A STUDY TO EVALUATE EFFICACY, SAFETY AND TOLERABILITY OF SINGLE DOSES OF *TIRASEMTIV* IN PATIENTS WITH MYASTHENIA GRAVIS

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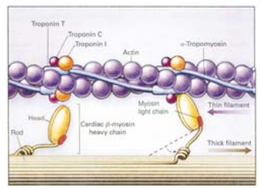
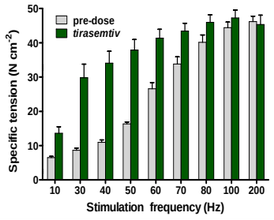
Introduction

Tirasemtiv selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium, thereby increasing skeletal muscle force in response to neuronal input and delaying the onset and reducing the degree of muscle fatigue. Increases in skeletal muscle strength and endurance have been observed after single doses of *tirasemtiv:*

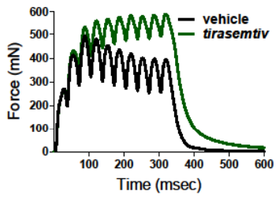
- In preclinical models
- In healthy volunteers
- In patients with ALS
- In patients with calf claudication

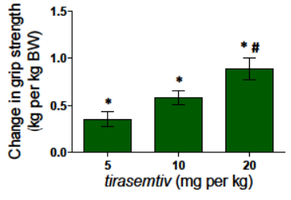
***Tirasemtiv* is a fast skeletal troponin activator, sensitizing the sarcomere to Ca^{2+}, thus amplifying the response of muscle to motor neuron input**





In a passive transfer rat model of myasthenia gravis, *tirasemtiv* decreased muscle fatigability, increased muscle force, and increased grip strength





Russell et al, Nature Medicine. (2012) 18(3) p. 452.

Objectives

- To demonstrate an effect of single doses of *tirasemtiv* on skeletal muscle function and fatigability in patients with MG
- Hypothesis-generating study; no specified primary endpoint

Inclusion Criteria

- Established diagnosis of MG, with clinical evidence of muscle weakness and +AChR-binding antibody
- Ability to refrain from IVIg during the study
- Ability to refrain from cholinesterase inhibitors for 12 hours before each dose of study drug
- Ability to perform all elements of the QMG
- QMG Grade 2 or 3 in two or more of the following muscle groups:
  - Right or left arm outstretched
  - Head lift
  - Right or left leg raise at 45°

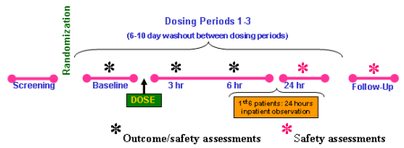
Exclusion Criteria

- IVIg or therapeutic plasma exchange <6 weeks before the first dose of study drug
- Changes to immunosuppressive treatments (i.e., prednisone) <6 weeks before the first dose of study drug
- Rituxan treatment <3 months before study entry

Methods

Design:

- Three-period crossover study
- Each patient received the following double-blind, single oral doses, in random order, about one week apart:
  - *Tirasemtiv* 250 mg
  - *Tirasemtiv* 500 mg
  - Placebo



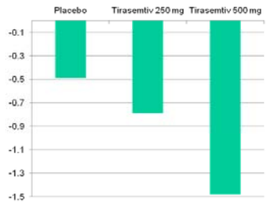
Outcome assessments

- Quantitative Myasthenia Gravis (QMG) score
- Vital Capacity (liters and % predicted)
- MG Manual Muscle Test
- MG Composite

Results

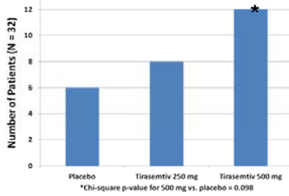
32 patients were randomized: all completed the study.

Mean QMG change from baseline at 6 hours after dosing



The QMG Score improved by 0.99 points vs. placebo (p=0.020) at 6 hours after the 500 mg dose. Decreases in the QMG Score were dose-related.

QMG improved >=3 points from baseline at 6 hours after dosing



Twice as many subjects improved at least 3 QMG points 6 hours after the 500 mg dose as after placebo (p=0.098).

- FVC (% predicted) was increased vs. placebo 6 hours after dosing.
  - *Tirasemtiv* 250 mg: 7.0 ± 2.1% (p = 0.0012)
  - *Tirasemtiv* 500 mg: 4.5 ± 2.1% (p = 0.034)
  - Dose trend: 2.2%/250 mg (p = 0.043)

- The MG Composite and Modified MG Symptom Assessments and Manual Muscle Testing were not affected by *tirasemtiv.*

- Both doses of *tirasemtiv* were well-tolerated; there were no premature terminations or serious adverse events. The most commonly reported adverse event was dizziness, which was mild in all but one case, which was classified as moderate.

Tirasemtiv in MG Study Group

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Conclusions

The results of this study suggest that *tirasemtiv* may improve function in MG and will be used to support further development of *tirasemtiv* in neuromuscular diseases.

Disclosures

Dr. Sanders:
- **Consultant to Accordant Health Services, Cytokinetics, UCB, GSK, Jacobus Pharmaceutical Co.**
- **Speakers' Program for Athena Diagnostics.**

Dr. Rosenfeld:
- **Consultant to Cytokinetics and Hill Rom, Inc.**
- **Research support from Hill Rom, Inc.**
- **Speakers panel for Avinir Pharmaceuticals**

Dr. Dimachkie:
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- **CSL-Behring advisory board meeting**
- **Biomarin LEMS Steering Committee member**

Drs. Meng & Malik::
- **Employees of Cytokinetics, with stock options.**