TNX-102 SL* for Treatment of Fibromyalgia: Approaches to Pain Measurement

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Introduction

- TNX-102 SL is a novel sublingual investigational formulation of low dose (2.8 mg) cyclobenzaprine designed for rapid absorption and routine bedtime use
- We recently completed a Phase 2b trial (BESTFIT) of TNX-102 SL, which was the first large scale evaluation of this therapeutic approach in fibromyalgia patients
- In addition to assessments of the efficacy of TNX-102 SL in reducing symptoms of fibromyalgia, we explored various methodological approaches to evaluation of changes in patient reported 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
- 205 participants in 17 centers in the United States
  - Placebo (n=102)
  - TNX-102 SL 2.8 mg (n=103)

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

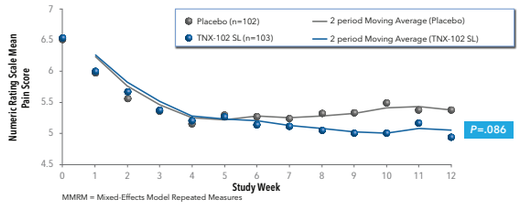
Key secondary efficacy endpoints

- Patient Global Impression of Change (PGIC)
- Fibromyalgia Impact Questionnaire-Revised (FIQ-R)
- Daily Sleep Diary
- PROMIS Sleep Disturbance Instrument

Safety Evaluation[1]

- Adverse events
- Oral adverse events

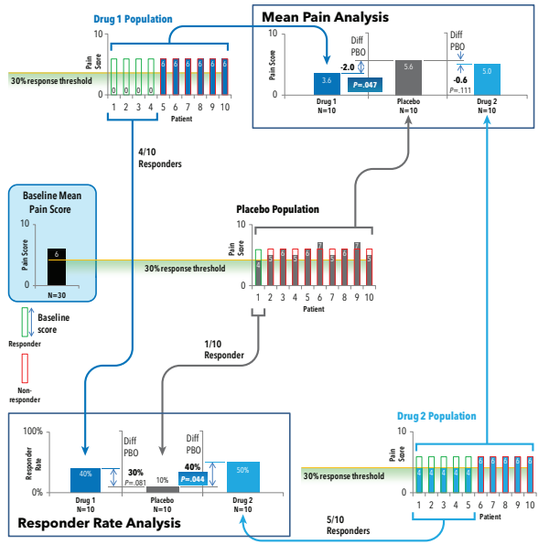
Change from Baseline (CFB) in Mean Pain over 12 Weeks Was Numerically Lower for TNX-102 SL Than for Placebo (MMRM)



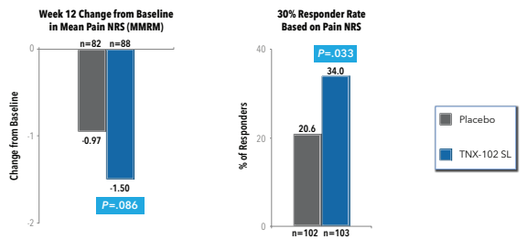
MMRM = Mixed-Effects Model Repeated Measures

Responder Analysis versus Mean Pain Analysis Has More Clinical Relevance and Greater Statistical Significance in Certain Cases

Hypothetical Clinical Trial Result

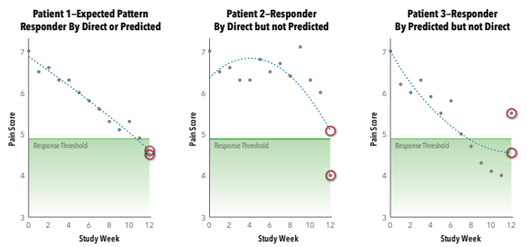


In BESTFIT, TNX-102 SL Had a Significant Effect on 30% Responder Rate but Not Mean Pain



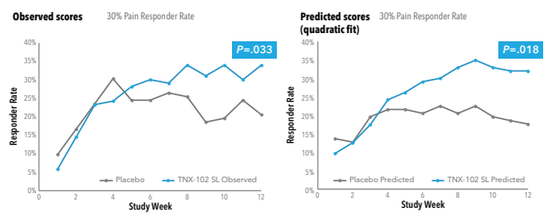
MMRM = Mixed-Effects Model Repeated Measures; NRS = Numeric Rating Scale

Quadratic Fitting Normalizes Anomalies That May Occur in Individual Pain Scores at Study Endpoint

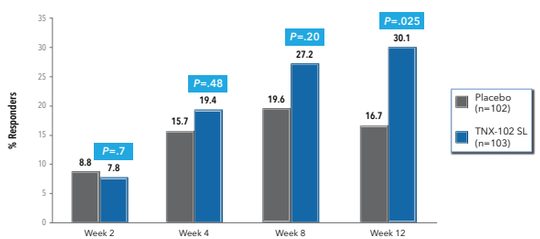


- Predicted values obtained by 2nd order line fitting normalizes anomalous results that may occur at individual study visits
- Because a patient's response is based on the week 12 score, anomalous results at week 12 can skew the response rate
- Response rates based on predicted pain scores can compensate for anomalous scores, leading to reduced variation and lower *P*-values

30% Responder Rate Predicted Scores Were More Significant than Observed Scores

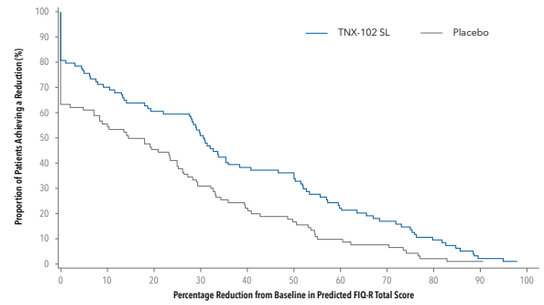


PGIC Response Rate Over Time



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

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



Conclusions

- To convey the benefits of a pain medication to patients and physicians, responder analysis is more clinically relevant and comprehensible than change from baseline
- Change from baseline analysis is often preferred because it generally has more power to detect a treatment effect, thus necessitating fewer patients in the study
- Using predicted pain score values for response categorization of individual patients may improve the statistical significance of the response rates
- TNX-102 was significantly better than placebo on the pain responder rates determined using the pain numeric rating scale
- The most common local adverse event was transient tongue or mouth numbness occurring in 42% of treated patients. No systemic adverse events were noted in >5% of treated patients.
- Regulators have recognized that responder analyses have face validity and are a viable alternative to mean change analyses to determine therapeutic efficacy

References

1. Lederman S, Clauw D, Gendreau J, et al. TNX-102 SL for the treatment of fibromyalgia: role of nonrestorative sleep on pain centralization. Annual European Congress of Rheumatology, Rome, Italy, 10–13 June 2015, Abstract THU0325.
2. Moore RA, Moore OA, Derry S, Peloso PM, Gammaitoni AR, Wang H. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Ann Rheum Dis.* 2010;69(2):374-379.
3. Data on file. Tonix Pharmaceuticals.

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

Gendreau RM, Clauw D, Gendreau J, Daugherty B, Lederman S. TNX-102 SL for treatment of fibromyalgia: approaches to pain measurement. Poster presented at: 16th EULAR Annual European Congress of Rheumatology; June 10-13, 2015; Rome, Italy.