Tolperisone for Acute Muscle Spasm: Dose-Ranging STAR 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, a centrally acting, nonopioid oral SMR, is available in Europe and Asia for the treatment of abnormally increased muscle tone
  - In Switzerland tolperisone is indicated for the treatment of muscle spasm at doses up to 600 mg/day
  - It is currently in clinical development in the United States for the treatment of symptoms associated with acute muscle spasm of the back
    - To date there have been 5 US studies in healthy volunteers, involving a total of 148 subjects
  - An ultra-pure formulation of tolperisone has been developed using a synthetic pathway that produces negligible levels of genotoxic impurities, such as 2-methyl-1-(4-methylphenyl)-propenone
  - In contrast with other centrally acting SMRs, tolperisone use does not appear to be associated with somnolence or cognitive impairment[9]
    - In a recent driving study, measures of weaving, driving ability, cognition, and psychomotor function were similar in participants receiving tolperisone (150 mg 3 times daily [TID]) or placebo[10]
    - In the same study, cyclobenzaprine, a widely used SMR, was found to significantly impair primary and secondary measures of driving ability

OBJECTIVE

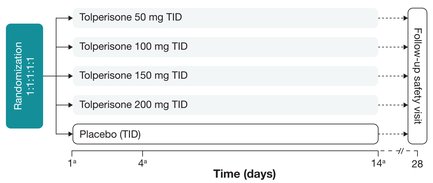
- To assess the safety and efficacy of tolperisone 50 mg, 100 mg, 150 mg, or 200 mg TID vs placebo for the treatment of acute muscle spasm of the back

METHODS

Study Design

- STAR was a double-blind, randomized, placebo-controlled, phase 2 dose-ranging study (NCT03802565) (**Figure 1**)
  - Subjects were randomly assigned (1:1:1:1:1) to tolperisone 50, 100, 150, or 200 mg TID or placebo for 14 days
  - Dosing diaries and electronic patient-reported outcome assessments were completed daily for 14 days
  - Subjects attended clinic assessments on study days 4 and 14, and on follow-up day 28
  - Use of acetaminophen 500 mg TID was permitted as rescue medication for subjects experiencing significant pain after randomization (rescue medication was not permitted on study days 4 and 14)
- The study was approved by the institutional review board at each site, and all subjects provided written informed consent

Figure 1. Study Design



TID, three times daily.
[a]A subject-rated pain assessment on a 10-point numerical rating scale was completed at baseline (study day 1), day 4, and day 14; electronic patient-reported outcomes and dosing diaries were completed daily on study days 1-14.

Inclusion Criteria

- Adult subjects aged 18-65 years with acute muscle spasm of the back were eligible
  - All subjects had BP and/or stiffness due to acute and painful muscle spasm starting ≤7 days prior to study entry and continuing for >8 weeks after the last episode
  - Pain was required to be localized below the neck and above the inferior gluteal folds with an intensity of ≥4 on the subject's "right now" rating of pain intensity on a 10-point numerical rating scale (NRS; 0 = no pain to 10 = worst possible pain)
- Subjects were required to discontinue all medications used for the treatment of pain or muscle spasm on day 1 of the study

Endpoints

- Safety
- Primary efficacy endpoint
  - Subject-rated pain "right now" using the 10-point NRS on day 14
- Secondary efficacy endpoints:
  - Subject-rated pain using the 10-point NRS to evaluate onset of action and duration of pain relief
  - Subject rating of medication usefulness
  - Clinician's global impression of severity/change
  - Patient's global impression of severity/change
  - Distance measured on fingertip-to-floor test
  - Pain and disability assessment on the Oswestry Disability Index (ODI)
  - Use of rescue medication

Statistical Analysis

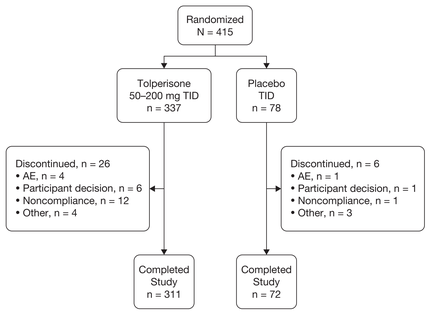
- The safety analysis was conducted on the safety population, which included all subjects who received ≥1 dose of study drug
- The primary efficacy analysis was conducted on the intent-to-treat population, which included all randomized subjects who received ≥1 dose of study medication
- A linear test of trend across all tolperisone doses was performed using a mixed-effect model for repeated measures with an unstructured covariance matrix; the model included factors for treatment group and visit as fixed effects, the treatment by visit interaction, and the baseline NRS rating as a covariate
- The observed NRS rating and change from baseline values are presented using descriptive statistics
  - Least squares mean (LSM) estimates and least squares mean differences (LSMDs) for each tolperisone dose level vs placebo are presented with 95% confidence intervals (CIs) of the LSMDs and associated *P* values for the observed values of the day-14 visit

RESULTS

Subject Disposition and Demographics

- 415 subjects were randomized to receive tolperisone (50 mg TID, n = 82; 100 mg TID, n = 87; 150 mg TID, n = 83; 200 mg TID, n = 85) or placebo (n = 78) (**Figure 2**)
  - 92.3% (311/337) of subjects randomized to tolperisone and 92.3% (72/78) of those randomized to placebo completed the study
  - Among subjects receiving tolperisone, noncompliance (n = 12) and participant decision (n = 6) were the most common reasons for early discontinuation

Figure 2. Study Disposition



AE, adverse event; TID, three times daily.

- Subject demographics and characteristics were well balanced across all treatment groups (**Table 1**)

Table 1. Subject Demographics

	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
Age, mean (SD), years	41.6 (12.37)	43.5 (12.58)	44.4 (12.20)	44.3 (12.09)	42.0 (11.96)	43.6 (12.19)
Age, years, n (%)						
18-49	52 (66.7)	54 (65.9)	52 (59.8)	50 (60.2)	61 (71.8)	217 (64.4)
50-65	26 (33.3)	28 (34.1)	35 (40.2)	33 (39.8)	24 (28.2)	120 (35.6)
Sex, n (%)						
Male	29 (37.2)	37 (45.1)	30 (34.5)	42 (50.6)	44 (51.8)	153 (45.4)
Female	49 (62.8)	45 (54.9)	57 (65.5)	41 (49.4)	41 (48.2)	184 (54.6)
Ethnicity, n (%)						
Hispanic or Latino	16 (20.5)	13 (15.9)	18 (20.7)	22 (26.5)	20 (23.5)	73 (21.7)
Not Hispanic or Latino	62 (79.5)	69 (84.1)	69 (79.3)	61 (73.5)	65 (76.5)	264 (78.3)
Race,[a] n (%)						
American Indian/ Alaska Native	3 (3.8)	1 (1.2)	0	1 (1.2)	0	2 (0.6)
Asian	4 (5.1)	1 (1.2)	4 (4.6)	2 (2.4)	4 (4.7)	11 (3.3)
Black or African American	30 (38.5)	29 (35.4)	32 (36.8)	30 (36.1)	35 (41.2)	126 (37.4)
Native Hawaiian/ Pacific Islander	0	1 (1.2)	1 (1.1)	1 (1.2)	0	3 (0.9)
White	44 (56.4)	50 (61.0)	50 (57.5)	50 (60.2)	45 (52.9)	195 (57.9)
Other	0	0	0	0	1 (1.2)	1 (0.3)
BMI						
Mean (SD)	28.53 (4.33)	28.23 (4.27)	28.48 (4.10)	28.34 (3.99)	28.45 (4.35)	28.38 (4.16)
Range	19.5-35.0	19.4-35.0	20.9-35.0	19.8-35.0	20.0-35.0	19.4-35.0

BMI, body mass index; SD, standard deviation.
[a]Subjects may have been included in >1 race category.

Safety

- Adverse events (AEs) were reported in 14.1% (11/78) of subjects receiving placebo and ranged from 12.2% (10/82) to 23.5% (20/85) in those receiving tolperisone 50 mg TID and tolperisone 200 mg TID, respectively (**Table 2**)
  - Headache was the most common AE in subjects receiving tolperisone, occurring in 3.7% (50 mg TID), 9.6% (150 mg TID), and 9.4% (200 mg TID) of subjects, respectively
    - Headache generally resolved over the first 24 to 48 hours of dosing
  - Somnolence and hypersensitivity are AEs typically associated with SMRs (**Table 3**)
    - Somnolence was reported by 1.2% of those receiving tolperisone and 2.6% of those receiving placebo
      - All events of somnolence were assessed as mild or moderate and were considered at least possibly related to the study drug; all resolved
    - Four subjects who received tolperisone reported hypersensitivity events
      - All were mild or moderate
      - Three events (urticaria, pruritus, and maculopapular rash) were considered at least possibly related to the study drug
      - The events of urticaria and maculopapular rash led to discontinuation of the study drug
      - One event (allergic dermatitis) was unrelated to the study drug, and the subject remained in the study
- Treatment-related AEs were reported in 13.4% and 6.4% of subjects receiving tolperisone and placebo, respectively
- There were no serious AEs or deaths reported during the study

Table 2. AEs (safety population[a])

	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
AEs, n	13	13	22	21	36	92
Subjects with ≥1 AE, n (%)	11 (14.1)	10 (12.2)	16 (18.4)	15 (18.1)	20 (23.5)	61 (18.1)
Mild[b]	8 (10.3)	6 (7.3)	13 (14.9)	8 (9.6)	12 (14.1)	39 (11.6)
Moderate[b]	3 (3.8)	4 (4.9)	3 (3.4)	5 (6.0)	6 (7.1)	18 (5.3)
Severe[b]	0	0	0	2 (2.4)	2 (2.4)	4 (1.2)
AE, n (%)						
Related to study drug[c]	5 (6.4)	5 (6.1)	13 (14.9)	13 (15.7)	14 (16.5)	45 (13.4)
Leading to study drug discontinuation[d]	1 (1.3)	0	1 (1.1)	2 (2.4)	2 (2.4)	5 (1.5)
Requiring dose interruption of study drug	0	0	0	0	1 (1.2)	1 (0.3)
Requiring dose interruption of study drug reduction	0	0	0	0	1 (1.2)	1 (0.3)
Death	0	0	0	0	0	0
Serious AEs, n	0	0	0	0	0	0

AE, adverse event; TID, three times daily.
AEs were events that began or worsened on or after the date of the first dose through 24 hours or 1 day after the date of the last dose.
[a]Included all subjects who received ≥1 dose of study drug. Treatment group assignment was based on the highest dose actually received.
[b]Subjects reporting ≥1 AE were counted only once, using the highest severity.
[c]Subjects reporting >1 AE were counted only once, using the closest relationship to the study drug. Related events included those reported as "possibly related" or "definitely related" to the study drug.
[d]One subject receiving placebo discontinued treatment due to an AE of blurred vision. Five subjects receiving tolperisone discontinued treatment, with a total of eight AEs (vertigo [n = 2], headache, nausea, vomiting, withdrawal syndrome, urticaria, and maculopapular rash).

Table 3. AEs Typically Associated With SMRs (safety population[a])

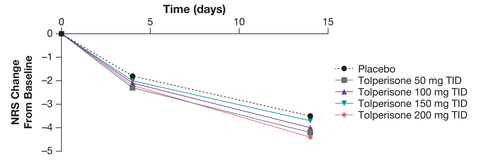
Category, n (%) Preferred term, n (%)	Placebo n = 78	Tolperisone 50 mg TID n = 82	Tolperisone 100 mg TID n = 87	Tolperisone 150 mg TID n = 83	Tolperisone 200 mg TID n = 85	Tolperisone Total n = 337
Somnolence	2 (2.6)	0	3 (3.4)	0	1 (1.2)	4 (1.2)
Hypersensitivity[b]	0	0	1 (1.1)	1 (1.2)	2 (2.4)	4 (1.2)
Dermatitis allergic	0	0	1 (1.1)	0	0	1 (0.3)
Pruritus	0	0	0	0	1 (1.2)	1 (0.3)
Maculopapular rash	0	0	0	0	1 (1.2)	1 (0.3)
Urticaria	0	0	0	1 (1.2)	0	1 (0.3)

AE, adverse event; SMR, skeletal muscle relaxant; TID, three times daily.
AEs were events that began or worsened on or after the date of the first dose through 24 hours or 1 day after the date of the last dose.
[a]Included all subjects who received ≥1 dose of study drug. Treatment group assignment was based on the highest dose actually received.
[b]AEs were coded to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1

Efficacy

- The overall trend in NRS rating of pain "right now" across dose groups at day 14 trended toward statistical significance ($P = 0.0539$) (**Figure 3**)

Figure 3. Change From Baseline NRS "Right Now" Scores

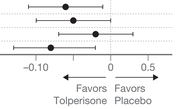


NRS, numerical rating scale; TID, three times daily.

- Analysis of pairwise LSM estimates and LSMDs (treatment – placebo) for each tolperisone dose vs placebo indicates significant reductions in NRS at day 14 for tolperisone 50 mg TID and 200 mg TID dose groups compared with placebo (**Figure 4**). The tolperisone 100 mg TID group trended toward significance compared with placebo (P=0.0506)
  - Three of four doses were within range of expected results, with the greatest numerical difference and statistical significance noted between tolperisone 200 mg TID and placebo

Figure 4. NRS "Right Now" LSMD (treatment – placebo): Mixed-Effect Model for Repeated Measures Estimate of NRS (95% CI)

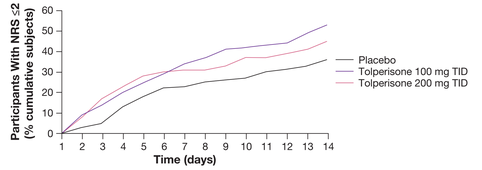
Tolperisone dose	LSMD (95% CI)	*P* value
50 mg TID	−0.6 (−1.1, −0.1)	0.0240
100 mg TID	−0.5 (−1.0, 0.0)	0.0560
150 mg TID	−0.2 (−0.7, 0.3)	0.4443
200 mg TID	−0.8 (−1.3, −0.2)	0.0040



LSMD, least squares mean difference; NRS, numerical rating scale; TID, three times daily.

- A number of secondary endpoints did not demonstrate a statistical significance between tolperisone and placebo treatment arms
  - Time to pain relief (NRS ≤2) was numerically faster in subjects receiving tolperisone at all doses vs placebo (**Figure 5**)

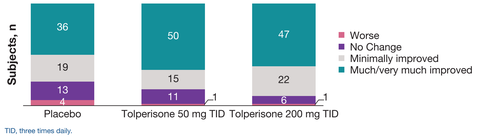
Figure 5. Time to Pain Relief



NRS, numerical rating scale; TID, three times daily.

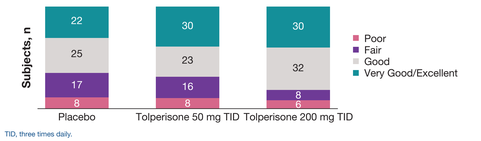
- Certain subcategories of the ODI (ie, personal care, walking, and social life) trended toward significance for the comparison of tolperisone 200 mg TID and placebo at day 14
- There were trends toward significant improvements in Patient's Global Impression of Change (**Figure 6**) and rating of medication helpfulness (rated from poor to excellent on a 5-point scale) (**Figure 7**) in subjects receiving tolperisone 200 mg TID compared with those receiving placebo
- The percentages of subjects receiving at least one caplet of rescue medication during the treatment period were 51.2%, 41.4%, 45.8%, 50.6%, and 52.6% in the tolperisone 50 mg TID, 100 mg TID, 150 mg TID, 200 mg TID, and placebo groups, respectively
  - During the first 7 days, 30% more subjects receiving placebo used rescue medication than those receiving tolperisone

Figure 6. Patient's Global Impression of Change at Day 14



TID, three times daily.

Figure 7. Rating of Medication Helpfulness at Day 14



TID, three times daily.

CONCLUSIONS

- Oral tolperisone at TID doses of 50 mg, 100 mg, 150 mg, and 200 mg for 14 days effectively reduced pain due to acute muscle spasm of the back at three of the four doses evaluated
  - The largest clinically meaningful decrease in NRS relative to placebo was seen in subjects receiving tolperisone 200 mg TID
- There were no treatment-related safety trends in subjects treated with tolperisone
  - The only AEs reported with an incidence of ≥2% in the total tolperisone group were headache and diarrhea
  - Few AEs led to discontinuation of tolperisone
  - The rates of somnolence and hypersensitivity with tolperisone were low and comparable to those of placebo
- Based on the efficacy and safety results from this study, a tolperisone dose of 200 mg TID may be a promising treatment for the management of acute muscle spasm without the somnolence typically experienced with SMRs

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DISCLOSURES

S. Nalamachu is a consultant for Neurana Pharmaceuticals, Pfizer, RedHill, and Lilly. R. Kaye is an employee of and owns stock in Neurana Pharmaceuticals. J. Pergolizzi is a consultant/speaker and researcher for Neurana Pharmaceuticals, US World Meds, BDSI, Salix, Enalare, Scilex, Pfizer, Lilly, Teva, Regeneron, Redhill, Grunenthal, and Neumentum.

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