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

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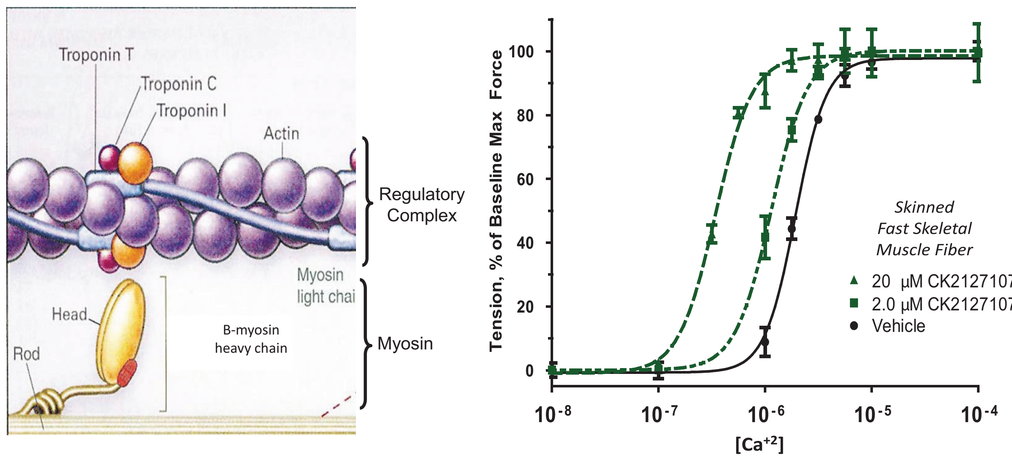
BACKGROUND

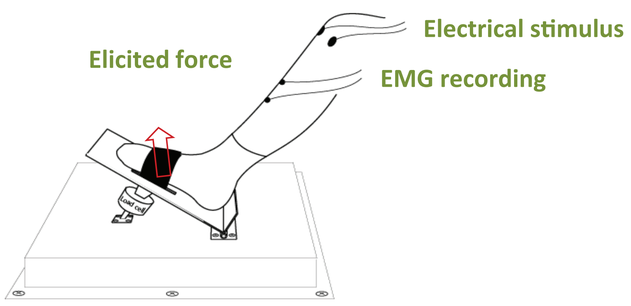
CK-2127107 Activates the Fast Skeletal Troponin Complex

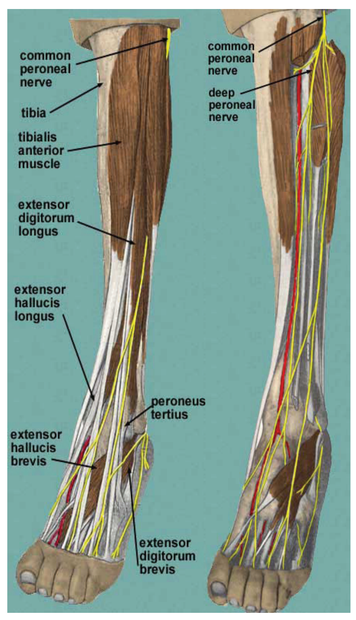
CK-2127107, a selective fast skeletal muscle troponin activator, slows the rate of calcium release from troponin C, sensitizing the sarcomere to calcium and increasing fast skeletal muscle contractility.



CY 5013: Methods and Rationale
Force Frequency Assessment by External Stimulation of Tibialis Anterior Muscle

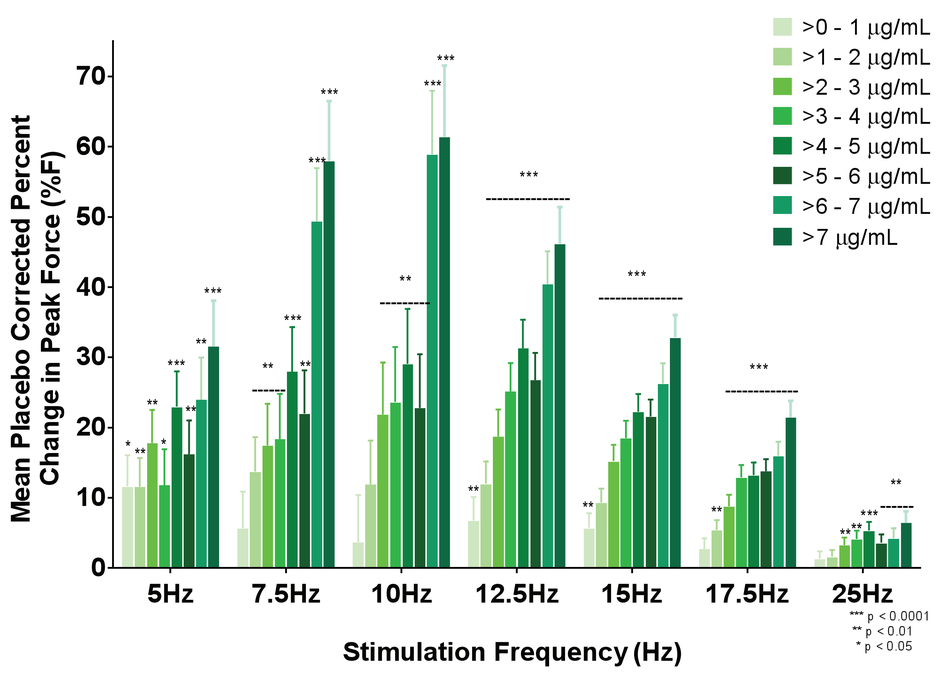
- Stimulate a nerve-muscle pair (peroneal nerve, anterior tibialis muscle) via external electrodes
- Measure isometric force at multiple nerve stimulation frequencies
- Reproducible when normalized to response to stimulation at 50 Hz (tetany)
- Voluntary contribution minimized





Anterior tibialis muscle ~ 25% fast (Type II) fibers

CY 5013: Translation of Mechanism into Humans
Frequency and Concentration Dependent Force Increases



CK-2127107: Phase I Clinical Trials Program

STUDY #	N	TRIAL OBJECTIVE	RESULTS
CY 5011	35	Assess safety and tolerability; Evaluate pharmacokinetics (increasing single doses)	Achieved highest planned dose; No emerging pattern of adverse events; Well tolerated
CY 5012	24	Assess safety, tolerability and pharmacokinetics in healthy young and elderly (multiple dose)	10-day courses of either 300 mg or 500 mg twice daily were well tolerated by young and older subjects; Plasma concentrations achieved steady state; No age-related differences in PK
CY 5013	16	Assess pharmacodynamic effects	Statistically significant increases (versus placebo) in peak force; Well tolerated
CY 5014	24	Assess pharmacokinetics of two different physical forms of API in suspension	Well tolerated at 300 mg and 1000 mg; Physical form selected
CY 5015	24	Assess pharmacokinetics of a tablet formulation; Fed vs. fasted	Well tolerated at 250 mg, 500 mg and 1000 mg; Tablet appropriate for use in potential future clinical trials

5 Phase I Clinical Trials Enrolling > 100 Healthy Subjects
Well Characterized Safety, Tolerability, PK/PD during Oral Administration

RESULTS

CY 5021: CK-2127107 Administered Orally to SMA patients

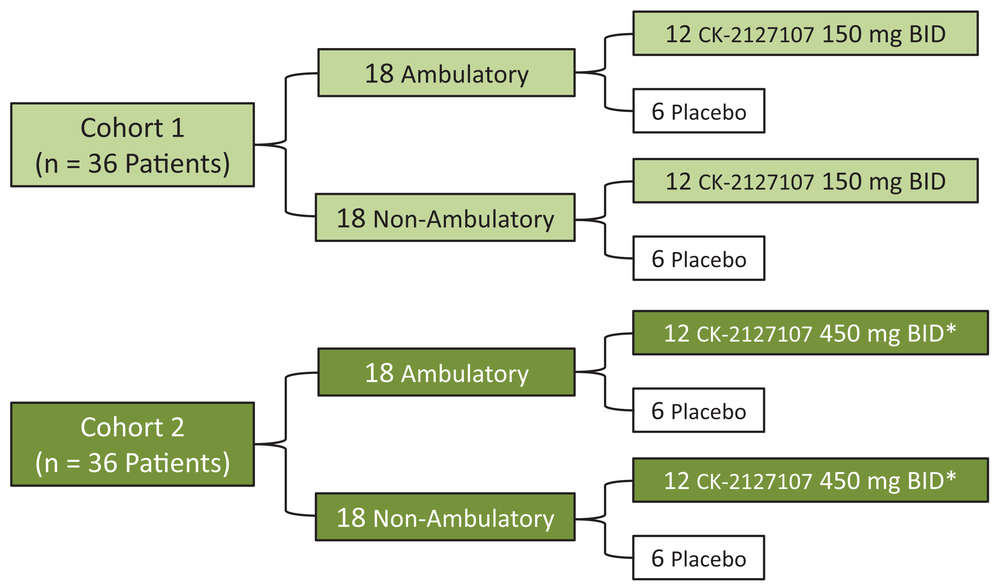
Study Objectives
- To evaluate the safety and tolerability
- To determine potential pharmacodynamic effects
- To evaluate the pharmacokinetics

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

- 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

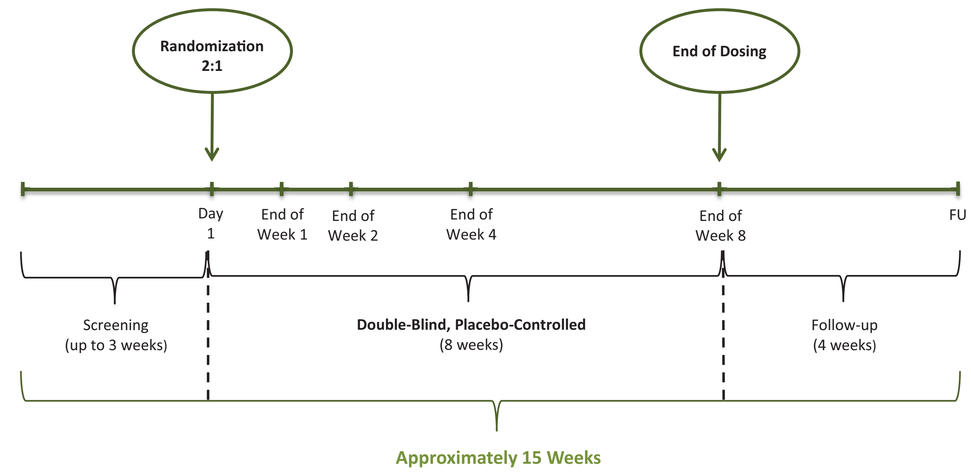
CY 5021: Study Design Diagram



or lower, pending the review of data from Cohort 1

CY 5021: Study Design Diagram

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



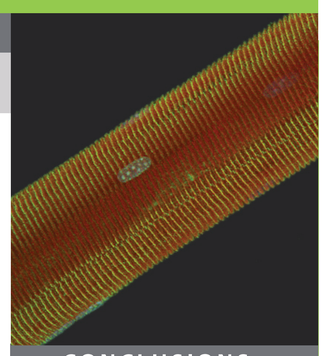
Outcome Measures

Respiratory
- Forced Vital Capacity
- Maximum Inspiratory Pressure
- Maximum Expiratory Pressure

Motor evaluations
- Hand held dynamometry
- Revised upper limb module (RULM)
- Hammersmith (HFMS-E) test
- Timed Up and Go (TUG)
- Six-minute walk test (6MWT)

Safety Monitoring

Pharmacokinetics



CONCLUSIONS

Based on safety, pharmacokinetics, and pharmacodynamics findings in Phase 1 studies, a Phase 2a clinical trial of CK-2127107 is currently enrolling patients in the US

DISCLOSURES

S Rudnicki J Andrews, F Malik, A Wolff are employees of Cytokinetics, Inc. J Day has served as a consultant to Cytokinetics

Cytokinetics

astellas