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ORIGINAL INVESTIGATION

A randomized, double-blind, placebo controlled, phase 1 study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of LB-102, a selective dopamine $D_{2/3}$/5-HT_7 inhibitor

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Abstract
LB-102 is an *N*-methylated analogue of amisulpride under development to treat schizophrenia. LB-102 was evaluated in a Phase 1, double-blind, placebo-controlled, clinical study to evaluate safety and pharmacokinetics. This was a first-in-human study examining single and multiple doses of LB-102 administered orally in 64 healthy volunteers. Dosing in the single ascending dose (SAD) portion of the study was initially planned to be 50, 100, 200, and 400 mg, with doses in the multiple ascending dose (MAD) portion to be determined based on observations in the SAD portion. As a result of two cases of EPS (acute dystonia) at 200 mg in the MAD portion of the study, dosing of that arm was discontinued and doses for the remaining cohort were decreased to 150 mg/day. Dose escalation was guided by safety and plasma concentrations of LB-102 compared to a translational model. LB-102 was generally safe and well-tolerated, and clinical lab values were unremarkable at all doses, save for prolactin which was transiently elevated in the majority of subjects treated with LB-102; there were no clinical observations associated with the increases in prolactin elevation. There was evidence of transient QT interval prolongation at the 200 mg dose, none of which resulted in clinical observation or triggered stopping criteria. There were four instances of EPS (acute dystonia), typically associated with dopamine receptor occupancy in excess of 80%, one at 100 mg QD, one at 75 mg BID, and two at 100 mg BID. A phase 2 clinical study of LB-102 in schizophrenia patients with PANSS as primary endpoint is being planned.

Keywords Schizophrenia · Pharmacologic intervention · Dopamine $D_{2/3}$ · $5HT_7$ · Antagonism · Clinical trial

Introduction

Schizophrenia is a chronic and debilitating mental illness that affects approximately 1% of the population (McCutcheon et al. 2020). Despite a surfeit of available drugs to treat schizophrenia, adequate treatment of the disorder remains a challenge. Non-adherence and discontinuation of treatment is a major issue; a review of randomized, double-blind, clinical trials involving schizophrenia or related disorders found that half of patients stopped their treatment at an early stage, with poor response or psychiatric symptom worsening as the main cause (Huhn et al. 2019). Discontinuation of treatment significantly increases the chance of relapse: estimated relapse rates are ~ 80% and 95% after discontinuing treatment for 12 and 24 months, respectively (Elmsley et al. 2013).

The standard pharmacologic mechanism of action for antipsychotic drugs is antagonism of dopamine receptors in the brain, (Meltzer and Stahl 1976; McCutcheon et al. 2019) and every current FDA-approved drug to treat schizophrenia interacts with dopamine receptors (Meyer 2018)—the only novel antipsychotic approved since 2018 has been lumateperone, also a dopamine receptor antagonist (Davis et al. 2015). Amisulpride is a dopamine receptor antagonist originally developed in France in the 1980s and is approved in more than 50 countries worldwide for the treatment of schizophrenia (and in certain countries for the treatment

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of dysthymia) (IMS report). Amisulpride elicits its activity in part by selectively blocking the human dopamine D_2 (K_i 2.8 nM) and D_3 (K_i 3.2 nM) receptors with negligible affinity for the D_1, D_4, and D_5 receptor subtypes (Curran and Perry 2001). Amisulpride also inhibits 5-HT_7 receptors with a Ki of 22 nM (Grattan et al. 2019). Though less well understood mechanistically, the 5-HT_7 receptor has been suggested to play a role in schizophrenia and depression (Hedlund 2009).

Amisulpride has repeatedly been demonstrated to be a clinically effective drug; in a recent meta-analysis of 32 schizophrenia drugs in 54,000 subjects (Huhn et al., 2019), amisulpride was second only to clozapine in antipsychotic efficacy and was second lowest in all-cause discontinuation rate—itself a composite measure of efficacy and tolerability (Rabinowitz et al. 2009), a result consistent with the EUFEST study (Kahn et al. 2008). In a more recent example, the BeStInTro study of 144 schizophrenia patients (Johnsen et al. 2020) found that amisulpride was more effective than either aripiprazole or olanzapine at reducing symptoms of schizophrenia.

A 2014 study (Dos Santos Pereira et al. 2014) demonstrated that passive diffusion of amisulpride across a PAMPA membrane—a common proxy for the blood–brain barrier (BBB)—was the lowest of 30 psychiatric drugs tested. Poor distribution into the brain could impact the drug's efficacy. One possible explanation for the relatively high dose of amisulpride required for efficacy (for example, amisulpride with a low single-digit nM K_i against dopamine $D_{2/3}$ receptors requires 400 to 800 mg/day for efficacy (Curran 2001) while risperidone with a similar dopamine K_i typically is dosed less than 10 mg/day) is that poor BBB permeability accounts for the relatively high daily dose of amisulpride needed for efficacy.

LB-102 (Fig. 1) is a methylated version of amisulpride designed to increase the lipophilicity of the drug while minimally altering its receptor binding characteristics. In in vitro studies, (Grattan et al. 2019) LB-102 and amisulpride displayed similar binding to dopamine and 5-HT_7 receptors and a similar lack of interaction with other common CNS receptors: for example muscarinic or histaminergic.

In vivo LB-102 was equivalent, or better than, amisulpride in three different animal behavioral models of schizophrenia (novel object recognition, locomotor activity, and apomorphine induced climbing) (Neill et al. 2017). In addition, amisulpride and LB-102 exhibited similar PK profiles, as measured by total benzamide concentration (in dogs and rodents, LB-102 was extensively demethylated into amisulpride), when dosed orally in rats and in mice. The Log P, a physicochemical measure of lipophilicity, of LB-102 at neutral pH was measured to be 1.72 while that of amisulpride was 1.52. In a previously published report (Dos Santos Pereira et al. 2014), a 10% increase in cLogP due to addition of a methyl group afforded substantial improvement in passive diffusion across a non-polar membrane. In a PET study in mice evaluating dopamine receptor occupancy, LB-102 had double the receptor occupancy of amisulpride in mouse brains. Given that the dopamine K_is for the two molecules are equivalent, this suggests that the extra lipophilicity of the methyl group may be the cause of the increased binding by increasing concentration of drug in the brain, and suggesting that LB-102 could be dosed at lower levels than amisulpride (Vaino et al. 2021).

The promising preclinical data on LB-102, in its own right and in comparison to the well-established efficacy of amisulpride, warranted further investigation as a potential treatment for schizophrenia in humans. A phase 1, placebo-controlled, randomized, double-blind, clinical study of LB-102 in healthy volunteers was conducted and is described.

Methods

Study design and subjects

This study (NCT04187560) was conducted at a single site (Medpace in Cincinnati, OH) in compliance with all Institutional Review Board regulations. All local regulations and Good Clinical Practices were observed. This was a double-blind,[1] placebo-controlled study.

Healthy females and males between 18 and 55 years of age with BMI ≥ 18 and ≤ 30 kg/m^2 were enrolled in the study. Main exclusion criteria included history or presence of psychiatric disorder, drug or alcohol abuse, history of QT prolongation or dysrhythmia, fasting blood glucose level of ≥ 126 mg/dL, or a known allergy to the drug or its metabolites. The study was planned as a two part study. Part A was comprised of 5 single ascending dose (SAD) cohorts, each of 8 subjects and Part B was comprised of 3 multiple ascending dose (MAD) cohorts each of 8 subjects, dosed twice daily for 7 days (13 doses in total), each of 8 subjects. Dosing in the SAD portion of the study began at 50 mg/day and selection of the next dose was determined based on plasma concentration of drug (this is described in greater detail in the Dose Selection section). Selection of subsequent doses was determined based on clinical observations. Starting dose in the MAD portion of the study was to be determined by observations in the SAD portion of the study, with each subsequent MAD dose determined by clinical observations in

[1] 1Neither the subject nor the Investigator or study staff members knew the identity of each subject's treatment. LB-102 was dispensed by an unblinded pharmacist to study staff for administration to the subjects. The blind was not broken during this study.

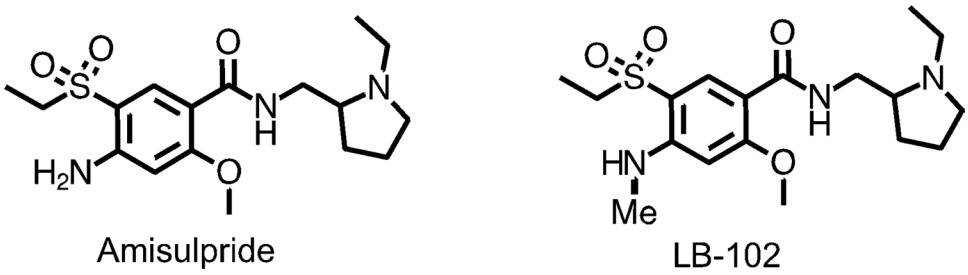

Fig. 1 Chemical structures of amisulpride and LB-102

the prior dose(s). The following stopping criteria were also established in the protocol:

- a serious adverse event (SAE) in one or more subjects that is clearly related to LB-102 or placebo
- one or more subjects experiencing a ≥ Grade 3 adverse event (AE) that is clearly related to LB-102 or placebo
- two or more subjects experiencing a ≥ Grade 2 AE in the same organ class clearly related to LB-102 or placebo
- any other event deemed by the investigator or sponsor to pose an unacceptable risk to subjects as a result of dose escalation.

Subjects were randomized on Day 1 of the treatment period 3:1 LB-102: placebo; that is, for each cohort 6 subjects received LB-102 and 2 received placebo. Subjects were randomized using Medpace's standard randomization scheme with numbers from 1001 to 1008 assigned to subjects in Cohort 1, from 2001 to 2008 in Cohort 2, and so on. No formal sample size calculations were made. The primary endpoint of the study was safety, specifically the percentage of subjects who experienced at least one treatment emergent adverse event (TEAE), with pharmacokinetics as a secondary objective.

Safety assessments

Adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECG), and the Columbia-Suicide Severity Rating Scale (CSSRS) were all monitored. The intensity of AEs was classified as mild, moderate, or severe, and each AE was classified according to its relation to the study drug. Laboratory tests evaluated hematology, serum chemistry, urine, and hormone levels. Vital signs were collected and ECGs were performed at screening, during the study, and after dosing ceased. Tables 1 and 2 present timing of above measures.

Dose selection

Based on toxicology studies in rats and dogs dosing for this Phase 1 study was initially planned to be 50, 100, 200, and 400 mg for the SAD portion of the study, with doses in the MAD portion to be determined based on observations in the SAD portion. Dose selection was based on comparison to amisulpride dosing, which is typically dosed between 400 and 800 mg per day (Curran and Perry 2001); in the EUFEST study (Kahn et al. 2008), the average daily dose of amisulpride was 451 mg/d and in the BeStInTro study it was 397 mg/day (Johnsen et al. 2020). As LB-102 had never been tested in humans, out of an abundance of caution, dosing in the second cohort of the study was to be based on comparison of observed plasma drug concentration in cohort 1 compared to a model based on animal PK data of LB-102 and published PK data on amisulpride. (Rosenzweig et al., 2002). Target concentrations for total plasma benzamide (in animals LB-102 was metabolized up to 50% to amisulpride) concentration in Cohort 1 (50 mg) are depicted in Table 3 (values in Table 3 were 5 × expected benzamide concentration from model at each dose).

If the starting dose (50 mg/day) for Cohort 1 (Part A) resulted in a total benzamide (amisulpride and LB-102) geometric mean Cmax greater than 173 ng/mL or a geometric mean of total benzamide exposure (AUC_{inf}) greater than 1,648 ng/mL*h, the dose for Cohort 2 was to be adjusted downward to the nearest 10 mg according to:

$$\text{Dose2} = 50\text{mg} * \text{Cmax35ng/mL/ObservedCmax(ng/mL)}$$

or

$$\text{Dose 2} = 50\text{ mg} * \text{AUCinf 655 ng/mL} * \text{h / Observed AUCinf (ng/mL} * \text{h)}$$

whichever produced the lowest dose.

On review of the 50 mg PK data in Cohort 1, the average plasma C_{max} was measured to be 176 ng/mL, in excess of the limit in Table 2, which triggered a prespecified decrease in dosing in Cohort 2 from the planned 100 to 10 mg. Dosing in subsequent cohorts was determined based on clinical observations. Dosing in Cohort 3 was 100 mg, Cohort 4 was 200 mg, and Cohort 5 was 150 mg. Dosing in the MAD portion of the study, which was to last 7 days for a total of 13 doses, was to be determined based on clinical observations in the SAD portion of the study. The first dose in the MAD portion of the study was 50 mg BID (i.e., 100 mg/day) and subsequent doses, namely 75 and 100 mg BID were chosen based on clinical observations in prior doses.

Table 1 Study design and schedule of assessments for MAD portion of study

	Check in	Treatment evaluation				Follow-up
	Day -28 to -1	Day 0	Day 1	Day 2	Day 3	Day 8 & 15
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Medical history	X	X				
Demographics	X					
Randomization			X			
Height, weight, BMI[a]	X					X (Day 8)
Physical examination	X	X		X		X (Day 8)
Vital signs[b]	X	X	X	X	X	X (Day 8)
Laboratory tests	X	X		X		X (Day 8)
Serum HbA_{1c}	X					
Serum prolactin	X				X	X
HIV, HBsAg, and HCV labs	X					
12-lead ECG[c]	X	X	X	X		
C-SSRS	X				X	
Urine drug screen	X	X				
Alcohol breathalyzer	X	X				
Pregnancy[d]	X	X				X (Day 8)
FSH[e]	X					
Plasma PK[f]			X	X	X	X
Dose subjects[g]			X			
Concomitant medication[h]	X	X	X	X	X	X
Adverse event assessment[h]		X	X	X	X	X

BMI Body Mass Index; *C-SSRS* Columbia-Suicide Severity Rating Scale; *ECG* Electrocardiogram; *FSH* follicle-stimulating hormone; *HbA1c* hemoglobin A1c; *HBsAg* hepatitis B surface antigen; *HCV* hepatitis C virus; *HIB* human immunodeficiency virus; *PK* pharmacokinetic

[a]Only weight was recorded at follow-up

[b]Vital Signs were measured at Screening, Check-in, Day 1 at pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 (±30 min) hours post-dose, and at Follow-up (Day 8)

[c]ECG was measured at Screening, Check-in, Day 1 at pre-dose and 1, 2, 3, 4, 5, 6, 8, and 24 (±30 min) hours post-dose. ECG was measured once at each time point for Cohorts 1–4 and in triplicate (approximately 1 min apart) for Cohort 5

[d]Serum pregnancy test at Screening and Urine pregnancy test at Day 0 and Day 8 for all females of childbearing potential

[e]FSH test for postmenopausal women

[f]Plasma PK samples were collected on Day 1 at pre-dose, 15, 30, and 45 min (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 h (±15 min) postdose, and Days 8 and 15

[g]Subjects were required to fast for approximately 12 h prior to the first Day 1 dose

[h]Concomitant Medication and AE Assessment were recorded once per day on the days indicated

Results

Two hundred eighty-eight subjects were screened for this study of which 64 were randomized. To be included in the study, subjects must be competent to voluntarily provide informed consent, have a BMI ≥ 18 and ≤ 30 kg/m^2 at screening visit, be in good physical health as determined by medical history and physical exam, have normal clinical lab test and ECG results, females of child bearing potential must agree to use two forms of acceptable contraception, and male subjects must be surgically sterile or practice at least one method of contraception and must also agree to abstain from sperm donation though 90 days after administration of last dose of study drug. Exclusion criteria included the following: subjects who were pregnant or lactating, had a history or presence of significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological, or psychiatric disorders which, in the opinion of the investigator, increases the risk of the study drug or may confound the interpretation of study measures, had a history of seizures, had any history of current evidence of suicidal behavior, were unwilling to complete any planned study assessment,

Table 2 Study design and schedule of assessments for MAD portion of study

	Check in	Treatment evaluation			Follow up	
	Day -28 to -1	Day 0	Day 1	Days 2–7	Days 8–9	Day 15
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Medical history	X	X				
Demographics	X					
Randomization			X			
Height, weight, BMI[a]	X					X
Physical examination	X	X		X (Days 2 & 4)	X (Day 8)	X
Vital signs[b]						
Laboratory tests	X	X		X (Day 4)	X (Day 8)	X
Serum HbA_{1c}	X					
Serum prolactin	X			X (Day 4)	X (Day 9)	X
HIV, HBsAg, and HCV labs	X					
12-lead ECG[c]	X	X	X	X	X (Day 8)	
C-SSRS	X			X (Day 4)	X (Day 8)	
Urine drug screen	X	X				
Alcohol breathalyzer	X	X				
Pregnancy[d]		X	X			X
FSH[e]		X				
Plasma PK[f]			X	X	X	
Dose subjects[g]			X	X		
Concomitant medication[h]	X	X	X	X	X	X
Adverse event assessment[h]		X	X	X	X	X

BMI body mass index; *C-SSRS* Columbia-Suicide Severity Rating Scale; *ECG* electrocardiogram; *FSH* follicle-stimulating hormone; *HbA1c* hemoglobin A1c; *HBsAg* hepatitis B surface antigen; *HCV* hepatitis C virus; *HIB* human immunodeficiency virus; *PK* pharmacokinetic

[a]Only weight was recorded at follow-up

[b]Vital Signs were measured at Screening, Check-in, Day 1 at pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, and 12 (±30 min) hours post first dose, prior to the first dose and 2 h (±30 min) post first dose on Days 2–7, 24, and 48 h (±30 min) post Day 7 dose, and at follow-up

[c]ECG was measured in triplicate at Screening, Check-in, Day 1 prior to the first dose and 1, 2, 3, 4, 5, 6, and 8 h (±30 min) hours post first dose, prior to first dose on Days 2–7, and Day 8 (24 h (±30 min) post Day 7 dose)

[d]Serum pregnancy test at Screening and Urine pregnancy test at Day 0 and Day 15 for all females of child-bearing potential

[e]FSH test for postmenopausal women

[f]Plasma PK samples were collected on Day 1 prior to the first dose, and 15, 30, and 45 min (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 h (±15 min) post first dose, Days 2–6: prior to first dose, Day 7 prior to the first dose and 15, 30, and 45 min (±5 min), and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 32, and 48 h (±15 min) post first dose

[g]Subjects were required to fast for approximately 12 h prior to the first Day 1 dose. On Days 1–6, subjects received 2 doses per day (8 AM and 8 PM ± 1 h) separated by approximately 12 h. On Day 7, subjects received 1 dose (8 AM ± 1 h)

[h]Concomitant Medication and AE Assessment were recorded once per day on the days indicated

recent (within last two years) history of drug or alcohol abuse, have donated > 500 mL blood in the 30 days prior to screening, received treatment with an investigational drug within 30 day prior to screening, used any prescription or over the counter medication, herbal medications, vitamins, or supplements within 14 days prior to study drug administration, have a positive test for human immunodeficiency virus (HIV) antibodies 1 and 2, Hepatitis B surface antigen or Hepatitis C antibody, or is known to be allergic to the study drug or any components of the study drug.

All subjects in Cohorts 1–6 (10, 50, 75, 100, 200 mg QD and 50 mg BID) completed the study. Three subjects in Cohort 7 (100 mg BID) withdrew consent due to personal/family or work reasons on Day 3. Two of these subjects

Table 3 Target Cmax and AUCinf for total benzamide plasma concentration resulting from dosing LB-102

Dose (mg)	C_{max} (ng/mL)	AUC $_{inf}$ (ng/mL*h)
10	35	330
50	173	1648
100	346	3297
200	692	6593

C_{max} maximum plasma concentration, AUC_{inf} plasma concentration is under curve to infinite time

subsequently reported an acute dystonic reaction (after taking their morning doses on Day 3). As a result of two subjects having a Grade 2 AE in the same organ class, thus meeting a stopping criterion, dosing in Cohort 7 was halted. As a result of meeting a stopping criterion at 100 mg BID, it was decided to dose the final cohort (Cohort 8) at 75 mg (dosing for each Cohort in the MAD was to be determined by clinical observations in the prior cohorts).

Demographics

A total of 64 healthy volunteers were enrolled in this study, and demographic data are summarized in Table 4. There were numerical differences between treatment and placebo groups in mean age and female/male ratio as well as a preponderance of African American/Black subjects: BMI was well-matched.

Safety

Overall LB-102 was well-tolerated, and there were no deaths or serious adverse events in this study. There were a total of 44 adverse events, including 5 in placebo subjects. All AEs were mild or moderate in severity. The most common AE was prolactin elevation, and there were 4 instances of acute dystonia, an extra-pyramidal symptom. Adverse events for this study are summarized in Table 5.

No changes in blood count, liver function, or kidney function were observed during this study. No clinically significant changes in blood count, liver function or kidney function were observed: cholesterol, lipid levels, or electrolytes were not measured in this Phase 1 study. Subjects in this study were not permitted to smoke or consume alcohol, so interactions with these could not be measured.

At the highest dose tested, Cohort 4 (SAD, 200 mg), transient increases in QTcF interval (on average up to 25 ms for cohort) in the first 4 h after dosing were observed; the average QTcF interval for this cohort decreased to normal 6 h post-dosing. None of the subjects in Cohort 4 experienced QTcF prolongation sufficient to trigger a stopping criterion

Table 4 Demographic characteristics of enrolled subjects

	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

Table 5 Summary adverse events

		Single ascending dose					Multiple ascending dose		
Adverse event	Placebo	10 mg	50 mg	100 mg	150 mg	200 mg	50 mg BID	75 mg BID	100 mg BID
n	**16**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
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								
Total AEs	4	3	5	4	1	9	2	9	7

AE adverse event

(an increase in QTcF of > 60 ms over baseline or an absolute value of > 500 ms). Out of an abundance of caution dosing in the 5th Cohort in the SAD was decreased to 150 mg from 200 mg in Cohort 4. In Cohort 7 (MAD,100 mg BID), there were two instances of acute dystonic reactions, an extrapyramidal symptom (EPS), that were judged to be drug related and occurred on Day 3 of dosing. Based on the protocol, these two AEs in the same organ class met a stopping criterion and dosing in this cohort was halted. As a result of the AEs at 100 mg BID, dosing in Cohort 8 was reduced to 75 mg BID. One subject in Cohort 8 experienced an acute dystonic reaction to LB-102 and this subject withdrew consent from the study. There were no clinically significant changes in vitals signs and laboratory parameters (except for prolactin elevations as described above). No subjects responded "yes" to any of the questions in the Columbia-Suicide Severity Rating Scale (C-SSRS).

Pharmacokinetics

In preclinical animal models, LB-102 was extensively, up to 50%, demethylated to amisulpride. In this clinical study, both LB-102 and amisulpride were measured in plasma. Metabolism of LB-102 to amisulpride was minimal (< 3%)

Table 6 Summary of PK parameters from SAD portion of Phase 1 study, mean (SD)

	10 mg	50 mg	100 mg	150 mg	200 mg
C_{max} (ng/mL)	24.1 (10.7)	176 (52.8)	348.2 (141.8)	596.5 (117.5)	975.7 (254)
T_{max} (h)	3	3	3	3	3
$T_{1/2}$ (h)	13.7 (3.9)	11.9 (1.8)	14.1 (4.0)	12.0 (1.9)	13.0 (3.6)
$AUC_{0\text{-inf}}$ (ngh/mL)	252.6 (69.9)	1595.9 (189.2)	2809.8 (477.8)	4636.6 (745.7)	7002.1 (820.7)
CL/F (L/h)	42.4 (12.6)	31.7 (3.8)	36.6 (6.9)	33.1 (5.3)	28.9 (3.4)

C_{max} maximum plasma concentration, T_{max} time of maximum concentration, $T_{1/2}$ half-life, $AUC_{0\text{-inf}}$ area under the curve from time = 0 to infinite time, *CL/F* over bioavailability

Table 7 Summary of PK parameters from MAD portion of Phase 1 study, mean (SD)

	50 mg BID	75 mg BID	100 mg BID
C_{max} (ng/mL) D1	125.5 (22.7)	267.3 (69.4)	325.2 (67.7)
T_{max} (h) D1	2.5	3	2.5
$T_{1/2}$ (h) D1	4.2 (0.4)	4.0 (0.5)	4.12 (0.6)
$AUC_{0\text{-inf}}$ (ngh/mL) D1	1012.6 (100.4)	1777.9 (309.0)	2152.9 (439.9)
C_{max} (ng/mL) D7	224.0 (39.9)	309.4 (149.1)	
T_{max} (h) D7	2.5	2	
$T_{1/2}$ (h) D7	14.3 (3.7)		
$AUC_{0\text{-inf}}$ (ngh/mL) D7	2489.1 (312.4)		
CL/F (L/h)	33.8 (3.1)	34.9 (8.8)	

C_{max} maximum plasma concentration, *T_{max}* time of maximum concentration, *$T_{1/2}$* half-life, *$AUC_{0\text{-inf}}$* area under the curve from time = 0 to infinite time, *CL/F* over bioavailability, D1 refers to day 1 and D7 to day 7. Note, for the 75 mg BID Cohort PK sampling was changed to Day 6 instead of Day 7 so $T_{1/2}$ and C_{max} could for D7 were not calculated. Dosing at 100 mg BID was discontinued on Day 3 so data were not obtained for Day 7

and represented a minor metabolite. Pharmacokinetic parameters for the SAD and MAD portions of this study are presented in Tables 6 and 7.

Plasma concentrations from the SAD portion of the study as a function of time are presented in Fig. 2.

Orally dosed LB-102 was rapidly absorbed and exposure increased in a slightly greater than dose proportional manner. In the MAD portion of the study trough concentrations of LB-102 plateaued prior to the morning dose on Day 4 and showed a slight to moderate accumulation of across dose levels.

Discussion

Orally dosed LB-102 was well-tolerated up to 150 mg/day in healthy volunteers, with acute dystonia (which occurred in 4/48 [8%] of subjects; as a comparison, the Australian label for Solian (amisulpride) lists EPS as occurring in 11% of those taking the drug) as a limiting factor. The most common AEs in this study, prolactin elevation and EPS, are known consequences of dopamine receptor antagonism in general. For LB-102, prolactin elevation was independent of dose, consistent with a recent study of prolactin elevation as a function of amisulpride plasma concentration that showed no meaningful correlation (Glatard et al. 2020). There were no clinical observations associated with increased prolactin (for example, galactorrhea, or menstrual irregularities), and levels returned to normal on discontinuation of treatment.

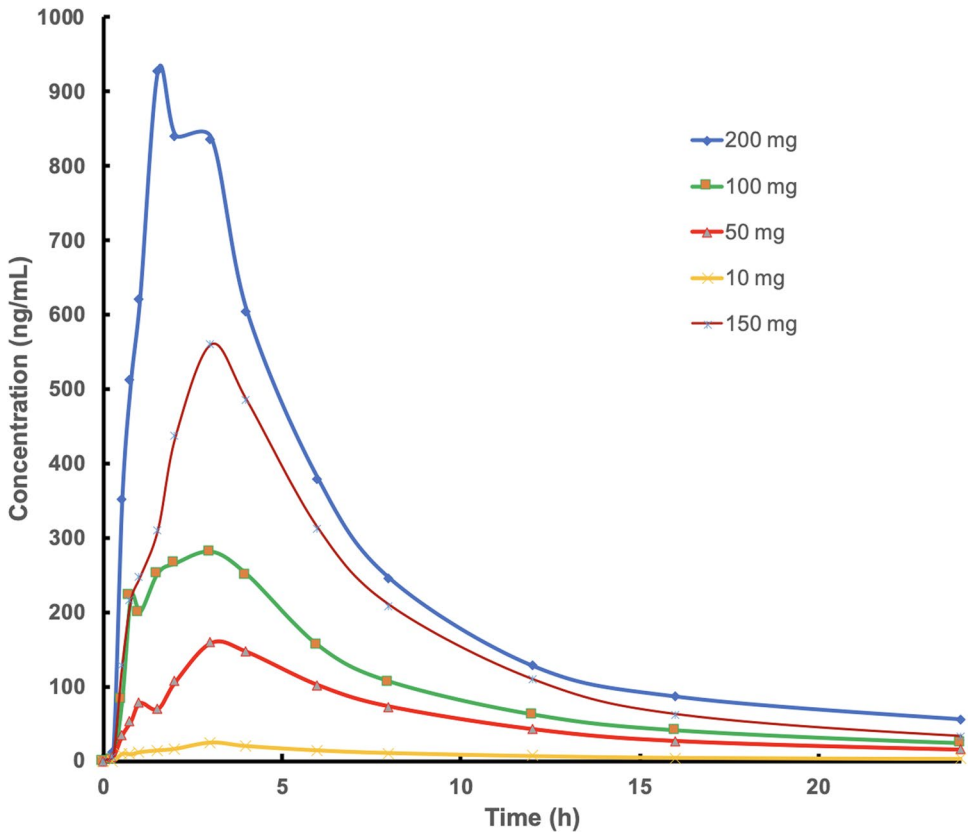

Fig. 2 Plasma concentration as a function of time for SAD portion of Phase 1 study

There are examples in the literature that healthy volunteers are more likely to be subject to adverse events, in particular EPS (Miller et al. 1993), when treated with antipsychotics than individuals with schizophrenia. (Othman et al. 2013; Cutler 2001; Glatard et al. 2020). EPS are typically observed as a consequence of > 80% dopamine D_2 receptor occupancy (Pani et al. 2007). One way to interpret the dystonic reactions observed in this study is that at 100 mg LB-102 BID more than 80% of dopamine receptors were engaged, resulting in the observed acute dystonia and suggesting a lower dose to obtain the desired 60 ~ 80% typically observed with dopamine receptor antagonists effective in treating schizophrenia.

Comparing the plasma PK data of LB-102 from the 50 mg single-dose cohort to published data (Curran and Perry 2001) for healthy volunteers receiving a single 50-mg oral dose of amisulpride showed that the plasma benzamide AUC was about 2.5 times greater for LB-102 (1595 ngh/mL versus 603 ngh/mL); one explanation for this difference is the increased lipophilicity of LB-102 over amisulpride. Having greater plasma concentration for LB-102 compared to amisulpride suggests that dosing could be substantially lower than the 400 mg to 800 mg per day amisulpride typically used to treat schizophrenia.

Observations of EPS, consistent with > 80% dopamine receptor occupancy, may provide an early glimpse of evidence that LB-102 is doing what it was designed to do, namely engage dopamine receptors at clinically relevant levels at lower doses than amisulpride. In a prior study (Meisenzhal et al. 2008), 600-mg amisulpride was required to achieve 80% dopamine receptor occupancy, well below doses of LB-102 examined. A clinical study measuring dopamine receptor occupancy of LB-102 using positron emission tomography is being completed and results from this study will be used to inform dosing in a subsequent Phase 2 clinical study of LB-102 in schizophrenia patients.

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Author contribution Vincent Grattan, Zachary Prensky, and Andrew Vaino invented LB-102. Lukasz Biernat, Mark Hixon, Zachary Prensky, and Andrew Vaino designed the study or were primarily responsible for oversight and conduct of the study. All authors contributed to and have approved the final manuscript.

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Declarations

Conflict of interest Vincent Grattan and Mark Hixon are consultants to, and shareholders of, LB Pharmaceuticals. Zachary Prensky and Andrew Vaino are employees and shareholders of LB Pharmaceuticals. Lukasz Biernat was an employee of Medpace Clinical Pharmacology LLC.

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