Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of ETX-018810 in Subjects with Lumbosacral Radicular Pain

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Synopsis

Protocol Title:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of ETX-018810 in Subjects with Lumbosacral Radicular Pain

Short Title:

Efficacy and Safety of ETX-018810 for the Treatment of Lumbosacral Radicular Pain

Rationale:

ETX-018810 is a new chemical entity that is under development as a non-opioid treatment for chronic pain syndromes. ETX-018810 is a prodrug of palmitoylethanolamide (PEA), an endogenous bioactive lipid that has shown efficacy in a broad range of nonclinical inflammatory and neuropathic pain models and in clinical trials in chronic pain indications, including lumbosacral radicular pain (LSRP). [redacted] The existing clinical validation of the efficacy of PEA, the safety and tolerability of ETX-018810 in nonclinical toxicology studies and in a Phase 1 single- and multiple-, ascending-dose study, and a post hoc analysis, which confirms the clinical efficacy of PEA on pain in patients with low back pain, support its potential as a treatment for LSRP, a pain condition for which there is high unmet medical need due to the suboptimal efficacy and unacceptable adverse effects of current therapies. This study is designed to evaluate the efficacy, safety, and tolerability of ETX-018810 for the treatment of LSRP.

Objectives and Endpoints:

The study objectives and endpoints are summarized in Table S-1.

Table S-1: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ETX-018810 for the treatment of lumbosacral radicular pain (LSRP)	• Change from baseline to Week 4 in the weekly average of the daily pain score on the 11-point Pain Intensity Numerical Rating Scale (PI-NRS)[2]
Secondary	
• To evaluate the efficacy of ETX-018810 on additional pain measures and assessments of disability	*Secondary efficacy endpoints in pain[2]:* • Response rate, defined as a ≥50% reduction from baseline to Weeks 1, 2, 3, and 4 in the weekly average of the daily pain score • Response rate, defined as a ≥30% reduction from baseline to Weeks 1, 2, 3, and 4 in the weekly average of the daily pain score • Change in the weekly average of the daily pain score from baseline to Weeks 1, 2, and 3 • Change from baseline to Week 4 for worst pain[4] *Secondary efficacy endpoints:* • Response rate on the Patient Global Impression of Change (PGIC) scale at Week 4, defined as the proportion of subjects who are "much improved" or "very much improved" • Response rate on the Clinical Global Impression of Change (CGIC) scale at Week 4, defined as the proportion of subjects who are "much improved" or "very much improved" • Change in the weekly average of the daily sleep score on the Daily Sleep Interference Scale (DSIS) from baseline to Weeks 1, 2, 3, and 4[3] • Change from baseline to Week 4 in the Brief Pain Inventory (BPI)[4] • Change from baseline to Week 4 in the Roland-Morris Disability Questionnaire • Amount of rescue mediation used (dosage/day)[5]
• To investigate the safety and tolerability of ETX-018810 in subjects with LSRP	• Nature, frequency, and severity of nonserious treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Frequency of discontinuations due to TEAEs or death

Table S-1: Study Objectives and Endpoints (Continued)

Objectives	Endpoints
• To characterize the pharmacokinetics (PK) of ETX-018810 in subjects with LSRP[1]	• Plasma concentrations and plasma PK parameters (maximum observed drug concentration [C_{max}] over the first 5 hours after dosing and area under the plasma concentration-time curve computed up to 5 hours after dosing [AUC_{0-5h}]) of palmitoylethanolamide (PEA)

1. Participation in the PK component of the study is optional.
2. Subjects will record the PI-NRS score that represents their overall pain in the index leg (most painful leg) over the last 24-hour period in the electronic diary (eDiary) once daily in the evening (when they take their second daily dose of investigational product).
3. Subjects will record their DSIS score in the eDiary, once daily in the morning (when they take their first daily dose of investigational product).
4. Subjects will record their worst pain via question 3 of the BPI on Days 1 and 28.
5. Subjects will record rescue medication (acetaminophen) use in the eDiary once daily in the evening (when they take their second daily dose of investigational product).

Overall Design:

This is prospective, Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of ETX-018810 in male and female subjects aged ≥18 and ≤75 years with a diagnosis of LSRP, with an onset ≥3 months before screening, and at least moderate pain intensity on the Patient Global Impression of Severity (PGI-S) scale. The study will include a screening period (maximum of 4 weeks), a 4-week treatment period, and a 1-week posttreatment follow-up period. Each subject will participate in the trial for up to approximately 9 weeks.

After providing written informed consent, potential study subjects will be screened for study eligibility during the maximum 4-week screening period. Subjects who meet the study entry criteria will be trained in the use of the electronic diary (eDiary)[1] and in the completion of the Pain Intensity Numeric Rating Scale (PI-NRS), completion of the Daily Sleep Interference Scale (DSIS), and documentation of rescue medication use (acetaminophen) and will be instructed to discontinue any prohibited medications at the screening visit.

Subjects will record their PI-NRS score over the last 24 hours once daily in the evening, their DSIS score once daily in the morning, and their rescue medication use once daily in the evening in the eDiary from screening until the baseline/Day 1 visit. Subjects will record their average pain intensity in their worst affected limb, as identified at screening, over the last 24 hours for their pain due to LSRP (pain in relation to the symptomatic nerve root(s), which is perceived in the lower limb).

The values that are recorded for the PI-NRS and DSIS on the last 7 days before the baseline/Day 1 visit will used to determine the baseline scores. Only the intensity of pain due to LSRP will be used to determine eligibility. Subjects whose average pain intensity over these

[redacted]

7 days meets the study-specified threshold, who completed the PI-NRS and DSIS in the eDiary on at least 5 of the 7 days before the baseline/Day 1 visit, and who continue to meet all other study eligibility criteria will be enrolled in the study. The baseline assessment of eligibility will be made using a computerized screening algorithm on the basis of the information that is recorded in the eDiary. The investigator, site team, and study monitors will be blinded to the screening algorithm. The investigator/site staff will be informed as to whether the algorithm classifies the subject as eligible or ineligible and will inform the subject if he/she is eligible to continue in the study. Subject will be randomized to receive double-blind treatment with ETX-018810 1000 mg or placebo twice daily (BID) for 4 weeks at the baseline/Day 1 visit. Subjects will be trained on scoring of their pain intensity at the baseline visit.

Subjects will continue to use the eDiary to record their LSRP pain score, as defined above, over the last 24 hours on the PI-NRS (once daily in the evening when they take their second daily dose of investigational product), their sleep interference as a result of their LSRP on the DSIS (once daily in the morning when they take their first daily dose of investigational product), and rescue medication use (once daily in the evening when they take their second daily dose of investigational product) throughout the 4-week double-blind treatment period. Subjects will be allowed to take acetaminophen at a dose of up to 2600 mg/day for up to 3 consecutive days, but for no more than a total of 7 days, for non-LSRP-related pain (headache, toothache, etc) or for breakthrough pain due to LSRP.

[redacted]

Subjects will be contacted by telephone to review their status at the end of Week 2 and will report to the clinic for an end-of-treatment (EOT) visit at the end of Week 4. A final posttreatment follow-up telephone contact will be made 1 week after the last dose of investigational product (Week 5) to inquire about adverse events (AEs) and concomitant medication use. Subjects who discontinue from the study before completing the planned 4 weeks of treatment will undergo an early termination visit, which will include the evaluations that are scheduled for the Week 4 visit. If an ongoing automated review of the eDiary reveals that the subject is not complying with study procedures, site personnel will contact the subject to discuss any issues in an effort to improve compliance.

Subjects will take their first dose of investigational product in the clinic on Day 1 (baseline),

[redacted]

Blood specimens for plasma concentrations of PEA and for calculation of plasma pharmacokinetic (PK) parameters of PEA will be obtained before

[redacted]

[redacted]

Disclosure Statement:

This is a double-blind, parallel-group study of ETX-018810 and placebo in subjects with LSRP. Treatment assignments will be blinded to the subjects, investigators and other study personnel, and all sponsor personnel that are involved in the conduct of the study or in the analysis of the study results. The subjects and investigators will be blinded to the study-specified baseline criteria that are necessary for randomization into the study.

Number of Subjects:

Approximately 203 subjects will be screened to achieve a minimum of 122 randomized subjects (61 per treatment group). Subjects for whom diary data is unavailable due to technical issues may be replaced.

Treatment Groups and Duration:

Each subject will participate in the study for approximately 9 weeks, including a screening period of up to 4 weeks; a 4-week, double-blind treatment period; and a 1-week posttreatment follow-up period. Subjects will be randomized in a 1:1 ratio to receive 1000 mg of ETX-018810 or placebo BID for 4 weeks.

Statistical Analysis Plan:

The analysis populations were defined as:

- Safety Population - All subjects who received at least 1 dose of study treatment.
- Intent-to-treat (ITT) Population - All randomized subjects who received at least 1 dose of study treatment.
- Modified intent-to-treat (mITT) Population - All subjects in the ITT population who had at least 4 postbaseline measurements for the Pain Intensity Numeric Rating Scale (PI-NRS) in the eDiary.

The mITT population was used for the primary analysis of the primary efficacy endpoint and for all other eDiary efficacy endpoints; the ITT population was used for the analyses of the secondary efficacy endpoints. The safety population was used for the safety analyses.

Continuous data were summarized using descriptive statistics (e.g., mean, standard deviation), and categorical data were summarized using counts and percentages.

For the PI-NRS and DSIS (for which scores were completed daily in the eDiary), the weekly average was the mean of the non-missing scores for the 7-day period; the weekly average was calculated if at least one score was recorded for the week.

The treatment comparison for the change from baseline at Week 4 was estimated using a Mixed Model Repeated Measures (MMRM), which included the baseline score as a covariate; treatment group, visit (week), and the treatment-by-visit (week) as fixed effects; and a repeated structure that acknowledged the visits within a subject using an unstructured covariance structure. The Kenward-Rogers (1997) approximation was used to estimate the denominator degrees of freedom. The estimate, standard error, 90% CI, and associated p-value (2-sided) were presented.