Response and Remission Outcomes of Lumateperone for Major Depressive Episodes With Mixed Features in Major Depressive Disorder and Bipolar I or Bipolar II Disorder

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Disclosures

- S. Durgam, W.R. Earley, J. Huo, and J.B. Edwards are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson Company. S.G. Kozauer is a former employee of Intra-Cellular Therapies, a Johnson & Johnson Company.

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Background: MDD and Bipolar Depression With Mixed Features

- Many patients (25%-35%) with MDD or bipolar depression experience mixed features[1]
  - Mixed features is defined as the presence of ≥3 of 7 manic/hypomanic symptoms during most days of an MDE (DSM-5 and DSM-5-TR)[2,3]
- Patients with mixed features have[1,4]:
  - Greater depression severity
  - Increased risk of comorbidities
  - Reduced treatment response compared with patients without mixed features
- Some pharmacological treatments (eg, antidepressant monotherapy) may worsen manic symptoms in patients with an MDE with mixed features[5]
- Thus, measuring simultaneous effects on depressive and manic symptoms is important when evaluating treatments for patients with MDD or bipolar depression with mixed features

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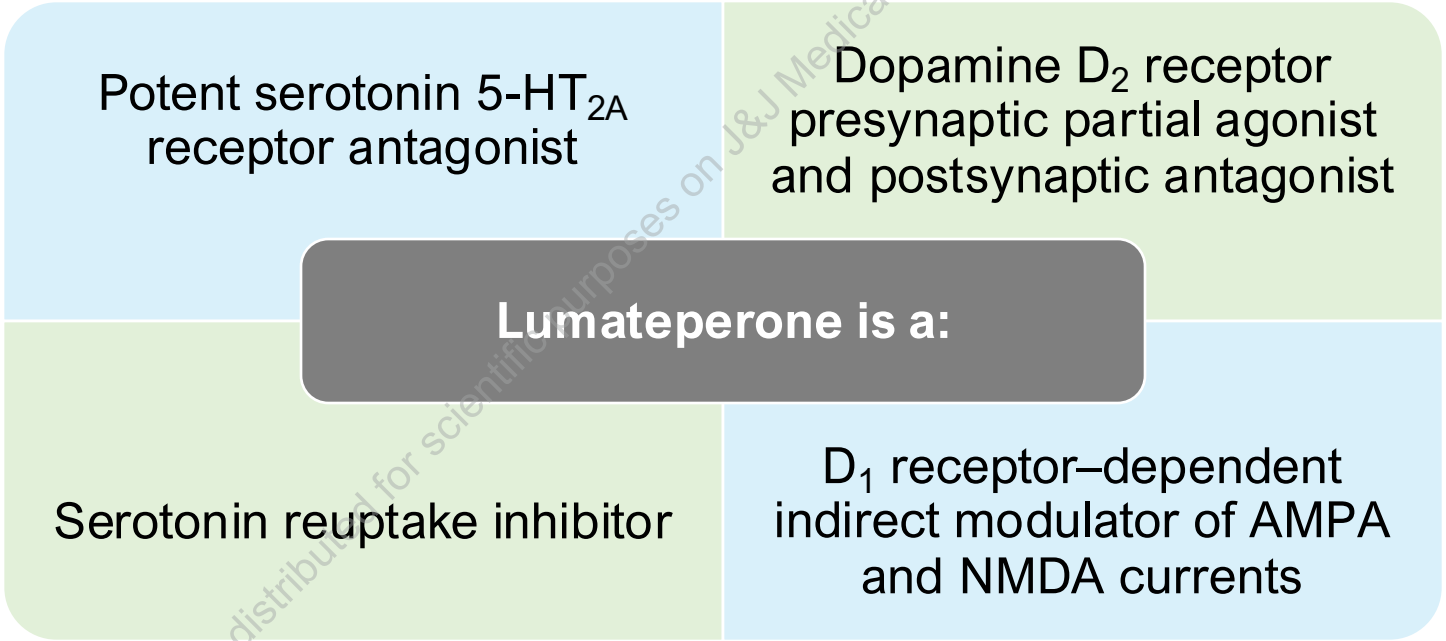
DSM-5-TR, Diagnostic and Statistical Manual, 5th ed, text revision; MDD, major depressive disorder; MDE, major depressive episode.

1. McIntyre RS, et al. *J Affect Disord*. 2015;172:259-264. 2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. 3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Text Revision. American Psychiatric Association; 2022. 4. McIntyre RS, et al. *Ther Adv Psychopharmacol*. 2018;8(1 suppl):1-16. 5. Stahl SM, et al. *CNS Spectrums*. 2017;22(2):203-219.

Background: Lumateperone

- Lumateperone is a mechanistically novel FDA-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder[1,2]
- Lumateperone simultaneously modulates serotonin, dopamine, and glutamate neurotransmission[2]



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AMPA, α-amino-3–hydroxy-5-methyl-4-isoxazolepropionic acid; FDA, US Food and Drug Administration; NMDA, *N*-methyl-D-aspartate.

1. Caplyta. Prescribing information. Intra-Cellular Therapies, Inc;2023. 2. Titulaer J, et al. *Eur Neuropsychopharmacol*. 2022;62:22-35.

Background: Efficacy and Safety of Lumateperone in Patients With Mixed Features

- A randomized, double-blind, placebo-controlled trial (NCT04285515) established the efficacy and safety of lumateperone 42 mg in patients with MDD or bipolar depression with mixed features[1]
  - Lumateperone 42 mg met the primary study endpoint, with significant improvement in MADRS Total score from baseline to Day 43 vs placebo
  - Disease severity and mania measured by CGI-S and YMRS Total score, respectively, also significantly improved with lumateperone 42 mg vs placebo
  - Lumateperone 42 mg was generally well tolerated, with minimal EPS or cardiometabolic risk and no mania/hypomania TEAEs

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CGI-S, Clinical Global Impression–Severity; EPS, extrapyramidal symptom; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; TEAE, treatment-emergent adverse event; YMRS, Young Mania Rating Scale.

1. Durgam S, et al. *J Clin Psychopharmacol.* 2025;45:67-75.

Study Design

- This post hoc analysis of Study 403 defined and measured response and remission based on reductions in both MADRS and YMRS scores in patients with MDEs with mixed features associated with MDD or bipolar disorder

Key Eligibility Criteria

- Age 18-75 years
- DSM-5–diagnosed MDD with mixed features or bipolar I or II disorder with mixed features
- Current MDE (MADRS Total score ≥24; CGI-S score ≥4)
- YMRS score 4-16

Study Design

Treatment randomized 1:1 to:
- Placebo
- Lumateperone 42 mg

Populations
- Combined MDD/bipolar depression
- Individual MDD
- Individual bipolar depression

Screening (≤2 weeks) → Double-blind treatment (6 weeks) → Follow-up (2 weeks)

Endpoints

Primary
- MADRS Total score

Key secondary
- CGI-S score

Additional
- YMRS Total score
- Composite MADRS and YMRS Total score response and remission

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CGI-S, Clinical Global Impression–Severity; DSM-5, Diagnostic and Statistical Manual, 5th ed; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; YMRS, Young Mania Rating Scale.

Patient Populations

- The mITT population comprised 383 patients
- Baseline demographics and clinical characteristics were similar between groups
- At baseline, patients had moderate to severe depression

mITT Population	Combined MDD/Bipolar Depression Population		MDD Population		Bipolar Depression Population	
	Lumateperone 42 mg	Placebo	Lumateperone 42 mg	Placebo	Lumateperone 42 mg	Placebo
Demographic Parameters	**n=192**	**n=191**	**n=92**	**n=92**	**n=100**	**n=99**
Age, mean (range), years	43.1 (18-73)	42.5 (18-70)	44.4 (18-73)	44.7 (18-69)	41.9 (18-72)	40.5 (18-70)
Sex, n (%)						
Female	119 (62.0)	117 (61.3)	55 (59.8)	54 (58.7)	64 (64.0)	63 (63.6)
Male	73 (38.0)	74 (38.7)	37 (40.2)	38 (41.3)	36 (36.0)	36 (36.4)
Race, n (%)						
White	168 (87.5)	155 (81.2)	82 (89.1)	76 (82.6)	86 (86.0)	79 (79.8)
Black	22 (11.5)	32 (16.8)	8 (8.7)	13 (14.1)	14 (14.0)	19 (19.2)
Other	2 (1.0)	4 (2.1)	2 (2.2)	3 (3.3)	0	1 (1.0)
Hispanic or Latino ethnicity, n (%)	18 (9.4)	18 (9.4)	11 (12.0)	14 (15.2)	7 (7.0)	4 (4.0)
Diagnosis, n (%)						
Bipolar I disorder	78 (40.6)	78 (40.8)	–	–	78 (78.0)	78 (78.8)
Bipolar II disorder	22 (11.5)	21 (11.0)	–	–	22 (22.0)	21 (21.2)
MDD	92 (47.9)	92 (48.2)	92 (100)	92 (100)	–	–
Baseline Efficacy Parameters	**n=192**	**n=191**	**n=92**	**n=92**	**n=100**	**n=99**
MADRS Total score, mean (SD)	31.3 (4.05)	31.1 (4.07)	30.8 (3.59)	31.2 (4.16)	31.8 (4.40)	31.1 (4.01)
CGI-S score, mean (SD)	4.5 (0.54)	4.5 (0.52)	4.4 (0.52)	4.4 (0.48)	4.6 (0.55)	4.6 (0.54)
YMRS score, mean (SD)	9.0 (2.40)	9.2 (2.46)	9.3 (2.24)	9.3 (2.09)	8.7 (2.52)	9.1 (2.76)

CGI-S, Clinical Global Impression–Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; mITT, modified intent-to-treat; YMRS, Young Mania Rating Scale.

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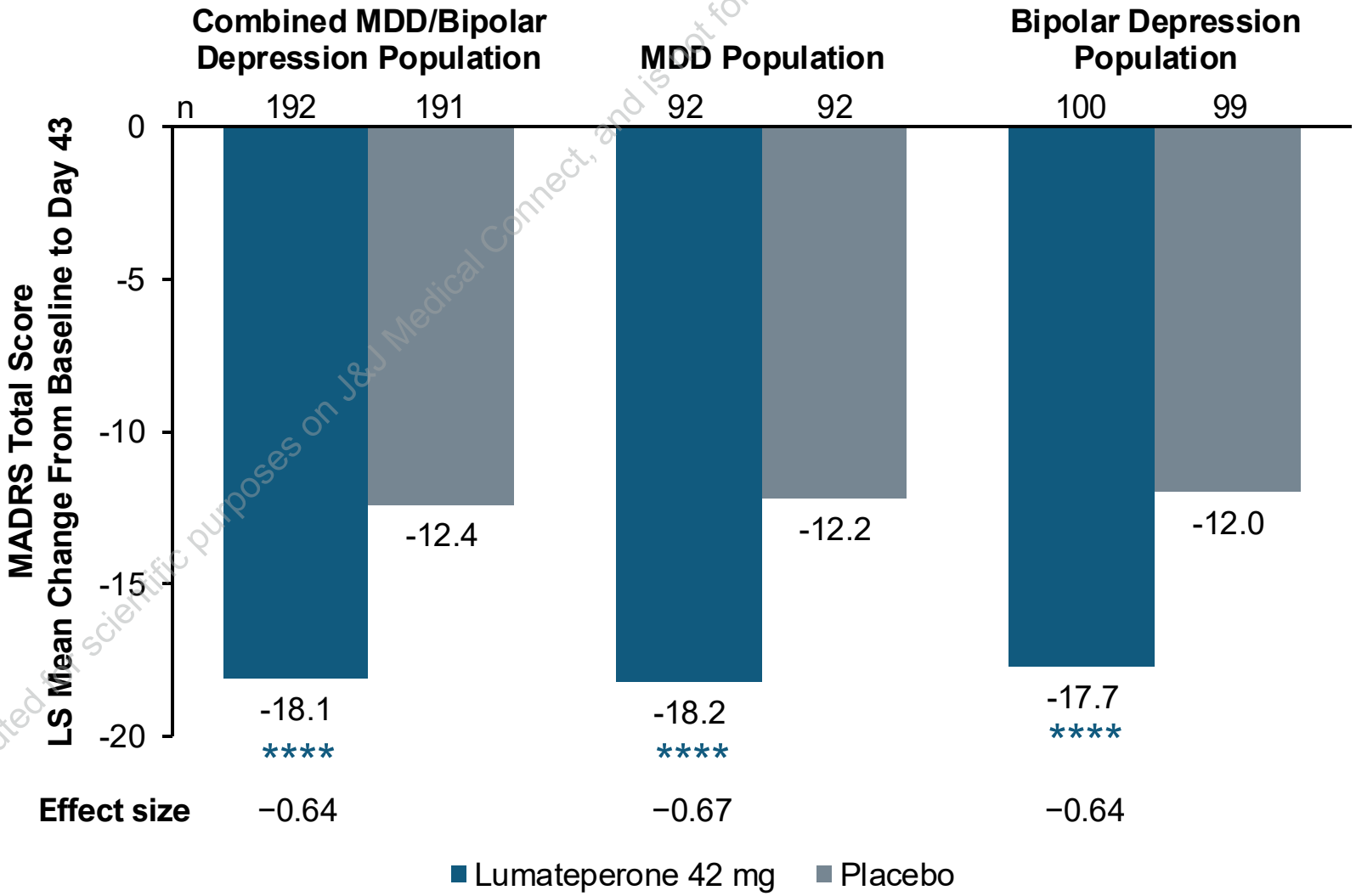
MADRS Total Score

- Lumateperone significantly improved MADRS Total score at Day 43 vs placebo in all 3 populations with mixed features



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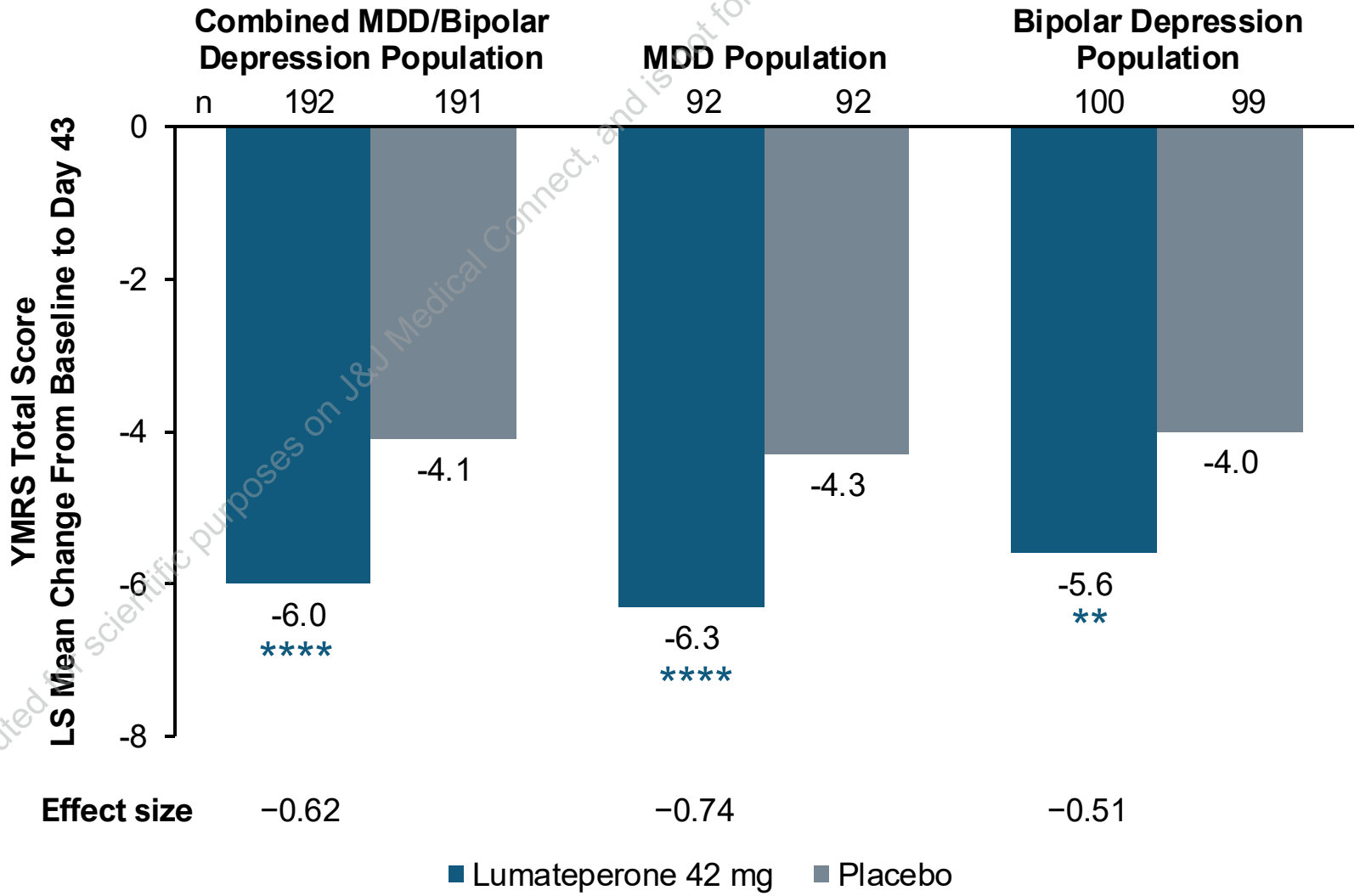
****P<.0001. LSMD vs placebo. MMRM. mITT population.

LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures. Durgam S, et al. *J Clin Psychopharmacol*. 2025;45:67-75.

YMRS Total Score

- Lumateperone significantly improved YMRS Total score at Day 43 vs placebo in all 3 populations with mixed features



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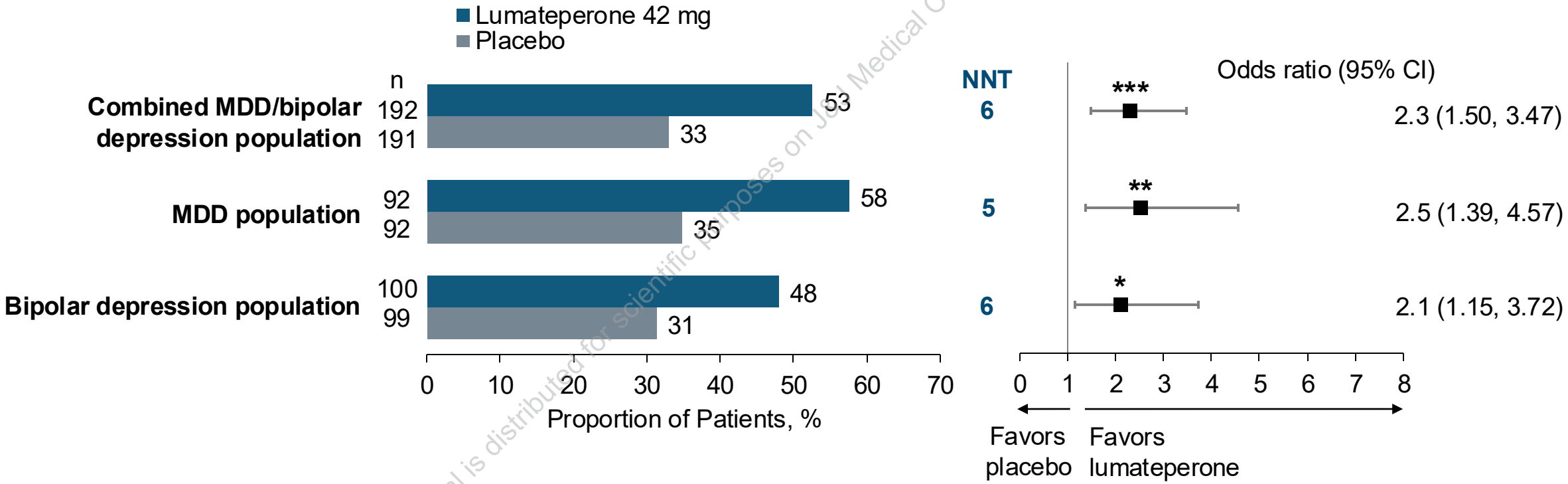
**P<.01 ****P<.0001. LSMD vs placebo. MMRM. mITT population.

LS, least squares; LSMD, least squares mean difference; MDD, major depressive disorder; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; YMRS, Young Mania Rating Scale. Durgam S, et al. *J Clin Psychopharmacol.* 2025;45:67-75.

Response: Composite MADRS Total Score and YMRS Total Score[a]

- Significantly greater composite MADRS and YMRS Total Score response rates at end of treatment were observed with lumateperone compared with placebo in all 3 populations



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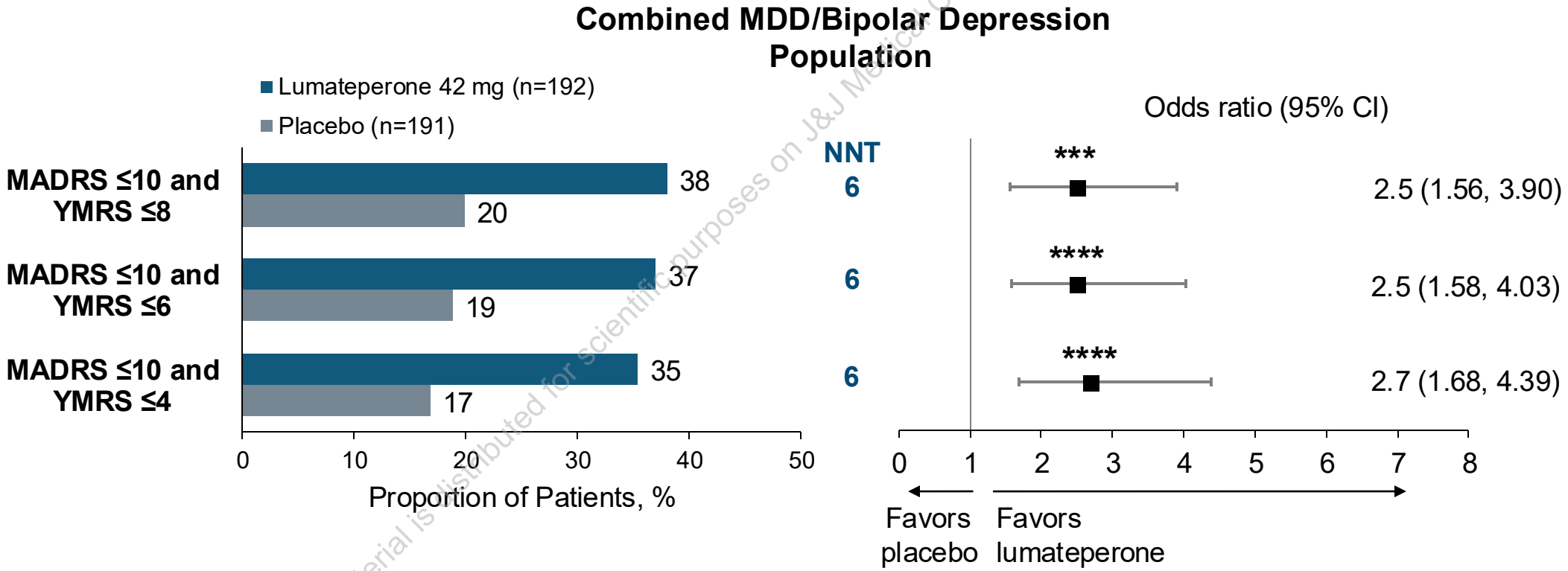
*P<.05 **P<.01 ***P<.001. Logistic regression. mITT population.
NNT = 1/(rate of lumateperone − rate of placebo).
[a] Response defined as both ≥50% MADRS Total score decrease from baseline to end of treatment and ≥50% YMRS Total score decrease from baseline to end of treatment.
MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; mITT, modified intent-to-treat; NNT, number needed to treat; YMRS, Young Mania Rating Scale.

Remission: Composite MADRS Total Score and YMRS Total Score

- Composite MADRS and YMRS Total Score remission rates at end of treatment were significantly greater with lumateperone compared with placebo in the combined population



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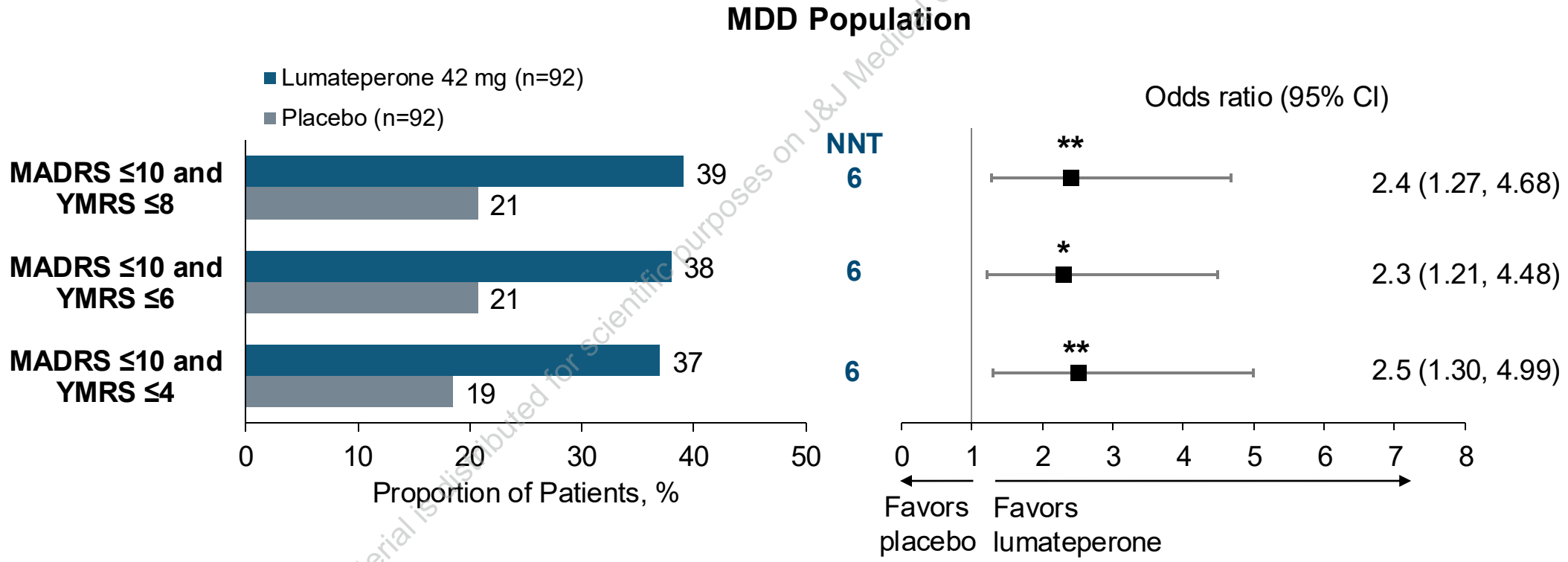
***P<.001 ****P<.0001. Logistic regression. mITT population.
NNT = 1/(rate of lumateperone − rate of placebo).
MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; mITT, modified intent-to-treat; NNT, number needed to treat; YMRS, Young Mania Rating Scale.

Remission: Composite MADRS Total Score and YMRS Total Score

- Composite MADRS and YMRS Total Score remission rates at end of treatment were significantly greater with lumateperone compared with placebo in the individual MDD population



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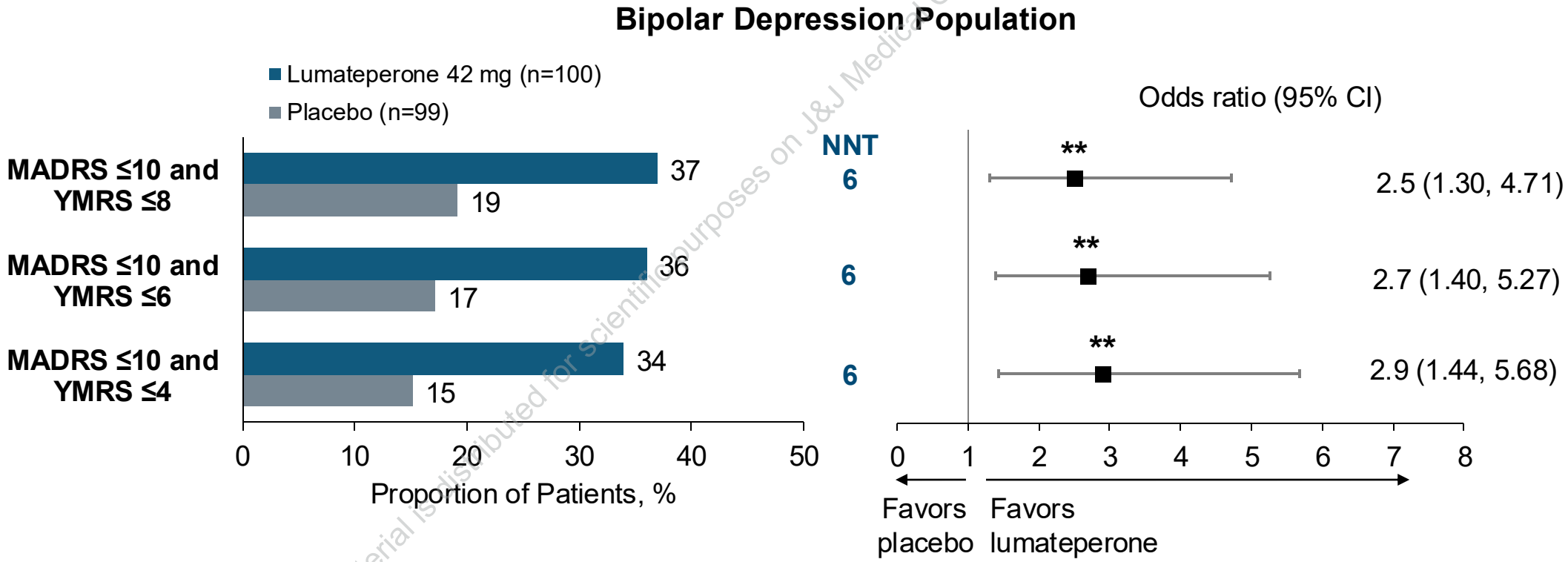
*P<.05 **P<.01. Logistic regression. mITT population.
NNT = 1/(rate of lumateperone − rate of placebo).
MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; mITT, modified intent-to-treat; NNT, number needed to treat; YMRS, Young Mania Rating Scale.

Remission: Composite MADRS Total Score and YMRS Total Score

- Composite MADRS and YMRS Total Score remission rates at end of treatment were significantly greater with lumateperone compared with placebo in the individual bipolar depression population



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**P<.01. Logistic regression. mITT population.
NNT = 1/(rate of lumateperone − rate of placebo).
MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; NNT, number needed to treat; YMRS, Young Mania Rating Scale.

Conclusions

- Lumateperone 42 mg significantly improved MADRS Total score and YMRS Total score compared with placebo in:
  - The combined population of patients with MDD or bipolar depression with mixed features
  - The individual population of patients with MDD with mixed features
  - The individual population of patients with bipolar depression with mixed features
- Lumateperone 42 mg concurrently improved both depressive and manic symptoms, as shown by significantly greater composite MADRS and YMRS Total score response and remission rates compared with placebo
- The results support lumateperone 42 mg as a promising treatment option in patients with an MDE with mixed features associated with MDD or bipolar I or bipolar II disorder

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MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; YMRS, Young Mania Rating Scale.

Thank you

The authors thank all study investigators, research staff, and patients for their participation

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