Lumateperone for the treatment of bipolar mania in patients with bipolar I disorder: results from a double-blind, placebo-controlled, randomized, Phase 3 trial

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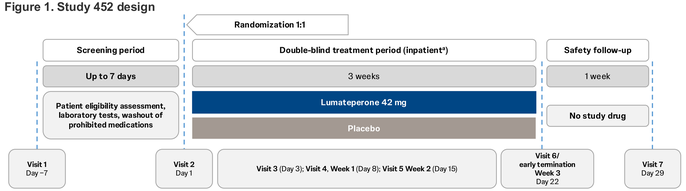
Background

- Bipolar I disorder is characterized by the occurrence of at least 1 manic episode, which may be preceded or followed by major depressive episodes and/or hypomanic episodes[1,2]
- A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting ≥1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary)[1,2]
  - Manic episodes with mixed features are also possible and can be exhibited by approximately one-third of patients with bipolar I disorder[3-5]
- Due to the heterogeneity of responses and tolerability with current treatments,[6-7] there remains a significant unmet need for new options that address all episode types associated with bipolar I disorder (depressive, mixed, and manic)
- Lumateperone is indicated for depressive episodes associated with bipolar I or II disorder, for schizophrenia, and as adjunctive therapy to antidepressant therapy in major depressive disorder[8]
- In a separate identically designed study (Study 451 [NCT06462586]), lumateperone 42 mg vs placebo demonstrated rapid onset and statistically significant improvement in acute manic symptoms in bipolar I disorder with and without mixed features[9]
- Study 452 was a randomized, double-blind, placebo-controlled, multicenter trial (NCT06462612) that investigated the efficacy and safety of lumateperone 42 mg for the treatment of bipolar mania in adults with bipolar I disorder

Methods

- Eligible adults (aged 18-75 years) were diagnosed per *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR) with bipolar I disorder and a current episode of mania with or without mixed features
- Patients were randomized 1:1 to either 3 weeks of lumateperone 42 mg or placebo (**Figure 1** and **Table 1**)
  - Patients received study treatment in an inpatient setting

Figure 1. Study 452 design



*Patients could be discharged to outpatient status after the completion of Visit 5 (Week 2) per investigator discretion.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Adults hospitalized because of the current manic episode • DSM-5-TR–diagnosed bipolar I with a current episode of mania or mania with mixed features ≤4 weeks prior to Visit 1 with or without psychotic symptoms • YMRS total score ≥20 (a total score ≥25 was considered severely ill[10]), plus: • YMRS score ≥4 on 2 key items at Visits 1 and 2 (irritability, speech, content, or disruptive/aggressive behavior), plus: • CGI-S score ≥4 at Visits 1 and 2	• Patient's primary DSM-5-TR psychiatric diagnosis was anything other than bipolar disorder • Patient was experiencing their first manic episode • Patient had a significant risk for suicidal behavior in the opinion of the investigator

CGI-S, Clinical Global Impression–Severity; DSM-5-TR, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision*; YMRS, Young Mania Rating Scale.

- Efficacy assessments
  - The primary endpoint was change from baseline (ie, Day 1, prerandomization) to end of Week 3 (Day 22) in Young Mania Rating Scale (YMRS) total score
    - The key secondary endpoint was the change from baseline to end of Week 3 (Day 22) in Clinical Global Impression–Severity (CGI-S) score
  - Efficacy assessments were controlled for multiple comparisons via fixed sequence testing: Primary → key secondary → Week 1 (Day 8) YMRS → Day 3 YMRS
  - Efficacy assessments were analyzed using an analysis of covariance model
  - Intercurrent events and corresponding strategy considered data missing not at random for dropouts due to lack of efficacy and/or initiation of a new therapy in the lumateperone 42 mg group and missing at random for dropouts due to other reasons in either treatment group
- Safety and tolerability were evaluated throughout the treatment period and for 1 week afterward
- Study populations
  - Safety population: all randomized patients who received ≥1 dose of study treatment
  - Intent-to-treat (ITT) population: all randomized patients who received ≥1 dose of study treatment and had a baseline YMRS total score

Results

Patient population

- Of 351 patients treated (lumateperone 42 mg, n=173; placebo, n=178), 311 (88.6%) completed treatment
- The mean age at the start of the study was 46.1 years, and 56.1% were male (**Table 2**)
- Approximately 44% of patients had experienced ≤5 lifetime manic episodes (43.6%), and 31.3% were diagnosed with mixed features according to the DSM-5-TR (**Table 2**)
- Mean YMRS total score at baseline indicated severe mania in both groups (32.9 in the lumateperone 42-mg group and 32.8 in the placebo group) (**Table 2**)
- Baseline demographics and psychiatric history were balanced between treatment groups

Table 2. Baseline demographics and clinical characteristics (safety population[a])

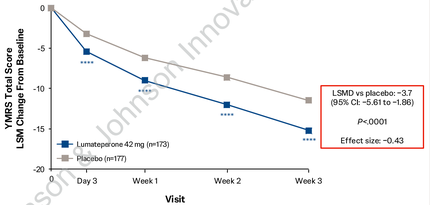
	Lumateperone 42 mg (n=173)	Placebo (n=178)	Total (N=351)
Age, mean (SD), years	46.0 (12.37)	46.2 (11.59)	46.1 (11.96)
Male, n (%)	105 (60.7)	92 (51.7)	197 (56.1)
Race, n (%)			
White	113 (65.3)	107 (60.1)	220 (62.7)
Black or African American	55 (31.8)	67 (37.6)	122 (34.8)
Other[b]	5 (2.9)	4 (2.2)	9 (2.6)
Hispanic or Latino ethnicity, n (%)	34 (19.7)	39 (21.9)	73 (20.8)
Any specifiers associated with current episode, n (%)			
Yes	93 (53.8)	91 (51.1)	184 (52.4)
No	80 (46.2)	87 (48.9)	167 (47.6)
Mixed features, yes, n (%)[c]	54 (31.2)	56 (31.5)	110 (31.3)
Psychotic features, yes, n (%)[d]	58 (33.5)	64 (36.0)	122 (34.8)
Time since start of current manic episode, mean (SD), days	15.6 (5.53)	15.6 (5.33)	15.6 (5.42)
Lifetime manic episodes (including the current one), n (%)			
≤5	74 (42.8)	79 (44.4)	153 (43.6)
>5 and ≤10	61 (35.3)	60 (33.7)	121 (34.5)
>10 and ≤20	26 (15.0)	25 (14.0)	51 (14.5)
>20	4 (2.3)	9 (5.1)	13 (3.7)
Unknown	8 (4.6)	5 (2.8)	13 (3.7)
Age at first bipolar disorder diagnosis, mean (SD), years	29.2 (11.12)	28.0 (10.72)	28.6 (10.92)
YMRS total score, mean (SD)[e]	32.9 (5.75)	32.8 (5.75)	32.8 (5.74)
CGI-S score, mean (SD)[e]	4.8 (0.59)	4.8 (0.64)	4.8 (0.61)
MADRS total score, mean (SD)[e]	11.2 (7.88)	11.5 (8.21)	11.4 (8.04)

[a]The safety population included all randomized patients who received ≥1 dose of study treatment.
[b]Other includes American Indian or Alaska Native, multiple, or other. There were no Asian patients.
[c]Of patients with assessments for mixed features.
[d]Of patients with assessments for psychotic features.
[e]ITT population (lumateperone 42 mg, n=173; placebo, n=177).
CGI-S, Clinical Global Impression–Severity; MADRS, Montgomery Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

Efficacy

- The primary endpoint was met; the superiority of lumateperone 42 mg over placebo was demonstrated with a least squares mean difference (LSMD) in change from baseline to end of Week 3 in YMRS total score of −3.7 (effect size, −0.43; *P*<.0001)
  - Treatment differences were observed starting at Day 3 (*P*<.0001) and maintained from Week 1 (*P*<.0001) onward (**Figure 2**)

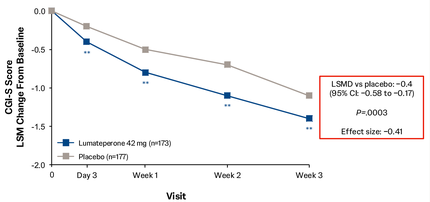
Figure 2. Change from baseline in YMRS total score (ITT population[a])



Negative values indicate improvement in symptom severity.
****P<.0001. LSMD vs placebo. Analysis of covariance in the ITT population. Data following intercurrent events were considered missing not at random for dropouts due to lack of efficacy and/or initiation of a new therapy in the lumateperone 42 mg group and missing at random for dropouts due to other reasons in either treatment group.
[a]ITT population included all randomized patients who received ≥1 dose of study treatment and had baseline YMRS total score.
ITT, intent-to-treat; LSM, least squares mean; LSMD, least squares mean difference; YMRS, Young Mania Rating Scale.

- Lumateperone 42 mg demonstrated superiority over placebo for the change in CGI-S score from baseline to the end of Week 3 with a LSMD of −0.4 (effect size, −0.41; *P*=.0003) (**Figure 3**)
  - Treatment differences were observed starting at Day 3 (nominal *P*=.0003) and were maintained from Week 1 (nominal *P*=.0001) onward

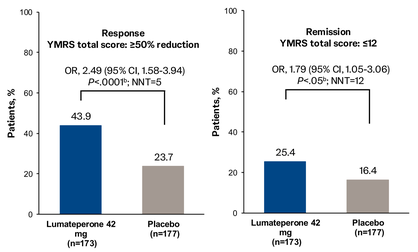
Figure 3. Change from baseline in CGI-S score (ITT population[a])



Negative values indicate improvement in symptom severity.
**P<.001 (nominal *P* values for Day 3, Week 1, and Week 2). LSMD vs placebo. Analysis of covariance in the ITT population. Data following intercurrent events were considered missing not at random for dropouts due to lack of efficacy and/or initiation of a new therapy in the lumateperone 42 mg group and missing at random for dropouts due to other reasons in either treatment group.
[a]ITT population included all randomized patients who received ≥1 dose of study treatment and had baseline YMRS total score.
CGI-S, Clinical Global Impression–Severity; ITT, intent-to-treat; LSM, least squares mean; LSMD, least squares mean difference.

- Lumateperone 42 mg vs placebo showed significantly greater response rates (YMRS total score ≥50% decrease; 43.9% vs 23.7%; nominal *P*<.0001) (**Figure 4**)
- Lumateperone 42 mg vs placebo showed significantly greater remission rates (YMRS total score ≤12; 25.4% vs 16.4%; nominal *P*=.0330) (**Figure 4**)
- The number needed to treat for lumateperone 42 mg was 5 to achieve response and 12 to achieve remission

Figure 4. YMRS total score response and remission rates at Week 3 (ITT population[a])



Response was defined as ≥50% decrease from baseline YMRS total score at Week 3; remission was defined as a YMRS total score ≤12 at Week 3.
Logistic regression in the ITT population: These endpoints were not adjusted for multiple comparisons; therefore, the *P* values displayed are nominal, and statistical significance has not been established.
[a]ITT population included all randomized patients who received ≥1 dose of study treatment and had baseline YMRS total score.
[b]Nominal *P* value.
ITT, intent-to-treat; NNT, number needed to treat; OR, odds ratio; YMRS, Young Mania Rating Scale.

Safety

- The safety profile of lumateperone 42 mg revealed no new safety concerns
- There were 2 serious adverse events (AEs), 1 in each treatment group (lumateperone 42 mg, urinary retention; placebo, bipolar I disorder)
  - No deaths were reported
- The most common treatment-emergent AEs with lumateperone 42 mg (rate ≥5% with lumateperone 42 mg and >2× placebo) were dizziness (10.4% vs 1.7%), dry mouth (5.8% vs 1.1%), and somnolence (5.2% vs 1.7%) (**Table 3**)
- Discontinuation rates due to AEs were low (lumateperone, 4.0%; placebo, 3.4%)

Table 3. Treatment-emergent adverse events with frequency ≥5% and >2× rate of placebo throughout the double-blind treatment period (safety population[a])

Preferred term, n (%)	Lumateperone 42 mg (n=173)	Placebo (n=178)
Dizziness	18 (10.4)	3 (1.7)
Dry mouth	10 (5.8)	2 (1.1)
Somnolence	9 (5.2)	3 (1.7)

[a]Safety population included all randomized patients who received ≥1 dose of study treatment.

Conclusions

- Lumateperone 42 mg demonstrated rapid onset at Day 3 (2 days after treatment initiation), compared with placebo in YMRS total score and CGI-S score in patients with bipolar mania with or without mixed features, consistent with previous results[9]
- Effects on YMRS total score and CGI-S score were significant at Day 3 and Week 1 and were maintained throughout the treatment period
- More patients receiving lumateperone 42 mg than those receiving placebo achieved YMRS response and remission by the end of treatment
- Lumateperone 42 mg was generally safe and well tolerated with no new safety concerns, consistent with previous results[9]
- Along with the identically designed Study 451, these results strengthen the overall efficacy profile in bipolar I disorder and address an important evidence gap for an established treatment for bipolar depression by extending demonstrated efficacy across bipolar I disorder–associated depressive, manic, and mixed episodes[8,9]

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Disclosures

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Willie R. Earley is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company.

Robert Hayes, Yifan Mo, and Andrea C. Wilson are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company.

Mauricio Tohen was an employee of Lilly (1997-2008) and has received honoraria from or consulted for Abbott, AbbVie, AstraZeneca, Alkermes, Atai, Biohaven Pharmaceuticals, Squibb, Rapport Neurosciences, Lilly, Johnson & Johnson, Otsuka, Merck, Sunovion, Intra-Cellular Therapies, NeuroRX, Roche, Elan, Lundbeck, Teva, Minerva, Neurocrine Biosciences, NoemaPharma, Pfizer, and Synapse Medical Communications; his spouse was a full-time employee at Lilly (1998-2013).

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