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

Jennifer Szegda, Brooke Hegarty MSHS, Laura Rosen MD PhD, Glenn F. Short III PhD, Jennifer Cermak PhD, Christoph Westphal MD PhD and Tom Wessel MD PhD

Flex Pharma Inc, Boston MA 02199

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 restless legs syndrome (RLS). FLX-787 was found to reduce the frequency and intensity of cramps and spasms related to restless legs syndrome as well as decrease subjective sleep disturbance.

Objective: The study is a randomized, double-blind, placebo-controlled, cross-over study to evaluate the effects of FLX-787 on cramp/spasm frequency in patients with MS. The study was conducted in accordance with the Declaration of Helsinki and all regulatory requirements.

Methods: A total of 25 MS patients were enrolled in the study. The study design was a randomized, double-blind, placebo-controlled, cross-over design with a 28-day washout period in between the two treatments. The study was divided into two treatment periods of 28 days each, with a 14-day period of exposure to FLX-787 followed by a 14-day period of exposure to placebo, and a 28-day washout period between the two treatments. The patients were randomized into two groups: one group received FLX-787 first, followed by placebo, and the other group received placebo first, followed by FLX-787. The study was conducted in accordance with the Declaration of Helsinki and all regulatory requirements.

Results: The mean pain score (0-10) was 4.2 for the FLX-787 group and 3.8 for the placebo group. The mean pain score (0-10) was 4.2 for the FLX-787 group and 3.8 for the placebo group. The mean cramp/spasm frequency was 82 cramps/spasms.

Conclusions: FLX-787 was well tolerated, and no treatment-related AEs were reported in clinical studies to date. In the study population, cramp/spasm frequencies were strongly associated with pain. 40% of subjects who experience high prevalence of cramps/spasms also experience more pain, which may affect overall quality of life.

The presence of muscle cramps is a common symptom in patients with MS, and FLX-787 limits cramp/spasm frequency in patients with MS. The beneficial characteristic of very low systemic exposure may reduce the risk of drug-drug interactions and systemic effects seen with other MS agents.

Efficacy of FLX-787

EIC Efficacy of FLX-787

NLC Efficacy of FLX-787

Low Systemic Exposure of FLX-787

Cramp/Spasm & Pain Prevalence

Correlation Analysis

Objectives and Endpoints

Objective: To assess the safety, tolerability, and exploratory efficacy of FLX-787 in MS patients with subjectivity and muscle cramps/spasms as assessed by the following endpoints:

Efficacy:
1) Cramp/spasm frequency (collected by daily IVRS);
2) Modified Ashworth Scale (MMS);
3) Tardieu Scale (TS);
4) Numerical Rating Scale (NRS) which includes: spasticity severity (SIV), spasms severity (SIVs), pain intensity (IIV), fatigue, tremors, bladder symptoms, edema; and
5) Barthel Activities of Daily Living (ADL)
6) Times 25-Foot Walk (T25-FW);
7) Clinical Global Impressions - Global Improvement (CGI-I Scale);
8) Quality of Life (QoL) questionnaires – 36-Item Short Form Survey (SF-36) and Multiple Sclerosis Quality Scale (MSQ-Q);
9) Incomplete Motor Score (IMS) Index Scale Survey.

Safety:
1) Percentage of subjects with treatment-emergent AEs;
2) Change in vital signs or physical examination findings from screening;
3) Change in laboratory or ECG findings from screening;
4) Change in neurological examination or other neurological examination findings from screening;
5) Change in disease activity from baseline measurement.

Flex-201 Methods

Spasticity and Muscle Cramps/Spasms in MS

- 25-3058 people with MS in the US. (7)
- Current anti-spastic treatments provide incomplete resolution of spasticity and cramps/spasms.
- Abnormal u-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 oral solution containing 15 mg.

Figure 6. Number of Cramps/Spasms Experienced Over a 2-Week Period

- 92% (27/30) of subjects experienced at least one episode of cramps/spasms during the two-week period.
- 40% (15/30) of subjects experienced pain associated cramps/spasms.
- Of the 40% of subjects (12/30) who experienced ≥3 cramps/spasms over the 2-week period, the mean cramp/spasm frequency was 80 cramps/spasms.
- The mean pain score (0-10 scale) was 4.2.

- Pearson Correlation analysis reveals a strong correlation between cramp/spasm occurrence and pain (r = 0.04).
- Strong correlation between stiffness and spasticity self-reported scores (r = 0.0001).
- Correlation between pain and stiffness (r = 0.0452).

References

- 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 u-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 N/C study.
- FLX-787 is well tolerated, and no treatment-related AEs 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 affect overall quality of life.
- Given the observed correlations, if FLX-787 limits cramp/spasm frequency 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.

- Pearson Correlation Coefficient, N/C, and in vivo Tissue (2019).