CK-2127107, A Selective Activator of the Fast Skeletal Muscle Troponin Complex, for the Potential Treatment of Spinal Muscular Atrophy

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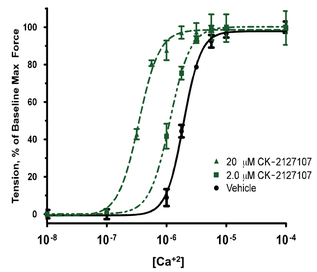
BACKGROUND

- Selective fast skeletal muscle activators are hypothesized to improve function in individuals with neuromuscular disorders
- *Tirasemtiv*, a potent, selective, fast skeletal muscle troponin activator, is currently in phase 3 clinical trial for ALS
- CK-2127107, also known as CK-107, is a next generation fast skeletal muscle troponin activator that may improve muscle function and physical performance in people with SMA
- CK-107 has been the subject of five completed Phase 1 clinical trials in healthy volunteers, which evaluated safety, tolerability, bioavailability, pharmacokinetics, and pharmacodynamics
- Cytokinetics started a Phase 2 clinical trial of CK-107 in patients with SMA in Q4 2015

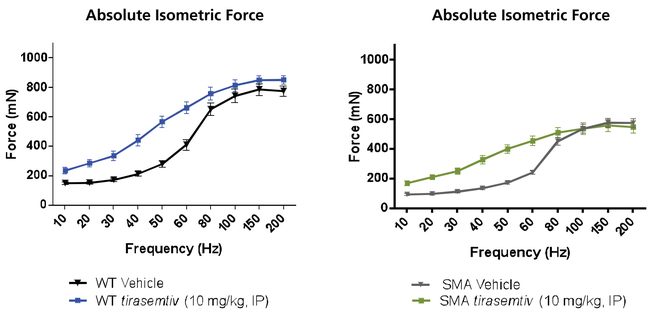
PRECLINICAL DATA

Skinned Fast Skeletal Muscle Fiber

CK-107, a selective fast skeletal muscle troponin activator, slows the rate of calcium release from troponin C, sensitizing the sarcomere to calcium and increasing fast skeletal muscle contractility

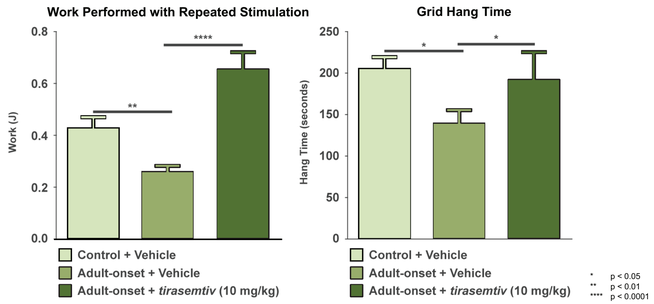


Troponin Activation in a Adult Onset Mouse Model of SMA



Collaboration with Dr. Christine DiDonato, Lurie Children's Hospital of Chicago; funded by Cure SMA

Troponin Activation in a Adult Onset Mouse Model of SMA



PHASE 1

Clinical Trials Program

STUDY	N	OBJECTIVE	RESULTS
CY 5011	35	Single dose: safety, tolerability, pharmacokinetics	Achieved highest planned dose; well tolerated; no emerging pattern of adverse events
CY 5012	24	Multiple dose: safety, tolerability and pharmacokinetics	Well tolerated; plasma concentrations achieved steady state; no age-related differences in PK
CY 5013	16	Pharmacodynamic effects	Statistically significant increases in peak force; well tolerated
CY 5014	24	Pharmacokinetics of two different physical forms in suspension	Well tolerated at 300 mg and 1000 mg; physical form selected
CY 5015	24	Assess pharmacokinetics tablet formulation; fed vs. fasted	Well tolerated at 250 mg, 500 mg and 1000 mg; tablet appropriate for use in clinical trials

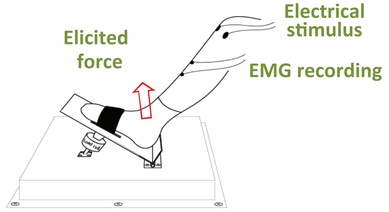
Well Characterized Safety, Tolerability, PK/PD during Oral Administration

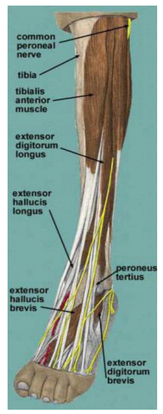
Clinical Trial (CY 5013)

Pharmacodynamic Study In Healthy Subjects

Force Frequency assessment by stimulation of the peroneal nerve and recording force generated by the tibialis anterior muscle

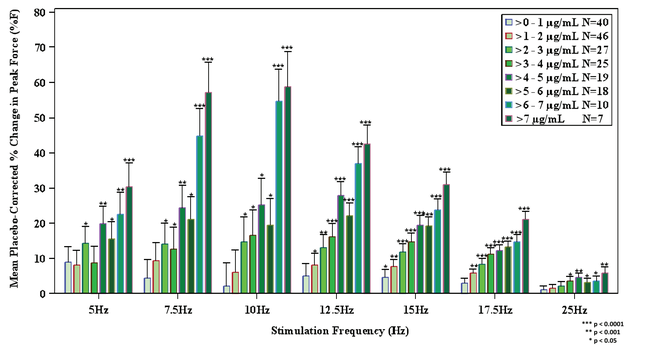
- Stimulate a nerve-muscle pair (peroneal nerve, anterior tibialis muscle) via external electrodes
- Measure isometric force at multiple nerve stimulation frequencies
- Reproducible when normalized to response to stimulation at 50 Hz (tetany)
- Voluntary contribution minimized





Pharmacodynamic Study Results

Mean Placebo Corrected % Change from Baseline in Force/Frequency



Augmentation of force in response to motor nerve stimulation

PHASE 2

Study Design (CY 5021)

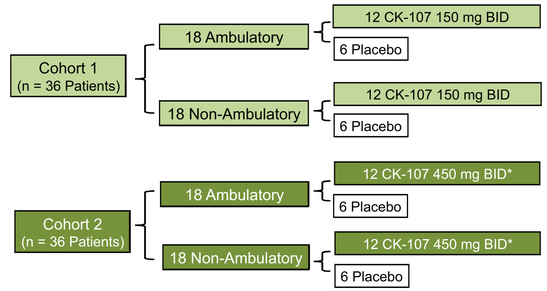
CK-107 Administered Orally to SMA Patients

- **Study Objectives**
  - To evaluate the safety and tolerability
  - To determine potential pharmacodynamic effects
  - To evaluate the pharmacokinetics
- **Sequential dose escalation, randomized, double blind placebo controlled study**
  - Cohort 1: 150 mg bid compared to placebo
  - Cohort 2: 450 mg bid (proposed) compared to placebo
    - At end of cohort 1, safety, tolerability and pharmacodynamics reviewed to establish dose for Cohort 2

Patient Population (CY 5021)

- **Patients 12 years of age and older**
- **Genetically confirmed spinal muscular atrophy Types II, III, or IV**
- **72 patients equally divided between ambulatory and non-ambulatory status**

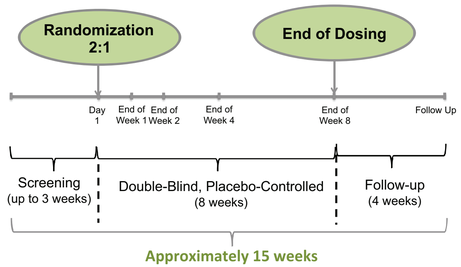
Study Design Diagram (CY 5021)



*Or lower, pending the review of data from Cohort 1

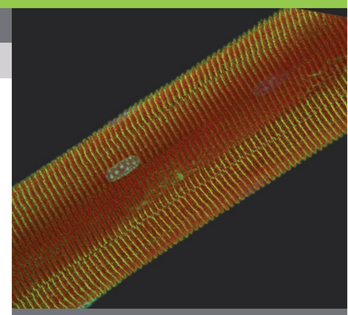
Patient Visit Diagram (CY 5021)

- Screening: up to 3 weeks
- Dosing: 8 weeks
- Follow-Up: 4 weeks after last dose



Outcome Measures (CY 5021)

Respiratory	Motor Evaluation	Other
Forced Vital Capacity	Hand held dynamometry	Safety Monitoring
Maximum Inspiratory Pressure	Revised upper limb module (RULM)	Pharmacokinetics
Maximum Expiratory Pressure	Hammersmith Functional Motor Score (HFMS-E)	
	Timed Up and Go (TUG)	
	Six-minute walk test (6MWT)	



CONCLUSIONS

- In preclinical models, CK-107 increased muscle contractility
- Phase I studies characterized its tolerability and pharmacodynamic effect on muscle
- Cytokinetics is conducting a Phase 2 clinical trial of CK-107 in patients with SMA

DISCLOSURES

S Rudnicki, J Andrews, F Malik, A Wolff are employees of and own stock in Cytokinetics, Inc.

J Day has served as a consultant to Cytokinetics

Cytokinetics

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