CY 4025: A Study to Evaluate Safety and Tolerability of CK-2017357 in Patients with Amyotrophic Lateral Sclerosis (ALS) Using a Twice-Daily, Dose-Titration Regimen

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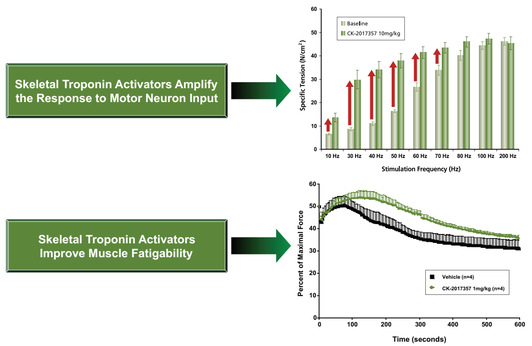
Background

- CK-2017357 selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium which increases the force response of muscle to neuronal input and reduces fatigability.
- Previous clinical trials of CK-2017357 in ALS have shown an acceptable tolerability profile with dizziness as the most frequently reported adverse event, and trends toward improvements in global assessments, muscle fatigability, and pulmonary function.
- This clinical trial was designed to determine if the maximum tolerable total daily dose of CK-2017357 could be increased by …
  - Dividing the daily dose into two portions (morning and evening), and
  - Beginning treatment with a low dose and titrating upward to a target of 250 mg twice daily

The Effects of Skeletal Troponin Activation on Skeletal Muscle Function



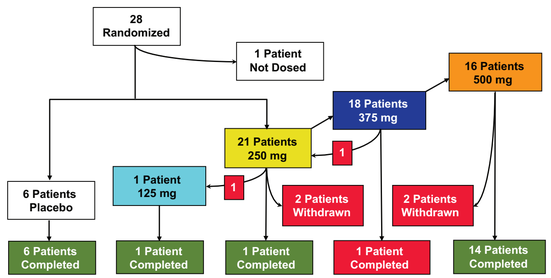
Methods

Study Design

- Randomized, double-blind, and placebo-controlled
- 7-day stabilization period for riluzole at a reduced dose of 50 mg QD
- Patients then randomized 3:1 to CK-2017357 or placebo for 3 weeks
- CK-2017357 titration regimen:
  - Dosing initiated at 125 mg twice daily for 7 days (250 mg total daily dose)
  - On Day 8, up titration to 125 mg in the morning and 250 mg in the evening (375 mg total daily dose)
  - On Day 15, up titration to 250 mg twice daily (500 mg total daily dose) continued through the morning dose on Day 22
  - Patients who did not tolerate a dose escalation returned to the previous tolerated dose level and remained at that dose level to complete the study
  - Placebo patients underwent a similar dummy dose titration to maintain the blind

Results

Patient Disposition



In the figure above, CK-2017357 doses are shown as the total daily dose, divided as described under "Study Design" above, except for the 125 mg total daily dose which was administered as 125 mg once daily. See "Safety and Tolerability", below, for an explanation of withdrawals and down-titrations.

Results (contd.)

Demographics and Baseline Characteristics

(Mean ± SD) *(unless otherwise noted)*	Placebo (N=6)	CK-2017357 (N=21)
Age (years)	54 (12.7)	56 (13.7)
Sex [Male (%)]	4 (67%)	12 (57%)
Body Mass Index (kg/m^2)	27 (3.5)	26 (3.9)
Months from Diagnosis	27 (24.6)	24 (21.4)
Months from 1st Symptom	18 (24.3)	12 (19.8)
ALS Function Rating Scale – Revised	34 (5.2)	39 (4.9)
Slow Vital Capacity (% Predicted)	66 (15.0)	89 (17.0)
Maximal Ventilatory Volume (L/min)	64 (41.1)	76 (45.7)

Slow Vital Capacity was higher in the CK-2017357 treatment group (p = 0.0075). There were no other statistically significant baseline differences between the two treatment groups.

Safety

Safety and Tolerability

- Of 21 patients randomized to treatment with CK-2017357, 14 were escalated to the highest total daily dose of 500 mg and completed three weeks of dosing
- 2 patients terminated the study prematurely while receiving the 500 mg total daily dose due to adverse events that required hospitalization
  - 1 with ataxia and confusion believed to be related to treatment with CK-2017357
  - 1 with cellulitis believed to be unrelated to treatment with CK-2017357
- 1 patient was withdrawn prematurely after completing treatment at the 375 mg total daily dose of CK-2017357 due to hospitalization with an upper respiratory infection believed to be unrelated to treatment with CK-2017357
- 2 patients withdrew from study for non-serious adverse events while receiving the 250 mg total daily dose of CK-2017357
  - 1 with dysarthria
  - 1 with unsteadiness, decreased appetite, fatigue, dizziness, and nausea
- 2 patients completed the study after a downward dose titration
- Adverse events reported by at least 3 patients overall are shown in the table below

Adverse Events Reported by at least 3 Patients

Number of patients (%)		Total Daily Dose of CK-2017357 at which Adverse Event Began*				
Preferred Term	Placebo (N=6)	125 mg (N=1)	250 mg (N=21)	375 mg (N=18)	500 mg (N=16)	All (N=21)
Any Adverse Event	4 (67)	1 (100)	14 (67)	10 (56)	10 (63)	20 (95)
Dizziness	0	0	10 (47.6)	3 (16.7)	0	12 (57.1)
Fatigue	0	0	2 (9.5)	2 (11.1)	2 (12.5)	6 (28.6)
Nausea	0	0	3 (14.3)	1 (5.6)	1 (6.3)	5 (23.8)
Contusion	0	0	1 (4.8)	2 (11.1)	1 (6.3)	4 (19.0)
Somnolence	1 (16.7)	0	3 (14.3)	0	1 (6.3)	3 (14.3)
Asthenia	0	0	1 (4.8)	1 (5.6)	1 (6.3)	3 (14.3)
Headache	0	0	1 (4.8)	0	2 (12.5)	3 (14.3)

Severe Adverse Events**

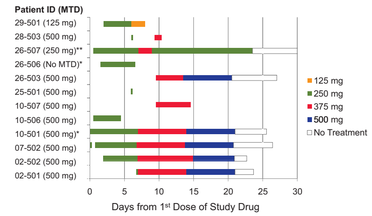
Number of patients (%)			Total Daily Dose of CK-2017357 at which Adverse Event Began*				
Preferred Term	Grade	Placebo (N=6)	125 mg (N=1)	250 mg (N=21)	375 mg (N=18)	500 mg (N=16)	All (N=21)
Any Adverse Event	3			1 (4.8)	1 (5.6)	2 (12.5)	3 (14.3)
	2	1 (16.7)		6 (28.6)	4 (22.2)	2 (12.5)	11 (52.4)
	1	4 (66.7)	1 (100)	12 (57.1)	10 (55.6)	9 (56.3)	18 (85.7)
Fatigue	3					1 (6.3)	1 (4.8)
	2			2 (9.5)		1 (6.3)	3 (14.3)
	1				2 (11.1)		2 (9.5)
Ataxia	3					1 (6.3)	1 (4.8)
Confusional state	3					1 (6.3)	1 (4.8)
Dysarthria	3					1 (6.3)	1 (4.8)
Muscle contractions involuntary	3			1 (4.8)			1 (4.8)
Cellulitis	3				1 (5.6)		1 (4.8)
International normalised ratio increased	3				1 (5.6)		1 (4.8)

*Patients whose adverse event continued at the same severity after upward or downward dose titration are counted only once, at the dose level at which the adverse event began. Patients whose adverse event either continued but increased in severity at a different dose level, or resolved but then recurred at a different dose level, are counted at the dose level at which the adverse event first began and again at any dose level at which the adverse event worsened in severity or recurred.

**CTCAE Grade 3. Patients who reported more than one occurrence of the same adverse event at the same dose level but with different severities are included only once at the maximum severity.

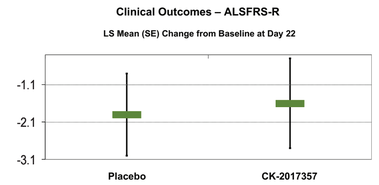
Safety (contd.)

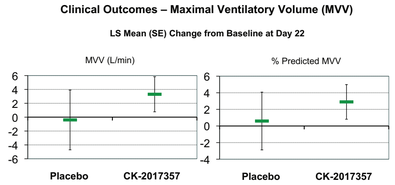
Dizziness During CY 4025

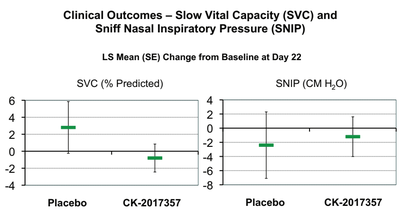


*Two patients reported Grade 2 dizziness. All others experienced Grade 1 dizziness.
**One patient had a Grade 1 dizziness ongoing through the follow-up visit.

Clinical Outcome Measures

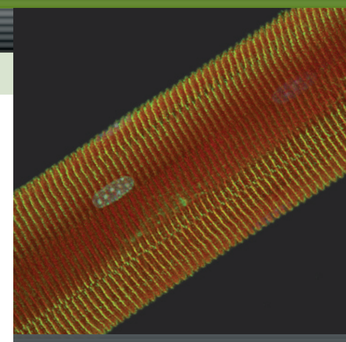






Test-Retest Reliability of Outcome Measures

Two Baseline Measures	Correlation Coefficient (p-value)
ALSFRS-R	0.88 (<0.0001)
% Predicted SVC	0.90 (<0.0001)
MVV	0.92 (<0.0001)
SNIP	0.86 (<0.0001)
Weaker Side Maximum Grip	0.97 (<0.0001)
Weaker Hand Fatigability at 60% of Sub-maximal Grip Strength Target	0.65 (0.0003)



Summary and Conclusions

CK-2017357 administered in the twice-daily, dose titration regimen studied in this trial appeared to be safe and well tolerated

The majority of patients could be titrated successfully to highest CK-2017357 dose level of 250 mg twice daily

The most commonly reported treatment-emergent adverse event was dizziness, which was

- Mild in 10 of the 12 patients in whom it occurred and only moderate in the other 2
- Self-limited in 6 of 12 patients in whom it occurred

The study was not designed to detect statistically significant differences in clinical outcome measures; however, encouraging trends toward increases in the ALSFRS-R score and MVV were observed on CK-2017357 relative to placebo

Acknowledgements

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