# LB-102, a novel benzamide for the treatment of schizophrenia: safety and dopamine receptor occupancy data from two clinical studies

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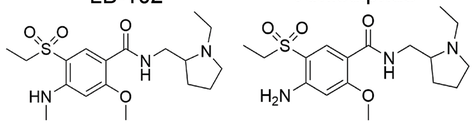
## LB-102 Background

LB-102 is a novel benzamide analogue of amisulpride. LB-102, like amisulpride, is a strong dopamine $D_{2/3}$ antagonist ($K_i$ < 1 nM) and moderate 5-$HT_7$ antagonist ($K_i$ ~30 nM). In preclinical assays LB-102 had properties similar to amisulpride in terms of CNS receptor binding, pharmacokinetics, and behavioral modification in animal models of schizophrenia while exhibiting greater dopamine receptor occupancy in the brain. LB-102 has successfully completed a Phase 1 safety/PK study (NCT04187560) in 64 healthy volunteers and a positron emission tomography study (NCT04588129) in 16 healthy volunteers to measure dopamine receptor occupancy in humans. Based on the above data a Phase 2 study (NCT06179108) of LB-102 is underway at 25 sites in the US, enrolling 350 schizophrenia patients randomized 3:3:3:1 placebo:50 mg:75 mg:100 mg.

LB-102 Amisulpride

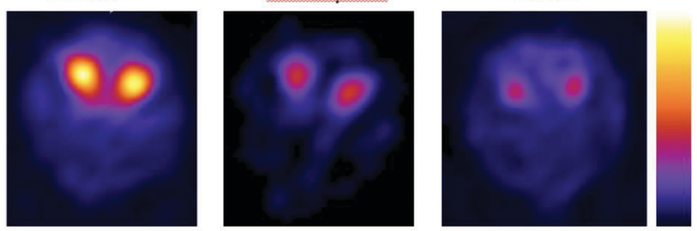


### *Preclinical*

In preclinical assays evaluating LB-102 the molecule had:

- Similar potency as amisulpride at important CNS receptors; specifically binding dopamine $D_{2/3}$ with single digit nM $K_i$ and $5HT_7$ with low double digit nM $K_i$
- Plasma PK profiles in rats and mice superimposable (in rodents LB-102 is ~50% demethylated to amisulpride)
- LB-102 had a Log P 1.72, which is more lipophilic than amisulpride (log P 1.52)
- Similar or better efficacy in behavioral models of schizophrenia, Novel Object Recognition, LocoMotor Activity, or Apomorphine Induced Climbing LB-102 was as good as, or better than, amisulpride
- Twice the dopamine $D_{2/3}$ receptor occupancy in a Positron Emission Tomography study in mice as amisulpride:

Vehicle Amisulpride LB102



## Clinical Studies

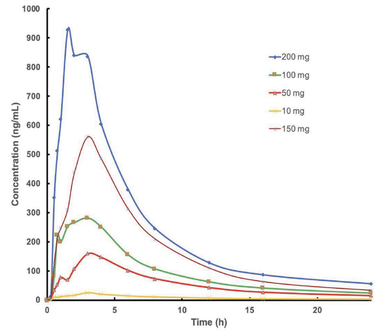
### Phase 1

This was a clinical study designed to evaluate the safety and pharmacokinetics of LB-102 in healthy volunteers. This study enrolled 64 healthy volunteers at a single site (Medpace in Cincinnati). Subjects were randomized 3:1 to LB-102:placebo. In the single ascending dose (SAD) portion of this study subjects were dosed at 10, 50, 100, 150, or 200 mg. In the multiple ascending dose (MAD) groups subjects were dosed at 100, 150, or 200 mg/day in two divided doses. Subject disposition is summarized below:

| | Part A (SAD) | | | | | Part B (MAD) | | | Averages | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cohort 1 (50 mg QD) | Cohort 2 (10 mg QD) | Cohort 3 100 mg QD) | Cohort 4 (200 mg QD) | Cohort 5 (150 mg QD) | Cohort 6 (50 mg BID) | Cohort 7 (100 mg BID) | Cohort 8 (75 mg BID) | LB-102 | Placebo |
| N | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 16 |
| Age, Mean (SD) | 37.2 (8.2) | 31.3 (10.7) | 35 (9.8) | 28.8 (11.7) | 31 (11.5) | 31.7 (4.9) | 34.8 (9.8) | 44 (8.7) | 34.2 (9.4) | 40.1 (12.3) |
| % Female | 66.7 | 33.3 | 33.3 | 33.3 | 33.3 | 0 | 16.7 | 33.3 | 31.2 | 25 |
| % Asian | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % Black or African American | 33.3 | 50 | 66.7 | 100 | 83.3 | 66.7 | 83.3 | 33.3 | 68 | 56.3 |
| % White | 50 | 50 | 33.3 | 0 | 16.7 | 33.3 | 16.7 | 66.7 | 33 | 43.8 |
| BMI (kg/m2), Mean (SD) | 25.7 (3.2) | 23.9 (3.1) | 25.3 (4.2) | 24.2 (3.3) | 24.3 (2.1) | 26 (2.5) | 22.8 (3.1) | 24.1 (2) | 24.5 (2.9) | 25.1 (2.4) |

*QD* once daily dosing, *BID* twice daily dosing, *SD* standard deviation, *BMI* body mass index

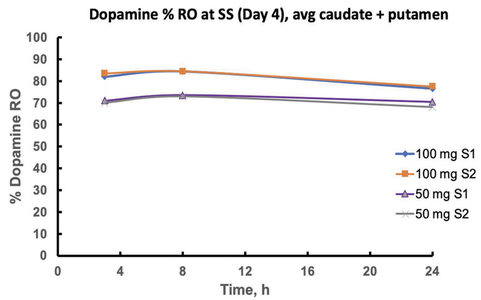
- The plasma PK profile (right) showed dose-linearity and suggested once daily dosing (amisulpride is typically dosed twice a day) is feasible
- Dosing at 100 mg BID was discontinued due to 2 cases of acute dystonia (EPS), consistent with dopamine receptor occupancy > 80%
- LB-102 was generally safe and well-tolerated, no serious adverse events were reported (below)




| Adverse event | Placebo | Single ascending dose 10 mg | 50 mg | 100 mg | 150 mg | 200 mg | Multiple ascending dose 50 mg BID | 75 mg BID | 100 mg BID |
|---|---|---|---|---|---|---|---|---|---|
| n | 16 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Elevated prolactin | | 2 | 3 | 1 | 1 | 1 | 2 | 2 | 1 |
| Diarrhea | | | 1 | | | | | | |
| Upper respiratory infection | | | 1 | 1 | | | | | |
| Abdominal pain | 1 | 1 | | 1 | | | | | |
| Nausea | | | | | | 1 | | 1 | 1 |
| Urticaria | | | | 1 | | | | | |
| Acute dystonia | | | | | | 1 | | 1 | 2 |
| QT prolongation | | | | | | 1 | | | |
| Insomnia | | | | | | 1 | | 1 | |
| Gastroesophageal reflux | | | | | | 1 | | | |
| Headache | 1 | | | | | 1 | | | |
| Oropharyngeal pain | | | | | | 1 | | | |
| Heart palpitations | | | | | | 1 | | | |
| Vomiting | | | | | | | | | 1 |
| Dry mouth | | | | | | | | | 1 |
| Somnolence | | | | | | | | 1 | 1 |
| Dizziness | | | | | | | | 1 | |
| Migraine | | | | | | | | 1 | |
| Back pain | 1 | | | | | | | 1 | |
| Bug bite | 1 | | | | | | | | |

### PET study

This was a clinical study designed to measure the dopamine receptor occupancy (RO) of LB-102 in healthy volunteers by measuring 11C raclopride displacement using PET. This study enrolled 16 healthy volunteers at a single site (Washington University in St. Louis). Subjects in the first 3 cohorts were given a single dose of 50, 75, or 100 mg of LB-102. RO in these subjects ranged from 40% to 80%. Unlike most anti-psychotics, dopamine RO was uncorrelated with plasma drug concentration, with significant binding continuing even as plasma concentration approached 10% of $C_{max}$. In the final cohort subjects were dosed with 50 or 100 mg LB-102 once daily for 4 days to achieve steady state concentration, RO for these subjects is depicted below:




### Conclusion and future directions

- LB-102 was generally safe and well-tolerated and provided consistent dopamine RO in the desired 60-80% range over a full day after dosing
- Based on the present data a 350 patient, double-blind, placebo-controlled, study of LB-102 began in patients with acutely exacerbated schizophrenia in November 2023
- Three treatment arms: 50, 75, and 100 mg
- Patients will be dosed for 28 days with PANSS total score as primary endpoint
- Data are expected in the first half of 2025, and will guide planning of Phase 3 studies

**Conflict of Interest/funding**

Disclosure statement: AE, AV, VG, and ZP are employees and shareholders of LB Pharmaceuticals. JK is a consultant to and shareholder of LB Pharmaceuticals.