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Lead 'tonic' for Tonix targets fibromyalgia in phase III study

By Marie Powers, News Editor

Tonix Pharmaceuticals Holding Corp. took a giant step toward moving its lead compound, TNX-102, across the goal line by launching the phase III AFFIRM study in patients with fibromyalgia. The randomized, double-blind, placebo-controlled study is evaluating TNX-102 – a low-dose, sublingual formulation of the muscle relaxant cyclobenzaprine – taken daily at bedtime in improving pain, sleep quality and other clinical measures, as well as safety.

The pivotal study is expected to enroll approximately 500 patients at up to 35 U.S. centers, with top-line data due to report in the second half of next year.

The trial was designed with input from the FDA, which agreed to accept a pain responder analysis – defined as the proportion of patients who report at least a 30 percent reduction in pain from baseline at the end of the 12-week treatment period – as the primary endpoint., according to Seth Lederman, the company's co-founder, chairman and CEO. A dozen secondary endpoints include changes from baseline in the weekly average of patient-reported sleep quality and pain severity, the Patient-Reported Outcomes Measurement System for sleep disturbance, the total score on the Fibromyalgia Impact Questionnaire (FIQ-R), the proportion of patients with a Patient's Global Impression of Change rating of "very much improved" or "much improved," and various safety factors – all after 12 weeks of treatment.

The technology underlying TNX-102 germinated more than 15 years ago at Vela Pharmaceuticals Inc., of Lawrenceville, N.J., whose co-founders included Lederman and Donald Landry – later Tonix co-founders. Vela (originally named Janus Pharmaceuticals Inc.) was a venture-backed start-up developing medicines for central nervous system disorders that "took a turn" in the early 2000s into gastrointestinal disorders, Lederman said. In 2006, Vela was acquired by Pharmos Corp. in a deal valued at about $29.7 million, mainly to gain access to Vela's phase II irritable bowel syndrome candidate, R-tofisopam. At that time, the rights to the cyclobenzaprine technology were returned to Lederman and Landry. (See *BioWorld Today*, Nov. 2, 2000, and March 16, 2006.)

The two immediately tried to form a company around the technology but were side-tracked by the financial crisis. Using private money, they finally got Tonix off the ground in 2009, picking up many of Vela's former managers and directors, including Ernest Mario, former deputy chairman and CEO of Glaxo Holdings plc.

Lacking an IPO alternative in the early years of recovery from the Great Recession, in 2011 Tonix completed a reverse merger with a shell to gain access to the public markets, where its shares (NASDAQ:TNXP) now trade, closing up 2 cents on Wednesday at $6.19.

New York-based Tonix has been out of the limelight, Lederman acknowledged, because "we're not in the mainstream of what's exciting," with a small pipeline – just two assets – targeting three enormous indications: fibromyalgia, which affects 5 million to 15 million patients in the U.S.; post-traumatic stress disorder (PTSD), which affects some 8.5 million; and tension headache, which affects some 70 million, or nearly 1 in 3 U.S. adults.

Lederman, who directed basic science research in molecular immunology, infectious diseases and the development of therapeutics for autoimmune diseases at Columbia University and maintains an appointment there as associate professor, admitted that he was a skeptic about fibromyalgia – now the flagship program at Tonix – until he treated patients and gained an appreciation for the unmet medical need.

The condition is characterized primarily by chronic widespread pain and non-restorative sleep, resulting in unrelenting fatigue. But an equally large challenge for these patients, Lederman said, is "central sensitization" – the amplification of every sensory input, resulting in an outsized response to a range of stimuli, including bright light, noxious odors, loud sounds and bitter tastes.

Existing therapies for fibromyalgia also are limited by tolerability, according to Lederman. TNX-102 addresses not only the need for long-term tolerability but also the central sensitization issue with an "elegant" formulation that, when taken at bedtime, reduces the delay in absorption compared to an oral tablet.

"The sublingual characteristics are essential to making this work," he told *BioWorld Today*.

POSITIONING DRUG TO BE 'FIRST-LINE PLATFORM THERAPY'

The technology, which was developed at the angstrom level – 1,000 times smaller than a nanometer – is based on a eutectic system in which the active ingredient, cyclobenzaprine, is co-penetrated with another crystal to form a protective sheath. The upshot is that the formulation drives sublingual transmucosal absorption, creating a rapidly acting drug.

Tonix has filed multiple patents on the technology, giving the company strong intellectual property protection until at least 2030, according to Lederman.

In addition to AFFIRM, Tonix completed a phase IIb study, dubbed BESTFIT, that was designed as a registration study and enrolled 200 patients. BESTFIT showed a statistically significant effect of TNX-102 on pain by a 30 percent responder analysis of the primary pain data – the primary endpoint of AFFIRM – but did not achieve statistical significance in its primary efficacy endpoint of change in average daily pain score at week 12. However, TNX-102 also showed statistically significant improvements in secondary measures of patient global impression of change, FIQ-R total score and sleep quality.

Although Tonix likely will launch an additional phase III while AFFIRM is under way, because the BESTFIT responder analysis was positive, "we believe there's a chance the FDA will consider AFFIRM as a pivotal study with BESTFIT as highly supportive," Lederman said. "If we show a very significant effect with AFFIRM, we might be able to argue that one pivotal study might be enough. The position of the agency is that they won't know until they see the AFFIRM data."

In the meantime, the company is conducting a 12-month open-label extension study of BESTFIT primarily to collect additional human exposure data for its filing. Tonix – the name refers to an old usage of "tonic," or gentle, soothing medicine – plans to file its new drug application (NDA) through the 505(b)(2) pathway.

TNX-102 could become what Lederman called a "first-line platform therapy" not only for fibromyalgia but also for PTSD, which shares a "curious and unexplained" clinical overlap, especially with respect to pain and non-restorative sleep. Although pain is not considered an indicator in the diagnosis of PTSD, "pain is an important part of the experience" of the disorder, he said.

Tonix is currently running the randomized, double-blind, placebo-controlled, fixed-dose, parallel-group phase II AtEase study of TNX-102 in PTSD, also designed as a "registration quality" trial, with approximately 220 patients expected to be enrolled at up to 24 U.S. sites.

Although Lederman characterized AtEase as a proof-of-concept study, the primary endpoint is an evaluation of efficacy using the DSM-5 total symptom severity score over 12 weeks. If the data are positive, Tonix hopes the FDA will accept the study as the first of two pivotals.

The company also could seek breakthrough therapy designation for TNX-102 in PTSD, which is associated with high rates of suicide among patients.

The company's second asset, TNX-201, is in a phase I study in healthy volunteers and is expected to move into a phase II study this quarter in patients with episodic tension-type headaches.

Tonix will likely stay focused in clinical development, according to Lederman, although he didn't rule out an internal commercial effort for TNX-102 in PTSD by partnering with the U.S. military through a restricted distribution license.

In general, "we're going for such large indications that it's really not practical for us to contemplate even in our wildest dreams to market these drugs," Lederman admitted. "We're actively seeking commercialization partners, although we're funded to get to the next points in all of these studies so we don't have any need to do a deal in the short term."