PROTOCOL CY 5021

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTIPLE DOSE STUDY OF CK-2127107 IN TWO ASCENDING DOSE COHORTS OF PATIENTS WITH SPINAL MUSCULAR ATROPHY (SMA)

Product: CK-2127107

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Cytokinetics.
- Not to amend the protocol without agreement, prior review, and written approval from the Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard to the patients.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol and any other information provided by the Sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document.
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Cytokinetics investigational product(s) and of their study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the Sponsor or the investigational product, and more generally about his/her financial ties with the Sponsor. Cytokinetics will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply Cytokinetics with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study; and
- Agree that Cytokinetics may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Investigator Name: _____

Investigator Signature: _____ Date: _____

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
6MWT	6-minute walk test
AE	adverse event
ALT	alanine aminotransferase (alanine transaminase)
ANCOVA	analysis of co-variance
ANOVA	analysis of variance
API	active pharmaceutical ingredient
AST	aspartate aminotransferase (aspartate transaminase)
AT	aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice daily
BDI	Beck Depression Inventory
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{trough}	pre-dose plasma concentration
eCRF	electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
ECG	electrocardiogram
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	Good Clinical Practices
HFMS-E	Hammersmith Functional Motor Scale-Expanded
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
INR	International normalized ratio

Abbreviation or Specialist Term	Explanation
IUD	intrauterine device
IUS	intrauterine system
IRB	Institutional Review Board
LA-CRF	liver abnormality case report form
LFT	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
MEP	maximum expiratory pressure
MIP	maximum inspiratory pressure
NASH	non-alcoholic steatohepatitis
NCI	National Cancer Institute
NOAEL	no observed adverse effects level
PD	pharmacodynamic
PDS	pharmacodynamic analysis set
PET	polyethylene terephthalate
PIBA	press-in-bottle adapters
PK	pharmacokinetic
PKS	pharmacokinetics analysis set
QTc	corrected QT interval
RULM	revised upper limb module
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SDD	spray dried dispersion
SMA	spinal muscular atrophy
SMA-HI	Spinal Muscular Atrophy-Health Index
TBL	total bilirubin
TEAE	treatment emergent adverse event
TUG	timed up and go
UA	urinalysis
ULN	upper limit of normal
WBC	white blood cells
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

CK-2127107, a small molecule activator of the fast skeletal muscle troponin complex, is being developed to improve skeletal muscle function in disease states associated with muscular weakness and/or muscle fatigue. CK-2127107 slows the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers resulting in a sensitization of the sarcomere to calcium. It is highly selective for fast skeletal muscle troponin, with similar potencies in muscle fibers from preclinical species and human fast skeletal muscle fibers; accordingly, it is much less effective in activating slow skeletal muscle and cardiac muscle. In intact rat skeletal muscle in vivo, CK-2127107 increases muscle force at sub-maximal nerve stimulation frequencies, increases muscle power, and decreases muscle fatigability. Dosing of CK-2127107 increased running performance in a preclinical rat model of heart failure produced by myocardial infarction.

Spinal Muscular Atrophy (SMA) is a severe neuromuscular disease that occurs in 1 in every 6,000 to 10,000 live births each year and is one of the most common fatal genetic disorders. Spinal muscular atrophy manifests in various degrees of severity as progressive muscle weakness resulting in respiratory and mobility impairment. There are four types of SMA, named for time of the initial onset of muscle weakness and related symptoms: Type I (Infantile), Type II (Intermediate), Type III (Juvenile) and Type IV (Adult onset). Life expectancy and disease severity varies by type of SMA from Type I, who have the worst prognosis and a life expectancy of no more than 2 years from birth, to the Type IV, who have a normal life span but with gradual weakness in the proximal muscles of the extremities resulting in mobility issues. Few treatment options exist for these patients, resulting in a high unmet need for new therapeutic options to address symptoms and modify disease progression.

In mice with late or “adult” onset SMA, a compound with the same mechanism of action as CK-2127107, *tirasemtiv,* increased muscle force at submaximal nerve stimulation frequencies and increased muscle work during repetitive stimulation. Mice were able to hang longer from an inverted grid following dosing with *tirasemtiv*. Thus, the pharmacological profile of CK-2127107 is novel approach to the treatment of SMA in that it is a direct functional activator of fast skeletal muscle; as such, it could benefit patients with a wide variety of disorders characterized by muscular weakness and/or muscle fatigue including SMA.

This clinical protocol is a double-blind, randomized, placebo-controlled, multiple dose study to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of CK-2127107 in patients with SMA.

1.2. Overview of CK-2127107 Nonclinical Studies

CK-2127107 was evaluated in a series of nonclinical safety studies in rat and monkey, including single- and repeat-dose (28 days and 13 weeks) toxicity studies, safety pharmacology studies, and a core battery of genotoxicity tests.

The toxicology studies conducted in rat and monkey with CK-2127107 demonstrated an acceptable safety profile, and supported Phase 1 clinical trials in healthy volunteers. Based on in vitro metabolism studies, the monkey was selected as the non-rodent toxicology species since the

metabolism of CK-2127107 in monkeys was qualitatively comparable to that in humans, in particular with respect to the production of CK-2127106, an identified inactive metabolite of CK-2127107. In definitive 28-day and 13-week repeat-dose toxicity and toxicokinetic studies, the no observed adverse effect level (NOAEL) for CK-2127107 (formulated from a spray dried dispersion (SDD) containing 50% CK-2127107) was 600 mg/kg/day, the highest dose level evaluated, in both rats and monkeys.

The core battery of safety pharmacology studies conducted with CK-2127107 indicated no functional changes in vital organs or systems which are likely to be of importance in clinical studies of CK-2127107.

The results of the bacterial reverse mutation, in vitro cytogenetic and in vivo rodent bone marrow micronucleus studies conducted with CK-2127107 indicated a lack of genotoxic hazard. CK-2127106 was equivocal in an in vitro cytogenetic assay conducted in human peripheral blood lymphocytes; in this assay, a statistically significant increase in the incidence of aberrant cells, compared to the vehicle control, was noted only at the highest CK-2127106 concentration evaluated (386 µg/mL) in the 21-hour regime.

Additional information concerning the pharmacology, PK, and toxicology of CK-2127107 is available in the Investigator's Brochure (IB).

1.3. Overview of CK-2127107 Clinical Studies

Five Phase 1 studies have been completed to date in healthy subjects, a first in human, single ascending dose study (Study CY 5011), a multiple ascending dose study in young vs. elderly subjects (CY 5012), a PK/PD study (CY 5013), a formulation study (CY 5014) and a food effect study (CY 5015).

CY 5011, a phase 1, double-blind, randomized, placebo-controlled, single ascending dose study of CK-2127107 in healthy male volunteers, is complete. The primary objective of CY 5011 was to determine the safety and tolerability of single doses of CK-2127107 administered orally as an amorphous SDD formulation to healthy male volunteers. The secondary objective of CY 5011 was to evaluate the PK profile of single doses of CK-2127107 and its inactive metabolite, CK-2127106. Volunteers received oral doses up to 4000 mg of CK-2127107 in a crossover fashion, which was generally well tolerated and no serious adverse events (SAEs) were reported. The most common non-serious adverse event at the highest dose of 4000 mg was grade 1 (mild) dizziness which resolved spontaneously and in all cases resolved within 24 hours of onset. One subject described a "lightheaded" sensation while others described their dizziness as an intermittent fleeting sensation of dizziness with movement of the head. Table 1 summarizes the most common treatment emergent adverse events (TEAEs). Exposure to CK-2127107 ranged from 150 to 10,000 ng/mL for maximum observed plasma concentration (C_{max}) and 860 to 142,000 ng*hr/mL for $AUC_{0\text{-}inf}$, over the dose range of 30 to 4000 mg. Mean exposure to the inactive metabolite, CK-2127106, ranged from 4% to 19% of CK-2127107 across all doses as measured by area under the plasma concentration-time curve (AUC). Linear dose-proportional PK was observed up to 4000 mg of CK-2127107.

Table 1: CY 5011 – Treatment Emergent Adverse Events (≥2 occurrences)

Adverse Event	Placebo N=35 n(%)	30 mg N=8 n(%)	90 mg N=8 n(%)	270 mg N=8 n(%)	500 mg N=8 n(%)	1000 mg N=8 n(%)	1500 mg N=8 n(%)	2250 mg N=8 n(%)	3000 mg N=7 n(%)	4000 mg N=7 n(%)
Dizziness	0	0	0	0	0	0	0	3(37.5)	2(28.6)	4(57.1)
Headache	1(2.9)	0	0	0	0	1(12.5)	1(12.5)	1(12.5)	2(28.6)	3(42.9)
Visual Impairment	1(2.9)	0	0	0	0	0	0	1(12.5)	0	1(14.3)
Nausea	0	0	0	0	0	0	0	0	1(14.3)	1(14.3)
Cough	0	0	0	0	1(12.5)	0	0	0	1(14.3)	0
Diarrhea	0	0	0	0	0	1(12.5)	0	1(12.5)	0	0

CY 5012, a phase 1, double-blind, randomized, placebo-controlled, multiple ascending dose, parallel group study to evaluate the safety, tolerability, and PK of CK-2127107 in healthy young and elderly male and female volunteers, is complete. The objectives of this study were to determine the safety and tolerability of CK-2127107 in suspension after multiple oral doses in healthy young and elderly men and women and to determine the PK profile of the parent compound and its inactive metabolite, CK-2127106, after a single dose and at steady-state, as well as any PK differences between young vs. elderly subjects. It consisted of three cohorts of 12 young (age 18-55) healthy subjects each, and two cohorts of 12 elderly (age 65-85) healthy subjects each.

A total of 59 subjects were enrolled in the study and were randomized as follows: 20 to placebo, 16 to the CK-2127107 300 mg dose, and 23 to the CK-2127107 500 mg dose (see Table 2 for the study design and dosing regimens). Fifty-eight subjects (98.3%) completed the study as planned, and one subject (1.7%) withdrew consent after receiving one dose of CK-2127107 500 mg but did not experience any adverse events (AEs). Although steady-state was essentially achieved by Day 10 for CK-2127107, this was not the case for the metabolite, CK-2127106. Hence, a fifth cohort was added to allow a longer dosing duration of 17 days.

Table 2: CY 5012 Study Design and Dosing Regimen

Cohort	Age Group	CK-2127107 or placebo Randomized 2:1
1	18-55	300 mg QD on Days 1 and 10 300 mg BID on Days 2–9
2	65-85	300 mg QD on Days 1 and 10 300 mg BID on Days 2–9
3	18-55	500 mg QD on Days 1 and 10 500 mg BID on Days 2–9
4	65-81	500 mg QD on Days 1 and 10 500 mg BID on Days 2–9
5	18-55	500 mg QD on Days 1 and 17 500 mg BID on Days 2–16

At steady-state, the median t_{max} of CK 2127107 was 2 to 3 h and the mean $t_{1/2}$ ranged from 10.5 to 12.8 h. Exposure (C_{max} and AUC) for CK 2127107 increased with dose, and slope estimates suggested a somewhat higher than dose proportional exposure as the dose increased from 300 to 500 mg. C_{max} and AUC_{0-12} for CK 2127107 were higher at steady-state than after a single dose on Day 1 with an accumulation ratio of approximately 3 to 4 at 300 mg and 4 to 5 at 500 mg. Exposure to the inactive metabolite, CK-2127106, was also higher at steady-state than after a single dose with mean accumulation ratios >20, consistent with its longer $t_{1/2}$ of about 40 h. Average CK-2127107 drug exposure tended to be somewhat higher in women than in men but there were no differences in the PK of CK-2127107 between the young vs. elderly age group. On the other hand, mean exposure to the metabolite, CK-2127106, was higher in elderly subjects.

Table 3: CK-2127107 PK Parameters after the Last Dose on Day 10/17 (Study CY 5012)

	C_{max} (ng/mL) Geometric Mean CV (%)	AUC_{0-12} (h×ng/mL) Geometric Mean CV (%)	$t_{1/2}$ (h) Geometric Mean CV (%)	t_{max} (h) Geometric Mean CV (%)
Elderly 300 mg (n=8)	3369.16 22.33	26516.61 26.39	7.72 82.06	2.33 21.22
Young 300 mg (n=8)	3329.17 30.98	28101.65 37.25	9.15 59.08	3.17 23.05
Elderly 500 mg (n=7)	6299.46 29.65	53899.94 34.33	11.61 51.82	2.99 20.71
Young 500 mg (n=15)	7300.43 39.54	65497.98 48.19	10.38 49.51	3.20 24.69

There were no SAEs or discontinuations due to an AE. Four of the 20 subjects on placebo (20.0%) and 17 of the 39 subjects on CK-2127107 (43.6%) had a TEAE. Among the 17 subjects treated with CK-2127107 who had an AE, five had received the 300 mg dose and 12 had received the 500 mg dose. TEAEs reported for >1 subject on active drug were vessel puncture site pain (in two subjects on 500 mg), liver enzyme elevation (three subjects on 500 mg and one on placebo), diarrhea (three on 300 mg and one on placebo), and headache (two on 300 mg and one on 500 mg). An additional four subjects (one treated with CK-2127107 300 mg and three treated with CK-2127107 500 mg) had at least one out-of-range value for a liver enzyme that was not considered to be an AE. Of the total of eight subjects with an abnormal liver function test, some of whom also had modest bilirubin elevations, none had values that met Hy's Law criteria.

While most other laboratory tests during the study generally remained consistent with baseline values, serum creatinine values increased following CK-2127107 dosing. On Day 11, subjects treated with CK-2127107 had a mean increase from baseline in serum creatinine of 36.4 μmol/L compared with a mean change of 4.9 μmol/L for subjects treated with placebo. Changes in serum creatinine were generally similar between the two age groups. The elevated values returned toward normal and there were no associated symptoms or AEs reported. All abnormal values were deemed not clinically significant by the investigator. A possible explanation for these

findings is that CK-2127107 or one of its metabolites, may interfere with either the creatinine assay or may inhibit the renal tubular secretion of creatinine, as has been reported with other drugs.

Vital signs and electrocardiogram (ECG) intervals centrally read at a core laboratory generally remained consistent with baseline values. There were no abnormal findings during physical and neurological examinations.

CY 5013, a phase 1, double-blind, randomized, placebo-controlled, single dose, 4-period crossover study to evaluate the PK and PD of CK-2127107 in healthy male volunteers, is complete. The primary objective of this study was to determine the force-frequency profile in relationship to dose and plasma concentrations of CK-2127107 in healthy men. Twelve healthy men received placebo, CK-2127107 300 mg, 1000 mg and 3000 mg, each dose separated by a 7-day washout period. The sequence of study drug administration was randomized.

PK and PD at matched time points were obtained after each dosing regimen. The PD readout obtained at each dose level consisted of a standardized determination of the force-frequency relationship in the tibialis anterior muscle after peroneal nerve stimulation (Hotz, Wilson et al. 1997; Mela, Veltink et al. 2001; Baudry and Duchateau 2004; Hansen, Saikali et al. 2014). There were no SAEs or discontinuations due to an AE. Ten of the 16 subjects (62.5%) had a TEAE, two subjects (12.5%) on placebo, three subjects (18.8%) on 300 mg, five subjects (31.3%) on 1000 mg, and seven subjects (43.8%) on 3000 mg. Commonly reported TEAEs were headache (6 subjects [37.5%]) and dizziness (4 subjects [25.0%]); all other AEs were reported for one or two subjects. None of the AEs were classified as severe.

CY 5014, a phase 1, randomized, open-label, 2-period crossover study of two oral forms of CK-2127107 in healthy male volunteers, is complete. The primary objective of CY 5014 was to assess the relative oral bioavailability and PK profiles of the stabilized amorphous form of CK-2127107 formulated as an SDD and the crystalline form of CK-2127107 API in suspension following single doses of 300 and 1000 mg. Volunteers received all planned doses of CK-2127107 SDD in suspension and API in suspension and no SAEs were reported. Exposure following dosing of the crystalline API compared to the SDD form was similar at the 300 mg dose but was decreased about 33% at the 1000 mg dose. The crystalline form was selected for further use in clinical studies. Other results of this study are summarized in the IB.

CY 5015, a phase 1, open-label, randomized, single dose study to evaluate the PK in a fed and fasted state of an oral tablet form of CK-2127107 in healthy male volunteers, is complete. The objectives of this study were to assess the relative oral bioavailability and PK profile of the crystalline form of CK-2127107 API formulated as an immediate release, 250 mg strength tablet (API tablet) or in a suspension (API suspension) as well as to determine the effect of a high fat breakfast on the PK of CK-2127107 healthy men.

There were no SAEs and no subject discontinued due to an AE. A significant food effect was demonstrated as exposure (C_{max} and $AUC_{0\text{-}inf}$) increased 2.6- and 1.6-fold, respectively, when tablets (250 mg x 2 [500 mg total dose]) were administered with food. Other results of this study are summarized in the IB.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to determine the potential PD effects of CK-2127107 suspension after multiple oral doses in patients with SMA.

2.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of multiple doses of CK-2127107 administered orally to SMA patients
- To evaluate the PK of CK-2127107 administered orally to SMA patients

3. STUDY OVERVIEW

3.1. Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled, multiple dose, study of CK-2127107 in two sequential ascending dose cohorts of patients with Type II, Type III, or Type IV SMA. Within each cohort, randomization will be stratified by ambulatory status versus non-ambulatory status.

The CK-2127107 Granules for Oral Suspension will be constituted by the site pharmacy for patient use as an oral suspension.

At least 72 male or female patients (two cohorts of at least 36 patients each) will receive twice daily doses of CK-2127107 suspension for 8 weeks.

An overview of the general study design is provided in Table 4:

Table 4: CY 5021 Study Design

Cohort	N	CK-2127107 Doses
1	18	Group 1: Approximately 18 ambulatory patients ≥ 12 years of age with Type III or Type IV SMA randomized 2:1 to CK-2127107 150 mg versus placebo single dose on Day 1 and then twice daily (BID) for remainder of 8 weeks
	18	Group 2: Approximately 18 non-ambulatory patients ≥ 12 years of age with Type II or Type III SMA randomized 2:1 to CK-2127107 150 mg versus placebo single dose on Day 1 and then twice daily (BID) for remainder of 8 weeks
After 30 patients in Cohort 1 have received at least one dose of study drug and have either completed the End of Week 8 visit or have permanently discontinued study drug, the safety and PK data available at that time from Cohort 1 will be reviewed, to confirm the dose level or reduce the dose level of CK-2127107 to be administered in Cohort 2 (Section 8.8)		
2	18	Group 1: Approximately 18 ambulatory patients ≥ 12 years of age with Type III or Type IV SMA randomized 2:1 to CK-2127107 450 mg (or lower) versus placebo single dose on Day 1 and then twice daily (BID) for remainder of 8 weeks
	18	Group 2: Approximately 18 non-ambulatory patients ≥ 12 years of age with Type II or Type III SMA randomized 2:1 to CK-2127107 450 mg (or lower) versus placebo single dose on Day 1 and then twice daily (BID) for remainder of 8 weeks

*Ambulatory and Non-Ambulatory patients are defined in the Inclusion Criteria (Section 4.1)

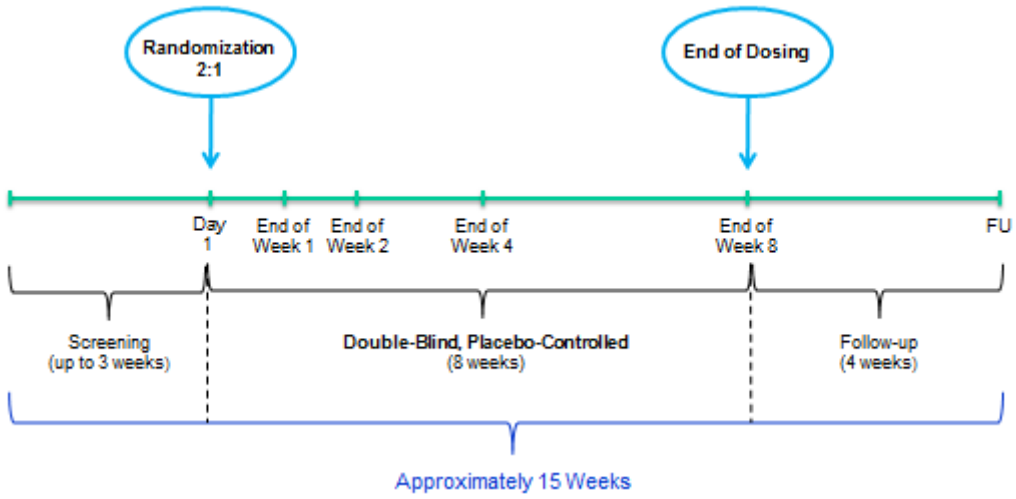
Screening for the study will be no more than 21 days in duration. Once patients have completed screening and are considered eligible for the appropriate cohort, they will be randomized as described above, stratified by ambulatory versus non-ambulatory. Consequently, at the conclusion of the study, approximately 24 patients (12 ambulatory and 12 non-ambulatory) will have been randomized to placebo, approximately 24 patients to CK-2127107 150 mg BID (also

divided equally between ambulatory and non-ambulatory patients), and approximately 24 to CK-2127107 450 mg BID (or lower, pending the review of data from Cohort 1).

There will be a total of seven study visits for patients in each cohort:

- Screening
- Start of Dosing (Day 1)
- End of Week 1 (Day 8)
- End of Week 2 (Day 15)
- End of Week 4 (Day 29)
- End of Week 8 (Day 57)
- Follow-Up Visit (4 weeks after last dose of study drug)

Figure 1: Study Design



For Cohort 1, on Day 1, patients in Group 1 and Group 2 will be randomized to receive a single dose on Day 1 followed by twice daily doses of 150 mg CK-2127107 suspension or placebo.

After 30 patients in Cohort 1 have received at least one dose of study drug and have either completed the End of Week 8 visit or have permanently discontinued study drug, the safety and PK data available at that time from Cohort 1 will be reviewed, to confirm the dose level or reduce the dose level of CK-2127107 to be administered in Cohort 2.

For Cohort 2, on Day 1, patients in Group 1 and Group 2 will be randomized to receive a single dose on Day 1 followed by twice daily doses of 450 mg (or lower) CK-2127107 suspension or placebo.

A Follow-Up Visit will occur 4 weeks after the patient's final dose of study drug.

Pharmacodynamic measures, vital signs, ECGs, and clinical laboratory evaluations will be performed at Screening and at specified times during each cohort. Patients will be evaluated at each study visit for signs and symptoms of intolerance to study drug.

3.2. Study Rationale

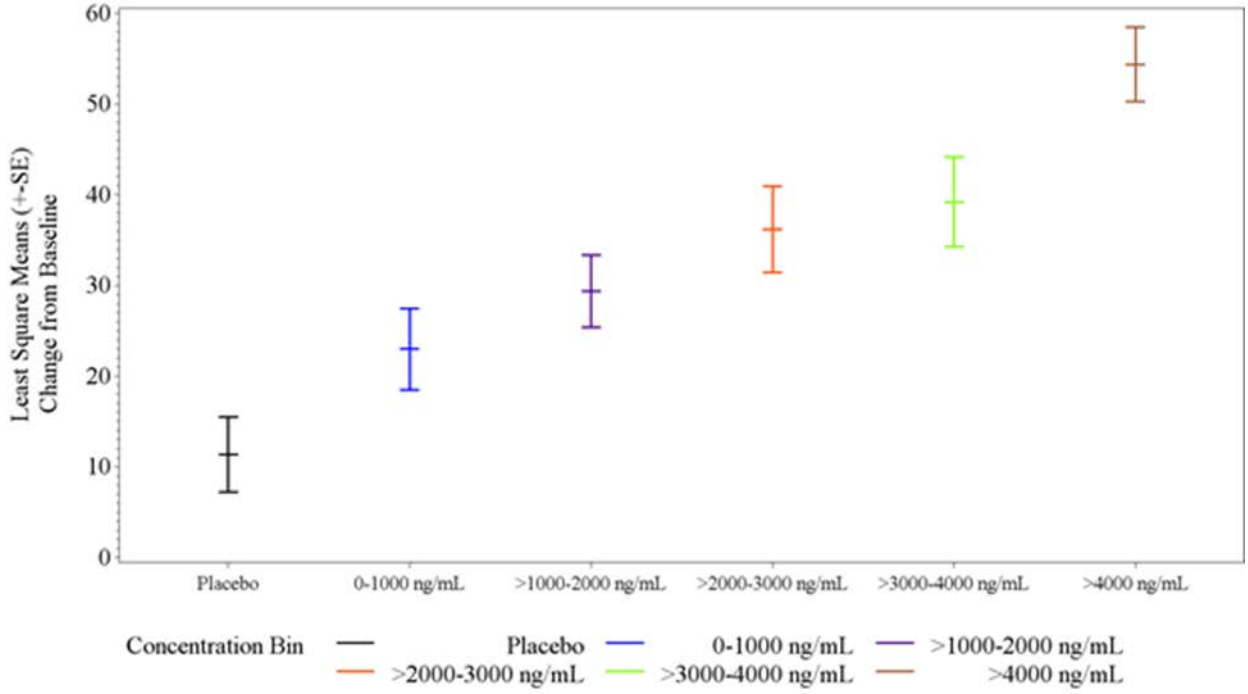
CK-2127107 is being investigated as a potential new therapy for improving muscular weakness and muscle fatigue in patients with SMA. This is the first study being conducted in these patients and is designed to assess the effect of 8 weeks of dosing of CK-2127107 on measures of muscle function in both ambulatory and non-ambulatory patients with SMA. The plasma concentration of CK-2127107 will be measured at selected time points during the course of dosing and the plasma concentrations obtained in this study may be used to conduct exposure-response analysis. The results of this study will inform further clinical development of this mechanism of action in SMA.

3.3. Dose Rationale

CK-2127107 will be administered as an oral suspension at a dose of 150 mg twice daily in Cohort 1 and 450 mg (or lower, pending the review of data from Cohort 1) twice daily in Cohort 2. At steady-state, C_{max} at the lower dose is estimated to be ~2 µg/mL and at the higher dose C_{max} is estimated to be ~6 µg/mL. In Study CY 5013, plasma concentrations were sampled at the time of nerve stimulation in order to construct a PK/PD relationship. Figure 2 shows that these plasma concentrations produce significant concentration-dependent increases in force at submaximal stimulation frequencies with the largest force increases at 10 Hz. The doses selected in the current study should produce plasma concentrations that span the PD range measured in this healthy volunteer population.

In the current study, a dose escalating design will be employed; the PK in Cohort 1 at the lower dose will be determined prior to dosing the higher dose in Cohort 2. A dose adjustment downward in Cohort 2 may be employed if the dose in Cohort 1 produces exposures that are higher than anticipated.

Figure 2: CY 5013: Increases in Force during Nerve Stimulation in Healthy Volunteers



The safety, tolerability, and PK of CK-2127107 were previously explored in the Phase 1. Single doses of 30 to 4000 mg were well tolerated by the healthy male subjects enrolled in CY 5011 and no maximum tolerated dose was established. Similarly, 10-17 day courses of 300 mg and 500 mg twice daily were well tolerated by young and elderly healthy men and women although eight subjects (1 on placebo and 7 on CK-2127107) had a transient elevation of liver enzymes after approximately 10 days of dosing, none of which satisfied Hy's Law criteria. The IB contains further details of these cases. Consequently, this study will monitor the liver enzymes of patients following 2 weeks of dosing to allow for drug discontinuation if deemed necessary by the clinical investigator.

Based on this prior clinical experience, the doses selected for this study are expected to be well tolerated and the information obtained in this study will guide the selection of doses in future clinical studies of patients.

4. STUDY POPULATION

Approximately 72 patients who fulfill the eligibility criteria will be enrolled in the study.

4.1. Inclusion Criteria

Patients who meet all of the following criteria may be included in the study:

1. Able to comprehend and willing to sign an Informed Consent Form (ICF) for patients 18 years of age and older. For patients less than 18 years of age, parent(s)/legal guardian(s) of patients must provide written informed consent prior to participation in the study and informed assent will be obtained from minors at least 12 years of age when required by regulation.
2. Males or females with genetically confirmed diagnosis of SMA who are Type II, III or IV and at least 12 years of age
3. Ambulatory patients, once having achieved a standing position independently, must be able to complete at least one lap in the 6-minute walk test (at least 50 meters) within 6 minutes without assistance
4. Non-ambulatory patients (defined as individuals who are effectively requiring a wheelchair for all mobility needs; they may be able to stand or walk short distances, but unable to walk 50 meters without assistance in 6 minutes). Non-ambulatory patients must be able to tolerate an upright sitting position, with support, continuously for 3 hours
5. Forced vital capacity (FVC) > 20% predicted at screening
6. Hammersmith Functional Motor Scale-Expanded (HFMS-E) score ≥ 10 and ≤ 54 at screening
7. Contracture of the elbow flexion and knee flexion ≤ 90 degrees
8. Pre-study clinical laboratory findings within the normal range or, if outside the normal range, deemed not clinically significant by the Investigator
9. Able to swallow an oral suspension and in the opinion of the Investigator, is expected to continue to be able to do so for the duration of the trial. Administration via a feeding tube is not allowed.
10. Male patients who have reached puberty must agree to do either of the following from Screening until 10 weeks after the last dose of the investigational product unless they have had a vasectomy and confirmed sperm count is zero:
    - Abstain from sexual intercourse, OR
    - If having heterosexual intercourse, must use a condom and their female partners who are of childbearing potential must use a highly effective contraception method*
11. Female patients who have had their first period will be considered of childbearing potential unless they are anatomically and physiologically incapable of becoming pregnant. If of childbearing potential, the female patients must:
    - Have a negative urine/serum pregnancy test at Screening AND

- Abstain from heterosexual intercourse from Screening until 10 weeks after the last dose of investigational product, OR
  - If having heterosexual intercourse, must use a highly effective contraception method* and require the male partners to use a condom from Screening until 10 weeks after the last dose of investigational product

*Highly effective contraception methods include:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

12. Male patients must agree to refrain from sperm donation from Screening until 10 weeks after the final study drug administration

4.2. Exclusion Criteria

Any of the following will exclude potential patients from the study:

1. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator
2. Hospitalization within 2 months of Screening
3. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (appendectomy, hernia repair, and/or cholecystectomy will be allowed)
4. A clinically significant illness, including but not limited to cardiac, pulmonary, GI, musculoskeletal, or psychiatric illness, that might interfere with the patient's ability to comply with study procedures or that might confound the interpretation of clinical safety or efficacy data, within 4 weeks of Screening
5. History of alcoholism or drug addiction within 2 years prior to Screening
6. History of smoking more than 10 cigarettes (or equivalent amount of tobacco) per day within 3 months prior to Screening
7. Patient has used a strong CYP3A4 inhibitor within 7 days prior to first dose of study drug or a strong CYP3A4 inducer within 14 days prior to first dose of study drug
8. Any other medical condition that would interfere with performance of testing including (but not limited to) significant joint pain or arthritis limiting mobility, and chronic neuromuscular pain sufficient to require ongoing analgesic medication
9. Participation by two people at the same time that are living in the same household
10. Taking any other investigational study drug as a clinical trial participant, within 30 days or five half-lives, whichever is greater, prior to Screening
11. An ALT or AST greater than 2-fold the upper limit of normal (ULN) or has total bilirubin greater than the ULN at screening. These assessments may be repeated once at the investigator's discretion (within the screening window)

12. Currently taking nusinersin, or has taken it in the past, or plans to take it during the course the study

5. STUDY PROCEDURES

5.1. Screening

A signed ICF will be obtained from each patient prior to performing any study-specific procedures. A copy of the ICF will be retained in the study file and a copy will be provided to the patient.

The following screening procedures will be performed for all potential patients at a visit conducted within 21 days of study entry:

1. Demographic data, including tobacco and alcohol usage
2. Medical history, including review of concomitant medications
3. Review of inclusion/exclusion criteria
4. Height, ulna length, body weight, and calculation of body mass index (BMI)
5. Routine physical examination
6. Neurological examination
7. 12-lead ECG
8. Vital signs, including oral temperature, heart rate and blood pressure measured after the patient has been resting for at least 3 minutes
9. Clinical laboratory evaluations (collected after the patient has fasted), including complete blood count (CBC) and white blood cells (WBC) with differential, serum chemistries and urinalysis (UA)
10. Pregnancy test for all females of childbearing potential
11. Pulmonary function assessments
12. Muscle strength measurements
13. Hammersmith Functional Motor Scale-Expanded (HFMS-E)
14. Revised upper limb module (RULM)
15. Timed up and go (TUG) test (for ambulatory patients)
16. 6-minute walk test (6MWT) (for ambulatory patients)
17. Beck Depression Inventory (BDI®) FastScreen

Once a patient is confirmed eligible to participate and before the first dose on Day 1, patients will be randomized to receive either CK-2127107 or placebo.

5.2. First Dosing Day (Day 1)

Patients will be instructed to have breakfast before coming to the clinic on Day 1. Prior to study drug dosing on the morning of Day 1, the following procedures will be performed:

1. 12-lead ECG

2. Vital signs, including heart rate and blood pressure measured after the patient has been resting for at least 3 minutes
3. Weight
4. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries and UA
5. PK blood sample
6. Pulmonary function assessments
7. Muscle strength measurements
8. HFMS-E
9. RULM
10. TUG test (for ambulatory patients)
11. 6MWT (for ambulatory patients)
12. SMA-HI

Following a 3-hour fast from food (not including water), patients will receive their first dose of study drug (CK-2127107 or placebo), and will be followed by a fast from food (not including water) for at least 1 hour post-dose.

The following assessments will be performed after the first dose of study drug is given:

13. PK blood samples at 1 and 3 hours post-dose
14. AE/SAE evaluation and concomitant medication assessment (since last visit)
15. BDI® FastScreen

Patients will be given an adequate supply of study drug (CK-2127107 or placebo) to take twice daily for 2 weeks at home starting on Day 2 but will return to the clinic 1 week later at the end of Week 1. A dosing diary will be provided for patients to record the date and time of twice daily study drug administration.

5.3. End of Week 1 Visit

Patients will be instructed to be fasting for at least 3 hours (not including water) when arriving at the clinic for the End of Week 1 Visit. Prior to study drug dosing on the morning of the End of Week 1 Visit, the following procedures will be performed:

1. Vital signs, including heart rate and blood pressure measured after the patient has been resting for at least 3 minutes
2. Weight
3. PK blood sample

Patients will receive their morning dose of study drug (CK-2127107 or placebo), and will be followed by a fast from food (not including water) for at least 1 hour post-dose. Patients will be reminded to bring their morning dose of study drug with them to take while at the clinic. The

following assessments will be performed 1 hour after the morning dose of study drug is given and the patient has eaten:

4. Pulmonary function assessments
5. Muscle strength measurements
6. HFMS-E
7. RULM
8. AE/SAE evaluation and concomitant medication assessment (since last visit)
9. BDI® FastScreen

Patients will have already been given their supply of study drug (CK-2127107 or placebo) to take twice daily at home until their next clinic visit at the end of Week 2. A dosing diary will be provided for patients to record the date and time of twice daily study drug administration.

5.4. End of Week 2 Visit

Patients will be instructed to be fasting for at least 3 hours (not including water) when arriving at the clinic for the End of Week 2 Visit. Prior to study drug dosing on the morning of the End of Week 2 Visit, the following procedures will be performed:

1. 12-lead ECG
2. Vital signs, including heart rate and blood pressure measured after the patient has been resting for at least 3 minutes
3. Weight
4. PK blood sample
5. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries and UA

Patients will receive their morning dose of study drug (CK-2127107 or placebo), and will be followed by a fast from food (not including water) for at least 1 hour post-dose. The following assessments will be performed 1 hour after the morning dose of study drug is given and the patient has eaten:

6. Pulmonary function assessments
7. Muscle strength measurements
8. HFMS-E
9. RULM
10. Global assessments
11. PK blood samples at 1 and 3 hours post-dose
12. AE/SAE evaluation and concomitant medication assessment (since last visit)
13. BDI® FastScreen

Patients will be given an adequate supply of study drug (CK-2127107 or placebo) to take twice daily for 2 weeks at home until their next clinic visit at the end of Week 4. A dosing diary will be provided for patients to record the date and time of twice daily study drug administration.

5.5. End of Week 4 Visit

Patients will be instructed to be fasting for at least 3 hours (not including water) when arriving at the clinic for the End of Week 4 Visit. Prior to study drug dosing on the morning of the End of Week 4 Visit, the following procedures will be performed:

1. Vital signs, including heart rate and blood pressure measured after the patient has been resting for at least 3 minutes
2. Weight
3. PK blood sample

Patients will receive their morning dose of study drug (CK-2127107 or placebo), and will be followed by a fast from food (not including water) for at least 1 hour post-dose. The following assessments will be performed 1 hour after the morning dose of study drug is given and the patient has eaten:

4. Pulmonary function assessments
5. Muscle strength measurements
6. HFMS-E
7. RULM
8. TUG test (for ambulatory patients)
9. 6MWT (for ambulatory patients)
10. AE/SAE evaluation and concomitant medication assessment (since last visit)
11. BDI® FastScreen

Patients will be given an adequate supply of study drug (CK-2127107 or placebo) to take twice daily for 2 weeks at home. Study drug will need to be picked up in the clinic at the end of Week 6 for 2 more weeks of dosing until the next clinic visit at the end of Week 8. A dosing diary will be provided for patients to record the date and time of twice daily study drug administration.

5.6. End of Week 8 Visit

Patients will be instructed to be fasting for at least 3 hours (not including water) when arriving at the clinic for the End of Week 8 Visit. Prior to the last dose of study drug on the morning of the End of Week 8 Visit, the following procedures will be performed:

1. 12-lead ECG
2. Vital signs, including heart rate and blood pressure measured after the patient has been resting for at least 3 minutes
3. Weight

4. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries and UA
5. PK blood sample

Patients will receive their last morning dose of study drug (CK-2127107 or placebo), and will be followed by a fast from food (not including water) for at least 1 hour post-dose. The following assessments will be performed 1 hour after the last morning dose of study drug is given and the patient has eaten:

6. Pulmonary function assessments
7. Muscle strength measurements
8. HFMS-E
9. RULM
10. TUG test (for ambulatory patients)
11. 6MWT (for ambulatory patients)
12. Global assessments
13. SMA-HI
14. PK blood samples at 1, 3 and 6 hours post-dose
15. AE/SAE evaluation and concomitant medication assessment (since last visit)
16. BDI® FastScreen

5.7. Follow-Up Visit

The following procedures will be performed at a Follow-Up Visit 4 weeks after each patient's final dose of study drug:

1. 12-lead ECG
2. Vital signs including heart rate and blood pressure measured after the patient has been resting for at least 3 minutes
3. Weight
4. Abbreviated physical examination
5. Neurological examination
6. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries and UA
7. Pulmonary function assessments
8. Muscle strength measurements
9. HFMS-E
10. RULM
11. TUG test (for ambulatory patients)

12. 6MWT (for ambulatory patients)
13. Global assessments
14. AE/SAE evaluation and concomitant medication assessment (since last visit)
15. BDI® FastScreen

5.8. Visit Windows

To aid in scheduling patient visits, the following study visit windows are considered acceptable (Table 5). If a patient visit must be scheduled outside the visit window, the Medical Monitor should be contacted.

Table 5: Visit Windows

Visit	Visit Window
Screening	Up to 21 days prior to Day 1 visit (as per protocol)
Day 1	First day of randomized, double-blind dosing
End of Week 1 (Day 8)	- 1 day
End of Week 2 (Day 15)	- 1 day
End of Week 4 (Day 29)	- 1 day
End of Week 6 (Day 43) (for study drug pick-up only)	- 1 day
End of Week 8 (Day 57)	+/- 1 day
Follow-Up	4 weeks after last dose of study drug +/- 3 days

5.9. Diet Control

All doses of study drug should be taken after fasting from food at least 3 hours and following the dose, patients should also fast from food (not including water) for at least 1 hour.

Subjects will abstain from consuming grapefruit-containing foods or beverages from Day 1 through the Follow-Up visit.

5.10. Concomitant Medications

All prescription drugs, over-the-counter medications, nutriceuticals and herbal remedies taken by the patient from the time of screening through the Follow-Up visit should be entered into the electronic case report form (eCRF). Medications that inhibit the activity of CYP3A4 should be avoided from 7 days before the start of dosing (Day 1) through the last day of dosing (End of Week 8). Medications that induce the activity of CYP3A4 should be avoided from 14 days before the start of dosing (Day 1) through the last day of dosing (End of Week 8).

5.11. Pharmacokinetic Sampling

Blood samples for plasma PK analysis of CK-2127107 and its metabolites (if applicable) will be collected from patients at the nominal time points listed in Table 6.

Table 6: Pharmacokinetic (PK) Samples

Day	Sample Time Points
Day 1	Pre-dose (-30 min), 1 (+/-30 min) and 3 (+/-30 min) hours post-dose
End of Week 1	Pre-dose (-30 min)
End of Week 2	Pre-dose (-30 min), 1 (+/-30 min) and 3 (+/-30 min) hours post-dose
End of Week 4	Pre-dose (-30 min)
End of Week 8	Pre-dose (-30 min), 1 (+/-30 min), 3 (+/-30 min) and 6 (+/-30 min) hours post-dose

If an indwelling catheter is used, saline flushes will be used.

After completion of bioanalysis, remaining plasma samples will be retained consistent with the Sponsor's standard operating procedures. These samples will not be used for pharmacogenomic testing.

5.12. Clinical Safety Assessments

5.12.1. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be collected at Screening, Day 1, End of Week 2 visit, End of Week 8 visit, and at the Follow-Up Visit.

5.12.2. 12-Lead Electrocardiograms

A 12-lead ECG, including ECG parameters of RR, PR, QRS, QT and QTc intervals as well as significant findings will be obtained at Screening, Day 1, End of Week 2 visit, End of Week 8 visit, and at the Follow-Up Visit.

When 12-lead ECGs are scheduled at the same time as blood draws, the order of evaluation will be ECG, vital signs, and then blood draw.

5.12.3. Vital Signs

Vital signs, including heart rate and blood pressure measured after the patient has been resting for at least 3 minutes will be obtained at every visit. Resting vital signs (sitting or supine) should be collected the same way for each patient throughout their participation. Oral temperature, height, and ulna length will also be obtained at the Screening visit. Weight will be obtained at each visit and BMI calculation only at Screening.

When vital signs are scheduled at the same time as blood draws, the order of evaluation will be ECG, vital signs, and then blood draw.

5.12.4. AE Assessments

Patients will be asked how they are feeling from the first administration of study drug through the Follow-Up visit (see Section 7.2). Patients will also be encouraged to voluntarily report any AEs they experience during the study.

5.12.5. Physical Examinations

A routine physical examination will be performed at Screening, and an abbreviated physical examination (consisting of an examination of general appearance, skin, lungs, cardiovascular and abdomen) will be performed at the Follow-Up Visit.

5.12.6. Neurological Examinations

A neurological examination will be administered at Screening and at the Follow-Up Visit as described in the Study Manual.

5.12.7. Beck Depression Inventory (BDI®)

The BDI-FastScreen will be assessed at all study visits as described in the Study Manual.

5.13. Clinical and Pharmacodynamic Outcome Measures

5.13.1. Pulmonary Function Assessments

The pulmonary function assessments in this study will include forced vital capacity (FVC), maximum inspiratory pressure (MIP), and maximum expiratory pressure (MEP). Pulmonary function assessments will be performed at each study visit as described in the Study Manual.

5.13.2. Hand-Held Dynamometry

Muscle strength measurements of selected muscles will be performed using hand-held dynamometry (HHD) at each study visit as described in the Study Manual.

5.13.3. Hammersmith Functional Motor Scale-Expanded (HFMS-E)

The HFMS-E will be performed at each study visit as described in the Study Manual.

5.13.4. Revised Upper Limb Module (RULM)

The RULM will be performed at each study visit as described in the Study Manual.

5.13.5. Timed Up and Go (TUG) Test

The TUG test (for ambulatory patients only) will be performed at Screening, Day 1 visit (baseline), End of Week 4 visit, End of Week 8 visit, and at the Follow-Up Visit as described in the Study Manual.

5.13.6. 6-Minute Walk Test (6MWT)

The 6MWT (for ambulatory patients only) will be performed at Screening, Day 1 visit (baseline), End of Week 4 visit, End of Week 8 visit, and at the Follow-Up Visit as described in the Study Manual.

5.13.7. Global Assessments

Both a patient and Investigator global assessment will be performed at the End of Week 2 visit, at the End of Week 8 visit, and at the Follow-Up Visit.

Patient Global Assessment:

Patients will be asked to assess whether they feel the same, better, or worse as compared to how they felt pre-dose on Day 1.

Investigator Global Assessment:

The Investigator will assess whether the patient appears the same, better, or worse as compared to the patient's status at pre-dose on Day 1.

5.13.8. SMA-HI

The SMA-HI (Health Index) is a patient reported outcome measure that will be performed at Day 1 and End of Week 8 visits as described in the Study Manual.

5.14. Removal of Patients from Study Participation

Patients will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator may remove a patient from the study if, in the Investigator's opinion, it is not in the best interest of the patient to continue the study. Patients may be discontinued due to the following:

a. A change in compliance with inclusion/exclusion criteria that is clinically relevant and/or affects patient safety, and/or study assessments/objectives, etc.
b. Occurrence of intolerable AEs
c. Changes in vital signs, ECGs, or clinical laboratory results that, in the opinion of the Investigator, pose a significant health risk
d. Intake of non-permitted concomitant medication that might affect patient safety or study assessments/objectives, etc.
e. Cystatin C increase from baseline (defined as Day 1 or Screening if Day 1 value is not available) to ≥1.2 times the upper limit of normal

Notification of discontinuation will immediately be made to the Sponsor's Medical Monitor. In case of premature discontinuation of study drug, every effort should be made for the patient to be seen in the clinic as soon as possible following discontinuation of study drug to perform an early termination visit which should include the same assessments done at the Follow-Up visit (Section 5.7). The official Follow-Up visit should be conducted 4 weeks after patient's final dose of study drug. The date the patient is withdrawn from the study and the reason for discontinuation will be recorded on the patient's Case Report Form (CRF). All patients who prematurely discontinue from the study for AEs will be followed for up to 30 days, until the AE resolves, or until the unresolved AE is judged by the Investigator to have stabilized.

The primary reason for a patient prematurely withdrawing from the study should be selected from the following categories and documented in the source documents:

a. Patient Death
b. Adverse Event: One or more clinical or laboratory events which, in the medical judgment of the Investigator, are grounds for discontinuation even if the event does not appear to be related to study medication. The patient may withdraw because of an AE even if the Investigator does not feel that the event is grounds for discontinuation.

c. Protocol Violation: The patient's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements
d. Patient Withdrawal of Consent: Patient desires to withdraw from further participation in the study.
e. Administrative/Other: Any cause of premature termination from the study other than the above, such as illness of investigator, loss of study drug, or termination of study by Cytokinetics.

5.15. Assessment of Safety

An independent Data Monitoring Committee (DMC) will periodically assess patient safety in an unblinded manner during the course of the study. No unblinded data will be accessible to site staff, the Sponsor, study monitors, and personnel of the electronic data capture (EDC) vendors before the database is locked. The specific activities and responsibilities of the DMC are defined in the DMC Charter for CY 5021.

Dosing of an individual will be stopped and not resumed if treatment-related AEs, changes in vital signs, ECGs, or clinical laboratory results are observed and these changes pose a significant health risk, in the opinion of either the Investigator or the Sponsor Medical Monitor. A blood sample for PK analysis should be collected at the time of the event or as close as possible to the time of the event.

In the event of a confirmed, marked hepatic abnormality as defined in Appendix C (Liver Safety Monitoring and Assessment), it is the Investigator's responsibility to ensure contact with the Sponsor immediately (i.e., within 24 hours of awareness or at the earliest possible time point). Patients with AEs of hepatic origin accompanied by Liver Function Test (LFT) abnormalities should be carefully monitored.

5.16. Replacement of Patients

For patients who are discontinued by the Investigator or who voluntarily withdraw prematurely from the study, replacement patients may be enrolled as necessary to ensure that at least 36 patients in each Cohort are evaluable for PK and safety.

5.17. Study Discontinuation

The study may be discontinued by the Sponsor for the following reasons:

- Excessive rates of AEs
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- A decision to cease or delay further development of the drug

6. INVESTIGATIONAL PRODUCT

6.1. Description of Investigational Product

This is a double-blind, placebo-controlled study. As such, the site pharmacy staff, the Investigator, the patient, and remaining study site clinical staff will be blinded to treatment assignment.

Study drug will be supplied to the sites as CK-2127107 Granules for Oral Suspension and Placebo for CK-2127107 Granules for Oral Suspension. Study drug will be constituted by the site pharmacy for patient use.

The Sponsor, or designee, will provide the pharmacist with adequate quantities of CK-2127107 and matching placebo bottles as follows:

Table 7: Study Drug

Study Drug	CK-2127107 Granules for Oral Suspension	Placebo for CK-2127107 Granules for Oral Suspension
Form	Granules for Oral Suspension	Granules for Oral Suspension
Manufacturer	Patheon, Inc. Toronto Regional Operations (TRO) 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada	Patheon, Inc. Toronto Regional Operations (TRO) 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada

CK-2127107 Granules for Oral Suspension and Placebo for CK-2127107 Granules for Oral Suspension will be supplied to the clinical site in 240 mL polyethylene terephthalate (PET) amber bottles containing 12 g of granules per bottle with an induction sealed aluminum foil and child resistant cap. Each bottle contains sufficient drug for 1 week of dosing plus overage. Bottles of CK-2127107 Granules for Oral Suspension and Placebo for CK-2127107 Granules for Oral Suspension are to be stored at controlled room temperature (20-25°C; 68-77°F) with temporary excursions allowed between 15-30°C; 59-86°F.

The Sponsor, or designee, will also provide clear 10 mL oral syringes and press-in-bottle adapters (PIBA). The pharmacy will provide USP Purified Water for constitution.

6.2. Dose Preparation and Administration

The dry granules are constituted in the bottle by the pharmacy staff by adding 126 mL of USP purified water, followed by 2 minutes vigorous shaking, holding the suspension at ambient temperature for 60 minutes and then inverting the bottle 20 times. The bottle is held at ambient temperature for another 60 minutes and then inverted another 20 times. The final volume of the prepared suspension is 135 mL. Each bottle contains 15 doses of 9 mL/dose of the oral suspension for weekly BID dosing. After constitution, the PIBA is inserted into the bottle opening and recapped. The constituted suspension is stored refrigerated 2-8°C; 36-46°F.

Patients will take home the bottles of prepared oral suspension and clear 10 mL oral syringes. The constituted suspension is stored refrigerated. Prior to administration, the bottle is inverted

five times to assure the homogeneity of the suspension. A clear 10 mL oral syringe is inserted into the PIBA and used to withdraw a 9 mL dose to be administered orally.

Study drug (CK-2127107 or placebo) should be taken in the morning (on study visit days it will be taken in the clinic) and in the evening, approximately 12 hours apart. All doses of study drug should be taken after fasting from food at least 3 hours and following the dose, patients should also fast from food (not including water) for at least 1 hour. Unused study drug should be returned to the clinic at each study visit.

If the dose is decreased in Cohort 2 (see Section 8.8 for discussion), the volume of administration may be decreased as a means to adjust dose. The pharmacy manual will be updated to reflect any changes and provided to sites with appropriate training prior to the start of Cohort 2.

6.3. Dosing Diary

A dosing diary will be maintained by the patient to record date and time of twice daily study drug administration. The dosing diary should be returned at each clinic visit.

6.4. Randomization

A randomization schedule will be centrally generated for each cohort. The randomization schedule will be available for the pharmacy staff to prepare the study drug accordingly. Patients will be randomized 2:1 to CK-2127107 or placebo and they will also be stratified by ambulatory versus non-ambulatory status.

6.5. Study Drug Accountability and Disposal

The site pharmacist or other qualified person responsible for managing study drug supplies will maintain an accurate record of the receipt of the investigational study drug as shipped by the Sponsor (or designee), including the kit number and date received. One copy of this receipt will be returned to the Sponsor when the contents of the investigational study drug shipment have been verified. An accurate drug disposition record will be kept, specifying the study drug provided to each patient and the dates of dose administration. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

All used and unused drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinical research unit, per the Sponsor's (or designee's) instructions.

7. ADVERSE EVENTS

7.1. Definitions

7.1.1. Adverse Event

As defined by the International Conference on Harmonisation (ICH), an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product, whether or not the event is considered related to the investigational product. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the investigational product.

Examples of an AE:

- Conditions newly detected or diagnosed after administration of study drug, including conditions that may have been present but undetected prior to the start of the study
- Conditions known to have been present prior to the start of the study that increase in severity or frequency after administration of study drug
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose (overdose per se should not be reported as an AE term)
- Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., ECGs, vital signs, etc.) that are considered by the Investigator as a clinically significant change after the first dose of study drug. The Investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is a clinically significant change after the first dose of study drug.

Issues Not Considered AEs:

- Medical or surgical procedures (e.g., appendectomy); the condition that leads to the procedure (e.g., appendicitis) is the AE if it qualifies according to the definition above
- Hospitalizations where an untoward medical occurrence did not occur (e.g., convenience admissions to a hospital)
- Fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant change after the first dose of study drug
- Abnormal laboratory or test findings that are not assessed by the Investigator as a clinically significant change after the first dose of study drug.

7.1.2. Serious Adverse Event

A serious adverse event (SAE) is any AE that:

a. Results in death

NOTE: Death is selected as a serious criterion ONLY when the event is the cause of death. Death is an outcome and the event which led to death should be the reported event term.

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe, prolonged, or untreated.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: Hospitalization signifies that the subject has been admitted to the hospital as an in-patient for any length of time. Emergency room treatment does not qualify for this category, but may be appropriately included in category f (see below). Complications that occur during hospitalization are usually AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event will be considered as serious. When in doubt as to whether 'hospitalization' occurred, consult the Medical Monitor.

Hospitalization will not be considered an AE in itself. It will be considered an outcome of an AE. Therefore, if there is no associated AE, there is no SAE. For example, hospitalization for elective treatment of a pre-existing condition that did not worsen after the first dose of study drug will not be considered an AE.

d. Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) that may temporarily interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

NOTE: Medical and scientific judgment should be exercised in deciding if an event should be reported as serious. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition may be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. If in doubt as to whether or not an event qualifies as an "important medical event", consult the Sponsor's Medical Monitor.

7.2. Collection of AEs/SAEs

During each scheduled visit, ask about potential AEs or SAEs using the following standard questions:

1. Have you had any medical problems since your last visit?
2. Have you taken any new medications since your last visit?

7.3. Recording and Reporting of AEs/SAEs

7.3.1. Recording and Reporting of AEs

Events occurring between the Screening Visit and just prior to the first dose of study drug on Day 1 should not be recorded in the AE eCRF. They should be recorded in the Medical History eCRF.

AEs will be documented from the first administration of study drug through the Follow-Up Visit. The Investigator will review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) relevant to the event. A diagnosis will then be determined based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be reported as the AE term.

7.3.2. Recording and Reporting of SAEs

If an AE meets any of the seriousness criteria (see Section 7.1.2), it must be reported using the SAE report form **within 24 hours of the site's knowledge**. At a minimum, the following information should be included:

- Patient number
- Event term, including an onset date and stop date, if applicable, and a brief description
- Seriousness criterion/criteria
- Causality assessment in relation to the investigational product

If all information regarding the SAE is not initially available, the site should still report the SAE within 24 hours of awareness/discovery. Additional information should be reported when it becomes available and no later than 24 hours after receipt of such information.

7.4. Evaluating AEs and SAEs

7.4.1. Assessment of Severity

The Investigator should assess the severity of each AE/SAE. The severity of AEs/SAEs will be assessed by assigning a Grade of 1, 2, 3, 4 or 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The CTCAE is available at the following link:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

When an AE/SAE cannot be graded by CTCAE, the following severity grade may be used:

- Grade 1 (Mild): Aware of sign or symptom, but easily tolerated and intervention is not indicated
- Grade 2 (Moderate): Discomfort enough to cause interference with usual activity, local or non-invasive intervention is indicated
- Grade 3 (Severe): Incapacitating with inability to work or do usual activity, not immediately life-threatening; hospitalization or prolongation of hospitalization may be indicated
- Grade 4 (Life-Threatening): Refers to an event in which the patient was, in the view of the Investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.); urgent intervention is indicated
- Grade 5 (Fatal): Death related to AE

Severity should not be confused with seriousness. Severity is a category for rating the intensity of an event, and an event becomes serious when it meets one of the outcomes described in Section 7.1.2 . "Serious Adverse Event"

7.4.2. Assessment of Causality

The Investigator will assign causality to each SAE (related or unrelated). When assessing relationship to study drug, the Investigator will consider the following factors:

- Temporal association between administration of the study drug and the event
- Cessation of the AE following discontinuation of dosing
- Recurrence of the AE with reintroduction of study drug, if performed
- Similarity to known class effects
- Alternative causes, such as:
  - Known effects of concomitant medications
  - Pre-existing risk factors
  - Concurrent illnesses

The assessment of causality will be based on the information available, and may be changed upon receipt of additional information.

7.5. Follow-Up of AEs and SAEs

After the initial recording of an AE/SAE, the Investigator should proactively follow the patient. Non-serious AEs that are still ongoing at the end of the study should be reviewed to determine if further follow up is required. The Investigator will document on the AE eCRF any/all ongoing non-serious AEs that will not be followed up further after the patient exits the study. If in doubt, the Investigator should consult the Sponsor's Medical Monitor.

All SAEs should be followed until resolution, until the condition stabilizes, or until the patient is lost to follow-up. Once the seriousness criterion no longer applies to the SAE (e.g., patient was discharged), the corresponding AE eCRF page should be updated. All relevant additional information collected regarding an SAE, including laboratory test reports, consultation reports from other health care professionals, discharge summaries, or other information should be transmitted to Cytokinetics with the follow-up SAE report form **within 24 hours of receipt or awareness**.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of any AE/SAE.

If a patient dies during participation in the study or during the follow-up period, the Investigator will provide Cytokinetics with a copy of any post-mortem findings, including an autopsy report if obtainable.

7.6. Post-Study AEs/SAEs

A post-study AE/SAE is defined as any event that occurs outside of the AE detection period defined in Section 7.3.1.

Investigators are not obligated to actively solicit AEs from former study participants. However, if the Investigator learns of an SAE at any time after a patient has been discharged from the study that he/she considers reasonably related to the investigational product, the Investigator will promptly notify Cytokinetics.

7.7. Pregnancy

Pregnancy is not an AE; however, information on pregnant female study participants and female partners of male study participants will be collected if the pregnancy occurs from the first dose of the investigational product until 10 weeks after the last dose. The pregnancy information and its outcome will be collected using the Pregnancy Report Form. If the pregnancy occurs in a partner of a male study participant, the partner's consent will be obtained before collecting information regarding the pregnancy and its outcome.

If the pregnancy test (urine or serum) is positive, the pregnancy should be immediately reported to the Investigator and Cytokinetics. Any patient who becomes pregnant during the study is not eligible to continue the study and should complete the study procedures as soon as possible. The male participant, who have not had a vasectomy with a confirmed zero sperm count, will be advised to use barrier method (condom) during the study and up to 10 weeks after the last dose of the investigational product to prevent pregnancy of female partners of child bearing potential and/or fetal exposure if the partner is pregnant.

Accidental, therapeutic, or spontaneous abortions and congenital anomalies or birth defects will be reported as SAEs.

8. STATISTICAL METHODS

8.1. General Considerations

8.1.1. General Approach

The primary objective of this study is to determine the potential PD effects of CK-2127107 suspension after multiple oral doses in patients with SMA.

The secondary objectives of this study are:

- To evaluate the safety and tolerability of multiple doses of CK-2127107 administered orally to SMA patients
- To evaluate the PK of CK-2127107 administered orally to SMA patients

All statistical tests will be two-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be two-sided 95% confidence intervals, unless stated otherwise. No adjustments for multiple comparisons will be made.

Summary statistics for continuous variables will include numbers of patients, means, medians, standard deviations, minima, and maxima, overall and by treatment, cohort, and ambulatory and non-ambulatory patients. For categorical variables, frequencies and percentages will be given overall and by treatment, dose, and ambulatory and non-ambulatory patients. Assumptions for statistical models will be evaluated. If assumptions are substantially violated, alternative analysis methods will be considered. Missing data will not be imputed unless specified. Baseline is defined as the last available measurement taken before the first dose unless otherwise specified.

8.1.2. Sample Size and Randomization

With a two-tailed alpha error of 0.05, at least 72 patients (24 on placebo and 48 on CK-2127107) are expected to complete the 8 weeks of double-blind treatment, which is estimated to provide 84% power to detect a treatment difference of three points in HFMS-E score change from baseline to the end of the 8-week double-blind treatment between placebo and all CK-2127107 dose groups pooled with a common standard deviation of four points (Swoboda, Scott et al. 2010). Stratified by ambulatory and non-ambulatory condition, at least 36 patients (approximately 18 ambulatory and 18 non-ambulatory patients) for each of the two cohorts will be randomized to receive CK-2127107 and placebo in a treatment allocation ratio of 2:1. Replacement patients will be enrolled as necessary to ensure that at least 36 patients complete each Cohort (approximately 18 patients in each of the ambulatory group or the non-ambulatory group) and are evaluable for PD effect of CK-2127107. In order to ensure this, replacement patients may be recruited after one dropout has occurred. Each replacement patient will be assigned to the same treatment for the same ambulatory or non-ambulatory condition as the patient being replaced.

8.2. Analysis Populations

8.2.1. Safety Analysis Set (SAS)

The safety population will consist of all patients who receive at least one dose of study medication.

8.2.2. Pharmacokinetics Analysis Set (PKS)

The PKS will consist of all patients who have at least one evaluable PK plasma profile, provided they have no major protocol violations that could affect the PK of CK-2127107.

8.2.3. Pharmacodynamic Analysis Set (PDS)

The PDS consists of all patients in the SAS who have at least one non-missing post-baseline assessment of the PD endpoints, provided they have no major protocol violations that could affect the PD effect of CK-2127107.

8.3. Statistical Analysis

8.3.1. Patient Disposition

The number of patients who are randomized, who complete the planned treatment, and who prematurely discontinue from the study, including replacement patients if any, will be presented. Reasons for premature discontinuation as recorded on the termination page of the eCRF will be summarized.

8.3.2. Demographics and Other Baseline Characteristics

Patient demographics and other baseline characteristics will be summarized descriptively.

8.4. Safety Analysis

Safety data will be summarized overall and by treatment dose as well as by ambulatory or non-ambulatory condition.

8.4.1. Study Drug Exposure

Study drug exposure will be summarized. The amount of study drug expected to have been administered, and the amount of each dose of study drug actually received will be presented.

8.4.2. Adverse Events

A TEAE is an AE with an onset after initiation of study drug dosing during the randomized treatment period, or an AE present at initiation of study drug dosing that worsens in severity during the randomized treatment period. AEs will be coded using MedDRA Preferred Terms and grouped by System Organ Class. The version of the MedDRA dictionary will be noted in the report.
AEs will be classified according to severity and relationship to study medication. The number and percentage of patients reporting AEs will be tabulated. The number and percentage of patients reporting AEs will also be tabulated by severity or relationship to study medication.

Only TEAEs with an onset from the first dose until the follow up visit will be summarized. All AEs will be included in patient listings.

8.4.3. Serious Adverse Events

Summaries of SAEs and SAEs by severity grade determined by the NCI-CTCAE version 4 as well as by relationship to study medication will be presented.

8.4.4. Concomitant Medications

Concomitant medications will be summarized and classified by drug class and preferred term using the WHO (World Health Organization) Drug dictionary. The version of the WHO Drug dictionary will be noted in the report.

8.4.5. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values and changes from baseline at each protocol specified assessment time point will be presented.

8.4.6. Vital Signs

Descriptive statistics for vital signs and changes from baseline at each protocol specified assessment time point will be presented.

8.4.7. Electrocardiogram (ECG)

Descriptive statistics for ECG parameters (e.g., heart rate, PR interval, QRS interval, QT interval, and QTc interval [both Bazett's and Fridericia's corrections) and changes from baseline at each protocol specified assessment time point will be presented.

8.5. Pharmacodynamic Analysis

PD analyses will be based on the PDS. The following pharmacodynamic endpoints are categorized by the pharmacodynamic assessments below:

8.5.1. Forced Vital Capacity (FVC)

- Change from baseline in FVC at the end of Week 8 treatment
- Slope of FVC change from baseline to the end of Week 8 treatment

8.5.2. Maximum Inspiratory Pressure (MIP) / Maximum Expiratory Pressure (MEP)

- Change from baseline in MIP/MEP at the end of Week 8 treatment
- Slope of MIP/MEP change from baseline to the end of Week 8 treatment

8.5.3. Hand-Held Dynamometry

- Change from baseline in muscle megascore at the end of Week 8 treatment
- Slope of muscle megascore change from baseline to the end of Week 8 treatment

8.5.4. Hammersmith Functional Motor Scale-Expanded (HFMS-E)

- Change from baseline in HFMS-E score at the end of Week 8 treatment
- Slope of HFMS-E score change from baseline to the end of Week 8 treatment

8.5.5. Revised Upper Limb Module (RULM)

- Change from baseline in upper limb module-revised score at the end of Week 8 treatment
- Slope of upper limb module-revised score change from baseline to the end of Week 8 treatment

8.5.6. Timed Up and Go (TUG) Test

- Change from baseline in time up and go at the end of Week 8 treatment
- Slope of time up and go change from baseline to the end of Week 8 treatment

8.5.7. 6-Minute Walk Test (6MWT)

- Change from baseline in 6-Minute Walk distance at the end of Week 8 treatment
- Slope of 6-Minite Walk distance change from baseline to the end of Week 8 treatment

8.5.8. Global Assessments

- Responder is defined as an improvement response at the end of Week 8 treatment

8.5.9. SMA-HI

- Change from baseline to end of Week 8

Pharmacological effects by dose and by plasma concentrations of CK-2127107 will be investigated. Test-retest data between screening and Day 1 will be investigated for data reliability and consistency.

Statistical analysis will be performed on change from baseline PD assessments for all patients on CK-2127107 compared to placebo. For continuous endpoints, with assessments at the end of Week 2, 4, and/or 8, analysis of PD assessments will be performed using an analysis of co-variance (ANCOVA) model with treatment and time as fixed effects, their interaction, the baseline value of the variable being analyzed as a covariate, accounting for repeated measures within patients. The primary comparison will be between all patients on CK-2127107 vs. placebo, at the end of Week 8, regardless of each patient's dosage level. For categorical endpoints, analysis of PD assessments will be performed using the appropriate chi-square test. A logistic regression will be used to model responder variables, providing odds ratio and 95% CI for odds ratio for treatment differences between active dose levels and placebo. The odds ratio estimated from GEE models will also be provided for responder variables with repeated measures. Additional analyses based on dose and plasma concentration relationships will be performed with similar models, with treatment replaced by dose, plasma concentration**,** and/or concentration bins. All p-values provided will be considered nominal and are for descriptive purposes only.

A detailed description of the analyses will be presented in the Statistical Analysis Plan.

8.6. Pharmacokinetic Analysis

PK analysis will be based on the PKS. For each patient, the following PK parameters and time to reach steady-state will be calculated, whenever possible, based on the plasma concentrations of CK-2127107 and its metabolites (if applicable) using non-compartmental PK methods:

C_{max}	Maximum observed plasma concentration
C_{trough}	Pre-dose plasma concentration
AUC_{0-t}	Area under the plasma concentration-time curve from pre-dose to the last measurable plasma concentration
AUC_{avg}	Area under the plasma concentration-time curve at steady-state will be the average AUC_{0-24} at the end of Week 2 and 8

8.7. Statistical Analysis of Pharmacokinetic Data

Descriptive statistics in terms of mean, standard deviation (SD), geometric mean, coefficient of variation (CV), median, and range will be provided for concentrations at all planned sampling time points and all PK parameters listed above by dose, cohort, ambulatory and non-ambulatory condition, and adolescence (12 to < 18 years old) and adult (≥ 18 years old) patients. Individual or mean concentrations over time will be graphically displayed. The least square difference of natural log-transformed C_{max} and AUC_{avg} at the end of Week 2 and 8 between adolescence (12 to < 18 years old) and adult (≥ 18 years old) patients and the associated 90% confidence interval (CI) will be examined using analysis of variance (ANOVA) model including terms of dose, gender, and ambulatory and non-ambulatory condition, using adult patients as the reference, respectively. Back-transformation will provide point estimates and conventional 90% CIs for the geometric mean ratio of C_{max} and AUC_{avg} between adolescence and adult patients. Similar method will be used to examine the differences in C_{max} between ambulatory and non-ambulatory condition, controlling for dose, age, and gender as using ambulatory condition as the reference. Graphs with PK parameters by dose and adolescence and adult patients will be provided.

8.8. Interim Analysis and Dose Level Review

After 30 patients in Cohort 1 have received at least one dose of study drug and have either completed the End of Week 8 visit or have permanently discontinued study drug, representatives of the Sponsor, the Sponsor's collaborator (Astellas), and one of the Study Investigators will review the safety and PK data available at that time from Cohort 1, including blinded pharmacokinetic data, to confirm the dose level or reduce the dose level of CK-2127107 to be administered in Cohort 2. After the last patient in Cohort 1 completes 2 weeks of dosing, the recommendation along with the safety data from the last 6 patients will be forwarded to the DMC for their endorsement of the dose selected and the decision to proceed to Cohort 2. The DMC may also indicate the need to alter study conduct. If the aggregate blinded data do not allow a decision to proceed to Cohort 2 to be made, the database for Cohort 1 will be locked. An unblinded interim analysis will be conducted and the recommendation on how to proceed forwarded to the DMC before Cohort 2 is commenced. In addition, upon completion of dosing

in Cohort 1 or Cohort 2, the database may be locked or frozen and an interim analysis of the data may be conducted for planning future development.

8.9. Statistical Software

Statistical analyses will be performed using SAS® version 9.3 or greater.

8.10. Changes in Statistical Methods

All changes in statistical methods that are described in the statistical analysis plan will be documented in the clinical study report.

9. ADMINISTRATIVE ASPECTS

9.1. Change in Protocol

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator. There will be no alterations in the protocol without the express written approval of the Sponsor, Investigator, and the Institutional Review Board (IRB).

9.2. Initiation Visit

Prior to the start of the clinical study at each site, the representative(s) of the Sponsor will meet with the Investigator(s) and appropriate clinical staff to familiarize the Investigator and clinical staff with the materials necessary for conducting the clinical study.

9.3. Disclosure

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (e.g., articles in journals or newspapers, oral presentations, abstracts, etc.) by the Investigator(s) or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

9.4. Monitoring

The Sponsor will designate site monitors who will be responsible for monitoring this clinical trial. The site monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the site monitor have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the site monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and other study personnel will be expected to cooperate with the site monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

9.5. Institutional Review Board

In accordance with the US Code of Federal Regulations, 21 CFR 56, the protocol, subject recruitment advertisements (if applicable), and ICF will be submitted to the IRB for review and subsequent written approval by the IRB must be received before proceeding. The Sponsor will supply relevant material for the Investigator to submit to the IRB for the protocol's review and approval. Verification of the IRB unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator.

The IRB will be informed by the Investigator of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the

Investigator. If requested, the Investigator will permit audits by the IRB and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

9.6. Informed Consent

Before protocol-specific procedures are carried out, written informed consent for the study will be obtained from patients who are 18 years of age and older and for minors who are at least 12 years of age, parental permission and child assent will be required. The ICF and parental permission and assent generated by the Investigator (or designee) will be approved (along with the protocol) by the IRB and will be acceptable to the Sponsor.

The Investigator (or designee) will explain the nature of the study and the action of the test product. The capable patients and parents/legal guardians of minors will be informed that participation is voluntary and that patients can withdraw from the study at any time. In accordance with 21 CFR 50, informed consent shall be documented by the use of a written ICF or parental permission and child assent approved by the IRB and will be signed by the patient and if the patient is a minor, the parental permission will be signed by the minor's parents/legal guardians prior to protocol-specific procedures being performed. A copy of the signed consent (or signed permission and assent), and the original will be maintained with the patient's records. A copy of the IRB approved ICF or parental permission and child assent must be sent to the Sponsor (or designee).

9.7. Records

The results from data collected during the study will be recorded in the patient's eCRF. To maintain confidentiality, the patient will be identified only by numbers.

The completed eCRFs will be transferred to the Sponsor or designee. All source documents, records, and reports will be retained by the study site in accordance with 21 CFR 312.62(c). All primary data, or copies thereof (e.g., laboratory records, source documents, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives.

9.8. Reference to Declaration of Helsinki/Basic Principles

The study procedures outlined in this protocol will be conducted in accordance with the CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for FDA Approval to Market a New Drug (21 CFR 314), as appropriate. As such, these sections of U.S. Title 21 CFR, along with the applicable ICH Guidelines, are commonly known as Good Clinical Practices (GCP), which are consistent with the Declaration of Helsinki, 1996.

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APPENDIX A. SCHEDULE OF EVENTS

Study Procedures	Screening	Day 1	End of Week 1	End of Week 2	End of Week 4	End of Week 8	FU Visit
Informed Consent	X						
Incl/Excl Criteria	X						
Demographics	X						
Medical History	X						
Concomitant Meds	X	X	X	X	X	X	X
Physical Exam [a]	X						X
Neurological Exam	X						X
Height, Ulna Length	X						
Weight, BMI [b]	X	X	X	X	X	X	X
12-Lead ECG	X	X		X		X	X
Vital Signs [c]	X	X	X	X	X	X	X
Clinical Safety Labs	X	X		X		X	X
Pregnancy Test [d]	X						
PK Sample [e]		X	X	X	X	X	
Pulmonary Function Tests	X	X	X	X	X	X	X
Muscle Strength	X	X	X	X	X	X	X
HFMS-E	X	X	X	X	X	X	X
RULM	X	X	X	X	X	X	X
TUG Test [f]	X	X			X	X	X
6MWT [f]	X	X			X	X	X
Global Assessments				X		X	X
Study Drug Dosing		X	X	X	X	X	
AE/SAE Evaluations		X	X	X	X	X	X
BDI® FastScreen	X	X	X	X	X	X	X
SMA-HI		X				X	

[a] Complete physical examination at Screening Visit, abbreviated physical examination at FU visit
[b] BMI only at Screening
[c] Oral temperature only at Screening
[d] Only for females of childbearing potential
[e] PK sampling on Day 1 visit, End of Week 1 visit, End of Week 2 visit, End of Week 4 visit, and End of Week 8 visit; refer to Table 6 in protocol
[f] For ambulatory patients only

APPENDIX B. CYP3A4 INHIBITORS AND CYP3A4 INDUCERS

CYP3A4 Inhibitors	CYP3A4 Inducers
Strong Inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	phenobarbital
clarithromycin	phenytoin
itraconazole	pioglitazone
ketoconazole	rifabutin
nefazodone	rifampin
	St. John's Wort
Moderate Inhibitors:	troglitazone
erythromycin	
grapefruit juice	
verapamil	
suboxone	
diltiazem	
Weak Inhibitors:	
cimetidine	

APPENDIX C. LIVER SAFETY MONITORING AND ASSESSMENT

Any patient enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN, or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 24 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the Investigator, study monitor and study team. Patients should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3× ULN	or	> 2× ULN
Severe	> 3× ULN	and	> 2× ULN

In addition, the patient should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8× ULN
- ALT or AST > 5× ULN for more than 2 weeks
- ALT or AST > 3× ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal LFTs, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) or an appropriate document. Patients with confirmed abnormal LFTs should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The Sponsor should be contacted and informed of all patients for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the eCRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the patient's history, other testing may be appropriate including:
  - acute viral hepatitis (A, B, C, D, E or other infectious agents)
  - ultrasound or other imaging to assess biliary tract disease
  - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the patient may be discontinued from the study. The investigator may determine that it is not in the patient's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST $\geq$ 3 × ULN or,
- ALT or AST $\geq$ 2 × ULN and ALT or AST > 5 × baseline value or,
- TBL $\geq$ 2 × ULN

In addition, if close monitoring for a patient with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

Hy's Law Definition - Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant) (Temple 2006; FDA 2009).

The two “requirements” for Hy’s Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 x ULN (“2 x ULN elevations are too common in treated and untreated patients to be discriminating”).
2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert’s syndrome.