BL-1020: First-in-Class GABA-Enhanced Antipsychotic For Schizophrenia

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Forward Looking Statements

This presentation contains "forward-looking statements." These statements include words like "may," "expects," "believes," “plans,” “scheduled,” and "intends," and describe opinions about future events. These forward-looking statements involve known and unknown risks and uncertainties that may cause the actual results, performance or achievements of BioLineRx to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements.
Cognitive Impairment in Schizophrenia (CIS) Pipeline

- CIS pipeline consists of ~30 clinical stage drug candidates, reflecting the intense interest in meeting this unmet need:
  - Most in phase II trials involving <200 patients
  - Designed for adjunctive therapy in stable patients
- Results of 10 trials published to date show no statistical separation or improvement in some cognitive areas
- BL-1020 is first dual action molecule to show clinically meaningful, statistically significant improvement in cognitive function in large clinical study
  - “BL-1020 is the first drug which has shown a benefit for cognition in schizophrenia in a controlled clinical trial. Although the study was not fully ideal for documenting the positive cognition profile, its consistent benefit for cognition in the controlled trial was striking.” Dr. Carol Tamminga Prof. Psychiatry
BL-1020 A Novel Dual Action Molecule

BL-1020 is a conjugate of the dopamine (DA) D₂ receptor antagonist, perphenazine, a classical antipsychotic drug, and the key inhibitory brain neurotransmitter GABA. The conjugate is broken down in the brain.

Perphenazine

[Chemical structure of perphenazine]

MW (free base)- 498.07 Dalton

Perphenazine is fully active in all standard models for antipsychotic activity.

Cortical GABAergic hypofunction has been postulated to be a major factor in CIS by disinhibiting the glutamatergic system in the brain – the loss of the ‘brake’

Direct administration of GABA is not feasible, due to poor GI & brain penetration.
CATIE: Perphenazine’s Robust Comparative Efficacy

GABA’s Role in CIS

Objective Findings In Schizophrenia

Expression of GABA synthetic enzyme, GAD67 in the DLPFC

GABA mediated cortical synchrony

Cognitive Impairment

Perphenazine’s Lipid Solubility Enables BL-1020 to Enter the Brain, Where GABA is Released
Evidence That BL-1020 Rapidly Enters and Accumulates in the Brain

Experimental design:
- BL-1020 was orally administered to rats, for 14 consecutive days
- Maximum dose 6mg/kg
- On day 14, samples from CSF, plasma and brain at intervals for 24 hours post administration (n=4-5 animals/time point)
- Control animals were administered vehicle; CSF, brain and plasma samples were collected 2 hours post administration
- Samples were analyzed using an LC/MS/MS

Results:
BL-1020 was not detected in CSF samples
Brain to plasma ratio of BL-1020 (AUC) = 110/43 = 256%
(Cmax) = 5.8/4.8 = 120%

Brain BL-1020 levels are stable - Only 23% reduction 24h post administration
BL-1020 Shows Potential for Improved Cognition In *In Vivo* Studies

**In vivo microdialysis dopamine efflux studies**

- DA is essential for normal cognition. Hypodopaminergia is key factor in cognitive impairment in schizophrenia, Parkinson’s disease and Alzheimer’s.
- Increased efflux of dopamine (DA) in the cortex and hippocampus has been shown to be effective to improve cognition in numerous animal models.
- Meltzer Laboratory (Northwestern University School of Medicine)

**Behavioral cognition studies**

- Phencyclidine (PCP) administration is the basis for the most accepted model of CIS.
- BL-1020 was assessed to reverse PCP-induced deficit in “novel object recognition” and “reversal learning” - measures of human long term memory and executive function.
- Prof. Jo Neill (School of Pharmacy, University of Bradford, UK)
In Vivo Microdialysis Data Show BL-1020 Enables Dopamine Efflux in mPFC

- Doses of 3mg/kg BL-1020 and equimolar doses of perphenazine were administered to rats. DA was tested every 30 minutes, and up to 3.5h post administration.

Studies were done in collaboration with Dr. Herbert Y. Meltzer, Northwestern University School of Medicine
PCP-Induced NOR Deficit Model

Acquisition

Normal rat

PCP-treated rat

PCP-treated rat with drug

Retention

Explore novel than familiar

Explore both objects

Reverse PCP-induced NOR deficit?
BL-1020 Ameliorates Cognitive Deficit

BL-1020 significantly increases the time rats spent exploring the novel object.

*Presented by Prof. Jo Neil at 2009 SOBP Vancouver*
PCP Induced Cognitive Impairment Model
Reversal Learning

Experimental

• Female Hooded-Lister rats are initially trained to respond to food in standard two lever Skinner boxes

• Reversal learning test consists of two phases: initial phase (same reward contingency same as previous training day) and reversal phase (opposite reward contingency to that of initial phase)

• Following a stable level of responding, rats are trained to respond to food in the presence of a visual cue-a stimulus light above the lever. At the start of each session, the house light is turned on, activation of one lever only will result in delivery of a food pellet

• Once rats have achieved at least 90% correct responding on initial task they are trained on the opposite reward contingency
Experimental

- **Cognitive impairment induction**
  - Cognitive impairment is induced by subchronic treatment with PCP
  - Cognitive impairment is present in the reversal phase as more errors and longer time to reversal,
  - the initial learning phase is unaffected by the subchronic PCP

- **Treatment groups (n=8-10)**
  - Vehicle (no PCP)
  - PCP
  - PCP+ BL-1020, 3mg/kg
  - PCP+ Perphenazine (equimolar dose)
"Trained" rats are given access to same reward contingency of previous day for 5 min. As expected, in this phase there is no difference in % correct responding.

In the reversal test, the reward contingency is reversed so that the animal responds in the opposite way. PCP impairs reversal learning (**P<0.001 vs. Vehicle);

BL-1020 improves reversal learning (P<0.05 vs. PCP); Perphenazine does not.
A GABA\textsubscript{A} Receptor Blockers Bicuculline and Picrotoxin Prevents the Improvement in Reversal Learning with BL-1020

- BL-1020 was administered alone or in combination with specific GABA\textsubscript{A} antagonists to rats with impaired cognition following PCP administration
  - GABA\textsubscript{A} antagonist bicuculline at 2 mg/kg, was administered i.p, 70 min. prior to testing.
  - GABA\textsubscript{A} antagonist picrotoxin at 0.5mg/kg, was administered i.p, 70 min. prior to testing.
  - BL-1020 at 3 mg/kg, was administered orally 10 min after either antagonist

- Cognition was assessed using “reversal learning”
MOA: BL-1020’s GABAergic Activity Results in Cognitive Improvement

BL-1020 is effective in reversing cognitive impairment
Selective GABA$_A$ antagonists (bicuculline and picrotoxin) block BL-1020’s effect on cognition

Initial phase - no significant differences between groups.
Significant reduction in % correct responding in reversal phase of drug treatment groups in comparison to vehicle group. *** p<0.001
Significant improvement in responding compared to PCP alone in the reversal phase ## p<0.01 ANOVA followed by Dunnett's t-test
Conclusions

- BL-1020 is the first in class antipsychotic drug to directly target the deficit in brain GABA which has been reliably demonstrated in schizophrenia.
- BL-1020 couples the lipophilic antipsychotic perphenazine enabling this novel agent to be absorbed in the gut and then pass the blood brain barrier where it is cleaved to perphenazine and GABA.
- Perphenazine has been shown preclinically and clinically in the average schizophrenic patient to be as effective for psychopathology reduction as any antipsychotic drug and to have a low burden of parkinsonian symptoms.
- Preclinical data, using the rodent subchronic PCP model of CIS, shows BL-1020 is effective to ameliorate the PCP-induced cognitive deficit.
- BL-1020 was shown in the Eagle study to be significantly more beneficial for CIS than risperidone and placebo, indicating great promise as a single agent able to meet two key needs of patients with schizophrenia in a manner unlike that of any other marketed drug or drug in development.
Bench to Bedside to Partner