A STUDY TO EVALUATE SAFETY, TOLERABILITY AND CLINICAL OUTCOMES FOLLOWING REPEATED DOSES OF CK-2017357 (CK-357) IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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BACKGROUND

Skeletal Troponin Activators

Increase Muscle Power

Incubate the Response to 
Motor Neurons

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The Effects of Skeletal Troponin Activation on Skeletal Muscle Function

METHODS

Study Design and Objectives

• Study Design
  - Randomized, double-blind, placebo-controlled study
  - 28 week washout of placebo
  - Patients randomized into four parallel treatment groups (8 per 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 and 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 the relationship between plasma concentrations, if any, between the doses and plasma concentrations of CK-2017357 and its pharmacological effects
  - To evaluate the changes in muscle force, pulmonary function, and global assessments during treatment with CK-2017357 and placebo
  - To assess test-retest reliability of selected outcome measures

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

- Number 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 adverse events were reported during the study
- All TEAEs that were reported by ≥10% of patients in the combined CK-2017357 treatment groups are shown in the Table below

SAFETY

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

- Dizziness
  - Incidence and Dose-Relationship:
    - 14 episodes of dizziness were reported by 8 of 18 patients (44%) who received CK-2017357
    - 3 of 4 patients in the 125 mg dose group, 5 of 6 patients in the 250 mg dose group, and
      2 of 6 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 2; the remainder were Grade 1
    - Both patients who reported Grade 3 dizziness withdrew from the study during the first week
      - One 28 year old male in the 250 mg dose group reported dizziness, weakness and vomiting approximately
      5 hours after receiving his first dose of 250 mg of CK-2017357. Symptoms resolved within a day
      - Another patient in the 375 mg dose group complained of dizziness and lightheadedness shortly after taking his first dose of CK-2017357. Symptoms improved over the next 2 days. Her plasma level of CK-2017357 on day 1 was 151 µg/mL, the highest level observed in the study. Study drug was
      continued on day 2, and her symptoms improved promptly
    - Duration:
      - Episodes were self-limited, as shown in the figure below
      - The average duration of the initial episodes of dizziness increased with increasing dose of CK-2017357
      - Only one patient reported dizziness throughout the 2nd week of the study

- 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.

- ALRSFRS-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 ALRSFRS-R
    - As shown in the figure below, a post-hoc analysis found that each increase of 1 unit in the average plasma concentration of CK-2017357 predicted a 5% increase in the odds of a rise in the ALRSFRS-R score by at least 1 point (OR = 1.05, 95% CI 1.01, 1.09; p = 0.008 using a logistic regression model)

- Change in Maximum Voluntary Ventilation at Day 15
  - The 15 cm 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

- Enrollment is ongoing in a study to evaluate 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 QD daily, when administered on an ascending, twice-daily schedule
- The combined data from these studies will be used to select a dosing regimen for planned Phase 3 clinical trials

- We would also like to acknowledge the contributions of Tara Bergstresser, Michelle Cheung, and Eric Schachter, BSc at Cyteokinetics, Inc.