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

December 2012
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.
Background and Unmet Medical Need

- **Schizophrenia is characterized by 3 categories of symptoms:**
  - Positive symptoms - delusions, hallucinations, and disorganized speech/behavior
  - Negative symptoms - flat affect (decreased ability to express emotions), alogia (decreased speaking), avolition (lack of motivation), anhedonia (inability to feel pleasure), etc.
  - **Cognitive impairment**

- **Schizophrenia affects 0.5 - 1.5% of adults**

- **Current medications are primarily effective against positive symptoms only**
Background and Unmet Medical Need (cont.)

- Cognitive impairment is a core deficit in schizophrenia:
  - >90% of patients with schizophrenia are affected
  - Cognitive impairment is the major determinant of poor functional outcomes in the community

  - Patient preference is placed on reducing confusion and difficulty in concentrating (Rosenheck et al., 2005, BJP)
“There are currently no drugs that improve cognition in patients with schizophrenia. Any drug that can be demonstrated to have significant benefit for cognition will likely be utilized by physicians world-wide. If such a drug also has antipsychotic benefit, that would be even better.”

Prof. Richard Keefe, Director, Schizophrenia Research Group, Psychiatry & Behavioral Sciences, Division of Medical Psychology, School of Medicine, Duke University, USA. Member of the FDA’s cognition steering committee

Consultant to numerous pharmaceutical companies including Abbott, Astellas, BMS, Eli Lilly, EnVivo, Lundbeck, Merck, Pfizer, Roche
BL-1020 Background: A Novel Dual-Function Molecule

*Three* active components

**BL-1020**
A dual action (antipsychotic + pro-cognitive) agents

**Perphenazine**
1\textsuperscript{st} generation antipsychotic w/ certain 2\textsuperscript{nd} generation characteristics

**GABA**
Putative role in cognitive dysfunction in schizophrenia
BL-1020 Highlights

Indication: Schizophrenia; Cognitive Improvement in Schizophrenia (CIS)

• Cognition:
  – First dual action antipsychotic to show cognitive improvement

• Anti-Psychotic Efficacy:
  – Highly efficacious, similar to FGA and SGA on positive symptoms

• Safety:
  – **Overall**: clean safety profile; comparable to market leading SGAs
  – **Metabolic**: minimal metabolic side effects
  – **Movement Related (EPS)**: comparable to SGAs
  – **Cardiovascular**: minimal cardiac side effects (e.g. arrhythmias, QTc prolongation, tachycardia, BP, HR)

• **Status**: Phase II/III

FGA- First Generation Antipsychotics
SGA- Second Generation Antipsychotics
Phase 2b EAGLE Trial (Completed Sep 09)

Efficacy, safety and tolerability of BL-1020 in hospitalized patients with acute exacerbation of schizophrenia

**Main Trial**
- BL-1020 10 mg/day
- BL-1020 20-30 mg/day
- Risperidone 2-8 mg/day
- Placebo

363 patients

**Extension Trial**
- BL-1020 10 mg/day
- BL-1020 20-30 mg/day
- Risperidone 2-8 mg/day
- BL-1020 10mg/day
- BL-1020 20-30mg/day

75 patients

Primary Endpoint: **PANSS** (Positive And Negative Syndrome Scale)
Secondary: **CGI-S** (Clinical Global Impression – Severity), **CGI-C** (Clinical Global Impression – Change), **RDQ** (Readiness for Discharge Questionnaire), **Strauss Carpenter Scale**
Exploratory: Cognitive function (**BACS** - Brief Assessment of Cognition in Schizophrenia)

6 weeks 12 weeks

J Clin Psychiatry 2012;73:el168-el174
Antipsychotic Efficacy Demonstrated

PANSS Total Score Changes from Baseline to Week 6 in Main Trial

Change from Baseline (LSM)

Week

ANCOVA model: Change = Baseline Value Center Treatment (*p<0.05: compared with placebo)
Antipsychotic Efficacy Demonstrated Extension Trial

PANSS Total Score Changes from Baseline to Week 12 (LOCF)

All patients

Extension patients

Confidential
Brief Assessment of Cognition in Schizophrenia (BACS)

• BACS assesses aspects of cognition found to be most impaired and most strongly correlated with outcome in patients with schizophrenia.

• BACS battery comprises 4 of the 7 elements deemed necessary for measuring cognitive function as determined by the NIMH.

• Tests include:
  • List Learning (verbal memory)
  • Digit Sequencing Task (working memory)
  • Token Motor Task (processing speed)
  • Semantic and Letter Fluency (processing speed)
  • Symbol Coding Task (processing speed)
  • Tower of London (reasoning and problem solving)

• BACS composite score, calculated from the six measures, highly correlates with the MCCB.

<table>
<thead>
<tr>
<th>MCCB Cognitive Domains</th>
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<tr>
<td>Speed of processing</td>
</tr>
<tr>
<td>Attention/vigilance</td>
</tr>
<tr>
<td>Working memory</td>
</tr>
<tr>
<td>Verbal learning</td>
</tr>
<tr>
<td>Visual learning</td>
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<tr>
<td>Reasoning and problem solving</td>
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<tr>
<td>Social cognition</td>
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</table>
Evidence for BL-1020's Pro-Cognitive Effects in EAGLE Trial

BACS Composite Score Change from Baseline to Week 6 (LOCF)
(Uncorrected BACS Score)

- BL-1020 10mg
- BL-1020 30mg
- Risperidone
- Placebo

LS Mean Change of BACS Composite Score (Uncorrected)

- (n=61) p=0.027 vs PBO
- (n=53) p=0.027 vs Risp.
- (n=63)
- (n=51)
Improvement Demonstrated on all BACS Subscales

Cognitive benefit achieved following 6 weeks of treatment was maintained and even improved at 12 weeks.
CLARITY Phase II/III Trial Overview

- Aimed at determining the short (6 weeks) and long-term (6 months) cognitive and anti-psychotic efficacy, safety and tolerability of BL-1020 compared with Risperidone
- Cognition is primary endpoint
  - MCCB replaces BACS (correlation 0.8)
  - MCCB – current recommendation by FDA, NIMH, EMA
- Randomized, double-blinded, positive controlled
- Up to 450 patients with acute exacerbation of schizophrenia
- Interim results expected Q1 2013
- Final results expected H2 2013
- Full GCP trial
CLARITY Trial

Study design

**Acute Phase**
- BL-1020
  - Titrate to MTD (15-35)
- Risperidone
  - Titrate to MTD (2-6)

**Chronic Phase**
- BL-1020
- Risperidone

Up to 450 patients

Primary: Cognition (MATRICS)

6 weeks
6 months
CLARITY Trial Status

• Regulatory submissions – 43 sites
  – Romania - Active sites – 12, awaiting EC approval - 8 sites
  – India - Active sites - 13, awaiting EC approval - 7 sites
  – Moldova - awaiting EC approval - 3 sites

• Interim Analysis -
  – To be performed on data based on ~ 235 randomized patients from Romania and India
  – Results expected - Q1 2013

• Final study results expected H2 2013
Bench to Bedside to Partner