**ABSTRACT**

**THE EFFECTS OF FAST SKELETAL TROPONIN ACTIVATION ON SKELETAL MUSCLE FUNCTION**

- **Tirasemtiv** increases contraction force in healthy volunteers
- **Tirasemtiv** sensitizes the sarcosome to calcium
- **Tirasemtiv** increases contraction force in skeletal muscle

**Prior clinical trials of Tirasemtiv in ALS**

- CY 4021: Other Key Findings
  - **Tirasemtiv** increases contraction force in healthy volunteers
  - **Tirasemtiv** sensitizes the sarcosome to calcium

**BENEFIT-ALS: Key Design Elements**

- Randomize 400 patients with ALS
  - **Randomization**: 1:1 Tirasemtiv versus placebo stratified by riluzole use
  - **12 weeks of double-blind treatment**

- **Tirasemtiv** titrated versus placebo BD (similar to CY 4025)
  - More flexible: dosing interruptions or down-titrations permitted
  - More persistent: each titration step must be attempted at least twice

**Patients taking riluzole will receive**

- **Tirasemtiv** 50 mg twice daily if randomized to **Tirasemtiv**
- **Tirasemtiv** 50 mg once daily if randomized to **Tirasemtiv**

**The evening riluzole dose will be blinded to preserve the study blind**

**Primary endpoint**

- **Mean ALSFRS-R at 8 and 12 weeks**
- 80% power for a 1.58 point difference vs placebo, 2-tailed α = 0.05

**First secondary endpoint**

- **Maximum Voluntary Ventilation**

**Study Design**

- **Blinded Evaluation of Neuro muscular**
  - **Effects and Functional Improvement with Tirasemtiv in ALS**

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