Bedtime, Rapidly Absorbed Sublingual Cyclobenzaprine (TNX-102 SL) for the Treatment of Fibromyalgia: Results of a Phase 2b Randomized, Double-Blind, Placebo-Controlled Study

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Background

- Fibromyalgia is characterized by chronic widespread pain and sleep disturbance
- 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, including all of the following:
  a) Widespread Pain Index (WPI) ≥7 and Symptom Severity (SS) scale score ≥5; or WPI 3-6 and SS scale score ≥9; and
  b) Symptoms present at a similar level for at least 3 months; and
  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 daily diary pain score during week 12
- (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

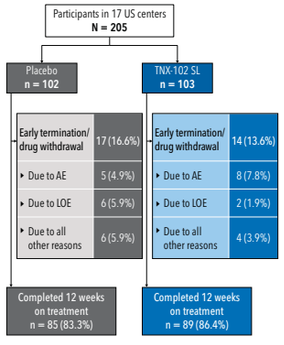
Safety Evaluation

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

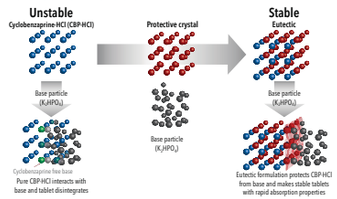
Baseline Characteristics

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)

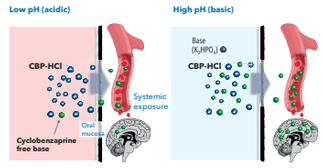
Patient Disposition



Proprietary Cyclobenzaprine Hydrochloride Eutectic Mixture Stabilizes Tablet Formulation

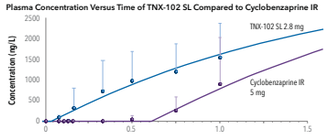


Base Increases Systemic Absorption of Cyclobenzaprine Free Base During Buccal Administration



Cyclobenzaprine is Detected in Plasma Within 20 Minutes Following Sublingual Administration of TNX-102 in Phase 1 Comparative Pharmacokinetic Study

Plasma Concentration Versus Time of TNX-102 SL Compared to Cyclobenzaprine IR

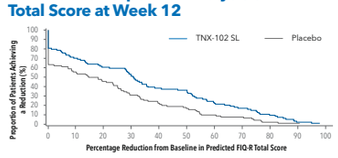


Pharmacokinetics of Cyclobenzaprine Formulations and Active Metabolite

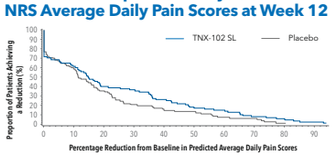
Parameter	TNX-102 2.8 mg SL	Oral IR CBP	Comparison
Dose	2.8 mg sublingual tablet	5 mg oral tablet	44% lower dose for SL
Absorption Lag Time (T_{lag})	0.050 hr (3 min)	0.622 hr (37 min)	12 x faster for SL
Relative Bioavailability (F_{rel})	154%		54% greater for SL
T_{max}	4.33 hr	4.00 hr	Similar
C_{max}	3.41 ng/mL	4.26 ng/mL	20% lower for SL
AUC 0-48	57.4 ng•hr/mL	69.5 ng•hr/mL	17% lower for SL
Active Metabolite	nCBP	nCBP	
C_{max}	0.81 ng/mL	1.71 ng/mL	53% lower for SL
AUC 0-48	30.5 ng•hr/mL	58.6 ng•hr/mL	48% lower for SL

TNX-102 SL Continuous Responder Analysis

Continuous Responder Analysis on FIQ-R Total Score at Week 12

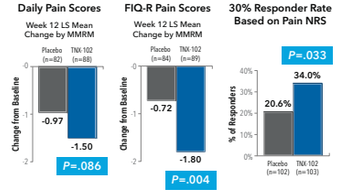


Continuous Responder Analysis on IVRS NRS Average Daily Pain Scores at Week 12



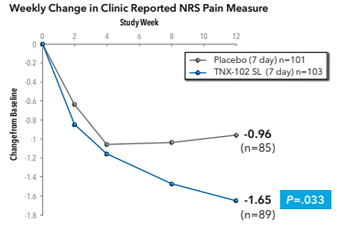
TNX-102 SL Provides Relief from Pain

Effect of TNX-102 SL on Pain Endpoints



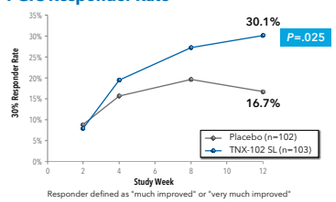
MMRM=Mixed model for repeated measures

Time Course of Pain Reduction



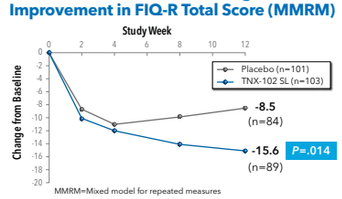
TNX-102 SL Improves Fibromyalgia Global and Functional Measures

PGIC Responder Rate



Responder defined as "much improved" or "very much improved"

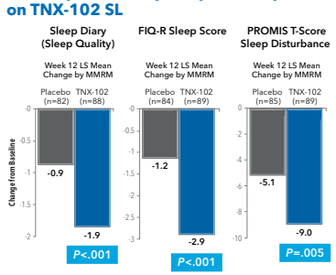
TNX-102 SL Demonstrated a Significant Improvement in FIQ-R Total Score (MMRM)



MMRM=Mixed model for repeated measures

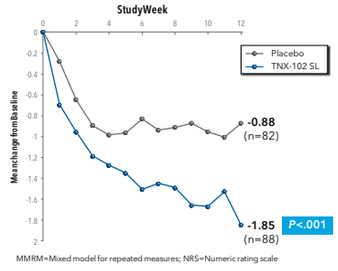
TNX-102 SL Improves Sleep Quality

All Sleep Secondary Endpoints Improved on TNX-102 SL



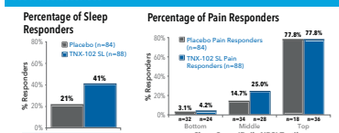
MMRM=Mixed model for repeated measures

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



MMRM=Mixed model for repeated measures; NRS=Numeric rating scale

TNX-102 SL Effect on Sleep Responders Supports Hypothesis of Restorative Sleep Mechanism



Tertiles of sleep score were analyzed based on total completer population
Phase 2b BESTFIT Results

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%)
	Diarrhoea	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

- TNX-102 SL provides multisymptom relief
- TNX-102 SL significantly improved global and functional measures such as PGIC and FIQ-R total score
- Systemic adverse events for TNX-102 SL were similar to placebo in the BESTFIT study
- 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
- TNX-102 SL has simple, once-daily dosing at bedtime with no need to titrate or adjust the dose
- TNX-102 SL increased sleep quality as evidenced by an increase in sleep responders
- Correlation of pain response with sleep response, regardless of treatment arm, suggests that improving sleep improves pain outcomes
- TNX-102 SL may be improving pain outcomes by improving restorative sleep

References

1. Data on file, Tonix Pharmaceuticals.

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