TNX-102 SL* for the Treatment of Fibromyalgia: Role of Nonrestorative Sleep on Pain Centralization

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Introduction

- In patients with fibromyalgia (FM), sleep quality has been shown to correlate to symptoms: when sleep is perceived as restful, patients report substantial improvement in their daytime symptoms
- Unfortunately, poor nighttime sleep has been considered as a predictor of a more painful day, and a more painful day in turn tends to be followed by poorer sleep at night, creating a vicious cycle
- The importance of nonrestorative sleep in the pathophysiology of FM suggests that treatments that improve sleep quality may improve FM globally by a mechanism distinct from that of centrally acting analgesics
- TNX-102 SL is an eutectic sublingual formulation of cyclobenzaprine (CBP) designed for rapid transmucocal absorption and bedtime use
- Phase 1 comparative pharmacokinetic study supports the advantage of the proprietary CBP eutectic formulation
- The current study was designed to evaluate the safety and efficacy of TNX-102 SL in the treatment of FM

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
- 205 participants in 17 centers in the United States
  - Placebo (n=102)
  - TNX-102 SL 2.8 mg (n=103)

Entry Criteria

- The patient had a diagnosis of primary fibromyalgia as defined by the 2010 ACR Preliminary Diagnostic Criteria for fibromyalgia defined as all of the following:
  a) WPI ≥7 and 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 daily diary pain score during week 12
- 11-point (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
- PROMIS Sleep Disturbance Instrument

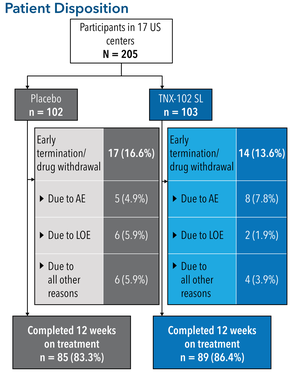
Safety Evaluation

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

Baseline Characteristics

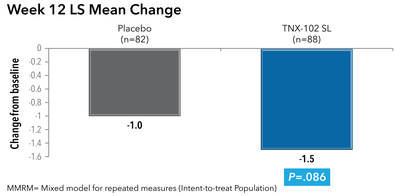
Characteristic	Placebo N=101	TNX-102 SL N=103
Age (SD)	49.7 (11.7)	50.7 (9.9)
Males (%)	3 (3%)	7 (6.8%)
Caucasian (%)	88 (87%)	91 (88%)
Weight, kg (SD)	80.9 (17.2)	80.6 (16.7)
BMI (SD)	30.0 (5.5)	30.0 (5.7)
Never smoked	68%	60%
Currently employed	55%	48%
College level or higher education	77%	85%

Patient Disposition



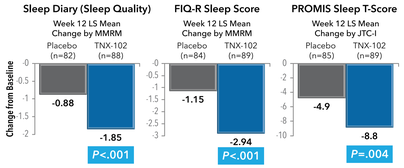
LOE = Lack of efficacy

TNX-102 SL Daily Pain Scores at Week 12 (MMRM)



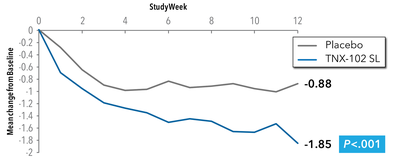
MMRM= Mixed model for repeated measures (Intent-to-treat Population)

All sleep secondary endpoints improved on TNX-102 SL



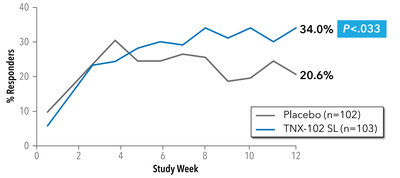
JTC-I = Jump To Control/Multiple Imputations (Intent-to-treat Population)
MMRM= Mixed model for repeated measures

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

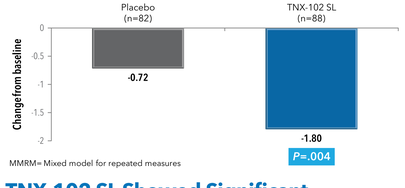


MMRM=Mixed model for repeated measures; NRS=Numeric rating scale

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

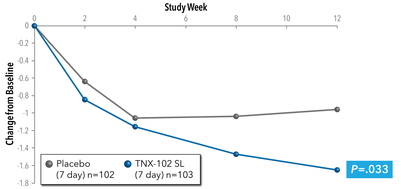


TNX-102 SL Improved FIQ-R Pain Scores

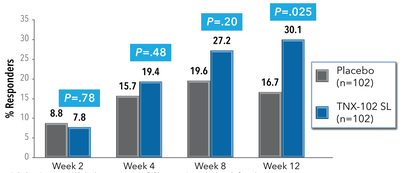


MMRM= Mixed model for repeated measures

TNX-102 SL Showed Significant Improvement on the Clinic-Reported Numeric Rating Scale Pain Measure

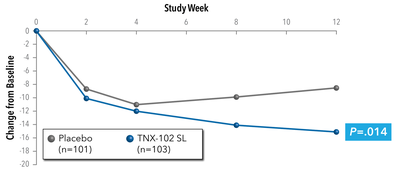


PGIC Response Rate Over Time



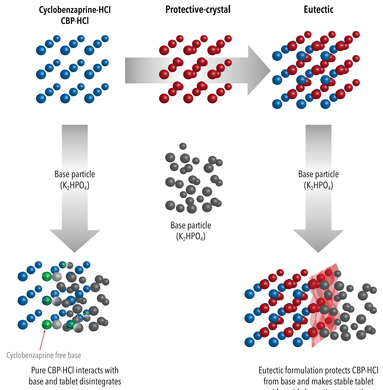
PGIC = Patients' Global Impression of Change, Responder defined as "Much Improved" or "Very Much Improved"

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



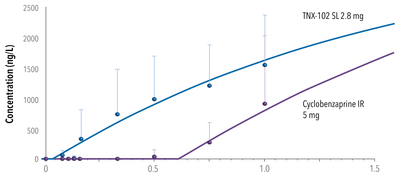
MMRM= Mixed model for repeated measures

Proprietary Cyclobenzaprine Hydrochloride Eutectic Mixture Stabilizes Tablet Formulation



Cyclobenzaprine Is Detected in Plasma Within 20 Minutes Following Sublingual Administration of TNX-102 SL 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
$AUC_{0\text{-}48}$	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
$AUC_{0\text{-}48}$	30.5 ng•hr/mL	58.6 ng•hr/mL	48% lower for SL

TNX-102 SL Adverse Events

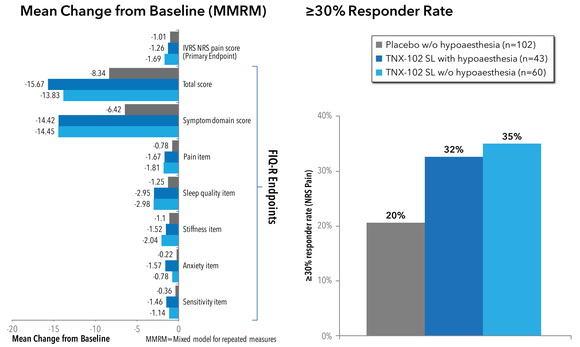
Systemic Adverse Events (>2 subjects in either group)

System Organ Class	Adverse Event Term	Placebo (n=101)	TNX-102 SL (n=103)
Gastrointestinal Disorders	At least 1 TEAE	58 (57.4%)	80 (77.7%)
	Hypoaesthesia oral	1 (1.0%)	43 (41.7%)
	Dry mouth	4 (4.0%)	4 (3.9%)
	Constipation	1 (1.0%)	4 (3.9%)
	Nausea	2 (2.0%)	3 (2.9%)
	Paraesthesia oral	0	3 (2.9%)
	Vomiting	0	3 (2.9%)
Infections and infestations	Sinusitis	3 (3.0%)	3 (2.9%)
	Nasopharyngitis	2 (2.0%)	3 (2.9%)
	Upper respiratory tract infection	2 (2.0%)	3 (2.9%)
	Urinary tract infection	1 (1.0%)	3 (2.9%)
	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

Oral Adverse Events (≥2 subjects in either group)

Adverse Event Term	Placebo (n=101)	TNX-102 SL (n=103)
Hypoaesthesia oral	1 (1.0%)	43 (41.7%)
Product taste abnormal	-	8 (7.8%)
Glossitis	1 (1.0%)	2 (1.9%)
Glossodynia	1 (1.0%)	2 (1.9%)
Paraesthesia oral (tingling)	-	3 (2.9%)
Swollen tongue	1 (1.0%)	2 (1.9%)
Aphthous stomatitis	1 (1.0%)	1 (1.0%)
Lip swelling	-	2 (1.9%)
Tongue ulceration	-	2 (1.9%)

Presence of Oral Adverse Events Did Not Lead to Significant Differences in Outcome Measures



MMRM= Mixed model for repeated measures

Conclusions

- TNX-102 SL, an eutectic sublingual formulation of CBP, administered at bedtime improved sleep quality by multiple measures
- Nonrestorative sleep has been linked to central sensitization, which is a process in which regional chronic pain leads to changes in central pain processing and interpretation
- Treatment with TNX-102 SL demonstrated improvement in sleep quality, which in turn led to a broad range of FM symptom improvements including PGIC, FIQ-R total score, as well as pain reduction (30% response)
- A Phase 3 study has been initiated based on this outcome

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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