Calming The Roller-Coaster Ride, Bipolar Disease: A Double-Blind, Active Controlled Trial Demonstrates Anti-Manic Efficacy Of A New Protein Kinase C Inhibitor Endoxifen

Ateeq Ahmad Ph.D.
Jina Pharmaceuticals Inc.,
USA
Drugs for Bipolar Disorder

- Protein Kinase C Inhibitors

Clinical Trial Design
- Safety & Efficacy

Efficacy
- YMRS

PK-PD (Exposure-Response)

Onset of Action Compared with Known Drugs

Summary
Drugs for Bipolar Disorder I

Common Drugs

- Lithium (0.6 - 2g/daily)
  - FDA 1970 for BPD
- Valproate (1g-2g/daily)
  - FDA 1995
- Olanzapine
  - FDA 2000
- Asenapine
  - FDA 2009
- Cariprazine
  - FDA 2015

Issues and Side Effects

- Weight Gain
- Extra Pyramidal Symptoms
  - Akathisia: “Inability to sit”
  - Pseudoparkinsonism

Narrow Therapeutic Index
Protein Kinase C Inhibitors for BPD

% PKC inhibition (Mean ± SEM)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Endoxifen (mM)</th>
<th>Tamoxifen (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

Chemical structures of Endoxifen and Tamoxifen with metabolic pathways involving CYP3A4, CYP2D6, and N-desmethyaltamoxifen and 4-hydroxytamoxifen.
Endoxifen - Clinical Trial Design

**BPD I Patients**

N = 42

Double-Blind Double-Dummy

**Endoxifen**

(4 mg/day)

21 days

n = 28

**Divalproex**

(1000 mg/day)

21 days

n = 14

**PRIMARY ENDPOINT:**
Young Mania Response Rating Score (YMRS)

**Stage I**

**Stage II**
Endoxifen - Safety & Efficacy

<table>
<thead>
<tr>
<th></th>
<th>E (4mg/d) N=27</th>
<th>E (8 mg/d) N=28</th>
<th>D (1 gm/d) N=28</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with at least one AE</td>
<td>8 (29.63)</td>
<td>7 (25)</td>
<td>12 (41.38)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (3.7)</td>
<td>1 (3.57)</td>
<td>5 (17.24)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (3.7)</td>
<td>2 (7.4)</td>
<td>5 (17.24)</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of Responders</td>
<td>12 (44.44)</td>
<td>18 (64.29)</td>
<td>21 (72.41)</td>
</tr>
</tbody>
</table>
Improvement in YMRS score for Endoxifen
Exposure-Response Analysis of Endoxifen

Exposure-Response Analysis of Endoxifen

### Endoxifen - Rapid Onset of Action

**Monotherapy Trials of drugs for the treatment of Bipolar Disorder I**

**Trial Duration (3 weeks)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline YMRS Score</th>
<th>Change from Baseline</th>
<th>Onset of Action (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Divalproex (1 g/day)</strong></td>
<td>28</td>
<td>-4.86</td>
<td>4</td>
</tr>
<tr>
<td><strong>Endoxifen (mg/day)</strong></td>
<td>24</td>
<td>-3.65</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>-5.66</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>-5.66</td>
<td>4</td>
</tr>
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</table>
Summary

- Endoxifen
  - Safe
  - Potent PKC inhibitor
  - Efficacy demonstrated by change in YMRS Score
  - Exposure-Response (PK-PD) Analysis shows proportionality
  - Rapid Onset of action in BPD patients

ateeq@jinapharma.com
(847) 573 0731