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

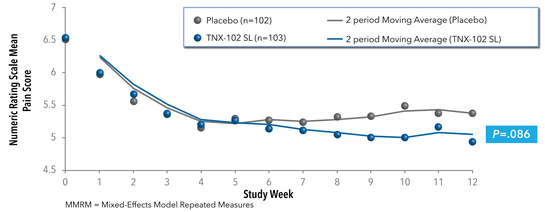
Key secondary efficacy endpoints

- 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

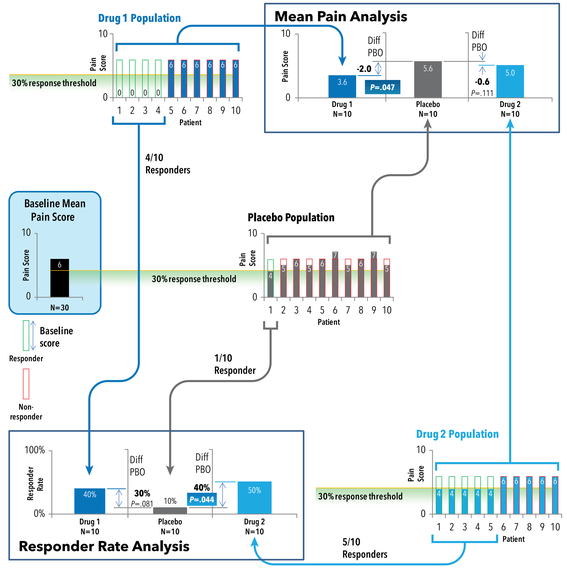
Change from Baseline (CFB) in Mean Pain over 12 Weeks Was Numerically Lower for TNX-102 SL Than for Placebo (MMRM)



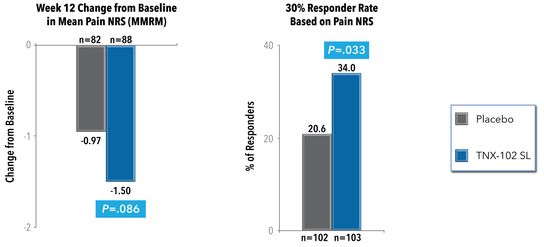
MMRM = Mixed-Effects Model Repeated Measures

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

Hypothetical Clinical Trial Result

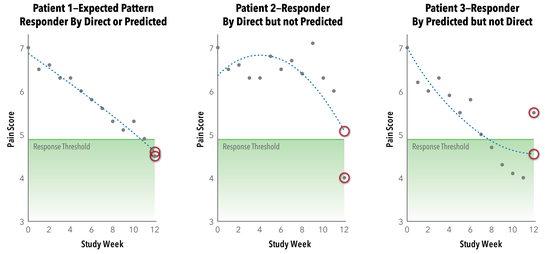


In BESTFIT, TNX-102 SL Had a Significant Effect on 30% Responder Rate but Not Mean Pain



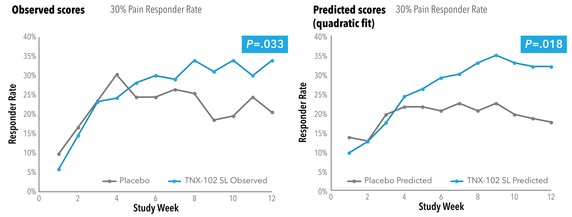
MMRM = Mixed-Effects Model Repeated Measures; NRS = Numeric Rating Scale

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

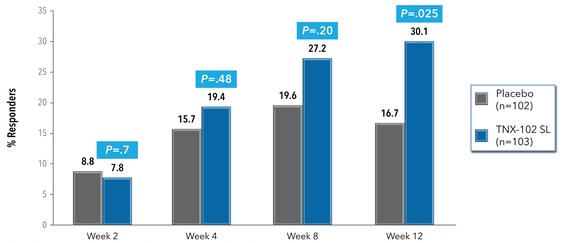


- Predicted values obtained by 2nd order line fitting normalizes anomalous results that may occur at individual study visits
- Because a patient's response is based on the week 12 score, anomalous results at week 12 can skew the response rate
- Response rates based on predicted pain scores can compensate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

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

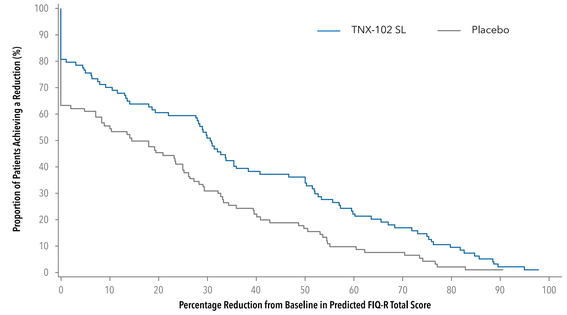


PGIC Response Rate Over Time



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.