Pre-clinical evaluation of two novel benzamides LB–102 and 103 for the treatment of schizophrenia

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DEVELOPING TREATMENTS FOR MENTAL ILLNESS

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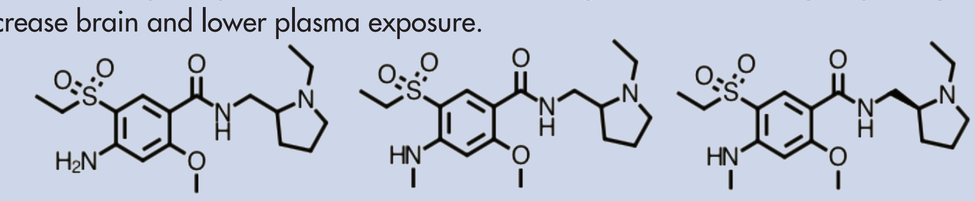
Pragmatic approaches to drug discovery challenges

BACKGROUND

Schizophrenia is a debilitating disease affecting ~1% of the population. Despite a surfeit of schizophrenia drugs, according to the APA, 60% of patients do not adequately respond to treatment. LB-102 and LB-103 are novel benzamides designed to improve the poor blood brain barrier (BBB) permeability of amisulpride, a well established dopamine antagonist used to treat schizophrenia.[1]

HYPOTHESIS

Selective *N*-methylation of amisulpride produces LB-102/LB-103, designed to decrease hydrophilicity to improve BBB permeability, increase brain and lower plasma exposure.



RECEPTOR BINDING DATA

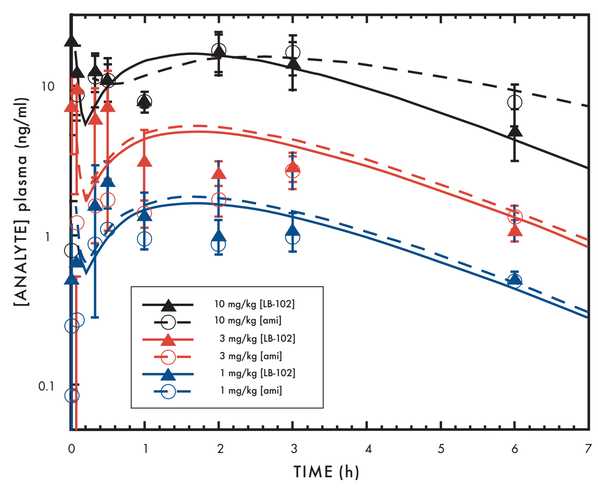
Inhibition constants (Ki) were determined from ligand displacement assays

	Ki (nM)		
	amisulpride	LB1012	LB1013
5-HT_{2a}	>1000[3]	490	530
5-HT_7	12-136[3]	27	
D_2	2.84[4]	<1	<1
D_3	3.24[4]	2.5	1.2

Binding to D_2 and D_3 receptors was similar to amisulpride (Ki of 2.8 nM against D_2 and 3.2 nM against D_3).

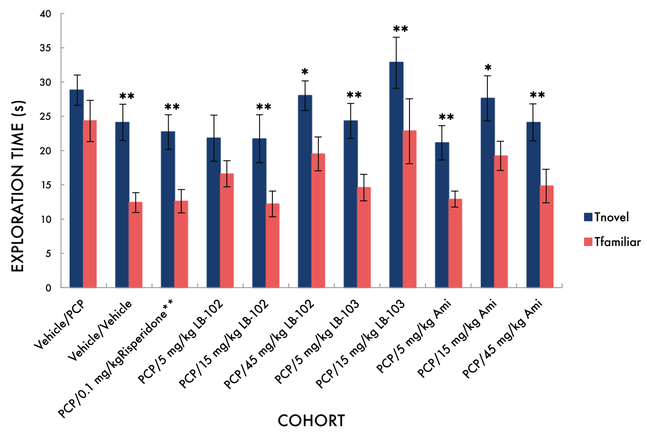
Notably, an initial screen at 10 mM showed weak inhibition (<50%) at the a_1, a_{1a}, a_{1b}, a_2d, H_1, m_1, m_2, 5HT2C, and hERG receptors.

RODENT PHARMACOKINETIC EFFICACY



Pharmacokinetics p.o. dosing of rats (3/grp) LB-102. LB-102 displays a demethylation burst (possibly 1st pass) followed by a steady state having equal proportions of LB-102 and demethylated metabolite (amisulpride). LB-102 affords exposures of active agents (parent and metabolite) equal to amisulpride. Mouse PK (not shown) was similar.

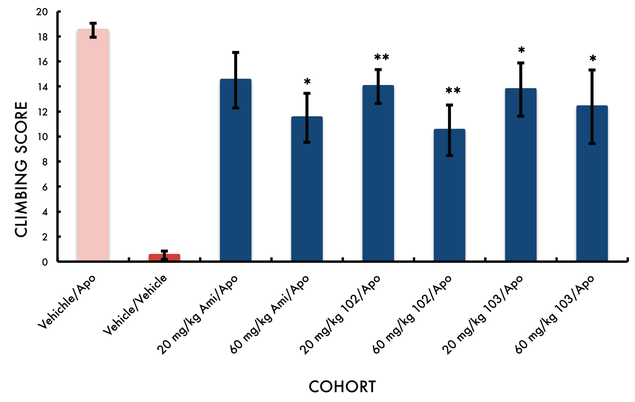
NOVEL OBJECT RECOGNITION (NOR)



Amisulpride, Risperidone, LB-102, and LB-103 dosed p.o.
* = p < 0.05 between Tn and Tf, ** = P < 0.01

NOR Object exploration data from a sub-chronic PCP NOR study in rats (2 mg/kg i.p. twice daily followed by 7 days drug free (n = 10/grp) measured 60-180 min post dose drug.

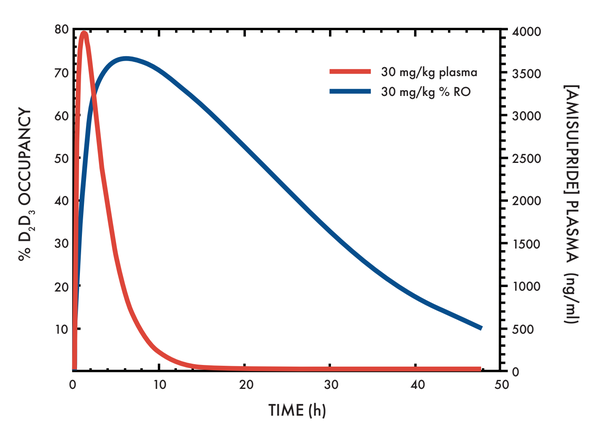
APOMORPHINE INDUCED CLIMBING (AIC)



Amisulpride, LB-102, and LB-103 dosed p.o.* = p < 0.1 (i.e. strongly trending) compared with cohort/Apo, ** = P < 0.05 (statistically significant).

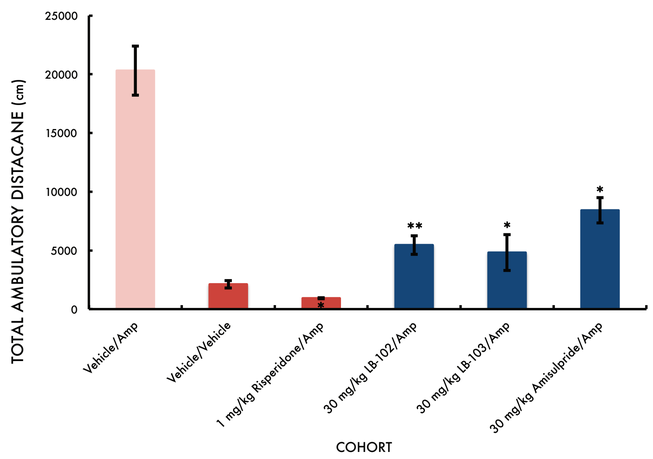
AIC Climbing Scores from an Apomorphine Induced Climbing (AIC) study in mice (n = 8/grp) showed that LB-102 significantly reduced apomorphine-induced climbing behaviour and was statistically indistinguishable from amisulpride.

PRELIMINARY PK-PD-RO MODEL



Preliminary PK-PD-E Model of Amisulpride based on published[2] and proprietary data the relationship between plasma concentration and apparent D2/D3 receptor occupancy (both D2 and D3) is plotted above. These data informed choice of dose and observation time for behavioural studies, and are expected to have application in selecting dosing for clinical studies.

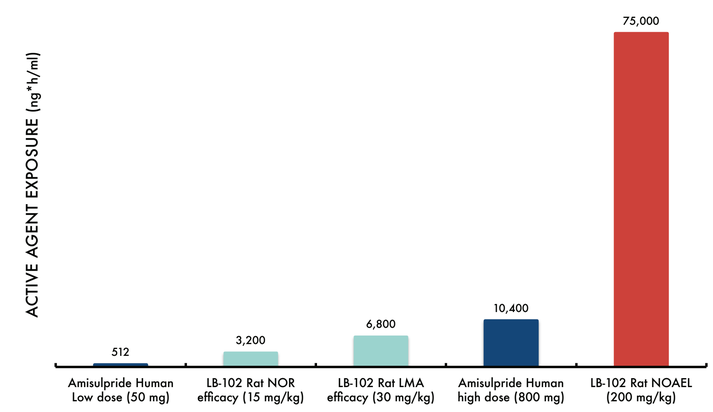
LOCOMOTOR ACTIVITY (LMA)



Amisulpride, Risperidone, LB-102, and LB-103 dosed p.o.

LMA Total Ambulatory Distance data from an amphetamine induced LMA rat study (n =10/grp) measured 6 h post-dose amphetamine dose over the course of an hour. Treatment groups marked with * were statistically superior to amphetamine (p < 0.01), and 30 mg/kg LB-102 (**) was astatistically superior to 30 mg/kg amisulpride (p < 0.05).

AMISULPRIDE/LB-102 EXPOSURE



Translation to the Clinic
LB-102 provides efficacy in rat and mouse behavioural studies consistent with amisulpride exposure known to provide clinical efficacy. Clinical dose selection will be guided by animal efficacy and receptor occupancy studies (ongoing) and amisulpride human dosing.

DISCUSSION

LB-102 and LB-103 are next generation analogs of amisulpride designed to retain the antipsychotic activity of amisulpride (an antipsychotic licensed for use in Europe since 1993) at lower doses, providing a potentially improved side effect profile. Studies to date with LB-102 and LB-103 demonstrate:

1. CNS receptor binding profiles comparable to amisulpride

2. Oral pharmacokinetic profiles (for active agent plus metabolite amisulpride) in rodents comparable to amisulpride

3. Similar-to-superior behavioural responses in animal models designed to recapitulate both positive and cognitive deficit symptoms of schizophrenia (object recognition deficits [NOR], hyperactivity [LMA], and stereotypy [AIC])

4. LB-102 14 day rat tox NOAEL was 200 mg/kg/d (same as amisulpride)[5]

5. In scPCP treated rats in a catalepsy test to measure EPS potential, no catalepsy was observed and LB-102 and LB-103 were indistinguishable from amisulpride

CONCLUSION

LB-102 and LB-103 have target level binding, DMPK, rodent behavioural model efficacy, and drug safety comparable-to-superior to amisulpride.

LB Pharmaceuticals expects to initiate Phase 1 clinical trials in early 2019.

DISCLOSURES

This work was funded by LB Pharmaceuticals Inc. and Rivopharm SA. JCN, BG, GP, and DC are employees of the University of Manchester. ZP and AV are employees of LB Pharmaceuticals. MB, VG, and MSH are consultants to LB Pharmaceuticals. MB, VG, MSH, ZP, and AV are shareholders of LB Pharmaceuticals.

[1] *The AAPS Journal*, **2014**, *16*, 1247–1258.
[2] *Schizophrenia Research*, **2008**, 105, 224-235.
[3] *The Neuroscientist*, **2000**, *6*, 252-262.
[4] *J. Pharmacol. Exp. Ther.*, **1997**, *280*, 83-97.
[5] Solian label.