Open-Label Phase 2 Trial of the Oral Neuroactive Steroid GABA Receptor Positive Allosteric Modulator Zuranolone in Bipolar Disorder I and II

**Introduction**

Bipolar disorder (BDP) is a chronic, episodic illness affecting nearly 50 million globally, with substantial disability due to depressive episodes. Bipolar depression treatment with antidepresants may be associated with risk of manic switching and rapid cycling. Zuranolone (SAGE-217) is an investigational oral neuroactive steroid GABA receptor positive allosteric modulator.

- **Zuranolone demonstrated improved depression in depressive symptoms in two double-blind, randomized, placebo-controlled trials in unipolar depression.**

- **Zuranolone binds to both synaptic and extrasynaptic GABA receptors, enhancing inhibitory activity of the GABAergic system, the major inhibitory neurotransmission system in the brain.**

This open-label Phase 2 trial (NCT03692910; ARCHWAY) evaluated zuranolone safety and tolerability in subjects with bipolar depression.

**Results**

**DEMOGRAPHICS & BASELINE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ZURANOLONE N=35</th>
<th>MADRS 30 MG N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>37.6 (10.4)</td>
<td>38.7 (11.7)</td>
</tr>
<tr>
<td>Race</td>
<td>White (91.4%)</td>
<td>White (90.6%)</td>
</tr>
<tr>
<td></td>
<td>Black/African American (4.3%)</td>
<td>Black/African American (6.2%)</td>
</tr>
<tr>
<td></td>
<td>Other (4.3%)</td>
<td>Other (3.1%)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (68.6%)</td>
<td>Male (59.4%)</td>
</tr>
<tr>
<td></td>
<td>Female (31.4%)</td>
<td>Female (40.6%)</td>
</tr>
<tr>
<td>Weight, kg (SD)</td>
<td>80.6 (17.6)</td>
<td>80.1 (15.9)</td>
</tr>
<tr>
<td>Height, cm (SD)</td>
<td>171.9 (8.4)</td>
<td>171.3 (8.2)</td>
</tr>
<tr>
<td>Baseline HAMD-17</td>
<td>29.3 (18.2)</td>
<td>28.8 (20.0)</td>
</tr>
<tr>
<td>Baseline Mood Stabilizer Use</td>
<td>Yes (94.3%)</td>
<td>Yes (93.8%)</td>
</tr>
<tr>
<td></td>
<td>No (5.7%)</td>
<td>No (6.2%)</td>
</tr>
<tr>
<td>Baseline Antidepressant Use</td>
<td>Yes (91.4%)</td>
<td>Yes (90.6%)</td>
</tr>
<tr>
<td></td>
<td>No (8.6%)</td>
<td>No (9.4%)</td>
</tr>
</tbody>
</table>

**Methods**

- Patients, aged 18-65 years old, with a documented history of mania or hypomania, a BPD I (characterized by manic episodes) or BPD II (characterized by hypomanic episodes) diagnosis, and a current major depressive episode, as well as a HAMD-17≥17 total score ≥22, and a MADRS total score ≥16 were included.

- Key exclusion criteria included a current depressive episode with mixed features or a history of rapid cycling BPD (occurrence of four or more mood disturbances within a single year).

- Stable antidepressant doses were permitted from 60 days prior to Day 1 through the treatment period.

- Open-label zuranolone 30 mg capsule was self-administered once daily for two weeks, as well as on follow-up through Day 42.

- The primary endpoint was safety and tolerability evaluated by treatment emergent adverse event (TEAE) reporting, the Young Mania Rating Scale, the Columbia Suicide Severity Rating Scale (C-SSRS), and standard clinical assessments.

- Secondary endpoints included the change from baseline (CFB) in the Montgomery-Asberg Depression Rating Scale (MADRS) and HAMD-17 in the treatment follow-up period.

- Least-square (LS) ± standard deviation (SD) are reported.

- HAMD-17 response (reduction ≥50%) was also assessed.

**ZURANOLONE WAS GENERALLY WELL TOLERATED**

- There were no serious or severe TEAEs and no discontinuations due to adverse events.

- 29 patients completed the study and 25 completed treatment.

- There were no dose reductions to 20 mg due to adverse events.

- No laboratory or vital sign-related TEAE was reported during the study.

- No mania was observed.

- Two cases of hypomania, considered to be mild in severity, occurred in the off-treatment follow-up period in two patients with BPD I.

- No signal for increased suicidal ideation or suicidal behavior compared to baseline, as measured by C-SSRS, was observed.

**Conclusion**

- In this open-label study, zuranolone was generally well tolerated with no severe or serious TEAEs, no mania, no increased signal for suicidal ideation or behavior and no discontinuations or dose reductions due to adverse events. TEAES in ≥5% of patients were somnolence, headache, sedation, hypomania, and diarrhea.

- Zuranolone may have the potential to offer a favorable safety and tolerability profile in patients with bipolar depression and may be associated with relatively rapid improvement or depressive symptoms.

- Zuranolone demonstrated increased percentage of patients achieving HAMD-17 response.

**ZURANOLONE REDUCED DEPRESSIVE SYMPTOMS COMPARED TO BASELINE**

- There was a reduction in MADRS total score, beginning at Day 3 (-7.7 ± 8.4).

- At Day 15, the mean MADRS CFB was -15.5 ± 13.7, and reductions in MADRS total score were sustained through Day 42 (-16.4 ± 10.4).

- There was a reduction in HAMD-17 total score, beginning at Day 3 (-6.5 ± 6.4).

- At Day 15, the mean HAMD-17 CFB was -11.4 ± 8.7 and reductions in HAMD-17 total score were sustained through Day 42 (-11.9 ± 7.4).

- HAMD-17 response defined as reduction of ≥50% from baseline.

**HAMD-17 RESPONSE RATES**

- Data shown are from the modified efficacy set.

- At Day 15, 45% of patients achieved HAM-D response, with 50% of patients showing HAM-D response at Day 42.