Responder Compared to Mean Change Analyses in a Fibromyalgia Phase 2b Clinical Study of Bedtime Rapidly Absorbed Sublingual Cyclobenzaprine (TNX-102 SL)

R Michael Gendreau,1 Daniel J. Clauw,2 Judith Gendreau,3 Bruce Daugherty,4 and Seth Lederman4

Gendreau Consulting LLC,1 University of Michigan,2 Tonix Pharmaceuticals,3 Tonix Pharmaceuticals, Inc.4

Background

- Fibromyalgia is associated with symptoms that include widespread pain and other descriptors.
- Clinical trials that rely on patient self-reported outcome measures such as pain scales may be influenced by bias and lack of precision.
- Chicken models highlighted the potential for pain relief with TNX-102 SL.

Methods

BESTFIT Study Characteristics and Endpoint Measures

- 12-week, randomized, double-blind, placebo-controlled study in patients diagnosed with fibromyalgia by 2010 ACR criteria.
- Defined as having 11 or more of the 18 ACR tender point criteria.
- Patients were randomized to either TNX-102 SL 2.8 mg or placebo.

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=103)</th>
<th>TNX-102 SL (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.7 (9.9)</td>
<td>49.7 (11.7)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>6.8%</td>
<td>3%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.6 (16.7)</td>
<td>80.9 (17.2)</td>
</tr>
<tr>
<td>SS, mean (SD)</td>
<td>8.9 (1.82)</td>
<td>8.8 (1.80)</td>
</tr>
</tbody>
</table>

Tender Point Count

- TNX-102 SL: n=45 (43.8%) of 103 treated patients
- Placebo: n=46 (44.8%) of 103 treated patients

Responder Analysis (≥30% Improvement from Baseline)

- 45 out of 103 treated patients (43.8%) in the TNX-102 SL group responded to treatment, compared to 46 out of 103 (44.8%) in the placebo group (P=0.984).

Primary Efficacy Endpoint

- Mean change from baseline in the weekly average daily diary pain score during week 12 for fibromyalgia as all of the following:

  - The patients had a diagnosis of primary fibromyalgia as defined by the 2010 ACR Preliminary Diagnostic Criteria for fibromyalgia
  - SS of 30 or greater

Other Efficacy Endpoints

- TNX-102 SL demonstrated significant improvement over Placebo for pain, sleep, and function at all times (P=0.014).

Safety Efficacy

- There were no serious adverse events, and no deaths were reported in the study.
- The most commonly reported adverse event was hypoaesthesia, which occurred in 2.9% of patients in the TNX-102 SL group and 2.4% of patients in the placebo group.

Conclusion

- Results from the Phase 2a trial support the finding that responder analyses for pain studies and other indicators relying on patient-reported outcomes may reveal significant and meaningful effects that are missed by group mean changes.
- Local site administration reactions of oral hypoaesthesia and abnormal product taste were the only commonly reported adverse events with an incidence of 1.5% and at least twice the rate of placebo.
- Although the primary endpoint for BESTFIT was based on an analysis of improvement in pain, the mechanistic action of this intervention is believed to be targeting of nervous system instability. Consistent with this mechanism, observed improvements in sleep quality preceded improvement in pain.
- An ongoing confirmatory Phase 3 study will utilize a responder analysis of pain as the primary endpoint. Key secondary endpoints will also be analyzed as responder analyses, which seem to be a more appropriate approach to the evaluation of TNX-102 SL in fibromyalgia.

References

3. Gendreau R, Clauw DJ, Gendreau J, Lederman S. TNX-102 is an investigational New Drug and has not been approved for any indication.