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2.6.2 PHARMACOLOGY WRITTEN SUMMARY

2.6.2.1 Brief Summary

The *in vitro* and *in vivo* pharmacodynamics of LB-102 have been evaluated. *In vitro* binding of LB-102 to important CNS receptors relevant to schizophrenia (e.g. androgenic, dopaminergic, histaminergic, muscarinic, and serotinergic) has been measured and the molecule demonstrated the strongest binding to the dopamine $D_{2/3}$ receptors, having a K_i of 1 nM; there was also some affinity for the 5-HT_7 receptor (K_i of 31 nM). In a Parallel Artificial Membrane Permeability Assay (PAMPA), a proxy for blood-brain barrier penetrating ability, LB-102 had ~200 X higher permeability across this membrane as compared to amisulpride.

Commonly used animal behavioral studies mimicking symptoms of schizophrenia were used to assess the *in vivo* efficacy of LB-102. These included Novel Object Recognition (NOR) in rats, a measure of cognition, Apomorphine Induced Climbing (AIC) in mice, a measure of climbing, and Locomotor Activity (LMA) in rats, a measure of hyperactivity. In two of these studies, NOR and AIC, LB-102 was statistically indistinguishable from amisulpride and in one of these studies (LMA) a 30 mg/kg dose of LB-102 was statistically superior to amisulpride.

A complete battery of Good Laboratory Practice (GLP)-compliant safety pharmacology studies has been performed.

No effects were noted on the respiratory system of rats at doses up to and including 200 mg/kg. A minor finding of increased grip strength was observed in rats at the highest dose tested, 200 mg/kg; no other central nervous system changes occurred at doses of 40 and 80 mg/kg. A dose-related inhibition of the hERG channel was observed with an IC_{50} of 16.7 µM. Based on allomeric scaling of the rodent and dog PK data and human amisulpride PK data, the projected C_{max} for a 400 mg dose of LB-102 is 280 ng/mL, or 0.7 µM. This is approximately 24 times lower than the IC_{50} observed for hERG inhibition. In dogs, the main toxicology finding was a dose-related, transient, and reversible increase in heart rate which was reported at all doses (1.5 to 15 mg/kg).

An overview of the safety pharmacology studies is provided in Table 2.6.3.1.

2.6.2.2 Primary Pharmacodynamics

2.6.2.2.1 In Vitro Studies

2.6.2.2.1.1 PAMPA Permeability of LB-102

Membrane permeability of LB-102 was measured using a Parallel Artificial Membrane Permeability Assay (PAMPA) at pH 5 and 7.4 (Study LB-102-PC-011). The PAMPA assay is often used as a screen to rank compounds by their ability to penetrate the blood brain barrier. (Di, et al., 2003) Specifically, 10 mM solutions of controls, ranitidine (3.5 mg in 1 mL DMSO) and propanolol (2.9 mg in 1 mL DMSO), as well as LB-102 (3.3 mg in 0.8 mL DMSO) and amisulpride (3.4 mg in 0.9 mL DMSO) were prepared, diluted in aqueous solution (pH 5 and 7.4) and placed on one side of the membrane which was made up of porcine brain lipids. Blank aqueous buffer was placed on the other side. After 15 to 20 hours of incubation, the donor and acceptor wells were sampled and analyzed by LC-MS/MS for drug content.

Retention (R) and the effective permeability (Pe) were calculated using the following formula:

$$P_e = -\frac{2.303V_D}{A(t-t_{LAG})}\left(\frac{1}{1+r_V}\right)\cdot\log_{10}\left[1-\left(\frac{1+r_V^{-1}}{1-R}\right)\cdot\frac{C_A(t)}{C_D(0)}\right]$$

where

- $C_A(t)$ and $C_D(0)$ – any concentration-proportional numbers (OD or AUC), the ratio $C_A(t)/C_D(0)$ should never exceed 0.495;
- $r_V = V_D/V_A = 1$;
- A – area of the filter, 0.3 cm^2;
- t – time, s;
- t_{LAG} – time needed to saturate the membrane with solute, it may be assumed 1200 s for 15 h PAMPA assay using porcine brain lipids (neutral) lipid model.
- Retention factor, $R = 1 - \frac{C_D(t)+C_A(t)}{C_D(0)}$

Permeability (P_e) results from this study are presented below.

Table 1: Permeability of LB-102, Amisulpride, Propanolol, and Ranitidine Through a PAMPA Membrane at pH 5 and pH 7.4

Compound	Permeability (cm/s) pH 5	Permeability (cm/s) pH 7.4
Amisulpride	2.4 X 10^{-10}	2.4 X 10^{-11}
LB-102	2.1 X 10^{-8}	5.2 X 10^{-9}
Propanolol	3.1 X 10^{-8}	7.8 X 10^{-6}
Ranitidine	1.1 X 10^{-10}	1.5 X 10^{-10}

In this study the control agents, propranolol and ranitidine, behaved as expected. Initial membrane diffusion studies showed that LB-102 passively diffused across the artificial brain membrane more effectively than amisulpride. As expected for LB-102 and amisulpride, permeation across the test membrane at neutral pH (7.4) was more effective than at acidic pH (5) due to amine protonation, which decreases lipophilicity.

2.6.2.2.1.2 CNS Receptor Binding Screen

An *in vitro* radioligand receptor binding displacement screen measured the percent binding inhibition of target ligands to a range of common CNS receptors at a 10 µM concentration LB-102 (Study Number LB-102-PC-001). Results of this study are presented in Table 2, and show that LB-102 has the potential to interact with the D_2 (long and short) receptors, the dopamine D_3 receptor, and the 5-HT_{2a} receptors while minimally affecting other CNS receptors.

Table 2: LB-102 In Vitro Binding (% Inhibition at 10 µM) Against a Panel of CNS Receptors

Receptor	Mean % Inhibition at 10 µM
a1	36
a1a	28
a1b	48
a1d	48
a2	100
a2a	94
a2c	90
d2s	101
d2l	99
d3	100
h1	4
m1	25
m2	22
5ht2a	90
5ht2c	63

Based on the data in Table 2, the next phase of this study was a more comprehensive examination to determine K_is, also by radioligand displacement. In this part of the study, binding of LB-102 and LB-103 (the *S* enantiomer of LB-102 [†]) was evaluated against receptors in the above study showing at least 80% inhibition at 10 µM (excluding the A_2 receptors) over a range of concentrations (1×10^{-9} to 1×10^{-5} M) that enabled determination of the inhibition constant (K_i). The decision to evaluate the *S* enantiomer of LB-102 for binding to the dopamine receptors was based on the prior observation for amisulpride (Castelli et al., 2001) that determined that the K_i of the *S* enantiomer for this drug was lower than that of the *R* enantiomer (see footnote below). Results of these second-stage ligand-displacement studies, summarized in Table 3, reiterated the findings from the initial screen: LB-102 is a potent receptor antagonist of dopamine D_2 and D_3 receptors, which are known to improve symptoms of schizophrenia.

[†] Specifically, the K_i for racemic amisulpride against the D_{2L} using ^{3}H-nemonapride as a ligand was 7.7 nM, compared to 4.4 nM for the *S* enantiomer and 151 nM for the *R* enantiomer.

Table 3: LB-102 Ki Values for Select CNS Receptors

Receptor	K_i (nM)	
	LB-102 (racemate)	**LB-103 (*S* enantiomer)**
a2a (non-selective)	41	6.7
a2a(h)	220	ND
a2b(h)	110	ND
a2c(h)	240	ND
5-HT_{2a}	200	410
D_{2L}	0.66	0.41
D_{2s}	3.4	0.56
D_3	2.5	1.2
ND = No data.		

In separate *in vitro* binding assays, the ability of LB-101 (racemic amisulpride), LB-102 (a racemic mixture) along with its *S* enantiomer (LB-103) and its *R* enantiomer (LB-104) were evaluated for their abilities to bind dopamine D_2 and 5-HT_7 receptors (both of which are thought to be responsible for the anti-psychotic activity of schizophrenia drugs) via displacement of a membrane potential dye at concentrations ranging from 0.3 nM to 100 nM (Study LB-102-PC-002, Study LB-102-PC-003). As mentioned above, dopamine antagonism is ubiquitous in all approved schizophrenia drugs to date. The 5-HT_7 receptor, however, is also thought to play a role in cognitive aspects of schizophrenia (Hedlund 2009; Pouzet et al., 2002). Prior data on amisulpride (Castelli et al.,2001) suggested that the *S* enantiomer of LB-102 would preferentially bind to the dopamine receptors as compared to the *R* enantiomer; this was confirmed (Study LB-102-PC-003) as shown in Table 4. Interestingly, when considering the binding of the LB-102 enantiomers to the 5-HT_7 receptor, it was noted that the *R* enantiomer was responsible for binding and the *S* enantiomer had no activity (K_i > 1000 nM). Thus, LB-102, the racemic mixture of *R* and *S* enantiomers, has the potential to offer benefits of both D_2 and 5-HT_7 binding in treating schizophrenia.

Table 4: K_i Values for LB-101, -102, -103, and -104 at D_2 and 5HT_7 Receptors

Receptor	K_i (nM)			
	LB-101	**LB-102**	**LB-103**	**LB-104**
D_2	1.1	0.82	0.4	14.4
5-HT_7	44	31	15.6	>1000

2.6.2.2.2 In Vivo Studies

LB-102 was evaluated in three well accepted animal models of schizophrenia: AIC (Wilcox et al., 1980), NOR (Neill et al., 2010; Neill et al., 2014; Neill et al., 2016) and LMA (Kay et al., 1987).

2.6.2.2.2.1 Apomorphine Induced Climbing in Mice

Efficacy of LB-102 was studied in the mouse AIC model AIC model (Study LB-102-PC-006). AIC is a model where animals are dosed with the dopamine agonist apomorphine which induces stereotypic climbing, a proxy for the stereotypy that is a common manifestation of schizophrenia.

In this AIC study, male C56Bl/6 mice (n = 8/group) were treated with 2.5 mg/kg apomorphine via subcutaneous (SC) injection followed by dosing with LB-102 or amisulpride at 20 and 60 mg/kg. Climbing behavior, over the course of 30 minutes, was measured 2 hours post dosing. As a positive control, mice were also dosed with 1 mg/kg haloperidol which rendered them completely cataleptic and unable to move. The endpoint of this study was total climbing score (the number of paws on the cage at each time point; mean ± standard error of the mean [SEM]). Total climbing scores from this AIC study are summarized below.

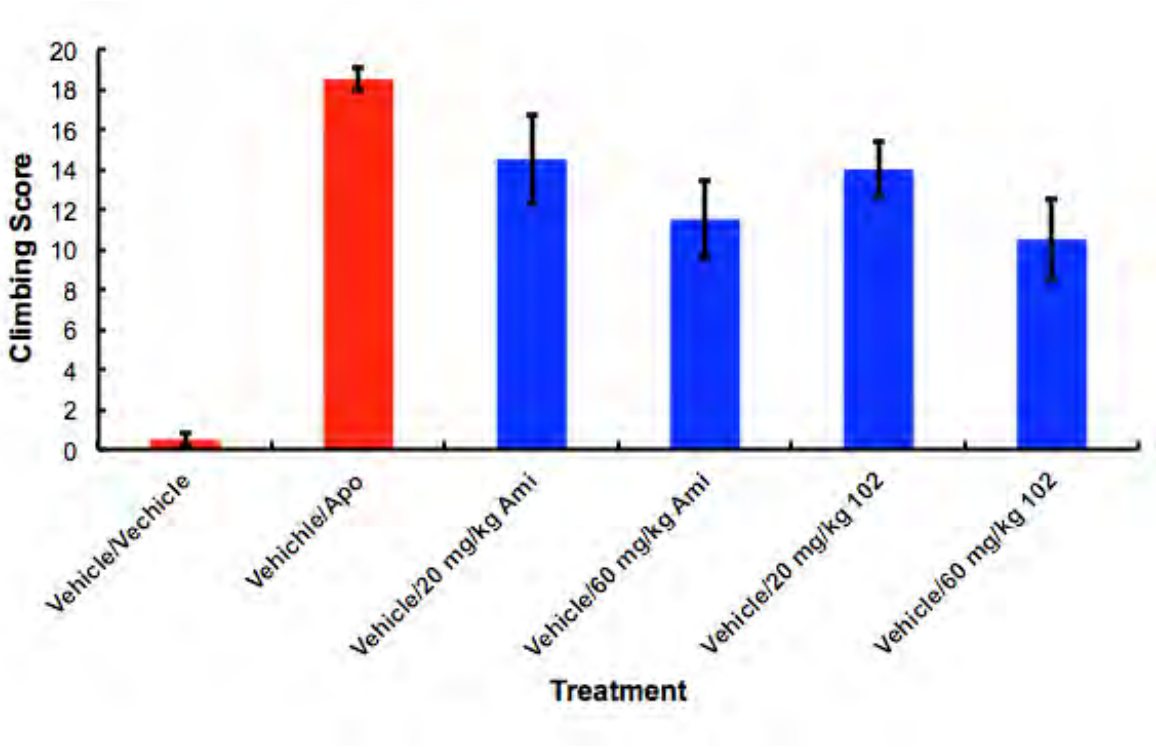

Figure 1: Climbing Scores in the AIC Mouse Model

In this AIC study in mice, LB-102 reversed apomorphine climbing in a manner that was consistent with amisulpride.

2.6.2.2.2.2 Locomotor Activity in Rats

Efficacy of LB-102 was studied in rats in an amphetamine-induced LMA assay, a measure of positive aspects (excitement) of the positive and negative syndrome scale for assessing schizophrenia (Study LB-102-PC-007). In the LMA assay, rats are observed in an open field arena for the distance moved. Rats are dosed with amphetamine or vehicle (negative/negative control) and with various treatments. Amphetamine alone produces hypermobility whereas dosing with antipsychotics produces more normal, calmer activity.

In this LMA study, Sprague-Dawley rats (n = 10/group) were treated with 1 mg/kg amphetamine SC to elicit hyperactivity at specified times following administration of the test articles. LB-102 and amisulpride were dosed orally at 3, 10, and 30 mg/kg (6 hours prior to amphetamine dosing), and risperidone was dosed SC at 1 mg/kg (1 hour prior to amphetamine dosing). Rats in the amphetamine group were dosed with vehicle during the experiment. Distance moved, over the course of an hour, was measured. The endpoint of this study was total ambulatory distance (the distance traveled by each animal). Total ambulatory distance data (mean ± SEM) from this LMA study are summarized below.

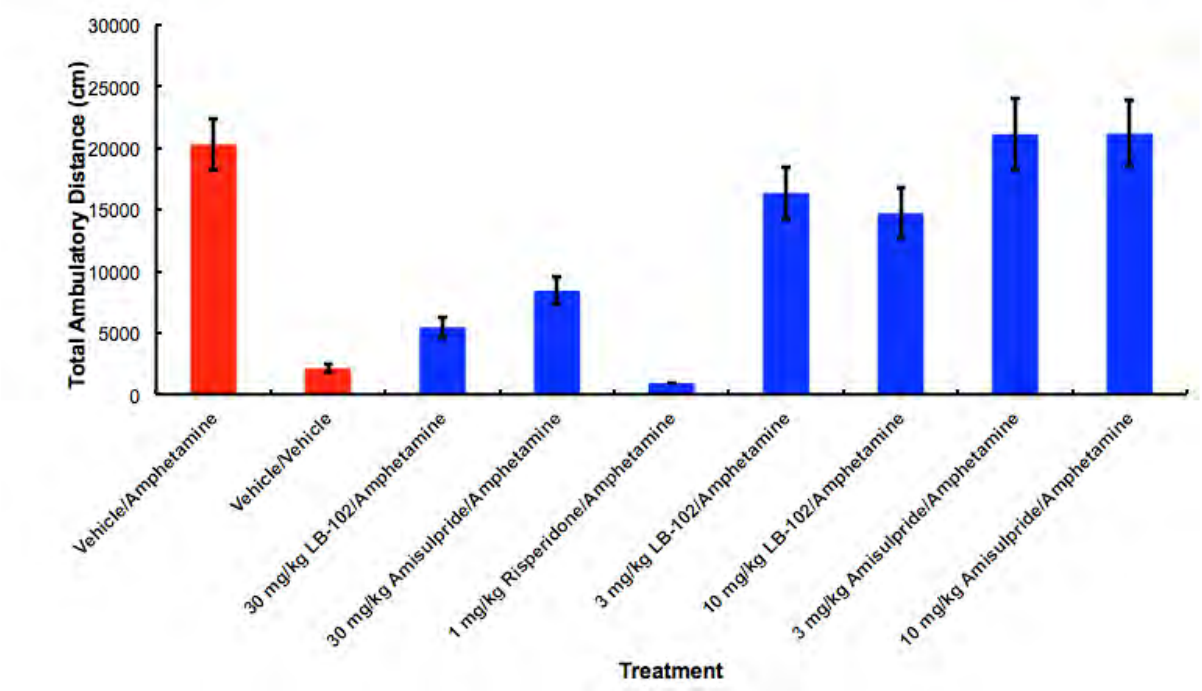

Figure 2: Total Ambulatory Distance in LMA Rat Model

In this LMA study in rats, at a dose of 30 mg/kg, LB-102 reversed amphetamine hyperactivity in a manner that was significantly superior to amisulpride.

2.6.2.2.2.3 Novel Object Recognition in Rats

Efficacy of LB-102 was evaluated in rats in a NOR assay, a well-established model recapitulating cognitive and negative aspects of schizophrenia (difficultly in abstract thinking) (Study LB-102-PC-005). In the NOR model, animals were treated for 7 days with a low dose of phencyclidine (PCP) which impaired the rat's ability to discern between novel and familiar objects. Typically rats, like humans, will spend more time exploring a novel object than a familiar one. Efficacy in this study is demonstrated by the ability of the test treatment to restore normal brain function as manifested by reversing the PCP impairment.

In this NOR study, LB-102, amisulpride, and risperidone were dosed to female Wistar hooded rats (n = 4-5/group) at 1.7, 5, 15, and 45 mg/kg for LB-102, 5, 15, and 45 mg/kg for amisulpride (additionally, one arm was dosed at 3 mg/kg via intraperitoneal [IP] injection), and 0.1 mg/kg for risperidone ; all doses were PO unless specified IP. Cognitive measurements were taken at 3 hours

post-dose for benzamides and 30 minutes post-dose for risperidone. The endpoint of this study was the Discrimination Index (DI), a normalized ratio of time spent exploring a novel object compared to a familiar one. DI results from this NOR study (mean ± SEM) are summarized in Figure 3.

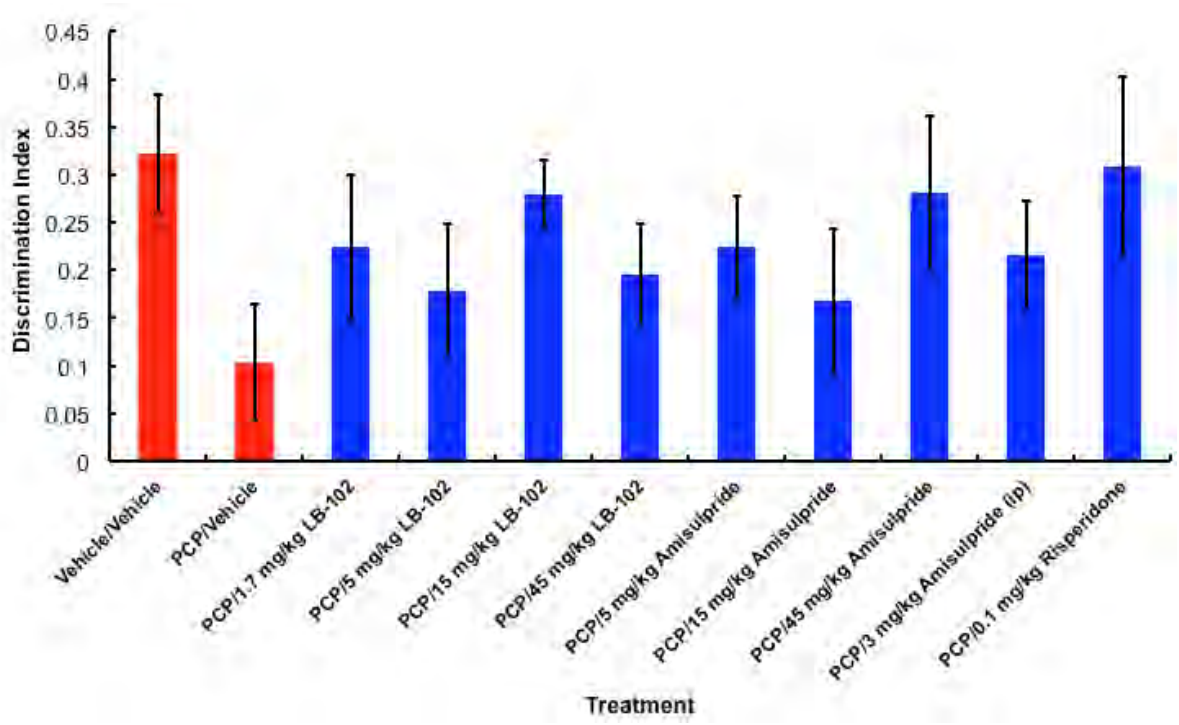

Figure 3: DI Scores in the NOR Rat Model

Results show that LB-102 restored cognitive function in a manner similar to amisulpride.

2.6.2.2.2.4 Bar Test (for Catalepsy) in Rats

Extrapyramidal effects are drug induced movement adverse events often associated with schizophrenia treatments. In animals, extrapyramidal effects can be studied by monitoring catalepsy (a state of muscle rigidity resulting in an inability to correct an imposed posture). To understand if catalepsy is a potential concern with LB-102, a catalepsy study using the bar model was performed (Study LB-102-PC-008). In this study design, following 7 days of twice daily administration of PCP, rats are forced into a pose having their front legs on a bar suspended above the floor of a cage (Hoffman and Donovan 1995). The degree of catalepsy is a function of the length of time the rat spends on the bar. This was evaluated for up to 5 hours post-dose.

Data (mean ± SEM) from the bar test for orally administered LB-102 (75 and 100 mg/kg) and amisulpride (75 and 100 mg/kg) are presented in Figure 4.

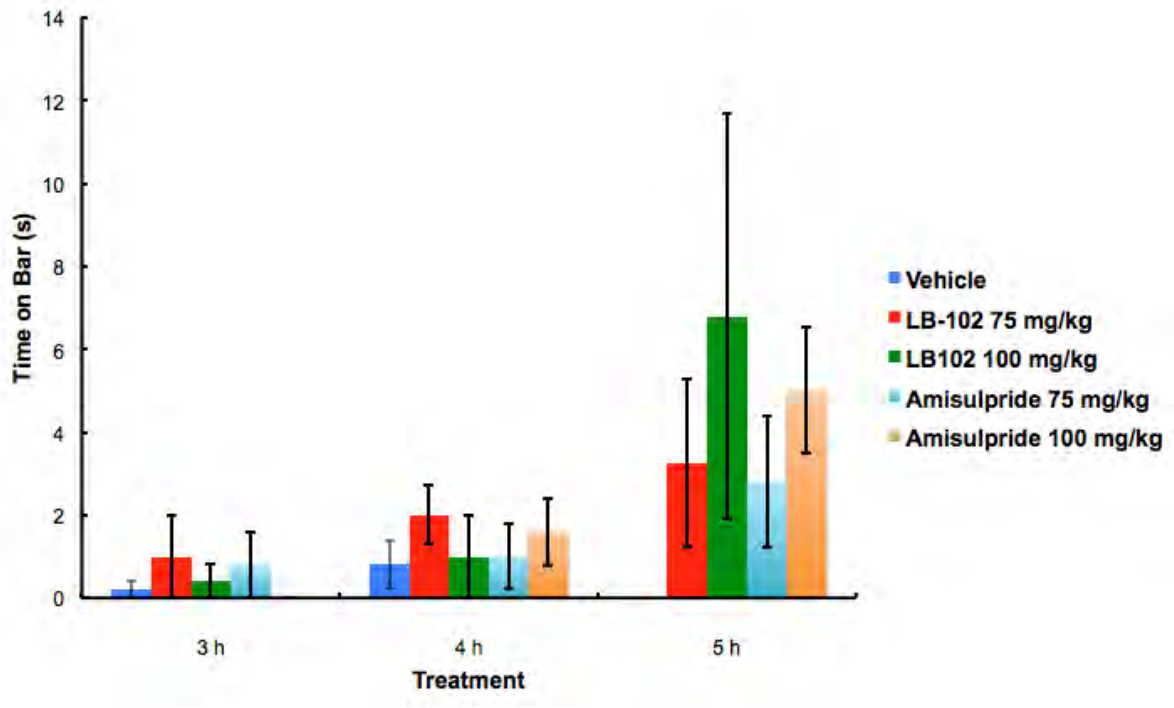

Figure 4: Bar Hang Mean Time for Rat Catalepsy Model

There were no significant differences in mean time on the bar, however, there was a trend for longer hang times for LB-102 and amisulpride. In this assay of catalepsy, the effects of LB-102 were consistent with amisulpride.

2.6.2.3 Secondary Pharmacodynamics

Figure 1 depicts a 'heat map' comparing the binding of LB-102 to a range of drugs used to treat schizophrenia over a myriad of receptors known to be important in the brain (Roth et al. 2000). In general, binding of LB-102 was similar to that of amisulpride. By comparison to the other approved schizophrenia drugs, LB-102 (and amisulpride) were less promiscuous. For example, Risperdal hits 10 receptors with K_is < 100 nM, Geodon hits 15, and Abilify hits 14 while amisulpride only hits 4. Of the receptors tested, LB-102 interacts meaningfully with dopamine $D_{2/3}$ and 5-HT_7. Hitting fewer off-target receptors should decrease the risk of unexpected adverse events.

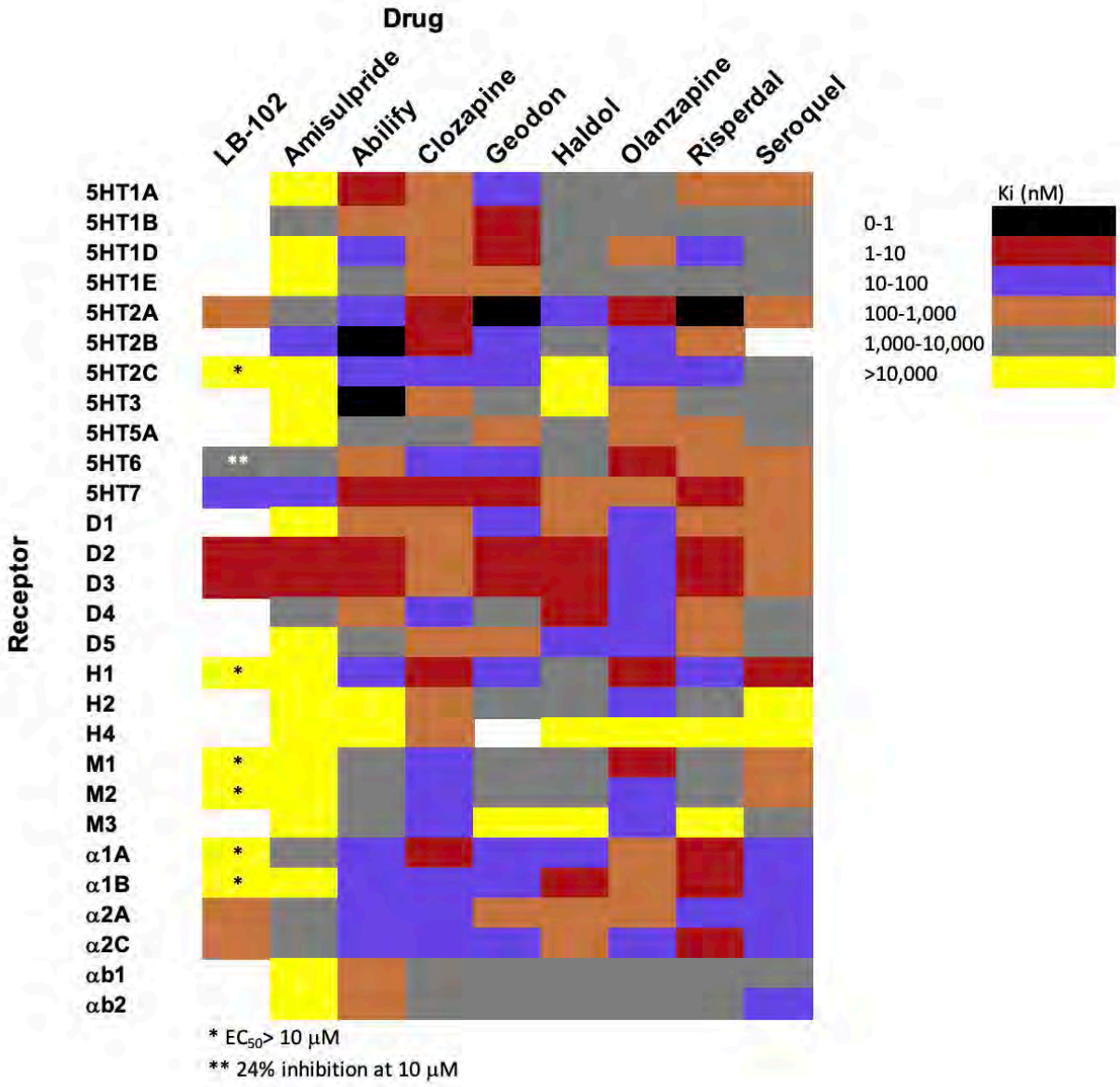

Figure 5: Heat Map Comparing Binding of LB-102 with Other Schizophrenia Drugs at Select CNS Receptors

2.6.2.4 Safety Pharmacology

Safety pharmacology studies have been conducted to assess potential effects on the core organ systems: central nervous system, cardiovascular system, and respiratory system. These studies were performed in compliance with GLPs and, for the *in vivo* studies, involved the clinically relevant route of administration, oral dosing. It is important to note that in these studies LB-102 was administered as a single daily dose. This is in contrast to the clinical dosing regimen which involves twice daily dosing (approximately 12 hours apart). As a result, the concentrations administered were higher than those used in the pivotal repeat-dose toxicity studies, which likely explains the findings in the dog cardiovascular study.

2.6.2.4.1 Central Nervous System

Male Wistar Han rats (n = 8/group) received single oral doses of LB-102 at 0 (0.5% methylcellulose [MC]), 40, 80 and 200 mg/kg and functional observational batteries were performed pre-dose and at 2 and 24 hours post-dose (Study 2591-012, Table 2.6.3.2).

Dose formulation analyses revealed concentrations ranging from 96.5 to 102.9% of nominal, and the materials were homogenous.

There were no mortalities or adverse clinical signs. LB-102 was associated with increased grip strength (forelimb and hindlimb) at 200 mg/kg at 2 and 24 hours post-dose. None of the other neurobehavioral parameters were affected.

Based on these findings, the no-observed-effect-level (NOEL) for effects on neurobehavioral function in rats was 80 mg/kg.

2.6.2.4.2 Cardiovascular System

HEK-293 cells (n = 3/group) were incubated with LB-102 at concentrations of 0 (HEPES-buffered physiological saline in 0.3% dimethyl sulfoxide), 3, 10, 30 and 100 µM and effects on the hERG potassium channel were assessed using a patch clamp technique for whole cell recordings (Study 180920.MCQ, Table 2.6.3.2).

Dose formulation data revealed concentrations ranging from 95.1 to 98.2% of nominal; the materials were also homogenous.

A dose-related increase in inhibition of the hERG channel was observed: 0.3, 12.7, 36.4, 65.5 and 87.2% inhibition at 0, 3, 10, 30 and 100 µM, respectively. The IC_{50} was calculated to be 16.7 µM.

Four telemetrized male beagle dogs were administered single oral doses of LB-102 at 0, 1.5, 6 and 15 mg/kg with ECGs being collected continuously for 24 hours post-dose (Study 2591-011, Table 2.6.3.2).

Dose formulation analyses revealed concentrations ranging from 93 to 100.9% of nominal, and the materials were homogenous.

LB-102 did not produce mortality or effects on body weight, blood pressure, or qualitative ECGs at any dose. Clinical signs of panting were noted at 1 hour in two dogs receiving the high dose.

The primary finding was reversible, dose-dependent increases in mean heart rate at all doses beginning approximately 0.5 hours post-dose and resolving by 6 hours post-dose. The peak increases were as follows: 32% (+31 beats/minute) at 1.25 hours for 1.5 mg/kg; 85% (+73 beats/minute) at 1 hour for 6 mg/kg; and 117% (+101 beats/minute) at 1 hour for 15 mg/kg. The increases were statistically significant at 6 and 15 mg/kg; the increase at 1.5 mg/kg was largely due to a single animal. These changes were transient in nature (*i.e.*, relatively short in duration), did not progress to arrhythmias or result in clinical signs other than panting, and therefore, within the context of this study, were not considered to be adverse.

A series of additional findings were noted that were associated with LB-102 administration but were within physiological ranges or were below established levels of concern; these are discussed below. In conjunction with the increased heart rate, there was an associated decrease in mean PR (6 and 15 mg/kg) and uncorrected QT interval duration; this resolved within 2 to 6 hours post-dose. The PR and uncorrected QT changes were within physiological ranges. Reversible increases in mean body temperature were observed at ≥6 mg/kg beginning approximately 1 hour post-dose and resolving within 6 hours post-dose. The peak increase was 0.6ºC at 2.25 hours for 6 mg/kg and 0.8°C at 3 hours for 15 mg/kg. The body temperatures remained within physiological ranges. At 15 mg/kg, reversible increases in QRS duration that resolved within 6 hours post-dose and changes in QTc (initial decreases [up to 12%] during higher heart rates and corresponding increases of body temperature [1 to 3.25 hours postdose] followed by increases [up to 7%] starting at approximately 4 hours that resolved within 11 hours post-dose) were observed. The QRS increase remained within physiological ranges and the QTc decrease and increase were potentially related to the body temperature increase and remained below the peak level of concern, respectively.

It is likely that the more pronounced cardiovascular changes (e.g. heart rate effects) noted in this study were related to the higher C_{max} values achieved than occurred in the pivotal dog toxicology study (Study 2591-009). This was related to the single dose administration of LB-102 in the safety pharmacology study as compared to the twice daily dosing for the toxicity study. In the dog cardiovascular study, dose concentrations of 0.3, 1.2 and 3 mg/mL were administered (associated with doses of 1.5, 6 and 15 mg/kg) versus dose concentrations of 0.15, 0.6 and 1.5 mg/mL (associated with doses of 0.75, 3, and 7.5 mg/kg/dose) being administered twice daily in the 28-day repeat-dose study. To visualize this comparison, the following table summarizes relevant information from the two GLP dog studies including: dose concentrations used; Day 1 C_{max} values for males (after the first dose) at the two highest doses from the 28-day dog study (where heart rate effects were reported); extrapolated C_{max} values for the safety pharmacology study; and the correlating increase in mean heart rate as compared to the concurrent controls.

Table 5: Changes in Heart Rate as Related to C_{max} in Dogs

Study	Dose Concentration (mg/mL)	Dose (mg/kg/dose)	Day 1 C_{max} (ng/mL; after first dose)	Increased Heart Rate (BPM)
CV	0.3	1.5	192[a]	31
28-Day	0.6	3	384	25
CV	1.2	6	768[a]	73
28-Day	1.5	7.5	1047	36
CV	3	15	2100[b]	101

BPM = Beats per minute; CV = Cardiovascular.
a – Extrapolated assuming linear kinetics from C_{max} at 3 mg/kg/dose in 28-day study.
b – Extrapolated assuming linear kinetics from C_{max} at 7.5 mg/kg/dose in 28-day study.

There are a few important considerations to take into account when reviewing these data. First, the safety pharmacology study had a higher degree of sensitivity for capturing cardiovascular changes than the 28-day dog study based on the use of telemetry versus a standard 10 lead ECG. Second, there was a fair degree of inter-animal variability in the heart rate values and plasma data from the 28-day dog study. Third, the C_{max} values for the safety pharmacology studies were extrapolated and not directly measured. Despite these issues, the collective data generally show a trend to

increased heart rate with increasing C_{max} with pronounced changes at the 3 mg/mL concentration, less pronounced changes at 1.2 to 1.5 mg/mL and the smallest changes at 0.3 to 0.6 mg/mL. Importantly, the no-observed-adverse-effect-level (NOAEL) from the 28-day dog study is 15 mg/kg/day, which has a correlating Day 28 C_{max} of 1870 ng/mL. As dogs are the most sensitive species following repeat-dose administration of LB-102 as compared to rats, a 10-fold safety margin will be applied to the NOAEL which is anticipated to result in human peak plasma exposures that would not likely exceed approximately 200 ng/mL. Based on the data above, this is associated with a transient, low increase in heart rate and therefore a low safety risk for humans.

Overall, for the dog cardiovascular study, based on the relatively small magnitude and/or transient/reversible nature of the observations in this study, none of the cardiovascular changes was considered adverse. Of the cardiovascular changes that were outside the physiological range, no progression to arrhythmias occurred (heart rate and QTc) and the QTc prolongation was below the established level of concern (<10%). Therefore, the (NOAEL) for effects on cardiovascular function in dogs was 15 mg/kg, the highest dose level tested.

2.6.2.4.3 Respiratory System

Male Wistar Han rats (n = 8/group) received single oral doses of LB-102 at 0 (0.5% MC), 40, 80 and 200 mg/kg and respiratory function was assessed using whole body plethysmograph chambers pre-dose and continuously up to 6 hours post-dose (Study 2591-010, Table 2.6.3.2).

Dose formulation analyses revealed concentrations ranging from 98 to 100.8% of nominal, and the materials were homogenous.

LB-102 did not produce mortality or adverse clinical signs. No effects on respiratory parameters including respiratory rate, tidal volume and minute volume were observed.

Based on these data, the NOEL for effects on respiratory function in rats was 200 mg/kg.

2.6.2.5 Pharmacodynamic Drug Interactions

No pharmacodynamic drug interaction studies have been conducted.

2.6.2.6 Discussion and Conclusions

LB-102 was designed to be a novel molecule having similar biological activity to amisulpride but with increased blood-brain barrier permeability. To date, in a model of passive diffusion through a (PAMPA) membrane LB-102 was found to be better able than amisulpride to passively penetrate a membrane. In *in vitro* studies, LB-102 was a selective blocker of the human dopaminergic D_2 and D_3 receptors (the target of all approved schizophrenia drugs to date) and, similar to amisulpride, was also a 5-HT_7 antagonist (which may be important in cognitive aspects of schizophrenia). The *in vitro* activity and selectivity toward these receptors are similar to those of amisulpride.

In the rat NOR model of schizophrenia, LB-102 was equivalent to amisulpride in reversing the cognitive effects of PCP dosing. In the rat LMA model of schizophrenia, LB-102 was statistically superior to amisulpride at 30 mg/kg. In the mouse AIC model, LB-102 was equivalent to amisulpride at 20 mg/kg and 60 mg/kg. That LB-102 displayed similar efficacy to amisulpride in

animal models covering three aspects of schizophrenia in two different species, as well that it displayed comparable to better dopamine receptor occupancy *in vivo* supports the further development of this product for schizophrenia.

The safety pharmacology studies revealed a minor effect on the central nervous system (increased grip strength) in rats at a high dose that is of questionable significance to humans, no effects on the respiratory system (up to 200 mg/kg) in rats, and transient/reversible, non-adverse effects on the cardiovascular system in dogs that did not progress to arrhythmias. Furthermore, the cardiovascular changes are easily monitored in the clinic and the initial peak plasma concentrations that humans are anticipated to be exposed to are associated with small increases in heart rate. These data indicate minimal to no effects on the core organ systems.

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