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

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Synopsis

Title:

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

Short Title:

Efficacy and Safety of ETX-018810 for the Treatment of Diabetic Peripheral Neuropathic 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 diabetic peripheral neuropathic pain (DPNP). The existing published clinical validation of the efficacy of PEA and the safety and tolerability of ETX-018810 in nonclinical studies and in a Phase 1 single- and multiple-, ascending-dose study support its potential as a treatment for DPNP, a pain condition for which there is a 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 DPNP.

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 on neuropathic pain via daily pain measurements in subjects with diabetic peripheral neuropathic pain (DPNP)	• Change from baseline to Week 4 in the weekly average of the daily pain score as derived from the subject's responses on the Pain Intensity Numerical Rating Scale (PI-NRS)[2,3]
Secondary	
• To evaluate the efficacy of ETX-018810 on additional measures of pain and disability	• 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[2,3] • 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[2,3] • Change in the weekly average of the daily pain score from baseline to Weeks 1, 2, and 3[2,3] • 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" • 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" • 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[2,4] • Change in the Brief Pain Inventory (BPI) – Interference Scale from baseline to Week 4 • Change in the BPI-Pain Scale from baseline to Week 4 • Amount and pattern of acetaminophen use[5]
• To investigate the safety and tolerability of ETX-018810 in subjects with DPNP	• Nature, frequency, and severity of nonserious and serious treatment-emergent adverse events (TEAEs) • Frequency of discontinuations due to TEAEs or death • Nature, frequency, and severity of posttreatment adverse events (AEs)/serious adverse events (SAEs)

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

Objectives	Endpoints
• To characterize the pharmacokinetics (PK) of ETX-018810 in subjects with DPNP[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 their PI-NRS score over the last 24 hours once daily in the evening and their DSIS score once daily in the morning in the electronic diary (eDiary) from screening until the baseline/Day 1 visit. 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.
3. Subjects will record their PI-NRS score over the last 24 hours in the eDiary, once daily in the evening (when they take their second daily dose of investigational product).
4. Subjects will record their DSIS score in the eDiary once daily in the morning (when they take their first daily dose of investigational product).
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 type 1 or 2 diabetes mellitus; diabetic neuropathy of a symmetrical nature in the lower extremities for ≥6 months to ≤10 years, with a score of ≥3 on the Michigan Neuropathy Screening Instrument (MNSI); 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

[redacted]

until the baseline/Day 1 visit. 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. Subjects whose average pain intensity over these 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 continue to use the eDiary to record their average pain intensity 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 the neuropathic pain 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-DPNP-related pain (headache, toothache, etc) or for breakthrough pain due to DPNP.

[redacted]

Subjects will be contacted by telephone to review their status at the end of Week 2 t 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 DPNP. 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 410 subjects will be screened to achieve a minimum of 162 randomized subjects (81 per treatment group).

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.