Establishing a PK-PD-E Relationship for Clinical Candidate LB-102, a Next-Generation Benzamide Antipsychotic

Mark S. Hixon Consulting LLC
Pragmatic approaches to drug discovery challenges

Mark S. Hixon Ph.D.*, Andrew R. Vaino Ph.D., Zachary Prensky, and Vincent Grattan RPh.
LB Pharmaceuticals Inc., 575 Madison Ave., New York, NY 10022, USA

Background:

A retrospective analysis of Phase II clinical outcomes reveals less than a 30% success rate.[1] Probability of success was highest for those new molecular entities where investigators had high confidence in translation of drug exposure and pharmacology and of testing the mechanism of action. LB-102 is an *N*-methylated analog of amisulpride (an antipsychotic benzamide marketed worldwide though not in the U.S.). As a part of LB-102 development and in preparation and for clinical trials, a pharmacokinetic-pharmacodynamic-efficacy (PK-PD-E) relationship was established to enhance the clinical probability of success.

Methods:

PK-PD-E data were sourced from LB Pharmaceuticals-directed studies and literature reports on rodent amisulpride dose-$D_{2/3}$ receptor occupancy-efficacy studies. In addition, translation of the model to human relevance was accomplished by the retro-analysis of several clinical reports of amisulpride including a dopamine $D_{2/3}$ occupancy study. Rodent PK studies were directed by LB Pharmaceuticals. D_2, D_3 and $5HT_7$ receptor occupancy determinations were based on radiolabeled probe displacement studies. Rodent efficacy studies included behavioral models Apomorophine Induced Climbing [AIC], LocoMotor Activity [LMA], and Novel Object Recognition [NOR].

Results:

In rodents, robust responses were observed with oral doses of 30 mg/kg. LB-102 produces plasma level Cmax and exposures of active agents comparable to amisulpride. N-demethylation of LB-102 (generating amisulpride) is the dominate elimination pathway. Receptor occupancy and behavioral responses are delayed relative to plasma concentrations and persist much longer than predicted by plasma levels. Direct measurement of rodent brain concentrations indicates that blood brain barrier permeation is rate limiting and that brain concentrations lag behind and then persist beyond observed plasma concentrations. As well, $D_{2/3}$ occupancy and behavioral responses appear to be in rapid equilibrium with brain drug concentrations. As modeled in rodents, a 30 mg/kg dose of LB-102 achieves D_2 occupancy of 74% at peak occupancy and provides for 16 out of 24 hours of D_2 occupancy when analyzed as the Area Under the Response Curve (AURC). The human equivalent dose is 400 mg.

Conclusion:

LB-102 has affinity for $D_{2/3}$ receptors comparable to amisulpride and in rodent behavioral models comparable-to-superior efficacy. In rodents, a robust LB-102 PK-PD-E model has been established and by use of published and in-house amisulpride studies, translated in preparation for clinical trials.

LB Pharmaceuticals, Inc. directed these studies.

Disclosures

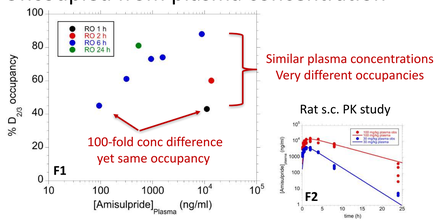
Dr. Vaino, Mr. Grattan & Mr. Prensky are employees of LB Pharmaceuticals
Dr. Hixon as been compensated by LB Pharmaceuticals in his capacity as a consultant

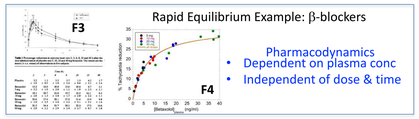
Citations

1) *Drug Discovery Today* **2012**, *17*, 419-424
2) Meta analysis of *Schizophrenia Research* **2008**, *105*, 224-235 and in-house directed PK studies; meta analysis of beta blockers: *Br. J. clin, Pharmac.* **1981**, *11*, 171-180, *Life Science Journal* **2007**, *4*, 30-33
3) Meta analysis of *Hum Psychopharmacol Clin Exp* **2002**; *17*, 1-13 and *Journal of Nuclear Medicine* **2005**, *46*, 1028-1033

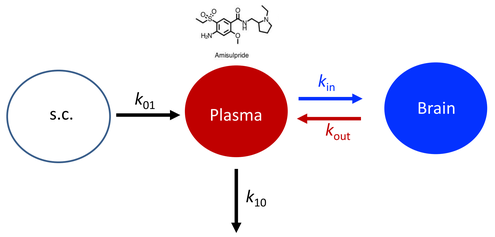
Building an Amisulpride PK-RO-E model from rat studies[2]

Efficacy & Receptor Occupancy are Uncoupled from plasma concentration



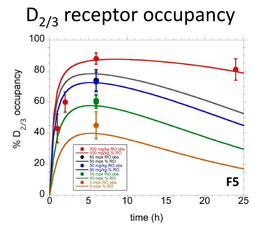


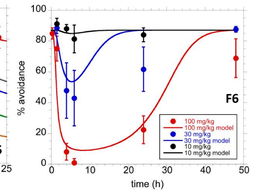
Proposed CNS PK model



Model: slow exchange into the CNS produces a time offset between plasma concentration, receptor occupancy, and efficacy

Modeled results v observations





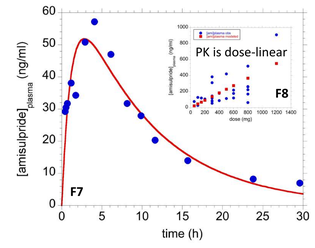
Optimized parameters

k_{01} = 0.138 h^{-1} k_{in} = 0.00522 h^{-1}
k_{10} = 0.31 h^{-1} k_{out} = 0.12 h^{-1}
Vd = 12.5 L/kg
EC_{50} = 10 ng/g Hill = 0.60

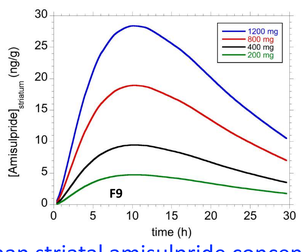
Slow exchange of amisulpride between plasma and the CNS can explain the observed delay and then persistence of receptor occupancy & efficacy v plasma concentration.

Translating the rodent PK-PD-E model to humans[3]

Amisulpride Human PK (50 mg p.o.)

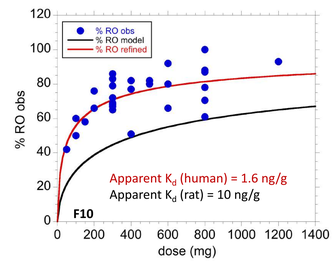


Modeled human striatal PK



Human striatal amisulpride concentrations are calculated from human plasma PK and rodent CNS partition rates.

Modeled and observed human $D_{2/3}$ % occupancy at 12 h post-dose

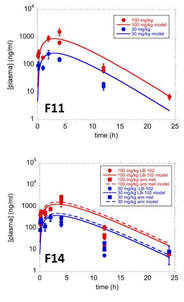


- $D_{2/3}$ % occupancy is calculated from striatal amisulpride concentration
- Rodent apparent K_d under-predicts observed human RO though Hill slope is consistent between species.
- Adjusting the human K_d to 1.6 ng/g produces excellent agreement

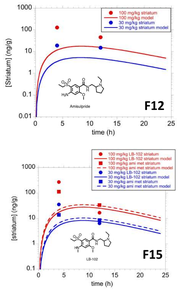
Translational bridge for LB-102

Amisulpride & LB-102
Rat PK-$D_{2/3}$ RO studies

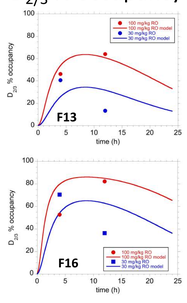
Plasma PK

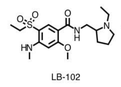


Striatal PK



$D_{2/3}$ % occupancy





- LB Pharma-directed rat PK-RO studies produced results generally consistent with previous reports.
- CNS PK model provided reasonable fits to the current amisulpride study data.
- LB-102 has a PK-RO relationship comparable to amisulpride

Translation to the Clinic

LB-102 provides efficacy in rodent behavioral studies at exposures where amisulpride has clinical efficacy. Clinical dose selection will be guided by these animal efficacy and receptor occupancy studies and amisupride human dosing.