Oral, Once-Daily LB-102: Recent Positive Results From a Phase 2 Study in Patients With Acute Schizophrenia

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Presented at

American Society of Clinical Psychopharmacology (ASCP)
May 27–30, 2025
Scottsdale, AZ, USA

W65

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LB-102

- LB-102 (*N*-methyl amisulpride) is a novel D_2/D_3/5-HT_7 receptor antagonist and potential first-in-class benzamide antipsychotic under development for schizophrenia (**Figure 1**).[1]
- Preclinical assays have shown equal, if not improved, receptor binding, pharmacokinetics, and behavioral modification properties for LB-102 compared to amisulpride with as good or better efficacy when compared to amisulpride in animal schizophrenia models (**Figure 2**).[2]
- A phase 1, double-blind, placebo-controlled study (NCT04187560) demonstrated that LB-102 was generally safe and well-tolerated in 64 healthy volunteers.[3]
- A phase 1, open-label PET study (NCT04588129) highlighted that LB-102 afforded dopamine receptor occupancy (RO) under steady-state conditions in the desired range of 60% to 80% required to treat schizophrenia in doses as low as 50 mg/day, and in a similar effect range as observed with amisulpride 400 mg (Data not shown) (**Figure 3**).[4]

Figure 1. LB-102: A Novel Benzamide to Treat Psychiatric Disorders

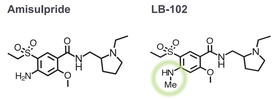
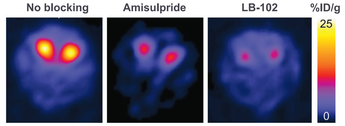
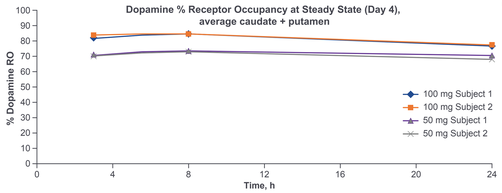


Figure 2. Dopamine Receptor Occupancy of LB-102 Compared With Amisulpride in Mice



PET scans taken 140 minutes after dosing either 100 mg/kg amisulpride or LB-102.

Figure 3. Target Receptor Occupancy Engagement With LB-102



- Subjects scanned 2.5, 7.5, and 23.5 hrs after 4 days of daily dosing
  - The observed dopamine receptor occupancy (RO) for 50 mg LB-102 was in the desired range for an effective schizophrenia drug
  - 50 mg LB-102 afforded same dopamine RO as 400 mg amisulpride per day (data not shown).

NOVA[1]: Phase 2 Study

- NOVA[1] was a phase 2, multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov: NCT06179108) conducted in the United States (**Figure 4**).
- Study schedule included:
  - Up to 14-day inpatient screening/washout period
  - 28-day inpatient treatment period
  - 5-day inpatient stabilization period
  - Outpatient safety follow-up visit ~2 weeks post-treatment
- Eligible participants were randomized (3:3:3:1) to oral once-daily placebo, LB-102 50 mg, LB-102 75 mg, or LB-102 100 mg, with the 100 mg dose considered exploratory.

Key Inclusion Criteria

- Adults 18–55 years diagnosed with schizophrenia and requiring hospitalization or continued hospitalization for a current acute exacerbation of psychotic symptoms
- Positive and Negative Syndrome Scale (PANSS) total score of 80–120
- PANSS positive subscale item scores of ≥4 on at least two key items
- Clinical Global Impression of Severity (CGI-S) score of ≥4

Key Exclusion Criteria

- Schizophrenia diagnosed ≤1 year ago
- History of treatment resistance
- Improvement of ≥20% from screening to baseline in PANSS total score

Outcomes and Analyses

- **Primary efficacy endpoint:** Change from baseline to Week 4 in PANSS total score
- **Secondary efficacy endpoints:** Change from baseline to Week 4 in CGI-S score, changes from baseline to Week 4 in PANSS positive and negative subscale scores
- **Safety:** Adverse event reporting and other safety assessments

Results

Disposition

- 359 participants were randomized and included in the safety and intent-to-treat populations.
  - 293 participants (82%) completed Week 4
  - 261 participants (73%) completed the trial
- Demographics and baseline characteristics were similar across treatment arms and reflective of an inpatient schizophrenia population (**Table 1**).
- The most commonly co-occurring medical conditions were insomnia (n=266, 74%), anxiety (n=211, 59%), headache (n=144, 40%), depression (n=118, 33%), and agitation (n=108, 30%).

Efficacy

- LB-102 met the primary endpoint, with all doses being statistically superior to placebo (**Figure 5**).
- Least-squares mean changes from baseline to Week 4 in PANSS total score were:
  - Placebo, −9.3
  - LB-102 50 mg, −14.3 (p=0.0009 vs placebo; effect size=0.61)
  - LB-102 75 mg, −14.0 (p=0.0022 vs placebo; effect size=0.41)
  - LB-102 100 mg, −16.1 (nominal p=0.0017 vs placebo; effect size=0.83)
- Secondary analysis of change from baseline to Week 4 of PANSS positive symptoms demonstrated a statistically significant reduction for LB-102 (all doses) compared to placebo (**Figure 7**).
- A treatment effect on PANSS total score was observed with LB-102 (all doses) as early as Week 1 and maintained throughout the 4-week treatment period (**Figure 5**).
- Analysis of change from baseline to Week 4 on the CGI-S score identified a statistically significant improvement for LB-102 (all doses) compared to placebo (**Figure 6**).

Safety and Tolerability

- Treatment-emergent adverse events (TEAEs) were reported in 56% (placebo), 69% (50 mg), 57% (75 mg), and 75% (100 mg) of participants (**Table 2**).
  - 10 participants (2.8%) experienced a TEAE that led to treatment withdrawal (**Table 2**).
  - 5 participants (1.4%) experienced a serious TEAE (**Table 2**).
- Insomnia was the most commonly reported TEAE across treatment arms, followed by headache, anxiety, and agitation (**Table 3**).
- A total of 25 participants treated with LB-102 experienced hyperprolactinemia or increased blood prolactin (**Table 3**).
  - 3 experienced galactorrhea (50 mg, n=2; 75 mg, n=1)
  - 1 experienced breast enlargement (100 mg)
  - 1 experienced erectile dysfunction (100 mg)
- There was an increase in weight across all treatment arms by the end of Week 4 (placebo, 2.1 kg; 50 mg, 4.6 kg; 75 mg, 3.5 kg; 100 mg, 3.7 kg).
  - Increases in weight and BMI were not associated with any change in cardiovascular or metabolic markers.
- There was no change in suicidal ideation or behavior at the end of Week 4, as measured by the Columbia–Suicide Severity Rating Scale (C-SSRS).

Figure 4. Trial Design

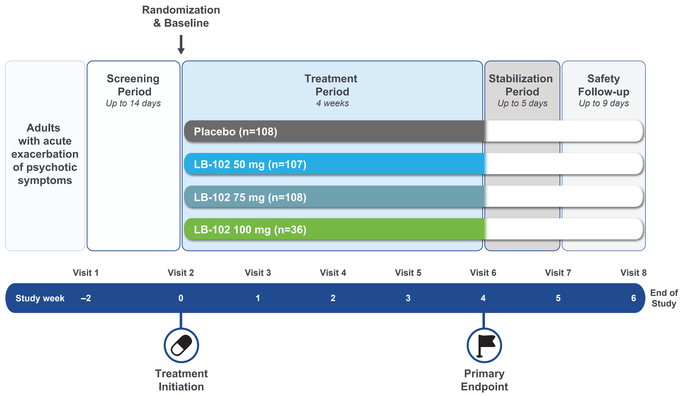
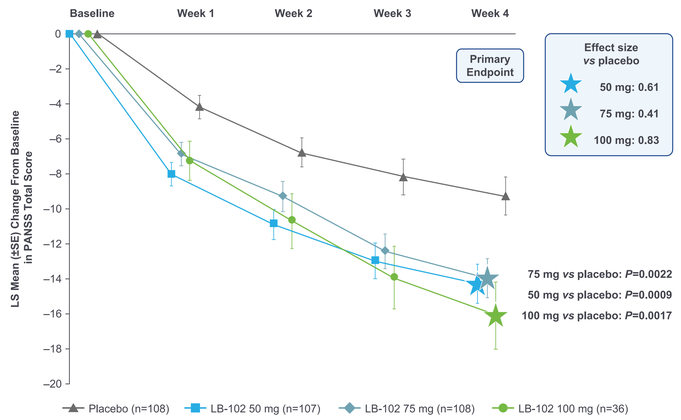


Table 1. Demographics and Baseline Characteristics

		Placebo (n=108)	50 mg (n=107)	75 mg (n=108)	100 mg (n=36)	Overall (N=359)
Age at informed consent, mean (SD)		39.1 (9.1)	39.0 (9.6)	39.2 (9.2)	39.1 (9.2)	39.1 (9.3)
Sex, n (%)	Male	85 (79%)	87 (81%)	90 (83%)	28 (78%)	290 (81%)
	Female	23 (21%)	20 (19%)	18 (17%)	8 (22%)	69 (19%)
Ethnicity, n (%)	Latino	17 (16%)	12 (11%)	8 (7%)	6 (17%)	43 (12%)
Race, n (%)	White	24 (22%)	17 (16%)	18 (17%)	9 (25%)	68 (19%)
	Black	80 (74%)	87 (81%)	83 (77%)	25 (69%)	275 (77%)
	Asian	1 (1%)	0	2 (2%)	0	3 (1%)
	Native American	0	0	2 (2%)	0	2 (1%)
Weight at baseline (kg), mean (SD)		85.6 (17.2)	84.0 (19.5)	88.4 (18.5)	85.9 (18.0)	86.0 (18.4)
BMI at baseline (kg/m^2), mean (SD)		28.2 (5.2)	27.4 (6.0)	28.8 (5.6)	28.0 (6.0)	28.1 (5.6)
Baseline PANSS total score at baseline, mean (SD)		93.8 (8.2)	93.9 (7.5)	93.6 (7.8)	93.9 (9.0)	–
Years since diagnosis, mean (range)		16.4 (2–41)	15.2 (2–38)	16.2 (2–39)	13.5 (2–36)	15.8 (2–41)

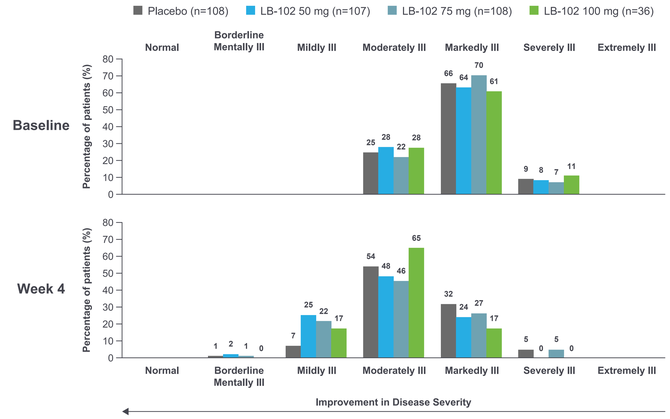
BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Figure 5. Change From Baseline in PANSS Total Score Over Time Through Week 4



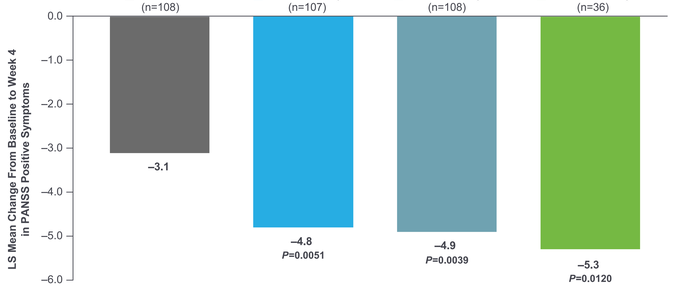
Analyzed using a mixed model for repeated measures (MMRM) that included treatment, visit, treatment-by-visit interaction, and study site as categorical effects, and baseline PANSS total score as continuous covariate.
LS, least squares; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Figure 6. Shift in CGI-S Score From Baseline to Week 4



Percentages may not sum to 100% due to rounding. CGI-S, Clinical Global Impressions–Severity of illness.

Figure 7. Mean Change From Baseline in PANSS Positive Symptoms at Week 4



LS, least squares; PANSS, Positive and Negative Syndrome Scale.

Table 2. Summary of Treatment-Emergent Adverse Events (TEAEs)

Participants, n (%)	Placebo (n=108)	50 mg (n=107)	75 mg (n=108)	100 mg (n=36)	Overall (N=359)
Any adverse event	67 (62%)	77 (72%)	68 (63%)	28 (78%)	240 (67%)
Any TEAE	60 (56%)	74 (69%)	62 (57%)	27 (75%)	223 (62%)
Any treatment-related TEAE	23 (21%)	49 (46%)	34 (31%)	17 (47%)	123 (34%)
Any TEAE leading to early withdrawal	2 (1.9%)	2 (1.9%)	3 (2.8%)	3 (8.3%)	10 (2.8%)
Any severe TEAE	3 (2.8%)	0	1 (0.9%)	1 (2.8%)	5 (1.4%)
Any serious TEAE	2 (1.9%)	1 (0.9%)	1 (0.9%)	1 (2.8%)	5 (1.4%)
Any serious treatment-related TEAE	0	1 (0.9%)	1 (0.9%)	0	2 (0.6%)
Any TEAE leading to death	1 (0.9%)	0	0	0	1 (0.3%)

Table 3. Treatment-Emergent Adverse Events Reported by ≥5% in Any Treatment Arm

Participants, n (%)	Placebo (n=108)	50 mg (n=107)	75 mg (n=108)	100 mg (n=36)
Insomnia	24 (22.2%)	27 (25.2%)	23 (21.3%)	14 (38.9%)
Headache	10 (9.3%)	12 (11.2%)	9 (8.3%)	2 (5.6%)
Anxiety	9 (8.3%)	10 (9.3%)	9 (8.3%)	4 (11.1%)
Agitation	10 (9.3%)	11 (10.3%)	6 (5.6%)	4 (11.1%)
Weight increased	4 (3.7%)	13 (12.1%)	8 (7.4%)	3 (8.3%)
Hyperprolactinemia[1]	0	11 (10.3%)	8 (7.4%)	6 (16.7%)
Blood creatine phosphokinase increased	3 (2.8%)	4 (3.7%)	1 (0.9%)	2 (5.6%)
Alanine aminotransferase increased	1 (0.9%)	3 (2.8%)	1 (0.9%)	2 (5.6%)
Somnolence	0	1 (0.9%)	4 (3.7%)	2 (5.6%)
Constipation	0	4 (3.7%)	1 (0.9%)	2 (5.6%)

[1]Sum of the preferred terms "hyperprolactinemia" and "blood prolactin increased."

CONCLUSION

- LB-102, a novel and potentially first-in-class benzamide D_2/D_3/5-HT_7 receptor antagonist, demonstrated statistically significant efficacy on PANSS improvement and was generally safe and well-tolerated.

DISCUSSION

- This phase 2 clinical trial provided rigorous evidence demonstrating the efficacy and safety of LB-102 for the treatment of adults with acute schizophrenia, supporting the continued clinical development of LB-102 for schizophrenia.
- A phase 3 clinical development program in schizophrenia is currently being planned.

References

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Acknowledgments

Medical writing and poster development support were provided by The Medicine Group, LLC (New Hope, PA, USA) in accordance with Good Publication Practice guidelines.

Funding

This study and poster development support were sponsored by LB Pharmaceuticals Inc, New York, NY, USA.

Disclosures

AE, LC, BL, and **AV** are full-time employees and shareholders of LB Pharmaceuticals. **NB** serves as a consultant to LB Pharmaceuticals. **ZP** is a co-founder and former Chief Executive Officer of LB Pharmaceuticals; he currently serves as a member of the Board of LB Pharmaceuticals. **JK** has served as a consultant to, received honoraria, received travel support, and/or participated in speakers' bureaus for AbbVie, Alkermes, Allergan, Boehringer-Ingelheim, Bristol Meyer-Squibb, Cerevel, Dainippon Sumitomo, HealthRhythms, HLS Therapeutics, Indivior, Intracellular Therapies, Janssen Pharmaceutical, Johnson & Johnson, LB Pharmaceuticals, Lundbeck, Mapi, Maplight, Merck, Minerva, Neurocrine, Newron, Novartis, NW PharmaTech, Otsuka, Roche, Saladax, Sunovion, and Teva; has participated on advisory boards for AbbVie, Alkermes, BMS, Boehringer-Ingelheim, Cerevel, Click Therapeutics, Lundbeck, Merck, Newron, Novartis, Otsuka, Sumitomo, Terran, and Teva; has received grant support from Lundbeck, Janssen, Otsuka, and Sunovion; holds stock or stock options in HealthRhythms, LB Pharmaceuticals, Medincell, North Shore Therapeutics, NW Pharmatech, Reviva, Saladax, Terran, and Vanguard Research Group; and receives royalties from UpToDate.