .001
Mania subscore	0.1 (0.03)	0.1 (0.03)	−0.0 (−0.06 to 0.06)	−0.01; *P* = .969	0.1 (0.04)	0.1 (0.04)	−0.0 (−0.14 to 0.07)	−0.09; *P* = .515
Depression subscore	−1.6 (0.15)	−2.0 (0.16)	−0.4 (−0.76 to −0.03)	−0.37; *P* < .05	−1.2 (0.11)	−1.8 (0.11)	−0.5 (−0.83 to −0.25)	−0.53; *P* < .001
Overall bipolar illness subscore	−1.4 (0.15)	−1.7 (0.15)	−0.4 (−0.70 to −0.01)	−0.35; *P* < .05	−1.2 (0.11)	−1.6 (0.11)	−0.5 (−0.75 to −0.19)	−0.48; *P* < .01
Q-LES-Q-SF percent score[a]	14.2 (2.90)	20.1 (2.82)	5.9 (1.09 to 10.71)	0.41; *P* < .05	16.1 (2.16)	18.7 (2.05)	2.6 (−2.05 to 7.21)	0.16; *P* = .273

[a]Analyzed with ANCOVA.

Abbreviations: ANCOVA = analysis of covariance, CGI-BP-S = Clinical Global Impression Scale-Bipolar Version-Severity, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-effects model for repeated measures, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, YMRS = Young Mania Rating Scale.

Figure 2. Change From Baseline in (A) MADRS Total Score and (B) CGI-BP-S Total Score in Patients With or Without Mixed Features[a]

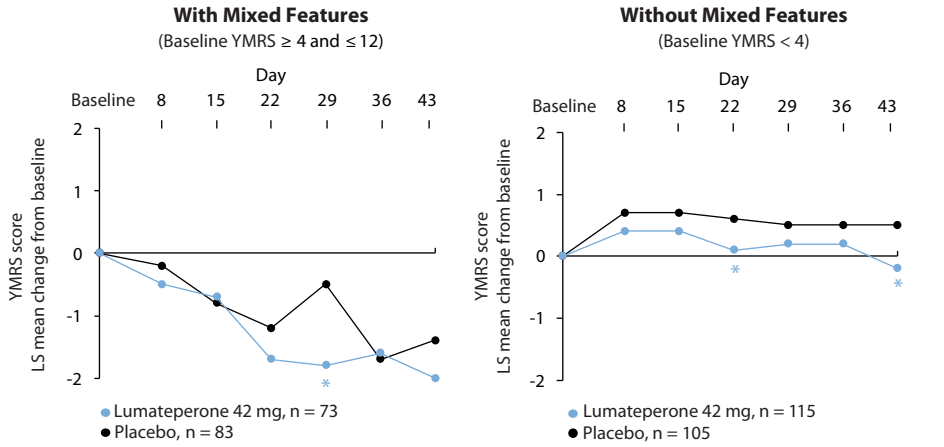


[a]LSMD vs placebo. MMRM.

*P < .05. **P < .01. ***P < .001.

Abbreviations: CGI-BP-S = Clinical Global Impression Scale-Bipolar Version-Severity, LS = least squares, LSMD = least squares mean difference, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-effects model for repeated measures, YMRS = Young Mania Rating Scale.

Figure 3. Change From Baseline in YMRS Score in Patients With or Without Mixed Features



Abbreviations: LS = least squares, YMRS = Young Mania Rating Scale.

CGI-BP-S Depression and Overall Bipolar Illness subscores significantly improved from baseline to day 43 for patients with or without mixed features (Table 2).

In the overall study population, Q-LES-Q-SF percent score significantly improved from baseline to day 43 with lumateperone compared with placebo (LS mean change, 19.4; LSMD, 4.6; 95% CI, 1.42 to 7.69; effect size, 0.31; $P < .01$).[38] A statistically significant improvement was also observed in LS mean Q-LES-Q-SF percent score at day 43 with lumateperone compared with placebo in the group with mixed features (LSMD, 5.9; 95% CI, 1.09 to 10.71; effect size, 0.41; $P < .05$) but not in the group without mixed features (LSMD, 2.6; 95% CI, −2.05 to 7.21; effect size, 0.16; $P = .273$) (Table 2).

Mania and Hypomania

Safety and tolerability findings have been previously published.[38] Briefly, the rate of treatment-emergent adverse events (TEAEs) was similar between the lumateperone 42-mg and placebo groups, and the majority of events were mild to moderate in severity.[38]

Rates of TEAEs were similar in patients who received ≥ 1 dose of study drug with mixed features (placebo, 51.8%; lumateperone, 54.8%) and without mixed features (placebo, 49.1%; lumateperone, 54.8%). TEAEs that occurred in ≥ 5% of the lumateperone group and more than twice the rate of placebo included somnolence and nausea for patients with mixed features and headache and dizziness postural for patients without mixed features (Supplementary Table 1).

TEAEs of mania occurred at similar rates in patients with mixed features (placebo, 2.4%; lumateperone, 1.4%) or without mixed features (placebo, 1.9%; lumateperone, 0.9%). All cases of mania were moderate in severity. Two cases of hypomania occurred during treatment; both cases were in the mixed features group (placebo, 1.2% [mild severity]; lumateperone, 1.4% [moderate severity]).

During the study, patients with mixed features had numerical, not statistically significant decreases in YMRS score, with the exception of a significant decrease with lumateperone compared with placebo on day 29 ($P < .05$) (Figure 3). YMRS score was generally stable in those without mixed features, with a reduction at day 43 in those treated with lumateperone compared with placebo (LSMD, −0.8; 95% CI, −1.43 to −0.07; effect size, −0.32; $P < .05$).

DISCUSSION

In this post hoc analysis of a phase 3, randomized, double-blind, placebo-controlled study, lumateperone 42-mg treatment significantly improved symptoms of depression and disease severity in patients with bipolar depression with or without mixed features. In bipolar I and II disorder, depressive symptoms are more predominant than manic or hypomanic symptoms, and bipolar depression is associated with a greater illness burden compared with bipolar mania.[2,47] An unmet need for treatment exists for patients with bipolar disorder with mixed features; treatment challenges include a limited patient response to available therapies and a risk for mood switching with therapies that are targeted at only 1 set of symptoms.[48]

The diagnostic criteria for mixed features have varied over time with regard to the severity, type, and number of symptoms, leading to controversy about the appropriate diagnosis of patients with combinations of symptoms.[10,12] Of the study population, 41.5% had mixed features, which is consistent with the prevalence rates reported previously.[7,8] A numerically greater percentage of women in the study had mixed features (64.1%) compared with those without mixed features (53.6%), and the data are in line with prior reports that observed a higher rate of female than male patients with mixed features.[49,50] Baseline characteristics describing disease severity were similar between patients with or without mixed features in this study, including age at onset of illness, number of lifetime depressive episodes, MADRS total score, CGI-BP-S total score, and Q-LES-Q-SF percent score.

Depending on the presentation of symptoms of mania and depression, patients are often prescribed antidepressants or antipsychotics.[11,12] Treatment must be chosen carefully in

patients with mixed features, as inappropriate antidepressant treatment for an MDE in these patients can trigger symptoms of mania and suicidality.[9,11] While several antipsychotics are approved for bipolar I disorder mania with mixed episodes (eg, aripiprazole,[51] cariprazine,[25] quetiapine extended-release,[26] risperidone,[52] olanzapine[53]), none are approved in bipolar depression with mixed episodes.[25–29,54] In recent years, several analyses investigated the use of antipsychotics in bipolar I depression with mixed manic episodes.[7,41] In this analysis in patients with bipolar I or bipolar II depression with or without mixed features, lumateperone significantly improved depressive symptoms and disease severity as measured by MADRS total score and CGI-BP-S total score. Additionally, lumateperone treatment significantly improved quality of life as measured by Q-LES-Q-SF percent score in patients with mixed features. The latter improvement is notable because, compared with other bipolar disorder states, patients experiencing mixed features have reported reduced quality of life across several domains.[3]

As previously published, 6-week treatment of lumateperone 42 mg was generally well tolerated in patients with bipolar disorder experiencing an MDE, with rates of TEAEs that were similar to those of placebo.[38] Because some treatments for bipolar depression can induce manic symptoms and several baseline variables can enhance the risk of manic switch,[14,55] it is important to monitor symptoms of mania in patients, particularly with mixed features. In this analysis, TEAEs of mania were rare, were moderate in severity, and occurred at similar rates in patients with or without mixed features. The 2 reported cases of hypomania in this study (placebo, 1; lumateperone 42 mg, 1) occurred in the group with mixed features and were mild or moderate in severity. Overall, the stable or reduced YMRS score from baseline indicates that lumateperone was not associated with an increase in manic symptoms in patients with or without mixed features.

A limitation is that this study was a post hoc analysis and not prospective in nature; as such, the presence or absence of mixed features was defined by YMRS score instead of a specific clinical assessment for mixed features. Because the mixed features criteria utilized baseline YMRS score, some patients in the mixed features group may not meet the criteria for mixed features as defined by the *DSM-5*. In addition, Study 404 excluded patients with treatment-resistant illness, imminent suicidal risk, and rapid cycling or serious comorbid psychiatric or medical illnesses, which may limit the generalizability of the findings.

In summary, lumateperone 42 mg significantly improved symptoms of depression and disease severity in patients experiencing bipolar depression, with or without mixed features, and did not induce mania. These results support lumateperone as a promising new treatment for MDEs associated with bipolar I or bipolar II disorder in patients with or without mixed features.

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Supplementary Material

Article Title: The Efficacy of Lumateperone in Patients With Bipolar Depression With Mixed Features

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List of Supplementary Material for the article

1. Table 1 TEAEs Occurring in the Lumateperone Group at ≥5% and More Than Twice the Rate of Placebo

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Supplementary Table 1. TEAEs occurring in the lumateperone group at ≥5% and more than twice the rate of placebo

n (%)	With Mixed Features (Baseline YMRS ≥4 and ≤12)		Without Mixed Features (Baseline YMRS <4)	
	Placebo (n=83)	Lumateperone 42 mg (n=73)	Placebo (n=106)	Lumateperone 42 mg (n=115)
Somnolence	1 (1.2)	11 (15.1)	1 (0.9)	5 (4.3)
Nausea	1 (1.2)	7 (9.6)	3 (2.8)	5 (4.3)
Headache	10 (12.0)	12 (16.4)	9 (8.5)	21 (18.3)
Dizziness postural	0	0	1 (0.9)	8 (7.0)

Abbreviations: TEAE = treatment-emergent adverse event, YMRS = Young Mania Rating Scale.