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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 the treatment of MDD in adults as an adjunct to ADT; the treatment of schizophrenia in adults; and the 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[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 Studies 501 and 502, both of which evaluated oral lumateperone 42 mg + ADT vs placebo + ADT in eligible adults (aged 18-65 years) who met the *Diagnostic and Statistical Manual of Mental Disorders, Fifth 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 to <25 kg/m²; overweight: ≥25 to <30 kg/m²; obese: ≥30 kg/m²)

Results

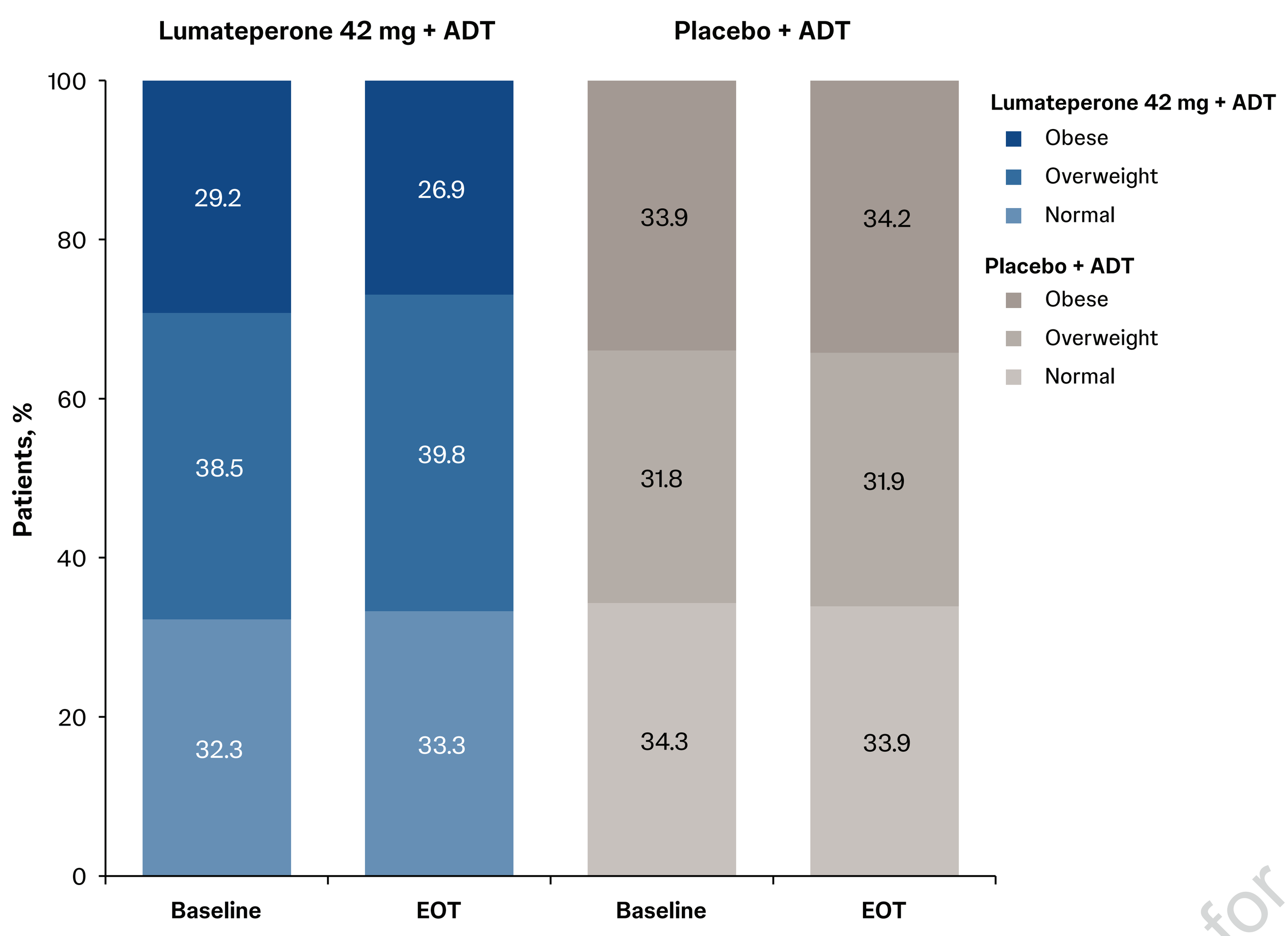
Overall Population

- 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
- Changes from baseline to end of treatment (EOT) were minimal with lumateperone + ADT vs placebo + ADT for weight (−0.1 vs +0.0 kg), BMI (−0.0 vs +0.0 kg/m²), and waist circumference (−0.2 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

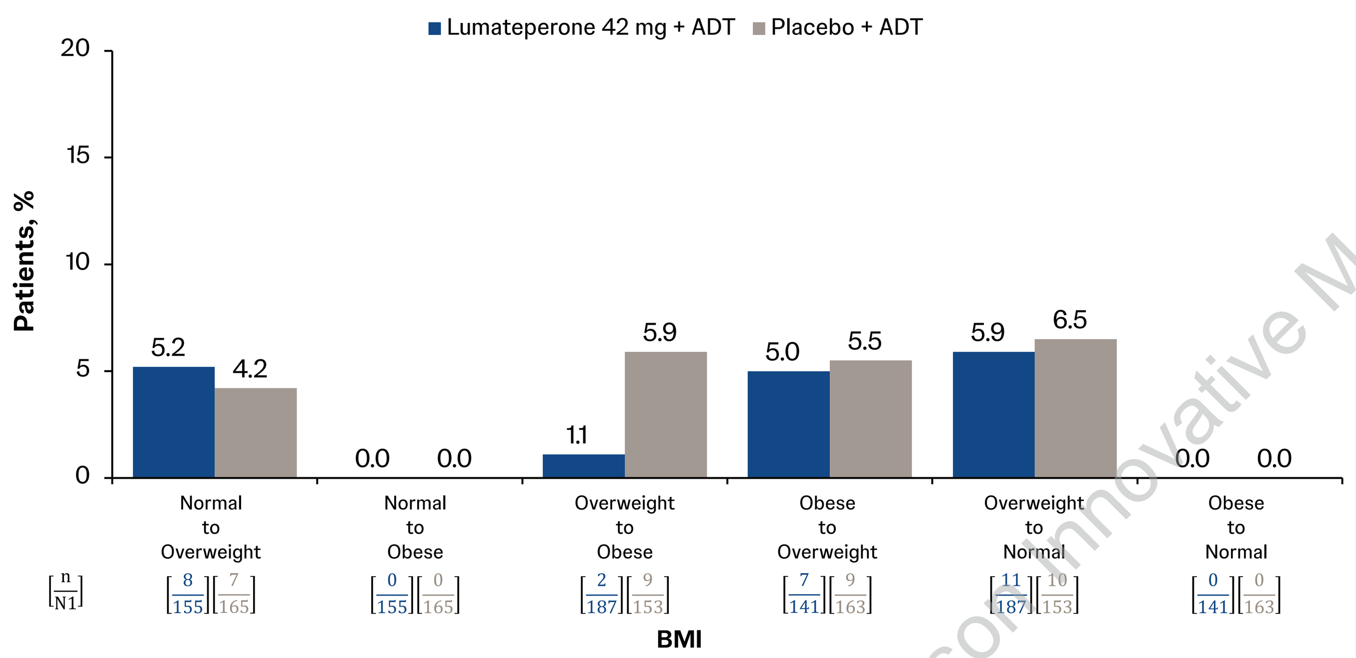
Figure 1. Proportion of Patients in BMI Categories at Baseline and EOT


Lumateperone 42 mg + ADT
Placebo + ADT
Patients, %
100
80
60
40
20
0
29.2
38.5
32.3
26.9
39.8
33.3
33.9
31.8
34.3
34.2
31.9
33.9
Baseline
EOT
Baseline
EOT
Lumateperone 42 mg + ADT
Obese
Overweight
Normal
Placebo + ADT
Obese
Overweight
Normal

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

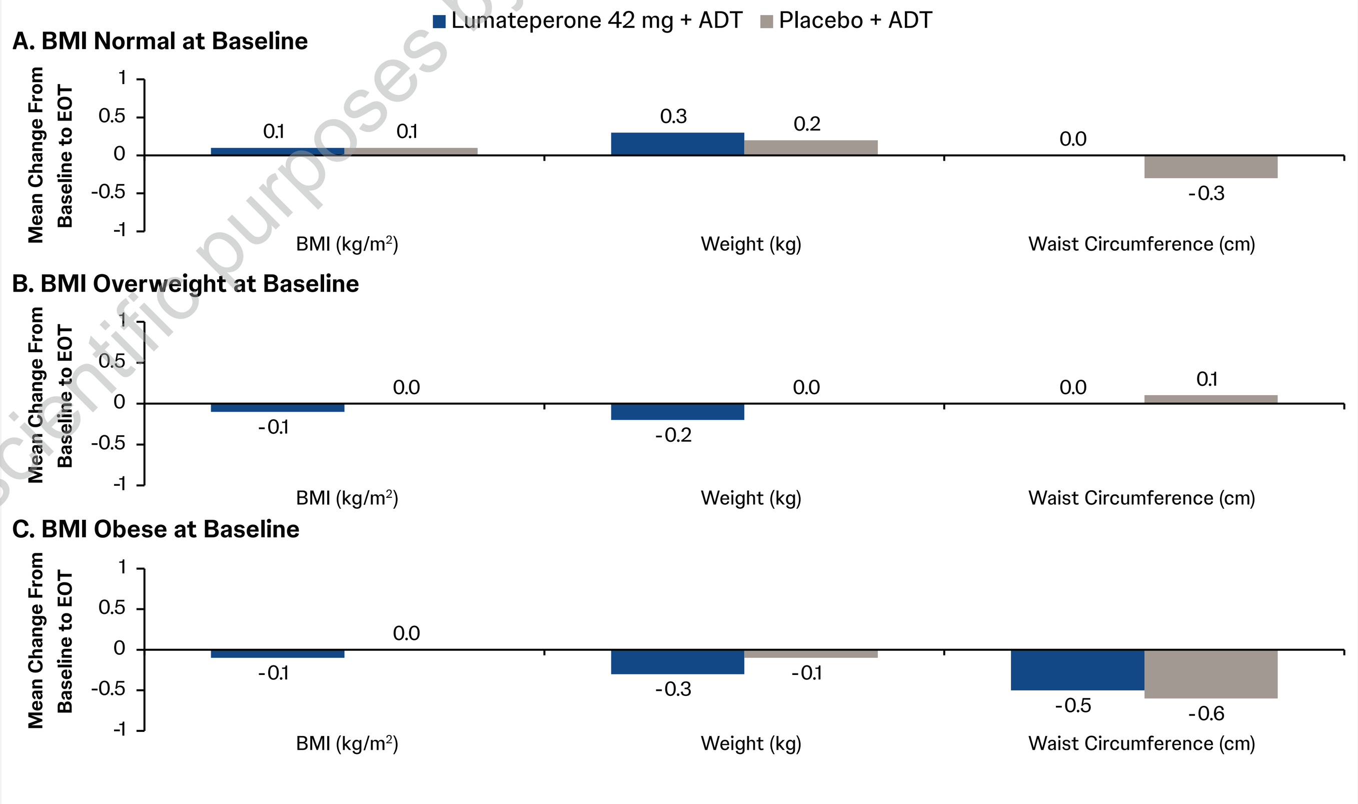

Lumateperone 42 mg + ADT
Placebo + ADT
Patients, %
20
15
10
5
0
5.2
4.2
0.0
0.0
1.1
5.9
5.0
5.5
5.9
6.5
0.0
0.0
Normal to Overweight
Normal to Obese
Overweight to Obese
Obese to Overweight
Overweight to Normal
Obese to Normal
n/N1
8/155 7/165
0/155 0/165
2/187 9/153
7/141 9/163
11/187 10/153
0/141 0/163
BMI

N1 = number of patients meeting the criteria at baseline.
Normal: ≥18.5 kg/m² and <25 kg/m²; Overweight: ≥25 kg/m² and <30 kg/m²; Obese: ≥30 kg/m².
BMI, body mass index; EOT, end of treatment.

Body Morphology Assessments

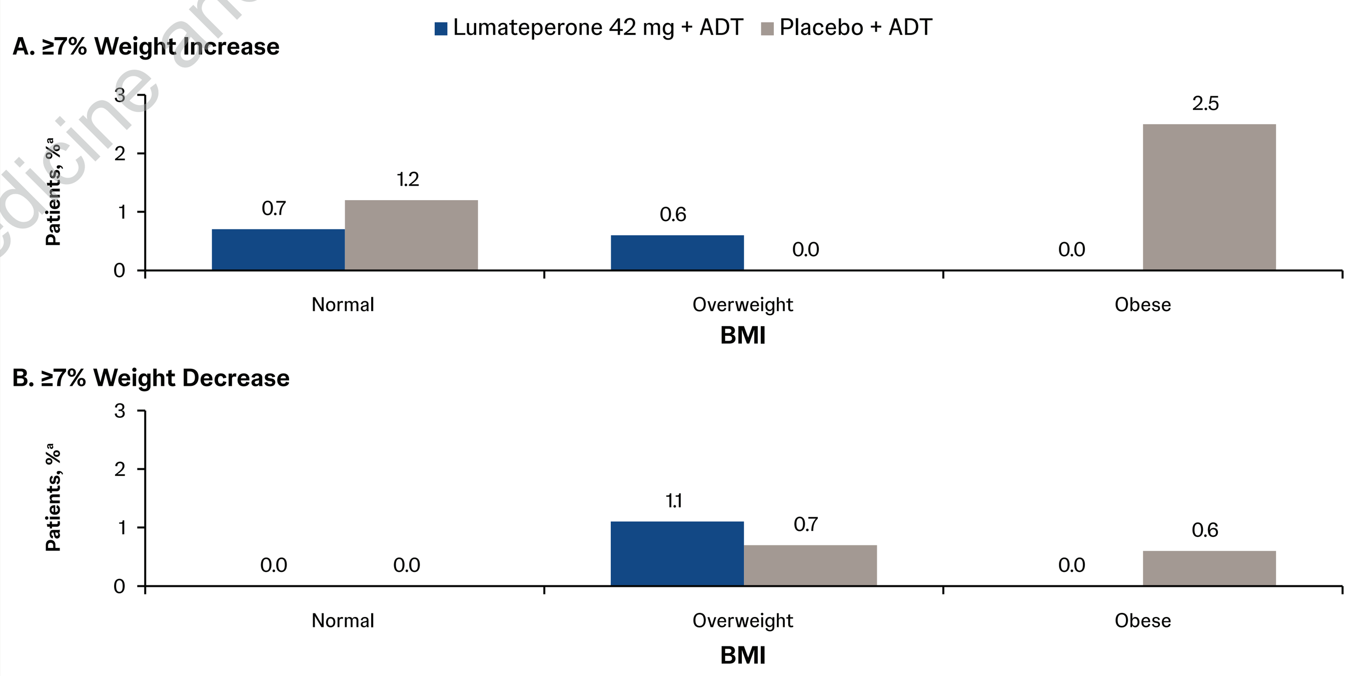
- Changes at EOT were minimal across BMI subgroups and treatment arms for BMI (−0.1 to +0.1 kg/m²), weight (−0.3 to +0.3 kg), and waist circumference (−0.6 to +0.1 cm) (**Figure 3**)
- PCS weight increase was rare with lumateperone + ADT vs placebo + ADT (normal weight: 0.7% vs 1.2%; overweight: 0.6% 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


Lumateperone 42 mg + ADT
Placebo + ADT
A. BMI Normal at Baseline
Mean Change From Baseline to EOT
0.1
0.1
0.3
0.2
0.0
-0.3
BMI (kg/m²)
Weight (kg)
Waist Circumference (cm)
B. BMI Overweight at Baseline
-0.1
0.0
-0.2
0.0
0.0
0.1
BMI (kg/m²)
Weight (kg)
Waist Circumference (cm)
C. BMI Obese at Baseline
-0.1
0.0
-0.3
-0.1
-0.5
-0.6
BMI (kg/m²)
Weight (kg)
Waist Circumference (cm)

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

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

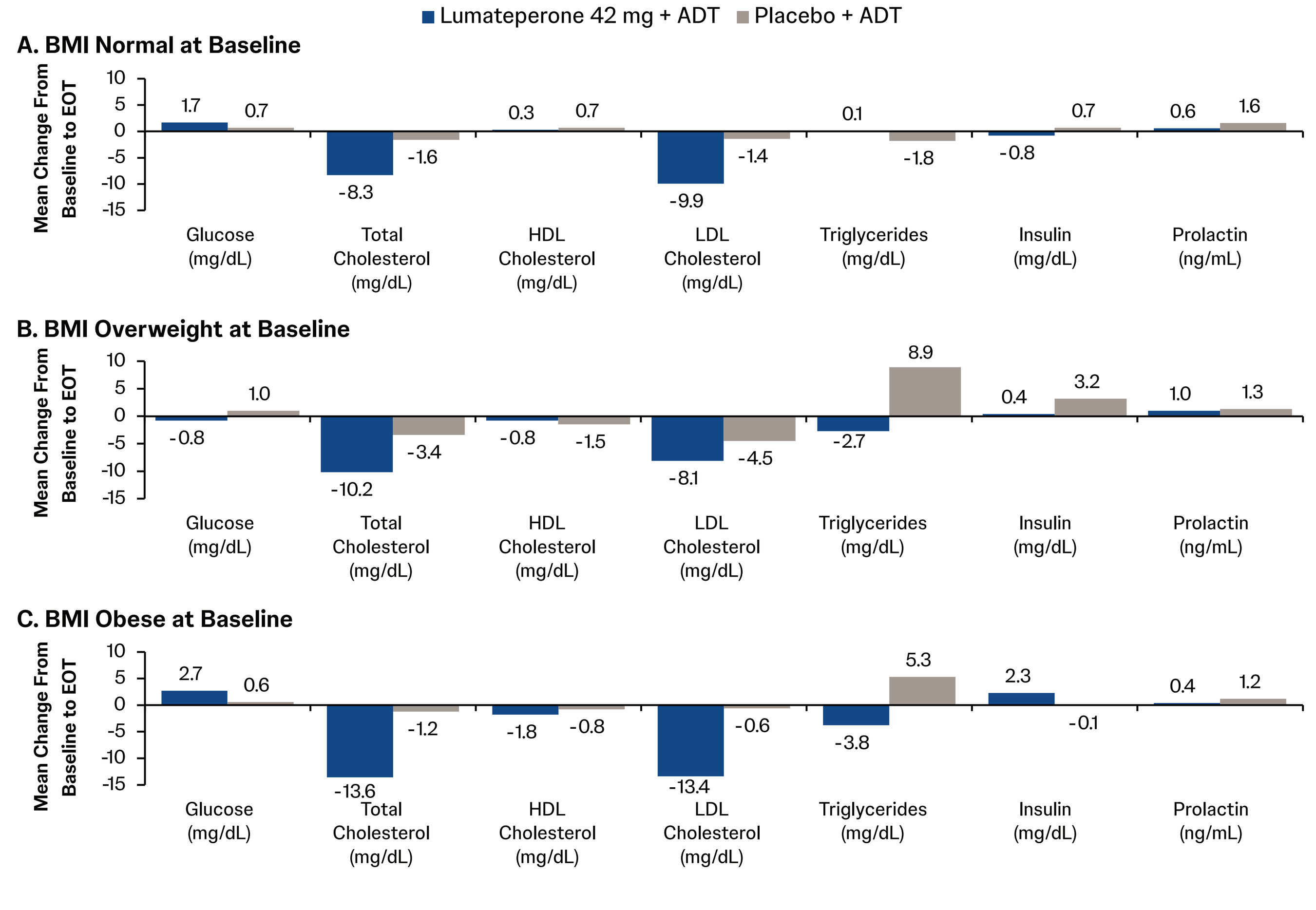

Lumateperone 42 mg + ADT
Placebo + ADT
A. ≥7% Weight Increase
Patients, %a
0.7
1.2
0.6
0.0
0.0
2.5
Normal
Overweight
Obese
BMI
B. ≥7% Weight Decrease
Patients, %a
0.0
0.0
1.1
0.7
0.0
0.6
Normal
Overweight
Obese
BMI

[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


Lumateperone 42 mg + ADT
Placebo + ADT
A. BMI Normal at Baseline
Mean Change From Baseline to EOT
1.7
0.7
-8.3
-1.6
0.3
0.7
-9.9
-1.4
0.1
-1.8
-0.8
0.7
0.6
1.6
Glucose (mg/dL)
Total Cholesterol (mg/dL)
HDL Cholesterol (mg/dL)
LDL Cholesterol (mg/dL)
Triglycerides (mg/dL)
Insulin (mg/dL)
Prolactin (ng/mL)
B. BMI Overweight at Baseline
-0.8
1.0
-10.2
-3.4
-0.8
-1.5
-8.1
-4.5
-2.7
8.9
0.4
3.2
1.0
1.3
C. BMI Obese at Baseline
2.7
0.6
-13.6
-1.2
-1.8
-0.8
-13.4
-0.6
-3.8
5.3
2.3
-0.1
0.4
1.2

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

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Disclosures

C Chepke has served on the advisory boards of AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol Myers Squibb, Corium, Eli Lilly, Idorsia, Intra-Cellular Therapies, Jazz, Johnson & Johnson, Lundbeck, Moderna, Neurocrine, Otsuka, Sage, Sumitomo, Teva; advisory boards (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 Therapies, 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.

WR Earley, R Migliore, and S Madi are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company. SG Kozauer is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company.

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