Tolperisone 100 and 200 mg Three Times Daily for Acute Muscle Spasm of the Back: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Phase 3 Study

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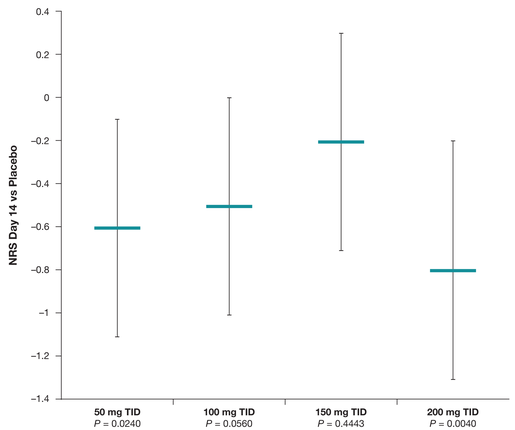
BACKGROUND

- Acute muscle spasm is a common condition that is often the cause of back pain[1]
  - Back pain, one of the most common reasons for a physician visit, is typically disabling and has a significant impact on an individual's quality of life
  - In a retrospective analysis of a US commercial database of more than 75 million individuals with newly diagnosed low back pain or lower extremity pain between 2008 and 2015, the total costs of care for those who did not undergo surgery were $1.8 billion[2]
  - Acute muscle spasm is typically treated with nonpharmacologic options (eg, superficial heat compress, physical therapy), over-the-counter oral or topical medications (eg, nonsteroidal anti-inflammatory drugs, acetaminophen, menthol), and skeletal muscle relaxants (SMRs)[1,3-5]
  - There are drawbacks to prescribing currently available SMRs, including side effects, such as somnolence
  - Office visits associated with a newly prescribed or continued SMR prescription nearly doubled, from 15.5 million in 2005 to 30.7 million in 2016[6]
    - Although office visits tied to new SMR prescriptions remained stable (~6 million per year), office visits with continued SMR drug therapy tripled, from 8.5 million visits in 2005 to 24.7 million visits in 2016
    - Current recommendations generally limit the duration of use of SMRs to a maximum of 2 to 3 weeks due to the risk of side effects
  - Opioids may be effective, but their use is associated with well-documented addiction and public health issues[7,8]

Tolperisone: an SMR that does not appear to be associated with somnolence

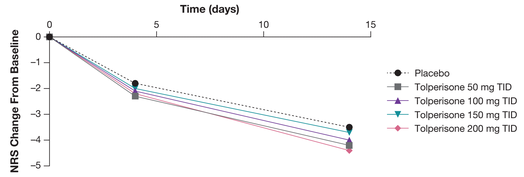
- Tolperisone, a centrally acting, non-opioid SMR, is in clinical development in the United States for the treatment of pain symptoms associated with acute muscle spasm of the back
  - Tolperisone has been available for decades in Europe and Asia for the therapeutic treatment of poststroke spasticity and in some countries for acute painful muscle spasm
  - In Switzerland, tolperisone is indicated for the treatment of muscle spasm, and is typically prescribed at a dose of 150 mg 3 times a day (TID) for an extended period (months)
  - Tolperisone has not been clinically developed in the United States due to a degradant that exceeds International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. However, because of an enhanced formulation pathway, an ultra-pure formulation has been developed for use in the United States
  - Importantly, clinical experience indicates that in contrast with other centrally acting SMRs, tolperisone use does not appear to be associated with somnolence or cognitive impairment[9]
  - The recently completed dose-ranging phase 2 STAR study (NCT03802565) evaluated tolperisone administered at 50, 100, 150, and 200 mg TID for 14 days in subjects with acute muscle spasm of the back
    - The overall trend in numeric rating scale (NRS) rating of pain "right now" across dose groups at day 14 trended toward statistical significance ($P = 0.0539$). Least-squares mean differences (LSMDs) (treatment-placebo) from the mixed-effect model for repeated measures estimates of NRS at day 14 were –0.6 ($P = 0.0240$), –0.5 ($P = 0.0506$), –0.2 ($P = 0.4443$), and –0.8 ($P = 0.0040$) in the tolperisone 50 mg TID, 100 mg TID, 150 mg TID, and 200 mg TID dose groups, respectively (**Figure 1**)

Figure 1. Numeric Rating Scale "Right Now" LSMDs (treatment-placebo) From the Mixed-Effect Model for Repeated Measures Estimate of Numeric Rating Scale (95% CI)



- Subject-rated pain "right now" demonstrated a mean decrease from baseline at day 14 of –4.4, –3.7, –4.0, and –4.2 in the tolperisone 50 mg TID, 100 mg TID, 150 mg TID, and 200 mg TID dose groups, respectively, versus –3.5 in the placebo group (**Figure 2**)

Figure 2. Change From Baseline NRS "Right Now" Scores



- Although the study was not sufficiently powered, a number of secondary efficacy end points also trended toward statistical significance at the tolperisone 200 mg TID dose
  - This included personal care, walking, and social life subcategories of the Oswestry Disability Index (ODI), and both the subject rating of medication helpfulness and Patient's Global Impression of Change (PGI-C)
- Tolperisone was well tolerated and its treatment-related adverse events (AEs) were similar to those of placebo (**Table 1**)
- The incidence of somnolence was comparable between subjects treated with tolperisone versus placebo (0%, 3.4%, 0%, and 1.2% of subjects in the tolperisone 50 mg TID, 100 mg TID, 150 mg TID, and 200 mg TID dose groups, respectively, compared with 2.6% of those in the placebo group)

Table 1. AEs Reported for ≥2 Subjects in the Placebo Group or Total Tolperisone Group

System organ class Preferred term	Placebo n = 78	Tolperisone 50 mg TID n = 82	Tolperisone 100 mg TID n = 87	Tolperisone 150 mg TID n = 83	Tolperisone 200 mg TID n = 85	Tolperisone Total n = 337
Number (%) of subjects reporting ≥1 AE	11 (14.1)	10 (12.2)	16 (18.4)	15 (18.1)	20 (23.5)	61 (18.1)
Nervous system disorders	6 (7.7)	5 (6.1)	13 (14.9)	8 (9.6)	11 (12.9)	37 (11.0)
Headache	3 (3.8)	3 (3.7)	5 (5.7)	8 (9.6)	8 (9.4)	24 (7.1)
Dizziness	0	1 (1.2)	2 (2.3)	0	2 (2.4)	5 (1.5)
Somnolence	2 (2.6)	0	3 (3.4)	0	1 (1.2)	4 (1.2)
Disturbance in attention	0	0	1 (1.1)	1 (1.2)	0	2 (0.6)
Head discomfort	0	0	1 (1.1)	0	1 (1.2)	2 (0.6)
Migraine	2 (2.6)	0	0	0	0	0
Gastrointestinal disorders	0	4 (4.9)	4 (4.6)	4 (4.8)	4 (4.7)	16 (4.7)
Diarrhea	0	2 (2.4)	2 (2.3)	3 (3.6)	1 (1.2)	8 (2.4)
Nausea	0	1 (1.2)	1 (1.1)	1 (1.2)	2 (2.4)	5 (1.5)
Dyspepsia	0	0	1 (1.1)	0	1 (1.2)	2 (0.6)
Vomiting	0	0	0	1 (1.2)	1 (1.2)	2 (0.6)
Ear and labyrinth disorders	0	1 (1.2)	0	2 (2.4)	1 (1.2)	4 (1.2)
Vertigo	0	1 (1.2)	0	1 (1.2)	1 (1.2)	3 (0.9)

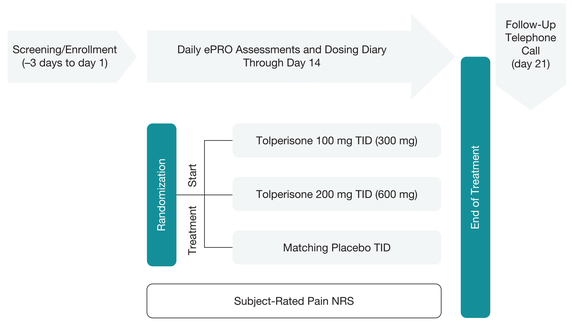
AEs defined as those that began or worsened on or after the date of the first dose through 24 hours or 1 day after the last dose.
At each level of summarization, subjects reporting >1 AE were counted only once.
AEs were coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

- Based on the results of the phase 2 STAR study and the safety and efficacy demonstrated by tolperisone, a pivotal phase 3 study has recently been initiated to evaluate the safety and efficacy of tolperisone (100 and 200 mg TID) for the relief of pain due to acute muscle spasm of the back
  - The tolperisone 200 mg TID dose was selected for the phase 3 study given the clinical efficacy signal observed and the balanced safety/tolerability profile from the phase 2 study
  - Selection of the 100 mg TID dose as the second dose of tolperisone in the phase 3 study was based on numerous inputs that are scientifically and clinically sound with a goal toward a two-fold difference between doses

The trial-in-progress: a double-blind, randomized, placebo-controlled, multicenter phase 3 study of tolperisone (100 and 200 mg TID) in subjects experiencing pain due to acute muscle spasm of the back

- Objectives of the study
  - Primary objective
    - To assess the efficacy and safety of tolperisone 100 mg and 200 mg TID for relief of pain due to acute back muscle spasm
  - Secondary objectives
    - To assess the tolerability of tolperisone in subjects with pain due to acute back muscle spasm
    - To determine onset of action of tolperisone in the treatment of pain due to acute back muscle spasm
    - To determine the need for rescue medication when treated with tolperisone for pain due to acute back muscle spasm
- Study Design
  - Subjects will be randomized 1:1:1 to tolperisone 100 mg TID or tolperisone 200 mg TID or placebo for 14 days (**Figure 3**)
  - Subjects can receive acetaminophen 500 mg TID as rescue medication, with use documented daily through day 14
  - The study will be approved by an institutional review board at each site

Figure 3. Study Design



ePRO, electronic patient-reported outcome.

- Study population
  - Key inclusion and exclusion criteria are presented in **Table 2**

Table 2. Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Ambulatory male or female, 18-64 years of age, inclusive
- Current acute back pain due to acute and painful muscle spasm starting within 7 days prior to study entry (day 1) and ≥8 weeks following the last episode of acute back pain
- Pain score of ≥4 on the subject "right now" rating of pain intensity NRS of 0-10 points at baseline
- Willingness to discontinue all previous or ongoing treatment of pain or muscle spasm on study entry at day 1 through the end of treatment, including medication, acupuncture, chiropractic adjustment, massage, transcutaneous electrical nerve stimulation, or physiotherapy
- Pain must be localized from the neck (C3 or lower) to the inferior gluteal folds and spasm assessed during the screening physical examination
- Body mass index range between 18 and 35 kg/m^2, inclusive

Exclusion Criteria

- Presence of acute or chronic back pain for the previous ≥8 days, where back pain is present on more days than not
- Presence of neurogenic pain in the back, neck, or upper or lower extremities, including pain from (or suspected from) nerve root compression or injury (radicular pain or "pinched nerve") or neuropathic pain. Evidence of these types of exclusionary pain includes pain that radiates beyond the back, chronic pain, and pain associated with abnormal sensation or loss of sensation in the back or extremities
- Presence of pain anywhere other than the target back pain that is bothersome, that interferes with activity, or for which pain relief is taken
- History of any neck, back, or pelvic surgery
- History within the previous 3 years of spinal fracture or spinal infection, inflammatory arthritis, degenerative spine disease, or any other back or spine condition that may reasonably contribute to current back pain
- Myasthenia gravis
- Subjects who are currently taking medications that are moderate to potent inhibitors of cytochrome P450 (CYP) isozymes CYP2D6 and are unable or unwilling to stop taking the medication for the duration of the clinical study. These medications are likely to cause drug interactions with tolperisone hydrochloride (eg, paroxetine, fluvoxamine)
- Moderate and severe renal insufficiency as determined by creatinine clearance or estimated glomerular filtration rate
- Subjects who are unable or unwilling to stop using any medication or dietary supplement to promote sleep, including over-the-counter sleep medications, during their participation in the study
- Subjects having any condition—past or present—that, in the opinion of the investigator, has a reasonable likelihood of unfavorably altering study risk–benefit, interfering with study compliance, or confounding safety or efficacy assessments

- Study endpoints
  - Data for the primary efficacy analysis will be assessed by the subject on the tablet provided for use in the clinic for screening/baseline day 1 (visit 1), day 4 (visit 2), and day 14 (visit 3)
  - Additional efficacy endpoints and dosing will be collected daily at specified times from the subjects via smartphone for ePROs
  - Baseline is defined as the last assessment prior to the first dose of study drug
  - Efficacy and safety endpoints are presented in **Table 3**

Table 3: Efficacy and Safety Endpoints

Primary Efficacy Endpoint

- Subject-rated pain reported "right now" due to acute back spasm using an NRS (0-10 scale, from no pain to worst pain imaginable) on day 14

Key Secondary Efficacy Endpoints

- Subject-rated pain "right now" due to acute back spasm using an NRS on day 4
- Subject-rated average pain "last hour" due to acute back spasm using an average daily (AM/PM) NRS over days 1 to 4
- Subject-rated average pain "last hour" due to acute back spasm using an average daily (AM/PM) NRS over days 1 to 7
- Time to relief of pain due to acute back spasm, defined as first occurrence of a subject rated NRS (0-10 scale) equal to ≤2 from subject-rated average pain "last hour" assessed on days 1 to 14
- PGI-C from baseline (1-7 scale, from very much worse to very much improved) on days 4 and 14
- Clinician's Global Impression of Change from baseline (1-7 scale from very much worse to very much improved) on days 4 and 14
- ODI questionnaire (10 questions with one answer each for pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life [if applicable], social life, and traveling) on days 4 and 14

Exploratory Efficacy Endpoints

- Use of rescue medications (measured daily, assessed as number of rescue tablets administered by the subject and documented via smartphone)
- Subject response to the satisfaction questions "Would you take this medication again?" and "Were you able to resume your usual activities?" (yes or no) on day 14 (visit 3)

Safety Endpoints

- Clinical evaluations
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature)
- Physical examinations
- 12-lead electrocardiograms
- Laboratory tests (blood chemistry, hematology, urinalysis, and urine pregnancy tests for women of childbearing potential)
- AEs
- Visual analogue scale score for subject-reported sleepiness measured in the clinic on day 4
- Epworth Sleepiness Scale measured in the clinic on day 14
- Columbia-Suicide Severity Rating Scale (C-SSRS)

RESULTS

- Approximately 750 subjects are planned to be enrolled at about 60 clinical sites in the United States, with the first subject expected to be enrolled in Fall 2020
- A second replicate phase 3 study will be initiated at a later date

CONCLUSIONS

- Given the increased clinical use of SMRs for acute muscle spasm of the back, physicians and patients require a safe and effective alternative option that is not associated with somnolence
- In clinical studies to date, tolperisone is both effective and well tolerated with somnolence rates comparable to placebo-treated subjects
- Similar to STAR study, this phase 3 study will be conducted in subjects experiencing pain due to acute muscle spasm of the back and is designed to confirm the safety and efficacy of tolperisone in a registration setting

FOR ALL QUESTIONS REGARDING THIS CLINICAL TRIAL OR THE TOLPERISONE CLINICAL DEVELOPMENT PLAN, PLEASE CONTACT NEURANA PHARMACEUTICALS, INC AT: contact@neuranapharma.com

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DISCLOSURES

This study is sponsored by Neurana Pharmaceuticals, Inc. R. Kaye and S. A. Vaughan are employees of and own stock in Neurana Pharmaceuticals. H. Riordan is an employee of and owns stock in Worldwide Clinical Trials. S. Nalamachu is a consultant for Neurana Pharmaceuticals, Pfizer, RedHill, and Lilly. J. Pergolizzi is a consultant/speaker and researcher for Neurana Pharmaceuticals, US WorldMeds, BDSI, Salix, Enalare, Scilex, Pfizer, Lilly, Teva, Regeneron, RedHill, Grunenthal, and Neumentum.

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