Building a translational bridge from animals to man for clinical candidate LB-102, a next-generation benzamide antipsychotic (P.101)

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Introduction:

Amisulpride is one of the most effective antipsychotics on the market outside of the USA [1]. Despite clear efficacy from clinical trials it has never been submitted as an antipsychotic for regulatory approval in the USA. LB-102 is an *N*-methylated analogue of amisulpride being developed as a potential treatment for schizophrenia in the US market and elsewhere. A retrospective analysis of Phase II clinical outcomes reveals less than a 30% success rate [2]: new molecular entities in which investigators had high confidence in translation of drug exposure and pharmacology had the highest probability of success. As a part of LB-102 development, and in preparation for clinical trials, a pharmacokinetic-pharmacodynamic-efficacy (PK-PD-E) relationship was established to improve clinical probability of success.

Methods:

PK-PD-E data were sourced from studies of LB-102 and amisulpride in dogs and rodents, as well as literature reports on rodent amisulpride dose-$D_{2/3}$ receptor occupancy-efficacy studies [3]. 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 [4-5]. 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 behavioral 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. Plasma levels of LB-102 in dogs followed were comparable. A metanalysis of published amisulpride studies reveals thtat receptor occupancy and behavioral responses are delayed relative to plasma drug 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). Results of a rat PK - $D_{2/3}$ receptor occupancy studies with amisulpride and LB-102 were generally consistent with published reports, i.e., with confirmation of brain permeation as a rate-limiting step. Meta-analysis of human $D_{2/3}$ occupancy studies indicated that rate constants for permeation of the human brain (k_{in} and k_{out}) were comparable to the rat but that amisulpride affinity for the human $D_{2/3}$ receptors is approximately 6-fold stronger than the rat.

Conclusion:

In both in vitro and in vivo studies LB-102 displayed 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.

References

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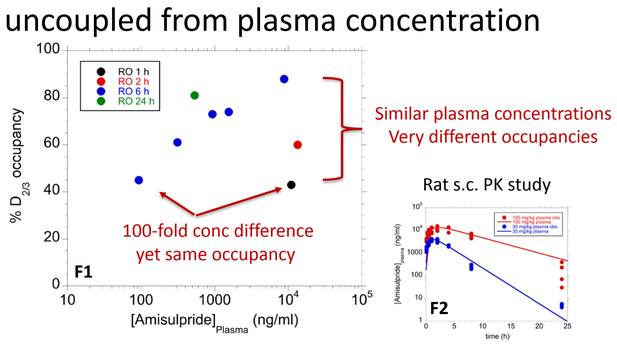
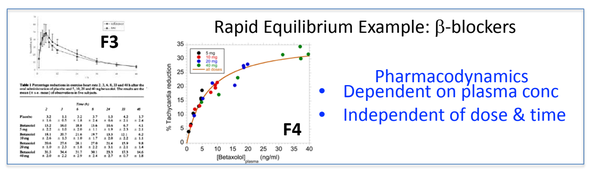
Conflict of interest:

Disclosure statement: VG and ZP are members of the Board of Directors and shareholders of LB Pharmaceuticals. ZP and AV are employees and shareholders of LB Pharmaceuticals. MH is a consultant to and a shareholder of LB Pharmaceuticals.

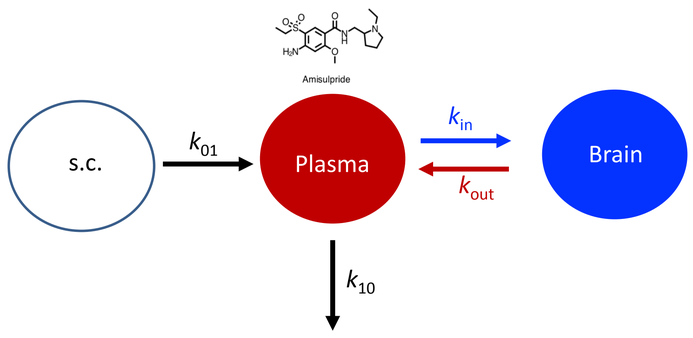
Building an Amisulpride PK-RO-E model from rat studies[2]

Efficacy & Receptor Occupancy are uncoupled from plasma concentration



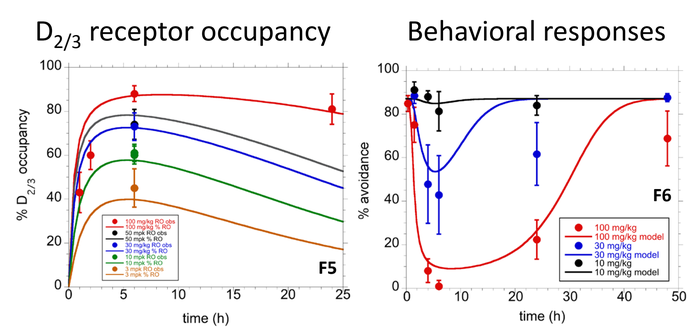


Proposed CNS PK model



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

Modeled results v observations



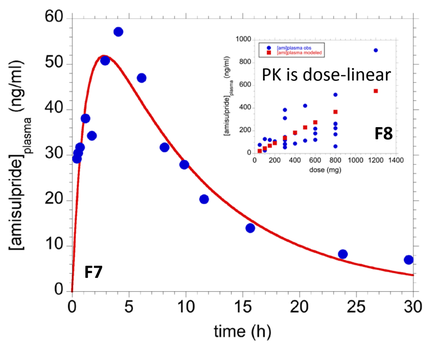
Optimized parameters

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

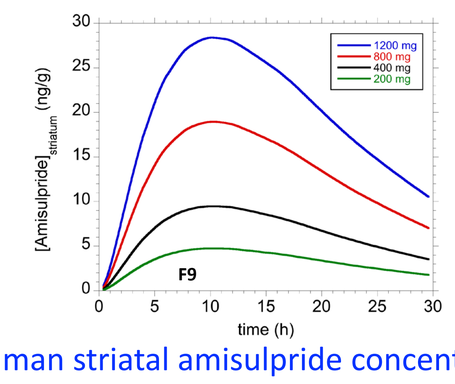
Slow exchange of amisulpride between plasma and the CNS can explain the observed delay and then persistence of receptor occupancy & efficacy v plasma concentration.

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

Amisulpride Human PK (50 mg p.o.)

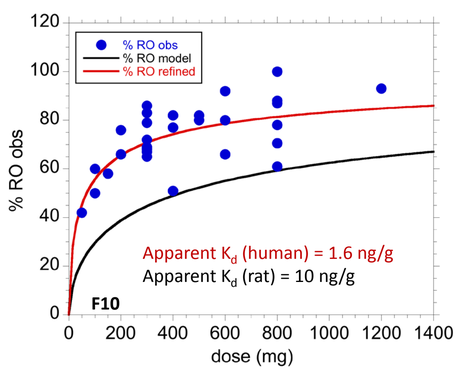


Modeled human striatal PK



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

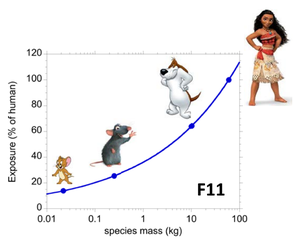
Modeled and observed human $D_{2/3}$ % occupancy at 12 h post-dose



- $D_{2/3}$ % 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

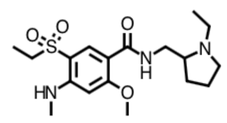
Translational bridge for LB-102

Allometry & Detrick transforms

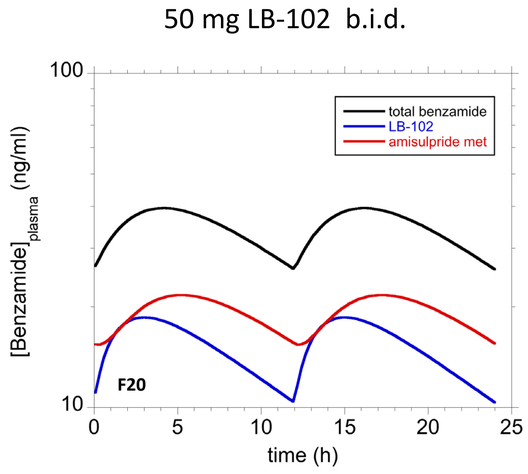


Predicting the PK of one species based on the PK of a second species

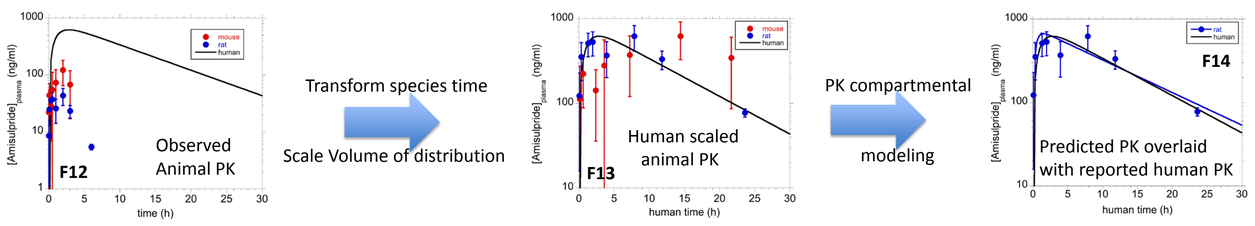
$$time_{species\ 2} = time_{specie\ 1}\left(\frac{Mass_{species\ 2}}{Mass_{species\ 1}}\right)^{0.25}$$



Predicted Human PK of 50 mg LB-102 b.i.d.

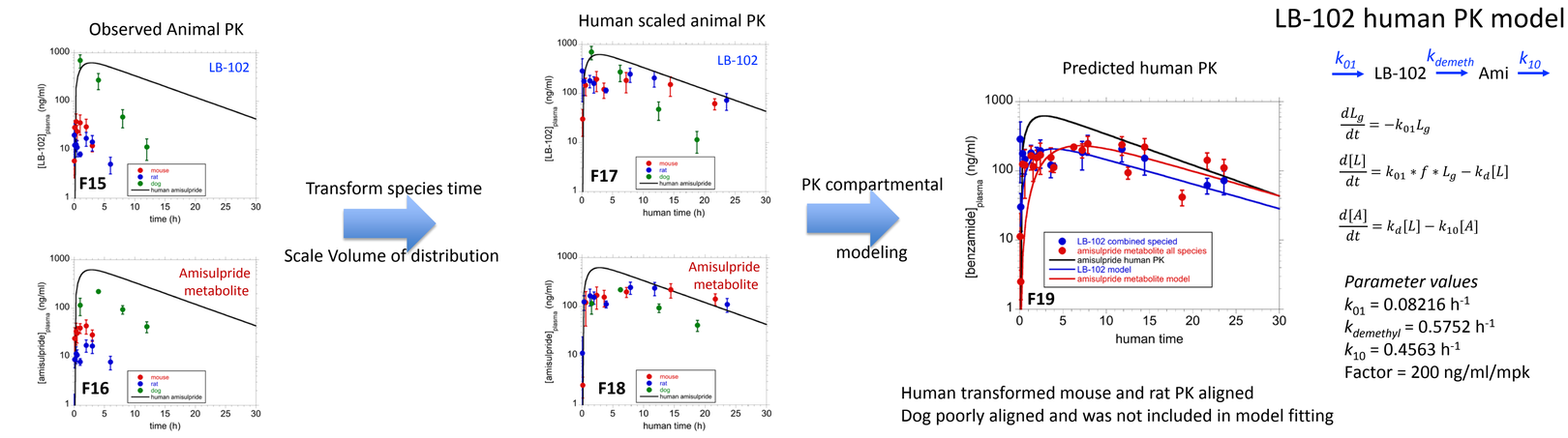


Method validation: Predicting amisulpride's human PK based on rodent PK



Rat transformed PK was predictive of reported human amisulpiride PK

Predicting the human PK of LB-102



Human transformed mouse and rat PK aligned
Dog poorly aligned and was not included in model fitting

LB-102 human PK model

k_{01} → LB-102 → (with k_{demeth}) Ami → (k_{10})

$$\frac{dL_g}{dt} = -k_{01}L_g$$

$$\frac{d[L]}{dt} = k_{01} * f * L_g - k_d[L]$$

$$\frac{d[A]}{dt} = k_d[L] - k_{10}[A]$$

Parameter values
k_{01} = 0.08216 h^{-1}
$k_{demethyl}$ = 0.5752 h^{-1}
k_{10} = 0.4563 h^{-1}
Factor = 200 ng/ml/mpk

Predicted $D_{2/3}$ occupancies v dose

Dose (mg)	$[Benzamide]_{steady\ state}$ (ng/ml)	$D_{2/3}$ (% occupancy)
50	54	45
100	109	62
200	220	76
400	440	87
800	880	93