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 approved as an antipsychotic for regulatory approval in the USA. LB-102 is an optimized analogs of amisulpride being developed as a potential treatment for schizophrenia in the US market and elsewhere. A retrospective analysis of Phase II clinical volumes revealed that a 30% success rate (30% new molecular entities) in which investigators had high confidence in translation of drug exposure and pharmacokinetics had the highest probability of success. As a part of LB-102 development, and in preparation for clinical trials, a pharmacometric-pharmacodynamic-occupancy (PK-PD-RO) relationship was established to improve clinical probability of success.

Methods:
PK-PD-RO data were sourced from studies of LB-102 and amisulpride in dogs and rodents, as well as literature reports on rodent amisulpride-dose-CO2, receptor occupancy efficacy studies [2]. In rodents, translation of the model to human reference was accomplished by the retro-analysis of several clinical reports of amisulpride including a dopamine D2/3 occupancy study [4-5]. D2, D3 and 5HT7 receptor occupancy determinations were based on radiolabeled probe displacement studies. Rodent efficacy studies included behavioral models Apomorphine 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. In rodents, 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.

Conclusion:
In both in vivo and in vitro studies LB-102 displayed efficacy for D2, D3 receptors comparable to amisulpride, and in rodent behavioral models comparable-to-superior efficacy. In rodents, a robust LB-102 PK-PD-RO-E model has been established and by use of published and in-house amisulpride studies, translated in preparation for clinical trials.

References:

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. M is a consultant to and a shareholder of LB Pharmaceuticals.