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Supplementary Material

Article Title: Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder: Results From a Randomized, Double-Blind, Phase 3 Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Methods

Full Inclusion and Exclusion Criteria

Inclusion Criteria

1. Written informed consent obtained from the patient before the initiation of any study specific procedures.
2. Male or female patients between the ages 18 and 65 years, inclusive
3. Met Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic criteria for major depressive disorder (MDD, a diagnosis of MDD with psychotic features was acceptable) as confirmed by the Investigator or Sponsor-approved rater using the Mini-International Neuropsychiatric Interview, and met all the following criteria:
    a. The start of the current major depressive episode (MDE) was at least 8 weeks but no more than 18 months prior to the screening (visit 1)
    b. Had at least moderate severity of illness, based on rater administered Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥ 24 at screening (visit 1) and at Baseline (visit 2)
    c. Had at least moderate severity of illness based on Clinical Global Impression Scale-Severity score of ≥4 at screening (visit 1) and at baseline (visit 2)
    d. Had a Quick Inventory of Depressive Symptomatology-Self Report-16 item (QIDS-SR-16) score of >14 at screening (visit 1) and at baseline (visit 2)
    e. Had sufficient history and medical record confirmation (as defined in the Study Reference Manual) verifying antidepressant therapy (ADT) and the current MDE is causing clinically significant distress or impairment in social, occupational, or other important areas of functioning
4. Was currently having an inadequate response to ADT (less than 50% improvement) as confirmed by the Investigator using Antidepressant Treatment Response Questionnaire and was taking at least the minimum effective dose (per package insert) of one of the following antidepressants as monotherapy treatment for at least 6 weeks duration:
    a. citalopram/escitalopram
    b. fluoxetine
    c. paroxetine
    d. sertraline
    e. duloxetine
    f. levomilnacipran/milnacipran (if locally approved for MDD)
    g. venlafaxine/desvenlafaxine
    h. bupropion
    i. vilazodone
    j. vortioxetine

5. Was an outpatient, and was anticipated to maintain outpatient status for the duration of the study
6. Had a body mass index of 19-40 kg/m^2, inclusive
7. Ability to follow study instructions and was likely to complete all required visits.

Exclusion criteria

Psychiatric Criteria

1. Within the patient's lifetime, had a confirmed DSM-5 psychiatric diagnosis other than MDD, including:
    a. Schizophrenia, Schizoaffective Disorder, Schizophreniform Disorder or other psychotic disorder
    b. Bipolar Disorder
2. Within 6 months of screening, had a confirmed DSM-5 psychiatric diagnosis other than MDD, including:
    a. Anxiety disorders such as Panic Disorder or Generalized Anxiety Disorder; Obsessive compulsive Disorder; Posttraumatic Stress Disorder as primary diagnoses. **Note:** anxiety symptoms may be allowed if secondary to MDD, provided these symptoms did not require concurrent treatment
    b. Eating disorder
    c. Substance use disorders (excluding nicotine)
    d. Personality disorder of sufficient severity to have a major impact on the patient's psychiatric status
    e. Within 12 months of screening, had any other psychiatric condition (other than MDD) that was the main focus of treatment
3. The patient experienced a ≥25% decrease in the MADRS total score between screening (visit 1) and baseline (visit 2)
4. The patient experienced a ≥25% decrease in the QIDS-SR-16 total score between screening (visit 1) and baseline (visit 2)
5. In the opinion of the Investigator, the patient had a significant risk for suicidal behavior during his/her participation in the study or
    a. At screening (visit 1), the patient scored "yes" on Suicidal Ideation Items 4 or 5 of the Columbia-Suicide Severity Rating Scale within 6 months prior to screening or, at baseline (visit 2), the patient scored "yes" on Suicidal Ideation Items 4 or 5 since the screening visit
    b. At screening (visit 1), the patient has had 1 or more suicidal attempts within the 2 years prior to screening
    c. At screening (visit 1) or baseline (visit 2), the patient scored ≥5 on MADRS Item 10 (Suicidal Thoughts)
    d. The patient was considered to be an imminent danger to him/herself or others.
6. The patient had a first MDE at age 60 years or older

Treatment Criteria

7. In the current MDE, the patient has had >2 ADTs administered at adequate dose (per product label) and for an adequate duration (at least 6 weeks)
8. In the current MDE, the patient had not responded to treatment with an antipsychotic for MDD administered at an adequate dose (per product label) and for an adequate duration (at least 3 weeks)
9. The patient was considered treatment-resistant, defined as having a lifetime history of treatment resistance (no remission) to ≥3 treatments 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)
10. The patient had received electroconvulsive therapy (ECT), vagal nerve stimulation, or repetitive transcranial magnetic stimulation within the past 5 years or had a failure in response to ECT at any time
11. The patient had known hypersensitivity or intolerance to lumateperone, or to any of the excipients
12. The patient was currently participating in psychotherapy, or had plans to initiate psychotherapy therapy during the study
13. The patient had used 1 of the following agents under the specified conditions:
    a. Any strong cytochrome P450 3A4 inhibitor or any P450 3A4 inducer within 7 days prior to the baseline visit
    b. Monoamine oxidase inhibitors within 14 days prior to the baseline visit
    c. Other drugs with known psychotropic properties or any non-psychotropic drugs with known or potentially significant central nervous system effects as reviewed by the Sponsor or designee, taken after screening, including, but not limited to:
        i. Benzodiazepines or sedative hypnotics (exceptions for zolpidem and other alternative treatments for insomnia)
        ii. Central opioid agonists/antagonists including tramadol
        iii. Anticonvulsants, mood stabilizers, antidepressants other than background antidepressant treatment, stimulants, antipsychotics, and nonbenzodiazepine anxiolytics
        iv. Dietary supplements and medical foods unless approved by the Sponsor or designee. Daily multivitamin use is not excluded
14. The patient had participated in a previous clinical trial with lumateperone, or had exposure to any investigational product within 3 months of the baseline visit or participated in the past 3 years in >2 clinical studies of an investigational product with a central nervous system indication
15. The patient was unable to be safely discontinued from prohibited psychotropic or nonpsychotropic medication (in the opinion of the Investigator)

Other Medical Criteria

16. The patient was male, or female of childbearing potential, and did not agree to use a highly effective method of birth control (defined as those methods, alone or in combination, that

result in a failure rate less than 1% per year when used consistently and correctly) beginning with signing the Informed Consent Form through the end-of-study follow-up period. Females of non-childbearing potential (defined as either permanently sterilized or post-menopausal females [defined as at least one year with no menses without an alternative medical explanation]) were exempt from the birth control requirement

17. The patient was breast-feeding or pregnant. Female patients of childbearing potential must have had a negative serum pregnancy test at screening (visit 1). On Day 1 (baseline/visit 2), female patients of childbearing potential must have had a negative urine pregnancy test prior to study treatment administration
18. The patient had a positive test for drugs of abuse (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methadone, opiates, or phencyclidine) at screening (visit 1). Exceptions included prescription treatments (eg, opioids, benzodiazepines) if the use was not chronic and was able to be discontinued as per the Investigator with the concurrence of the Sponsor or designee. A repeat drug test was allowed with the approval of the Sponsor or designee. A negative urine drug screen was required for randomization.
19. The patient had abnormal laboratory values or clinical findings at screening (visit 1) that were judged to be clinically significant including, but not limited to:
    a. Alanine aminotransferase and/or aspartate aminotransferase >2 × the upper limit of normal (ULN)
    b. Total bilirubin >1.5 × ULN
    c. Hemoglobin <8 g/dL (80 g/L) for females and <9 g/dL (90 g/L) for males
    d. Absolute neutrophil count <1200 cells/µL (1.2 × 109/L)
    e. Thyroid-stimulating hormone (TSH) outside of normal reference range AND free T3 or free T4 outside of the reference range. Free T3 and Free T4 were only be evaluated if TSH is outside of reference range
    f. HbA1c >7.5% [>58 mmol/mol]
    g. Positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M at screening; positive hepatitis C antibody at screening (visit 1), with the exception of a patient for whom the reflex HCV RNA test was negative
    h. Any other clinically significant abnormal laboratory result obtained at screening (visit 1)
20. The patient had corrected QT interval using the Fridericia formula >450 msec for males or >470 msec for females, corrected QT interval using the Bazett formula >450 msec for males or >470 msec for females, and/or heart rate <50 bpm, or evidence of clinically significant bundle-branch blocks
21. The patient had any of the following conditions:
    a. Cardiac: uncontrolled angina, or history of a myocardial infarction within 3 months prior to screening, or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced corrected QT interval prolongation
    b. Malignancy: Any diagnosis of cancer (except basal or squamous cell skin carcinoma), unless in remission for at least 5 years

c. Gastrointestinal: history of gastric bypass or any other condition that results in malabsorption
d. Endocrine: hypo- or hyperthyroidism unless treated and stable with no medication changes for at least three months prior to screening, diabetes, unless considered stable with no changes in treatment for at least three months prior to screening
e. Hepatic: Hepatitis B or Hepatitis C; moderate or severe hepatic impairment (Child-Pugh B or C)
f. Pulmonary: history of diagnosed and untreated obstructive sleep apnea
g. Neurological: history of epilepsy, seizure or convulsion, or electroencephalogram with clinically significant abnormalities, delirium, dementia, amnestic, or central sleep apnea, or significant brain trauma, or other cognitive disorder
h. Infectious: History of human immunodeficiency virus infection

   Note: Any other medical condition, or medical conditions that were stable with treatment (eg, hypertension, hypercholesterolemia, or thyroid abnormalities) were allowed as long as the condition has been stable for at least 3 months prior to screening (visit 1); treatments for these conditions were documented, kept stable, and were expected to be unchanged during the study; and the condition was not thought to affect safe participation in the study or relevant study outcomes in the opinion of the Investigator and confirmed by the Sponsor or designee

Other Criteria

22. The patient was judged by the Investigator to be inappropriate for the study
23. The patient was an employee of the Investigator or study site, or immediate family (ie, spouse, parent, child, or sibling, whether biological or legally adopted) of such employees, the Investigator, the Sponsor, or contract research organizations conducting the study

Randomization and Blinding

Independent external biostatistics personnel not participating in any study conduct generated the random patient treatment assignment using a permuted block randomization schedule using SAS software v9.4 for the interactive web response system, linking sequential patient randomization numbers to treatment codes. Randomization was stratified by site with a block size of 4. The clinical site staff and study team remained blinded from treatment assignment throughout the study.

Anxious Distress Specifier

According to Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria, the anxious distress specifier for depressive disorders is defined as the presence of ≥2 anxious symptoms (feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fearful something awful may happen, or feeling that the individual might lose control of himself or herself) during the majority of days of a major depressive episode.

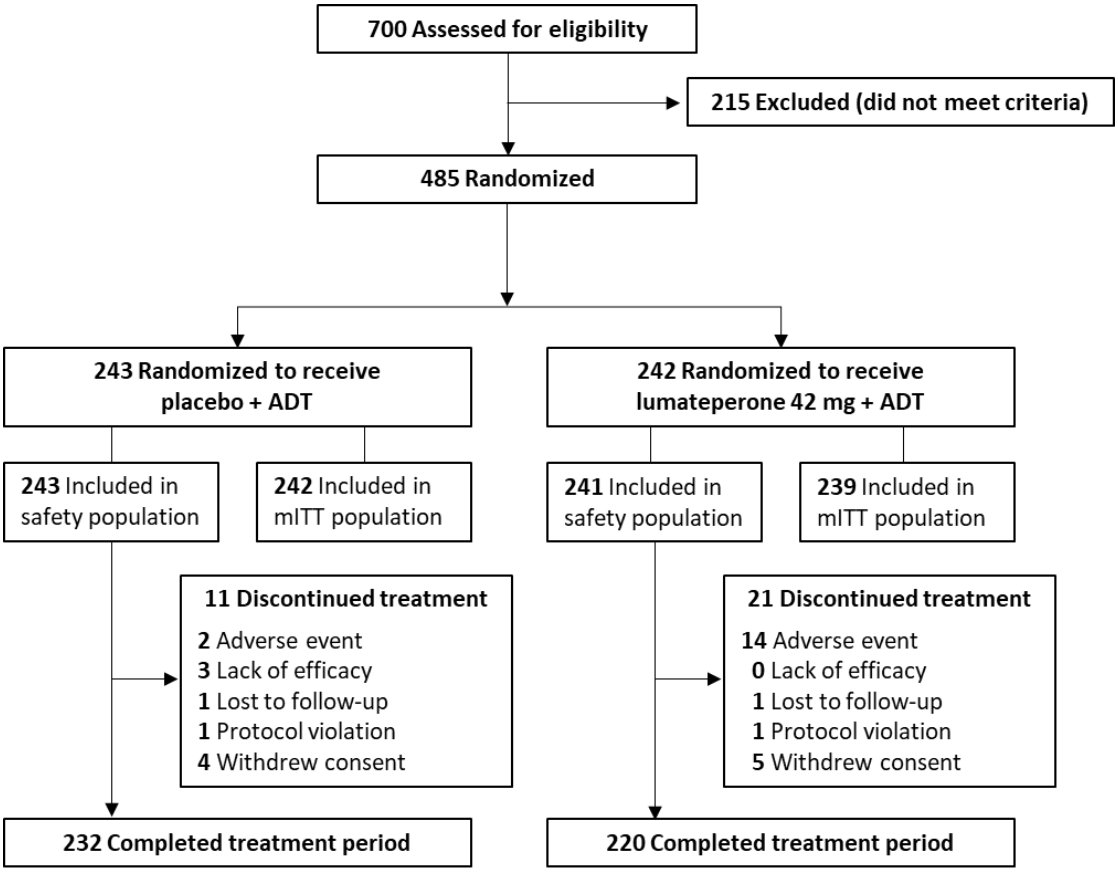
Statistical Analyses

The study was designed to have 90% power to detect a 0.33 effect size, corresponding to a 3.3-point difference in change from baseline to Day 43 in Montgomery-Åsberg Depression Rating Scale (MADRS) Total score between lumateperone + antidepressant therapy (ADT) and placebo + ADT.

Sensitivity of the primary analysis based on the mixed-effects model for repeated measures method for the change from baseline to Day 43 in MADRS Total score was performed under the assumption of missing not at random for the missing data based on the intent-to-treat population using pattern-

mixture model and a copy reference approach for the imputation of missing data. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Supplementary Figure 1. Patient Disposition



ADT, antidepressant therapy; mITT, modified intent-to-treat.

Supplementary Table 1. TEAEs Leading to Treatment Discontinuation (Safety Population)

n (%)	Placebo + ADT (n=243)	Lumateperone 42 mg + ADT (n=241)
≥1 TEAE leading to discontinuation	2 (0.8)	13 (5.4)
Vomiting	0	1 (0.4)
Abdominal pain upper	1 (0.4)	0
Fatigue	0	3 (1.2)
Dizziness	1 (0.4)	3 (1.2)
Sedation	0	2 (0.8)
Paresthesia	0	1 (0.4)
Tremor	0	1 (0.4)
Aggression	0	1 (0.4)
Anxiety	0	1 (0.4)

ADT, antidepressant therapy; TEAE, treatment-emergent adverse event.

Supplementary Table 2. Mean Change From Baseline and Categorical Shifts in Clinician-Rated Extrapyramidal Symptom–Related Scales at EOT (Safety Population)

	Placebo + ADT (n=243)		Lumateperone 42 mg + ADT (n=241)	
	Baseline Mean (SD)	**Mean Change at EOT (SE)**	**Baseline Mean (SD)**	**Mean Change at EOT (SE)**
AIMS	0.0 (0.20)	−0.0 (0.01)	0.1 (0.36)	−0.0 (0.02)
BARS	0.1 (0.39)	−0.0 (0.03)	0.1 (0.28)	0.0 (0.03)
SAS	0.1 (0.24)	−0.0 (0.01)	0.1 (0.40)	0.0 (0.02)
Shifts[a]	**n/N**	**%**	**n/N**	**%**
Baseline BARS ≤2 to BARS >2 during treatment	2/241	(0.8)	3/236	(1.3)
Baseline SAS ≤3 to SAS >3 during treatment	0/242	0	0/235	0

[a]N = Number of patients whose available baseline data did not meet the criterion and who had ≥1 postbaseline assessment during the double-blind treatment period.
ADT, antidepressant therapy; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; EOT, end of treatment; SAS, Simpson-Angus Scale.