PET clinical study of novel antipsychotic LB-102 demonstrates unexpectedly prolonged dopamine receptor engagement

D. F. Wong[1], A. Eramo[2], N. Caito[1], G. B. Chand[1], G. Nicol[1], M. S. Hixon[3], L. Tian[1], E. Lessie[1], I. Valenta[1], T. Schindler[1], V. T. Grattan[2], Z. Prensky[2], A. R. Vaino[2]

[1]Washington University, St. Louis, MO, USA [2]LB Pharmaceuticals Inc., New York, NY, USA [3]Mark S. Hixon Consulting LLC, San Diego, CA, USA

Washington University in St. Louis School of Medicine

MIR Mallinckrodt Institute of Radiology

Lab of CNS Neuropsychopharmacology and Multimodal Imaging

Objectives

- Using Positron Emission Tomography (PET), measure $D_{2/3}$ receptor occupancy (RO) of LB-102
- Assess safety and tolerability of LB-102

Background

- Treatment nonadherence is common in patients with schizophrenia, primarily related to medication effectiveness and tolerability
- Amisulpride, an atypical antipsychotic drug approved for the treatment of schizophrenia in Europe, is a selective antagonist at dopaminergic D_2 (Ki=2.8 nM) and D_3 (Ki=3.2 nM) receptors with negligible affinity for the D_1, D_4, and D_5 receptor subtypes (Ki > 1,000 nM). Amisulpride also acts as an antagonist at the
- 5-HT_7 receptor (Ki=11.5 nM)
- LB-102 is designed to improve upon the known membrane permeability issues with amisulpride, increasing ability to cross the blood-brain barrier (BBB)

Figure 1

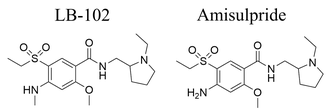


Figure 1.
LB-102 is an *N*-methylated version of amisulpride, which allows it to cross the blood-brain barrier more readily, possibly meaning lower doses are necessary to achieve the same effect.

Methodology

Participants and Study Design

Cohort	Treatment
1 (N=4)	LB-102 50 mg x 1 day
2 (N=4)	LB-102 100 mg x 1 day
3 (N=4)	LB-102 75 mg x 1 day
4 (N=4)	N=2, LB-102 100 mg, 4 x QD (Days 1-4; total of 4 doses) N=2, LB-102 50 mg, 4 x QD (Days 1-4; total of 4 doses)

- 18-55 years old with BMI ≤30 kg/m^2
- Subjects demonstrated good general health via medical history, physical examination, laboratory tests, and electrocardiogram
- No medications were allowed during the study period
- Monitored prolactin levels, QT interval, and suicidality
- Plasma samples collected ~0.5 hr pre-dose and at the following time points post-dose: 0.5 hr, 1 hr, 2 hrs, 3 hrs, 4 hrs, 8 hrs, 24 hrs, 25 hrs, and, in Cohort 3 only, 48 hrs and 49 hrs (±15 min)

Participant Demographics

Cohort	50 mg x 1	100 mg x 1	75 mg x 1	100 mg x 4	50 mg x 4
Mean Age (yrs)	31.25	36.75	28.25	44.5	23
Mean Weight (kg)	67.8	72.6	82.3	81.5	85.2
Sex	3 F, 1 M	3 F, 1 M	3 M, 1 F	2 M	2 M
Race	4 W	1 AfAm, 3 W	2 AfAm, 2 W	1 Asian, 1 W	2 W/Asian

PET Imaging

- Subjects received a total of 4 PET scans with [^{11}C]raclopride. The mean injected activity was 14.1 ± 0.31 mCi (SEM)
- 1 baseline PET scan (pre-dose) and 3 PET scans at several time points following final LB-102 dose
- Each PET scan lasted 90 minutes and collected ~30 frames

Funded by

pharmaceuticals

Conflict of Interest

Disclosure statement: AE, ARV, VG, and ZP are employees and shareholders of LB Pharmaceuticals. MSH is a consultant to and shareholder of LB Pharmaceuticals. GN has served as PI or Co-I on grants funded by Otsuka, Inc., Alkermes and Takeda, and has served as a consultant to Sunovion and Alkermes.

Results

Figure 2

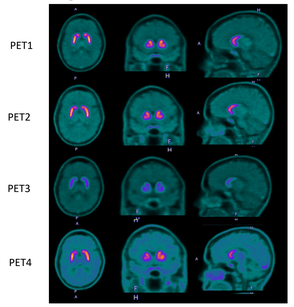
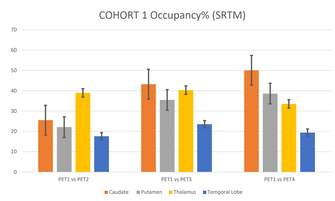
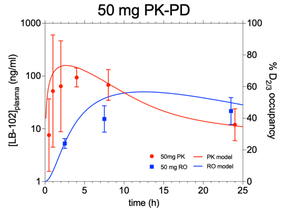


Figure 2. [C11]raclopride PET scans from a cohort 4 participant. This participant took a daily dose of 50 mg LB-102 for four days. PET 1 is a pre-dose baseline scan. Scans 2 through 4 occurred after the final dose (during steady state) at 2.5 hrs post-dose, 7.5 hrs post-dose, and 23.5 hrs post-dose, respectively.

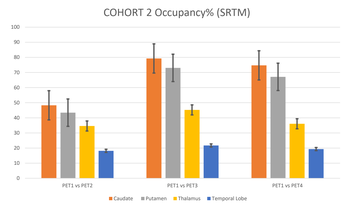
- Single 50 mg, 75 mg, and 100 mg oral doses of LB-102 demonstrated dopamine $D_{2/3}$ RO approaching 50%-75% in striatal regions (caudate/putamen)
- 4 QD oral doses (steady state) of 100 mg LB-102 demonstrated $D_{2/3}$ RO of 80% in caudate/putamen
- 4 QD oral doses (steady state) of 50 mg LB-102 demonstrated $D_{2/3}$ RO of 75% in caudate/putamen
- The acute dosing and confirmatory chronic dosing showed that 50 mg once daily will provide the desirable 75% occupancy in caudate/putamen
- There is also evidence of moderate occupancy in extra-striatal areas
- RO and pharmacokinetic (PK) data shown in the following graphs

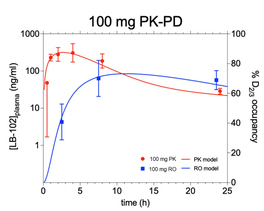
Cohort 1 (50 mg x 1 dose)



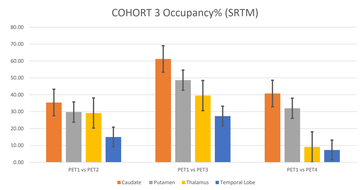


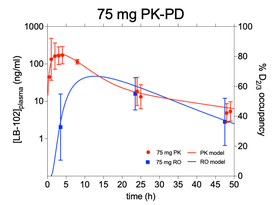
Cohort 2 (100 mg x 1 dose)





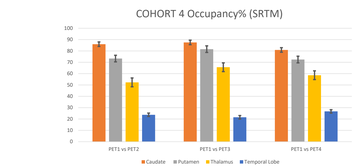
Cohort 3 (75 mg x 1 dose)

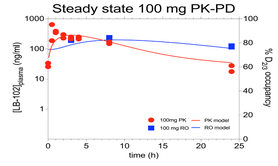




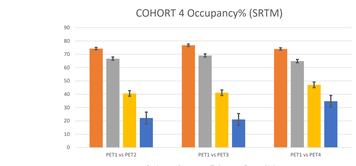
Cohort 4 (N=2, 100 mg x 4 doses; N=2, 50 mg x 4 doses)

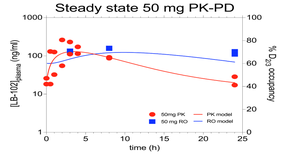
100 mg x 4 doses (steady state)





50 mg x 4 doses (steady state)





Treatment-Emergent Adverse Events

Possibly Related	Unrelated/remotely related	Not related
Headache (N=2)	Restlessness* (N=2)	Acid reflux (N=1)
Dizziness and lightheadedness (N=1)	Anxiety (N=1)	
	Sore throat (N=1)	
	Nasal congestion (N=1)	

*Determined not to be akathisia via clinical evaluation using the Barnes Akathisia Rating Scale

Several treatment-emergent adverse events were reported. The adverse events that were possibly drug-related included headache and dizziness/lightheadedness. Two instances of restlessness occurred during the multidose cohort. These were likely not akathisia and instead a consequence of the five day stay in the research unit.

Conclusions

- LB-102 was well-tolerated in a population of healthy adults
- Possible drug-related adverse events include headache and dizziness
- RO ranges of ~50%-80% were observed in caudate/putamen, with additional RO < 50 % in extra-striatal regions
- Results were generally consistent with our modeled expectations for LB-102 and are in the desired range (60% to 75% dopamine RO) for an effective schizophrenia drug
- By comparison, in a published study [1] of amisulpride, 75 % dopamine RO required > 400 mg of drug
- Single doses of 75 to 100 mg LB-102 produced sustained $D_{2/3}$ RO in the desired 60-75% range, a dose range that was well-tolerated in a Phase 1 clinical study of LB-102 [2]
- As anticipated from prior results [3], RO data above revealed uncoupling of $D_{2/3}$ receptor occupancy from the plasma PK over time, permitting reliable estimates of human CNS exchange kinetics
- The non-linear occupancy vs. PK concentrations suggests brain retention
- Cohort 4 data indicates that at steady state dosing, 50 - 75 mg LB-102 QD will achieve 65-75% $D_{2/3}$ RO. These results will guide dosing and drug administration schedule in a planned Phase 2 clinical study of LB-102 in adults with schizophrenia

[1] Meisenzahl, E. M., Schmitt, G., Gründer, G., Dresel, S., Frodl, T., la Fougère, C., Scheuerecker, J. Schwarz, M., Strauss, J. Hahn, K., and Möller, H.-J., 2008, "Striatal D2/ D3 Receptor Occupancy, Clinical Response and Side Effects with Amisulpride: An Iodine-123-Iodobenzamide SPET Study, *Pharmacopsychiatry*, *41*, 169-175.
[2] Vaino, A. R., Grattan, V. T., Prensky, Z., Hixon, M. S., Biernat, L. 2020. Safety, Pharmacokinetics, And Pharmacodynamics Of LB-102, A Selective D2/S-HT7, In Healthy Volunteers, 33rd European College of Neuropsychopharmacology meeting, Vienna, Austria.
[3] Vaino, A., Grattan, V., Prensky, Z., Hixon, M., 2019. Building A Translational Bridge From Animals To Man For Clinical Candidate LB-102, A Next-Generation Benzamide Antipsychotic, *European Neuropsychopharmacology* 29, S87-S88.