Efficacy and Tolerability of the Novel Fast Skeletal Muscle Troponin Activator, CK-2017357, in Patients with Claudication

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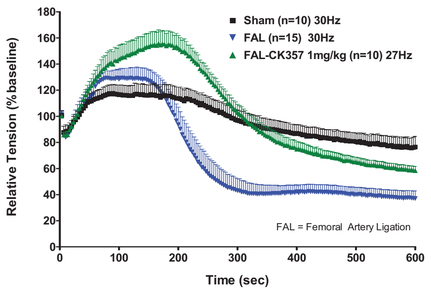
Introduction

CK-2017357 (CK-357), a novel small molecule activator of the fast skeletal muscle troponin complex, slows the rate of calcium release from troponin, resulting in sensitization of fast skeletal muscle fibers to calcium. In preclinical studies CK-357 increased muscle force and delayed the onset and reduced the extent of muscle fatigue under conditions of hypoxia *in vitro* and muscle ischemia *in situ* (Figure 1).

Figure 1: CK-2017357 Increases Force Generation and Decreases Fatigue in Rat Femoral Artery Ligation Model



Rat extensor digitorum longus (EDL) was stimulated at a frequency of 30 Hz, using 350 msec. trains every 3 seconds for 10 minutes *in situ* following femoral artery ligation (FAL) or a sham procedure. Animals that underwent FAL were studied prior to and following i.v. administration of 1 mg/kg CK-357 or vehicle. Baseline tension was matched prior to initiating the fatigue protocol by adjusting the stimulation frequency in CK-357 treated animals. Time to fatigue, indexed as time to 50% initial tension, as well as total tension generating capacity (AUC) were significantly reduced in vehicle-treated animals after FAL. CK-357 administration increased time to fatigue and tension generating capacity in FAL animals compared to vehicle treatment alone (Hinken, et al. Vascular Medicine 2010; 15:149).

Design

Double-blind, randomized, placebo-controlled, three-period cross-over, hypothesis-generating Phase II study in patients with peripheral artery disease and claudication.

Objectives

Primary: To demonstrate an effect of single doses of CK-357 on measures of skeletal muscle function and fatigability

Secondary

- To evaluate and characterize the relationship, if any, between the doses and plasma concentrations of CK-357 and its pharmacodynamic effects
- To evaluate the safety and tolerability of CK-357 administered as single doses

Key Inclusion Criteria

- Stable claudication for the last 6 months (Fontaine Stage II) in at least one calf muscle
- Peripheral artery disease: ankle–brachial index at rest < 0.90 in at least one leg in which the patient experiences claudication
- Ability to perform the bilateral heel raise test to claudication-limited maximum muscle performance at a contraction frequency of once every other second
- Ability to complete a 6-Minute Walk Test

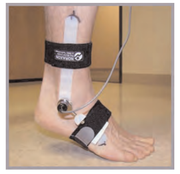
Key Exclusion Criteria

- Fontaine Stage III-IV leg ischemia (rest pain, tissue necrosis or gangrene)
- Leg, hip, or knee surgery within 6 months prior to randomization
- Within 3 months prior to randomization
  - Any revascularization procedure (coronary or peripheral)
  - Life-threatening ventricular arrhythmias, unstable angina, stroke, and/or myocardial infarction
  - NYHA Class III or IV heart failure
- Screening Heel Raise Test and 6-Minute Walk Test not limited by claudication

Methods

- Single doses of each of CK-357 375 mg, CK-357 750 mg and placebo were administered in random order with a 6 to 10 day wash out between each dose. The protocol was amended after 33 patients due to adverse events in two patients at 750 mg; the remainder received CK-357 500 mg instead of CK-357 750 mg
- Assessments:
  - Bilateral Heel Raise Test using electrogoniometry at 3 and 6 hours after dosing (See Figure 2 below and Poster #25* for details)
  - 6-Minute Walk Test at 4 hours after dosing
- Results were analyzed using a repeated-measures ANCOVA with treatment, sequence, period, baseline, and patient in the model. In the event of model assumption violations, non-parametric methods were utilized

Figure 2: Bilateral Heel Raise



The lateral aspect of the ankle on the dominant leg was instrumented with an electro-mechanical goniometer connected to a PC-based data collection system to monitor and record ankle angle position and range of motion (Noraxon U.S.A., Inc., Scottsdale, AZ)

Patients were instructed to perform heel raises at the frequency as directed by a metered, audible cue (1 heel raise every other second ~ 0.5Hz)

Patients reported the onset of claudication symptoms, and the test was performed to intolerable/maximal claudication pain and fatigue

The total number of heel raises, time, and a calculated index of work performed were assessed from the beginning of test to the onset of claudication and to maximal exercise

An index of work performed was calculated as follows: Heel Raise Work Index (HRWI) = (sinθ ∗ foot length) ∗ body mass

*Bauer et al., Bilateral Heel Raise Test: A Novel Functional Endpoint for Early Stage Clinical Trials in Peripheral Artery Disease (PAD). *Soc Vasc Med*, abstr 25, 2011.

Patient Population

Table 1. Patient Population

A. Demographic Characteristics

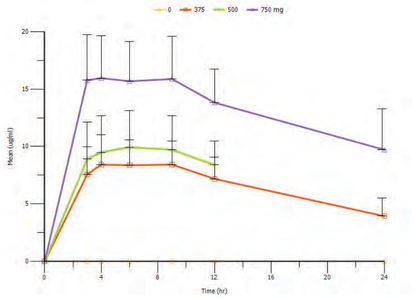
	Mean (SD) or n (Percent of Total)
Total N	**61 (100%)**
Age (years)	**67.3 (9.2)**
Sex, Female	**9 (14.8%)**
Male	**52 (85.2%)**
BMI (kg/m^2)	**26.4 (3.6)**
Smoking Status	
Current	**24 (39.3%)**
Former	**35 (57.4%)**
Never	**2 (3.3%)**
Tobacco Use (units/day)	**14.7 (11.0)**
Race:	
Asian	**1 (1.6%)**
Black	**7 (11.5%)**
White	**52 (85.2%)**
Other	**1 (1.6%)**
Ethnicity:	
Hispanic	**7 (11.5%)**
Non Hispanic	**54 (88.5%)**

B. Baseline Performance on Pharmacodynamic Outcome Measures

	Mean (SD)
Time to Claudication Onset (seconds)	**43.7 (17.9)**
Time to End of Test (seconds)	**78.4 (48.1)**
Number of Full Repetitions to Claudication Onset	**20.6 (8.6)**
Number of Full Repetitions Completed to End of Test	**36 (23.1)**
Work Index to Claudication Onset (kg-m)	**87.0 (39.1)**
Work Index Total to End of Test (kg-m)	**145.8 (74.3)**
6-Minute Walk Total Distance (feet)	**1078.8 (204.0)**

Pharmacokinetic Results

Figure 3: CK-2017357 Plasma Concentration-Time Profile



Mean (± SD) plasma concentrations over time. Mean plasma CK-357 concentrations showed relatively dose proportional increases. Mean plasma concentrations remained within the pharmacologically active range throughout the 24-hour observation period, even at the 375 mg dose.

Clinical Results

Figure 4A: Heel Raise Test: Time to Endpoint

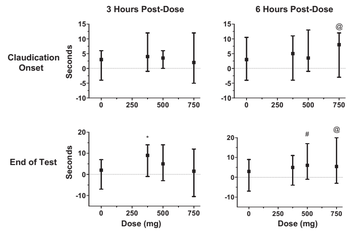


Figure 4B: Heel Raise Test: Repetitions to Endpoint

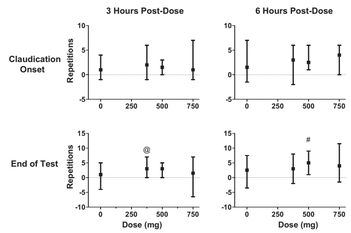
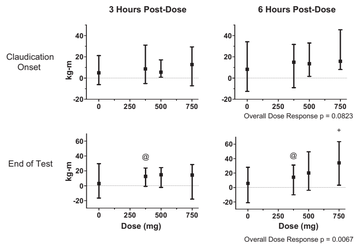
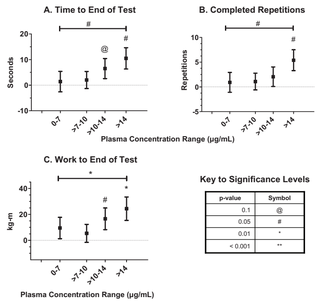


Figure 4C: Heel Raise Test: Work to Endpoint



Change from same-day baseline for **A**: Time to Onset of Claudication or End of Test (failure or intolerable claudication pain); **B**: Number of complete heel raise repetitions to Onset of Claudication or End of Test and **C**: Work done to Onset of Claudication and End of Test. All values are represented as median ± interquartile range. Symbols: @ $p < 0.10$; # $p < 0.05$; * $p < 0.01$; + $p < 0.002$.

Figure 5: PK/PD Analysis Shows Strong Relationship Between CK-357 Plasma Concentrations and Outcomes

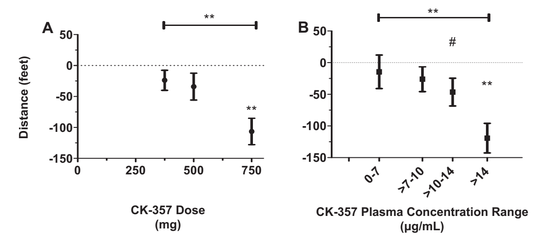


Key to Significance Levels

p-value	Symbol
0.1	@
0.05	#
0.01	*
< 0.001	**

Relationship of pharmacodynamic measures to plasma CK-357 concentrations. Pharmacokinetic samples were obtained at the time of each Heel Raise Test. All measured plasma CK-357 concentrations were divided into quartiles. The placebo-corrected LS mean change from baseline ± SEM for the simultaneously obtained value of each outcome measure is plotted at the mid-point of each concentration bin. There was a strong positive relationship between CK-357 plasma concentrations and all outcomes in the Heel Raise Test. Significance levels for individual comparisons to placebo are indicated on the table in the lower right-hand panel. Symbols above the horizontal bars on each graph indicate the p-value for the slope of the concentration-response relationship.

Figure 6: 6-Minute Walk Test: Placebo-Corrected Change from Baseline by Dose and CK-357 Plasma Concentration



Baseline Mean = 1079 feet

CK-357 administration was associated with a dose (**A**) and concentration (**B**) dependent decrease in the distance patients traversed during the 6-Minute Walk Test. Panel **A**: Values displayed are placebo-corrected LS mean changes from baseline ± SEM; ** $p < 0.0001$ for overall dose response (indicated by horizontal bar over the figure) and for comparison of the 750 mg dose to placebo. Panel **B**: All measured plasma CK-357 concentrations were divided into quartiles. The placebo-corrected LS mean change from baseline ± SEM for the simultaneously obtained value of each outcome measure was plotted at the mid-point of each concentration range. ** $p < 0.0001$ for overall concentration response (indicated by horizontal bar over the figure) and for comparison of the highest concentration range to placebo; # $p < 0.05$ for comparison of the second-highest range to placebo. Note that the placebo-corrected changes shown are small relative to the mean distance of 1079 feet traversed at the screening visit.

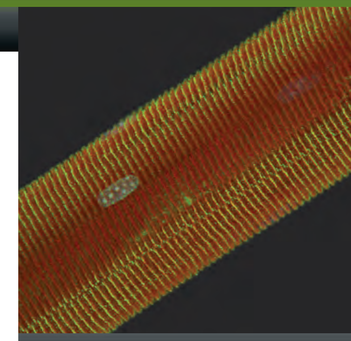
Safety

Serious Adverse Events

- 70-year-old woman hospitalized with severe dizziness and moderate dyskinesia after her 1st dose of study drug (750 mg)
  - Judged related to study drug
  - Recovered fully and spontaneously without intervention
- 85-year-old man hospitalized with severe dizziness and moderate mental confusion after his 2nd dose of study drug (750 mg)
  - Judged related to study drug
  - Recovered fully and spontaneously without intervention
- 70-year-old man hospitalized with severe worsening of cholecystitis after his 2nd dose of study drug (500 mg)
  - Judged unrelated to study drug
  - Recovered fully

Table 2. Treatment – Emergent Adverse Events Reported by > 5% of Patients

	Placebo (n=57) n (%)	375 mg (n=56) n (%)	500 mg (n=27) n (%)	750 mg (n=33) n (%)	Overall (n=61) N (%)
Dizziness	4 (7.0%)	29 (51.8%)	18 (66.7%)	27 (81.8%)	49 (80.3%)
Euphoric Mood	0	10 (17.9%)	7 (25.9%)	6 (18.2%)	16 (26.2%)
Fatigue	0	7 (12.5%)	5 (18.5%)	2 (6.1%)	11 (18.0%)
Gait Disturbance	0	1 (1.8%)	1 (3.7%)	8 (24.2%)	10 (16.4%)
Pain in Extremity	1 (1.8%)	3 (5.4%)	1 (3.7%)	4 (12.1%)	8 (13.1%)
Somnolence	1 (1.8%)	2 (3.6%)	0	5 (15.2%)	7 (11.5%)
Feeling Drunk	0	4 (7.1%)	1 (3.7%)	2 (6.1%)	6 (9.8%)
Blood CPK Increase	1 (1.8%)	3 (5.4%)	1 (3.7%)	1 (3.0%)	6 (9.8%)
Vision Blurred	0	2 (3.6%)	2 (7.4%)	3 (9.1%)	5 (8.2%)
Headache	1 (1.8%)	1 (1.8%)	1 (3.7%)	3 (9.1%)	5 (8.2%)
Nausea	0	2 (3.6%)	2 (7.4%)	2 (6.1%)	5 (8.2%)
Balance Disorder	0	2 (3.6%)	0	2 (6.1%)	4 (6.6%)
Hypertension	1 (1.8%)	0	1 (3.7%)	2 (6.1%)	4 (6.6%)



Conclusions

1. CK-357 increased calf muscle performance in patients with calf claudication as evidenced by heel raise testing.
2. Both increases in muscle performance and adverse events appear related to increasing both dose and plasma CK-357 concentration.
3. Performance on 6-Minute Walk Test was inversely related to dose and CK-357 plasma concentration. Dose related adverse events, particularly dizziness and others related to walking, may explain this negative effect on 6-Minute Walk.
4. CK-357 merits further study to establish a safe, well-tolerated and effective dosing regimen in repeat-dose studies.

Next Steps:

- Future studies will explore whether AEs (such as dizziness) abate with repeated dosing, alternate dosing regimens, and/or dose titration.
- Other fast skeletal muscle activators that penetrate the blood brain barrier less readily than CK-357 are in early development. Such compounds possibly may show an increase in muscle performance similar to CK-357 with better tolerability.

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