INVESTIGATOR'S BROCHURE

LB-102
(IND 137581)

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575 Madison Avenue
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Edition No.: 1
Release Date: 25Oct2019

Confidentiality Statement

SPONSOR SIGNATURE PAGE

LB-102 Investigator's Brochure

Edition No.: 1

Sponsor Signatory:

Zachary Prensky, CEO LB Pharmaceuticals Inc	**Date**

LB-102 Investigator's Brochure

Edition No.: 1

Data Cut-off Date: {dd Mmm yyyy}

Enclosed is an updated Investigator's Brochure for LB-102.

Substantial and non-substantial changes from the previous edition number {nn.n}, dated {dd Mmm yyyy}, are summarized in an accompanying Summary of Changes (SOC) document.

Record of IB Reviews and Updates

Date	Description of Change
{dd Mmm yyyy}	• Updated edition {nn.n} to be consistent with the new template format etc… • Revised Safety, Efficacy, pharmacokinetic (PK), etc…
{dd Mmm yyyy}	•

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Specialist Term	Definition
AE	adverse event
ALT	alanine aminotransferase
APD	action potential duration
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma-concentration time curve
BMI	Body Mass Index
BP	blood pressure
BPRS	Brief Psychiatric Rating Scale
bpm	beats per minute
Ca^{++}	calcium
CI	confidence interval
CL	total body clearance
Cl^{-}	chloride
C_{max}	peak drug concentration
CLr	renal clearance
CPK	creatine phosphokinase
C_{ss}	plasma concentration at steady state
CV	cardiovascular
CV%	% coefficient of variation
CYP	cytochrome P
D_2	Dopamine (D_2) Receptors
ECG	electrocardiogram
EPS	Extrapyramidal Side Effects
eq	equivalent
F	female
FGA	First Generation Antipsychotics
Fe^{++}	iron
FSH	Follicle-Stimulating Hormone
GGT	gamma-glutamyl transferase
HEK	human embryonic kidney
hERG	human ether-a-go-go-related gene

Abbreviation or Specialist Term	Definition
hr	hour
IC_{50}	inhibitory concentration 50% (concentration causing half-maximal inhibition)
IV	intravenous
K^+	potassium
K_i	inhibition constant
LD_{min}	minimum lethal dose
M	male
MAD	Multiple Ascending Doses
min	minute
msec	millisecond
N	total sample size
n	number representing a subset of N (the total sample size)
Na^+	sodium
NADPH	nicotinamide adenine dinucleotide phosphate
NC	not calculated
NOAEL	no observable adverse effect level
PD	pharmacodynamics
PK	pharmacokinetics
PO	Oral/by mouth
QD	Once Daily
QTc	QT interval corrected for heart rate
RBC	red blood cell
RH	relative humidity
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SC	subcutaneous
SD	standard deviation
SD rats	Sprague-Dawley rats
SGA	Second Generation Antipsychotics
$t_{1/2}$	terminal half-life
V_d	volume of distribution
V_{ss} or V_{dss}	volume of distribution at steady state

1. SUMMARY

Schizophrenia is a chronic and debilitating mental illness that affects 1.1% of the US population (NIMH, 2017). Schizophrenia manifests in delusional behavior, dysfunctional thinking, agitated body movement, social withdrawal, and depression. Furthermore, schizophrenia patients experience significantly higher rates of mortality and suicide compared the general population, as well as diminished quality of life (Harris and Barraclough, 1997; Olfson et al., 2015). Despite an abundance of treatment options approved by the FDA, adequate treatment for schizophrenia remains a challenge. In addition, non-adherence to treatment regimens, whether due to minimal or partial response to treatment or symptom worsening, increases the possibility of relapse. Therefore, there is a need for clinically efficacious treatments for schizophrenia.

LB Pharmaceuticals has designed LB-102 to be an improved version of the benzamide antipsychotic amisulpride. Amisulpride is indicated for the treatment of schizophrenia and has been approved in over 50 countries, as well as by the EMA. Amisulpride has demonstrated clinical efficacy similar to antipsychotics currently indicated for the treatment of schizophrenia. Furthermore, amisulpride has been shown to be safe, as demonstrated by the lowest all-cause discontinuation and sedation rate compared to 14 other FDA-approved antipsychotics (Leucht et al., 2013).

The investigational product LB-102 (IUPAC name: 4-methylamino-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-5-(ethylsulfonyl))-2-methoxybenzamide) is a white to off-white solid powder. LB-102 was synthesized through a 2-step process that adds a methyl group to the aniline nitrogen of amisulpride.

In vitro binding of LB-102 to important CNS receptors (androgenic, dopaminergic, histaminergic, muscarinic, and serotoninergic) has been measured and LB-102 bound most strongly to the dopamine D_2 and D_3 receptors, having low single digit nM K_is, and also showing some affinity for the 5-HT_7 receptor (K_i of 32 nM). Also *in vitro*, the ability of LB-102 to passively diffuse across a neutral membrane was compared to amisulpride which showed that LB-102 (amisulpride with an additional methyl group) was better able to penetrate said membrane by ~200 X.

An *in vitro* microsomal stability assay determined the stability of LB-102, in the presence of human, rat, mouse, dog, monkey, rabbit and minipig liver microsomes, and assessed the ability of LB-102 to inhibit Cytochrome P450 (CYP) isoforms. The microsomal stability data demonstrated that metabolism of LB-102 in dogs and rabbits display the highest fidelity to humans. Furthermore, LB-102 did exhibit inhibition beyond the top concentration of 100 µM in the presence of the CYP isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (Midazolam and Testosterone). In the presence of the CYP isoform CYP2C8, LB-102 exhibited slight inhibition, with an IC50 of 75.5 µM.

In vivo pharmacokinetic studies compared blood plasma levels of LB-102 and amisulpride in rats and mice. These data demonstrated that 1) LB-102 is partly decomposed to amisulpride, or another molecule with the same molecular weight---note, amisulpride itself is not further metabolized in rodents, and 2) that the total benzamide plasma concentration, i.e. concentration of LB-102 +

concentration of amisulpride, of mice or rats dosed with LB-102 was equivalent to mice or rats dosed with amisulpride.

Commonly used animal behavioral studies mimicking symptoms of schizophrenia, specifically Novel Object Recognition (NOR) in rats, a measure of cognition, Apomorphine Induced Climbing (AIC) in mice, a measure of stereotypy, and LocoMotor Activity (LMA) in rats, a measure of hyperactivity, were carried out to evaluate the efficacy of LB-102 to treat schizophrenia. In two of these studies, NOR and AIC, LB-102 was statistically indistinguishable from amisulpride. In the LMA study, a 30 mg/kg dose of LB-102 was statistically superior to the same dose of amisulpride.

In the comprehensive, GLP-compliant, 28-day, oral repeat-dose toxicity study in rats, doses of 0, 20, 40, and 100 mg/kg/dose (0, 40, 80, and 200 mg/kg/day) were administered BID approximately 12 hours apart with a 1-month recovery. LB-102-related effects in rats were associated with elevated levels of prolactin, which are presumed to occur with LB-102 based on its mechanism of action as a dopamine antagonist. These changes are unique to rodents, have been observed with other dopamine antagonists, were noted at all doses, and included hypertrophied corpora lutea (CLs), decreased CLs, interstitial cell hyperplasia and increased number of atretic follicles in the ovaries, mammary gland lobuloalveolar hyperplasia, and vaginal mucification in females, and mammary gland atrophy and prostatic inflammation in males. Tissue changes either completely resolved or showed a trend to resolution during the recovery period. Given the species-specific nature of the response, the no-observed-adverse-effect-level (NOAEL) was determined to be 200 mg/kg/day, the highest dose administered.

In dogs, the 28-day study used doses of 0, 0.75, 3, and 7.5 mg/kg/dose (0, 1.5, 6 and 15 mg/kg/day) administered BID approximately 12 hours apart; there was a 1-month post-dose recovery period. The main finding was an increase in heart rate at 6 and 15 mg/kg/day. The dogs remained in sinus rhythm and, due to the lack of correlating clinical/veterinary observations, clinical pathology findings, or histopathological findings, this change was not considered to be adverse. Furthermore, no cardiovascular alterations were noted after the recovery period. The NOAEL in dogs was determined to be 15 mg/kg/day, the highest dose administered.

In the *in vitro* Ames and micronucleus assays, LB-102 was neither mutagenic, clastogenic, nor aneugenic.

LB Pharmaceuticals is proposing a Phase 1 study for LB-102. The first study will be a Phase 1, placebo-controlled, double-blind study to evaluate the safety, tolerability, and pharmacokinetics (PK) of single (SAD) and multiple (MAD) ascending oral doses of LB-102 in healthy adult subjects. For the SAD study, subjects (n=40) will be divided into 5 sequential groups of 8 healthy subjects for LB-102 (n=6) or placebo (n=2) treatment. On Day 1, following a 12-hour overnight fast, subjects will receive 1 oral dose of placebo or LB-102 (50 mg/day). Blood samples will be collected at various times on Days 1-3 for PK analysis. Safety assessments including 12-lead ECG, clinical labs (hematology, chemistry, urinalysis), and vital signs will be recorded at multiple timepoints throughout the trial. Subjects will remain in the clinic from Check-in to Discharge on Day 3 and then return for a Follow-up Visit on Day 8. Dose escalation to 100, 200, 400, and

800 mg/day LB-102 will occur after Safety Review Committee (SRC) approval. Subsequent groups will follow the same study procedures for each dose escalation.

For the MAD study, subjects (n=24) will be divided into 3 sequential groups of 8 healthy subjects for LB-102 (n=6) or placebo (n=2) treatment. Subjects will receive 2 oral doses of placebo or LB-102, 12 hours apart, on Days 1-6 and one dose on Day 7 for a total of 13 oral doses. The doses for this study are dependent on the results of the SAD study. Blood samples will be collected at various times on Days 1-9 for PK analysis. Safety assessments including 12-lead ECG, clinical labs, and vital signs will be recorded at multiple timepoints throughout the trial. Subjects will remain in the clinic from Check-in to Discharge on Day 9 and then return for a Follow-up Visit on Day 14. Subsequent groups will be administered increasing doses of LB-102 that are dependent on the results of the SAD study, following the same study procedures.

2. INTRODUCTION

2.1 Details of the Condition

Schizophrenia is a chronic and debilitating mental illness that manifests in delusional behavior, dysfunctional thinking, agitated body movement, social withdrawal, and depression. Furthermore, schizophrenia affects 1.1% of the US population (NIMH, 2017). The course of schizophrenia is highly variable with periods of psychosis and stabilization of varying duration and intensity. Sustained remission of both positive and negative symptoms occurs in a minority of patients even with prolonged antipsychotic therapy. Patients with schizophrenia have a 3.5 times higher rate of mortality compared to the general population (Olfson et al., 2015). A study in 2013 of over 6 million Swedish adults (including 8300 patients with schizophrenia) found that females and males with schizophrenia died 12 and 15 years earlier than their counterparts in the general population, respectively (Crump et al., 2013).

Schizophrenia patients suffer a profoundly reduced quality of life and are 8 times more likely to commit suicide than the general population (Harris and Barraclough, 1997). In addition, meta analyses of suicide among schizophrenia patients estimate that 4-13% commit suicide (Miles, 1977; Caldwell and Gottesman, 1990; Inskip et al., 1998; Palmer et al., 2005). Half of suicides among patients with schizophrenia occur within the first two years of disease onset (Tandon and Jibson, 2003), pointing to the urgency for behavioral and pharmaceutical intervention. However, compliance with long-term medication is a significant problem due to dissatisfaction with antipsychotic side effects, or self-discontinuation of medication as a result of feeling better and no longer perceiving the need for continuous medication. Both of these issues contribute to relapse among schizophrenia patients.

According to IMS Health, there are over 60 million prescriptions written annually for anti-psychotics in the United States. In fact, there are at least 22 drugs (both first- and second-generation antipsychotics) approved by the FDA indicated for the treatment of schizophrenia (HHS, 2012; FDA 2015). Despite a seeming surfeit of available drugs to treat schizophrenia, adequate treatment of schizophrenia remains a challenge. First, non-adherence and discontinuation of treatment are major issues. This is due in part to the fact that majority of schizophrenia patients

are either unresponsive or only partially responsive to treatment with an antipsychotic. This was demonstrated by a review of randomized, double-blind clinical trials involving schizophrenia or related disorders. This review found that 53% of patients stopped their treatment at an early stage and the most prevalent reasons were poor response or psychiatric symptom worsening (Liu-Seifert et al., 2005). Discontinuation of treatment significantly increases the chance of relapse with an estimated relapse rates of approximately 80% and 95% after discontinuing treatment for 12 and 24 months, respectively (Emsley et al., 2013).

Leucht et al. suggested that at least a 26% improvement in PANSS score at week 4 was required to demonstrate a minimal improvement in treatment response (Leucht et al., 2005). However, a recent analysis of 16 clinical studies, covering over 6,000 patients, found that the overall nonresponse to drugs for the treatment of schizophrenia was 43% using a minimum 25% improvement in PANSS/BPRS and 67% if a 50% improvement in PANSS/BPRS was the goal (Samara et al., 2019). Despite 22 FDA approved drugs for the treatment of schizophrenia inadequate resolution of symptoms remains a serious medical need.

2.2 Rationale

The standard pharmacologic mechanism of action for antipsychotic drugs is antagonism of D_2 receptors in the limbic system of the brain (Meltzer and Stahl, 1976; Joyce and Meador-Woodruff, 1997; Wulff et al., 2015). This has remained largely unchanged since antipsychotics began use clinically in the 1950s. Second generation antipsychotics (SGAs), also known as Atypical Antipsychotics, are preferred by patients and clinicians and are used in the majority of patients. Older antipsychotics developed between 1950 and 1980 are referred to as first generation antipsychotics (FGAs) and are used primarily when patients have failed numerous SGAs. The primary advantage of SGAs is a lower incidence of extrapyramidal side effects (EPS) that resemble the types of movement disorders that occur in Parkinson's disease. Patients who experience EPS from a specific antipsychotic will often ask for a different drug or discontinue on their own. While SGAs were an important advance, these drugs are not free of the common side effects of many CNS drugs that arise from varying degrees of antagonism of dopamine, histamine, serotonin, muscarinic, hERG, and alpha receptors. Further, these drugs distribute widely throughout the CNS due to their ability to easily cross the blood brain barrier by passive diffusion allowing off-target effects to occur. SGA side effects, as a result of off-target receptor engagement, include weight gain, elevations in lipids and blood sugar, sedation, dry mouth, constipation, dizziness and falls due to low blood pressure, QT interval prolongation, cognitive impairment, and prolactin elevation. Until a disease modifying therapy is developed for schizophrenia, the ideal antipsychotic would be a drug that has selectivity for the limbic system and minimal to no engagement of receptors that cause side effects.

Amisulpride, originally developed in France in the 1980s (Thominet et al., 1983), is approved in more than 50 countries worldwide for the treatment of schizophrenia and in certain countries for the treatment of dysthymia (IMS, 2015). Amisulpride elicits its activity, in part, by selectively blocking the human D_2 (K_i 2.8 nM) and D_3 (K_i 3.2 nM) receptor subtypes with negligible affinity for the dopamine D_1, D_4, and D_5 receptor subtypes (K_i > 1,000 nM) and in part by its activity against the 5-HT_7 receptor (11.5 nM K_i). Amisulpride has been shown to have similar efficacy to antipsychotics currently indicated for the treatment of schizophrenia. Further, in a meta-analysis

amisulpride had the lowest all-cause discontinuation and sedation rate compared to 14 other antipsychotics (Leucht et al., 2013). Therefore, amisulpride is safe and effective for the treatment of schizophrenia.

While amisulpride is a clinically effective and safe drug, it demonstrates poor distribution to the brain. A 2014 study revealed that passive diffusion of amisulpride across a PAMPA membrane was the lowest of 30 psychiatric drugs tested (Dos Santos Pereira et al., 2014).

LB-102 was designed to be an improved version of the benzamide antipsychotic amisulpride having increased permeability across the blood-brain-barrier, potentially decreasing the plasma concentrations needed to achieve efficacy thereby decreasing the magnitude and frequency of adverse events typically observed in patients treated with amisulpride.

In vitro studies have confirmed that LB-102 is better able than amisulpride to passively penetrate a PAMPA membrane and exhibits similar activity and selectivity toward CNS receptors (D_2, D_3, and $5HT_7$ receptors) as amisulpride. *In vivo* studies have demonstrated that LB-102 has a favorable pharmacokinetic profile in rats and in mice, similar to amisulpride, as well as a similar or superior efficacy to amisulpride in animal models covering 3 aspects of schizophrenia. In summary, LB-102 is a proprietary molecule having similar physicochemical and biological characteristics equivalent to or better than amisulpride, an antipsychotic with an established decades-long clinical track-record

3. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1 Drug Substance

The investigational product LB-102 is a solid that appears as a white to off-white powder. LB-102 is synthesized through a 2-step process that adds a methyl group to the aniline nitrogen of amisulpride in a two-step process (Figure 1). Additional properties are listed in below.

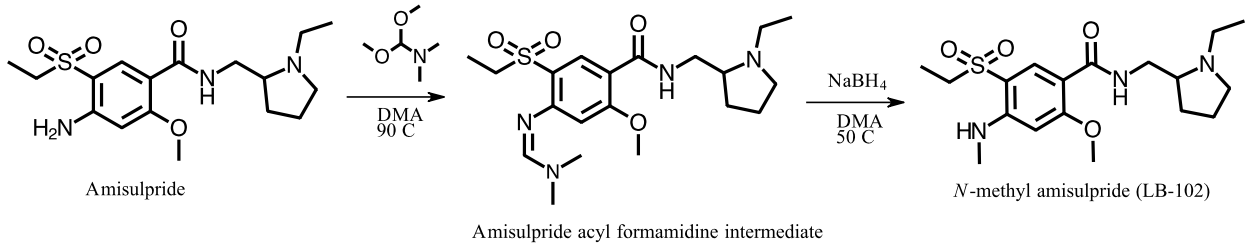

Figure 1: Structure of LB-102

Chemical Name: IUPAC name: 4-methylamino-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-5-(ethylsulfonyl))-2-methoxybenzamide

Appearance: White to off-white powder

Code Name: LB-102

Structural Formula: $C_{18}H_{29}N_3SO_4$

Molecular Weight: 383.51

Chirality: LB-102 is a racemic mixture

Table 1: Aqueous Solubility

Vehicle	HPLC Area of sample at 225 nM	Sample Concentration (mg/mL)	Calculated Solution Concentration (mg/mL)	Comment
30% DMF 70% pH 4.7 MES buffer	2796	0.44	44.0	100:1 dilution. pH of buffer is unchanged.
pH 4.7 MES buffer	3770	0.614	61.4	100:1 dilution. pH of buffer is unchanged.
pH 5 HCl	4990	0.839	83.9	100:1 dilution. pH of solution is unchanged.
pH 6 phosphate buffer	3827	0.625	625	1000:1 dilution. pH of buffer is unchanged.
pH 5 acetate buffer	Not determined	> 800 mg / mL	> 800 mg / mL	. pH of solution becomes 6.5

3.2 Drug Product

Not applicable.

3.3 Storage and Handling

No special transport or storage conditions are required for LB-102. In stability studies LB-102 has been demonstrated to be stable for nine months under standard (25°C/60% RH) conditions and for six months under accelerated (40°C/75% RH) conditions. Stability studies are ongoing.

4. NONCLINICAL STUDIES

4.1 Nonclinical Pharmacology

4.1.1 Primary Pharmacology

4.1.1.1 In Vitro Studies

4.1.1.1.1 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. After 15-20 hr incubation, the donor and acceptor wells were sampled and analyzed by LC-MS/MS. Permeability results from this study showed that more LB-102 passively diffused across an artificial membrane than did amisulpride (Table 2).

Table 2: Permeability of Amisulpride, Propanolol, and Ranitidine Through a PAMPA Membrane at pH 5 and pH 7.4

	Permeability (cm/s) pH 5	Permeability (cm/s) pH 7.4
Amisulpride	2.4×10^{-10}	2.4×10^{-11}
N-methyl amisulpride	2.1×10^{-8}	5.2×10^{-9}
Propanolol	3.1×10^{-8}	7.8×10^{-6}
Ranitidine	1.1×10^{-10}	1.5×10^{-10}

4.1.1.1.2 CNS Receptor Binding Screen

An in vitro radioligand receptor binding displacement screen measured the percent binding inhibition of target ligands to a range of important CNS receptors at a 10 µM concentration of LB-102. Results of this study are presented in Table 3 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 important CNS receptors.

Table 3: *In Vitro* Binding (% Inhibition at 10 µM) of LB-102 Against a Panel of Receptors Active in the CNS

Receptor	Mean % inhibition at 10 µM
a1	36
a1a	28
a1b	48
a1d	48
a2	100
a2a	94
a2b	100
a2c	90
d2s	101
d2l	99
d3	100
h1	4
m1	25
m2	22
5ht2a	90
5ht2c	63

As a follow up to the screen above, the binding of LB-102 to receptors with at least 80% inhibition at 10 µM (excluding A2 receptors) was further examined over a range of concentrations that enabled determination of the inhibition constant (Ki). Results of these ligand-displacement studies, summarized in Table 4, reiterated the findings from the initial screen: LB-102 is a potent receptor antagonist of dopamine D_2, D_3, (known to improves symptoms of schizophrenia) and 5-HT_7 with affinity similar to that of amisulpride.

Table 4: Ki Values for LB-102 for CNS Receptors with >80% Inhibition at 10 µM (Study 100030887)

Receptor	K_i (nM) LB-102
α-$_{2a}$ (non-selective)	41
α-$_{2a}$ (h)	220
α-$_{2B}$ (h)	110
α-$_{2C}$ (h)	240
5-HT-$_{2a}$	200
5-HT-$_{7}$	32
D_{2L}	0.66
D_{2S}	3.4
D_3	2.5

In separate *in vitro* binding assays, the ability of LB-102 (a racemic mixture), its S enantiomer (LB-103) and its R enantiomer (LB-104) were evaluated for their abilities to bind D_2 receptors and the 5-HT_7 receptor (thought to play a role in cognitive aspects of schizophrenia) (Hedlund, 2009; Pouzet et al., 2002). Prior data on amisulpride suggested that that the S enantiomer of LB-102 (i.e., LB-103) would bind to the dopamine receptors better than the R enantiomer and as depicted in Table 5 this proved to be the case (Castelli et al., 2001). Interestingly, in looking at binding of the enantiomers of LB-102 to the 5-HT_7 receptor, it was found that the R enantiomer was responsible for binding and the S enantiomer had no activity (Ki > 1000 nM). Thus, using a racemic mixture of R and S enantiomers of LB-102 has the potential to offer benefits of both D_2 and 5-HT_7 binding.

Table 5: K_i Values for Single Enantiomers of LB102 Against Dopamine D_2 and 5-HT_7 Receptors

	K_i (nM)	
Receptor	LB-103 (*S*)	LB-104 (*R*)
D_2	0.4	14.4
5-HT_7	>1000	15.6

Figure 2 depicts a heat map comparing the binding of LB-102 to a range of drugs used to treat schizophrenia over a myriad of CNS receptors (Roth et al., 2000). In general, binding of LB-102 is consistent with that of amisulpride. Furthermore, LB-102 exhibits less off-site binding to CNS receptors compared to other commonly prescribed antipsychotics.

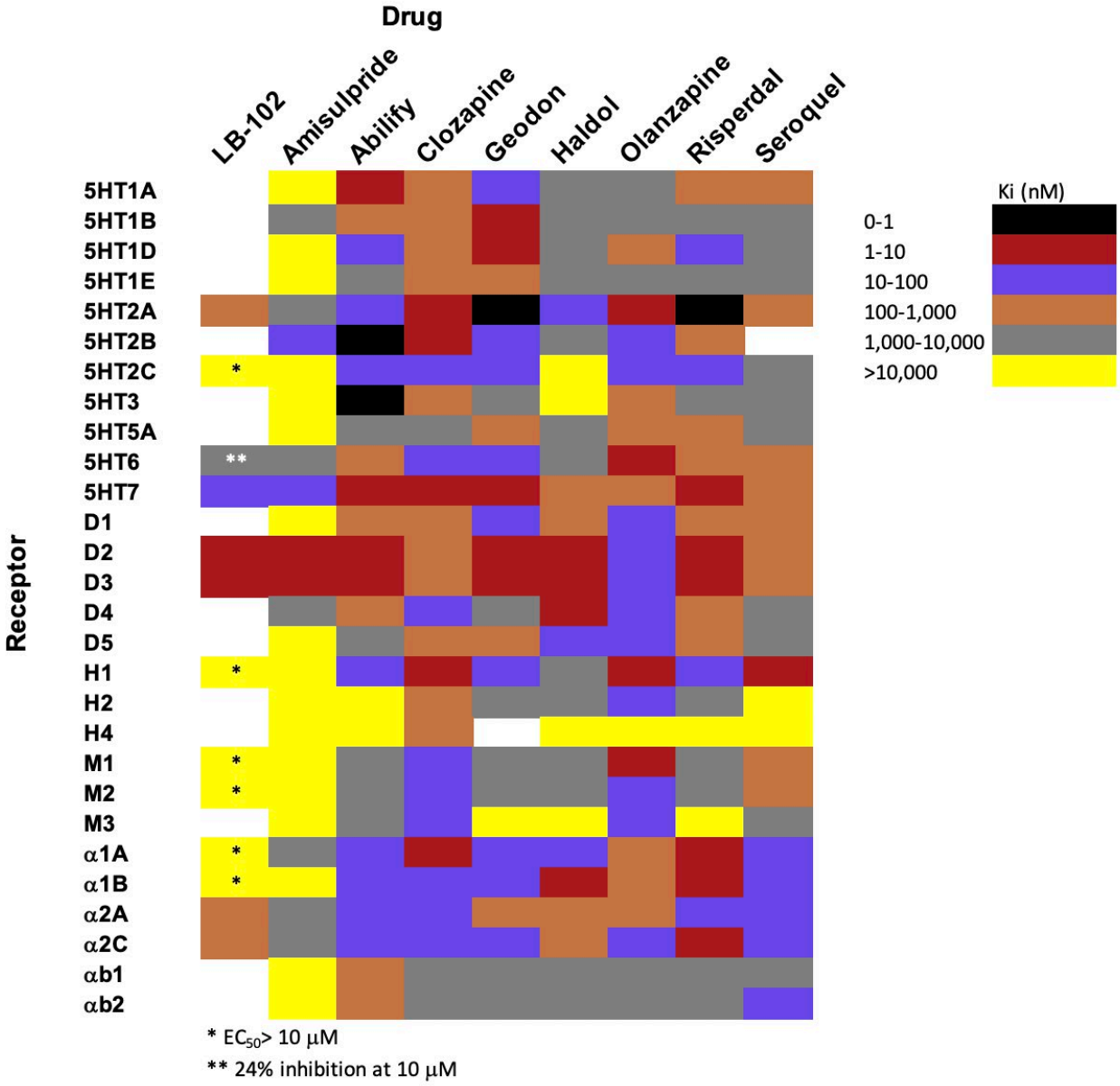

Figure 2: Comparison of CNS Receptor Binding of LB-102 to Other Commonly Prescribed Schizophrenia Treatments

4.1.1.1.3 LB-102 Liver Microsome Stability in Different Species

In an initial microsome stability screen, LB-102 was incubated with liver microsomes from humans, rats, mice, dogs, monkeys, rabbits, and minipigs over the course of 45 minutes. Concentration of LB-102 was measured at t = 0, 5, 15, 30, and 45 minutes. Results of this study are summarized in Figure 3. The microsomal stability data demonstrate that metabolism of LB-102 in dogs and rabbits displayed the highest fidelity to humans.

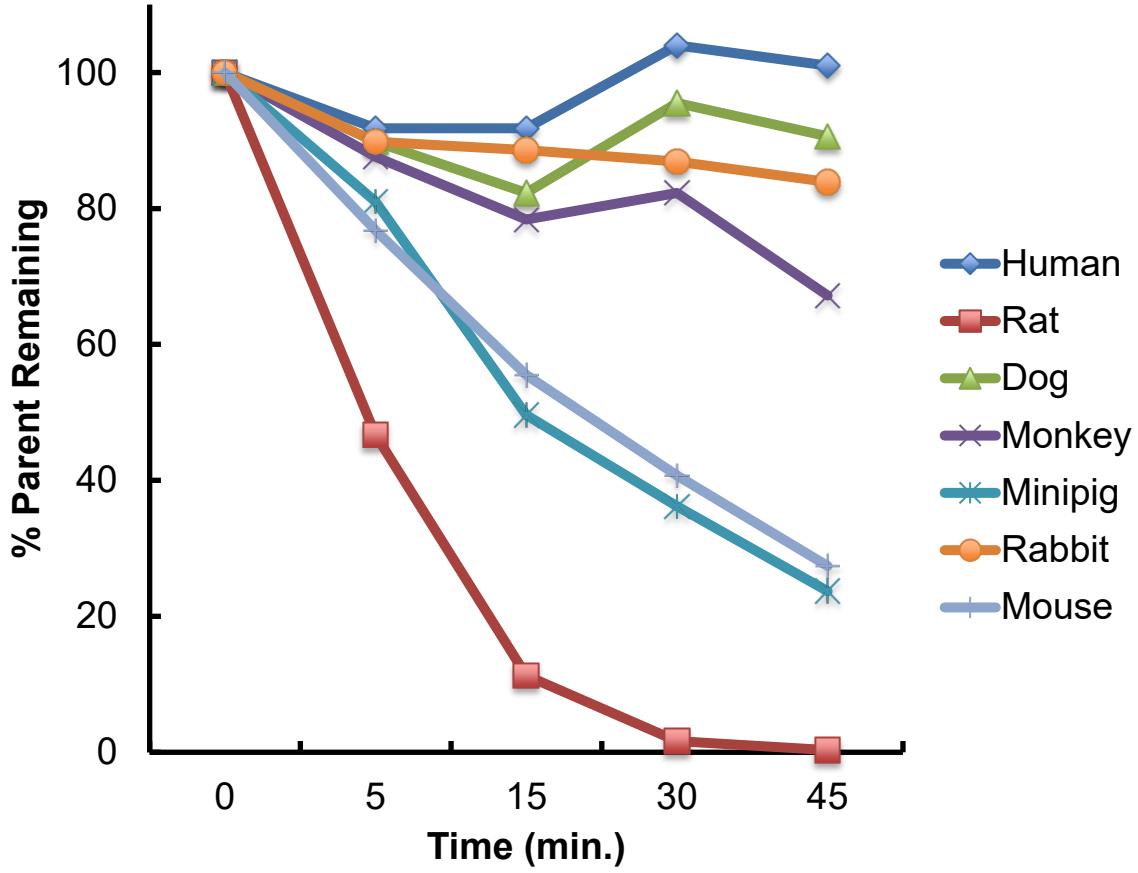

Figure 3: Stability of LB-102 in Various Mammalian Liver Microsome Samples

4.1.2 In Vivo Studies

4.1.2.1 Animal Behavior Studies

In vitro studies presented above suggest that LB-102 should behave as an effective schizophrenia drugs based on its ability to bind dopamine receptors. Initial PK studies (Section 4.2) showed that LB-102 would persist in the body long enough to interact with dopamine receptors. While both of these are important, it was still important to determine if LB-102 had any effect on the manifestations of schizophrenia. Three well accepted behavioral models of schizophrenia, apomorphine induced climbing, novel object recognition, and locomotor activity, were used to evaluate the potential of LB-102 to treat schizophrenia.

4.1.2.1.1 Apomorphine Induced Climbing Study

Efficacy of LB-102 was studied in an Apomorphine Induced Climbing (AIC) study in male mice (Wilcox et al., 1980). AIC is a model in which animals are dosed with the dopamine agonist apomorphine that induces stereotypic climbing, a proxy for stereotypy that is a common manifestation of schizophrenia.

In this AIC study, mice were treated with 2.5 mg/kg apomorphine (SC) followed by dosing with LB-102 or amisulpride orally in groups of 8 mice at 20 and 60 mg/kg. Climbing behavior, over the course of 30 minutes, was measured 2 hours post-dosing for LB-102 and amisulpride (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). Total climbing scores from this AIC study are summarized in Figure 4. In this AIC study in mice, LB-102 reversed apomorphine climbing in a manner that was consistent with amisulpride.

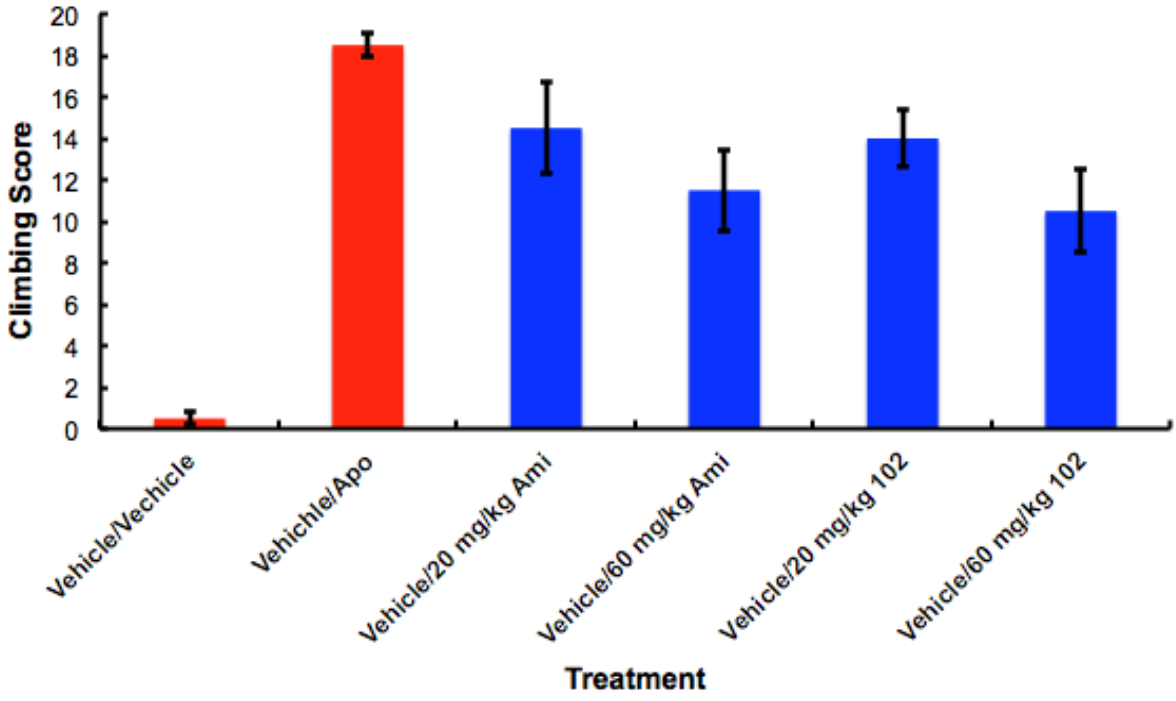

Figure 4: Climbing Score of Apomorphine Treated Mice (n=8/Group) ± SEM

4.1.2.1.2 Novel Object Recognition (NOR)

Efficacy of LB-102 was evaluated in rats in a Novel Object Recognition (NOR) assay, a well-established model recapitulating cognitive and negative aspects of schizophrenia, such as difficultly in abstract thinking (Neill et al., 2010; Neill et al., 2014; Neill et al., 2016). In the NOR model, animals were treated for several weeks 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 in groups of 10 rats at 1.7, 5, 15, and 45 mg/kg for LB-102 and 5, 15, 45 mg/kg for amisulpride (additionally, one arm was dosed at 3 mg/kg IP), risperidone was dosed at 0.1 mg/kg: all doses were PO unless specified IP. Cognitive measurements were taken at 3 hr. post-dose for benzamides and 30 min 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 are summarized in Figure 5. The results show that LB-102 restored cognitive function in a manner similar to amisulpride.

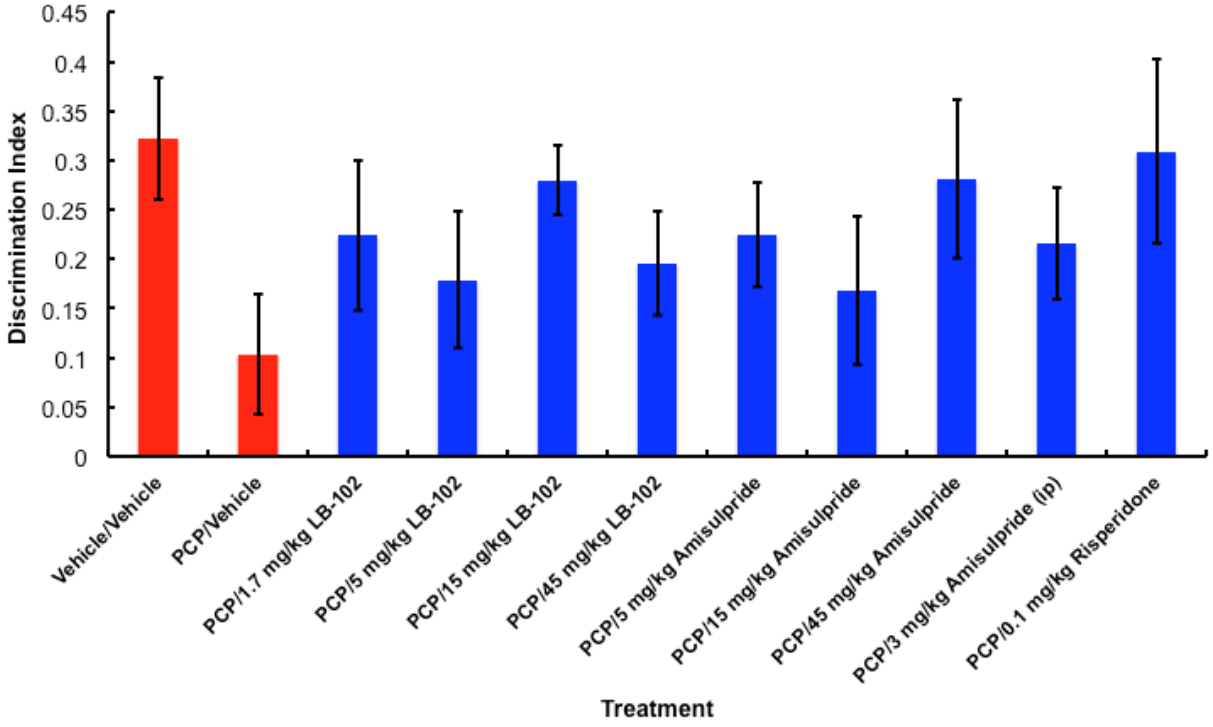

Figure 5: Discrimination Index (N = 10/Group) ((Time Spent Exploring Novel – Time Spent Exploring Familiar) /Total Exploration Time) ± SEM (n=10/Group)

4.1.2.1.3 Locomotor Activity (LMA)

Efficacy of LB-102 was studied in rats in an amphetamine-induced Locomotor Activity (LMA) assay, a measure of the positive aspects (excitement) of the PANSS (Positive and Negative Syndrome Scale) (Kay et al., 1987). In the LMA assay, rats were monitored in a cage to determine how far each rat moves. Rats were dosed with amphetamine or vehicle (negative/negative control) and with various treatment groups. Rats dosed with amphetamine alone display hypermobility while rats additionally dosed with antipsychotics show more normal, calmer, activity.

In this LMA study, rats were treated with 1 mg/kg amphetamine SC to elicit hyperactivity. LB-102, amisulpride, and risperidone were dosed orally in groups of 10 rats at 3, 10, and 30 mg/kg with LB-102 and amisulpride, and risperidone was dosed at 1 mg/kg. Rats in the amphetamine

group were dosed with vehicle during the experiment. Distance moved, over the course of an hour, was measured 6 hours post-dosing for LB-102 and amisulpride— risperidone was dosed 1 hour prior to measurement (note, the difference is due to slower brain penetration of amisulpride). The endpoint of this study was total ambulatory distance (the distance traveled by each animal in the cage). Total ambulatory distance data from this LMA study are summarized in Figure 6. In this LMA study in rats, LB-102 reversed amphetamine hyperactivity in a manner that was significantly superior at 30 mg/kg (LB-102 was statistically superior, having $p < 0.05$, p for LB-103 was 0.07) to amisulpride.

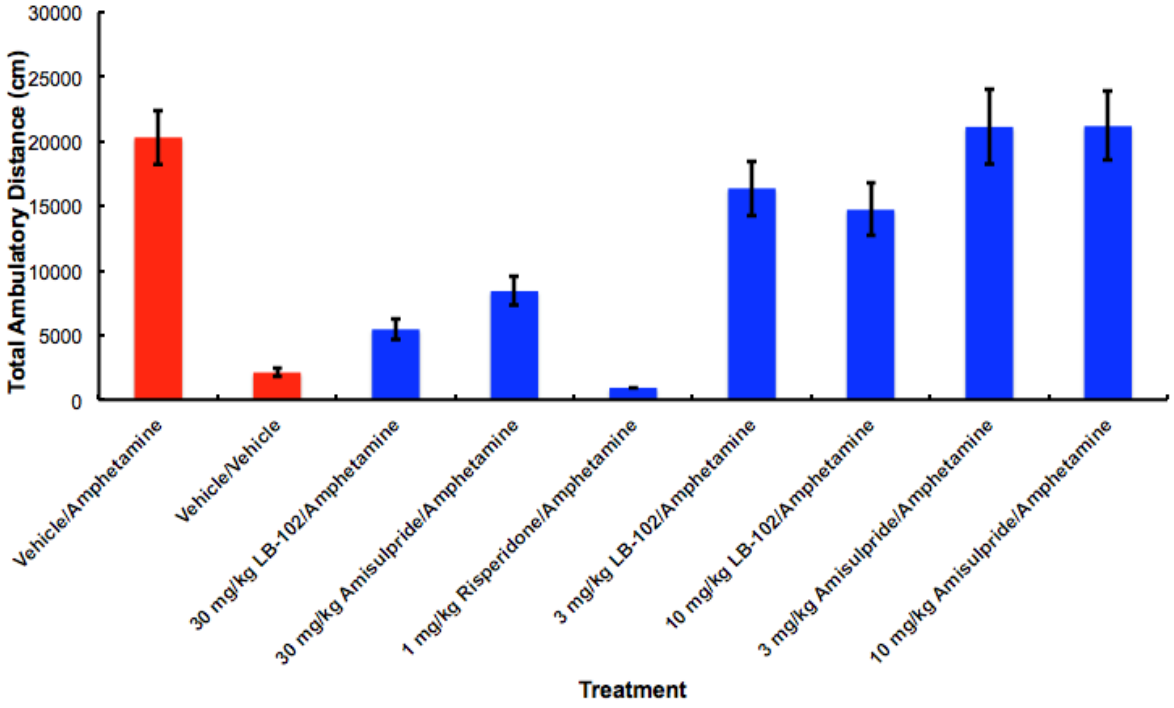

Figure 6: Total Ambulatory Distance (Over 1 Hour) ± SEM (n = 10/Group). Comparing 30 mg/kg LB-102 Activity to 30 mg/kg Amisulpride Activity Afforded $p < 0.05$

4.1.2.1.4 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. In this study, rats were 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.

Data from the bar test for LB-102 (75 and 100 mg/kg) and amisulpride (75 and 100 mg/kg) are presented in Figure 7. Of note is that there were no significant differences in mean time on bar after dose times for which a value was measurable (for 5 h vehicle dosing no observation of time

on bar was made). That is, in an assay for catalepsy, the effects of LB-102 were consistent with amisulpride: a well-tolerated drug with ~2 million prescriptions/year in the EU.

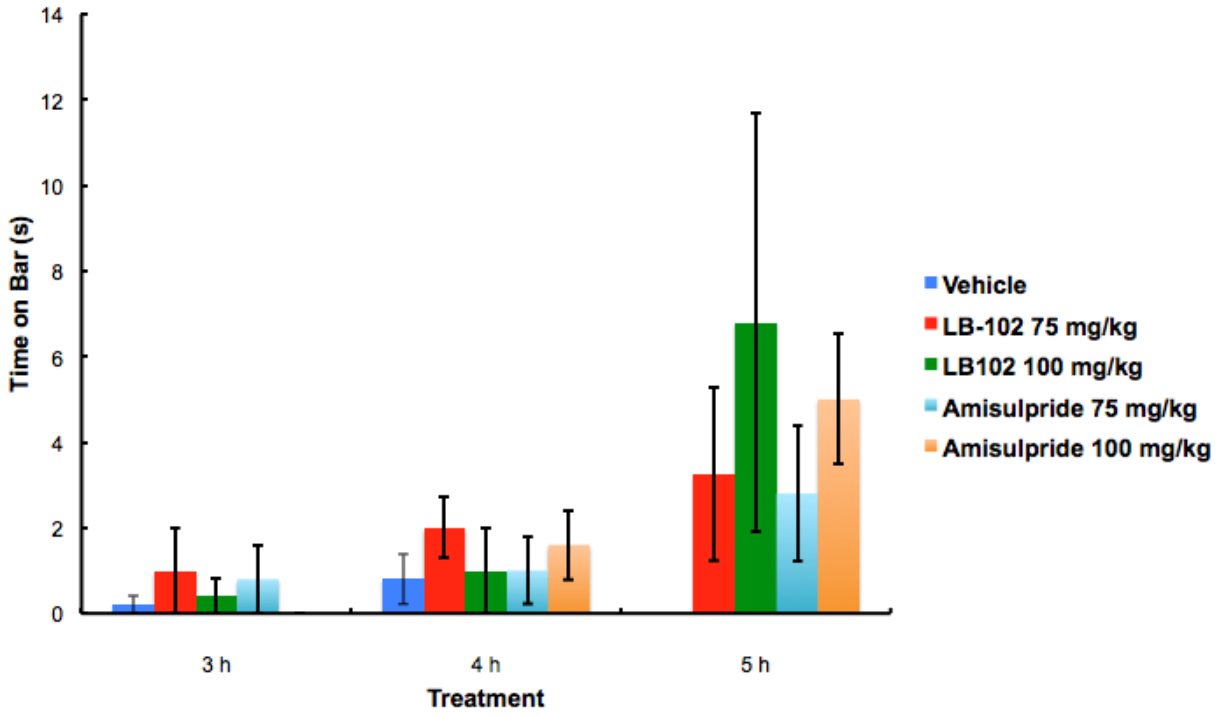

Figure 7: Mean Time (s) Spent on the Bar Following Acute Treatment with LB-102 (75 and 100 mg/kg, p.o.) and Amisulpride (75 and 100 mg/kg, p.o.)

4.1.3 Safety Pharmacology

4.1.3.1 General

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.

4.1.3.2 Cardiovascular and Respiratory Safety Pharmacology

4.1.3.2.1 Pulmonary

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).

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 no-observed-adverse-effect-level (NOAEL) for effects on respiratory function in rats was 200 mg/kg.

4.1.3.2.2 Cardiovascular

4.1.3.2.2.1 In Vitro

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).

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.

4.1.3.2.2.2 In Vivo

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).

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 post-dose] 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, Table 6 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 6: 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 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 were 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.

4.1.3.3 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).

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 NOAEL for effects on neurobehavioral function in rats was 80 mg/kg.

4.1.3.4 Renal Safety Pharmacology

No renal safety pharmacology studies have been conducted.

4.1.3.5 Drug Interaction Studies

No pharmacodynamic drug interaction studies have been conducted.

4.2 Pharmacokinetics and Product Metabolism in Animals

4.2.1 Single Dose Pharmacokinetics

Initial pharmacokinetic studies of LB-102 were performed in mice and in rats. Our expectation, based on chemical structure of LB-102, was that the molecule would be subject to *N* demethylation (likely P-450 mediated) to generate amisulpride *in vivo* (Figure 8).

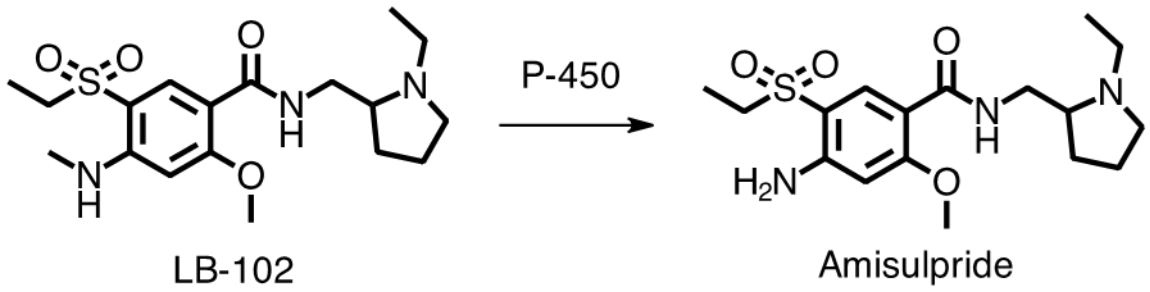

Figure 8: Proposed Metabolism of LB-102 into Amisulpride by Cytochrome P-450

4.2.1.1 Mouse Pharmacokinetic Study

A PK study of LB-102, in which mice were dosed orally with LB-102 or amisulpride at 30 mg/kg was conducted. Plasma concentrations were measured over the course of 3 hours and data for the total benzamide concentration [amisulpride] + [LB-102] are depicted in Figure 9. Consistent with rat PK data, about 50% of LB-102 was metabolized into amisulpride and the total plasma concentration of benzamide after oral dosing LB-102 in mice was consistent with that of amisulpride.

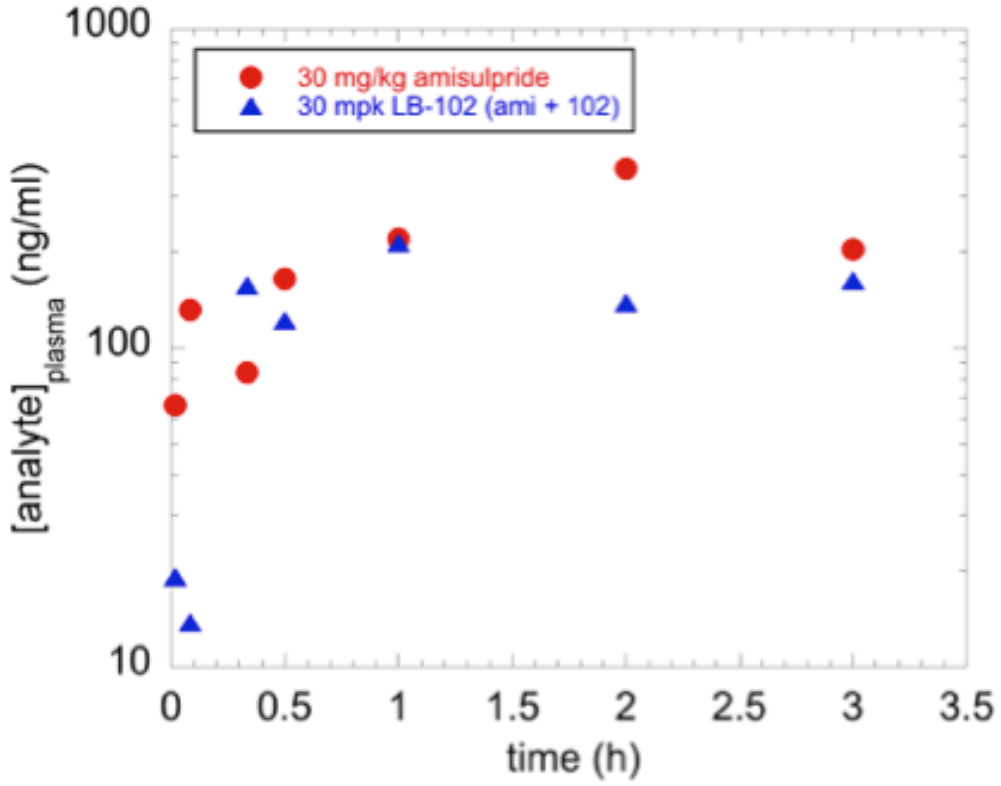

Figure 9: Pharmacokinetic Profile of 30 mg/kg Dose PO to Mice (n = 3/Group)

4.2.1.2 Rat Pharmacokinetic Study

In rats the pharmacokinetics of LB-102 displayed bi-phasic absorption and were dose-linear over the range of the doses examined, specifically 1 mg/kg, 3 mg/kg, and 10 mg/kg after oral dosing (Figure 10). The pharmacokinetics of amisulpride and LB-102 in rodents displayed biphasic absorption and were modeled as distributing into a single compartment.

The data from Figure 10 shows both intact LB-102 (triangles) and amisulpride (circles) resulting from the anticipated metabolic oxidation of LB-102 into amisulpride: this N-demethylation is not unexpected. At the three doses tested, the ratio of LB-102:amisulpride was consistently ~1:1. While the appearance of amisulpride decreases, in part, the effective dose of LB-102 the decrease is offset since the metabolite amisulpride is itself a potent antipsychotic.

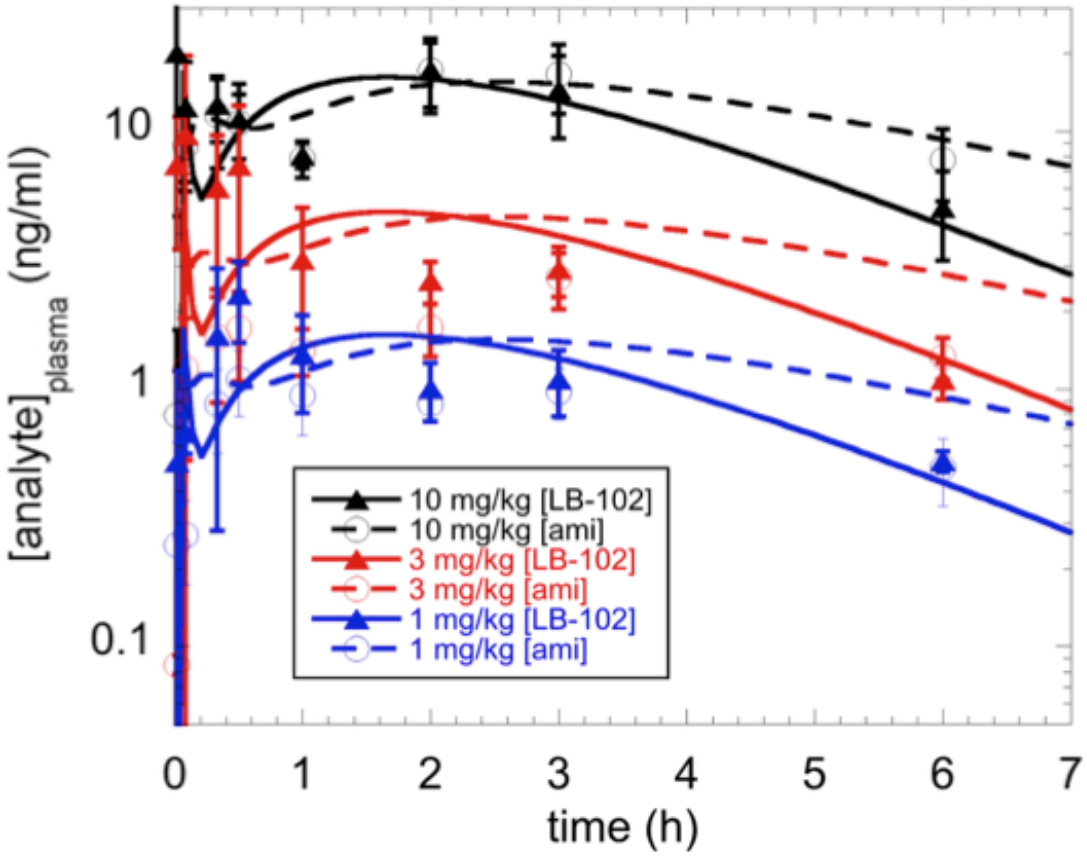

Figure 10: Concentration Versus Time for LB-102 and Demethylated LB-102 (Amisulpride) After Oral Dosing of Rats at 1, 3, and 10 mg/kg (n = 3/Group)

Note logarithmic Y-axis, and that triangles represent LB-102 and open circles represent amisulpride. Dashed and solid lines correspond to our PK model of LB-102.

A study was conducted to compare the pharmacokinetics of LB-102 to amisulpride in rats following a single oral dose at 3 mg/kg. Plasma exposures to LB-102 plus demethylated LB-102 (amisulpride) following a dose of LB-102 were equivalent to the exposure of amisulpride observed after a dose of amisulpride (Figure 11).

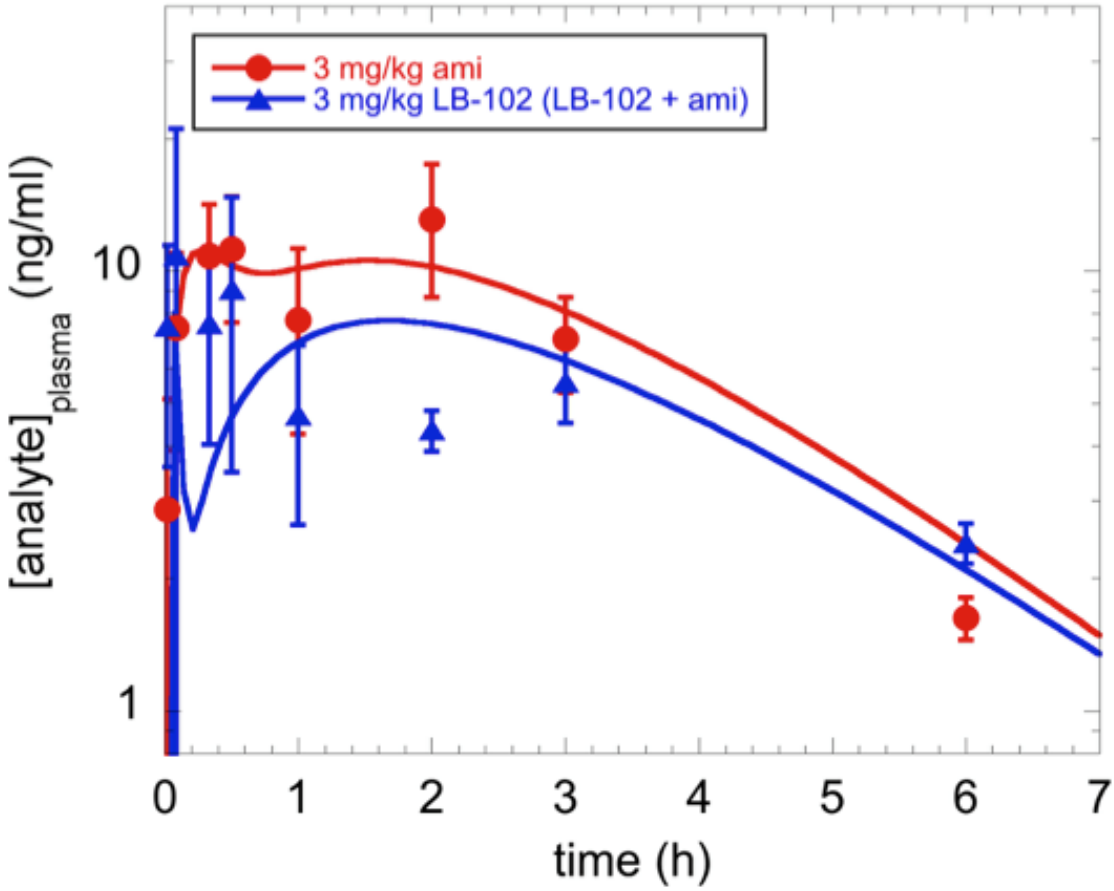

Figure 11: Plasma Concentration vs. Time Curves Following Single Oral Dose at 3 mg/kg of LB-012 (Exposures to Amisulpride Plus LB-102) or Amisulpride (Exposures to Amisulpride)

4.2.2 Metabolism

4.2.2.1 In vitro

The objective of this study was to determine the stability of the test compound, LB-102, in the presence of human, rat, mouse, dog, monkey, rabbit and minipig liver microsomes, and to assess the ability of LB-102 to inhibit Cytochrome P450 (CYP) isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

The results from the microsomal stability assay indicated that LB-102 gave intrinsic clearance values of -3.23, 256, 54.7, 1.15, 14.1, 6.03 and 62.5 µL/min/mg protein in the presence of human, rat, mouse, dog, monkey, rabbit and minipig liver microsomes respectively (Table 7).

Table 7: Microsomal Metabolic Stability Data for LB-102

Compound		Species	Metabolic Stability (Termination = ACN)			
Cyprotex ID	Customer ID		CL_{int} (µL/min/mg protein)	SE CL_{int}	$T_{1/2}$ (min)	n
CY0000211288	LB-102	Human	-3.23	3.24	-429	5
		Rat	256	8.81	5.42	5
		Mouse	54.7	4.22	25.3	5
		Dog	1.15	4.51	1200	5
		Monkey	14.1	4.09	98.5	5
		Rabbit	6.03	2.21	230	5
		Minipig	62.5	5.64	22.2	5

The results of the Cytochrome P450 Inhibition Assay demonstrated that LB-102 did exhibit inhibition beyond the top concentration of 100 µM in the presence of the CYP isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (Midazolam and Testosterone). In the presence of the CYP isoform CYP2C8, LB-102 exhibited slight inhibition, with an IC50 of 75.5 µM (Table 8).

Table 8: Cytochrome P450 Direct Inhibition (IC_{50} Determination) Data Summary

Inhibitor	Test Concentration	CYP3A4 – Midazolam	CYP3A4 – Testosterone	CYP 2C9	CYP 2D6	CYP 1A2	CYP2 C8	CYP 2B6	CYP 2C19
LB-102	0.1–100 µM	>100	>100	>100	75.5	>100	>100	>100	>100
Ketoconazole	0.001-10 µM	0.015	0.020						
Sulphaphenazole	0.001–10 µM			0.075					
Quinidine	0.001-10 µM				0.050				
a-Naphthoflavone	0.0001-10 µM					0.003			
Quercetin	0.01-50 µM						1.394		
Ticlopidine	0.01-50 µM							0.240	0.527

4.3 Toxicology

4.3.1 Single Dose

4.3.1.1 Non-GLP Rat Study

In a non-GLP study, Wistar rats (n = 3/sex/group) were administered single daily doses of 100, 300, 600, and 1200 mg/kg/dose BID approximately 12 hours apart (total daily doses of 200, 600, 1200, and 2400 mg/kg) and the animals were observed for 4 days (MPI Study Number 2591-001, Table 9). Parameters evaluated included clinical signs (daily), body weight (daily), and food consumption (daily).

Table 9: Overview of LB-102 Single Dose Toxicity in Rats and Dogs

Single-Dose Toxicity					Test Article: LB-102		
Species / Strain	**Method of Admin. (Vehicle/ Formulation)**	**Daily Doses[a] (mg/kg)**	**Gender and Number per Group**	**Observed Maximum Nonlethal Dose (mg/kg)**	**Approximate Lethal Dose (mg/kg)**	**Noteworthy Findings**	**Study Number**
Rat / Wistar	Oral (0.5% MC)	200, 600, 1200, 2400	3M, 3F	600	≥1200	**200 mg/kg:** None **600 mg/kg:** None **1200 mg/kg:** Mortality or MS (3M, 3F) **2400 mg/kg:** Mortality or MS (3M, 3F)	2591-001
Dog / Beagle	Oral (0.5% MC)	25, 50, 75, 100	1M, 1F[b]	>100	>100	**25 mg/kg:** None **50 mg/kg:** Transient weight loss **75 mg/kg:** Adverse clinical signs, weight loss and decreased FC **100 mg/kg:** Adverse clinical signs, weight loss and decreased FC MTD = 25 mg/kg	2591-007

F = Female; FC = Food consumption; M = Male; MC = Methylcellulose; MS = Moribund sacrifice; MTD = Maximum tolerated dose.
a – All doses were administered twice per day approximately 12 hours apart.
B – The same male and female dog received all doses with at least a 3-day washout between doses.

On Days 1 or 2 mortality and moribund sacrifice occurred for all animals following single doses of 1200 and 2400 mg/kg. Adverse clinical signs were noted in a few of these animals including decreased activity, ataxia, tremors, recumbency, and/or cold to touch. The only sign in surviving animals was cold to touch in one 600 mg/kg female. There was no effect on body weight or food consumption.

4.3.1.2 Non-GLP Dog Study

In a non-GLP study, one male and one female Beagle dog were administered single daily doses of 25, 50, 12.5, and 37.5 mg/kg/dose BID approximately 12 hours apart (total daily doses of 50, 100, 25 and 75 mg/kg) with at least a 3-day washout between doses (MPI Study Number 2591-007, Table 9). Parameters evaluated included detailed clinical signs (twice daily on dosing days, daily on non-dosing days), body weight (daily), and food consumption (daily).

No adverse effects were noted at 25 mg/kg; this dose was considered to be the maximum tolerated dose (MTD). Doses of ≥50 mg/kg were not tolerated. Transient weight loss and decreased food consumption occurred at 50 mg/kg. At ≥75 mg/kg, more pronounced body weight loss and decreased food consumption were accompanied by clinical signs of toxicity (decreased activity, salivation, trembling, warm to touch, and/or vomitus).

4.3.2 Repeat-Dose

4.3.2.1 Non-GLP Rat Dose-Range Finding Study

In the repeat-dose phase of the range-finding study, Wistar rats (n = 5/sex/group) were administered daily doses of 0 (0.5% MC), 50, 100, and 300 mg/kg/dose BID approximately 12 hours apart (total daily doses of 100 and 200 mg/kg/day) for 14 days (MPI Study Number 2591-001, Table 10). Due to unexpected toxicity and mortality at 300 mg/kg, all animals in this group received the first dose on Day 1 only but were retained for the remainder of the study. Parameters evaluated included clinical signs (daily), body weight (daily), food consumption (daily), clinical pathology (terminal necropsy), toxicokinetics (TK), gross pathology, and organ weights.

Dose formulation analyses revealed a wide range of variability in the preparations as follows: 2.73 to 34.8% of target for the low-dose; -16.2 to 26.7% of target for the mid-dose; and 22.3% of target for the high-dose.

At 300 mg/kg (after the first of the two daily doses on Day 1), three males and one female were moribund sacrificed; a cause of death could not be determined. In addition, two high-dose TK females were found dead or moribund sacrificed on Day 1. Minor effects were generally seen in the animals administered 100 and 200 mg/kg/day. These included: a slight decrease in body weight gain in males at 100 and 200 mg/kg/day; an initial decrease in food consumption in males at 200 mg/kg/day; minor clinical pathology changes (decreased reticulocytes at 100 and 200 mg/kg/day and mildly increased ALT at 200 mg/kg/day); and increases in pituitary weight (males at 100 and 200 mg/kg/day) and prostate weight (males at 100 mg/kg/day).

The MTD was reported to be 200 mg/kg/day.

Table 10: Design of the 14-Day Repeat-Dose Nonpivotal Study in Rats (Study 2591-001)

Species / Strain	Method of Admin. (Vehicle/ Formulation)	Duration of Dosing	Daily Doses (mg/kg[a])	Gender and Number per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rat / Wistar	Oral (0.5% MC)	14 Days	0, 100, 200, 300[b]	5M, 5F	NI	**100 mg/kg/day:** Slight decrease in weight gain (M); increased pituitary and prostate weights (M) **200 mg/kg/day:** Slight decrease in weight gain (M); initial decrease in FC (M); minor clinical pathology changes; increased pituitary weight (M) **300 mg/kg:** MS (3M, 1F) MTD = 200 mg/kg/day	2591-001

F = Female; FC = Food consumption; M = Male; MC = Methylcellulose; MS = Moribund sacrifice; MTD = Maximum tolerated dose; NI = Not identified.
a – All doses were administered twice per day approximately 12 hours apart.
b – Due to unexpected toxicity and mortality, animals in this group received a single dose of 300 mg/kg on Day 1 only.

4.3.2.2 28-Day Repeat-Dose GLP Rat Toxicity Study

In the GLP, 28-day repeat-dose study, Wistar rats (n = 16/sex/group) were administered LB-102 orally at doses of 0 (0.5% MC), 20, 40, and 100 mg/kg/dose BID approximately 12 hours apart (total daily doses of 40, 80, and 200 mg/kg/day) (MPI Study Number 2591-008, Table 11). Ten (10) rats per sex per group were sacrificed on Day 29 and the remaining 6/sex/group were maintained for a 4-week recovery. Parameters evaluated included detailed clinical signs (daily), body weight (daily), food consumption (daily), ophthalmology (pre-test and at terminal necropsy), clinical pathology (pre-test and at terminal and recovery necropsies), TK, gross pathology, organ weights and histopathology (full tissues for the control and high-dose animals at the terminal necropsy). The heart, mammary gland, adrenal glands, ovaries, vagina, uterus with cervix, and prostate gland were determined to be potential target organs and were examined at the terminal necropsy for the low- and mid-dose animals and for all recovery groups.

Table 11: Study Design for a 28-Day Oral Toxicity Study of LB-102 in Rats with a 28-Day Recovery Period

Daily Dose (mg/kg)	**0 (Control)**		**40**		**80**		**200**	
Gender	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number of Animals	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
Toxicokinetics: AUC (ng•hr/mL) (LB-102)								
Day 1	ND	ND	1170	1120	3500	3040	19400	11400
Day 28	ND	ND	1410	1020	7160	4230	37200	27300
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (%[a]) (Day 28)	355.4 g	191.2	-7*	+6	-10**	+8**	-11**	-5
Food Consumption (%[a]) (Days 21 to 28)	13.6 g/rat/day	8.4 g/rat/day	-38	-2	-43	+25	-65**	-101**

- = No noteworthy findings. AUC = Area under the curve; F = Female; M = Male; NA = Not applicable; ND = Not detected.

* $p<0.05$; **$p<0.01$ (Anova and Dunnett's test).

a At the end of dosing or recovery period. For controls, group means are shown. For treated groups, percent differences from controls are shown.

There were no LB-102-related mortalities or adverse test article-related effects on clinical signs, hematology, coagulation, clinical chemistry, urinalysis, or gross pathology. Although minor changes were noted in some of these parameters, they were considered to be non-adverse based on the small magnitude, lack of microscopic correlates, and reversibility.

LB-102-related decreases in body weight were noted in males ≥ 80 mg/kg/day. Body weight gain during the recovery period was similar to or exceeded control values indicating resolution. The effects noted during the treatment period were not considered adverse due to the minor magnitude and the full recovery that was apparent following the 28-day recovery period.

LB-102-related decreases in food consumption were noted in males at ≥ 80 mg/kg/day and females at 200 mg/kg/day. The effects noted during the treatment period were not considered adverse due to the minor magnitude and that full recovery was apparent following the 28-day recovery period.

At the terminal necropsy, several microscopic and organ weight findings were observed which were consistent with elevated levels of prolactin; these are secondary changes. Prolactinemia is a common finding observed with dopamine antagonists, such as LB-102, and these effects in rodents are well documented in the literature. In females at ≥ 40 mg/kg/day, the findings included decreased absolute ovarian weights, hypertrophied corpora lutea (CLs), decreased CLs, interstitial cell hyperplasia and increased number of atretic follicles in the ovaries, mammary gland lobuloalveolar hyperplasia, decreased uterus/cervix weights and vaginal mucification. The ovarian and uterine findings recovered fully, and the mammary changes had decreased in severity at recovery, showing a trend towards reversibility. These findings are specific to rodents when exposed to dopamine antagonists. Furthermore, due to the lack of degenerative findings and the overall similarity to changes normally occurring during pseudo-pregnancy and pregnancy and with other dopamine antagonists, this spectrum of findings was considered to be non-adverse.

Additional findings associated with elevated prolactin levels secondary to the intended pharmacology of LB-102 were noted in males at ≥40 mg/kg/day at the terminal necropsy. These included moderate to marked mammary gland atrophy, which exhibited decreased severity at recovery, demonstrating reversibility, and prostatic inflammation and increased prostate weights. The prostatic inflammation persisted through the end of the recovery period. Prostatic inflammation was of low severity, and the mammary gland atrophy was interpreted as non-harmful; thus, the findings in the males are also considered non-adverse.

LB-102 was well tolerated with no adverse findings in any parameter evaluated. Therefore, the NOAEL was considered to be 200 mg/kg/day (associated with Day 28 AUC values of 37200 and 27300 ng*hr/mL in males and females, respectively).

4.3.2.3 Non-GOP Dog Dose-Range Finding Study

In the 14-day repeat-dose phase of the range-finding study, Beagle dogs (n = 1/sex/group) received oral doses of 0 (0.5% MC), 2.5, 7.5, and 22.5 mg/kg/dose BID approximately 12 hours apart (total daily doses of 5, 15, and 45 mg/kg/day) (MPI Study Number 2591-007, Table 12). Parameters evaluated included detailed clinical signs (daily), body weight (daily), food consumption (daily), clinical pathology (pre-test and at terminal necropsy), toxicokinetics (TK), gross pathology, and organ weights.

Table 12: Design of the 14-Day Repeat-Dose Nonpivotal Study in Rats (Study 2591-007)

Species / Strain	Method of Admin. (Vehicle/ Formulation)	Duration of Dosing	Daily Doses (mg/kg[a])	Gender and Number per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Dog / Beagle	Oral (0.5% MC)	14 Days	0, 5, 15, 45	1M, 1F	NI	**5 mg/kg/day:** None **15 mg/kg/day:** Body weight loss; markedly decreased FC; **45 mg/kg/day:** Body weight loss (requiring food supplementation); markedly decreased FC MTD = 5 mg/kg/day	2591-007

F = Female; FC = Food consumption; M = Male; MC = Methylcellulose; MTD = Maximum tolerated dose; NI = Not identified.
a – All doses were administered twice per day approximately 12 hours apart.

The primary findings were a dose-related decrease in body weight, body weight gain, and food consumption. The effects at the low-dose were minimal whereas more pronounced/marked effects occurred at the mid- and high-doses. The high-dose dogs required food supplementation throughout most of the study based on the degree of weight loss that occurred. None of the other parameters were affected.

The MTD was determined to be 5 mg/kg/day.

4.3.2.4 28-Day Repeat-Dose GLP Toxicity Dog Study

In the GLP, 28-day study, Beagle dogs (n = 5/sex/group) were administered LB-102 orally at dose of 0 (0.5% MC), 0.75, 3 and 7.5 mg/kg/dose BID approximately 12 hours apart (total daily doses of 5, 15 and 45 mg/kg/day) (MPI Study Number 2591-009, Table 13). Three dogs per sex per group were sacrificed on Day 29 and the remaining 2/sex/group were maintained for a 4-week recovery. Parameters evaluated included detailed clinical signs (daily), body weight (daily), food consumption (daily), ophthalmology (pre-test and at terminal necropsy), eletrocardiography (pre-test and at terminal and recovery necropsies), clinical pathology (pre-test and at terminal, and recovery necropsies), TK, gross pathology, organ weights, and histopathology.

Table 13: Study Design for a 28-Day Oral Toxicity Study of LB-102 in Dogs with a 28-Day Recovery Period

Daily Dose (mg/kg)	**0 (Control)**		**1.5**		**6**		**15**	
Gender	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number of Animals	5	5	5	5	5	5	5	5
Toxicokinetics: AUC (ng•hr/mL) (LB-102)								
Day 1	ND	ND	658	749	2810	3110	9080	8670
Day 28	ND	ND	789	911	3670	3590	11800	10700
Noteworthy Findings								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (%[a]) (Day 27)	7.920 kg	6.290 kg	0.0	-1.1	-2.7	+0.5	-8.2	-2.5
Food Consumption (%[a]) (Days 27-28)	234.2 g/dog/day	161.4 g/dog/day	+6.6	-17.0	+8.2	+13.5	-12.0	+12.4

- = No noteworthy findings. AUC = Area under the curve; BPM = Beats per minute; F = Female; M = Male; ND = Not detected.
a – At the end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown.

All animals survived to their scheduled terminations. The only clinical sign was occasional emesis/vomitus in two males at 15 mg/kg/day; this was not considered to be adverse as there was no evidence of an adverse effect on the health status of the animals. An initial, slight, dose-related decrease in weight gain or weight loss occurred on Day 4, but by Day 6 animals were gaining weight at a comparable rate as the controls. Decreased food consumption was noted during Week 1 for males at ≥ 6 mg/kg/day. Decreased food consumption generally persisted until Week 3 or through Week 4 for males at 6 and 15 mg/kg/day, respectively. This finding was considered LB-102-related but was not considered adverse due to the minor magnitude and the lack of correlated test article effects on body weight or evidence of poor health in the animals.

LB-102 was associated with a dose-related increase in the heart rate and shortening of the RR interval at 6 and 15 mg/kg/day on Day 27. The increase in the heart rate was accompanied by a single instance of sinus tachycardia (a normal variant in dogs) for 1 of 5 high-dose males on Day 1 only and a physiologically appropriate shortening of the QT interval. There were no LB-102-related effects on the PR or QTc intervals or QRS duration. These findings were not considered to be adverse as the dogs were still in sinus rhythm and there was a lack of correlating

clinical/veterinary observations, clinical pathology findings, or histopathological findings. The quantitative ECG changes were not evident on the recovery ECGs indicating that these findings were reversible.

There were no effects on hematology, coagulation, or urinalysis parameters and only a minimal to mild increase in mean total cholesterol in both sexes at ≥ 6 mg/kg/day on Day 28. Total cholesterol concentrations had resolved following a 28-day recovery period. This finding was not considered adverse due to the minor magnitude and lack of histopathological correlates.

There were no test article-related effects on gross pathology, organ weights, or histopathology.

Based on these data, the NOAEL was considered to be 15 mg/kg/day (associated with Day 28, AUC values of 11800 and 10700 ng•hr/mL in males and females, respectively).

4.3.3 Carcinogenicity Studies

Studies to assess the carcinogenic potential of LB-102 will not be conducted with the IND enabling studies.

4.3.4 Reproductive Toxicity

Studies to assess the reproductive and developmental toxicity potential of LB-102 will not be conducted with the IND enabling studies.

4.3.5 Genotoxicity

4.3.5.1 Bacterial Mutagenicity

In vitro GLP- and ICH-compliant genetic toxicity studies have been performed on LB-102.

In the Ames assay, S. typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2uvrA were exposed to LB-102 at concentrations of 25 to 5000 µg/plate with and without metabolic activation (Charles River Study 01250001). The concentrations were selected after performing a range-finding assay.

Dose formulation analyses of the low, a mid and the high concentrations revealed values of 82.8, 96.5 and 97.2% of target, respectively. The back-up sample for the low concentration was analyzed and confirmed the low value. There was not a negative impact because the other two concentrations were acceptable, and the study was negative. Homogeneity samples confirmed that the dosing materials were homogenous.

LB-102 did not increase the number of revertant colonies at any concentration in any strain with or without metabolic activation and was concluded to be was negative for inducing mutagenicity in this assay. The positive controls produced the anticipated response.

4.3.5.2 In Vitro Micronucleus

In the *in vitro* micronucleus assay, TK6 cells were incubated with LB-102 at concentrations ranging from 12 to 384 µg/mL with and without metabolic activation (Charles River Study 01250003). Cells were incubated with drug for 4 hours with and without metabolic activation and for 27 hours without metabolic activation. Due to the lack of toxicity, the three highest concentrations were evaluated for micronuclei (96, 192, 384 µg/mL).

No increase in micronuclei was observed at any dose with or without metabolic activation. The positive controls produced the anticipated response. LB-102 was concluded to be negative for clastogenic and aneugenic activity in this assay.

5. EFFECTS IN HUMANS

5.1 Introduction

LB-102 currently has no previous human experience.

5.2 Pharmacokinetics and Product Metabolism in Humans

Not studied.

5.2.1 Pharmacokinetics

Not studied.

5.2.2 Bioavailability

Not studied.

5.2.3 Population Subgroups

Not studied.

5.2.4 Interactions

Not studied.

5.2.5 Other Pharmacokinetic Data

Not studied.

5.3 Safety and Efficacy

Not studied.

5.3.1 Efficacy Results in Clinical Studies

Not studied.

5.3.2 Safety Results in Clinical Studies

Not studied.

6. MARKETING EXPERIENCE

Not applicable.

7. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

Comprehensive GLP-compliant 28-day oral repeat-dose toxicity studies have been conducted on LB-102 in rats and dogs. LB-102 was split into 2 doses for rats (40, 80, or 200 mg/kg/day) and dogs (1.5, 6, or 15 mg/kg/day). For both species, LB-102 was administered using the intended clinical treatment regimen which included oral dosing twice per day approximately 12 hours apart. In rats, doses of 0, 20, 40 and 100 mg/kg/dose (0, 40, 80, and 200 mg/kg/day) and in dogs doses of 0, 0.75, 3 and 7.5 mg/kg/dose (0, 1.5, 6 and 15 mg/kg/day) were administered. For both species, a 1-month post-dose recovery period occurred following 28 days of treatment. LB-102-related effects in rats were associated with elevated levels of prolactin, which are presumed to occur with LB-102 based on its mechanism of action as a dopamine antagonist. These changes are unique to rodents, have been observed with other dopamine antagonists, were noted at all doses, and included hypertrophied corpora lutea (CLs), decreased CLs, interstitial cell hyperplasia and increased number of atretic follicles in the ovaries, mammary gland lobuloalveolar hyperplasia, and vaginal mucification in females and mammary gland atrophy and prostatic inflammation in males. Tissue changes either completely resolved or showed a trend to resolution during the recovery period. Given the species-specific nature of the response, the NOAEL was determined to be 200 mg/kg/day, the highest dose administered. In dogs, the main finding was an increase in heart rate at 6 and 15 mg/kg/day. The dogs remained in sinus rhythm and, due to the lack of correlating clinical/veterinary observations, clinical pathology findings, or histopathological findings, this change was not considered to be adverse. Furthermore, no cardiovascular alterations were noted after the recovery period. The NOAEL was determined to be 15 mg/kg/day, the highest dose administered.

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.

LB-102 currently has no previous human experience but was designed to have similar biological activity to amisulpride (see Section 4). An analysis of the clinical efficacy and safety of amisulpride for the treatment of schizophrenia are presented below.

Leucht and coworkers published a meta-analysis (Leucht et al., 2013) of 212 clinical studies, including 43,000 subjects, that compared the efficacy and adverse event profiles of 15 widely used antipsychotics. Drugs were rated using a SUCRA ranking (Surface Under the Cumulative Ranking), a measure that compared the efficacy of a drug to an intervention that was always the best (i.e. amisulpride is 92% as effective as Clozapine and 20% more effective than risperidone).

Each of the top 15 drugs (and a placebo), are presented in Figure 14. It is notable that amisulpride scored second highest to clozapine in efficacy using this measure.

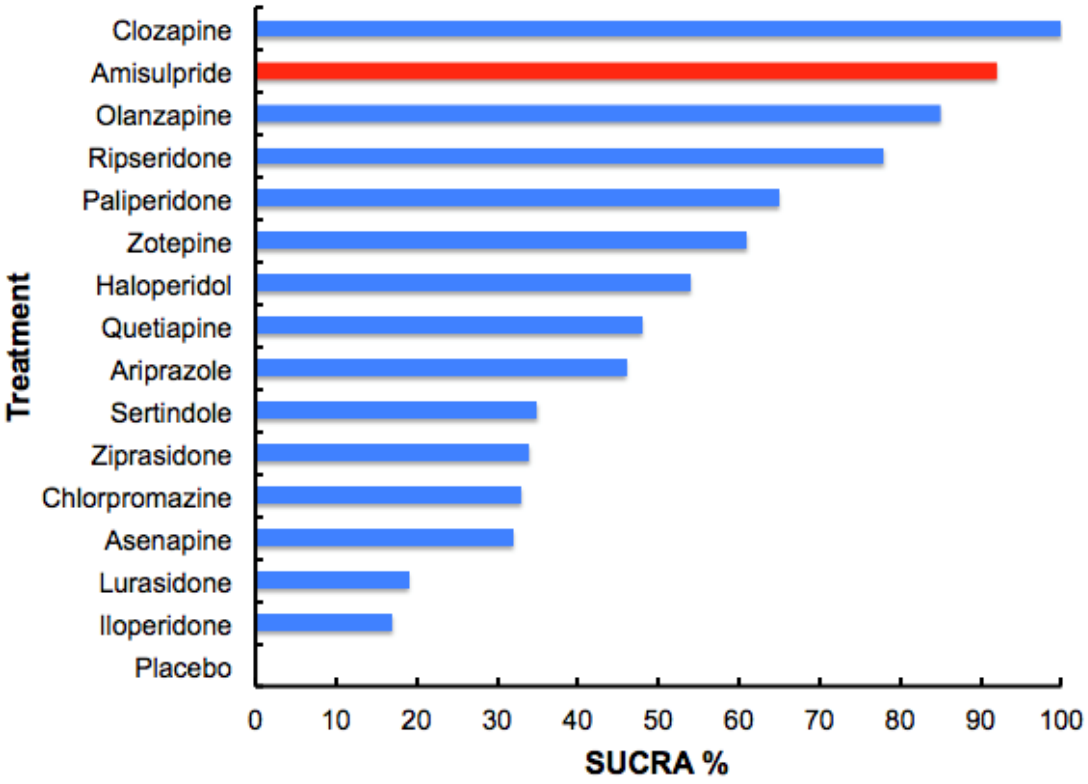

Figure 12: SUCRA Scores Comparing Efficacy of 15 Antipsychotic Drugs and Placebo

Source: Leucht et al., 2013

Of the 15 drugs evaluated, amisulpride had the lowest rate of discontinuation, compared to placebo, for any reason (Leucht et al., 2013; Figure 15).

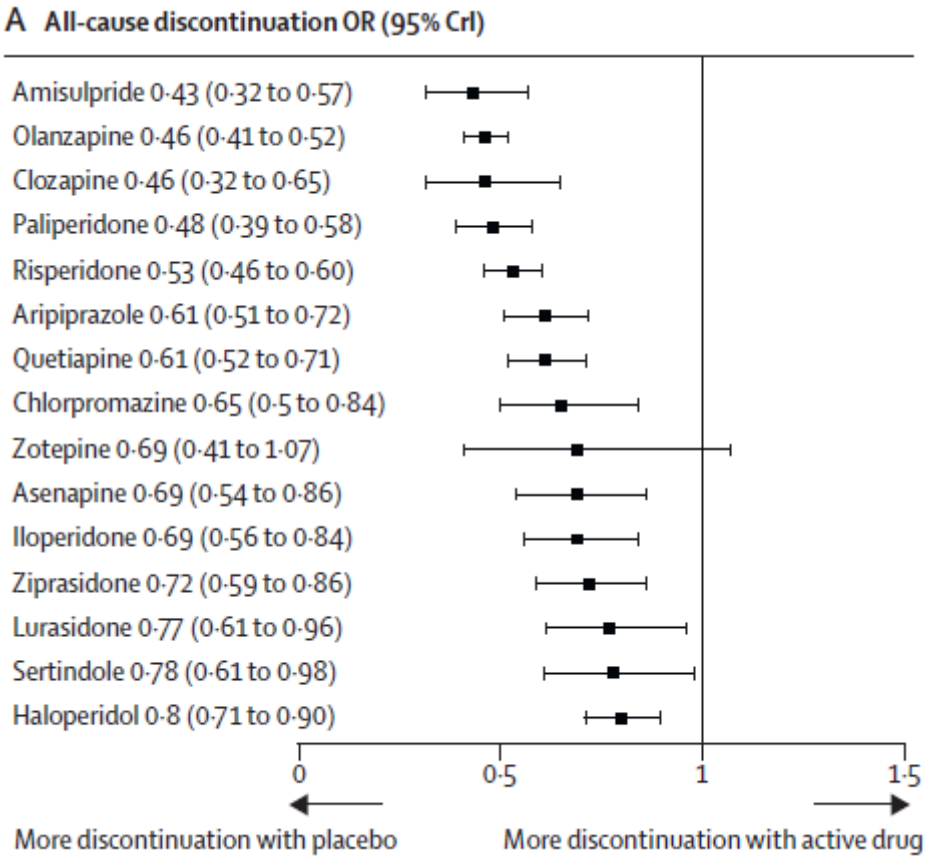

Figure 13: Odds Ratio of Discontinuation for any Reason, Compared to Placebo

Source: Leucht et al., 2013

The EUFEST clinical study enrolled 498 first episode schizophrenia patients randomized to receive haloperidol, amisulpride, olanzapine, quetiapine, or ziprasidone for one year (Kahn et al., 2008). One year discontinuation rates for this study, the primary endpoint for this study and an important measure of efficacy, are presented in Figure 16. Overall, amisulpride compared favorably to all drugs and only Olanzapine had a lower discontinuation rate.

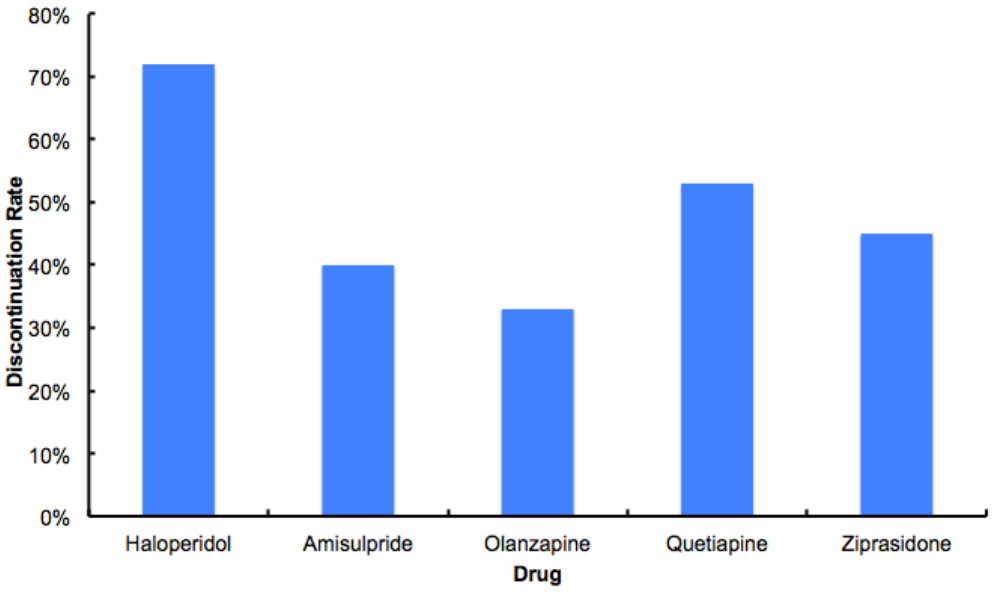

Figure 14: Discontinuation Rates at One Year for Antipsychotics in the EUFEST Study

Source: Kahn et al., 2008

Importantly, as depicted in Figure 17, amisulpride and olanzapine also had the lowest rates of discontinuation for lack of efficacy.

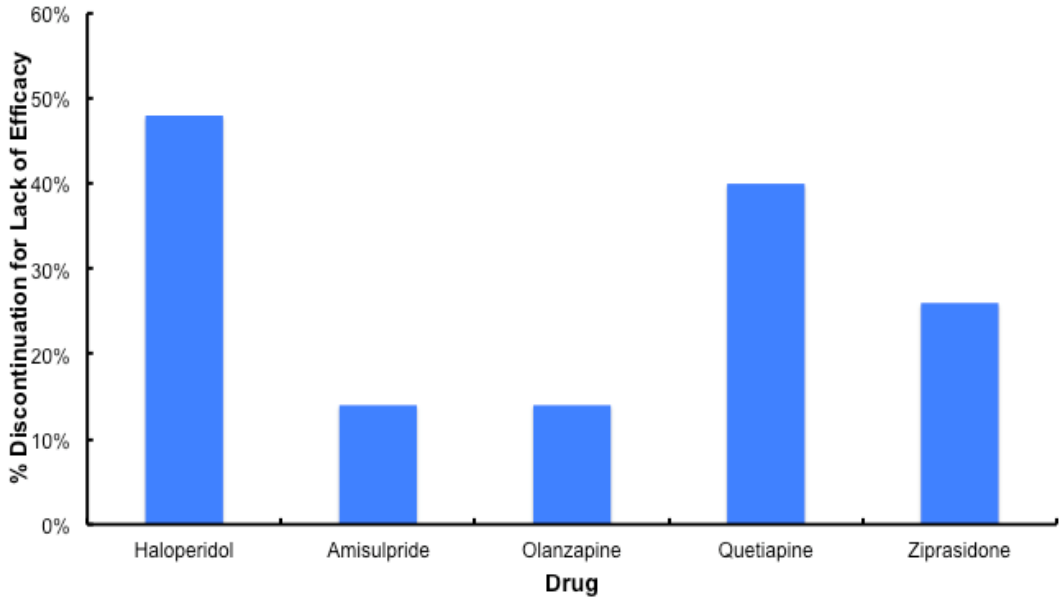

Figure 15: Discontinuation Rates at One Year Due to Lack of Efficacy for Antipsychotics in the EUFEST Study

Source: Kahn et al., 2008

Collectively the data from the EUFEST study shows that amisulpride is an effective and safe schizophrenia treatment.

The Schizophrenia Outpatients Health Outcomes (SOHO) study was an open label trial that included recovery and remission data on 6,642 patients with a maximum follow up period of 36 months (Novick et al., 2009). Patients entered the study if they had been recently switched to Olanzapine or another antipsychotic. The primary aim of this study was to compare the efficacy of Olanzapine to other available antipsychotics and, accordingly, the Olanzapine arm was intentionally larger than the other treatment arms. The primary treatments used by clinicians other than olanzapine (n=2,501) at the study endpoint included risperidone (n=966), amisulpride (n=208), quetiapine (n=292), and clozapine (n=272). Amisulpride was better on a number of measures compared to the other antipsychotics as depicted in Figure 18.

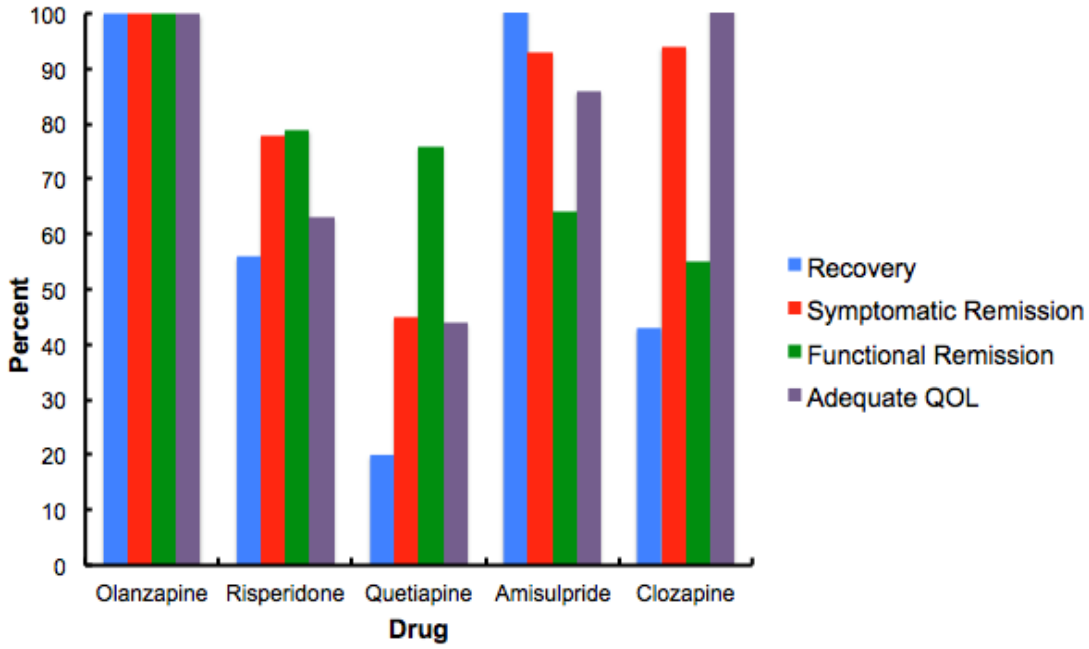

Figure 16: Percent of Patients in SOHO Study Achieving Various Endpoints

Source: Novick et al., 2009

Other more traditional drug trials have compared amisulpride to atypical antipsychotics such as risperidone or olanzapine. Sechter and coworkers (2002) conducted a 6 month, randomized, double-blind trial comparing risperidone (n=158) to amisulpride (n=152) on measures of efficacy and safety. Amisulpride was shown to be non-inferior to risperidone on the change in PANSS as shown in Figure 19. There were no significant differences between amisulpride and risperidone on safety measures in this study.

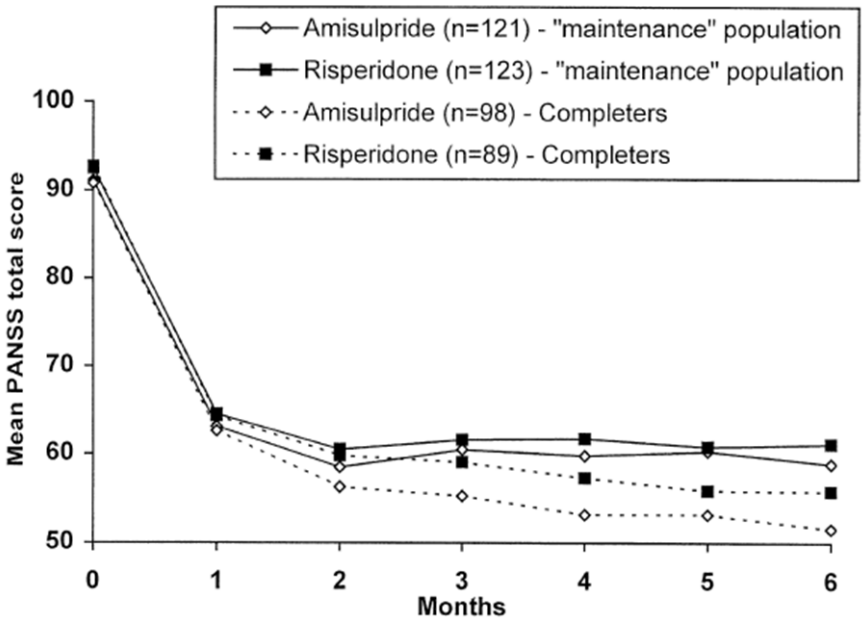

Figure 17: PANSS as a Function of Time

Source: Sechter et al., 2002.

In 2002, Martin and coworkers (2002) published results of a randomized, double-blind, head-to-head study comparing amisulpride (n=189) to olanzapine (n=188). The primary outcome of this study was change in BPRS with other outcomes reported including change in PANSS, body weight, and adverse events. There were no differences between amisulpride and olanzapine in the change in BPRS score at any time point (Figure 20).

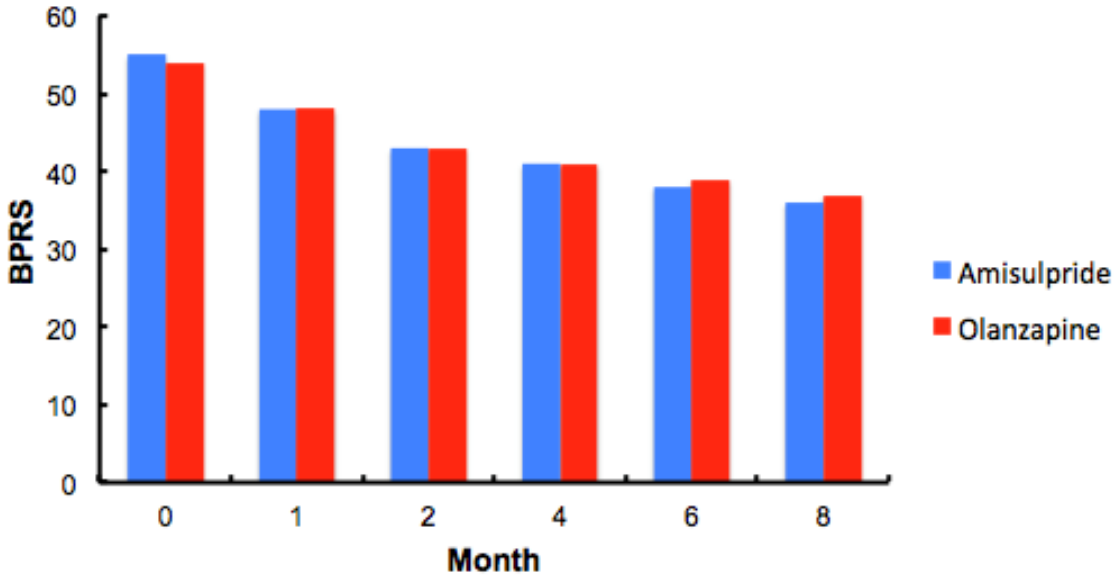

Figure 18: Comparison of BPRS After Treatment with Amisulpride or Olanzapine

Source: Martin et al., 2002

PANSS scores decreased by a mean of 39% in the amisulpride arm and 38% in the olanzapine arm. There were 8 withdrawals due to AEs in amisulpride treated patients compared to 7 in olanzapine treated patients. Olanzapine produced greater weight gain than observed in the amisulpride arm (Figure 21).

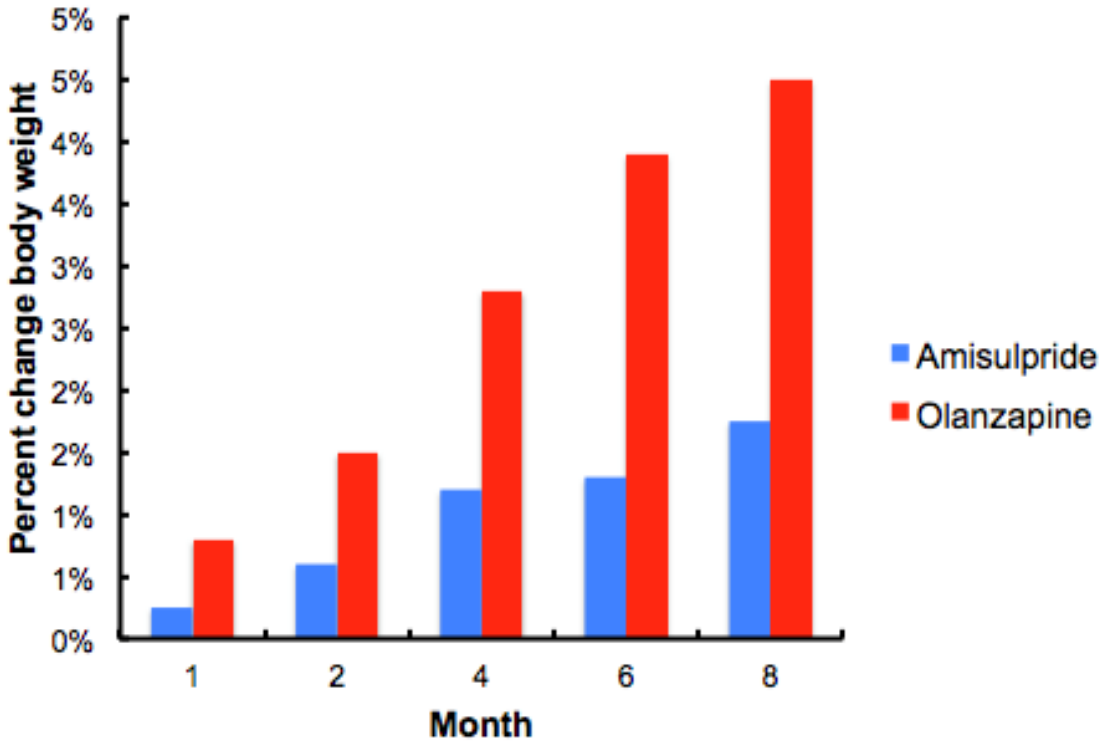

Figure 19: Percent Weight Gain by Month for Amisulpride and Olanzapine

Source: Martin et al., 2002

Amisulpride has been demonstrated to have a significant impact on the negative symptoms of schizophrenia which include impaired social functioning, lack of spontaneous speech, loss of interest in pleasurable activities, and cognitive deficits. Danion and coworkers conducted a 12 week study on low doses of amisulpride 50 mg/day (n = 84), 100 mg/day (n = 75) vs. placebo (n = 83) following a 4 week washout period in patients who were diagnosed with a schizophrenia subtype that presents primarily with negative symptoms (Danion et al., 1999). The Scale for the Assessment of Negative Symptoms (SANS) was used as the primary rating instrument in this study. As shown, patients treated with either dose showed substantial improvements in negative symptoms compared to placebo (Figure 22).

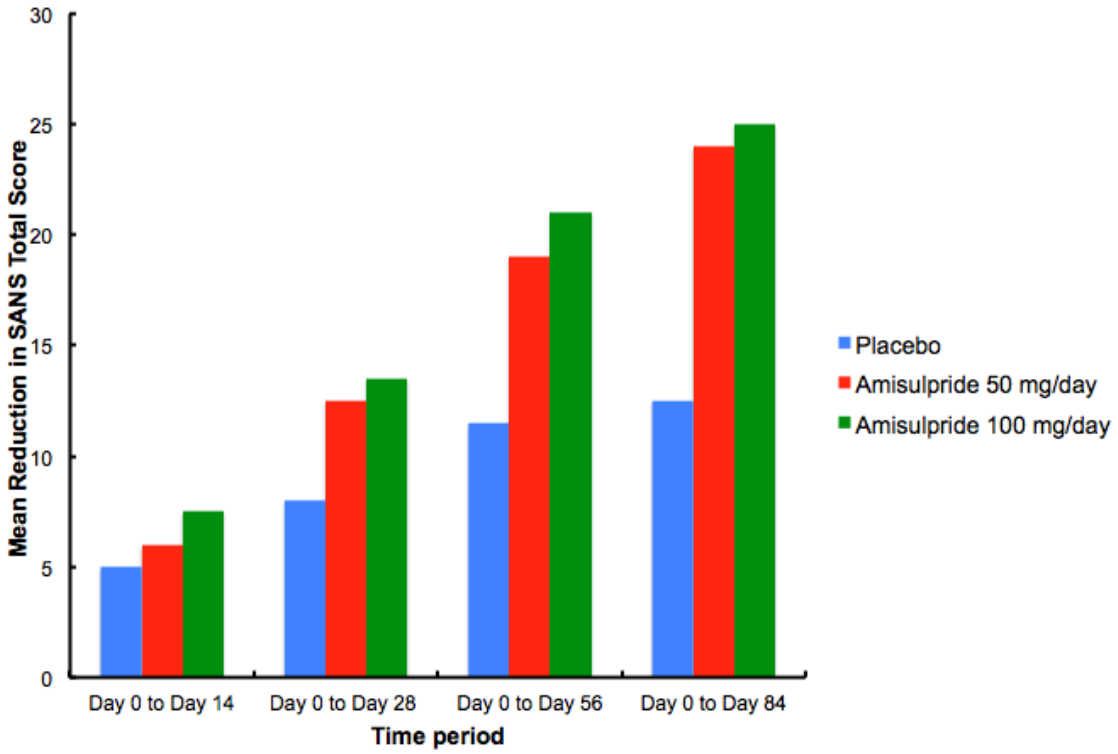

Figure 20: Changes in SANS Scores from Baseline After Treatment with Amisulpride Compared to Placebo

Source: Danion et al., 1999

In this study, amisulpride was statistically superior to placebo in all secondary measures, including: SAPS total score, BPRS, and Montgomery-Asperg Depression rating total score. These data suggest that amisulpride, at low doses, facilitates dopaminergic transmission by acting as either a partial dopamine agonist or presynaptic blocker of inhibitory dopamine autoreceptors in combination with 5-HT_7 antagonism, which may fill an unmet need in the treatment of schizophrenia by treating negative symptoms and improving depression.

In a study published in 1999, 228 patients with acute exacerbated schizophrenia were randomized to receive either amisulpride or risperidone (Peuskens et al., 1999). After 2 months patients in the amisulpride group had their BPRS scores improve by 38 points, similar to the 40-point improvement in the risperidone group.

A 3-month double-blind study conducted by Smeraldi compared fluoxetine (Prozac; 20 mg/day) to amisulpride (50 mg/day) in 281 patients with dysthymia or major depressive disorder in partial remission (Smeraldi, 1998). The primary rating instrument used in this study was the Montgomery Asberg Depression Rating Scale (MADRS). In the MADRS rating, amisulpride and fluoxetine were statistically indistinguishable.

The following adverse effects have been commonly observed in ≥5% of patients treated with amisulpride in controlled clinical trials (n=921): EPS disorders, insomnia, anxiety, agitation, and weight increase (Amisulpride PI, 2019).

Amisulpride is contraindicated for hypersensitivity to the active substance or to any of its excipients (maize starch, lactose monohydrate, methylcellulose 400cP, colloidal silica anhydrous, magnesium stearate), concomitant prolactin-dependent tumors (e.g., pituitary gland prolactinomas or breast cancer), pheochromocytoma, children before the onset of puberty, lactation, combination with levodopa, and combination with the following medication which could induce torsades de pointes: class Ia antiarrhythmic agents such as quinidine, disopyramide, procainamide, Class III antiarrhythmic agents such as amiodarone, sotalol, and other medicines such as bepidril, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin. Precautions should be taken when combining amisulpride with medications that can enhance torsades de pointes or could prolong QT interval, CNS depressants, antihypertensive drugs, and dopamine agonists (Amisulpride PI, 2019).

Special warnings and precautions to be aware of when administering amisulpride are the potential development of Neuroleptic Malignant Syndrome and hyperglycemia. Caution should be exercised when administering amisulpride to patients with renal insufficiency, a history of epilepsy, a history of QT prolongation or known cardiovascular condition, risk factors for stroke, dementia, risk factors for venous thromboembolism, a history or family history of breast cancer, being treated with antidopaminergic agents, or the elderly. Concomitant antipsychotics should be avoided. Treatment must be stopped if a patient is diagnosed with a pituitary tumor. Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including amisulpride. Unexplained infections or fever may be evidence of blood dyscrasia and requires immediate hematological investigation. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine (Amisulpride PI, 2019).

8. REFERENCE SAFETY INFORMATION (RSI)

The RSI provides a list of ADRs considered expected for the purposes of expedited reporting to Regulatory Authorities, i.e., to determine whether certain events would be deemed a Suspected Unexpected Serious Adverse Reaction (SUSAR) should a Serious Adverse Reaction (**SAR**) occur.

For the purposes of regulatory reporting, there are no events expected, any SAR would therefore be considered as SUSARs.

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