**FAST SKELETAL MUSCLE TROPONIN ACTIVATOR TIRASEMTIV INCREASES MUSCLE FUNCTION AND PERFORMANCE IN MOUSE MODELS OF SPINAL MUSCULAR ATROPHY**

**ABSTRACT**

Background: The small molecule drug tirasemtiv (CY90001) induces a local increase in cytosolic free calcium, leading to increased force production in skeletal muscle. The objective of this study was to investigate the effects of tirasemtiv on muscle function and performance in mouse models of spinal muscular atrophy (SMA).

Results: Male and female intermediate SMA (SMA1) mice exhibited nerve dysfunction, reduced muscle force, and muscle atrophy, and weakness. Single doses of tirasemtiv improved grip strength in intermediate SMA mice. In adult onset SMA mice, female (Vehicle: 24 ± 3.9 mN, 10 mg/kg: 28 ± 3.7 mN) and male (Vehicle: 24 ± 4.3 mN, 10 mg/kg: 34.9 ± 5.3 mN) intermediate SMA mice exhibited nerve dysfunction, muscle atrophy, and weakness. Single doses of tirasemtiv improved grip strength in intermediate SMA mice. In adult onset SMA mice, female (Vehicle: 24 ± 3.9 mN, 10 mg/kg: 28 ± 3.7 mN) and male (Vehicle: 24 ± 4.3 mN, 10 mg/kg: 34.9 ± 5.3 mN) intermediate SMA mice exhibited nerve dysfunction, muscle atrophy, and weakness. Single doses of tirasemtiv improved grip strength in intermediate SMA mice.

Discussion and conclusions: Intermediate and adult-onset SMA mice exhibited nerve dysfunction, muscle atrophy, and muscle weakness. Single doses of tirasemtiv improved grip strength in intermediate SMA mice. In adult onset SMA mice, female (Vehicle: 24 ± 3.9 mN, 10 mg/kg: 28 ± 3.7 mN) and male (Vehicle: 24 ± 4.3 mN, 10 mg/kg: 34.9 ± 5.3 mN) intermediate SMA mice exhibited nerve dysfunction, muscle atrophy, and weakness. Single doses of tirasemtiv improved grip strength in intermediate SMA mice. In adult onset SMA mice, female (Vehicle: 24 ± 3.9 mN, 10 mg/kg: 28 ± 3.7 mN) and male (Vehicle: 24 ± 4.3 mN, 10 mg/kg: 34.9 ± 5.3 mN) intermediate SMA mice exhibited nerve dysfunction, muscle atrophy, and weakness. Single doses of tirasemtiv improved grip strength in intermediate SMA mice.

**METHODS**

**SMA Mouse Models**

9-12 month old intermediate SMA and 13-14 month old adult-onset SMA mice were obtained from the laboratory of Dr. D. D. K. (Suzie) Chihilkikik (Department of Neurology, University of Chicago, Chicago, IL). Motor unit number estimation (MUNE) numbers were measured in control and SMA mice according to previously described methods.

**Assessment of Muscle Function in vivo**

The intermediate and adult-onset mice were killed in situ in intermediate SMA, adult-onset SMA, and their respective control mice. The presence of vehicle (0.5% gum Arabic, 0.5% gum Arabic) or tirasemtiv (10 mg/kg, IP) treatment in each case was assessed by measuring the force produced in response to submaximal nerve stimulations. The force produced by intermediate and adult-onset SMA mice was assessed at each stimulation frequency (from 0 to 20.1 Hz). The force produced by intermediate and adult-onset SMA mice was assessed at each stimulation frequency (from 0 to 20.1 Hz).

**Assessment of Grip Strength**

Male and female intermediate SMA (SMA1) mice were tested for grip strength in vivo on an inverted grid. The force produced by intermediate and adult-onset SMA mice was assessed at each stimulation frequency (from 0 to 20.1 Hz). The force produced by intermediate and adult-onset SMA mice was assessed at each stimulation frequency (from 0 to 20.1 Hz).

**DISCUSSION**

Intermediate and adult-onset SMA mice exhibited nerve dysfunction, muscle weakness, and atrophy. Single doses of tirasemtiv significantly increased muscle strength and fatigue resistance in in vivo response to submaximal nerve stimulation in both SMA mouse models. Tirasemtiv improved grip strength in vivo in intermediate and adult-onset SMA mice. These results suggest that tirasemtiv and other fast skeletal muscle troponin activators may be viable therapies for improving muscle function in spinal muscular atrophy.