A Study to Evaluate Safety, Tolerability and Clinical Outcomes Following Repeated Doses of CK-2017357 (CK-357) in Patients with Amyotrophic Lateral Sclerosis

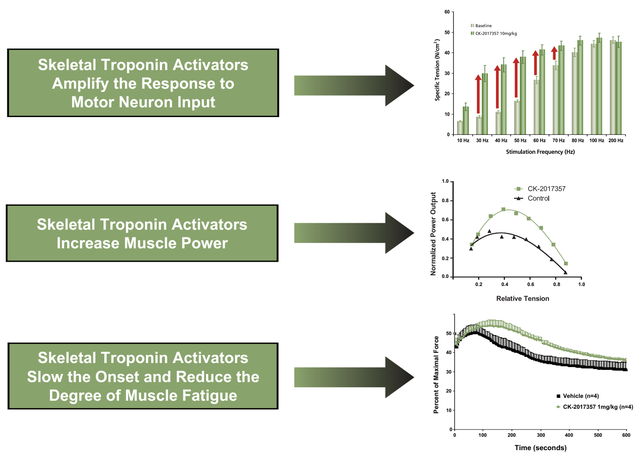
Jeremy Shefner[1], Benjamin Rix Brooks[2], Zachary Simmons[3], Hiroshi Mitsumoto[4], Andrew A Wolff[5], Jacqueline H Lee[5], Drew S Jones[5], John Mao[5], Lisa Meng[5], Jesse M Cedarbaum[5] for the CY 4024 Investigator Group

1. Department of Neurology, Upstate Medical University, Syracuse, NY. 2. Carolinas Medical Center, Charlotte, NC. 3. Penn State Hershey Medical Center, Hershey, PA.
4. Eleanor and Lou Gehrig MDA/ALS Research Center, Neurological Institute, Columbia University School of Medicine, New York, NY. 5. Cytokinetics, Inc., South San Francisco, CA.

Background

CK-2017357 is a selective activator of the fast skeletal muscle troponin complex. CK-2017357 increases the sensitivity of troponin to calcium, thereby increasing the force response of muscle to neuronal input, increasing power, and reducing fatigability.

The Effects of Skeletal Troponin Activation on Skeletal Muscle Function

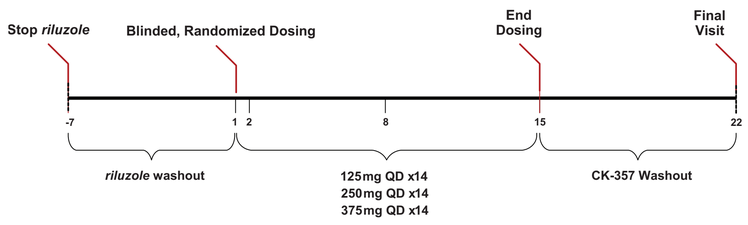


METHODS

Study Design and Objectives

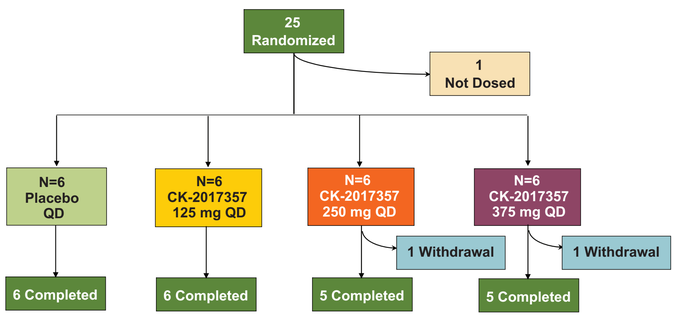
- **Study Design**
  - Randomized, double-blind, placebo-controlled study
  - 7-day washout of *riluzole*
  - Patients then randomized into four parallel groups (6 patients/group) to receive study medication for 14 days
    - Placebo
    - CK-2017357 125 mg QD
    - CK-2017357 250 mg QD
    - CK-2017357 375 mg QD
- **Primary Objective:**
  - To determine the safety & tolerability of CK-2017357 after multiple oral doses to steady state in patients with ALS
- **Secondary Objectives:**
  - To evaluate the pharmacokinetics of CK-2017357 after multiple oral doses to steady state
  - To evaluate and characterize the relationship, if any, between the doses and plasma concentrations of CK-2017357 and its pharmacological effects
  - To evaluate ALSFRS-R, muscle fatigue, pulmonary function and global assessments during treatment with CK-2017357 and placebo
  - To assess test-retest reliability of selected outcome measures

Study Flow Diagram



RESULTS

Patient Disposition



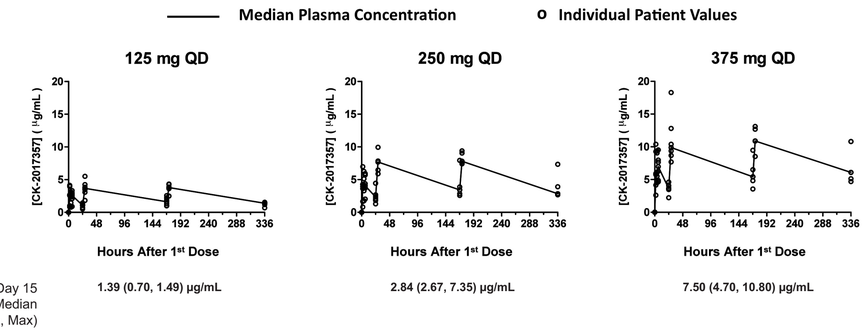
- One patient withdrew consent prior to the first dose of study drug
- Two patients withdrew from the study; one each at the 250 and 375 mg dose level, both due to adverse events.

Demographics and Baseline Disease Characteristics

(Mean ± SD) *(unless otherwise noted)*	Placebo (N=6)	Dose CK-2017357 125 mg (N=6)	250 mg (N=6)	375 mg (N=6)	Combined (N=18)
Age (years)	53 (12.5)	57 (14.4)	53 (14.8)	56 (12.3)	55 (13.1)
Sex [Male (%)]	3 (50%)	3 (50%)	3 (50%)	3 (50%)	9 (50%)
BMI (kg/m^2)	25.7 (4.9)	28.8 (5.7)	29.1(2.0)	27.1(7.2)	28.4(5.0)
Months from Diagnosis	17.1 (20.9)	20.2 (26.5)	15.8 (17.4)	34.8 (20.0)	23.6 (21.9)
Months from 1st Symptom	35.9 (19.8)	37.1 (21.1)	42.1 (29.1)	43.0 (25.9)	40.7 (24.2)
ALSFRS-R	38.2 (7.9)	32.3 (3.9)	35.8 (3.8)	30.5 (5.2)	32.9 (5.2)
SVC (% predicted)	73.0 (19.7)	78.8 (34.0)	75.1 (17.5)	66.9 (23.2)	73.6 (24.8)
MVV (L/min)*	85.5 (34.6)*	52.5 (18.4)	64.7 (20.3)	59.6 (29.4)	59.0 (22.4)

* Mean baseline MVV for the placebo group was significantly higher than for the combined CK-2017357 treatment groups (p<0.04). The difference in baseline ALSFRS-R scores was not significant.

Repeat-Dose Pharmacokinetics of CK-2017357



Day 15 Median (Min, Max)	125 mg QD	250 mg QD	375 mg QD
	1.39 (0.70, 1.49) µg/mL	2.84 (2.67, 7.35) µg/mL	7.50 (4.70, 10.80) µg/mL

Blood for measurement of CK-2017357 concentrations was obtained on Day 1 prior to the first dose of study drug and 2, 4 and 6 hrs post-dose; on Day 2 and 8 prior to dosing and 4 hrs post-dose, and finally at trough on Day 15, 24 hrs after the last dose of drug.

Safety

- 83% of patients in the combined CK-2017357 dose groups reported at least one Treatment-Emergent Adverse Event (TEAE), compared with 67% of placebo patients
- No treatment-emergent Serious Adverse Events were reported during the study
- AEs that were reported by > 10% of patients in the combined CK-2017357 treatment groups are shown in the Table below

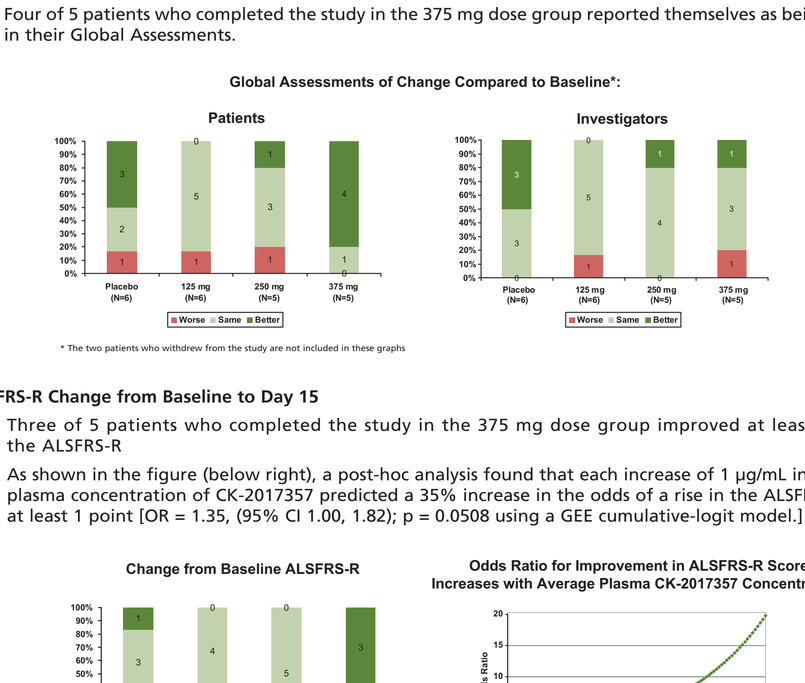
Most Common Adverse Events (> 10%) in Combined Active Treatment Groups
[number of pts (% of dose group)]

Preferred Term	Placebo (N=6)	Dose CK-2017357 125 mg (N=6)	250 mg (N=6)	375 mg (N=6)	Combined (N=18)
Any Adverse Event	4 (66.7)	3 (50)	6 (100)	6 (100)	15 (83.3)
Dizziness	0	1 (16.7)	3 (50.0)	4 (66.7)	8 (44.4)
Fatigue	2 (33.3)	1 (16.7)	2 (33.3)	2 (33.3)	5 (27.8)
Asthenia	0	1 (16.7)	1 (16.7)	0	2 (11.1)
Coordination abnormal	0	0	0	2 (33.3)	2 (11.1)
Euphoric mood	0	0	0	2 (33.3)	2 (11.1)
Muscle contractions involuntary	0	1 (16.7)	1 (16.7)	0	2 (11.1)
Nausea	0	1 (16.7)	1 (16.7)	0	2 (11.1)

Dizziness

- **Incidence and Dose-Relationship:**
  - 14 episodes of dizziness were reported by 8 of 18 patients (44%) who received CK-2017357
    - 2 by 1 patient in the 125 mg dose group,
    - 4 by 3 patients in the 250 mg dose group, and
    - 8 by 4 patients in the 375 mg dose group
  - The frequency of dizziness increased with increasing dose
- **Severity:**
  - One episode reported at 250 mg and one episode reported at 375 mg were assessed as Grade 3; the remainder were Grade 1
  - Both patients who reported Grade 3 dizziness withdrew from the study during the first week
    - A 28 year old male in the 250 mg dose group reported dizziness, weakness and vomiting approximately 5 hours after receiving his first and only dose of CK-2017357. Symptoms resolved within a day
    - A 65 year old female in the 375 mg dose group complained of shakiness and lightheadedness shortly after taking her first dose of CK-2017357. Symptoms increased in intensity over the next 2 days. Her plasma level of CK-2017357 on day 2 was 18.3 µg/ml, the highest level observed in the study. Study drug was discontinued on day 3, and her symptoms resolved promptly
- **Duration:**
  - Episodes were self-limited, as shown in the figure below
  - The average duration of the initial episode of dizziness increased with increasing dose of CK-2017357
  - Only one patient reported dizziness through the 2nd week of the study

Dizziness Began and Resolved Early in the Majority of Instances

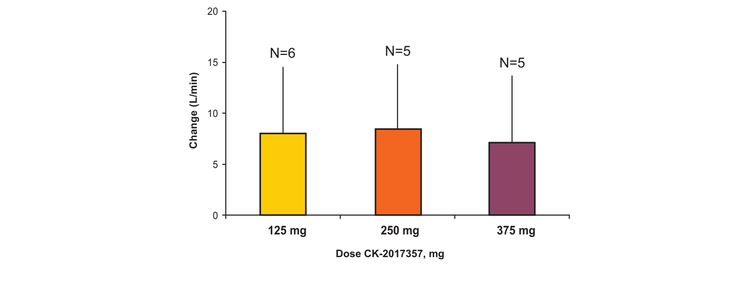


Clinical Outcome Measures

Due to its small sample size and short duration, as well as the large observed inter-patient variability, this study lacked statistical power to detect significant differences in the clinical outcome measures. Nevertheless, the following observations were made:

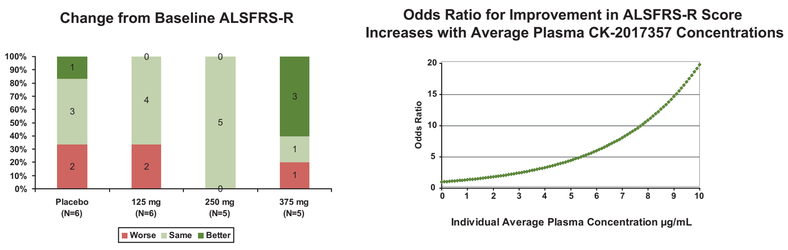
Clinical Outcomes at Day 15

- **Patient and Investigator Global Assessments of Change at Day 15**
  - Four of 5 patients who completed the study in the 375 mg dose group reported themselves as being improved in their Global Assessments.



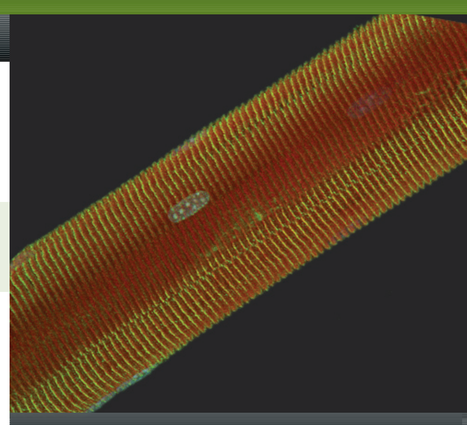
* The two patients who withdrew from the study are not included in these graphs

- **ALSFRS-R Change from Baseline to Day 15**
  - Three of 5 patients who completed the study in the 375 mg dose group improved at least 1 point on the ALSFRS-R
  - As shown in the figure (below right), a post-hoc analysis found that each increase of 1 µg/mL in the average plasma concentration of CK-2017357 predicted a 35% increase in the odds of a rise in the ALSFRS-R score by at least 1 point [OR = 1.35, (95% CI 1.00, 1.82); p = 0.0508 using a GEE cumulative-logit model.]



* The two patients who withdrew from the study in the 250 mg and 375 mg dose groups are not included

- **Change in Maximum Voluntary Ventilation at Day 15**
  - The LS mean change from baseline to Day 15 in MVV was numerically superior to placebo for all dose levels, but the results did not achieve statistical significance



Summary & Conclusions

- The study achieved its primary objective of defining the safety and tolerability, as well as the pharmacokinetic profile of CK-2017357 during two weeks of daily dosing in ALS patients
- CK-2017357 was well tolerated at all dose levels from 125 mg QD to 375 mg QD for two weeks
  - The most commonly reported TEAE in this study was dizziness
  - The incidence of dizziness was dose-related and most episodes were mild in intensity
  - Dizziness was self-limited in all but one patient, in whom it was mild in severity
- Both subjects who discontinued study participation did so due to Grade 3 AEs of dizziness
  - One of these patients had the highest CK-2017357 plasma concentrations observed in the study
  - The other had fever and laboratory test abnormalities suggesting these symptoms may not have been due to study drug
- Plasma concentrations of CK-2017357 increased with dose although there was considerable overlap in plasma concentrations of CK-2017357 across the dose levels studied
- As expected, due to its small sample size (N=6 per dose group), large inter-patient variability and short duration (2 weeks), the study lacked statistical power to detect significant differences in clinical outcome measures. Nevertheless, the following observations were made:
  - ALSFRS-R scores improved with increasing average plasma CK-2017357 concentrations.
  - MVV appeared improved at all dose levels compared to placebo

Next Steps in the Clinical Development of CK-2017357

- Enrollment is ongoing in a study to investigate safety and tolerability of 2 weeks' administration of CK-2017357 in conjunction with *riluzole*
- Another ongoing study will explore the safety and tolerability of CK-2017357 at doses up to 500 mg daily when administered on an ascending, twice-daily dosing schedule
- The combined data from these studies will be used to select a dosing regimen for planned Phase 3 clinical trials

CK-2017357 Investigators

- Deborah Bradshaw, MD - SUNY Upstate Medical Center, Syracuse, NY
- Zachary Simmons, MD - Penn State Hershey Medical Center, Hershey, PA
- Kevin Boylan, MD - Mayo Florida, Jacksonville, FL
- Terry Heiman-Patterson, MD - Drexel University, Philadelphia, PA
- Jonathan Katz, MD - California Pacific Medical Center, San Francisco, CA
- Nicholas Maragakis, MD - Johns Hopkins, Baltimore, MD
- Richard Barohn, MD - University of Kansas, Kansas City, KS
- Benjamin Brooks, MD - Carolinas Neuromuscular, Charlotte, NC
- Hiroshi Mitsumoto, MD - Columbia University Medical Center, New York, NY

- We would also like to acknowledge the contributions of Kara Burroughs, Michael Chen MS, Y-Ting Lin, Fady Malik MD, PhD and Jean Masonek RN, BSN at Cytokinetics, Inc.

UPSTATE MEDICAL UNIVERSITY