Human Efficacy of FLX-787, a Dual Activator of TRPV1 and TRPA1 Ion Channels, Reducing Muscle Cramp Frequency and Pain in Randomized Controlled Studies

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Summary

**Objective:** Night leg cramps (NLC) are painful spontaneous contractions caused by alpha-motor neuron hyperexcitability and lead to sleep disruptions and reduced quality of life. We have previously demonstrated that activation of TRPV1 and TRPA1 in leg muscles in the sheep models and epileptiform signs in humans significantly decrease electrically induced muscle cramps in healthy adults. We investigate whether this effect would translate to clinical improvements in subjects suffering from NLC. Using a QMF synthesized single-realistic muscle that is naturally-occurring on TRPV1/2/3 (laxion; FLX-787), we conducted an exploratory cross-over study with NLC to examine the impact on muscle cramp frequency and pain.

**Methods:** We investigated two doses of FLX-787 (37 mg and 25 mg) in an orally-administered tablet formulation (QMF) in a randomized, blinded, placebo-controlled two-part cross-over study in otherwise healthy subjects (cramps >60 nights per week) with QMF per week (n=17). At the conclusion of the study, we conducted a questionnaire in participants to determine if the NLC responders adhered to the diagnosis of NLC. FLX-787 at 37mg was well tolerated.

**Results:** FLX-787 QMF was safe and well-tolerated. Analysis restricted to the first cross-over period of each study part, together with subject selection based on NLC threshold, demonstrated efficacy. By “possible” and “probable” NLC criteria, combined active treatments demonstrated a 26% decrease in the mean weekly cramp frequency (p=0.05), 26% decrease in mean weekly cramp pain (p<0.01). As expected for subjects with likely NLC, no difference was observed in cramp frequency following placebo treatment.

**Conclusion:** FLX-787 QMF may be effective at reducing both cramp frequency and pain associated with NLC, but may not be useful in subjects without NLC. Careful adjudication of self-reported NLC must be performed prior to randomization to avoid confounding data from subjects with other sleep disorders. Hypothesis-generating conclusions, in conjunction with restricting study subjects to previously-identified NLC, will allow for improved clinical studies in NLC as well as in adult neurodegenerative neuroinflammation (ALS, MS, Carpal Tunnel syndrome) where cramping is prevalent.

**EIC Efficacy of FLX-787**

**NLC Questionnaire & Adjudication**

Post-hoc questionnaire was administered after study completion to identify if enrolled subjects displayed common NLC characteristics.

• Subjects were previously demonstrated increased cramp frequency, associated pain and cramp characterization.

- Pain episodes without evidence of muscle contraction

- Inconsistent pain and impact on sleep

- Probable diagnosis of NLC without evidence of painful cramps (pain <4 on a 0-10 scale)

- Pain episodes without evidence of muscle contraction

- 2 out of 63 Subjects

- Probable diagnosis of NLC

- Pain episodes without evidence of muscle contraction

- Pain episodes without evidence of muscle contraction

- Pain episodes without evidence of muscle contraction

**Efficacy of FLX-787**

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**Topical Chemical Neuro Stimulation**

**NLC Study Design**

- A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of a FLX-787 (norned ODT-164 in study) on NLC cramp frequency when administered ODM as a ODT.

- Six doses of FLX-787 ODT yield classic agonist dose curve (n=5, p<0.01). Efficacy saturates at ~32 mg FLX-787-ODT

- Initial human PK (n=10) indicates no measurable system exposure of parent drug in plasma at potential therapeutic dose.

- FLX-787 Inhibition of electrically-induced cramps in healthy subjects is dose-responsive.

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**Figure 2.** Example data demonstrating that FLX-787 (400 µg) in a single muscle that activates TRPV1 and TRPA1 where a decrease in electrically-induced muscle cramp frequency is demonstrated. The treatment effect was calculated by subtracting the cramp intensity of the control (c) from the cramp intensity of a surface EMG measurement at the conclusion of a peroneal biceps experiment (c+). FLX-787 treatment led to a 9-fold decrease in cramp intensity compared to the control.

**Figure 3.** NLC Questionnaire & Adjudication

43% of questionnaire respondents adjudicated as likely having NLC.

Single case identified as being discordant with other sites in the same cell with the lowest percentage (25%) of subjects adjudicated with NLC.

**Conclusions**

**Chemical Neuro Stimulation**

**FLX-787 reduces muscle cramp intensity in an EIC model of the foot.**

**FLX-787 is well tolerated, and no treatment-related SAEs have been reported in clinical studies to date.**

**Using an NLC questionnaire administered after study completion, a minority of study subjects (26 of 63) were diagnosed with possible or probable NLC.**

**Cross-over studies with FLX-787 as NLC may be hampered by carry-over effects limiting their interpretability.**

**Study data was previously identified as providing discordant data in comparison to the other study sites enrolled the fewest subjects diagnosed with NLC (8 out of 52 subjects).**

**In the diagnosed NLC cohort, FLX-787 reduced both cramp frequency (p<0.01) and pain (p<0.01) associated with NLC.**

**Effect size range of cramp frequency across NLC studies range from 0.46-0.84 in comparison to quinine literature at 0.32.**

**Inconsistent adjudication of self-reported NLC should be performed prior to randomization to confirm cramp frequency and the absence of consensuses such as RLS.**

**To minimize the impact of heterogeneous study populations as observed in NLC, we evaluated FLX-787 clinical studies on well-defined disease populations of MDS (ALS, RLS, SMA) and Charcot-Marie-Tooth Disease.**

**References**


