Lumateperone for the Prevention of Relapse in Patients with Schizophrenia: Results From a Double-Blind, Placebo-Controlled, Randomized Withdrawal, Phase 3 Trial

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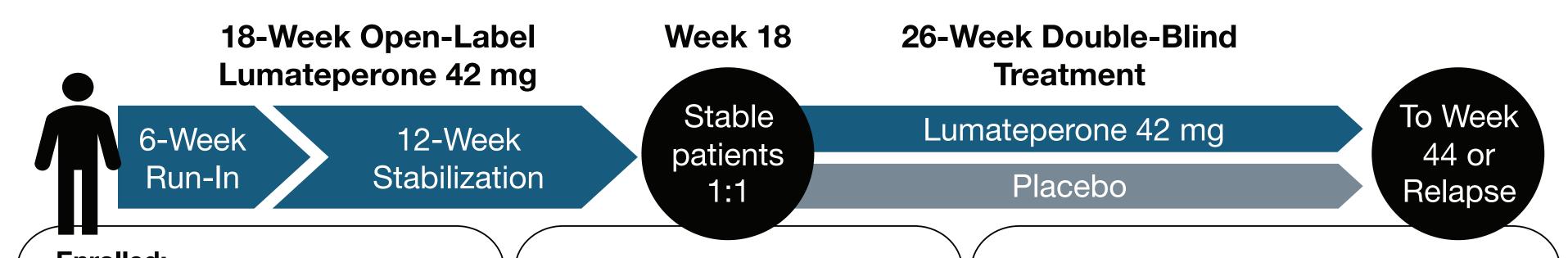
BACKGROUND

- Relapse is common in patients with schizophrenia and is associated with worsening symptoms, cognitive deterioration, poorer quality of life, and functional impairment¹
- Psychosocial outcomes and quality of life further decline with increasing frequency of relapse²
- Although maintenance antipsychotic treatment has shown efficacy in reducing relapse rate in patients with schizophrenia, current treatment options can be limited by adverse effects such as movement disorders and weight gain that may lead to nonadherence³
- Thus, a novel antipsychotic treatment that helps prevent relapse with a tolerable safety profile may lead to long-term benefits for
- Lumateperone is a mechanistically novel US Food and Drug Administration-approved antipsychotic to treat schizophrenia and depressive episodes associated with bipolar I or bipolar II disorder as monotherapy and as adjunctive therapy with lithium or valproate^{4,5}
- Lumateperone is a simultaneous modulator of serotonin, dopamine, and glutamate neurotransmission⁵
- Specifically, lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a dopamine D₂ receptor presynaptic partial agonist and postsynaptic antagonist, a D, receptor-dependent indirect modulator of glutamatergic AMPA and NMDA currents, and a serotonin
- This novel mechanism of action with multimodal effects may confer robust efficacy with improved tolerability compared with current treatment options
- This Phase 3, multicenter, multinational, double-blind, placebo-controlled, randomized withdrawal trial (Study 304, NCT04959032) investigated the efficacy and safety of lumateperone 42 mg for the prevention of relapse in adult patients with schizophrenia

METHODS

- Adults with schizophrenia experiencing a current psychotic episode received open-label, oral lumateperone 42 mg treatment once daily for 18 weeks
- Patients who achieved stability by the end of the 6-week run-in period and were still stable at Week 18 were randomized 1:1 to double-blind treatment with lumateperone 42 mg or placebo for 26 weeks or until relapse (Figure 1)

Figure 1. Study Design



Relapse defined as ≥1 of:

psychiatric care

Psychiatric hospitalization or increased

PANSS Total score increase by ≥30%

≥10 points (if <50 at randomization)

Aggressive/violent behavior or self-injury

(if score ≥50 at randomization) or

CGI-S score increase by ≥2 points

Score >4 on ≥1 of 7 PANSS items^b

Suicidal or homicidal ideation

and suicidality

Patient Population

treatment period

- 18-60 years (incl) DSM-5 schizophrenia ≥1 year
- PANSS Total score 70-120 (incl)
- at visit 1 and visit 2 Score ≥4 on ≥2 PANSS items^a
- at visit 1 and visit 2
- At the end of the run-in period stable patients continued treatment in stabilization period

and others were discontinued

CGI-S, Clinical Global Impression Scale-Severity; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition; incl, inclusive; PANSS, Positive and Negative Syndrome Scale.

in the safety and intent-to-treat populations (lumateperone, 110; placebo, 114)

The primary endpoint was the time to first symptom relapse during double-blind treatment

Stable defined as: PANSS Total score ≤60 ≥20% PANSS Total score

• The key secondary endpoint was time to all-cause discontinuation (including relapse) during double-blind treatment

- Of patients in the double-blind treatment phase, 130 (58%) completed double-blind treatment without relapse

• Safety assessments included adverse events (AEs), body morphology, laboratory parameters, extrapyramidal symptoms (EPS),

• CGI-S score ≤4

decrease from baseline

 Score ≤4 on 7 PANSS items^b No suicidal or homicidal No tolerability issues

• Demographics and baseline characteristics were generally similar between groups (**Table 1**)

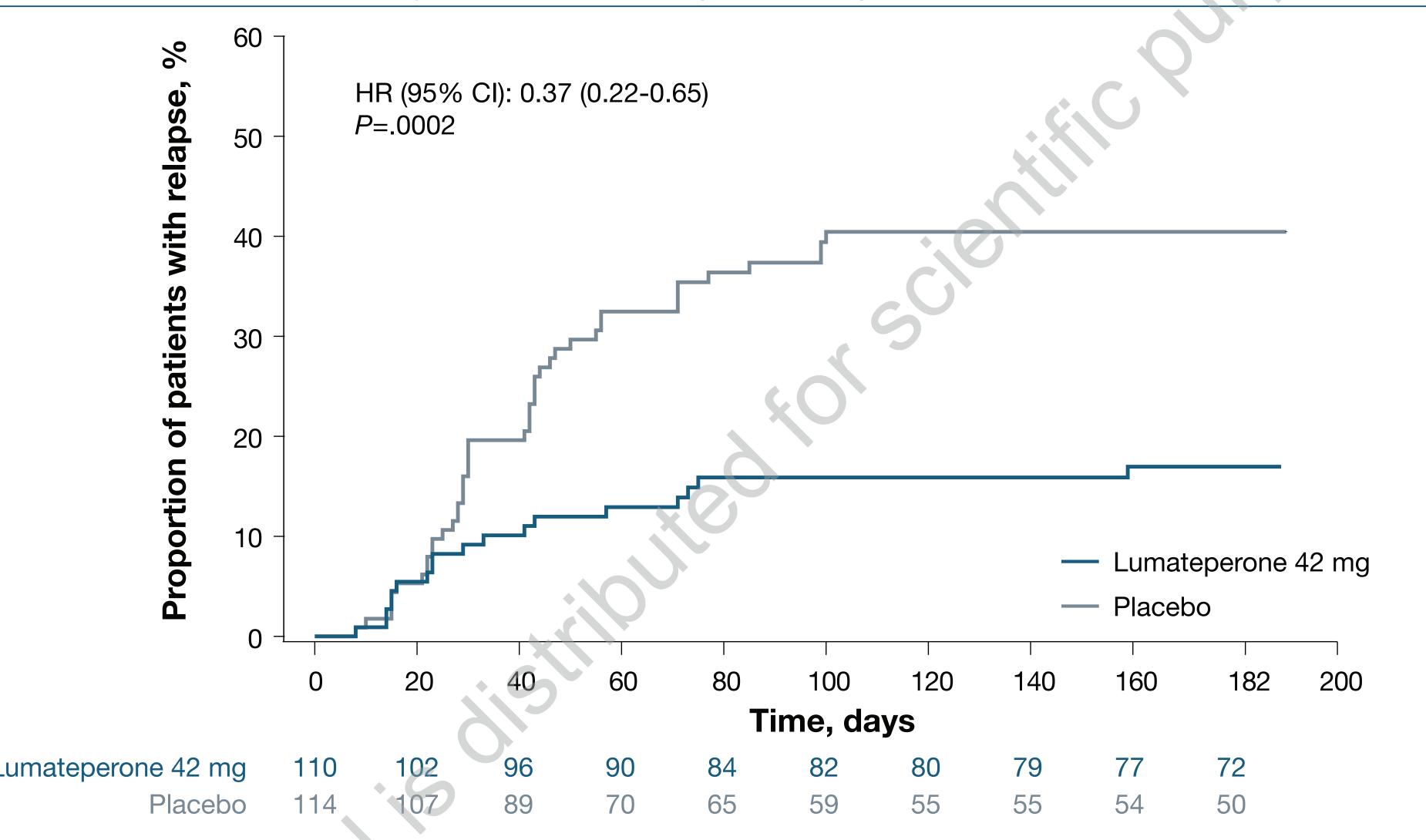
- Compared with the population in the open-label treatment phase, a greater proportion of White patients continued to the double-blind treatment phase
- As expected, mean Positive and Negative Syndrome Scale (PANSS) Total scores improved from the open-label treatment period baseline (91.5) to the double-blind treatment period baseline (lumateperone, 50.8; placebo, 51.3)

Table 1. Baseline Demographics and Disease Characteristics (Safety Population)

	Open-Label Treatment	Double-Blind Treatment	
	Lumateperone 42 mg (n=592)	Lumateperone 42 mg (n=110)	Placebo (n=114)
Age, mean (range), years	42.5 (18-60)	44.9 (23-60)	45.4 (25-60)
Sex, n (%)			
Male	414 (69.9)	73 (66.4)	70 (61.4)
Female	178 (30.1)	37 (33.6)	44 (38.6)
Race, n (%)			
White	299 (50.5)	77 (70.0)	84 (73.7)
Black	277 (46.8)	31 (28.2)	29 (25.4)
Asian	8 (1.4)	2 (1.8)	0
Other	8 (1.4)	0	1 (0.9)
Hispanic or Latino ethnicity, n (%)	45 (7.6)	4 (3.6)	6 (5.3)
No. previous psychiatric hospitalizations, mean (range)	5.0 (0-45)	4.9 (0-27)	5.6 (0-26)

- Lumateperone met the primary endpoint, significantly delaying the time to relapse vs placebo during double-blind treatment (Figure 2)
- Fewer relapses occurred with lumateperone (18 [16.4%]) than placebo (44 [38.6%]), corresponding to a number needed to treat (NNT) of 5
- The most common reason for relapse in both groups was PANSS Total score increase (lumateperone, 17 [15.5%]; placebo, 44 [38.6%]), followed by score >4 on ≥1 of 7 PANSS items (lumateperone, 12 [10.9%]; placebo, 19 [16.7%]) and ≥2 point CGI-S score increase in the Visit 14 score (lumateperone, 9 [8.2%]; placebo, 28 [24.6%])

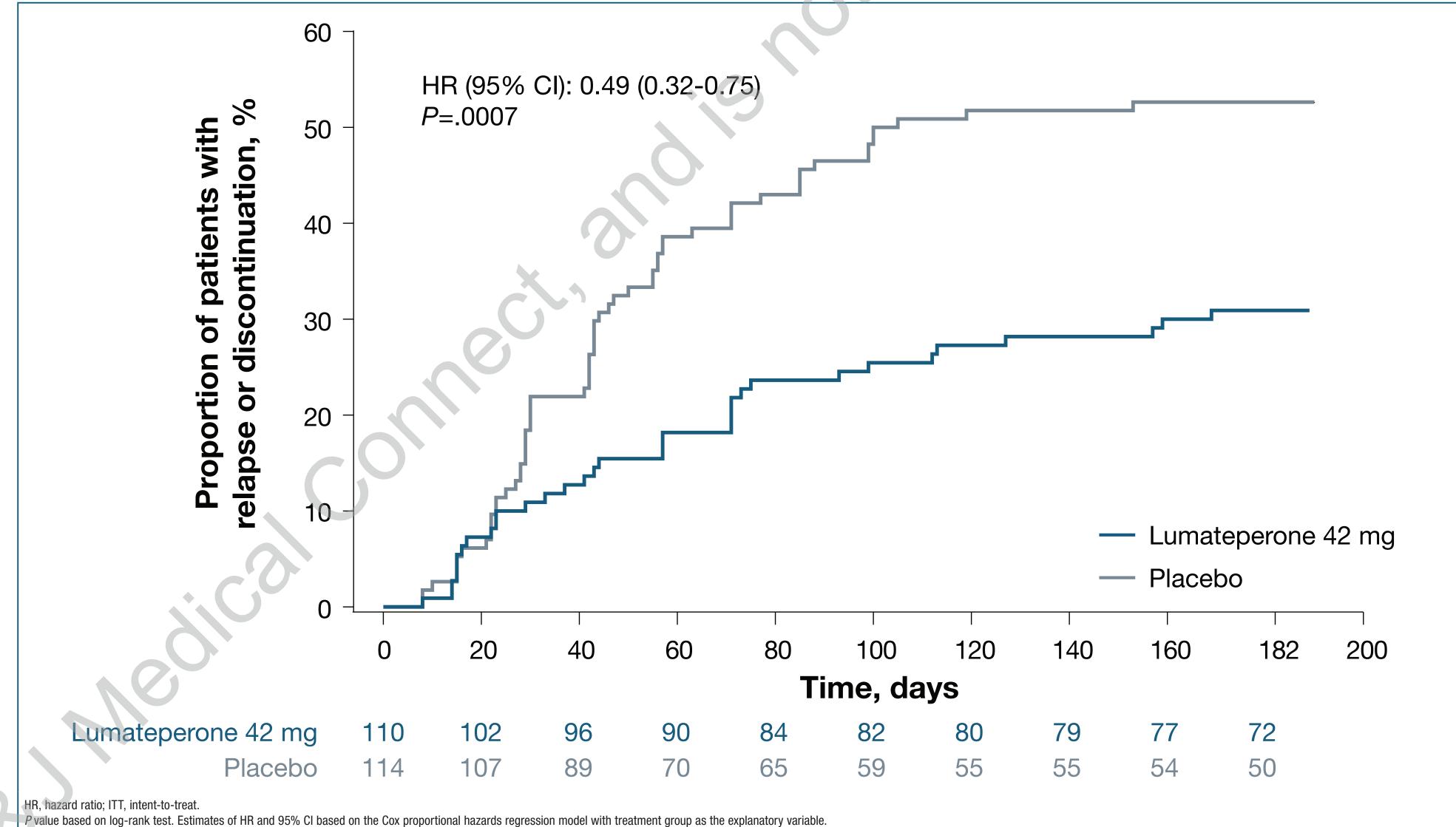
Figure 2. Cumulative Rate of Relapse During Double-Blind Treatment (ITT Population)



P value for prespecified primary analysis using the log-rank test. Estimates of HR and 95% CI based on the Cox proportional hazards model with treatment group as the explanatory variable.

• Lumateperone treatment also significantly delayed time to all-cause discontinuation (including relapse) compared with placebo (Figure 3) - The rate of all-cause discontinuation was lower with lumateperone (34 [30.9%]) than placebo (60 [52.6%]) corresponding to an NNT of 5

Figure 3. Cumulative Rate of All Cause Discontinuation During Double-Blind Treatment (ITT Population)



- During the double-blind treatment period mean treatment duration was 144.5 days for the lumateperone group and 111.9 days for the
- Treatment-emergent AEs (TEAEs) occurred in 52% of patients in the open-label treatment period and in similar frequencies in the lumateperone (33.6%) and placebo (30.7%) groups in the double-blind treatment period (**Table 2**)
- The most common TEAE was headache in both the open-label and double-blind treatment periods
- For most patients, TEAEs were mild or moderate in severity
- The rate of EPS-related TEAEs was low and similar to placebo during double-blind treatment (Table 2)
- There were no notable changes from baseline in EPS during the study as assessed by the Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson-Angus Scale

Table 2. Adverse Events Summary (Safety Population)

	Open-Label Treatment	Double-Blind Treatment		
Patients, n (%)	Lumateperone 42 mg (n=592)	Lumateperone 42 mg (n=110)	Placebo (n=114)	
≥1 TEAE	308 (52.0)	37 (33.6)	35 (30.7)	
Drug-related TEAE	144 (24.3)	10 (9.1)	10 (8.8)	
Discontinued treatment due to AE	52 (8.8)	2 (1.8)	2 (1.8)	
SAE	23 (3.9)	1 (0.9)	7 (6.1)	
Death	1 (0.2) ^a	0	0	
TEAEs in ≥5% of the lumateperone group ^b				
Headache	78 (13.2)	9 (8.2)	4 (3.5)	
EPS-related TEAEs ^c	16 (2.7)	1 (0.9)	1 (0.9)	

- Body morphology parameters remained stable with lumateperone from the baseline of the open-label treatment period to the end of the double-blind treatment period (Table 3)
- Potentially clinically significant weight increase and decrease (≥7% change from open-label treatment baseline) occurred at similar rates in the lumateperone group (11.8% increase and 13.6% decrease) and placebo group (both 9.7%) at the end of

- There were no clinically relevant increases at the end of the double-blind treatment period in prolactin or cardiometabolic parameters
- Based on the Columbia-Suicide Severity Rating Scale, suicidal behavior was rare (open-label treatment, 0.3%; double-blind treatment, 0%) - Emergence of suicidal ideation was low during open-label treatment (2.3%) and double-blind treatment (lumateperone, 0.9%;

Table 3. Mean Change From Baseline in Body Morphology, Prolactin, and Cardiometabolic Parameters During Double-Blind Treatment

	Double-Blind Treatment				
	Lumateperone 42 mg (n=110)		Placebo (n=114)		
	Baseline Mean (SD) ^a	Mean Change at EOT (SD) ^b	Baseline Mean (SD) ^a	Mean Change at EO1 (SD) ^b	
Weight, kg	80.5 (18.08)	0.2 (5.23)	82.9 (19.32)	-0.1 (4.14)	
BMI, kg/m²	27.0 (5.35)	0.1 (1.76)	27.8 (5.52)	0.0 (1.47)	
Waist circumference, cm	95.2 (13.59)	0.4 (5.16)	95.5 (13.97)	-1.1 (5.34)	
Prolactin, ng/mL	17.8 (18.58)	-3.3 (20.01)	15.6 (18.29)	-2.9 (14.44)	
Cholesterol, mg/dL					
Total	184.5 (39.15)	-6.1 (37.32)	189.1 (43.03)	-0.8 (40.10)	
HDL	47.6 (11.08)	2.0 (12.26)	47.2 (13.04)	4.9 (15.25)	
LDL	127.9 (39.90)	-4.8 (35.06)	132.0 (43.03)	-2.9 (41.04)	
Triglycerides, mg/dL	149.4 (87.28)	–11.0 (83.88)	154.5 (119.74)	-3.3 (132.86)	
Glucose, mg/dL	91.3 (12.68)	2.0 (15.73)	97.5 (42.78)	-2.3 (37.99)	
Insulin, mIU/L	15.9 (19.78)	3.2 (31.61)	17.3 (25.46)	2.6 (40.37)	

CONCLUSIONS

- Lumateperone 42 mg demonstrated efficacy as a maintenance treatment in patients with schizophrenia, significantly delaying the time to relapse compared with placebo (P=.0002) The relative risk of time to relapse with lumateperone 42 mg was reduced by 63% compared with placebo (HR 0.37)
- Lumateperone 42 mg also reduced absolute relapse rates compared with placebo, translating to
- Lumateperone 42 mg was generally safe and well tolerated with minimal EPS risk and no notable changes in prolactin or cardiometabolic parameters, consistent with prior lumateperone trials
- These results support the benefit of continued long-term treatment with lumateperone 42 mg in adults with schizophrenia

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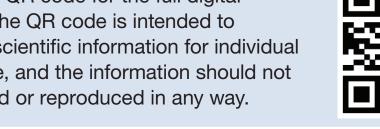
DISCLOSURES AND ACKNOWLEDGMENTS

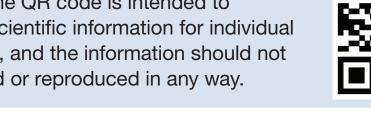
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Kendall Foote, PhD, of Nucleus Global, an Inizio company, funded by Intra-Cellular Therapies, a Johnson & Johnson Company.

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- A total of 228 patients were stable at Week 18 and randomized in the double-blind treatment phase, 224 were treated and included

2 were in the open-label safety population and 228 (39%) patients completed the open-label lumateperone