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Flex-201: A Multicenter, Randomized, Blinded Study to Evaluate the Efficacy and Tolerability of FLX-787 in MS.

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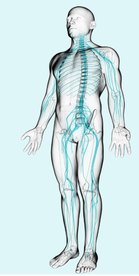
Novel Treatments for Neuromuscular Conditions



Summary

Background: FLX-787 is a TRPA1/TRPV1 ion channel activator that is efficacious in decreasing muscle cramp intensity in an electrically-induced cramp (EIC) model in healthy volunteers and cramp frequency in otherwise healthy subjects with nocturnal leg cramps (NLC). To understand the potential safety and efficacy of FLX-787 in indications where spasticity is prevalent, the Flex-201 study was initiated in patients with Multiple Sclerosis (MS).

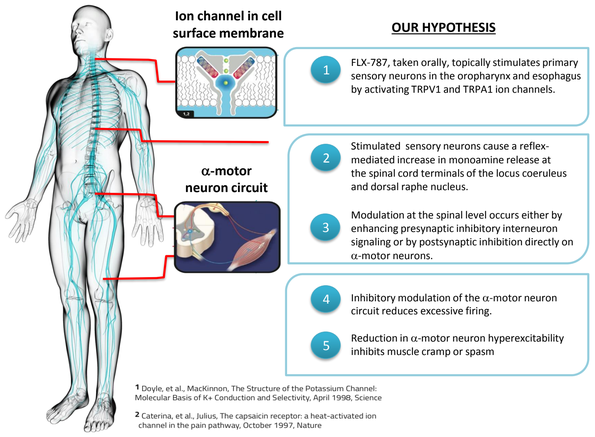
Objectives: Flex-201 has been designed to assess the efficacy and tolerability of FLX-787 as measured by: 1.) cramp/spasm frequency; 2.) Modified Ashworth Scale; 3.) Tardieu Scale; 4.) Numerical Rating Scale; 5.) Barthel Activities of Daily Living; 6.) Timed 25-Foot Walk; 7.) Clinical Global Impression; 8.) Quality of Life questionnaires (SF-36 and MSSS-88); and 9.) the Insomnia Severity Index Sleep Survey.

Methods: Flex-201 is a multicenter, randomized, blinded, cross-over study to investigate the effects of FLX-787 in subjects with MS and symptoms of spasticity, spasms and cramps (n=50 subjects). After a 2-week Run-in period to establish baseline spasticity and cramp/spasm frequency, subjects were dosed with either FLX-787 or placebo for 14-days followed by a 7-day intervening wash-out period and then crossed-over for an additional 14-days of dosing with the other treatment.

Results: In this exploratory phase 2 study, FLX-787 will be assessed on both the initial parallel portion of the study and the crossover period.

Conclusion: Results in human studies suggest that repeat dosing of FLX-787 may cause a general increase in the inhibitory tone of spinal circuits, and limit cramps, spasms and potentially spasticity in those living with MS. The beneficial characteristic of very low systemic exposure to unconjugated FLX-787 may also reduce the risk of drug-drug interactions and systemic effects seen with other MS agents.

Topical Chemical Neuro Stimulation



OUR HYPOTHESIS

1. FLX-787, taken orally, topically stimulates primary sensory neurons in the oropharynx and esophagus by activating TRPV1 and TRPA1 ion channels.
2. Stimulated sensory neurons cause a reflex-mediated increase in monoamine release at the spinal cord terminals of the locus coeruleus and dorsal raphe nucleus.
3. Modulation at the spinal level occurs either by enhancing presynaptic inhibitory interneuron signaling or by postsynaptic inhibition directly on α-motor neurons.
4. Inhibitory modulation of the α-motor neuron circuit reduces excessive firing.
5. Reduction in α-motor neuron hyperexcitability inhibits muscle cramp or spasm

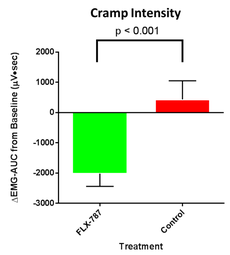
1 Doyle, et al., MacKinnon, The Structure of the Potassium Channel: Molecular Basis of K+ Conduction and Selectivity, April 1998, Science

2 Caterina, et al., Julius, The capsaicin receptor: a heat-activated ion channel in the pain pathway, October 1997, Nature

Figure 1. Overview of suspected mechanism of muscle cramps and methods of cramp inhibition by activation of TRP ion channels. Muscle cramping is caused by the uncontrolled and repetitive firing of α-motor neurons in the spinal cord (1), resulting in maintained contraction of the muscle. FLX-787 is thought to exploit a general principle of neural circuits whereby strong excitatory sensory input from one source enhances overall inhibitory tone by increased recruitment of inhibitory neurons, thereby reducing excitability in other parts of the circuit (3). FLX-787 stimulates primary sensory neurons in the mouth, esophagus and stomach by activating TRPV1 and TRPA1 ion channels (4,5). When activated, these sensory neurons, which project both directly and indirectly to the spinal cord, enhance the inhibitory tone in spinal cord circuits to reduce repetitive firing of α-motor neurons which prevents or reduces the frequency and intensity of muscle cramps and spasms.

EIC Efficacy of FLX-787

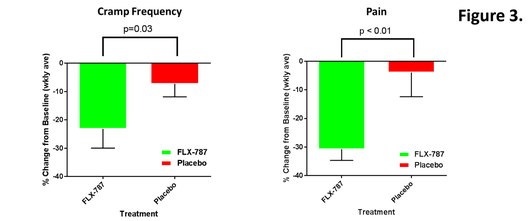
Figure 2.



Exemplary dataset demonstrating that FLX-787 (29 mg), a single molecule that co-activates TRPA1 and TRPV1, affords a decrease in electrically-induced muscle cramp intensity. The treatment effect was calculated based upon the area under the curve (AUC) of a surface EMG measurement of cramping relative to a pre-treatment baseline cramp (n=9). FLX-787 treatment led to a 5-fold reduction in delta-AUC compared to a study specific vehicle control. FLX-787 treatment demonstrated a significant difference from vehicle control (ANOVA, p < 0.001).

NLC Efficacy of FLX-787

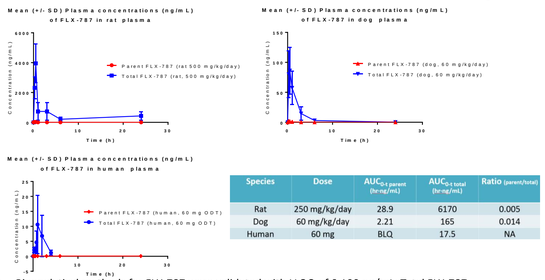
Figure 3.



- A cross-over, randomized, blinded, placebo-controlled study (n=72) was performed to study the effect of FLX-787 orally disintegrating tablet (ODT) in night leg cramps.
- An exploratory ANOVA sub-analysis was performed limited to subjects likely to have night leg cramps based upon a post hoc questionnaire administered after study completion.
  - 26 of 63 questionnaire respondents were independently adjudicated as having likely NLC.
  - To avoid potential influence of carry-over effects observed during cross-over analysis, ANOVA was restricted to the first treatment exposure.
  - The analysis is based on the overall active (17 + 25 mg FLX-787) vs placebo (aspartame + 0.8 mg FLX-787) comparison.
- Effect size based on analysis: Cramp Frequency: **0.53** and Pain: **0.83**
- Average effect size of cramp frequency derived from quinine literature is **0.12** (95%CI[-3.5,-1.36]). (6)

Low Systemic Exposure of FLX-787

Figure 4.



Species	Dose	$AUC_{0-t\ parent}$ (hr·ng/mL)	$AUC_{0-t\ total}$ (hr·ng/mL)	Ratio (parent/total)
Rat	250 mg/kg/day	28.9	6170	0.005
Dog	60 mg/kg/day	2.21	165	0.014
Human	60 mg	BLQ	17.5	NA

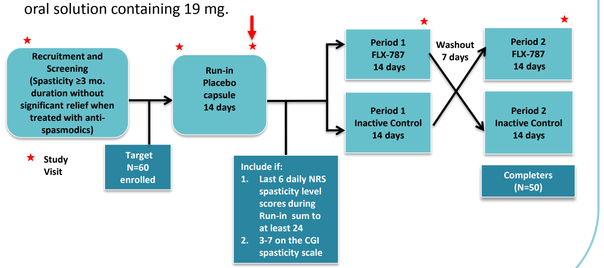
- Bioanalytical methods for FLX-787 were validated with LLOQ of 0.100 ng/mL; Total FLX-787 methods are semi-quantitative with LLOQ of <0.200 ng/mL
- The variability noted in the metabolic conversion of FLX-787 to conjugates suggests rapid and extensive phase 2 metabolism (first pass likely at the enterocyte level)

Flex-201 Methods

Spasticity and Muscle Cramps/Spasms in MS

- 250-350k people with MS in the US. (7)
- Current anti-spasmodic therapies provide incomplete resolution of spasticity and cramps/spasms.
- Aberrant α-motor neuron hyperexcitability is likely responsible for spasticity and muscle cramps/spasms in MS patients.
- While common symptoms in MS, little data exists on the prevalence of muscle cramps and spasms in the literature.

Figure 5. Multi-Center Trial in MS: A randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of a FLX-787 on the frequency of spasticity and muscle cramps/spasms when self-administered twice daily as a oral solution containing 19 mg.



Objectives and Endpoints

Objective: To assess the safety, tolerability, and exploratory efficacy of FLX-787 vs. inactive control over a 2-week period in MS subjects with spasticity and muscle cramps/spasms as assessed by the following endpoints:

Efficacy:

1) Cramp/spasm frequency (**collected by daily IVRS**);
2) Modified Ashworth Scale (MAS);
3) Tardieu Scale (TS);
4) Numerical Rating Scale (NRS which includes: spasticity severity (**IVRS**), spasm severity (**IVRS**), pain intensity (**IVRS**), fatigue, tremors, bladder symptoms, sleep);
5) Barthel Activities of Daily Living (ADL);
6) Timed 25-Foot Walk (T25-FW);
7) Clinical Global Impression - Global Improvement (CGI-I) Scale;
8) Quality of Life (QoL) questionnaires – 36-Item Short Form Survey (SF-36) and Multiple Sclerosis Spasticity Scale (MSSS-88);
9) Insomnia Severity Index (ISI) Sleep Survey.

Safety:

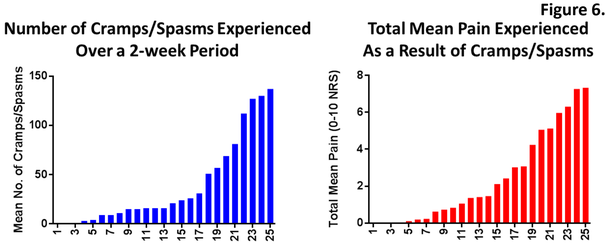
1) Percentage of subjects with treatment-emergent AEs
2) Change in vital signs or physical exam findings from Screening
3) Change in laboratory or ECG findings from screening

Run-In Analysis

- Subject-reported muscle Cramp/Spasm frequency and overall pain is being recorded by daily IVRS Collection.
- Mid-point analysis (n=25) was performed on Run-in IVRS data to understand the overall prevalence of muscle cramps and spasms, as well as associated pain, in the study population.
- Pearson Correlation Coefficient analysis performed to understand any correlations which may exist between IVRS endpoints.

Cramp/Spasm & Pain Prevalence

Figure 6.



- 92% (23/25) of subjects experienced at least one episode of cramps/spasms during the two week Run-in Period.
- 84% (21/25) of subjects experienced pain associated cramps/spasms.
- Of the 40% of subjects (10/25) who experienced ≥ 25 cramps/spasms over the 2-week period:
  - The mean cramp/spasm frequency was 82 cramps/spasms.
  - The mean pain score (0-10 scale) was 4.2.

Correlation Analysis

Figure 7.

Pearson Correlation Coefficients, N=25
Prob > |r| under H0; Rho=0

	Cramp/ Spasm Frequency	Spasticity Self-report (0-10)	Stiffness Self-report (0-10)	Pain Self-report (0-10)
Cramp/ Spasm Frequency	1.0000	0.18348 *0.3800*	0.33688 *0.0996*	0.67626 *0.0002*
Spasticity Self-report (0-10)	0.18348 *0.3800*	1.0000	0.68831 *0.0001*	0.15250 *0.4668*
Stiffness Self-report (0-10)	0.33688 *0.0996*	0.68831 *0.0001*	1.0000	0.44671 *0.0252*
Pain Self-report (0-10)	0.67626 *0.0002*	0.15250 0.4668	0.44671 *0.0252*	1.0000

- Pearson Correlation analysis reveals a strong correlation between cramp/ spasm occurrence and pain (p = 0.0002).
- Strong correlation between stiffness and spasticity self-reported scores (p = 0.0001).
- Correlation between pain and stiffness (p = 0.0252).

Conclusions

- Chemical Neuro Stimulation of TRPA1/TRPV1 by FLX-787 is a local, topical phenomenon that does not require systemic bioavailability and may result in indirect inhibition of α-motor neuron hyperexcitability.
- FLX-787 reduces muscle cramp intensity in an EIC-model of the foot.
- FLX-787 has shown the potential to reduce cramp frequency and pain in an exploratory human NLC study.
- FLX-787 is well tolerated, and no treatment-related SAEs have been reported in clinical studies to date.
- In the study population, cramps/spasms are strongly associated with pain.
- 40% of subjects who experience high prevalence of cramps/spasms also experience more pain, which may effect overall quality of life.
- Given the observed correlations, if FLX-787 limits cramps/spasms in patients with MS it could potentially reduce pain and stiffness as well.
- An exploratory Phase 2 study in MS, Flex-201, is currently underway with planned data readout expected by year end.

References

1. Minetto MA, Holobar A, Botter A, and Farina D. *Exerc. Sport Sci. Rev.* 41(1): 3-10, 2013.
2. Milanov, I. *Electromyogr Clin Neurophysiol.* 32 (2): 73-9, 1994.
3. Okun, M. & Lampl, I. *Nature Neurosci.* 11: 535–537, 2008.
4. Beilefeldt et al., *Am J Physiol Gastrointest Liver Physiol* 294: G130–G138, 2008.
5. Yu et al., *Am J Physiol Gastrointest Liver Physiol 297*: G34–G42, 2009.
6. El-Tawil S. et al., *Cochrane Database of Systematic Reviews* Issue 12, Art. No.: CD005044,2010.
7. National Institute of Neurological Disorders and Stroke