

# CK-2127107 AMPLIFIES SKELETAL MUSCLE RESPONSE TO NERVE ACTIVATION IN HUMANS

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**ABSTRACT:** *Introduction:* Three studies evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of CK-2127107 (CK-107), a next-generation fast skeletal muscle troponin activator (FSTA), in healthy participants. We tested the hypothesis that CK-107 would amplify the force-frequency response of muscle in humans. *Methods:* To assess the force-frequency response, participants received single doses of CK-107 and placebo in a randomized, double-blind, 4-period, crossover study. The force-frequency response of foot dorsiflexion following stimulation of the deep fibular nerve to activate the tibialis anterior muscle was assessed. *Results:* CK-107 significantly increased tibialis anterior muscle response with increasing dose and plasma concentration in a frequency-dependent manner; the largest increase in peak force was ~60% at 10 Hz. *Discussion:* CK-107 appears more potent and produced larger increases in force than tirasemtiv—a first-generation FSTA—in a similar pharmacodynamic study, thereby supporting its development for improvement of muscle function of patients.

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**D**ysfunction of nerve and/or muscle leading to muscle weakness or muscle fatigue can produce significant disability and/or play a role in increased mortality in a wide variety of debilitating diseases such as spinal muscular atrophy (SMA),<sup>1</sup> amyotrophic

lateral sclerosis (ALS),<sup>2–4</sup> Charcot–Marie–Tooth disease,<sup>5,6</sup> and myasthenia gravis.<sup>7</sup> Primary muscle dysfunction also occurs secondary to genetic muscle diseases and as a consequence of several medical conditions. For example, chronic obstructive pulmonary disease (COPD) can lead to dysfunction and atrophy of limb muscles,<sup>8</sup> a switch to a type 2 glycolytic fiber phenotype, and exercise intolerance.<sup>9</sup> There are limited or no therapeutic options for the treatment of muscle weakness and fatigue. Selective fast skeletal muscle troponin activators (FSTA) may provide a new therapeutic approach to improving motor function in individuals with muscle and neuromuscular disorders resulting in muscle weakness by increasing the production of muscle force.<sup>10</sup>

Acting as an FSTA, tirasemtiv has been shown to increase the calcium sensitivity of fast skeletal muscle, thereby increasing production of muscle force at submaximal nerve stimulation rates. The effect of tirasemtiv on muscle function was assessed in healthy participants by evaluating change in isometric force-frequency response of the tibialis anterior muscle following external electrical stimulation of the deep fibular nerve.<sup>11</sup> Tirasemtiv amplified the response of skeletal muscle to nerve input in a dose-, concentration-, and frequency-dependent manner at submaximal stimulation frequencies. In subsequent clinical development, results of a phase 2b, randomized, double-blind, placebo-controlled trial in patients with ALS suggested that tirasemtiv slowed the decline in respiratory muscle function as measured by vital capacity and slowed the decline in skeletal muscle strength as measured by muscle strength megascore, despite the trial not meeting its primary endpoint of change from baseline in the ALS Functional Rating Scale-Revised.<sup>12</sup> Tirasemtiv is currently being studied in a phase 3 clinical trial in patients with ALS, VITALITY-ALS (NCT02496767).

CK-2127107 (CK-107) is a next-generation FSTA that also may improve muscle function and physical performance. Like tirasemtiv, CK-107 slows the rate of calcium release from the troponin complex, sensitizing the sarcomere to calcium and increasing fast skeletal muscle contractility.<sup>13</sup> CK-107 is highly selective for fast skeletal muscle, with little to no effect on slow skeletal or cardiac muscle. In a preclinical rodent model of heart failure, CK-107 increased

Additional supporting information may be found in the online version of this article.

**Abbreviations:** AE, adverse event; ALS, amyotrophic lateral sclerosis; ALT, alanine transaminase; ANCOVA, analysis of covariance; AST, aspartate transaminase; AUC, area under the curve; BMI, body mass index; CK-107, CK-2127107; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EMG, electromyography; FSTA, fast skeletal muscle troponin activator; SMA, spinal muscular atrophy; SOC, system organ class; ULN, upper level of normal

**Key words:** CK-2127107; fast skeletal muscle troponin activator; force-frequency relationship; phase 1; skeletal muscle

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exercise performance, suggesting that the mechanism of action may have therapeutic application in non-neuromuscular conditions<sup>13</sup> in which secondary myopathies may contribute to exercise intolerance. CK-107 was advanced into clinical development for its potential to demonstrate increased efficacy relative to tirasemtiv as well as improved tolerability and less potential for drug-drug interactions.

Here we report the results from a series of 3 phase 1 clinical trials designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of CK-107 in healthy participants, including the impact of single doses of CK-107 on the force-frequency response of muscle, using the same methods that were employed in evaluating the effect of tirasemtiv on the force-frequency relationship in normal skeletal muscle.

## MATERIALS AND METHODS

**Study Designs.** Overall. Three double-blind, randomized, placebo-controlled phase 1 studies were conducted (CY 5011, CY 5012, and CY 5013). Active doses for all studies consisted of a spray-dried dispersion of CK-107 prepared as a suspension in Ora-Sweet flavored syrup vehicle (Paddock Laboratories, Minneapolis, MN), and placebo consisted of Avicel PH-200 and Avicel PH-105 (microcrystalline cellulose; FMC BioPolymer, Philadelphia, PA) suspended in Ora-Sweet flavored syrup. Safety assessments included adverse events (AE), laboratory results, vital signs, electrocardiogram (ECG) findings, and neurological and physical examinations. Participants were judged by the investigator to be in good health from history, physical and laboratory examination, and ECG results. Participants who had had a clinically significant illness within 4 weeks of screening were excluded.

**CY 5011.** CY 5011 was a single ascending dose, cross-over study performed to determine the safety and tolerability of doses of CK-107, which ranged from 30 to 4,000 mg, administered orally to healthy male participants ( $n = 35$ ) 18–50 years old with a body mass index (BMI) between 18.0 and 32.0 kg/m<sup>2</sup>. There were 3 treatment periods, each to enroll a cohort of 12 participants (randomized to achieve 8 active drug and 4 placebo participants per treatment period). Three successive cohorts were studied. Each participant received 2 ascending, active doses and a placebo dose, 1 in each of the 3 treatment periods (Supp. Info. Table 1). At completion of each dose period, evaluation of the overall participant experience (safety and tolerability) determined whether dose escalation proceeded in the next treatment period. The maximum tolerated dose was determined when the number of intolerant participants on the active drug was  $\geq 2$  and there were no participants intolerant of the placebo. If at least 1 participant was intolerant of the placebo, then the maximum tolerated dose was determined when the pattern of intolerance clearly distinguished the active drug from the placebo or the number of participants intolerant of the dose level in question was at least 2 more than the number of participants intolerant of the placebo.

**CY 5012.** CY 5012 was a multiple ascending dose, parallel group study that evaluated the safety, tolerability, and pharmacokinetics of CK-107 in healthy young and elderly male and female participants. This study enrolled

59 healthy young (18–55-year old) and elderly (65–85-year old) participants with BMI between 18.5 and 32.0 kg/m<sup>2</sup> and studied doses of either 300 or 500 mg. Cohorts of participants consisted of 12 participants each (8 randomized to active drug [4 men and 4 women] and 4 randomized to placebo [2 men and 2 women]). Three cohorts enrolled young participants, and 2 cohorts enrolled elderly participants; 4 cohorts received treatment for 10 days (young participants, 300 or 500 mg; elderly participants, 300 or 500 mg), and 1 cohort (young participants, 500 mg) received treatment for 17 days. Participants received the same dose of CK-107 throughout, once daily on the first and last study day to facilitate pharmacokinetic sampling and twice daily on days in between.

**CY 5013.** CY 5013 was a single-dose, 4-period cross-over study evaluating the pharmacokinetics and pharmacodynamics of CK-107 in 16 healthy male participants 18–50 years old with a BMI between 18.5 and 32.0 kg/m<sup>2</sup>. The primary objective was to determine the change in the force-frequency profile, a measure of pharmacodynamic activity, and its relationship to dose and plasma concentrations when CK-107 was administered. Participants received placebo and 300, 1,000, or 3,000 mg of CK-107 in random order, with a minimum washout period of 7 days between each dose.

## Protocol Approvals, Conduct, and Patient Consent.

The institutional review board governing the phase 1 clinical sites (Covance; Evansville, IN and Dallas, TX) approved all protocols and procedures. All studies were conducted in accordance with the applicable US Code of Federal Regulations 21 CFR 50 *Protection of Human Subjects*.<sup>14</sup> Written informed consent was obtained from all participants prior to study participation.

**Pharmacodynamic Assessment—CY 5013.** The force-frequency relationship of tibialis anterior muscle contraction elicited by transcutaneous electrical stimulation of the deep fibular nerve was used to evaluate the pharmacodynamic response to CK-107 in CY 5013. The sponsor used the same methods and statistical analyses detailed below, previously employed to evaluate tirasemtiv,<sup>11</sup> to evaluate the pharmacodynamic response to CK-107.

Each participant was fitted into an adjustable, rigid chair frame with integrated footplates incorporating a force sensor, and the right foot was strapped firmly to the footplate with the lower leg and knee immobilized. The chairs were constructed so that, when seated, the participant's knees were bent approximately 60°, and the ankle angle was fixed at 105° (shin to bottom of foot). A strain gauge containing a load cell (MLP-75; Transducer Techniques, Temecula, CA) coupled to the bottom of the footplate was used to measure dorsiflexion force (Supp. Info. Fig. 1).

An adhesive surface electrode (61-2510; ConMed, Utica, NY) fixed to the lateral aspect of the upper leg just below the head of the fibula acted as the cathode and delivered stimulation pulses transcutaneously to the deep fibular nerve. The anode was placed on the medial aspect of the knee. To identify optimal cathode placement, a handheld, nonadhesive electrode through which low-intensity stimulation pulses were delivered was used to activate the nerve without stimulating antagonistic muscle groups, as determined by palpation. The stimulus intensity was set by slowly increasing the electrical current during each stimulation pulse until the magnitude of the tibialis anterior twitch force and the resulting electromyography (EMG) signal did

not increase in magnitude. The final stimulus current was then set approximately 20% greater to ensure maximal nerve activation throughout the dosing period.

The force-frequency response of each participant was measured at baseline and at 1, 3, 5, and 7 h postdose during each of the 4 dosing periods in CY 5013. Each stimulation protocol consisted of 5-, 7.5-, 10-, 12.5-, 15-, 17.5-, 30-, and 50-Hz stimulation trains of 0.5-ms pulse width and 800-ms duration. The stimulation frequency was delivered in random order so that participants could not anticipate the intensity of the stimulus, with a single stimulus pulse delivered 5 s before and 5 s after each stimulus train to elicit a twitch response. Twitch–train–twitch sequences were separated by 30 s. At each assessment time point, the stimulation protocol was performed in triplicate, and concurrent blood samples were taken to measure CK-107 plasma concentrations.

The data acquisition system used to create stimulation pulse trains, amplify the EMG, and measure the strain-gauge output was custom designed. The measurement device and control software were validated to meet 21 CFR 11 regulatory requirements<sup>15</sup> to ensure patient safety, confidentiality, and data integrity for use in a clinical trial.

**Statistical Analyses.** *Overall.* AEs were classified by system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (versions used: CY 5011, 16.0; CY 5012, 16.1; CY 5013, 17.0). The number and the percentage of participants with treatment-emergent AEs were summarized by SOC, preferred term, treatment and dose. Noncompartmental pharmacokinetic methods were used for pharmacokinetic analysis of plasma concentration-time profiles to determine maximum plasma concentration, area under the curve (AUC) by using model-independent methods, and other pharmacokinetic parameters. Pharmacokinetic parameters are presented as geometric mean (geometric coefficient of variation) unless otherwise specified. Statistical analysis of the data was completed in commercial statistics software (SAS version 9.4; SAS, Cary, NC).

**CY 5013.** As previously described,<sup>11</sup> the force-frequency profile was obtained by using a custom analysis software application to identify the peak force value before CY 5013 was unblinded. The brief description of this method and derivation rules of force-frequency data to be fitted into the model are provided in the Supporting Information.

Data were analyzed in 2 ways. First, the percentage change in force from baseline for each assessment time point in each dosing period was summed over stimulation frequencies from 5 to 25 Hz ( $\% \Sigma F_i$ ) and analyzed with a repeated-measures analysis of covariance (ANCOVA) model that included treatment (dose), sequence, and period as fixed effects; baseline as a covariate; and assuming random participant intercept. Placebo-corrected least-squares mean differences and *P*-values were reported for each assessment time point after each dose of CK-107 administered.

A second concentration–response analysis examined the effects of CK-107 at each stimulation frequency. The percentage change in peak force from baseline at each stimulation frequency,  $\%F(v)$ , was paired with coincidentally measured plasma concentrations of CK-107 by assigning each observation to a CK-107 concentration range (i.e., in  $\mu\text{g/ml}$ ; 0–1, >1–2, >2–3, >3–4, >4–5, >5–6, >6–7, and >7) depending on the sampled plasma concentration of CK-107 at the time of measurement for all dosing periods in which the drug was

given, regardless of dose or time point, and concentration ranges were analyzed as separate groups. All placebo observations were similarly pooled. The repeated-measures ANCOVA model included concentration range, sequence, and dose period as fixed effects; baseline peak force as a covariate; and participant as a random effect. Least-squares mean differences from placebo and calculated *P*-values were reported for each stimulation frequency as a function of concentration range. In addition, the concentration response of change in the normalized peak force was also analyzed with a regression repeated-measures ANCOVA model that included sequence and period as fixed effects, baseline and concentration as covariates, assuming random subject intercept, and random slope effect. No adjustments were made for multiple comparisons.

## RESULTS

**CY 5011.** In CY 5011, 35 male participants were enrolled and received single oral doses of study medication. CK-107 was well tolerated at all dose levels, ranging from 30 mg to the maximum administered dose of 4,000 mg (Supp. Info. Table 2). Mild dizziness, which was not associated with vertigo or other neurological symptoms and was not associated with any cardiovascular symptoms, was reported by 6 of 35 participants and appeared to be dose related, occurring in those receiving 1 of the 3 highest doses in the study. There were no reports of dizziness on placebo. Headache also appeared to be dose related, reported by 5 of 35 participants receiving CK-107 and by 1 participant receiving placebo. Other AEs reported in  $\geq 2$  CK-107-treated patients included cough, nausea, and diarrhea. All AEs were mild or moderate in severity; there were no serious AEs or discontinuations due to an AE. No clinically meaningful changes from baseline were observed in the neurological examination, walk test, laboratory values, vital signs, ECG parameters, or pulse oximetry. Exposure to CK-107 (i.e., AUC) increased approximately dose proportionally (Supp. Info. Fig. 2). The median apparent plasma terminal elimination half-life was lower at doses  $\leq 270$  mg than at higher doses (Table 1).

**CY 5012.** In CY 5012, CK-107 was generally well tolerated at all doses administered. Headache and diarrhea were the most frequently reported AEs. All AEs were mild or moderate in severity, and the percentage of participants with AEs increased with dose and age (Supp. Info. Table 3). Vessel puncture site pain was also reported in 2 CK-107-treated patients. No serious AEs occurred, and there were no discontinuations due to an AE. Four participants (2 elderly [1 placebo, 1 CK-107 500 mg]; 2 young [both CK-107 500 mg]) had an AE related to elevation of alanine transaminase (ALT) and had aspartate transaminase (AST), between 2 and 5 times the upper limits of normal (ULN). None met Hy's law criteria (ALT or AST  $> 3 \times \text{ULN}$ , associated with total bilirubin  $> 2 \times \text{ULN}$ , and without initial findings of

**Table 1.** CY 5011—pharmacokinetics of CK-107.\*

PK parameters	30 mg	90 mg	270 mg	500 mg	1,000 mg	1,500 mg	2,250 mg	3,000 mg	4,000 mg
$C_{max}$ , $\mu\text{g/ml}$	0.15 (33.68)	0.40 (29.59)	1.42 (28.04)	1.88 (21.28)	3.87 (17.08)	5.29 (22.13)	6.48 (22.26)	6.22 (21.81)	10.02 (24.46)
$AUC_{last}$ , $\mu\text{g} \cdot \text{h/ml}$	0.79 (52.35)	2.58 (35.76)	10.43 (34.85)	17.04 (32.17)	38.85 (19.38)	57.21 (36.54)	69.21 (27.88)	94.15 (36.12)	140.34 (56.84)
$AUC_{0-\infty}$ , $\mu\text{g} \cdot \text{h/ml}$	0.86 (49.52)	2.69 (35.68)	10.56 (34.29)	17.51 (32.70)	39.84 (17.72)	57.93 (35.61)	70.77 (27.60)	94.85 (36.10)	141.74 (56.77)
$t_{1/2}$ , $\text{h}^\dagger$	2.96	3.39	3.98	10.72	10.20	9.31	14.24	11.61	8.85

$AUC_{0-\infty}$  = area under the concentration-time curve extrapolated to infinity;  $AUC_{last}$ , area under the concentration-time curve from h 0 to the last measurable plasma concentration; CK-107, CK-2127107;  $C_{max}$ , maximum observed plasma concentration.

CV%, coefficient of variation; PK, pharmacokinetics;  $t_{1/2}$ , apparent plasma terminal elimination half-life.

\*Values are geometric mean (geometric CV%).

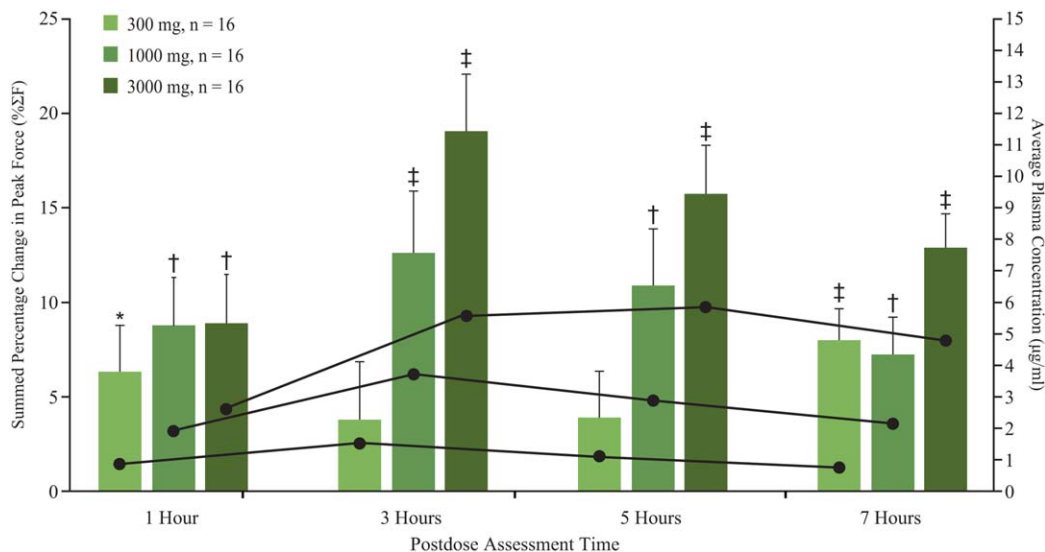
$^\dagger$ Presented as median.

cholestasis [elevated serum alkaline phosphatase]).<sup>16</sup> All elevations resolved between 6 and 17 days after onset. Overall, no other clinically meaningful changes from baseline were observed in other laboratory values, neurological examination, vital signs, or ECG parameters. The pharmacokinetic parameters of CK-107 were similar between young and elderly participants (Supp. Info. Table 4, Supp. Info. Figs. 3, 4). AUC increased somewhat greater than dose proportionally following multiple dosing, and mean exposure was higher in women versus men (data not shown). Analysis of the trough concentration at the last 3 dosing periods showed that steady state was achieved in elderly participants who received 300 mg for 10 days and young participants taking 500 mg for 17 days.

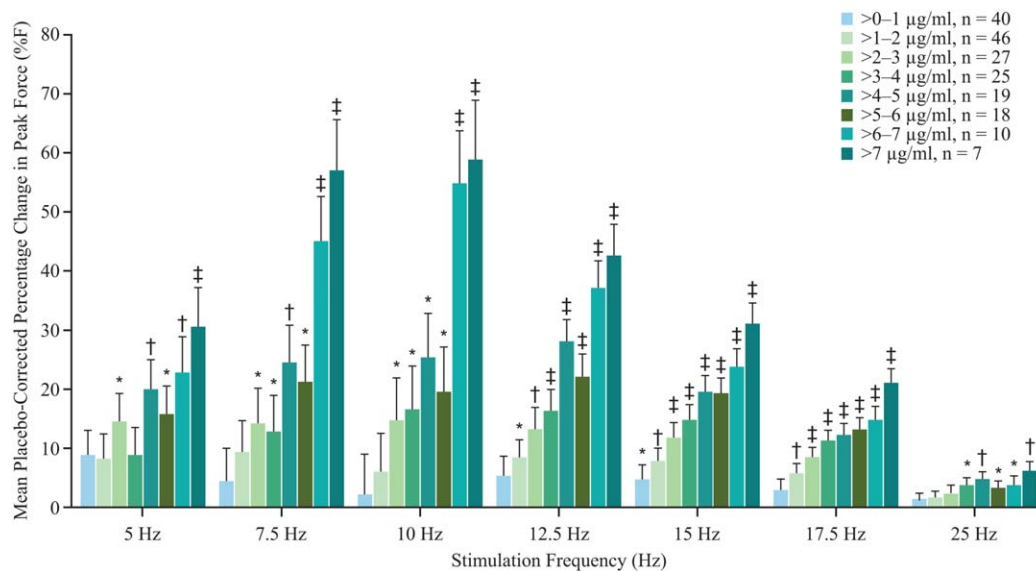
**CY 5013.** In CY 5013, 16 healthy men were enrolled and completed the study. The placebo-corrected summed percentage change from baseline of peak force ( $\Sigma F$ ) increased in a dose-

dependent manner at 1, 3, and 5 h after receiving CK-107 (Fig. 1). The response to CK-107 was also analyzed according to stimulus frequency and plasma concentration (Fig. 2). A (least-squares mean [SE]) 58.7% (10.2%) increase in peak force was the overall largest response, which occurred at 10 Hz and was associated with the highest CK-107 plasma concentration range of  $>7 \mu\text{g/ml}$ . Table 2 presents pharmacokinetic parameters for each dose of CK-107 in this study.

In agreement with CY 5011 and CY 5012, in CY 5013, single doses of CK-107 appeared well-tolerated by healthy participants (Table 3). Headache and dizziness were apparently dose related and also were the most commonly reported AEs. Other AEs reported in  $\geq 2$  CK-107-treated patients were asthenopia, visual impairment, nausea, and exco-riation. All AEs were mild (56.3%) or moderate (12.5%) in severity; no serious AEs occurred. Most laboratory values were consistent with baseline, and no laboratory abnormalities were reported as AEs.



**FIGURE 1.** Placebo-corrected summed percentage change from baseline (SEM) of peak force ( $\Sigma F$ ) with CK-107 treatment by time. \* $P < 0.05$ ,  $^\dagger P < 0.01$ ,  $^\ddagger P < 0.001$  for least-squares mean difference from placebo. CK-107, CK-2127107.



**FIGURE 2.** Placebo-corrected percent changes in peak force (%F) at each frequency by CK-107 concentration range. \* $P < 0.05$ , † $P < 0.001$ , ‡ $P < 0.0001$  for least-squares mean difference from placebo. CK-107, CK-2127107.

**Table 2.** CY 5013—pharmacokinetics of CK-107 by dose.\*

Dose, mg	$C_{max}$ , µg/ml	$AUC_{0-t}$ , µg · h/ml	$AUC_{0-\infty}$ , µg · h/ml	$t_{1/2}$ , h†
300	1.51 (24.31)	11.10 (37.81)	11.58 (40.64)	4.76
1,000	3.68 (29.26)	33.77 (41.69)	37.80 (46.62)	6.47
3,000	6.43 (22.67)	74.27 (25.88)	87.61 (40.98)	7.04

$AUC_{0-t}$ , area under the plasma concentration-time curve from pre-dose to the last measurable plasma concentration;  $AUC_{0-\infty}$ , area under the plasma concentration-time curve extrapolated to infinity; CK-107, CK-2127107;  $C_{max}$ , maximum observed plasma concentration; CV%, coefficient of variation;  $t_{1/2}$ , apparent plasma terminal elimination half-life.

\*Values are geometric mean (geometric CV%).

†Presented as median.

No clinically meaningful changes occurred in neurological examinations, vital signs, or ECG parameters.

## DISCUSSION

These 3 studies assessed the effects of CK-107 in healthy humans. CY 5011 established the safety, tolerability, and pharmacokinetics of single doses of CK-107 ranging from 30 to 4,000 mg. CY 5012 evaluated the same effects of CK-107 over multiple doses in both young and elderly participants. CK-

107 was found to have a half-life of approximately 8–12 h. There were no clinically meaningful differences in pharmacokinetics found between the young and the elderly.

The impact of CK-107 on muscle response to nerve activation was assessed in CY 5013, in which administration of CK-107 resulted in significant increases in force elicited by external electrical stimulation of the deep fibular nerve that were consistent with amplification of muscle response to

**Table 3.** CY 5013—TEAEs reported in  $\geq 2$  participants treated with CK-107.\*

AE	Participants, n (%)			
	Placebo	300 mg	1,000 mg	3,000 mg
Participants with at least 1 TEAE	2 (12.5)	3 (18.8)	5 (31.3)	7 (43.8)
Headache	1 (6.3)	0	2 (12.5)	4 (25.0)
Dizziness	0	0	1 (6.3)	4 (25.0)
Asthenopia	0	0	0	2 (12.5)
Nausea	0	1 (6.3)	0	2 (12.5)
Excoriation	0	1 (6.3)	0	1 (6.3)
Visual impairment	0	1 (6.3)	1 (6.3)	0

AE, adverse event; CK-107, CK-2127107; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

\*MedDRA version 17.0 was used to code TEAEs.

nerve input. Increases in the response of the tibialis anterior muscle to neuronal input increased with both the dose and the plasma concentration of CK-107. The effect of CK-107 on the force-frequency relationship was also related to the stimulation frequency, being greatest at approximately the rate that motor units typically discharge during daily physical activity<sup>17</sup> and reduced at higher stimulus frequencies that approach tetany. These force-frequency response findings parallel those observed in a preclinical rodent model,<sup>13</sup> supporting the translation into humans of CK-107 as an FSTA that improves muscle function.

Tirasemtiv was the first FSTA studied in humans. In a study of the effect of tirasemtiv on muscle function in healthy participants, tirasemtiv amplified skeletal muscle response to nerve input in a dose-, concentration-, and frequency-dependent manner.<sup>11</sup> CK-107 produced a similar dose-, concentration-, and frequency-dependent amplification of skeletal muscle response by using the same study paradigm as the pharmacodynamic study of tirasemtiv in healthy participants. CK-107 has shown comparable effects at less than half the concentration of tirasemtiv<sup>11</sup> and has generated more than twice the increase in peak force at electrical stimulations approximating typical motor unit discharge during physical activity. Thus, in comparable assays, CK-107 appears to be more potent than tirasemtiv and produces a larger effect, thereby supporting its development as a next-generation FSTA.

By directly increasing skeletal muscle force production, with maximal effects in the middle of the 5–15 Hz range where most normal daily human muscle activity occurs,<sup>17,18</sup> CK-107 may enhance physical performance not only in patients with neuromuscular diseases but also in patients with non-neuromuscular diseases, such as COPD, frailty, or heart failure in which weakness and fatigue are the result of reduced skeletal muscle force production. CK-107 is currently being studied in 4 mid-stage clinical trials; 1 trial is evaluating its effect on multiple measures of muscle function in patients with type II, type III, or type IV SMA (NCT02644668), 1 is evaluating its effect on respiratory function and other measures of muscle function in patients with ALS (NCT03160898), and 2 are evaluating its effect on physical function and exercise tolerance in patients with COPD (NCT02662582) and in the elderly with limited mobility (NCT03065959). Overall, these studies further reinforce the concept that FSTAs that sensitize the sarcomere to calcium and increase fast skeletal muscle contractility provide promise as

novel therapeutic approaches for improvement of muscle function for patients with diseases and conditions characterized by skeletal muscle weakness and fatigue.

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Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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