Metabolic Profile of Adjunctive Lumateperone 42 mg in Major Depressive Disorder: A Pooled Analysis of 2 Randomized Placebo-Controlled Trials

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Background

- Major depressive disorder (MDD) is a highly prevalent and disabling condition characterized by persistent low mood, anhedonia, and cognitive and physical symptoms that impair daily functioning[1-3]
- Importantly, MDD is frequently associated with comorbidities, including cardiovascular and metabolic disorders[4-6]
- First-line treatment for MDD typically includes antidepressant therapy (ADT), such as a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor; however, currently available treatments are associated with weight gain and metabolic disturbances[7,8]
- Approximately 50% of patients with MDD have an inadequate ADT response, defined as not achieving ≥50% improvement in depression severity after ≥6-8 weeks of treatment[9]
- Although augmenting ADTs with atypical antipsychotics has received increased attention in recent years, this treatment regimen has been associated with safety concerns, including extrapyramidal symptoms, metabolic effects, and weight gain[10-12]
- Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of MDD in adults as adjunct to ADT[13]
- Two Phase 3, randomized, double-blind, placebo-controlled studies (Study 501 [NCT04985942] and Study 502 [NCT05061706]) demonstrated the efficacy and safety of lumateperone 42 mg + ADT in patients with MDD with an inadequate ADT response[14,15]
  - In both trials, lumateperone 42 mg + ADT met primary and key secondary efficacy endpoints, significantly improving Montgomery-Åsberg Depression Rating Scale (MADRS) Total score and Clinical Global Impression–Severity (CGI-S) score from baseline to Day 43 compared with placebo + ADT
- A pooled analysis of these studies evaluated the metabolic profile associated with lumateperone 42 mg adjunctive to ADT

Methods

- In this post hoc analysis, safety data were pooled from Study 501 and Study 502, both of which evaluated oral lumateperone 42 mg + ADT vs placebo + ADT in eligible adults (18-65 years) who met the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* criteria for MDD with an inadequate response to 1-2 ADTs in the current depressive episode[14,15]
- Patients with MADRS Total score ≥24, CGI-S score ≥4, and Quick Inventory of Depressive Symptomatology-Self Report-16 item score ≥14 were randomized to 6-week lumateperone 42 mg + ADT or placebo + ADT[14,15]
- Assessments included changes in body mass index (BMI), weight, waist circumference, cardiometabolic laboratory parameters (glucose, cholesterol [total, high-density lipoprotein, low-density lipoprotein], triglycerides, insulin), and prolactin levels
  - Subgroups were analyzed by baseline BMI category (normal weight: ≥18.5 kg/m^2 to <25 kg/m^2; overweight: ≥25 kg/m^2 to <30 kg/m^2; obese: ≥30 kg/m^2)

Results

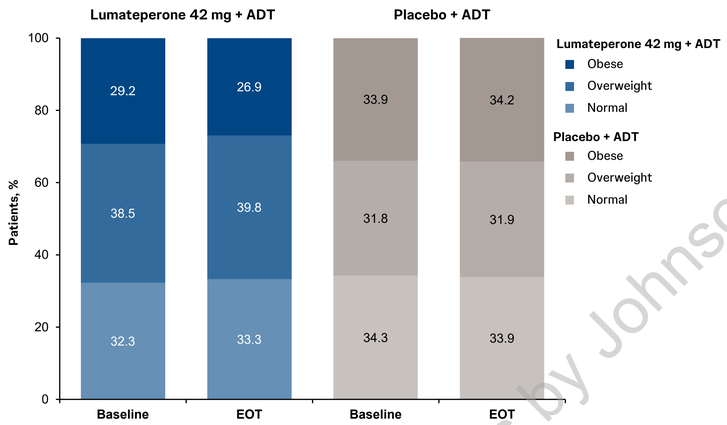
Overall Population

- The pooled safety population comprised 964 patients (lumateperone + ADT, n=483; placebo + ADT, n=481) and 91.4% completed treatment
- Demographics and baseline characteristics were similar between groups
  - The majority of patients were female and White
- Changes from baseline to end of treatment (EOT) were minimal with lumateperone + ADT vs placebo + ADT for weight (−0.1 kg vs +0.0 kg), BMI (−0.0 kg/m^2 vs +0.0 kg/m^2), and waist circumference (−0.2 cm vs −0.3 cm)
- Potentially clinically significant (PCS) weight increase (≥7% from baseline) was rare during treatment (lumateperone + ADT, 0.4%; placebo + ADT, 1.3%)
- No clinically meaningful changes were observed in cardiometabolic parameters or prolactin levels

Shift in BMI Categories

- At baseline, the proportions of patients across BMI categories were similar: normal weight (lumateperone + ADT, 32.3% vs placebo + ADT, 34.3%), overweight (38.5% vs 31.8%), and obese (29.2% vs 33.9%) (**Figure 1**)
  - The proportion of patients across BMI subgroups at EOT was also similar between lumateperone + ADT and placebo + ADT arms

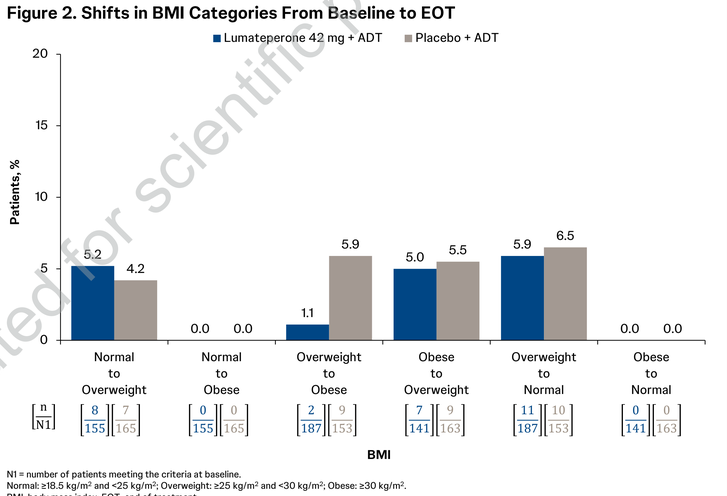
Figure 1. Proportion of Patients in BMI Categories at Baseline and EOT



ADT, antidepressant therapy; BMI, body mass index; EOT, end of treatment.

- Most patients remained in their BMI category at EOT (normal weight: lumateperone + ADT, 91.0% vs placebo + ADT, 95.2%; overweight: 89.8% vs 86.9%; obese: 91.5% vs 94.5%)
  - Shifts in BMI categories from baseline to EOT were similar between the lumateperone + ADT and placebo + ADT groups (**Figure 2**)

Figure 2. Shifts in BMI Categories From Baseline to EOT

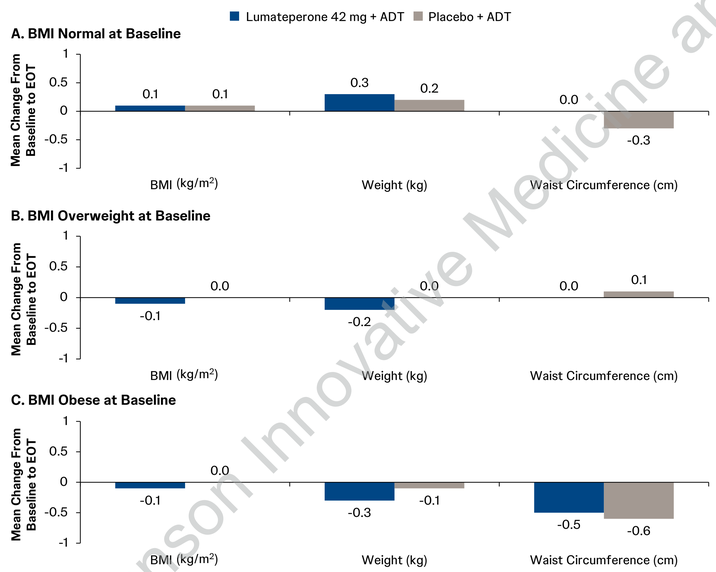


N1 = number of patients meeting the criteria at baseline.
Normal: ≥18.5 kg/m^2 and <25 kg/m^2; Overweight: ≥25 kg/m^2 and <30 kg/m^2; Obese: ≥30 kg/m^2.
BMI, body mass index; EOT, end of treatment.

Body Morphology Assessments

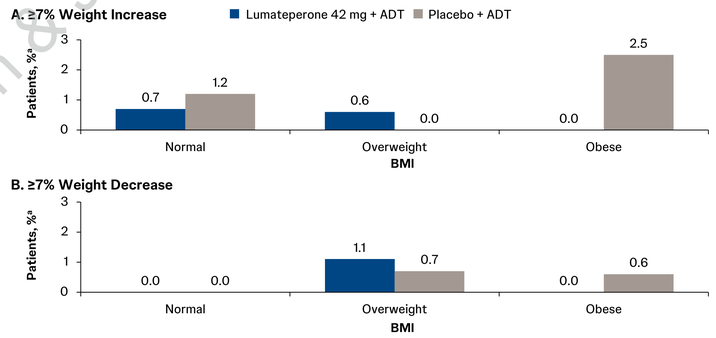
- Changes at EOT were minimal across BMI subgroups and treatment arms for BMI (−0.1 kg/m^2 to +0.1 kg/m^2), weight (−0.3 kg to +0.3 kg), and waist circumference (−0.6 cm to +0.1 cm) (**Figure 3**)
- PCS weight increase was rare with lumateperone + ADT vs placebo + ADT (normal weight: 0.7% vs 1.2%; overweight: 0.6% vs 0%; obese: 0% vs 2.5%) (**Figure 4A**)
  - PCS weight decrease (≥7%) was also rare during treatment (**Figure 4B**)

Figure 3. Changes in BMI, Weight, and Waist Circumference by Baseline BMI Category



ADT, antidepressant therapy; BMI, body mass index; EOT, end of treatment.

Figure 4. Incidence of PCS Weight Changes by Baseline BMI Category

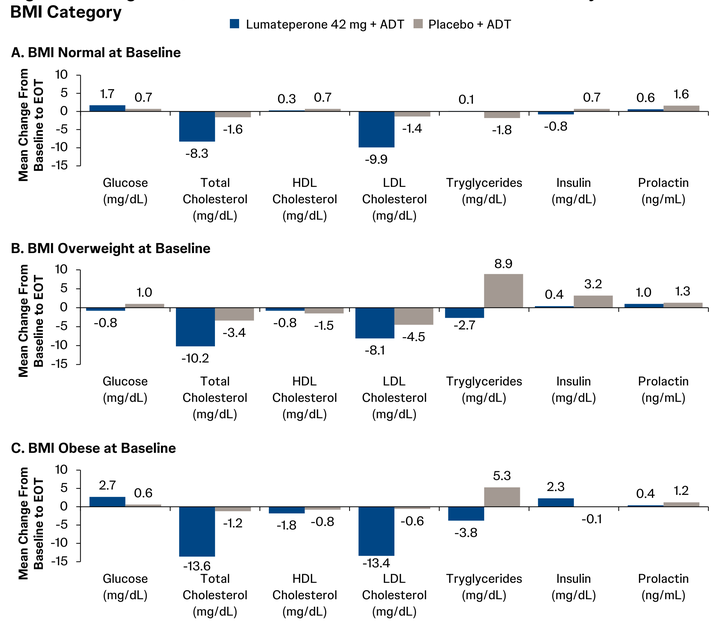


[a]Percentage is n/N1, with n = number of patients who met the criterion at least once during the double-blind treatment period and N1 = number of patients with baseline BMI in the category with ≥1 postbaseline assessment during the double-blind treatment period.
ADT, antidepressant therapy; BMI, body mass index; PCS, potentially clinically significant.

Cardiometabolic Parameters and Prolactin Levels

- Changes in cardiometabolic parameters and prolactin levels at EOT were not clinically relevant across BMI subgroups and treatment arms (**Figure 5**)

Figure 5. Changes in Cardiometabolic Parameters and Prolactin Levels by Baseline BMI Category



ADT, antidepressant therapy; BMI, body mass index; EOT, end of treatment; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Conclusions

- In this pooled analysis, 6-week treatment with lumateperone 42 mg + ADT had a favorable safety profile
- Minimal changes in body morphology, cardiometabolic parameters, and prolactin levels were observed across BMI subgroups
- Most patients remained in the same BMI category from baseline to EOT
- PCS weight changes were rare with lumateperone 42 mg + ADT
- These results indicate that lumateperone 42 mg may be a well-tolerated adjunctive treatment for patients with MDD with inadequate ADT response

Acknowledgments

The authors thank all study investigators, research staff, and patients for their participation. Medical writing support was provided by Thato Motlhalamme, PhD, of Nucleus Global, an Inizio company, funded by Intra-Cellular Therapies, a Johnson & Johnson company.

Disclosures

WR Earley, S Madi, and M Smith are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company. S Durgam and SG Kozauer are former employees of Intra-Cellular Therapies, a Johnson & Johnson company.

C Chepke has served on the Advisory Board of AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol Myers Squibb, Corium, Eli Lilly, Idorsia, Intra-Cellular, Jazz, Johnson & Johnson, Lundbeck, Moderna, Neurocrine, Otsuka, Sage, Sumitomo, Teva; Advisory Board (spouse): Bristol Myers Squibb, Otsuka; has been a consultant for: AbbVie, Acadia, Alkermes, Axsome, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Eli Lilly, Intra-Cellular, Johnson & Johnson, Lundbeck, Medincell, Moderna, Neurocrine, Otsuka, Sage, Sumitomo, Supernus, Teva; has received research grants from: Acadia, Axsome, Harmony, Neurocrine, Teva; has received speaker/promotional honoraria from: AbbVie, Acadia, Alkermes, Axsome, Bristol Myers Squibb, Corium, Intra-Cellular, Johnson & Johnson, Lundbeck, Luye, Merck, Neurocrine, Otsuka, Sumitomo, Teva; has no stocks/stock options/ ownership Interest/patents.

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Presented at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 26-29, 2026, Miami, FL

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