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

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Background

- Fibromyalgia is characterized by symptoms that include widespread pain and sleep disruption
- Clinical studies that rely on patient self-reported outcome measures such as pain scales may be analyzed by responder analysis (comparisons of proportions of treated patients achieving a predefined clinically meaningful improvement threshold) and by group mean changes
- In a phase 2b trial of TNX-102 SL,* a proprietary eutectic sublingual (SL) tablet formulation of low-dose cyclobenzaprine HCl (2.8 mg) in fibromyalgia patients (BESTFIT), we compared responder analyses to group mean change analyses for the evaluation of changes in pain and fibromyalgia symptoms

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 as 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
- Pain was measured on a 0-10 Numerical Rating Scale (NRS) that was completed every evening using a telephonic system
- Topline results from BESTFIT are presented elsewhere

Responder Analysis vs Mean Change from Baseline

- Responders for comparison to group mean changes are defined as follows:
  - Pain: ≥30% improvement from baseline
  - Patient Global Impression of Change (PGIC): score of 1 or 2 on the 1-7 score
  - Fibromyalgia Impact Questionnaire-Revised (FIQ-R) total score, pain item and domain scores: ≥30% improvement from baseline

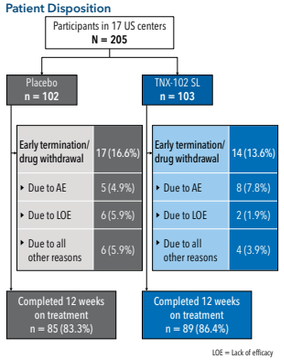
Safety Evaluation

- 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



Efficacy Measurements

Numerical Rating Scale (NRS) of average pain intensity

- Patients assessed using a daily telephone diary (interactive voice response system [IVRS])
  On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your average pain over the past 24 hours?

Please rate your average pain	No pain 0 1 2 3 4 5 6 7 8 9 10 Worst possible pain

Patient Global Impression of Change (PGIC)

- Patients assessed at weeks 2, 4, 8 and 12
  Overall, since the start of the study, my fibromyalgia is:

	Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	Very much worse
Score	1	2	3	4	5	6	7

Fibromyalgia Impact Questionnaire-Revised (FIQ-R)

- Assess the impact of fibromyalgia on a patient's well-being
- 7-day recall
- Patients assessed at weeks 2, 4, 8 and 12

Functional Domain

Brush/comb hair
Walk continuously for 20 minutes
Prepare homemade meal
Vacuum, scrub, sweep floors
Lift/carry bag full of groceries
Climb 1 flight of stairs
Change bed sheets
Sit in chair for 45 minutes
Shop for groceries

No difficulty NA 0 — Very difficult 10

Overall Impact Domain

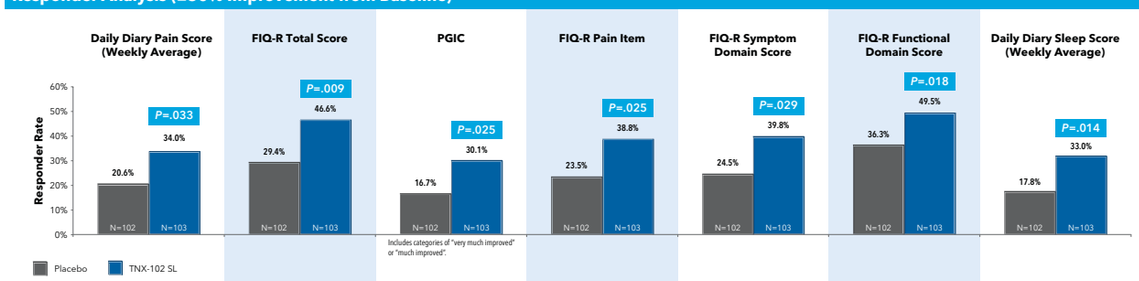
Fibromyalgia prevented goal accomplishment
Completely overwhelmed by fibromyalgia symptoms

Never 0 — Always 10

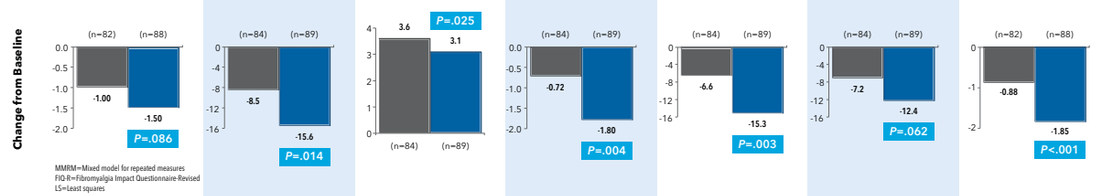
Symptoms Domain

	0	10
Level of pain	No pain	Unbearable pain
Level of energy	Lots of energy	No energy
Level of stiffness	No stiffness	Severe stiffness
Quality of sleep	Awoke rested	Awoke very tired
Level of depression	No depression	Very depressed
Level of memory problems	Good memory	Very poor memory
Level of anxiety	Not anxious	Very anxious
Level of tenderness to touch	No tenderness	Very tender
Level of balance problems	No imbalance	Severe imbalance
Level of sensitivity to loud noises, bright lights, odors, and cold	No sensitivity	Extreme sensitivity

Responder Analysis (≥30% Improvement from Baseline)



Mean Change from Baseline at Week 12 (MMRM)



MMRM=Mixed model for repeated measures
FIQ-R=Fibromyalgia Impact Questionnaire-Revised
LS=Least squares

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

- Results from this Phase 2b trial support the finding that responder analyses for pain studies and other indications relying on patient-reported outcomes may reveal significant and meaningful effects that are missed by group mean changes[1]
- 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
- Although the primary endpoint for BESTFIT was based on analysis of improvements in pain, the mechanism of action of this intervention is believed to be targeting of nonrestorative sleep. 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 seems to be a more appropriate approach to the evaluation of TNX-102 SL in fibromyalgia

References

1. Witter J, Simon LS, Dianne R. Are means meaningless? The application of individual responder analysis to analgesic drug development. *APS Bulletin*. 2003;13:4-7.
2. 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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