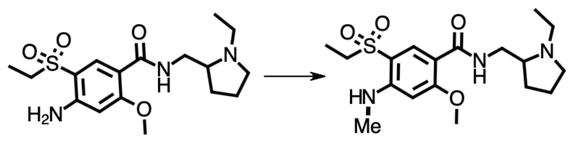
LB-102 displays superior dopamine receptor occupancy compared to amisulpride in mouse and human PET studies (P.0830)

A. R. Vaino[1], A. Mintz[2], A. Eramo[1], N. Caito[3], G. B. Chand[3], G. Nicol[3], M. S. Hixon[4], V. T. Grattan[1], Z. Prensky[1], A. Molotkov[2], M. Dolan[2], S. Oya[2], M. Cabrera[5], Luxi Wang[5], D. F. Wong[3]

[1]LB Pharmaceuticals Inc., New York, NY, USA, [2]Columbia University Medical Center, New York, NY, USA, [3]Washington University, Saint Louis, MO, USA, [4]Mark S. Hixon Consulting LLC, San Diego, CA, USA, [5]Target Health Inc., New York, NY, USA

Introduction:

LB-102 is novel derivative of the well-known—and highly effective—antipsychotic amisulpride. LB-102, like amisulpride, is a strong dopamine $D_{2/3}$ inhibitor (K_i < 1 nM) and moderate 5-HT_7 inhibitor (K_i ~30 nM). In a Phase 1 clinical study [1] in healthy volunteers, LB-102 was dosed up to 200 mg/day. Dopamine receptor occupancy (RO) has been used in clinical development as a marker of atypical antipsychotic efficacy and safety: in predominantly $D_{2/3}$ antagonists, 60 to 75% RO correlates to meaningful improvements in PANSS scores in schizophrenia patients [2]. The aim of these studies was to measure dopamine $D_{2/3}$ receptor occupancy of LB-102 relative to amisulpride to inform dosing in a planned Phase 2 clinical study.



Amisulpride
Log P 1.5 (pH 7)

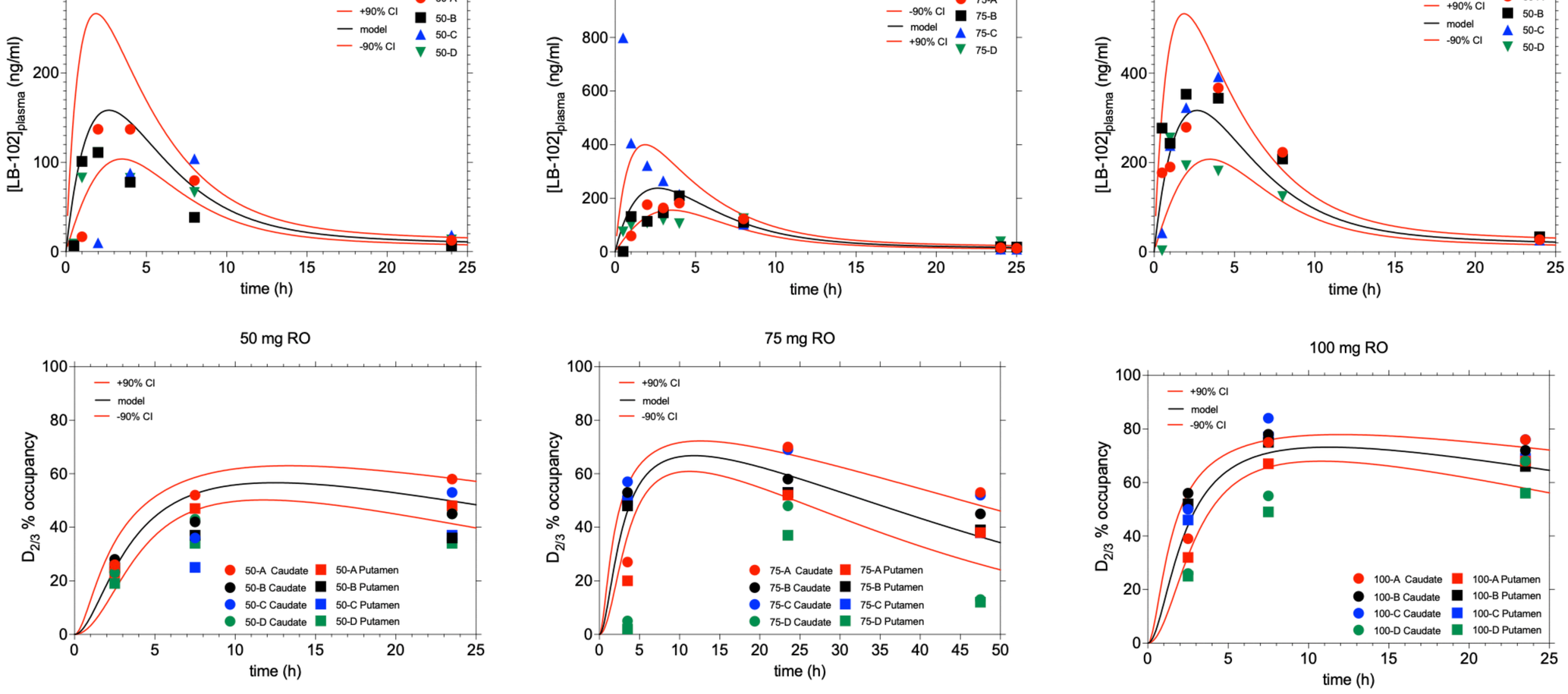
LB-102
Log P 1.7 (pH 7)

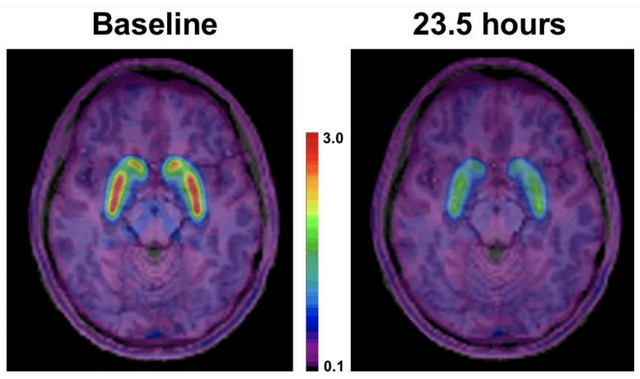
Methods:

Mice were dosed with LB-102 or amisulpride and static ^{11}C raclopride PET scans were obtained at baseline and 2 h post oral drug administration. In a clinical study (NCT04588129), healthy volunteers were dosed orally with single doses of either 50, 75, or 100 mg LB-102 and dynamic ^{11}C raclopride PET scans were obtained at baseline, 2.5, 7.5, 23.5 h, and 47.5 after LB-102 administration. Blood samples were drawn at 0, 0.5, 1, 2, 4, 8, 24 and 48 h post dose for PK analysis, both of LB-102 and amisulpride (a minor metabolite).

Results (pharmacokinetic and receptor occupancy data):

In the clinical study, single 50 mg, 75 mg and 100 mg oral doses of LB-102 demonstrated dopamine $D_{2/3}$ RO approaching 50% and ~75% in striatal regions, respectively. These results were generally consistent with our modeled expectations [3] 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 [4] of amisulpride 75 % dopamine RO required > 400 mg of drug. Charts showing PK and RO data are presented below.





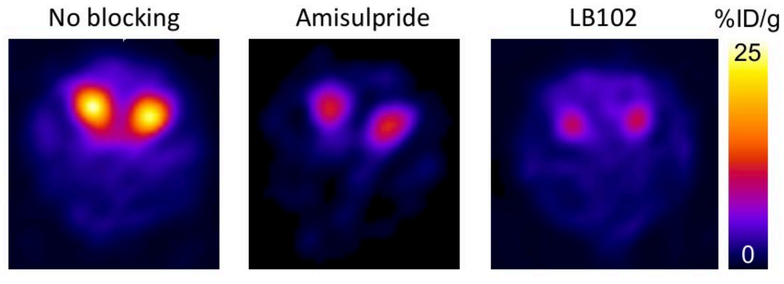
PET scans taken at baseline and 24 h after dosing either 50 mg LB-102

Results (safety, demographics, and PET scans):

There were three adverse events in this study, all mild: two incidences of mild headache and one incidence of moderate lightheadedness/dizziness: these all resolved without intervention. Demographic information for subjects is presented in the Table below.

	Cohort	50 mg QD	75 mg QD	100 mg QD
Age	Average age (yrs)	32.3	37.8	29.0
Weight	Average weight (kg)	67.8	72.6	82.3
Sex	Female	3	3	1
	Male	1	1	3
Race	White	4	3	2
	Black		1	2

Dopamine $D_{2/3}$ receptor occupancies in mice, presented below, resulting from 100 mg/kg oral doses of LB-102 and amisulpride in mice were determined to be 68% and 38%, respectively, consistent with greater Log P and increased plasma concentrations of LB-102 observed in a Phase 1 clinical study [1].



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

Conclusion:

In mice LB-102 showed better dopamine receptor occupancy than amisulpride at the same dose, possibly due to greater lipophilicity. In humans, single doses of 75 to 100 mg LB-102 produce 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 [1]. RO data above revealed uncoupling of $D_{2/3}$ receptor occupancy from the plasma PK over time, as expected from previous modeling work [3] and permitted reliable estimates of human CNS exchange kinetics. Our analysis indicates that at steady state dosing, 75 mg LB-102 QD will achieve 75% $D_{2/3}$ RO—amisulpride requires a 400 mg dose to achieve comparable occupancy [4]. The presented studies and their evaluation are being used to guide determination of dose and schedule of cohorts in a planned Phase 2 clinical study of LB-102 in schizophrenia patients.

References

[1] A. R. Vaino, A. R., Grattan, V. T., Prensky, Z., Hixon, M. S., Biernat, L. Safety, Pharmacokinetics, And Pharmacodynamics Of LB-102, A Selective D_2/5-HT_7, In Healthy Volunteers, 33rd European College of Neuropsychopharmacology meeting, Vienna, Austria.
[2] Pani, L., Pira, L., Marchese, G., 2007. “Antipsychotic efficacy: Relationship to optimal D_2-receptor occupancy”, *European Psychiatry*, *22*, 267-275.
[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 Neuropsychoparmacology* 29, S87-S88.
[4] 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.

Conflict of interest:

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