Pre-clinical evaluation of two novel benzamides LB–102 and 103 for the treatment of schizophrenia

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BACKGROUND

Schizophrenia is a debilitating disease affecting ~1% of the population. Despite a surfeit of schizophrenia drugs, according to the APA, 60% of patients do not adequately respond to treatment. LB–102 and LB–103 are novel benzamides designed to improve the poor blood brain barrier (BBB) permeability of amisulpride, a well established dopamine antagonist used to treat schizophrenia.

HYPOTHESIS

Selective N-methylation of amisulpride produces LB–102/LB–103, designed to decrease hydrophobicity to improve BBB permeability, increase brain and lower plasma exposure.

RECEPTOR BINDING DATA

Inhibition constants (Ki) were determined from ligand displacement assays.

DISCUSSION

LB–102 and LB–103 are next generation analogs of amisulpride designed to retain the antipsychotic activity of amisulpride (an antipsychotic licensed for use in Europe since 1993) at lower doses, providing a potentially improved side effect profile.

Studies to date with LB–102 and LB–103 demonstrate:

1. CNS receptor binding profiles comparable to amisulpride
2. Oral pharmacokinetic profiles (for active agent plus metabolite amisulpride) in rodents comparable to amisulpride
3. Similar-to-superior behavioural responses in animal models designed to recapitulate both positive and cognitive deficit symptoms of schizophrenia (object recognition deficits [NOR], hyperactivity [LMA], and stereotypy [AIC])
4. LB–102 14 day rat tox NOAEL was 200 mg/kg/d (same as amisulpride)
5. In scPCP treated rats in a catalepsy test to measure EPS potential, no catalepsy was observed and LB–102 and LB–103 were indistinguishable from amisulpride.

Conclusion

LB–102 and LB–103 have target level binding, DMPK, rodent behavioural model efficacy, and drug safety comparable-to-superior to amisulpride. LB Pharmaceuticals expects to initiate Phase 1 clinical trials in early 2019.

Disclosures

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