TNX-102 SL FOR THE TREATMENT OF FIBROMYALGIA

COMPARISON OF 30% PAIN RESPONDER ANALYSIS WITH OMERACT DRAFT COMPOSITE RESPONDER ENDPOINT ANALYSES

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Background

Novel responder definitions for fibromyalgia (FM) clinical trials have been proposed by the Outcome Measures in Rheumatology (OMERACT) FM subcommittee as alternative methods by which to assess efficacy. These definitions include key symptom and functional domains relevant to FM patients, and were validated using outcome data from 12 previous registration trials of 4 medications – milnacipran, pregabalin, duloxetine and sodium oxybate (Arnold L et al, Arth Rheum 64:885, 2012.)[1] TNX-102 SL* is a proprietary sublingual formulation of cyclobenzaprine designed for rapid absorption and bedtime use. It showed improvements in pain and other symptoms in a Phase 2B study.[2]

The BESTFIT study was a 12-week, randomized, double-blind, placebo-controlled trial conducted at 17 US sites, designed to evaluate TNX-102 SL as a potential treatment for FM. 205 participants were randomized (TNX-102 SL=103; placebo=102). The outcome results of BESTFIT were reanalyzed using four variants of the measures proposed by OMERACT, and these results were then compared to the primary outcomes used in BESTFIT.

Methods

OMERACT initially evaluated 24 different response definitions in an attempt to find constructs that assessed multiple domains important to fibromyalgia patients, and when used to evaluate clinical trial results were efficient in separating treatment responses from placebo responses. Using clinical data from 12 registration-quality, randomized, placebo-controlled trials of 4 different medications for the treatment of FM, each definition was evaluated. Two definitions performed best in these pooled analyses: the FM30 short version and the FM30 long version.

Both definitions required a ≥30% reduction in pain and ≥10% improvement in physical function. The definitions differed in that one (≥30% improvement in FM [FM30] short version) required ≥30% improvement in sleep or fatigue, and the other (FM30 long version) required ≥30% improvement in 2 of the following symptoms: sleep, fatigue, depression, anxiety, or cognition. Each of these definitions, with two alternative measures used to assess physical function, were evaluated in this analysis of BESTFIT data. Figure 1 below illustrates the two responder definitions evaluated for this analysis.

Results

Table 1 below presents the response rates obtained when each of the proposed definitions was evaluated with the data from BESTFIT.

Figure 1 graphically compares the standard pain responder analysis used in BESTFIT (≥30% improvement in pain from baseline based on daily diary recorded pain scores) to the alternative composite responder definitions proposed by OMERACT.

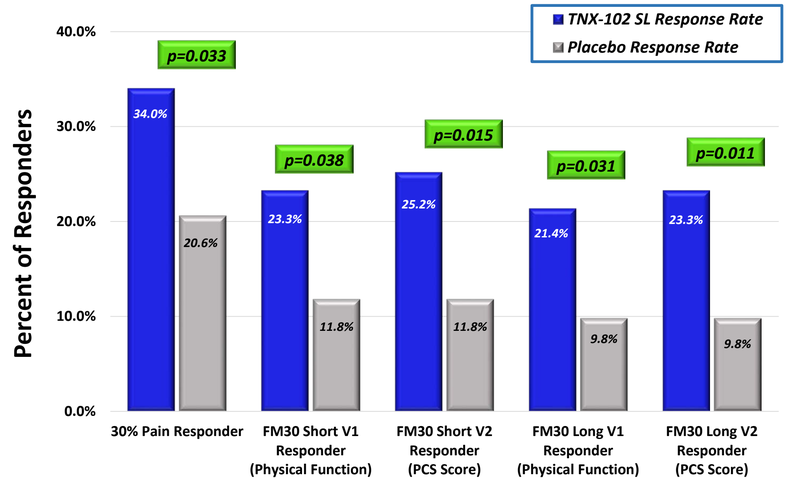
To the far right, Figure 2 presents the effects of TNX-102 SL on a number of sleep and function measures and Figure 3 presents additional responder analyses on key secondary measures from BESTFIT.

Table 1. Comparison of a Pain Responder Analysis to Alternative Composite Responder Definitions

Responder Definition/ Result	Physical Function Measure	Additional Symptom Measures	TNX-102 SL Responders	Placebo Responders	p-value
30% Pain Responder#	----	----	34.0%	20.6%	p= 0.033
FM30 Short Version 1	SF-36 Physical Function	FIQR energy or FIQR sleep quality	23.3%	11.8%	p= 0.038
FM30 Short Version 2	SF-36 PCS Score		25.2%	11.8%	p= 0.015
FM30 Long Version 1	SF-36 Physical Function	Any 2 of the following FIQR measures: Energy, Sleep quality, Depression, Anxiety	21.4%	9.8%	p= 0.031
FM30 Long Version 2	SF-36 PCS Score		23.3%	9.8%	p= 0.011

#*based on daily diary responses*
PCS: Physical Component Summary; *FIQR*: Fibromyalgia Impact Questionnaire (Revised)

Figure 1. Comparison of a Pain Responder Analysis to Alternative Composite Responder Definitions

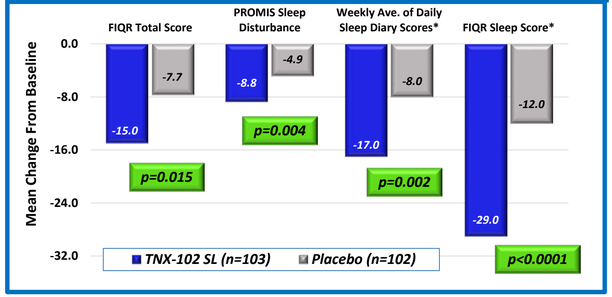


Systemic adverse events reported were similar to placebo. The most common local adverse event was transient tongue or mouth numbness, reported by 44% of TNX-102 SL patients and 2% of placebo patients.

Patient Global Impression of Change (PGIC) assesses the patient's perception of change in fibromyalgia using a 7-point Likert scale. "Response" is defined as a score of 1 (very much improved) or 2 (much improved) on the scale.

FIQR is made up of 3 domains: function (9 questions), overall impact (2 questions), and symptoms (10 questions); within the domains, each question is measured on an 11-point scale on a 7-day recall basis.

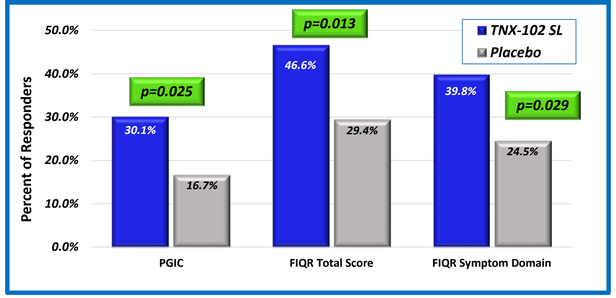
Figure 2. Effects of TNX-102 SL on Sleep and Function Measures

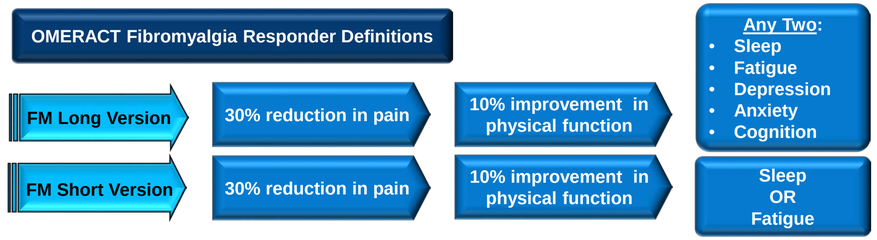


**For presentation purpose, responses are provided on the same scale. Actual results were -1.7 and -0.8 for TNX-102 SL and placebo (Diary sleep scores) and -2.9 and -1.2 (FIQR Sleep scores).*

PROMIS: Patient Reported Outcomes Measurement Information; Analyses performed using least squares mean (LS Mean) change from Baseline at Week 12

Figure 3. Responder Analysis (≥30% Improvement from Baseline)





Conclusion

In the BESTFIT trial, bedtime TNX-102 SL improved multiple domains of FM, including sleep, pain and physical function. Applying composite responder criteria developed by OMERACT to the results of this study gave results consistent with the conclusions of BESTFIT; namely that the improvements in FM symptoms seen with TNX-102 SL treatment are not limited only to an analgesic response, since these composite criteria require improvement in other somatic and functional symptoms. The proposed OMERACT response criteria provide an additional method by which to assess clinical benefit in fibromyalgia clinical trials.

References:
1. Arnold, Lesley M., et al. "Development of responder definitions for fibromyalgia clinical trials." *Arthritis & Rheumatism* 64.3 (2012): 885-894.
2. Gendreau, Michael R., et al. Responder Compared to Mean Change Analyses in a Fibromyalgia Phase 2b Clinical Study of Bedtime Rapidly Absorbed Sublingual Cyclobenzaprine (TNX-102 SL). Poster session presented at: 2015 American College of Rheumatology Annual Meeting; 2015 Nov 7-11; San Francisco, CA.
3. Data on file, Tonix Pharmaceuticals

Disclosure of Interest: None declared

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