Long-Term Adjunctive Lumateperone Treatment in Major Depressive Disorder: Results From a Six-Month Open-Label Extension Study

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Faculty Conflict of Interest Disclosure

We have the following potential conflict(s) of interest to report:

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Participation in a company sponsored speaker's bureau	Andrew J. Cutler has served on a speaker's bureau for: AbbVie, Alfasigma, Alkermes, Axsome, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular Therapies, Ironshore Pharmaceuticals, J&J, Lundbeck, Neurocrine, Noven, Otsuka, Supernus, Teva, Tris Pharma, and Vanda Pharmaceuticals
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Spouse/partner	None
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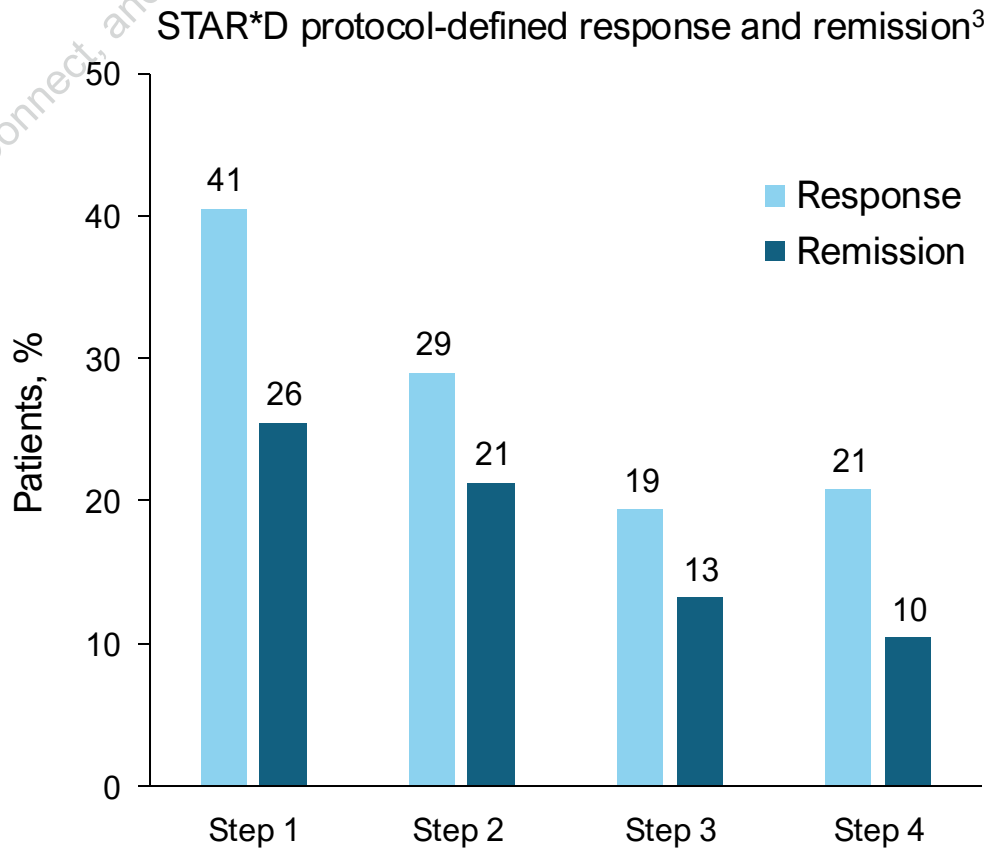
Background: Major Depressive Disorder (MDD)

- MDD is a highly burdensome illness that is associated with[1]
  - Functional impairment
  - Comorbidities
  - Reduced quality of life
- MDD is often chronic, with a high risk of relapse and recurrence that may require long-term or lifetime treatment[2]
- With first-line anti-depressant treatment, most patients fail to achieve remission (~75%) and remission rates decrease with each successive treatment[3]
- Current treatments for MDD are often limited by undesirable side effects, including weight gain and metabolic disturbances[4]



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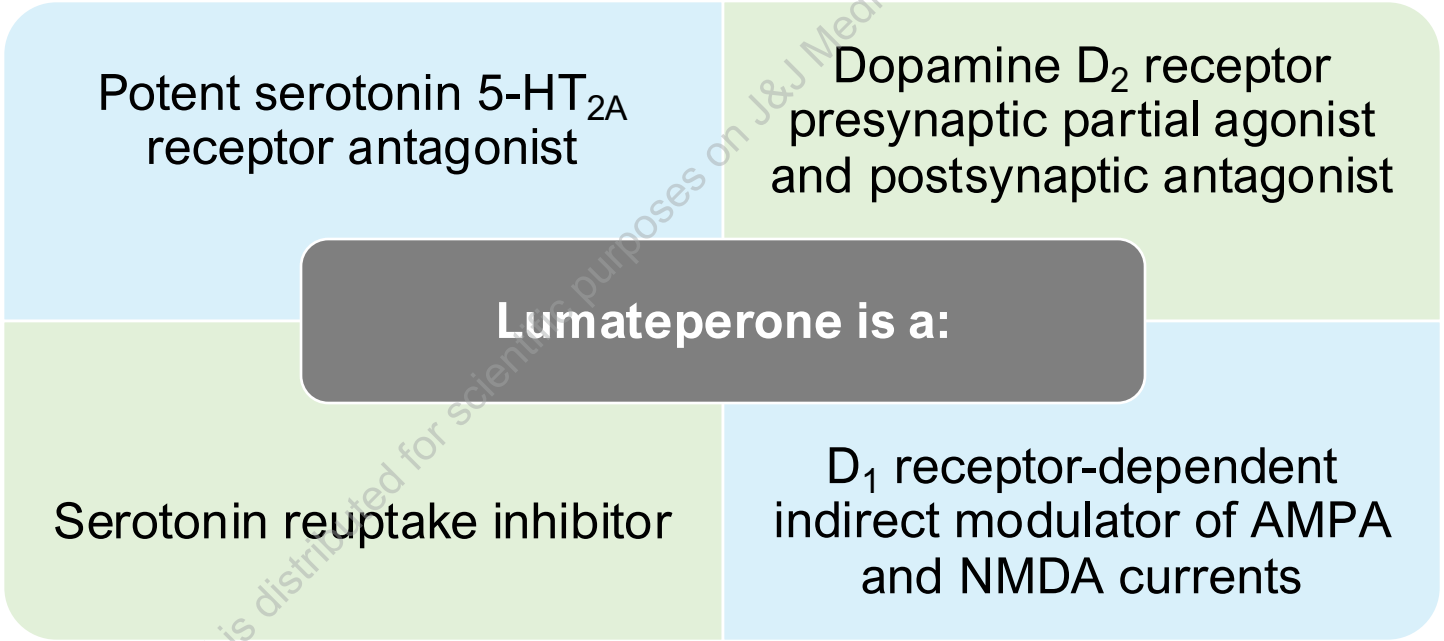
MDD, major depressive disorder.

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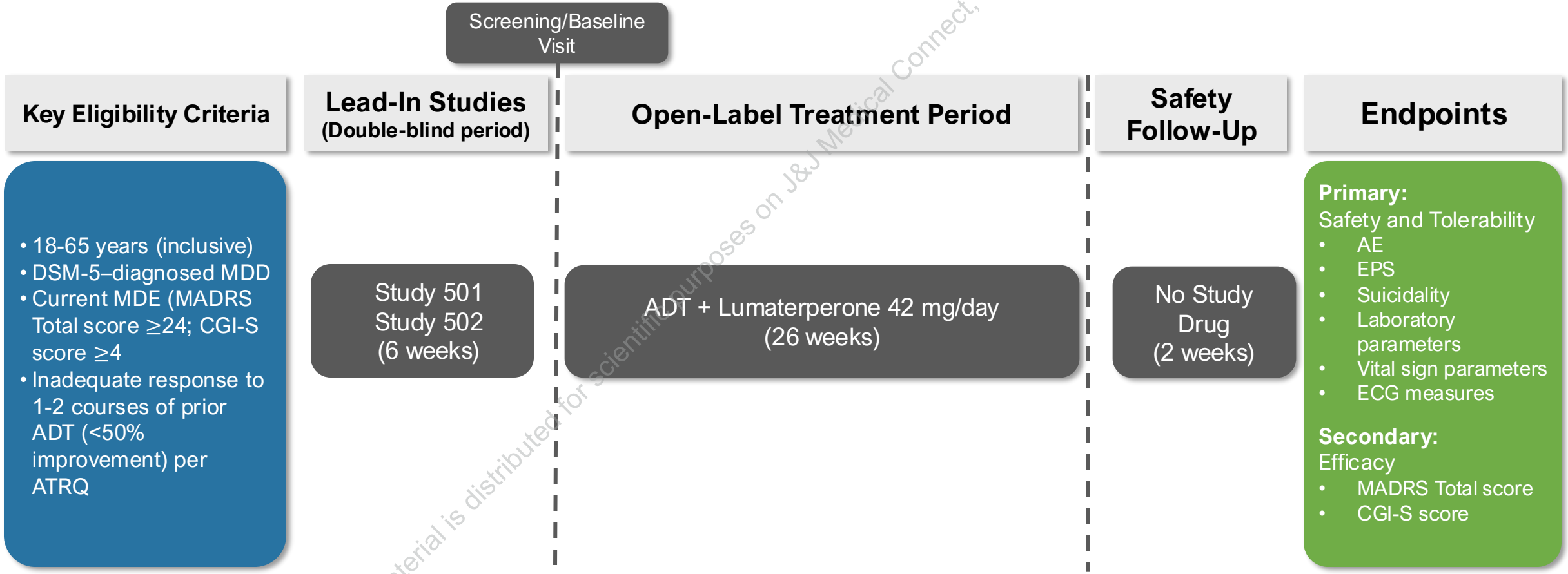
AMPA, α-amino-3–hydroxy-5-methyl-4-isoxazolepropionic acid; FDA, US Food and Drug Administration; NMDA, *N*-methyl-D-aspartate.

Study Design

- Patients who safely completed the 6-week double-blind treatment period could enroll in Study 503, which was a long-term OLE study to support FDA approval



ADT, antidepressant therapy; AE, adverse event; ATRQ, Antidepressant Treatment Response Questionnaire; CGI-S, Clinical Global Impression-Severity; DSM-5, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; ECG, electrocardiogram; EPS, extrapyramidal symptoms; FDA, US Food and Drug Administration; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; OLE, open-label extension.

Patient Disposition of Safety Population

- Of the 809 patients enrolled in the OLE safety population, 84.5% completed the treatment period
- The most common reasons for treatment discontinuation were adverse events (7.4%) and withdrawal of consent (5.1%)

	Lumateperone 42 mg + ADT
Enrolled in OLE, n	812
Safety population, n	809
Discontinued treatment, n (%)[a]	125 (15.5)
Adverse event	60 (7.4)
Patient withdrew consent	41 (5.1)
Protocol violation	8 (1.0)
Lack of efficacy	7 (0.9)
Lost to follow up	5 (0.6)
Other	4 (0.5)
Completed the OLE treatment period, n (%)[a]	648 (84.5)

[a] Proportion of patients treated.
ADT, antidepressant therapy; OLE, open-label extension.

Baseline Demographics and Disease Characteristics

- Demographics and baseline characteristics were similar to patients in the 6-week DB placebo-controlled treatment periods
- The most common SSRI was citalopram/escitalopram (30.4%) and the most common SNRI was venlafaxine/desvenlafaxine (18.7%)
- Mean MADRS and CGI-S scores at DB baseline indicated moderate-to-severe depression

	Lumateperone 42 mg + ADT (N=809)
Age, mean (range), years	46.2 (18-66)
Sex, n (%)	
Female	549 (67.9)
Male	260 (32.1)
Race, n (%)	
White	703 (86.9)
Asian	61 (7.5)
Black	37 (4.6)
Other	8 (1.0)
Hispanic or Latino ethnicity, n (%)	86 (10.6)
No. of lifetime depressive episodes, mean (range)	3.8 (1-36)
No. of lifetime of treatment failures n (%)[a]	
1	596 (73.7)
2	213 (26.3)
Background ADT during the OLE	
SSRI	535 (66.1)
SNRI	224 (27.7)
Other (bupropion)	50 (6.2)
MADRS Total score	
At DB Baseline, mean (SD)	30.7 (3.8)
At OLE Baseline, mean (SD)	18.2 (8.6)
CGI-S score	
At DB Baseline, mean (SD)	4.7 (0.6)
At OLE Baseline, mean (SD)	3.4 (1.1)

[a] Includes the current episode. Treatment failure defined as no remission with medications approved for the treatment of MDD at an adequate dose (per product label) and for an adequate duration of at least 6 weeks for monotherapy and 3 weeks for adjunctive therapy.
ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity; DB, double-blind; MADRS, Montgomery-Åsberg Depression Rating Scale; OLE, open-Label extension; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Safety: Adverse Events in Safety Population During OLE Period[a]

- 548 (67.7%) had ≥1 TEAE during the OLE
  - Most TEAEs (>98%) were mild or moderate in severity
  - Serious adverse events were 1.0%
- AEs led to discontinuation in 7.4% of patients
  - Only dizziness led to discontinuation in more than 1% of patients (1.1%)
- No suicidal behavior or suicidality serious AEs were reported in the study

Event, n (%)	Lumateperone 42 mg + ADT (N=809)
≥1 TEAE	548 (67.7)
Drug-related TEAE[a]	292 (36.1)
SAE	8 (1.0)
Discontinued treatment due to AE	60 (7.4)
Deaths	0
TEAEs occurring in ≥ 5% of patients	
Headache	134 (16.6)
Dizziness	86 (10.6)
Dry mouth	65 (8.0)
Nausea	62 (7.7)
Somnolence	58 (7.2)
Diarrhea	50 (6.2)
Nasopharyngitis	42 (5.2)

[a] An AE that occurred during the open-label treatment period was considered a TEAE if it started as a new event or if its severity increased during the OLE period; an AE that occurred more than 1 day after the date of the last dose of open-label lumateperone was not counted as a TEAE.
ADT, antidepressant therapy; AE, adverse event; OLE, open-label extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Safety: Body Morphology, Metabolic, Prolactin, and Vital Sign Assessments

- Changes in body morphology were small
- Potentially clinically significant weight increase or decrease was low and similar
- There were minimal changes in cardiometabolic parameters
  - Mean changes in blood pressure, heart rate, and respiratory rate were minimal
- Mean changes in prolactin levels at end of treatment were low, similar to what was seen in DB studies, and not clinically relevant

	Lumateperone 42 mg + ADT (N=483)	
	Baseline Mean (SD)	Mean Change from Baseline to EOT (SD)
Weight, kg	78.96 (16.9)	–0.16 (3.72)
BMI, kg/m^2	27.8 (5.02)	–0.05 (1.33)
Waist circumference, cm	92.96 (13.79)	–0.54 (5.50)
Cholesterol, mg/dL		
Total	199.7 (42.10)	–8.2 (32.30)
LDL	138.4 (41.24)	–9.6 (30.42)
HDL	56.7 (16.94)	0.1 (11.79)
Triglycerides, mg/dL	137.3 (81.66)	-0.2 (84.26)
Glucose, mg/dL	93.3 (14.75)	1.1 (15.56)
Insulin, µIU/L	14.51 (19.96)	-0.41 (22.41)
Prolactin, ng/mL	10.07 (12.98)	1.13 (13.01)
PCS Criterion	**n/N (%)**	
≥7% increase in weight	66/779 (8.5)	
≥7% decrease in weight	75/779 (9.6)	

ADT, antidepressant therapy; BMI, body mass index; DB, double-blind; EOT, end of treatment; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCS, potentially clinically significant.

Safety: Extrapyramidal Symptoms Assessments

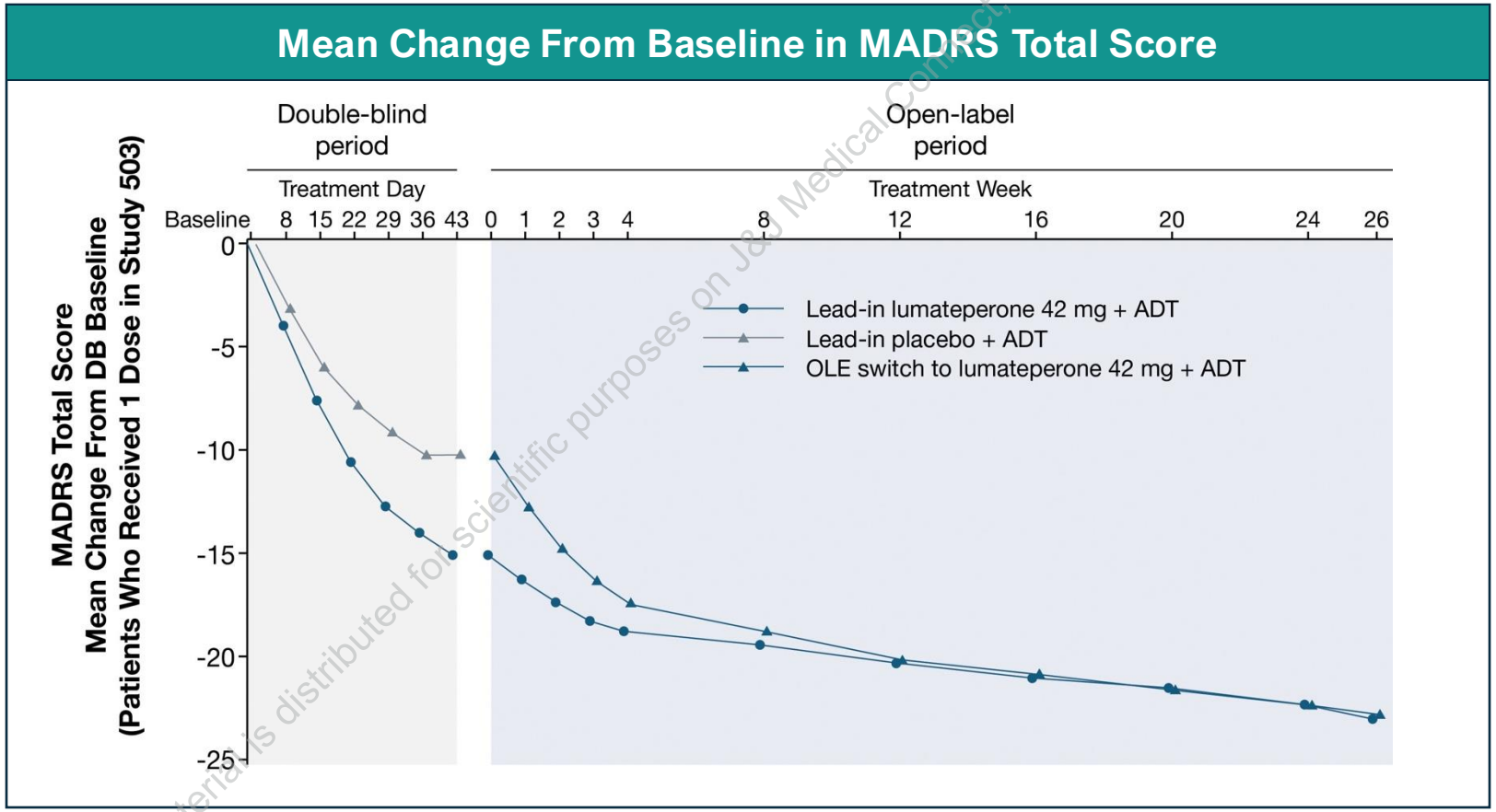
- There were no notable changes in EPS as assessed by clinician-rated scales during the study
- EPS as defined by categorical shifts in the BARS or SAS scales were rare
- The frequency of EPS-related TEAEs was 3.8%

	Lumateperone 42 mg + ADT (n=809)	
	Baseline Mean (SD)	Mean Change to EOT (SD)
BARS Total score	0.1 (0.52)	–0.1 (0.53)
AIMS Total score	0.0 (0.37)	–0.0 (0.38)
SAS Total score	0.1 (0.36)	–0.0 (0.38)
EPS defined by categorical shifts	**n/N (%)[a]**	
Parkinsonism: Baseline SAS >3 during treatment	4/776 (0.5)	
Akathisia: Baseline BARS >2 during treatment	14/770 (1.8)	

[a] n = number of patients who met criteria at least once during the OLE period; N = the number of patients with available baseline assessments that did not meet the criteria and had at least one assessment during the OLE period.
ADT, antidepressant therapy; AIMS, Abnormal Involuntary Movement Scale; BARS; Barnes Akathisia Rating Scale; EOT, end of treatment; EPS, extrapyramidal symptoms; OLE, open-label extension; SAS, Simpson-Angus Scale; TEAE, treatment-emergent adverse events.

Assessment of Depression Symptoms: MADRS Total Score

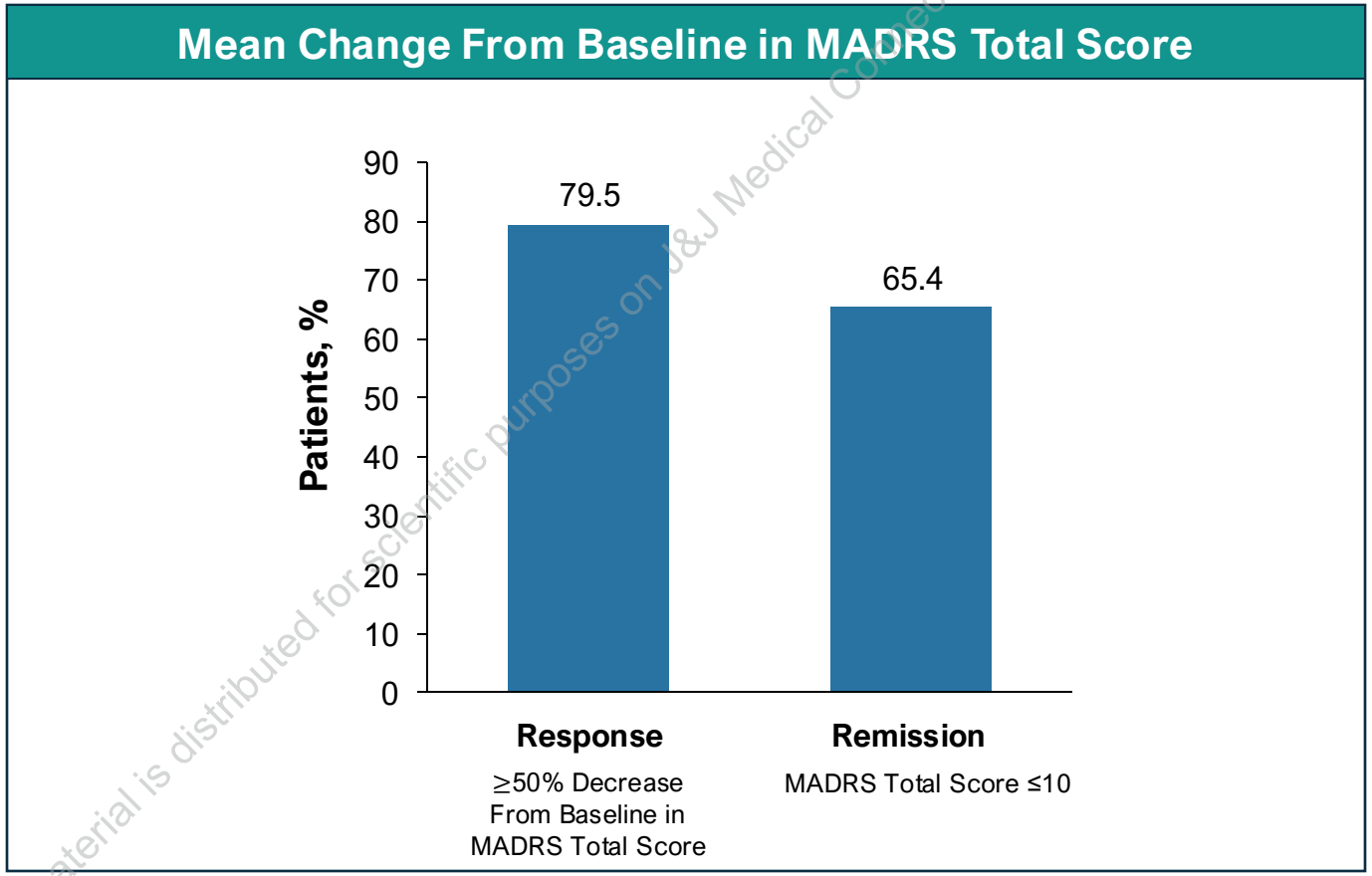
- Symptoms of depression continued to improve in the open-label treatment period



ADT, antidepressant therapy; DB, double-blind; EOLTP, end of long-term treatment period; MADRS, Montgomery-Åsberg Depression Rating Scale; OLE, open-label extension.

Assessment of Depression Symptoms: MADRS Response and Remission

- Most patients showed clinically meaningful improvements as assessed by MADRS response (79.5%) and remission (65.4%) criteria



MADRS, Montgomery-Åsberg Depression Rating Scale.

Conclusions

- Lumateperone 42 mg adjunctive to ADT was generally safe and well tolerated in long-term treatment in patients with MDD
  - There were no new safety findings, and AEs and safety parameters were consistent with the short-term 501 and 502 studies
- Over 26 weeks of treatment, lumateperone 42 mg adjunctive to ADT was associated with low risk of weight gain, cardiometabolic effects, and EPS
- In patients treated long-term with lumateperone 42 mg adjunctive to ADT, efficacy was maintained, and symptoms of depression improved throughout the study
- These results support the long-term safety and effectiveness of lumateperone 42 mg adjunctive to ADT in patients with MDD and inadequate ADT response

ADT, antidepressant therapy; AE, adverse events; EPS, extrapyramidal symptoms; MDD, major depressive disorder.

Thank you

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