Relationship of Sleep Quality and Fibromyalgia Outcomes in a Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study of Bedtime, Rapidly Absorbed, Sublingual Cyclobenzaprine (TNX-102 SL)

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Background

- Fibromyalgia is characterized by chronic widespread pain and sleep disturbance
- Nonrestorative sleep is believed to play an important role in the pathophysiology of fibromyalgia
- Treatments that improve sleep quality in fibromyalgia patients may improve fibromyalgia by a mechanism distinct from centrally acting analgesics
- TNX-102 SL* is a proprietary eutectic sublingual (SL) tablet formulation of low-dose cyclobenzaprine HCl (2.8 mg) designed for rapid absorption and long-term bedtime use
- This double-blind, randomized, placebo-controlled multicenter study (BESTFIT) evaluated the safety and efficacy of TNX-102 SL in fibromyalgia

Methods

BESTFIT Study Characteristics and Endpoint Measures

BESTFIT = Bedtime Sublingual TNX-102 SL as Fibromyalgia Intervention Therapy

- 12-week, randomized, double-blind, placebo-controlled study in patients diagnosed with fibromyalgia by 2010 ACR criteria
- 1:1 randomization of 205 participants in 17 centers in the United States
  - Placebo (n=102)
  - TNX-102 SL 2.8 mg (n=103)

Entry Criteria

- The patients had a diagnosis of primary fibromyalgia as defined by the 2010 ACR Preliminary Diagnostic Criteria for fibromyalgia, meeting all of the following criteria:
  a) Widespread pain index (WPI) ≥7 and Symptom Severity (SS) scale score ≥5; or WPI 3-6 and SS scale score ≥9
  b) Symptoms present at a similar level for at least 3 months
  c) Patients did not have a disorder that would have otherwise explained their pain

Primary efficacy endpoint

- Mean change from baseline in the weekly average of pain scores collected nightly on a telephonic diary system after 12 weeks
- (0-10) Numerical Rating Scale (NRS) to assess prior 24-hour average pain intensity.

Key secondary efficacy endpoints

- Patient Global Impression of Change (PGIC)
- Fibromyalgia Impact Questionnaire-Revised (FIQ-R)
- Daily Sleep Diary (0-10 NRS averaged weekly)
- Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Instrument

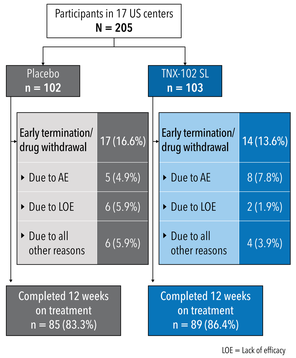
Safety Evaluation

- Adverse Events (AEs)
- Administration site reactions/local oral adverse events

Baseline Characteristics

Characteristic	Placebo N=101	TNX-102 SL N=103
Age	49.7 (11.7)	50.7 (9.9)
Males (%)	3 (3%)	7 (6.8%)
Caucasian (%)	88 (87%)	91 (88%)
Weight, kg (SD)	80.9 (17.2)	80.6 (16.7)
BMI (SD)	30.0 (5.5)	30.0 (5.7)
WPI, mean (SD)	12.9 (3.43)	12.9 (3.54)
SS, mean (SD)	8.8 (1.80)	8.9 (1.82)
Tender Point Count, mean (SD)	14.2 (2.90)	14.7 (2.56)

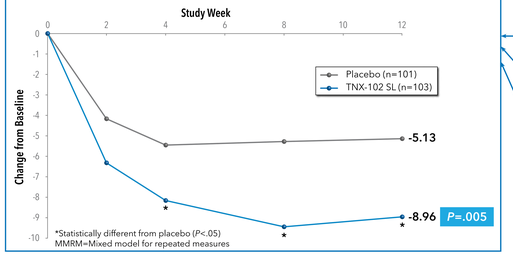
Patient Disposition



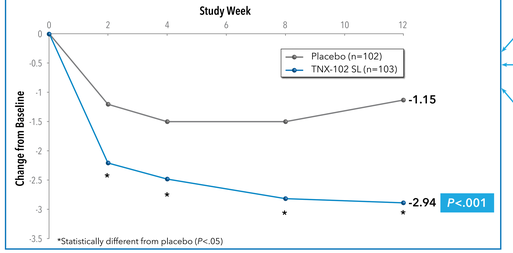
LOE = Lack of efficacy

Sleep Outcomes

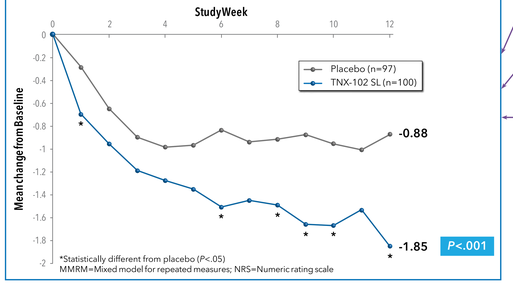
Change from Baseline in PROMIS Sleep Disturbance Scale (MMRM)



Change from Baseline in FIQ-R Quality of Sleep Scale



Change from Baseline in NRS Weekly Average of Daily Sleep Quality Scores (MMRM)

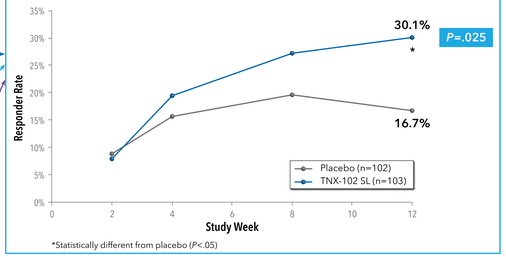


Correlations between sleep and other fibromyalgia endpoints at Week 12

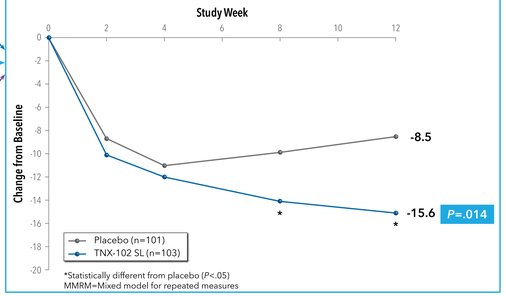
R=0.6 P≤.001
R=0.5 P≤.001
R=0.3 P≤.001
R=0.6 P<.001
R=0.7 P<.001
R=0.5 P<.001
R=0.5 P≤.001
R=0.6 P≤.001
R=0.6 P≤.001

Fibromyalgia and Pain Outcomes

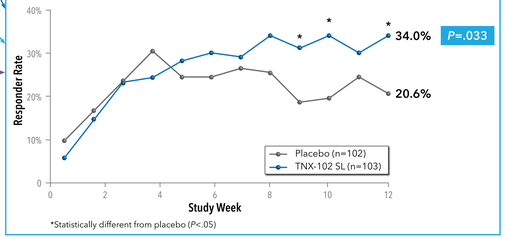
PGIC Favorable Response



TNX-102 SL Demonstrated a Significant Improvement in FIQ-R Total Score (MMRM)



30% Responder Rate on Daily Diary Pain Score Was Higher for TNX-102 SL



Prior Sleep Quality Affects Pain

- For up to 5 previous days in advance, the average measure of sleep quality is increasingly predictive of the current day's pain
- Pain and fatigue responders to TNX-102 SL show greater advanced improvement in sleep quality than with placebo. (Lead-lag statistical analyses: *P*<.001)

TNX-102 SL Adverse Events

Adverse Events Reported in More than 2 Subjects in Either Group

System Organ Class	Adverse Event Term	Placebo (n=101)	TNX-102 SL (n=103)
	At least 1 TEAE	59 (58.4%)	82 (79.6%)
Gastrointestinal disorders	Hypoaesthesia oral	2 (2.0%)	45 (43.7%)
	Dry mouth	4 (4.0%)	4 (3.9%)
	Nausea	2 (2.0%)	5 (4.9%)
	Constipation	1 (1.0%)	4 (3.9%)
	Glossitis	1 (1.0%)	3 (2.9%)
	Vomiting	0	4 (3.9%)
	Diarrhea	0	3 (2.9%)
	Paraesthesia oral	0	3 (2.9%)
Infections and infestations	Sinusitis	3 (3.0%)	4 (3.9%)
	Nasopharyngitis	2 (2.0%)	3 (2.9%)
	Upper respiratory tract infection	2 (2.0%)	3 (2.9%)
	Urinary tract infection	1 (1.0%)	4 (3.9%)
	Bronchitis	1 (1.0%)	3 (2.9%)
	Gastroenteritis viral	0	3 (2.9%)
Nervous system disorders	Somnolence	7 (6.9%)	2 (1.9%)
	Dizziness	3 (3.0%)	3 (2.9%)
Musculoskeletal and connective tissue disorders	Back pain	3 (3.0%)	5 (4.9%)
General disorders and administration site conditions	Product taste abnormal	0	8 (7.8%)
Psychiatric disorders	Abnormal dreams	2 (2.0%)	3 (2.9%)
	Anxiety	4 (4.0%)	1 (1.0%)
	Insomnia	3 (3.0%)	1 (1.0%)
Respiratory, thoracic and mediastinal disorders	Cough	3 (3.0%)	0

- Local administration site oral hypoaesthesia (transient tongue or sublingual numbness) was reported in 45 out of 103 treated patients
- Only 3 patients withdrew from participation in the study due to local adverse events

Conclusions

- Improvements in measures of sleep quality with bedtime administration of TNX-102 SL correlate with reductions in fibromyalgia pain symptoms
- Local site administration reactions of oral hypoaesthesia and abnormal product taste were the only commonly reported adverse events with an incidence of >5% and at least twice the rate of placebo
- Sleep quality improvements during preceding nights positively influences subsequent fibromyalgia pain. Increasing duration (up to 5 prior days) of sleep improvements increasingly predicts current pain reduction
- Sleep quality improvements with TNX-102 SL were associated with higher responder rates based on daytime pain and global fibromyalgia measures

References

1. Data on file, Tonix Pharmaceuticals.

*TNX-102 SL is an Investigational New Drug and has not been approved for any indication.

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