Pharmacokinetics and Pharmacodynamics of the Selective Fast Skeletal Muscle Troponin Activator, CK-2127107

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Background

Mechanism of Action

- CK-2127107, a selective fast skeletal muscle troponin activator, slows the rate of calcium release from the troponin complex (Figure 1), thus sensitizing the sarcomere to calcium and increasing fast skeletal muscle contractility (Figure 2)

Figure 1

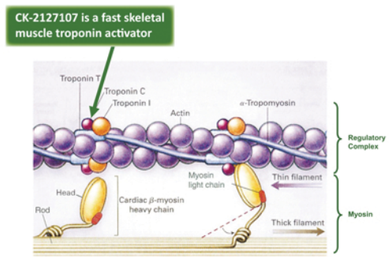
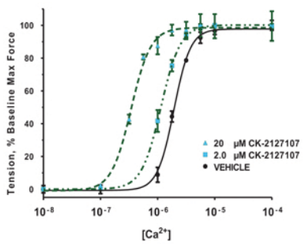


Figure 2: CK-2127107 Increases Tension in Skinned Fast Skeletal Muscle Fibers

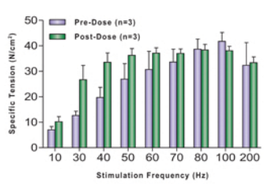


Rationale

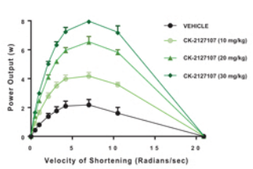
- CK-2127107 has demonstrated pharmacological activity that may lead to new treatments for neuromuscular diseases or conditions associated with muscle weakness and wasting (Figures 3A, 3B and 3C)
- By directly increasing skeletal muscle function, CK-2127107 may enhance physical performance in patients with neuromuscular diseases including spinal muscular atrophy (SMA); this possibility warrants a Phase 2 study in patients with SMA

Figure 3: The Effect of CK-2127107 on Skeletal Muscle Function in Rat

3A: Troponin activators augment force development in response to nerve stimulation

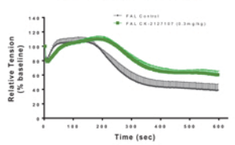


3B: CK-2127107 Increases Power Output



Power = force x velocity

3C: Troponin activators delay the onset and reduce the degree of muscle fatigue in a model of vascular insufficiency



Fatigue Stimulation after Femoral Artery Ligation (FAL) (Rat Extensor Digitorum Longus *in situ*)

Results

Introduction

The safety, tolerability, and pharmacokinetics (PK) of CK-2127107 and the relationship between its plasma concentrations and increases in skeletal muscle force have been studied in three double-blind, randomized, placebo-controlled studies in healthy volunteers.

First Time in Humans Study (CY 5011)

- Single ascending oral doses of CK-2127107 (or matching placebo) were administered to healthy adult males in a three period, escalating dose, crossover study
- Doses up to 4000 mg, the highest dose administered in this trial, were well-tolerated without an emerging pattern of adverse events (Table 1)
- The PK profile of CK-2127107 was linear and dose-proportional across the dose range studied with a mean terminal half-life compatible with once or twice daily dosing (Figure 4, Table 2)

Table 1: Adverse Events in CY 5011

n (%)	Placebo (N=35)	30 mg (N=8)	90 mg (N=8)	270 mg (N=8)	500 mg (N=8)	1000 mg (N=8)	1500 mg (N=8)	2250 mg (N=8)	3000 mg (N=7)	4000 mg (N=7)
Subjects with ≥ 1 TEAE	2 (5.7)	1 (12.5)	1 (12.5)	0	1 (12.5)	1 (12.5)	1 (12.5)	3 (37.5)	3 (42.9)	4 (57.1)
Dizziness	0	0	0	0	0	0	0	3 (37.5)	2 (28.6)	4 (57.1)
Headache	1 (2.9)	0	0	0	0	1 (12.5)	1 (12.5)	1 (12.5)	2 (28.6)	3 (42.9)
Ocular discomfort	0	0	0	0	0	0	0	0	0	1 (14.3)
Visual impairment	1 (2.9)	0	0	0	0	0	0	1 (12.5)	0	1 (14.3)
Nausea	0	0	0	0	0	0	0	0	1 (14.3)	1 (14.3)
Vomiting	0	0	0	0	0	0	0	0	1 (14.3)	0
Cough	0	0	0	0	1 (12.5)	0	0	0	1 (14.3)	0
Abdominal pain	0	0	0	0	0	0	0	1 (12.5)	0	0
Diarrhoea	0	0	0	0	0	1 (12.5)	0	1 (12.5)	0	0
Ecchymosis	0	0	0	0	0	0	0	1 (12.5)	0	0
Dermatitis	0	0	1 (12.5)	0	0	0	0	0	0	0
Tendonitis	0	1 (12.5)	0	0	0	0	0	0	0	0
Dyspnoea	1 (2.9)	0	0	0	0	0	0	0	0	0

Figure 4: Plasma Concentrations of CK–2127107 (ng/mL) Over Time by Dose in CY 5011

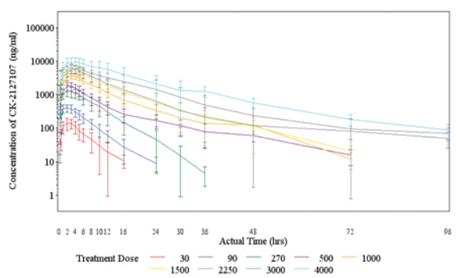


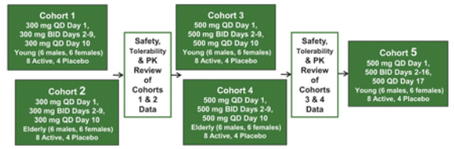
Table 2: CK-2127107 Single Dose PK in CY 5011

Dose (N)	C_{max} (ng/mL) Arithmetic Mean (SD)	t_{max} (hr) Median (SD)	$AUC_{0-\infty}$ (hr*mg/mL) Arithmetic Mean (SD)	$t_{1/2}$ (hr) Arithmetic Mean (SD)
30 mg (8)	154.1 (46.4)	2.00 (0.89)	979.4 (453.5)	2.98 (0.52)
90 mg (8)	418.3 (106.2)	2.00 (0.64)	2904.5 (913.1)	3.67 (1.45)
270 mg (8)	1469.4 (397.0)	2.00 (1.06)	11184.4 (3825.3)	4.03 (0.76)
500 mg (8)	1920.0 (402.4)	2.50 (0.74)	18646.4 (6106.0)	12.2 (7.51)
1000 mg (8)	3913.8 (641.8)	3.00 (0.83)	40851.6 (7026.7)	12.2 (8.23)
1500 mg (8)	5407.5 (1226.7)	3.00 (1.31)	61450.5 (20081.2)	9.27 (3.37)
2250 mg (8)	6616.3 (1419.0)	3.00 (0.76)	73380.1 (21356.6)	15.4 (12.4)
3000 mg (7)	6340.0 (1370.0)	3.00 (1.86)	100532.0 (39042.1)	14.3 (7.89)
4000 mg (7)	10284.3 (2658.3)	4.00 (2.57)	159091.8 (78146.5)	12.9 (8.29)

Multiple Ascending Dose Study (CY 5012)

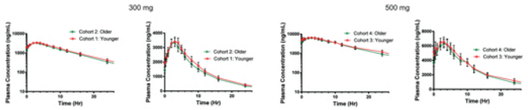
- Study design (Figure 5)
  - Three ascending dose cohorts of 12 younger volunteers (ages 18-55) and two ascending dose cohorts of 12 older volunteers (ages 65-85)
  - 6 men and 6 women in each cohort
  - Randomized to 2:1 to CK-2127107 or placebo
- CK-2127107 at 300 mg and 500 mg twice daily was well tolerated by both younger and older subjects
- The PK profile of CK-2127107 was linear and dose-proportional across the dose range studied with a mean terminal half-life compatible with once or twice daily dosing (Figure 6)

Figure 5: CY 5012 Study Design



- Screening within 21 days prior to Check-In (Day -2)
- In Phase I Unit from Day -2 through Day 11 (12 nights, 19 in Cohort 5)
- Intensive PK sampling on Day 1 & Day 10 (Day 17 in Cohort 5)
- Follow-Up Visit 7 days after last dose

Figure 6: Plasma Concentrations of CK-2127107 (ng/mL) Over Time by Dose in Younger and Older Volunteers in CY 5012

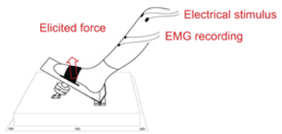


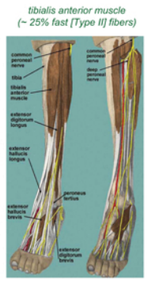
Translational Study in Healthy Volunteers (CY 5013)

CY 5013: Methods and Rationale

Force-frequency assessment by external stimulation of tibialis anterior muscle

- Stimulate a nerve-muscle pair (peroneal nerve, tibialis anterior 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





CY 5013: Study Design

- Subjects received all 4 of the following treatments in a randomized order, in a double-blind, 4-period crossover design:
  - Treatment A: Placebo
  - Treatment B: 300 mg CK-107
  - Treatment C: 1000 mg CK-107
  - Treatment D: 3000 mg CK-107
- Subjects were randomized to receive one of the 4 sequences, with each period separated by at least a 7-day washout:

	Period I	Period 2	Period 3	Period 4
Sequence 1	D	C	A	B
Sequence 2	C	B	D	A
Sequence 3	B	A	C	D
Sequence 4	A	D	B	C

- 16 healthy male volunteers, 4 per sequence
  - BMI within 18.5 to 32 kg/m2
  - Age between 19 and 50 years
  - Can tolerate force frequency assessment

Translational Study in Healthy Volunteers (CY 5013) (contd.)

Figure 7: Translation of the Mechanism into Humans in CY 5013

Frequency and Concentration Dependent Force Increases

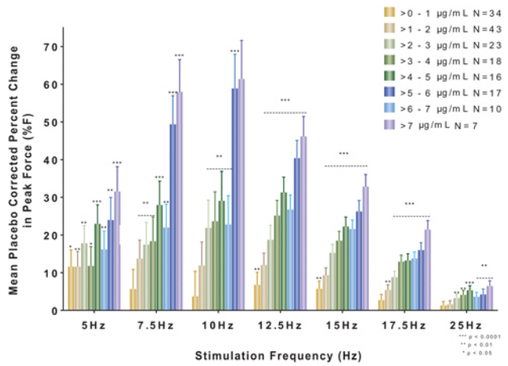


Figure 8: Translation of the Mechanism into Humans in CY 5013

Time and Dose Dependent Force Increases

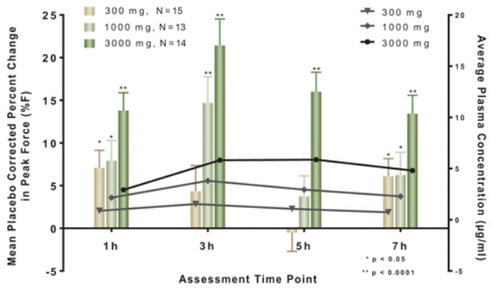
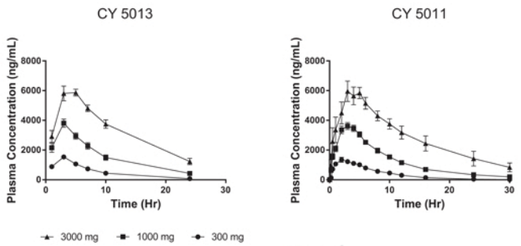
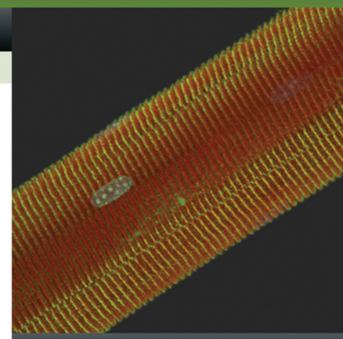


Figure 9: Plasma Concentrations of CK-2127107 (ng/mL) Over Time by Dose in CY 5013

Virtually Identical to Data after Single Doses in CY 5011





Conclusions

- CK-2127107 was well-tolerated in healthy volunteers at single doses up to 4000 mg
- Exposures increased generally proportionally up to 4000 mg
- CK-2127107 increased the response of muscle to neuronal input with increasing dose and plasma concentration
- By directly increasing skeletal muscle function, CK-2127107 may enhance physical performance in patients with neuromuscular diseases including spinal muscular atrophy (SMA); this possibility warrants a Phase 2 study in patients with SMA

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