Orally-administered TRPV1 and TRPA1 Activators Reduce Night Leg Cramps in a Randomized, Blinded, Placebo-Controlled, Crossover Human Trial

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Summary

Nocturnal leg cramps (NLC) affect millions of Americans, and there are no FDA-approved drug therapies. Recent experimental evidence argues that hyperexcitability of alpha-motor neurons is central to generating muscle cramps. Initial observations in athletes led to the hypothesis that activation of TRPV1/ TRPA1 ion channels in muscular membranes of the oropharynx/lipper GI tract increases inhibitory tone in the spinal cord, damping motor neuron hyperexcitability. Recent evidence in electrically- and volitionally-induced cramps in humans supports this hypothesis.

We investigated the safety and efficacy of a proprietary formulation of TRP activators (TRP-Stim) in NLC in a randomized, blinded, placebo-controlled, crossover trial in subjects with cramps at least 4 nights/week. After an initial placebo run-in period, 51 evaluable subjects (50-77 years) were randomized to either placebo or TRP-Stim for two weeks, then crossed over for two weeks.

Statistically significant effects were detected (p<0.05): cramp frequency (p=0.01), cramp-free days (p=0.03), the physician-rated Clinical Global Impression of Change (p=0.01), and sleep disturbance (p=0.05) and pain measures (p=0.01). The product appeared to be safe and well-tolerated, with no serious adverse events. The magnitude of cramp reduction appears to be similar to published “Class 1 level” quinine efficacy studies (quinine was banned by the FDA for leg cramps due to safety issues). Finally, a subset of subjects had a pronounced clinical benefit.

These results demonstrate that TRP activation can reduce NLC. This supports the novel concept of Chemical Neuro Stimulation, a process whereby small molecules activate TRP ion channels topically, leading to sensory stimulation that in turn reduces hyperexcitability at multiple levels in the spinal cord. The human efficacy signals generated in this study hold promise as a new approach in treating NLC and cramps in neurological disorders. Based upon these results, we plan to initiate studies with a chemically-synthesized single molecule TRP activator in potential indications such as NLC, MS and ALS.

Objectives & Endpoints

Objective: To assess the safety, tolerability, and exploratory efficacy of TRP-stimulator versus placebo over a 2-week period in nocturnal leg cramps (NLC) as assessed by the following endpoints:

- Change from baseline in:
  - Total number of cramps per period
  - Cramp pain/intensity assessments
  - Quality of Life SF-36
  - Inosine Severity Index

Safety: Safety endpoints will be the reported SAEs and unexpected AEs to the study treatment, vital signs, and laboratory assessments.

Disposition and Demographics

- Of the 51 subjects enrolled in the placebo run-in period, 13 subjects discontinued after placebo run-in:
  - 1 subject withdrew consent
  - 1 for VOMS incompliance, 1 for nonsignificant inhibitory responses, 1 for non-compliance with study drug regimen, 1 for NSAID abuse
  - 1 subject was randomized to Periods 1 & 2
  - 50% subjects completed the study

- Of the 38 subjects randomized to the treatment period:
  - 1 subject due to adverse event

Demographics:

- Mean age 59.1 ± 13.7 years (range 25-87)
- Male: 62.1% (n=24)
- Female: 37.9% (n=14)

Table 1. Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>TRP-Stim</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>59±11</td>
<td>60±10</td>
</tr>
<tr>
<td>Gender</td>
<td>49.4%</td>
<td>40.3%</td>
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<tr>
<td>Race</td>
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<td>75.8%</td>
</tr>
</tbody>
</table>

Table 2. Baseline characteristics of study population

Results

Figure 2. TRP-Stim treatment results in significant differences relative to placebo across multiple clinically meaningful endpoints.

Table 3. TRP-Stim treatment results in significant differences relative to placebo across multiple clinically meaningful endpoints.

Table 4. Percentage of participants who experienced at least a 25%, 50%, or 75% decrease in the total number of cramps over the two week study period.

Table 5. Percentage of participants who experienced at least a 25%, 50%, or 75% decrease in the total number of cramps over the two week study period.

Results, cont.

- Nocturnal leg cramps affect millions of Americans, but no approved drug therapy for NLC currently exists (quinine was banned by the FDA for leg cramps due to safety issues).
- Flex-100 investigated the safety and efficacy of TRP activators in a randomized, blinded, placebo-controlled, cross-over study in healthy subjects (50-77 years) suffering ≥ 4 night leg cramps/week.
- Treatment with TRP activators resulted in statistically significant effects on clinically meaningful endpoints: cramp frequency (p<0.05), cramp-free days (p<0.01), physician-rated Clinical Global Impression of Change (p<0.01), "difficulty staying asleep" (p<0.05) and VAS pain intensity over the last 3 days of each treatment period (p<0.01).
- 12% of subjects when treated with TRP activators experienced a ≥ 75% decrease in total cramps experienced over the two week treatment period.
- There were no serious adverse events; all adverse events reported were mild or moderate and related primarily to gastrointestinal: “tingling lips” and “dysgeusia” were the most frequent.
- The magnitude of cramp reduction appears to be similar to published “Class 1 level” quinine efficacy studies.
- Chemical Neuro Stimulation of TRPV1 and TRPA1 channels in the oral mucosa may be a generally applicable method to treat disorders stemming from α-motor neuron hyperexcitability.
- Clinical studies will be initiated using the chemically-synthesized single molecule TRP activator in potential indications such as NLC, MS and ALS.

Background

Figure 1. Overview of suspected mechanism of muscle cramps and methods of cramp inhibition by activation of TRP ion channels

- Muscle cramping and spasticity is thought to be caused by the uncontrollable and repetitive firing of α-motor neurons in the spinal cord, resulting in sustained contraction of the muscle. Flex Pharma’s proprietary products exploit a general principle of neural circuits whereby strong excitatory sensory input from one source enhances overall excitability through feedforward tone by increased recruitment of other parts of the circuit. TRPA1 and TRPV1 are promiscuous TRP channels in the mouth, esophagus and distally by activating TRPV1 and TRPA1 ion channels (5,6).

- 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 a-motor neurons which prevents or reduces the frequency and intensity of muscle cramps and spasms.

Methods

- To determine the safety and efficacy of TRP-Stimulator, a double-blind, placebo-controlled, crossover study was conducted in healthy adults suffering ≥ 4 night leg cramps/week.

- Subjects were randomized to placebo or TRP-Stimulator, and crossed over after two weeks.

- The study design involved a placebo run-in period, followed by two weeks of treatment with either placebo or TRP-Stimulator.

- The primary endpoint was the change from baseline in total number of leg cramps per treatment period.

- The secondary endpoints included changes in cramp frequency, pain intensity, and quality of life measures.

- Data were analyzed using statistical methods such as ANOVA and t-tests.

- Safety assessments included monitoring for adverse events and laboratory tests.

- The study was funded by Flex Pharma, Inc.

- The results of this study were submitted to the FDA for consideration.

References


Poster No. 013

Novel Treatments for Neuromuscular Conditions

Figure 3. Overview of suspected TRP activator in potential indications such as NLC, MS and ALS.

Figure 4. Graphical representation of the mean daily cramp frequency for each cross-over period (Periods 1 and 2). The TRP-Stim treatment arms display normal increasing efficacy over the course of each crossover period, whereas the placebo arms show no improvement over the 14-day periods.

Figure 5. Percentage of participants who experienced at least a 25%, 50%, or 75% decrease in total number of cramps over the two week study period.

Figure 6. Clinical Global Impression of Change (CGI-C) by Treatment. Responders were defined as those who scored 1 or 2 on the CGI-C, as assessed by the site principal investigators. TRP-stimulator treatment led to 40% of subjects being considered Responders vs. only 24% with Placebo treatment.

Figure 7. Baseline measures at the start of 2-week run-in period.