Efficacy of Adjunctive Lumateperone in Patients With Major Depressive Disorder: A Pooled Post Hoc Analysis of Patients With Clinical Features Associated With a More Challenging Disease Course

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Background

- Major depressive disorder (MDD) is a common and disabling psychiatric condition associated with considerable complexity and substantial burden that can impair functioning and quality of life[1]
 - Some clinical characteristics may be associated with greater disease burden and poorer outcomes in patients with MDD[2]
 - These may include recurrent major depressive episodes (MDEs), longer MDE duration, and history of psychiatric hospitalization[2,3]
 - A significant proportion of patients have suboptimal response to antidepressant therapy (ADT); for these patients, adjunctive treatment may be an option[4-8]
- Lumateperone is FDA approved for the treatment of MDD in adults as an adjunctive therapy to ADT; treatment of schizophrenia in adults; and treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as an adjunctive therapy with lithium or valproate[9]
 - Lumateperone is a mechanistically novel, multimodal antipsychotic that modulates serotonergic, dopaminergic, and, indirectly, glutamatergic neurotransmission[9,10]
- In 2 Phase 3, randomized, double-blind, placebo-controlled studies (Study 501, NCT04985942; Study 502, NCT05061706), adjunctive lumateperone 42 mg provided superior efficacy versus adjunctive placebo, with meaningful and significant improvements in depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS] Total score), disease severity (Clinical Global Impression–Severity [CGI-S score]), and patient reported outcomes (Quick Inventory of Depressive Symptomatology-Self Report-16 item [QIDS-SR-16])[11,12]
- This pooled analysis of Studies 501 and 502 evaluated the efficacy of adjunctive lumateperone 42 mg across subgroups defined by clinical characteristics associated with more challenging disease course, including a higher number of prior MDEs, longer duration of the current MDE, and prior psychiatric hospitalization

Methods

- Eligible adults (aged 18-65 years) in Studies 501 and 502 met *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for MDD with inadequate response to 1 or 2 ADT courses (<50% improvement on the Antidepressant Treatment Response Questionnaire) in the current MDE and had MADRS Total score ≥24, CGI-S score ≥4, and QIDS-SR-16 Total score ≥14[11,12]
 - Patients were randomized (1:1) to receive 6 weeks of oral lumateperone 42 mg or placebo per day adjunctive to ADT[11,12]
- Subgroups were defined based on prior number of MDEs (<5 prior MDEs/≥5 prior MDEs), current MDE duration (<6 months/≥6 months), history of psychiatric hospitalization (no/yes), number of ADT treatment failures in the current MDE (1 ADT/2 ADTs), and age of MDD onset (<22 years/≥22 years)
- Mean changes from baseline to end of treatment (EOT) were evaluated in the modified intent-to-treat (mITT) population using mixed-effects model for repeated measures (MMRM; MADRS and CGI-S) or analysis of covariance (ANCOVA; QIDS-SR-16)
- All *P* values were nominal and were not adjusted for multiplicity

Results

Patient Population

- The pooled mITT population comprised 950 patients (lumateperone 42 mg + ADT, n=471; placebo + ADT, n=479)[13]
- Baseline characteristics were generally similar between treatment arms overall (**Table 1**) and within subgroups (**Table 2**)

Table 1. Baseline Demographics and Clinical Characteristics (mITT Population)[13]

	Lumateperone 42 mg + ADT (n=471)	Placebo + ADT (n=479)
Age, mean (range), years	45.2 (18-65)	45.8 (18-65)
Sex, n (%)		
Female	318 (67.5)	325 (67.8)
Male, n (%)	153 (32.5)	154 (32.2)
Race, n (%)		
White	404 (85.8)	413 (86.2)
Asian	41 (8.7)	35 (7.3)
Black	25 (5.3)	24 (5.0)
Other[a]	1 (0.2)	7 (1.5)
Hispanic or Latino ethnicity, n (%)	50 (10.6)	49 (10.2)
Number of lifetime depressive episodes, mean (range)	3.6 (1-30)	4.0 (1-36)
Lifetime history of treatment failures including the current MDE, n (%)		
1	352 (74.7)	352 (73.5)
2	119 (25.3)	127 (26.5)
Prior psychiatric hospitalization, n (%)		
Yes	87 (18.5)	88 (18.4)
No	384 (81.5)	391 (81.6)
MADRS Total score, mean (SD)[b]	30.6 (3.82)	30.8 (3.80)
CGI-S score, mean (SD)[b]	4.7 (0.57)	4.6 (0.57)
QIDS-SR-16 Total score, mean (SD)[c]	18.0 (2.42)	17.8 (2.40)

[a]Other includes Native Hawaiian or other Pacific Islander, multiple, or other. [b]Baseline mean MADRS Total score (lumateperone 42 mg + ADT, 30.6; placebo + ADT, 30.8) and CGI-S score (lumateperone 42 mg + ADT, 4.7; placebo + ADT, 4.6). [c]ITT population (lumateperone 42 mg + ADT n=483, placebo + ADT n=481).
ADT, antidepressant therapy; CGI-S, Clinical Global Impressions–Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; MDE, major depressive episode; mITT, modified intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Table 2. Baseline Demographics and Clinical Characteristics by Subgroup

	Lumateperone 42 mg + ADT	Placebo + ADT	Lumateperone 42 mg + ADT	Placebo + ADT
Number of Prior MDEs	**<5 Prior MDEs**		**≥5 Prior MDEs**	
	n=353	n=352	n=118	n=127
Age, mean (range), years	43.3 (18-65)	44.1 (18-65)	51.1 (23-65)	50.4 (18-65)
Female, n (%)	236 (66.9)	227 (64.5)	82 (69.5)	98 (77.2)
White, n (%)	301 (85.3)	299 (84.9)	103 (87.3)	114 (89.8)
Number of lifetime MDEs, mean (range)	2.5 (1-4)	2.6 (1-4)	6.7 (5-30)	7.8 (5-36)
Duration of current MDE, mean (range), months	7.2 (2-18)	7.0 (2-18)	6.6 (2-18)	6.4 (2-18)
Current MDE Duration	**<6 Months**		**≥6 Months**	
	n=250	n=261	n=221	n=218
Age, mean (range), years	46.1 (18-65)	46.7 (18-65)	44.3 (18-65)	44.8 (18-65)
Female, n (%)	160 (64.0)	177 (67.8)	158 (71.5)	148 (67.9)
White, n (%)	218 (87.2)	232 (88.9)	186 (84.2)	181 (83.0)
Number of lifetime MDEs, mean (range)	3.8 (1-30)	4.0 (1-20)	3.3 (1-11)	4.0 (1-36)
Duration of current MDE, mean (range), months	3.6 (1.8-6.0)	3.6 (1.6-6.0)	10.6 (6.0-17.9)	10.7 (6.1-17.7)
History of Psychiatric Hospitalization	**No**		**Yes**	
	n=384	n=391	n=87	n=88
Age, mean (range), years	44.6 (18-65)	45.1 (18-65)	48.2 (18-65)	49.0 (18-65)
Female, n (%)	263 (68.5)	267 (68.3)	55 (63.2)	58 (65.9)
White, n (%)	323 (84.1)	329 (84.1)	81 (93.1)	84 (95.5)
Number of lifetime MDEs, mean (range)	3.2 (1-15)	3.5 (1-36)	5.2 (1-30)	6.0 (1-20)
Duration of current MDE, mean (range), months	7.4 (1.9-17.8)	7.1 (1.6-17.7)	5.5 (1.8-17.9)	5.6 (1.9-17.5)
Number of ADT Treatment Failures in the Current MDE	**1 ADT Failure**		**2 ADT Failures**	
	n=424	n=418	n=47	n=61
Age, mean (range), years	45.5 (18-65)	46.4 (18-65)	43.1 (18-65)	41.6 (19-64)
Female, n (%)	284 (67.0)	285 (68.2)	34 (72.3)	40 (65.6)
White, n (%)	363 (85.6)	360 (86.1)	41 (87.2)	53 (86.9)
Number of lifetime MDEs, mean (range)	3.6 (1-30)	4.1 (1-36)	3.0 (1-10)	3.2 (1-11)
Duration of current MDE, mean (range), months	6.8 (1.8-17.9)	6.4 (1.6-17.7)	9.4 (3.8-17.2)	10.1 (2.9-17.7)
Age of MDD Onset	**<22 Years**		**≥22 Years**	
	n=81	n=78	n=390	n=401
Age, mean (range), years	33.6 (18-64)	33.7 (18-65)	47.7 (23-65)	48.2 (22-65)
Female, n (%)	56 (69.1)	56 (71.8)	262 (67.2)	269 (67.1)
White, n (%)	69 (85.2)	62 (79.5)	335 (85.9)	351 (87.5)
Number of lifetime MDEs, mean (range)	3.6 (1-11)	4.3 (1-20)	3.6 (1-30)	3.9 (1-36)
Duration of current MDE, mean (range), months	8.6 (2.0-17.2)	8.8 (2.6-17.4)	6.7 (1.8-17.9)	6.5 (1.6-17.7)

ADT, antidepressant therapy; MDD, major depressive disorder; MDE, major depressive episode.

Number of Prior MDEs

- Lumateperone 42 mg + ADT versus placebo + ADT significantly improved MADRS Total score, CGI-S score, and QIDS-SR-16 Total score from baseline to EOT regardless of the number of prior MDEs:
 - MADRS Total score least squares mean difference versus placebo (LSMD): <5 prior MDEs, −4.2; ≥5 prior MDEs, −5.7; both *P*<.0001 (**Figure 1**)
 - CGI-S score LSMD: <5 prior MDEs, −0.6; ≥5 prior MDEs, −0.7; both *P*<.0001 (**Figure 2**)
 - QIDS-SR-16 LSMD: <5 prior MDEs, −2.1; ≥5 prior MDEs, −3.1; both *P*<.001 (**Figure 3**)

Current MDE Duration

- Lumateperone 42 mg + ADT versus placebo + ADT significantly improved MADRS Total score, CGI-S score, and QIDS-SR-16 Total score from baseline to EOT both for patients with current MDE duration of <6 months and for those with current MDE duration ≥6 months
 - MADRS Total score LSMD: <6 months, −4.3; ≥6 months, −5.0; both *P*<.0001 (**Figure 1**)
 - CGI-S score LSMD: <6 months, −0.6; ≥6 months, −0.7; both *P*<.0001 (**Figure 2**)
 - QIDS-SR-16 LSMD: <6 months, −2.5; ≥6 months, −2.2; both *P*<.001 (**Figure 3**)

History of Psychiatric Hospitalization

- Similar results were observed for subgroups with and without prior psychiatric hospitalization
 - MADRS Total score LSMD: no, −4.2; yes, −6.3; both *P*<.0001 (**Figure 1**)
 - CGI-S score LSMD: no, −0.6; yes, −0.7; both *P*<.0001 (**Figure 2**)
 - QIDS-SR-16 Total score LSMD: no, −2.1; yes, −3.6; both *P*<.001 (**Figure 3**)

Number of ADT Treatment Failures in the Current MDE

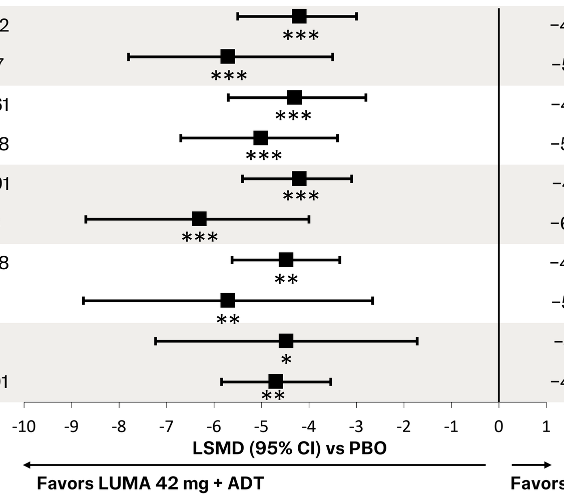
- Lumateperone 42 mg + ADT versus placebo + ADT significantly improved depression severity from baseline to EOT for patients with 1 or 2 ADT treatment failures in the current MDE
 - MADRS Total score LSMD: 1 ADT failure, −4.5; 2 ADT failures, −5.7; both *P*<.001 (**Figure 1**)
 - CGI-S score LSMD: 1 ADT failure, −0.6; 2 ADT failures, −0.9; both *P*<.001 (**Figure 2**)
 - QIDS-SR-16 Total score LSMD: 1 ADT failure, −2.1; 2 ADT failures, −4.4; both *P*<.001 (**Figure 3**)

Age of MDD Onset

- Lumateperone 42 mg + ADT versus placebo + ADT improved MADRS Total score, CGI-S score, and QIDS-SR-16 Total score from baseline to EOT for patients with age of MDD onset <22 years and for those with age of MDD onset ≥22 years; all comparisons were significant except for QIDS-SR-16 Total score for those with MDD onset <22 years of age
 - MADRS Total score LSMD: onset <22 years of age, −4.5 (*P*<.01); MDD onset ≥22 years of age, −4.7 (*P*<.001) (**Figure 1**)
 - CGI-S score LSMD: onset <22 years of age, −0.6; MDD onset ≥22 years of age, −0.6; both *P*<.001 (**Figure 2**)
 - QIDS-SR-16 Total score LSMD: MDD onset <22 years of age, −1.4 (*P*=.064); MDD onset ≥22 years of age, −2.6 (*P*<.001) (**Figure 3**)

Figure 1. Changes From Baseline to EOT in MADRS Total Score by Subgroup

	LUMA 42 mg + ADT n/N1	PBO + ADT n/N1	LSMD (95% CI)	ES
<5 prior MDEs	314/353	331/352	−4.2 (−5.5, −3.0)	−0.52
≥5 prior MDEs	105/118	119/127	−5.7 (−7.8, −3.5)	−0.68
Current MDE duration <6 mo	230/250	245/261	−4.3 (−5.7, −2.8)	−0.52
Current MDE duration ≥6 mo	189/221	205/218	−5.0 (−6.7, −3.4)	−0.60
No prior psychiatric hospitalization	340/384	368/391	−4.2 (−5.4, −3.1)	−0.51
Prior psychiatric hospitalization	79/87	82/88	−6.3 (−8.7, −4.0)	−0.82
1 ADT failure in current MDE	376/424	392/418	−4.5 (−5.6, −3.4)	−0.55
2 ADT failures in current MDE	43/47	58/61	−5.7 (−8.8, −2.7)	−0.73
MDD onset at age <22 years	66/81	73/78	−4.5 (−7.2, −1.7)	−0.53
MDD onset at age ≥22 years	353/390	377/401	−4.7 (−5.8, −3.5)	−0.58

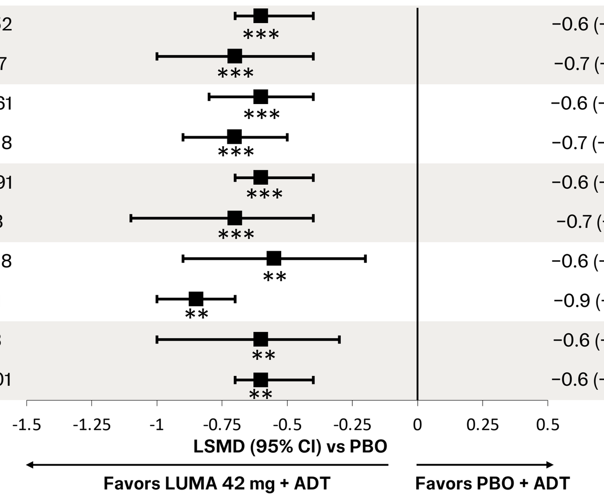


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-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1
LSMD (95% CI) vs PBO
Favors LUMA 42 mg + ADT
Favors PBO + ADT

* *P*<.01 ** *P*<.001 *** *P*<.0001. Mixed-effects model for repeated measures in the mITT population. ADT, antidepressant therapy; EOT, end of treatment; ES, effect size; LSMD, least squares mean difference; LUMA, lumateperone; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; mITT, modified intent-to-treat; n, number of patients with Day 43 assessment; N1, number of mITT patients in each group at baseline; PBO, placebo.

Figure 2. Changes From Baseline to EOT in CGI-S Score by Subgroup

	LUMA 42 mg + ADT n/N1	PBO + ADT n/N1	LSMD (95% CI)	ES
<5 prior MDEs	314/353	331/352	−0.6 (−0.7, −0.4)	−0.55
≥5 prior MDEs	105/118	119/127	−0.7 (−1.0, −0.4)	−0.61
Current MDE duration <6 mo	230/250	245/261	−0.6 (−0.8, −0.4)	−0.52
Current MDE duration ≥6 mo	189/221	205/218	−0.7 (−0.9, −0.5)	−0.62
No prior psychiatric hospitalization	340/384	368/391	−0.6 (−0.7, −0.4)	−0.53
Prior psychiatric hospitalization	79/87	82/88	−0.7 (−1.1, −0.4)	−0.74
1 ADT failure in current MDE	376/424	392/418	−0.6 (−0.7, −0.4)	−0.52
2 ADT failures in current MDE	43/47	58/61	−0.9 (−1.2, −0.5)	−0.56
MDD onset at age <22 years	66/81	73/78	−0.6 (−1.0, −0.3)	−0.57
MDD onset at age ≥22 years	353/390	377/401	−0.6 (−0.7, −0.4)	−0.56

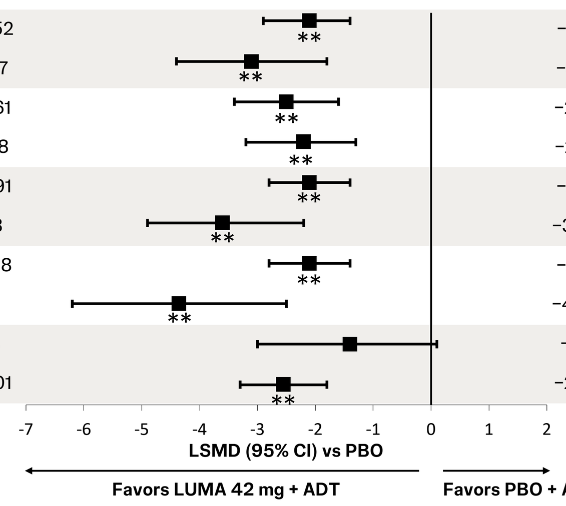


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-1.5 -1.25 -1 -0.75 -0.5 -0.25 0 0.25 0.5
LSMD (95% CI) vs PBO
Favors LUMA 42 mg + ADT
Favors PBO + ADT

** *P*<.001 *** *P*<.0001. Mixed-effects model for repeated measures in the mITT population. ADT, antidepressant therapy; CGI-S, Clinical Global Impressions–Severity; EOT, end of treatment; ES, effect size; LSMD, least squares mean difference; LUMA, lumateperone; MDD, major depressive disorder; MDE, major depressive episode; mITT, modified intent-to-treat; n, number of patients with Day 43 assessment; N1, number of mITT patients in each group at baseline; PBO, placebo.

Figure 3. Changes From Baseline to EOT in QIDS-SR-16 Total Score by Subgroup

	LUMA 42 mg + ADT n/N1	PBO + ADT n/N1	LSMD (95% CI)	ES
<5 prior MDEs	346/353	345/352	−2.1 (−2.9, −1.4)	−0.42
≥5 prior MDEs	114/118	125/127	−3.1 (−4.4, −1.8)	−0.61
Current MDE duration <6 mo	245/250	256/261	−2.5 (−3.4, −1.6)	−0.50
Current MDE duration ≥6 mo	215/221	214/218	−2.2 (−3.2, −1.3)	−0.44
No prior psychiatric hospitalization	374/384	384/391	−2.1 (−2.8, −1.4)	−0.41
Prior psychiatric hospitalization	86/87	86/88	−3.6 (−4.9, −2.2)	−0.78
1 ADT failure in current MDE	413/424	409/418	−2.1 (−2.8, −1.4)	−0.41
2 ADT failures in current MDE	47/47	61/61	−4.4 (−6.2, −2.5)	−0.90
MDD onset at age <22 years	78/81	77/78	−1.4 (−3.0, 0.1)	−0.30
MDD onset at age ≥22 years	382/390	393/401	−2.6 (−3.3, −1.8)	−0.51


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-7 -6 -5 -4 -3 -2 -1 0 1 2
LSMD (95% CI) vs PBO
Favors LUMA 42 mg + ADT
Favors PBO + ADT

** *P*<.001. Analysis of covariance in the mITT population. ADT, antidepressant therapy; EOT, end of treatment; ES, effect size; LSMD, least squares mean difference; LUMA, lumateperone; MDD, major depressive disorder; MDE, major depressive episode; mITT, modified intent-to-treat; n, number of patients with Day 43 assessment; N1, number of mITT patients in each group at baseline; PBO, placebo; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Conclusions

- Lumateperone 42 mg + ADT significantly improved MADRS Total score, CGI-S score, and QIDS-SR-16 Total score versus placebo + ADT across subgroups defined by prior number of MDEs (<5 prior MDEs and ≥5 prior MDEs), current MDE duration (<6 months and ≥6 months), history of psychiatric hospitalization (no and yes), number of ADT treatment failures in the current MDE (1 ADT and 2 ADTs), and age of MDD onset (≥22 years)
 - Significant improvements in MADRS Total score and CGI-S score were also observed in the subgroup with age of MDD onset <22 years
- These findings support adjunctive lumateperone 42 mg as an effective treatment option for patients with MDD with high or low clinical burden, both early- and late-illness patients, including those with clinical features associated with a more challenging disease course

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I Turkoz, B Curcio, KR Dorsey, Z Zhang, and C Edelstein are employees of Johnson & Johnson.

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