Tirasemtiv Increases Skeletal Muscle Performance in SMA Mice

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**INTRODUCTION**

- The majority of new therapeutic approaches for spinal muscular atrophy (SMA) focus on increasing SMN2 levels
- Directly activating fast skeletal troponin may provide a novel, and potentially complimentary, method of improving muscle function in SMA
- To examine this hypothesis, we tested the fast skeletal troponin activator, *tirasemtiv*, in two different SMA mouse models that resemble the Type II/III intermediate and Type IV adult-onset human condition.

**EXPERIMENTAL AIMS FOR TIRASEMTIV IN SMA RESEARCH**

Our specific experimental aims are:

- Determine the effect of *tirasemtiv* on skeletal muscle strength in mouse models of SMA
- Determine the effect of *tirasemtiv* on muscle performance in mouse models of SMA

**RESULTS**

**Characterization of SMA Mouse Models**

- "Intermediate" SMA mice
  - Weakness by 3 months of age
  - Muscle atrophy
  - Increased fasciculations
  - Gross progressive loss of function across species

- "Adult-onset" SMA mice
  - Weakness by 6 months of age
  - Reduced number of motor units
  - Contractures with significant muscle atrophy
  - More profound atrophy, function is most affected in lower motor neurons/related spinal cord changes

**Tirasemtiv Improves Strength and Endurance in a Mouse Model of SMA**

**Grip Strength Apparatus**

- Healthy mice and SMA mice are lowered onto the triangle bar until they grab the bar
- Mice are pulled gently by the tail until they release the bar
- The grip meter measures how much force it takes to pull the mouse from the triangle bar

**Grid Cage Hang Apparatus**

- The mice hang on as long as they can
- The grid is then inverted
- The mice hang on as long as they can

**Conclusions**

- *Tirasemtiv* is unique because it directly activates skeletal muscle and could be of benefit to patients with a wide variety of disorders characterized by muscle weakness and fatigue
- In this current study, *tirasemtiv* improved submaximal calf muscle strength, grip strength and grid hang time in SMA mice that resembled the Intermediate and Adult-onset human condition
- Significance of the Project:
  - Current treatment of SMA consists primarily of supportive measures. Thus, there remains a significant unmet medical need for a therapy that can improve muscle function, including respiratory muscle function
  - Based on our current results in SMA mouse models, *tirasemtiv* may ameliorate symptoms associated with muscle weakness in patients with SMA and thereby improve self-care abilities and quality of life