JBPOS0101: A New Generation mGluR- and BBB-Targeted AED for the Treatment of Super-Refractory Status Epilepticus (SRSE)

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Director of Pharmacology
Who We Are

• Bio-Pharm Solutions Co., Ltd. is a privately-owned drug discovery and development company based in South Korea

• Dr. Yong Moon Choi, CEO, has a track record in the field of epilepsy, including orphan epilepsies:
  - Involved in the development of Felbamate, currently used in the treatment Lennox-Gastaut Syndrome
  - Invented YKP3089, currently in late-stage clinical development at SK for refractory partial-onset seizures
  - Invented Carisbamate, a drug candidate for refractory partial-onset seizures which reached the NDA stage
JBPOS0101 Overview of SRSE

- A unique mechanism of action (metabotropic glutamate receptors) not presently associated with currently-used antiepileptic drugs
- Potent efficacy in the pharmaco-resistant status epilepticus (BDZ-resistant)
- Antiepileptogensis through suppressing spontaneous recurrent seizures
- Neuroprotection through blocking hemorrhages in the blood-brain barrier (BBB) of treatment-naive rats
- Potent anticonvulsant properties in a broad spectrum of epilepsy models
- Applications of JBPOS0101 go beyond orphan indications
  - JBPOS0101 has potential applications in infantile spasms based on preclinical pharmacology
Prevalence of Status Epilepticus

- Reported to be between 20 - 40 / 100,000
- Assuming a population of about 322,000,000, there are up to about 130,000 individuals with status epilepticus in the United States
- An estimated 15% of all cases of status epilepticus will become super-refractory*

*Shorvon and Ferlisi, Brain, 2011, 134:2802-18
Disease Overview: Super-Refractory Status Epilepticus

- Status epilepticus (SE) is defined as continuous seizure activity for ≥ 5 min
- One-third of patients with refractory and super-refractory SE will die, and another one-third will suffer chronic neurologic or other deficits
- No approved treatments for super-refractory SE at this time

**Early SE**
- Treat with 1st line AEDs (benzodiazepines)

**Established SE**
- Treat with 2nd line AEDs (phenytoin, phenobarbital, valproate, etc.)

**Refractory SE**
- Treat with 3rd line general anesthesia (propofol, midazolam, etc.)

**Super-Refractory SE**
- Failure to terminate SE after weaning 3rd line treatment

Modified from Shorvon and Ferlisi, Brain, 2011, 134:2802-18
JBPOS0101’s Efficacy in Lithium-Pilocarpine-Induced SE

**Prevention**
- Lithium (128 mg/kg, ip) 2 h before seizure induction
- Scopolamine (2 mg/kg, ip) 30 min before seizure onset

**Intervention**
- Pilocarpine (43 mg/kg, ip) At seizure onset
- 30 min after seizure onset

**Administration**
- **Injection route**
  - ip
  - iv
  - ip

**Observation**
- **Observation time after seizure onset**
  - 90 min

**ED$_{50}$ (mg/kg)**
- 19.1
- 20.4
- 54.3
- 80.4

**Summary**
JBPOS0101 shows potent efficacy in benzodiazepine-resistant SE
Efficacy of JBPOS0101 in Benzodiazepine-Resistant Electrographic SE

Benzodiazepine-resistant electrographic status epilepticus rat model: Gamma wave power (20-70 Hz) on EEG for 10 hours

Lithium (128 mg/kg, ip) & Pilocarpine (50 mg/kg, ip) & Scopolamine (1 mg/kg, ip) & Single injection (ip) & ~ 24 hours

EEG Implant 1 week ago & ~ 24 hr & 30 min & Seizure onset & EEG Recording

Conducted by: NINDS Anticonvulsant Screening Program


Solid line: mean, Shaded area: 95% confidence intervals, Mann-Whitney U-test, *p<0.05

JBPOS0101 suppresses benzodiazepine-resistant electrographic SE
Antiepileptogenic Effect of JBPOS0101 Following Benzodiazepine-Resistant SE

Monitoring of spontaneous recurrent seizures for 14 days

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Control 50 mg/kg 7days</th>
<th>JBPOS0101 50 mg/kg 7days</th>
<th>100 mg/kg</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>8 / 8</td>
<td>8 / 8</td>
<td>4 / 8</td>
</tr>
<tr>
<td>Day 2</td>
<td>5 / 7</td>
<td>7 / 8</td>
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</tr>
<tr>
<td>Day 6</td>
<td>3 / 7</td>
<td>0 / 8</td>
<td>0 / 8</td>
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<tr>
<td>Day 7</td>
<td>5 / 7</td>
<td>0 / 8</td>
<td>0 / 8</td>
</tr>
<tr>
<td>Day 8</td>
<td>3 / 7</td>
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<td>Day 13</td>
<td>5 / 5</td>
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<td>0 / 8</td>
</tr>
<tr>
<td>Day 14</td>
<td>4 / 4</td>
<td>1 / 8</td>
<td>0 / 8</td>
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</table>

JBPOS0101 suppresses spontaneous recurrent seizures and shows evidence of antiepileptogenesis
Survival Rate and Body Weight in Lithium-Pilocarpine-Induced SE

Survival Rate and Change in Body Weight for 14 days

- Survival rate
- Body weight

Data were represented as mean ± S.E.M. Statistical analysis were performed by Two-way ANOVA test and followed Bonferroni Test as a post hoc analysis using Prism.

JBPOS0101 improves survival rate and body weight in SE
BBB Hemorrhages caused by Lithium-Pilocarpine-Induced SE

Examples of HE staining showing BBB hemorrhages

JBPOS0101 reduces the number and size of hemorrhages in the BBB caused by SE
Neuroprotective Effect of JBPOS0101 in Benzodiazepine-Resistant SE

Status epilepticus-induced hippocampal cell loss after 14 days

- Lithium (128 mg/kg, ip)
- Pilocarpine (50 mg/kg, ip)
- Scopolamine (1 mg/kg, ip)

Single injection (ip)
Hippocampus Cell Counting

~ 24 hr
30 min
Seizure onset
14 days

JBPOS0101 protects hippocampus against status epilepticus-induced cell death
Effect of JBPOS0101 in SE-Induced Memory Deficits

Assessment of spatial memory and learning in SE-induced rats in the Morris Water Maze

- Lithium (128 mg/kg, ip)
- Pilocarpine (50 mg/kg, ip)
- Single 65 mg/kg (ip)

Seizure onset

- 15 min
- 14 days

Conducted by: NINDS Anticonvulsant Screening Program

Two-way ANOVA with Bonferroni’s multiple comparison test, *p<0.05

JBPOS0101 improves spatial memory and learning functions in rats with SE
## Comparison of Antiepileptic Activity in Animal Models

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MES (ip)</th>
<th>PTZ (ip)</th>
<th>scBIC (ip)</th>
<th>scPIC (ip)</th>
<th>Stry-Chnine (ip)</th>
<th>MES (po)</th>
<th>PTZ (po)</th>
<th>Li-Pilo Prevention (ip)</th>
<th>Li-Pilo Intervention (iv)</th>
<th>TD50 (po)</th>
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<tr>
<td>JBPOS0101</td>
<td>9.4 (po)</td>
<td>14.4</td>
<td>18.1</td>
<td>18.8</td>
<td>36.0</td>
<td>1.2</td>
<td>21.3</td>
<td>18</td>
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<td>Allopregnanolone</td>
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<td>4.1</td>
<td>31.7</td>
<td>&gt;300</td>
<td>&gt;40</td>
<td>&gt;10</td>
<td>6.8</td>
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<td>27.3 (ip)</td>
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<td>28.1</td>
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<td>Lamotrigine</td>
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<td>Topiramate</td>
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<td>Felbamate</td>
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</tbody>
</table>

NA: Not Available

JBPOS0101 shows broad spectrum and potent efficacy
Phase 1 Trial: Safety, Tolerability, and PK in Young Healthy Subjects

- **Phase 1 Protocol**
  - Approved by US FDA and Health Canada and conducted in Toronto, Canada
  - Single Dose: 30 - 1100 mg, 64 subjects (8 subjects/8 groups, 6 active/2 placebo)
  - Multiple Dose: 240 - 960 mg per day for 10 days, 24 subjects (8 subjects/3 groups, 6 active/2 placebo)

- **Phase 1 Results**
  - No effects on vital signs
  - PK data shows a dose-dependent linear relationship (Cmax, AUC)
  - Half-life \( (T_{1/2}) = 18 - 23 \) h
  - Mild/transient adverse effects at the highest doses: headache, somnolence, dizziness, euphoria
  - Very well tolerated by phase 1 volunteers
Summary

- **JBPOS0101**
  - New AED with novel mechanisms
  - Active in models of pharmaco-resistant status epilepticus
  - Evidence of antiepileptogenic & neuroprotective activity
  - Broad spectrum of antiepileptic activity
  - Other indications: neuroprotection, pain, anxiety, and depression

- **Current plan**
  - Super-refractory status epilepticus
    - Phase II study (open-label, single-center, adjunctive therapy)
    - Will be performed in USA and South Korea
    - Phase II study initiation in 2017
  - Infantile spasms
    - Protocol development/US FDA meeting preparation in progress
  - Response to treatment can be assessed quickly for both clinical trials