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

**Donald B. Sanders, Durham, NC; Jeffrey Rosenfeld, Fresno, CA; Mazen Dimachkie, Kansas City, KS; Lisa Meng, San Francisco, CA; Fady I. Malik, San Francisco, CA, for the Tirasesmtiv in Myasthenia Gravis Study Group**

**Introduction**

Tirasesmtiv 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 fatigability. Increases in skeletal muscle strength and endurance have been observed after single doses of tirasesmtiv:
- In preclinical models
- In healthy volunteers
- In patients with ALS
- In patients with cleft claudication

**Objective:**

To demonstrate an effect of single doses of tirasesmtiv 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**

- IVlg 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:
  - **Tirasesmtiv:** 250 mg
  - **Tirasesmtiv:** 500 mg
  - **Placebo**

**Outcome assessments**

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

**Results**

32 patients were randomized: all completed the study.

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.

- FVC (% predicted) was increased vs. placebo 6 hours after dosing.
- **Tirasesmtiv:** 250 mg: 7.0 ± 2.1% (p = 0.0012)
- **Tirasesmtiv:** 500 mg: 4.5 ± 2.1% (p = 0.034)
- **Dose trend:** 2.2%±0.250 mg (p = 0.043)

The MG Composite and Modified MG Symptom Assessments and Manual Muscle Testing were not affected by tirasesmtiv.

- Both doses of tirasesmtiv 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.

**Conclusions**

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

**Disclosures**

Dr. Sanders:
- Consultant to Accurand 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 Aviv Pharmaceutical

Dr. Dimachkie:
- Pfizer Depomed and Merck Speaker Bureau,
- CSL Behring advisory board meeting
- Biomarin LEMS Steering Committee member

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