# Effect of Bedtime Sublingual Cyclobenzaprine (TNX-102 SL) on Pain, Sleep, Fatigue and Cognition in Fibromyalgia-Type Long COVID: Results of a Double-Blind Randomized Proof-of-Concept Phase 2 Study

Herb Harris MD PhD[1], Jean Engels MS[1], Ben Vaughn, MS[2], Candace Flint[1], Seth Lederman MD[1], and Gregory Sullivan MD[1]

[1]Tonix Pharmaceuticals, Inc., Chatham, NJ [2]Rho, Inc, Chapel Hill, NC

*TNX-102 SL is an investigational drug and has not been approved for any indication

## BACKGROUND & AIMS

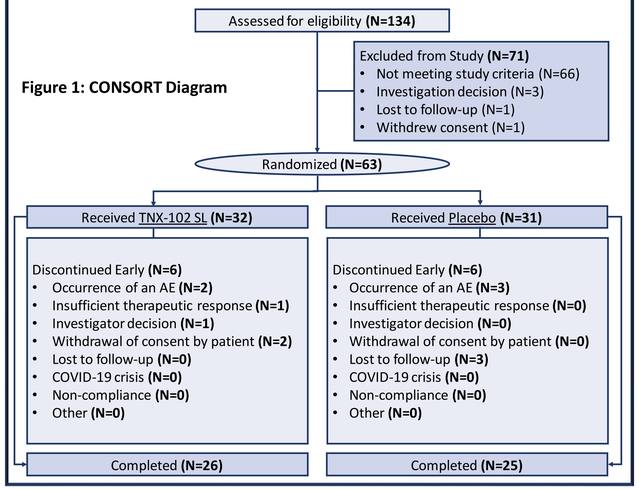
Chronic, widespread pain is a salient complaint for many Long COVID patients. Patients presenting with diffuse pain post-SARS-CoV-2 infection typically have other symptoms, such as fatigue, sleep disturbances, and cognitive symptoms that suggest clinical overlap with Fibromyalgia and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. We have termed this syndrome fibromyalgia (FM)-type Long COVID. We have hypothesized that FM-type Long COVID involves nociplastic pain mechanisms similar to those operative in FM. TNX-102 SL is a sublingual, transmucosal formulation of cyclobenzaprine (CBP) designed for bedtime administration to improve sleep quality. CBP is a tricyclic antagonist of 5-HT2A, α1 adrenergic, H1 histaminergic, and M1 muscarinic receptors. The sublingual route bypasses first-pass hepatic metabolism, making the pharmacokinetics of both CBP and its active metabolite norcyclobenzaprine distinct from the oral formulation. Treatment with TNX-102 SL has been shown to reduce pain in two statistically significant Phase 3 studies in FM. We believe that bedtime TNX-102 SL may improve sleep quality in FM-type Long COVID, leading to broad syndromal improvement in pain, fatigue, and cognitive function. The present Phase 2 proof-of-concept study tested TNX-102 SL for the treatment of FM-type Long COVID.

## METHODS

PREVAIL was a Phase 2, double-blind, multicenter, randomized, placebo-controlled, 14-week proof-of-concept trial at 19 US sites. The study enrolled Long COVID patients with multi-site pain defined as pain in at least 4 out of 7 body regions on a modified version of the Michigan Body Map (mMBM). A confirmed history of SARS-CoV-2 infection at least three months prior to enrollment was required. Patients were male or female, 18 to 65 years of age. Their COVID-19 infection severity rating was required to be < 6 on the World Health Organization COVID-19 8-Category Ordinal Scale of Disease Severity. A total of 63 patients were randomized in a 1:1 ratio to either: TNX-102 SL 2.8 mg for two weeks, followed by 5.6 mg for 12 weeks (n=32); or to matching placebo for 14 weeks (n=31). The primary endpoint, Week 14 change from baseline in weekly average of daily diary worst Long COVID numerical rating scale (NRS) pain scores, and all continuous endpoints were analyzed by mixed model repeated measures. PGIC responder analysis was assessed using a Pearson Chi-Squared test.

## RESULTS

**Figure 1: CONSORT Diagram**



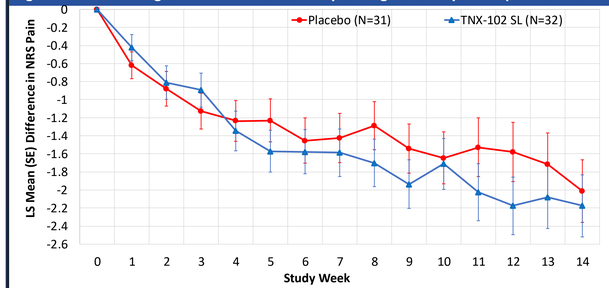

As seen in **Table 1**, no clinically important differences in baseline demographic or clinical characteristics were identified between groups.

**Table 1: Demographics and Baseline Characteristics in Safety Population**

| | TNX-102 SL (N=32) | Placebo (N=31) | Total (N=63) |
|---|---|---|---|
| Females | 65.6% | 80.6% | 73.0% |
| Males | 34.4% | 19.4% | 27.0% |
| White | 65.6% | 77.4% | 71.4% |
| Not Hispanic or Latino | 93.8% | 90.3% | 92.1% |
| Avg. age, years | 48.6 | 51.4 | 50.0 |
| BMI (kg/m$^2$) | 29.8 | 29.5 | 29.6 |
| Currently Employed | 78.1% | 83.9% | 81.0% |
| % Unemployed due to Long COVID | 9.4% | 3.2% | 6.3% |
| Current Alcohol User | 62.5% | 80.6% | 71.4% |
| Current THC User | 15.6% | 12.9% | 14.3% |

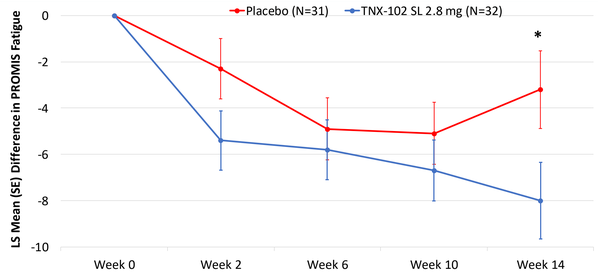
## Topline Results of the PREVAIL Study

**Figure 2: Mean Change from Baseline in Weekly Averages of Daily Widespread Pain Scores**



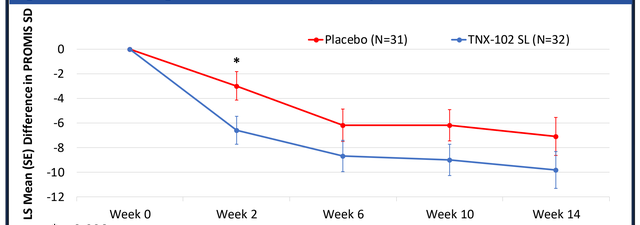

At Week 14, the primary efficacy endpoint of mean change from baseline to Week 14 in weekly average of daily worst pain intensity NRS scores was not significantly different from placebo (p=0.74, effect size [ES] = 0.08) **(Figure 2);** but TNX-102 SL showed a numerically greater reduction from Week 4 through 14.

**Figure 3: MCFB in PROMIS Fatigue**



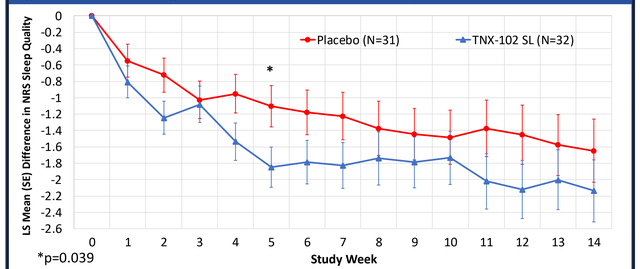

*p=0.045, effect size = 0.50

**Figure 4A: Mean Change from Baseline PROMIS Sleep Disturbance**




*p=0.028

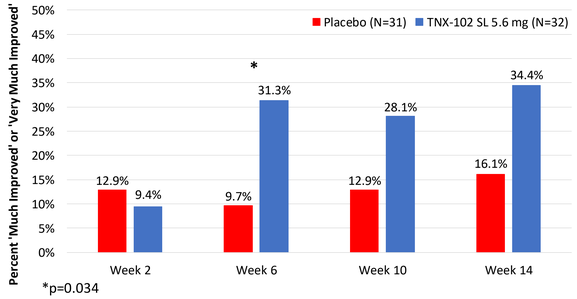
**Figures 4B: Mean Change from Baseline Daily Sleep Quality**




*p=0.039

The PROMIS Sleep Disturbance scale reached nominal statistical significance at Week 2 (**Figure 4A**). A trend favoring active treatment over placebo continued through Week 14 (ES=0.32). Consistent with this finding, trends favoring active treatment over placebo were observed in the daily sleep quality diary (**Figure 4B,** Week 14 ES=0.23).

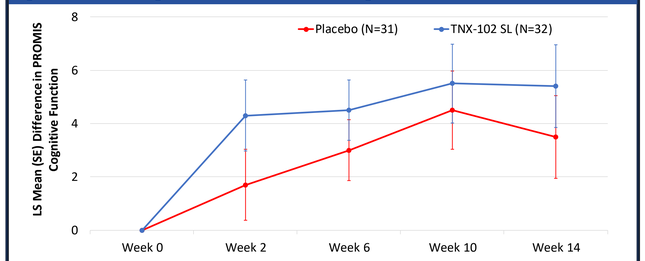
**Figures 5: Patient Global Impression of Change (PGIC) Responder Analysis**




*p=0.034

Evidence of robust global clinical benefit was seen in the PGIC responder rate. The proportion of patients reporting 'very much improved' or 'much improved' for TNX-102 SL compared to placebo was (31.3% vs. 9.7%, difference=21.6%) at Week 6, (28.1% vs. 12.9%, difference=15.2%) at Week 10, and (34.4% vs. 16.1%, difference=18.3%) at Week 14 (**Figure 5**).

**Figure 6: Mean Change from Baseline in PROMIS Cognition**




A trend favoring active treatment over placebo was observed in PROMIS Cognitive Function (ES=0.21 at Week 14)

## Safety Profile

TNX-102 SL demonstrated a favorable safety and tolerability profile over 14 weeks of treatment with no new safety signals. Most common adverse events are shown in **Table 2**. Only one TEAE was rated severe, gastritis in the TNX-102 SL group. There were no SAEs. The local administration site reaction of hypoaesthesia oral was the most common AE with TNX-102 SL (18.8%) versus placebo (0%), and was temporally related to dosing, transient, self-limited, and rated mild in all cases.

**Table 2: Adverse Events (AEs) Occurring in ≥ 3% of Patients in TNX 102 SL Treatment Group**

| | TNX-102 SL (N=32) | | Placebo (N=31) | | Total (N=63) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| ≥1 Treatment Emergent AE (TEAE) | 18 | 56.3% | 12 | 38.7% | 30 | 47.6% |
| ≥1 TEAE leading to study discontinuation | 2 | 6.3% | 3 | 9.7% | 5 | 7.9% |
| Any Oral Cavity AE | 14 | 43.8% | 2 | 6.5% | 16 | 25.4% |
| Hypoaesthesia Oral | 6 | 18.8% | 0 | 0% | 6 | 9.5% |
| Paraesthesia Oral | 2 | 6.3% | 0 | 0% | 2 | 3.2% |
| Product Taste Abnormal | 3 | 9.4% | 0 | 0% | 3 | 4.8% |

## DISCUSSION & CONCLUSIONS

- Bedtime TNX-102 SL treatment targets non-restorative sleep and, in FM-type Long COVID, resulted in an activity signal in ***fatigue, sleep and cognitive function.***
- The pain primary did not separate from placebo, however, changes from baseline in NRS score in both groups were large (-2.0 for placebo at Week 14), indicating a substantial placebo response in pain. We note that the magnitude of improvement for the active treatment group was numerically greater than placebo for Weeks 4-14. This placebo response was greater than that typically seen in FM studies employing the same endpoint.
- Given the small sample recruited over 19 sites, we pre-specified that an effect size > 0.2 would be considered of interest for further study for this disabling disorder without current treatments. The endpoints reaching this effect size criterion included the sleep quality diary (ES =0.23), PROMIS Sleep Disturbance (ES=0.32), PROMIS Fatigue (ES=0.50), PROMIS Cognitive Function (ES=0.21), the Insomnia Severity Index (ES=0.24) and the Sheehan Disability Scale (ES=0.26).
- The results of TNX-102 SL therapy observed in the PREVAIL study support the hypotheses that (1) common mechanisms underly FM-type Long COVID and FM and (2) addressing the sleep disturbance in FM-type Long COVID has the potential to result in broad syndromal improvement.



Presented at the American Society of Clinical Psychopharmacology (ASCP) 2024 Annual Meeting, May 28-31, 2024; Poster Session II, Thursday, May 30, 12:30PM ET