PROTOCOL CY 4033

A Phase 3, Open-Label Extension Study of *Tirasemtiv* for Patients with Amyotrophic Lateral Sclerosis (ALS) Who Completed VITALITY-ALS (CY 4031)

Product Number:	CK-2017357
Product Name:	*tirasemtiv*
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Sponsor:	Cytokinetics, Inc. 280 East Grand Avenue South San Francisco, California 94080
Original Protocol:	13 July 2016

Sponsor (Medical Monitor) Signature: _____

Lead Investigator Signature: _____

STUDY IDENTIFICATION

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Study Site	Multi-National

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), Research Ethics Board (REB), or Ethics Committee (EC), except where necessary to eliminate an immediate hazard to the patients.
- That I am thoroughly familiar with the appropriate use of the investigational product (*tirasemtiv*), 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 (*tirasemtiv*) 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 (*tirasemtiv*), 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 1 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: _____

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Abbreviation	Definition
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase (alanine transaminase)
ALSFRS-R	ALS Functional Rating Scale-Revised
AST	aspartate aminotransferase (aspartate transaminase)
AUC_{inf}	area under the concentration-time curve (extrapolated to infinity)
AUC	area under the plasma concentration-time curve (during dosing interval)
BID	twice a day
BMI	body mass index
CBC	Complete blood count (hematology clinical laboratory evaluations)
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CPK	creatine phosphokinase
C_{max}	maximum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
DPS	diaphragm pacing system
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
hERG	human ether-à-go-go related gene
IB	Investigator's Brochure
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation
INR	international normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
K_I	inactivation constant
k_{inact}	maximum rate constant for inactivation
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MTD	maximum tolerated dose
MVIC	Maximum Voluntary Isometric Contraction
MVV	Maximum Voluntary Ventilation
NADPH	nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
PD	Pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetic(s)
PKS	pharmacokinetic set
QD	once daily
REB	Research Ethics Board
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SE	standard error
SNIP	Sniff Nasal Inspiratory Pressure
SOP	standard operating procedure
SVC	slow vital capacity
t_{max}	time to maximum plasma concentration
TEAE	treatment-emergent adverse event
TnC	troponin C
TSH	thyroid stimulating hormone
UA	Urinalysis
WHO	World Health Organization

1. INTRODUCTION

1.1. Background on *Tirasemtiv*

Tirasemtiv (formerly CK-2017357) is a novel small molecule activator of fast skeletal muscle troponin, intended to improve skeletal muscle function in disease states associated with muscular weakness or fatigue, including amyotrophic lateral sclerosis (ALS), without affecting the structure of muscle itself. *Tirasemtiv* selectively binds to the fast skeletal muscle troponin complex and slows the rate of calcium release from troponin C (TnC). This increases the affinity of TnC for calcium and thus sensitizes the sarcomere to calcium. *Tirasemtiv* is selective for fast skeletal muscle troponin with little effect on slow skeletal muscle troponin and no effect on cardiac muscle troponin. By sensitizing the fast skeletal muscle troponin complex to calcium, *tirasemtiv* shifts the calcium-force relationship of muscle fibers leftward, amplifying the response of muscle to submaximal nerve stimulation and thereby increasing muscle force. *Tirasemtiv* decreases muscle fatigability in several preclinical models of exercise performance, presumably by reducing the energetic requirements of calcium cycling during muscle contraction (Russell, Hartman et al. 2012). In a transgenic mouse model of ALS with functional deficits, single doses of *tirasemtiv* significantly increased submaximal isometric force, forelimb grip strength, grid hang time, and running performance on a rotating rod. Additionally, diaphragm force and tidal volume were significantly higher (Hwee, Kennedy et al. 2014). Acute and reversible clinical signs of intolerance were the dose-limiting toxicities in preclinical testing. The pharmacological profile of *tirasemtiv* is unique in that it is a direct and selective functional activator of fast skeletal muscle; as such, it could benefit patients with a wide variety of disorders characterized by muscle weakness or fatigue.

In a Phase 2b study that enrolled 711 patients with ALS, CY 4026, also known as BENEFIT-ALS, 12 weeks' treatment with *tirasemtiv* was associated with statistically significant and potentially clinically meaningful reductions in the decline in slow vital capacity (SVC) versus placebo (see Section 1.4.2). This observation led to CY 4031, also known as VITALITY-ALS, a Phase 3 double-blind placebo-controlled study of *tirasemtiv* administered for 52 weeks with a projected enrollment of 600 patients. The current study, CY 4033, is the open label extension for those patients who complete participation on study drug in the CY 4031 (VITALITY-ALS) study.

1.2. Rationale for *Tirasemtiv* in the Potential Treatment of Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis, or ALS, is a disease of the nerve cells in the brain and spinal cord that control voluntary muscle movement. In ALS, progressive death of motor neurons leads to denervation of skeletal muscles. Surviving motor units attempt to compensate for dying ones by innervating more muscle fibers (a process called sprouting) but are only partially successful (Kiernan, Vucic et al. 2011). Over time, progressive denervation and its consequent skeletal muscle atrophy lead to weakness, fatigue, and eventually complete paralysis and death, primarily from respiratory complications.

No curative therapies for ALS exist. Rilutek® (riluzole, Sanofi-Aventis U.S. LLC) is the only medication approved for the treatment of ALS, and has a modest benefit on survival (Lacomblez, Bensimon et al. 1996). Two interventions that contribute greatly to the overall welfare and survival of ALS patients are the use of enteral feeding and ventilatory support.

To date, there are no available treatments that can improve skeletal muscle function, and in particular respiratory function. Because *tirasemtiv* has been demonstrated both to amplify skeletal muscle force production in response to diminished neuronal input and to delay the onset and reduce the magnitude of skeletal muscle fatigue during repeated or sustained efforts, it may be useful in the treatment of patients with ALS.

1.3. Overview of *Tirasemtiv* Nonclinical Studies

A brief summary of the nonclinical safety and pharmacokinetics (PK) of *tirasemtiv* is provided in this section. Additional information concerning nonclinical assessments of the pharmacology, PK, and safety of *tirasemtiv* is available in the Investigator's Brochure (IB).

Tirasemtiv was evaluated in a series of Good Laboratory Practices (GLP) nonclinical safety pharmacology and toxicology studies, including single- and repeat-dose toxicity studies performed in Sprague-Dawley rats up to 26 weeks and beagle dogs up to 39 weeks, teratology studies in rats and rabbits, single-dose phototoxicity studies in rats, and a core battery of genotoxicity tests.

In rats, following administration of *tirasemtiv* for 26 weeks at dose levels of 0, 5, 15 and 30 mg/kg/day, target organ effects were observed at levels of 15 and 30 mg/kg/day and consisted of fibrosis and/or atrophy of the mandibular salivary glands and hepatocellular hypertrophy of the liver. The finding in the liver was fully recovered and the findings in the salivary glands were partially recovered at 30 mg/kg/day following the recovery period. The no observed adverse effect level (NOAEL) in rats was considered to be 15 mg/kg/day in this study. The exposures at the end of the study attained at the NOAEL are shown in Table 1 below.

In dogs, administration of *tirasemtiv* for 39 weeks at dose levels of 0, 6, 20 and 50 mg/kg/day resulted in adverse but reversible clinical signs at 50 mg/kg/day, non-adverse effects on body weight at all dose levels, and a decrease in food consumption at the high dose. *Tirasemtiv* caused partially reversible increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at 50 mg/kg/day, with a reversible increase in total bilirubin in females at 50 mg/kg/day and a reversible increase in creatine kinase and aldolase activities in individual males and females at 50 mg/kg/day. The NOAEL in dogs was considered to be 20 mg/kg/day in this study. The exposures at the end of the study attained at the NOAEL are shown in Table 1 below.

Table 1: Exposure to *Tirasemtiv* at the NOAEL in Rat and Dog

	26-Week Rat Toxicity Study		**39-Week Dog Toxicity Study**	
	M	**F**	**M**	**F**
Dose (mg/kg/day)	15	15	20	20
C_{max} (µg/mL)	25.1	46.5	27.0	20.9
AUC (µg•h/mL)	228.5	589.0	128.8	80.6

There was no evidence of genotoxicity in bacterial reverse mutation, human lymphocyte chromosomal aberration, or rat micronucleus assays. There was no evidence of phototoxicity in single-dose studies in rat or of embryolethality, fetotoxicity, or teratogenicity in rats and rabbits. There was little effect of *tirasemtiv* on the human ether-à-go-go related gene (hERG) channel (inhibition of 19.5% at 250 µM). Findings in cardiovascular, central nervous system (CNS), and respiratory safety pharmacology studies of *tirasemtiv* were not considered adverse because of their mild severity and/or limited duration.

The potential of *tirasemtiv* to inhibit cytochrome P450 (CYP) enzymes (CYP1A2, 2A6, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1) was studied *in vitro* in human liver microsomes at concentrations up to 100 - 200 µM. Both direct and time-dependent inhibitions were assessed. *Tirasemtiv* did not inhibit CYP3A4, 2D6, 2A6, or 2E1 with each half maximal inhibitory concentration (IC_{50}) exceeding the highest concentrations tested. *Tirasemtiv* was found to be a direct and time-dependent inhibitor of multiple CYP450 isoforms (CYP1A2, 2B6, 2C8, 2C9, and 2C19). Kinetic parameters for the time-dependent inhibition, including the time-dependent IC_{50} (inhibitory constant following 20 or 30 minute pre-incubation with microsomes + NADPH), maximum rate constant for inactivation (k_{inact}) and inactivation constant (K_I), are shown in Table 2.

Table 2: Estimated IC_{50}, k_{inact}, and K_I Values for *Tirasemtiv* Time-Dependent Inhibition

CYP Isoform	Time-Dependent IC_{50} (µM)	k_{inact} (min^{-1})	K_I (µM)
CYP1A2	5.5	0.031	1.9
CYP2B6	21	0.035	26
CYP2C8	80	0.057	46
CYP2C9	69	0.021	34
CYP2C19	4	0.051	11

1.4. Overview of *Tirasemtiv* Clinical Studies

1.4.1. Phase 1 and Phase 2a Studies

Tirasemtiv has been evaluated in three completed Phase 1 clinical trials in healthy volunteers (CY 4011, CY 4012 and CY 4013), three Phase 2a clinical trials (CY 4021, CY 4024, and CY 4025) in patients with ALS; a Phase 2a clinical trial in patients with claudication secondary to peripheral artery disease (CY 4022) and a Phase 2a clinical trial in patients with myasthenia gravis (CY 4023) have also been completed. The Phase 1 and Phase 2a clinical studies are summarized in Table 4. Additional details are available in the IB.

1.4.2. Phase 2b Clinical Trial in Patients with ALS (CY 4026; BENEFIT-ALS)

CY 4026, also known as BENEFIT-ALS (**B**linded **E**valuation of **N**euromuscular **E**ffects and **F**unctional **I**mprovement with ***Tirasemtiv*** in **ALS**), was a Phase 2b clinical trial in which 711 patients with ALS were enrolled from 73 centers in North America and Western Europe into open-label treatment with *tirasemtiv* 125 mg twice a day. Subsequently, patients who completed one week of open-label treatment were randomized 1:1 to double-blind treatment with either

tirasemtiv (titrated at weekly intervals to each patient's maximum tolerated dose ≤ 250 mg twice daily) or placebo for 12 weeks. Clinical assessments were made at baseline (i.e., prior to treatment with open-label *tirasemtiv*), after 4, 8, and 12 weeks of double-blind treatment, and 1 and 4 weeks after the last dose of double-blind study drug. Safety and efficacy were assessed among the 295 patients randomized to placebo who received at least one dose of double-blind study drug and the 301 patients randomized to *tirasemtiv* who received at least one dose of double-blind study drug.

The primary endpoint in CY 4026, the mean change from baseline in the ALS Functional Rating Scale in its revised form (ALSFRS-R), was not statistically different between treatment groups. The least squares mean (LSM) changes from baseline were −2.40 in the placebo group and −2.98 in the *tirasemtiv* group. The LSM ± standard error (SE) difference between treatment groups (i.e., *tirasemtiv* response minus placebo response) was −0.58 ± 0.366 (95% confidence interval (CI): −1.30, 0.14; p = 0.114). Although CY 4026 did not achieve its primary efficacy endpoint, two pre-specified secondary endpoints, both reflective of skeletal muscle function, were positively impacted.

Treatment with *tirasemtiv* resulted in a statistically significant and potentially clinically meaningful reduction in the decline of vital capacity (measured as SVC) which assesses strength of the skeletal muscles responsible for breathing. The percent predicted SVC declined -3.12 percentage points (±0.90) from the baseline value over 12 weeks on *tirasemtiv* compared to a decline of -8.66 percentage points (±0.80) in the placebo group (p= <0.0001). This pre-specified secondary efficacy endpoint declined less on *tirasemtiv* than on placebo at each assessment time point and this difference persisted through 28 days after discontinuation of double-blind treatment (Figure 1, Table 3). Vital capacity has been shown to be an important predictor of disease progression and survival in prior clinical trials of patients with ALS.

Figure 1: Changes from Baseline in Percent Predicted Slow Vital Capacity in BENEFIT-ALS

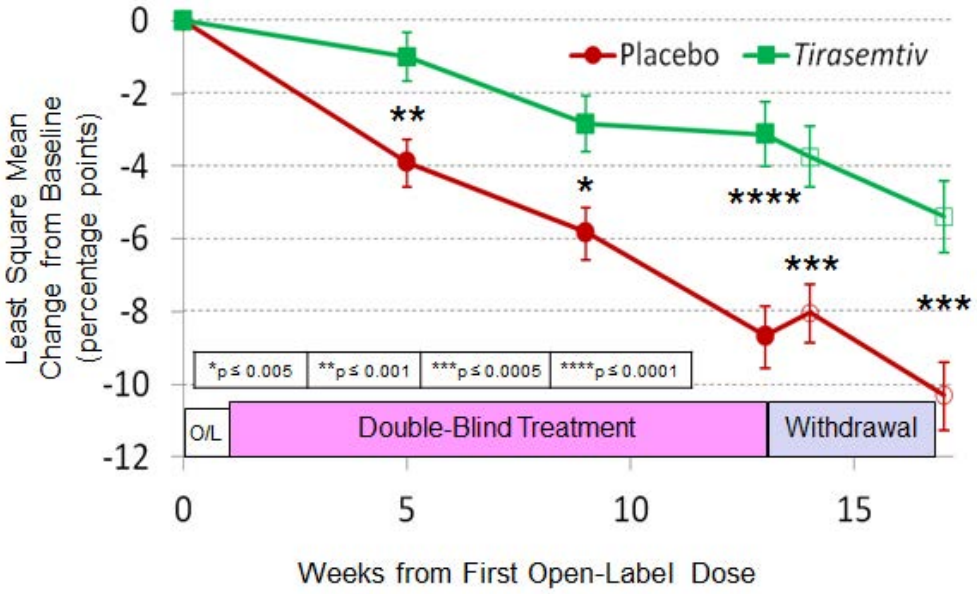
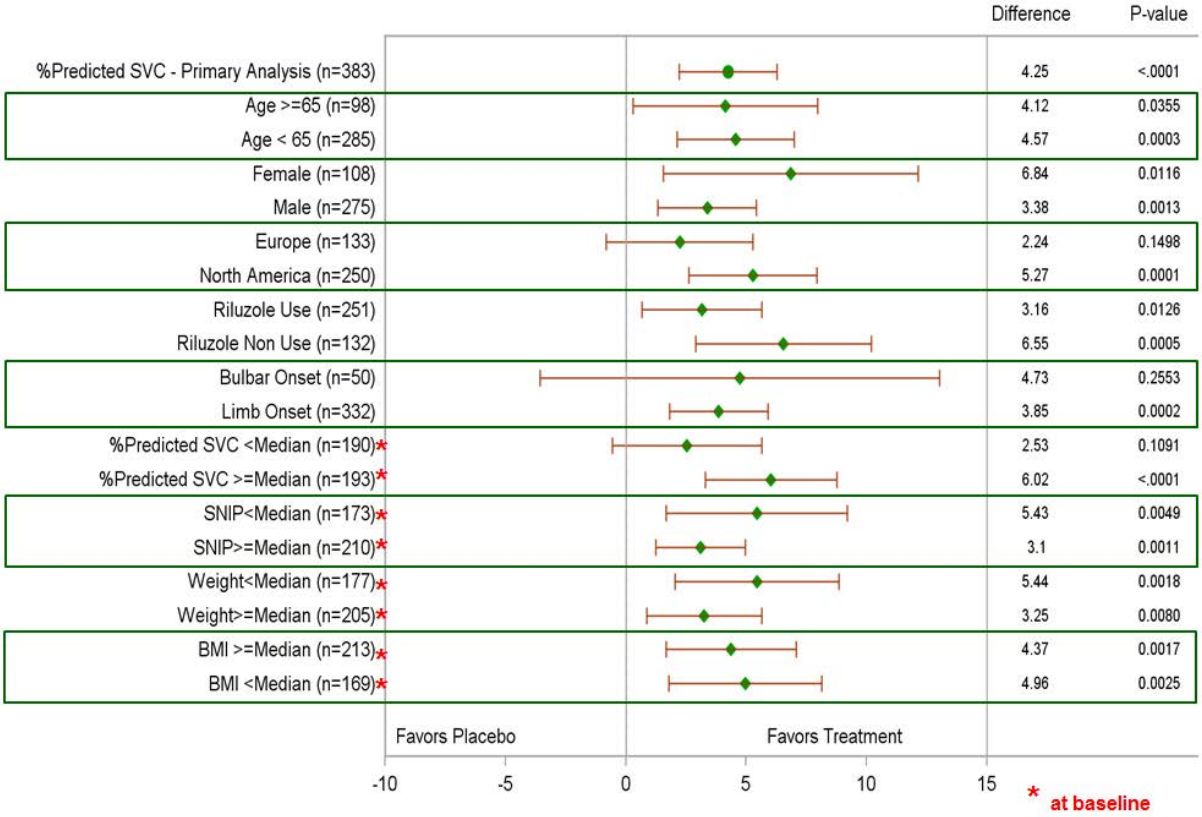


Table 3: Percent Predicted Slow Vital Capacity in BENEFIT-ALS

Slow Vital Capacity	**Placebo (n = 210)**	***Tirasemtiv* (n = 178)**	**All (N = 388)**
Baseline (prior to the one week Open-Label phase) (% Predicted, mean ± Standard Deviation [SD])	89.7 (17.2)	85.7 (19.3)	87.8 (18.3)
Time Point during the Double-Blind Treatment	**Changes from Baseline (LSM ± SE)**		**p-value**
Week 4	-3.89 (0.62)	-0.99 (0.68)	0.001
Week 8	-5.81 (0.68)	-2.85 (0.77)	0.004
Week 12	-8.66 (0.80)	-3.12 (0.90)	<0.0001
	Slope of decline (Percentage Points per day)		
Baseline to Week 12	-0.0905	-0.0394	0.0006
	Changes from Baseline (LSM ± SE)		
Week 13 (1 week after last DB dose)	-8.03 (0.77)	-3.75 (0.84)	0.0002
Week 16 (4 weeks after last DB dose)	-10.30 (0.90)	-5.39 (0.98)	0.0002

As shown in Figure 2, *tirasemtiv* reduced the decline in SVC compared to placebo regardless of age, gender, riluzole use, or body mass index (BMI). Subgroups with the largest and most significant differences in SVC on *tirasemtiv* versus placebo (change from baseline to mean SVC after 8 and 12 weeks of double-blind treatment) were: females (6.84%, $p = 0.012$); non-riluzole users (6.55%, $p = 0.0005$); and patients with baseline SVC ≥ median at baseline (6.02%, $p < 0.0001$).

Figure 2: Change from Baseline to Average after 8 and 12 Weeks in Percent Predicted Slow Vital Capacity



The results of other secondary endpoints assessed in this trial were mixed. The Muscle Strength Mega-Score, a measure of strength based on the percent change from baseline from several muscle groups in each patient, declined more slowly on *tirasemtiv* versus placebo ($p = 0.016$ for the difference in slope of decline); however, there were no differences at any time point that reached statistical significance. The rate of decline for Sniff Nasal Inspiratory Pressure (SNIP) was not statistically significantly different between *tirasemtiv* and placebo ($p = 0. 21$); however, SNIP decreased statistically significantly more on *tirasemtiv* compared with placebo at 4 and 12 weeks (p values at 4, 8, and 12 weeks were 0.012, 0.066, 0.050, respectively). No differences in Maximum Voluntary Ventilation (MVV) and Hand Grip Fatigue were observed on *tirasemtiv* versus placebo.

Serious adverse events (SAEs) during double-blind treatment were more frequent on *tirasemtiv* than on placebo (9.0% vs. 5.4%). The most common SAE was respiratory failure, which occurred in one patient on *tirasemtiv* and three patients on placebo, while confusional state and delirium occurred in two patients on *tirasemtiv* and no patients on placebo. Of patients receiving at least one dose of double-blind study drug, more patients on *tirasemtiv* withdrew from the trial following randomization than on placebo (97 vs. 26 patients, respectively). Adverse events (AEs) more common on *tirasemtiv* than on placebo (> 10% difference) were dizziness (50.8% vs. 19.7%), fatigue (33.2% vs. 14.2%), and nausea (21.9% vs. 7.8%).

Patients on *tirasemtiv* lost more weight than patients on placebo (change from baseline to Week 12: -1.70 kg vs. -0.79 kg; $p = 0.006$). Weight loss was significantly greater in patients

with gastrointestinal AEs (e.g., nausea and decreased appetite) on either treatment. However, such AEs occurred more frequently on *tirasemtiv* than on placebo (43.5% vs. 25.8%).

The statistically significant effect to reduce the decline in vital capacity observed in CY 4026 is a unique finding that has not been observed in any prior, sizable clinical trial in ALS patients. Vital capacity is a quantitative measure of respiratory muscle function in ALS and has been shown to predict disease progression in prior clinical trials. The significant results on SVC demonstrated in CY 4026 show that *tirasemtiv* has a biological effect. The cardinal symptom of ALS that directly affects survival is weakness of the skeletal muscles necessary for respiration. Therefore, the significant reduction in the decline in vital capacity seen in this trial over 12 weeks is clinically relevant to patients with ALS. Furthermore, the difference in vital capacity (measured by SVC) between *tirasemtiv* and placebo was maintained four weeks after discontinuation of double-blind treatment. This suggests that *tirasemtiv* may have a durable impact on this measure of respiratory function in patients with ALS. These effects, if persistent over longer periods of time, suggest that *tirasemtiv* may reduce progressive respiratory decline in patients with ALS.

1.4.3. Phase 3 Clinical Trial in Patients with ALS (CY 4031; VITALITY-ALS)

CY 4031, also known as VITALITY-ALS (**V**entilatory **I**nvestigation of ***Tirasemtiv*** and **A**ssessments of **L**ongitudindal **I**ndices after **T**reatment for a **Y**ear in **ALS**), is an ongoing Phase 3 clinical trial enrolling patients with ALS from about 80 centers in North America and Western Europe.

CY 4031 is a multi-national, double-blind, randomized, placebo-controlled, stratified, parallel group study with the selective fast skeletal muscle troponin activator, *tirasemtiv*, in patients with ALS who can complete two weeks of treatment with open-label *tirasemtiv* (125 mg twice daily). Both patients who are currently taking riluzole and those who are not are enrolled in the study. Patients taking riluzole randomized to *tirasemtiv* have had their riluzole dose decreased to 50 mg/day (half the approved dose) in a double-blind fashion, since previous studies demonstrated that administration of *tirasemtiv* approximately doubles the exposure to concomitant riluzole.

CY 4031 includes three phases; an open-label phase, a double-blind, placebo-controlled phase, and a double-blind, placebo-controlled *tirasemtiv* withdrawal phase.

Following completion of two weeks of treatment with open-label *tirasemtiv*, patients are randomized 3:2:2:2 to placebo and three different dose levels of *tirasemtiv*.

Approximately 600 patients are expected to be enrolled in the open-label phase. Approximately 477 of the patients enrolled onto open-label treatment are expected to be randomized in the double-blind, placebo-controlled phase.

An independent Data Monitoring Committee (DMC) has periodically assessed patient safety in an unblinded manner during the course of the study and there have been no changes to study conduct.

Study CY 4031 began enrollment in September 2015 and is currently ongoing. Additional information about the study can be found at www.clinicaltrials.gov.

Table 4: Completed Phase 1 and Phase 2a Clinical Studies with *Tirasemtiv*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Healthy Male Volunteers Phase 1 (CY 4011A)	57	• Double-blind, placebo-controlled; parallel dosing; *tirasemtiv* vs. placebo • Determine safety, tolerability and PK of increasing single doses • Determine maximum tolerated dose (MTD) and plasma concentration	• Single doses up to 2500 mg administered – Solid active pharmaceutical ingredient in capsule: 20 mg to 1250 mg – Liquid suspension: 640 mg to 2500 mg • MTD determined to be 2000 mg; mean C_{max} = 29.24 µg/mL • Median T_{max} 5.0 hr for both formulations • Terminal $t_{1/2}$ averaged 12.2 and 11.5 hours for the solid and liquid formulation, respectively • Dose proportional increase in AUC_{inf} over the dose range of 20 to 2500 mg • *tirasemtiv* was generally well tolerated; no SAEs	07 May 2009 to 17 Feb 2010
Healthy Male Volunteers Phase 1 (CY 4011B)	12	• Double-blind, randomized, placebo-controlled • 4-period, cross-over; single doses of 250, 500, 1000 mg and placebo in random order • Assess pharmacodynamic (PD) effects • Relate any effects observed to associated plasma concentrations	• Statistically significant increases versus placebo in peak force generated by the tibialis anterior muscle during transcutaneous stimulation of the common peroneal nerve that were related to nerve stimulation frequency and to *tirasemtiv* dose and plasma concentration • *Tirasemtiv* was generally well tolerated; no SAEs	07 Oct 2009 to 21 Dec 2009

Table 4: Completed Phase 1 and Phase 2a Clinical Studies with *Tirasemtiv (Continued)*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Healthy Male Volunteers Phase 1 (CY 4012)	24	• Double-blind, randomized, placebo-controlled • Once daily dosing for 7 days • Two cohorts, parallel dosing: – *tirasemtiv* 250 mg vs. placebo – *tirasemtiv* 375 mg vs. placebo • After multiple doses to steady-state: – Assess safety and tolerability – Evaluate the PK profile	• Dose proportional C_{max} and AUC_{24hr} • Modest (~70%) accumulation from single-dose to steady-state – Mean C_{max} of 6.34 and 8.22 µg/mL after single doses of 250 mg and 375 mg, respectively – Mean C_{max} of 9.13 and 13.39 µ/mL after dosing to steady-state with 250 mg QD and 375 mg QD, respectively • Mean $t_{1/2}$ of 8.99 hr and 12.28 hr after dosing to steady-state with 250 mg QD and 375 mg QD, respectively • Systemic exposures were high; inter-subject variability was low • *Tirasemtiv* was generally well tolerated; no SAEs	28 Oct 2009 to 17 Dec 2009

Table 4: Completed Phase 1 and Phase 2a Clinical Studies with *Tirasemtiv (Continued)*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Healthy Male or Female Volunteers Phase 1 (CY 4013)	39	Open-label, drug-drug interaction (DDI) and food effect study (2 part study) Part A • steady-state administration of *tirasemtiv* on the PK of single doses of riluzole Part B • steady-state administration of *tirasemtiv* on the PK of single doses of a warfarin + rosiglitazone cocktail • effect of food on a single dose of *tirasemtiv* • safety and tolerability of multiple doses of *tirasemtiv*	Part A • Steady-state *tirasemtiv* (250 mg) raised the mean C_{max} of riluzole approximately 2.04-fold, mean AUC_{inf} approximately 3.77-fold compared with riluzole alone • Mean $t_{1/2}$ of riluzole increased from 7.52 hours to 14.72 hours in the presence of steady-state *tirasemtiv* • Co-administration of *tirasemtiv* reduced the inter-subject variability of riluzole C_{max} and clearance Part B • Analysis of PK data from Part B of the study indicated that the AUC_{inf} for rosiglitazone and both S-warfarin and R-warfarin increased approximately 2-fold in the presence of steady-state plasma *tirasemtiv* achieved by daily dosing at a dosage of 250 mg once daily • Food had no effect on $t_{max,}$ or AUC • Administration of a high-fat meal increased the C_{max} of *tirasemtiv* by approximately 55%	15 Mar 2011 to 27 Jun 2011

Table 4: Completed Phase 1 and Phase 2a Clinical Studies with *Tirasemtiv (Continued)*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Patients with ALS Phase 2a (CY 4021)	67	• Double-blind, randomized, placebo-controlled • 3-period, crossover study • Single doses of *tirasemtiv* (250 mg, 500 mg) and placebo	• Single doses of *tirasemtiv* were safe and generally well tolerated • Dizziness, which was generally mild, was the most frequently reported and most clearly dose-related adverse event • Both patients and investigators perceived a dose- and concentration-dependent improvement in the patients' overall status at 6 hours after dosing • Statistically significant improvement in Maximum Voluntary Ventilation (MVV) at 6 and 24 hours after a single 500 mg dose; Sniff Nasal Inspiratory Pressure (SNIP) also trended to increase • Trend to increase in sub-maximum grip strength endurance • Small but statistically significant increases in Maximum Voluntary Isometric Contraction (MVIC) strength of some but not all muscles studied	29 Mar 2010 to 2 Nov 2010

Table 4: Completed Phase 1 and Phase 2a Clinical Studies with *Tirasemtiv (Continued)*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Patients with Claudication Phase 2a (CY 4022)	61	• Double-blind, randomized, placebo-controlled • 3-period cross-over study • Single doses of *tirasemtiv* (375 mg, 750 mg) and placebo; the protocol was amended to reduce the 750 mg dose to 500 mg	• Single doses of 375mg and 500 mg were safe and generally well tolerated • Two patients experienced SAEs including severe dizziness, prompting a protocol amendment to reduce the 750 mg dose to 500 mg • Statistically significant and dose-related increases in total calf muscle work assessed by heel raise testing • Statistically significant and dose-related decreases in 6 minute walk distance, possibly due to AEs such as dizziness that interfered with performance of the test	28 May 2010 to 31 Mar 2011

Table 4: Completed Phase 1 and Phase 2a Clinical Studies with *Tirasemtiv (Continued)*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Patients with ALS Phase 2a (CY 4024)	49	• Double-blind, randomized, placebo-controlled study to evaluate the safety and tolerability of 14 days dosing of *tirasemtiv* without and with the concomitant administration of riluzole • 14 days of once daily oral dosing with *tirasemtiv* or placebo • Four parallel treatment groups – Placebo – *tirasemtiv* 125 mg – *tirasemtiv* 250 mg – *tirasemtiv* 375 mg • Part A (no riluzole): 7-day washout of riluzole followed by 14 days of *tirasemtiv* or placebo • Part B: All patients took riluzole 50 mg once daily for 7 days before and during the 14 days of double-blind, once daily *tirasemtiv* or placebo	• 49 patients treated – Placebo: 6 Part A, 7 Part B – *tirasemtiv* 125 mg: 6 Part A, 6 Part B – *tirasemtiv* 250 mg: 6 Part A, 6 Part B – *tirasemtiv* 375 mg: 6 Part A, 6 Part B • *Tirasemtiv* appeared to be safe and well tolerated at once daily doses of 125 mg, 250 mg, and 375 mg daily for 14 days • Plasma concentrations of *tirasemtiv* were unaffected by co-administration with riluzole, while plasma concentrations of riluzole approximately doubled during co-administration with *tirasemtiv* • AEs and clinical outcome measures during treatment with *tirasemtiv* appeared similar with or without co-administration of riluzole 50 mg daily • The most frequently reported adverse event was dizziness. Most episodes were mild in intensity and began and resolved early after initiation of treatment and during continued dosing • Encouraging trends to increase the ALS Functional Rating Scale-Revised score and MVV were observed in patients treated with *tirasemtiv*	Part A: 20 Jun 2011 to 10 Nov 2011 Part B: 05 Oct 2011 to 02 Mar 2012

Table 4: Completed Phase 1 and Phase 2a Clinical Studies with *Tirasemtiv (Continued)*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Patients with ALS Phase 2a (CY 4025)	27	• Double-blind, randomized, placebo-controlled study to evaluate the safety and tolerability of 21 days dosing of *tirasemtiv* administered according to a twice-daily, dose titration regimen with the concomitant administration of riluzole • 21 days of twice daily oral dosing with *tirasemtiv* or placebo • Two parallel treatment groups – Placebo dose titration – Week 1: 1 tablet twice daily – Week 2: 1 tablet in the morning and 2 tablets in the evening – Week 3: 2 tablets twice daily – *Tirasemtiv* dose titration – Week 1: 125 mg twice daily – Week 2: 125 mg in the morning and 250 mg in the evening – Week 3: 250 mg twice daily • All patients took riluzole 50 mg once daily for 7 days before and during the 21 days of double-blind, twice-daily dose titration with *tirasemtiv* or placebo	• 27 patients treated – Placebo titration: 6 – *tirasemtiv* titration: 21 • *Tirasemtiv* administered in the twice-daily, dose titration regimen studied appeared to be safe and well tolerated • 14 of 21 patients randomized to *tirasemtiv* were titrated to *tirasemtiv* 250 mg twice daily and completed the study at that dose level • Dizziness was the most frequent adverse event, reported by 12 of 21 patients on *tirasemtiv* – Mild in 10 patients, moderate in 2 patients – Resolved during continued dosing in 6 patients • Encouraging trends to increase the ALS Functional Rating Scale-Revised score and MVV were observed in patients treated with *tirasemtiv*	18 Nov 2011 to 16 Mar 2012

Table 4: Completed Phase 1 and Phase 2a Clinical Studies with *Tirasemtiv (Continued)*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Patients with Myasthenia Gravis Phase 2a (CY 4023)	32	• Double-blind, randomized, placebo-controlled • 3-period cross-over study • Single doses of *tirasemtiv* (250 mg, 500 mg) and placebo	• Single doses of *tirasemtiv* were safe and generally well tolerated • Dizziness, which was generally mild, was the most commonly reported adverse event • There were no premature terminations and no SAEs reported • Quantitative Myasthenia Gravis (QMG) score decreased in a dose-related fashion • Forced Vital Capacity (FVC) increased versus placebo at 6 hours after dosing	29 Dec 2010 to 10 Oct 2012

Table 5: Completed Phase 2b Clinical Studies with *Tirasemtiv*

Population Phase (Study #)	N	Trial Design	Results	Start/End Start = First screened End = Last visit
Patients with ALS BENEFIT-ALS Phase 2b, (CY 4026)	711	• Double-blind, randomized (1:1), placebo-controlled study to evaluate the safety and tolerability of 12 weeks of 250-500 mg *tirasemtiv* administered according to a twice daily dose titration regimen – Open-label period: following screening and confirmation of eligibility, patients are enrolled in the study and receive 125 mg *tirasemtiv* twice daily for 1 week – Dose-titration period: patients randomized to *tirasemtiv* or placebo and are titrated to their MTD with a target dose of 250 mg BID over 3 weeks – MTD period: patients maintained at their MTD for 9 weeks • Patients randomized to *tirasemtiv* who were taking riluzole had a blinded dose reduction to 50 mg once daily • Primary objective: assess effect of *tirasemtiv* on ALSFRS-R total score • Secondary objectives: alternate assessments of effect on change from baseline in ALFRS-R and effect on respiratory function and other measures of skeletal muscle function	The efficacy assessments showed: • *Tirasemtiv* had no impact on changes from baseline in ALSFRS-R total score compared with placebo • Compared with placebo, treatment with *tirasemtiv* showed a statistically significant reduction in the decline in SVC, no impact on MVV, and a mixed effect on SNIP, with no effect on the rate of decline, but a statistically significantly greater decrease at the end of Weeks 4 and 12 • Treatment with *tirasemtiv* had no effect on handgrip fatigue and a mixed effect on muscle strength mega-score, with a significantly slower rate of decline, but no statistical difference at any measured time point The safety and tolerability assessments obtained during the study showed: • A greater proportion of patients treated with *tirasemtiv* had AEs and AEs leading to discontinuation from the study than patients treated with placebo • Commonly reported AEs with *tirasemtiv* treatment were dizziness, fatigue, and nausea; all were reported more frequently with *tirasemtiv* than placebo	23 Oct 2012 to 21 Mar 2014

Table 5: Completed Phase 2b Clinical Studies with *Tirasemtiv (Continued)*

			• Patients treated with *tirasemtiv* experienced dizziness sooner than patients treated with placebo, and the duration of the dizziness episode was longer with *tirasemtiv* than placebo • Patients treated with *tirasemtiv* lost more weight than those treated with placebo; weight loss appeared to be associated with gastrointestinal AEs • Laboratory parameters, vital signs, and ECG intervals were stable over the course of the study	

Table 6: Ongoing Phase 3 Clinical Study with *Tirasemtiv*

Population **Phase** **(Study #)**	**N**	**Trial Design**	**Results**	**Start/End** Start = First screened End = Last visit
Patients with ALS VITALITY-ALS Phase 3 (CY 4031)	600	• Multi-national, double-blind, randomized, placebo-controlled, stratified, parallel group, study with *tirasemtiv* treatment up to 52 weeks in ALS • Only those patients who tolerated two weeks of open-label *tirasemtiv* (125 mg BID), are randomized to the blinded phase • Patients randomized 3:2:2:2 to placebo and three total daily dose levels of *tirasemtiv* (250, 375 and 500 mg) for 48 weeks with gradual dose titration over the first 6 weeks • Following the 48 weeks, patients on *tirasemtiv* are re-randomized 1:1 to either their same dose of *tirasemtiv* or to placebo for the next 4 weeks (to Week 52). Patients originally randomized to placebo will continue to receive placebo • After completion of study drug, there is a final follow-up visit at Week 56	Study Ongoing	28 Aug 2015 Ongoing

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to assess the long-term safety and tolerability of *tirasemtiv,* in patients with ALS.

2.1.1. Primary Endpoint

The primary endpoint is the incidence of adverse events (AEs) in the patient population.

2.2. Secondary Objectives

The secondary objectives are:

- To compare the clinical course of patients who completed treatment with *tirasemtiv* in CY 4031 with those who completed treatment with placebo in CY 4031 during continued treatment of both groups with *tirasemtiv* during CY 4033
- To compare the clinical course of patients who completed treatment with *tirasemtiv* in CY 4031 during that study with their clinical course during continued treatment with *tirasemtiv* during CY 4033
- To compare the clinical course of patients who completed treatment with placebo in CY 4031 during that study with their clinical course during treatment with *tirasemtiv* during CY 4033

2.2.1. Secondary Endpoints

The secondary endpoints are:

- Time to first use of assisted ventilation or death
- Time to the first occurrence of respiratory insufficiency (defined as tracheostomy or the use of non-invasive ventilation for ≥22 hours per day for ≥10 consecutive days) or death
- Time to death
- Decline in percent predicted SVC from baseline
- Decline in ALSFRS-R score from baseline
- Slope of the change from baseline in percent predicted SVC
- Slope of the change from baseline in ALSFRS-R

The time to event endpoints will be assessed from the start of CY 4031 and from the start of CY 4033 to the end of CY 4033. The change from baseline endpoints will be assessed from the start of CY 4031 and from the start of CY 4033 to Week 24 and Week 48 of CY 4033. The slope of change endpoints will be assessed during the first 24 weeks and first 48 weeks of either CY 4031 or CY 4033.

See Section 8.3.2.1 for detailed descriptions of the secondary endpoint measures and their analyses.

3. STUDY OVERVIEW

CY 4033 is an open-label extension study with the selective fast skeletal muscle troponin activator, *tirasemtiv*, in patients with ALS who finished double-blind study drug and completed participation (through Week 56) in the CY 4031 study (VITALITY-ALS). Approximately 350 patients from the sites that participated in CY 4031 study are expected to be enrolled in the open-label extension study, CY 4033.

Following enrollment, patients will begin dosing of *tirasemtiv* 125 mg twice daily (250 mg/day) for a period of 4 weeks and will titrate to their tolerated dose, the maximum dose being 250 mg twice daily (500 mg/day) (Table 7). The Principal Investigator (PI), or designee with prescriptive authority in their local jurisdiction, may decide to up-titrate, maintain dose, or down-titrate the patient to the previously tolerated dose of *tirasemtiv*. Please see Section 6.3 for further guidance on dose adjustment.

Table 7: Study Dosing Plan

Initial Dose (Day 1 Clinic Visit)	**Planned Up-Titration (Week 4 Clinic Visit)**	**Planned Up-Titration (Week 6 Phone Call)**
250 mg *tirasemtiv* total daily dose First dose: 1 tablet (125 mg) of *tirasemtiv* Second dose: 1 tablet (125 mg) of *tirasemtiv* (approximately 12 hours apart)	375 mg *tirasemtiv* total daily dose First dose: 1 tablet (125 mg) of *tirasemtiv* Second dose: 2 tablets (250 mg) of *tirasemtiv* (approximately 12 hours apart)	500 mg *tirasemtiv* total daily dose First dose: 2 tablets (250 mg) of *tirasemtiv* Second dose: 2 tablets (250 mg) of *tirasemtiv* (approximately 12 hours apart)

Patient clinic visits will occur at Day 1, Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, and every 12 weeks thereafter. Patients will be contacted by phone to assess their tolerability at Week 2, Week 6, and Week 10. If a patient decides to discontinue *tirasemtiv,* the patient will come into the clinic for the *Tirasemtiv* Discontinuation Visit and the 28 Day Safety Follow-up Visit if the patient is able; otherwise the patient will be contacted by phone for these visits (Table 3).

Figure 3: Study Visit Diagram

3.1. *Tirasemtiv* Dose Rationale in the Open Label Extension Study

In the Phase 3 study of *tirasemtiv* in patients with ALS, CY 4031 (VITALITY-ALS), following a 2 week open-label run-in period at 250 mg/day, patients were randomized 3:2:2:2 to placebo and three different maximum dose levels of *tirasemtiv*, 250 mg/day (125 mg twice daily), 375 mg/day (125 mg in the morning and 250 mg in the evening), and 500 mg/day (250 mg twice daily).

In CY 4031, for patients randomized to 500 mg/day, the initiation and titration of dosing was done as follows:

- Open label treatment for 2 weeks at 250 mg/day (125 mg twice daily)
- Following randomization, treatment for another 2 weeks at 250 mg/day (125 mg twice daily)
- If well tolerated, up-titration to 375 mg/day (125 mg in the morning and 250 mg in the evening) for 2 weeks
- If well tolerated, up-titration to the final dose of 500 mg/day (250 mg twice daily)

In this open label extension study, the maximum dose level for all patients will be 500 mg/day. Initiation and titration of dosing will follow the same schedule employed in CY 4031 as follows:

- Treatment for 4 weeks at 250 mg/day (125 mg twice daily)
- If well tolerated, up-titration to 375 mg/day (125 mg in the morning and 250 mg in the evening) for 2 weeks
- If well tolerated, up-titration to the final dose of 500 mg/day (250 mg twice daily)

It is important to note that patients will not escalate their dose if signs of intolerability are present. Patients who do not tolerate a dose escalation due to symptoms believed to be due to treatment with study drug will be returned to a previously tolerated dose level.

To date, the DMC has not asked for any change in the study conduct of CY 4031, thus the 500 mg/day dose is being employed in this study as it may maximize efficacy and will maximize the evaluation of the safety and tolerability of *tirasemtiv*.

3.2. Riluzole Dose Adjustment Rationale

Tirasemtiv is a mechanism-based inhibitor of the drug metabolizing enzyme CYP1A2, the major pathway of elimination for riluzole; consequently, when *tirasemtiv* is administered concomitantly with riluzole, plasma riluzole concentrations are increased relative to when riluzole is administered in the absence of *tirasemtiv*. In CY 4031, patients taking riluzole who were randomized to double-blind *tirasemtiv* had their riluzole dose decreased from 50 mg twice daily to 50 mg once daily in a double-blind manner.

In the current study, CY 4033, all patients will be taking *tirasemtiv*. Thus, patients also taking riluzole will be advised to skip their evening dose of riluzole. Patients who take riluzole will use their own supply of riluzole (described in Section 5.16, Concomitant Medications).

4. STUDY POPULATION

Approximately 350 patients who fulfill the eligibility criteria will be enrolled in the study.

4.1. Inclusion Criteria

1. Able to comprehend and willing to sign an Informed Consent Form (ICF). If verbal consent is given, a Legal Designee of the patient must sign the ICF form
2. Completed participation on study drug and the Follow-Up Visit in the CY 4031 study
3. Male patients, who have not had a vasectomy AND confirmed zero sperm count, must agree for the duration of their participation in the study to either:
   a. Use a condom during sexual intercourse with female partners who are of childbearing potential (i.e., following menarche until post-menopausal if not anatomically and physiologically incapable of becoming pregnant) AND to have female partners use a highly effective means of contraception (see below):

   OR

   b. Abstain from sexual intercourse during participation in the study.
4. Female patients who are not post-menopausal (≥ 1 year) or sterilized, must:
   a. Not be breastfeeding
   b. Have a negative pregnancy test
   c. Have no intention to become pregnant during participation in the study,

   AND

   d. Practice sexual abstinence, defined as refraining from intercourse during the duration of the study OR if male partners are not vasectomized with a confirmed zero sperm count, require use of a condom AND use of a highly effective contraceptive measure, for the duration of the study such as:
      - Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
      - Progestogen-only oral, injectable, or implantable hormonal contraception associated with inhibition of ovulation
      - Intrauterine device (IUD)
      - Intrauterine hormone-releasing system (IUS)
      - Bilateral tubal occlusion

4.2. Exclusion Criteria

1. Has a diaphragm pacing system (DPS) at study entry or anticipate DPS placement during the course of the study
2. Has taken any investigational study drug (other than *tirasemtiv*) prior to dosing, within 30 days or five half-lives of the prior agent, whichever is greater

3. Use of tizanidine and theophylline-containing medications during study participation
4. Participation or planning to participate in another clinical trial involving stem cell therapy for the treatment of ALS or another investigational drug

5. STUDY PROCEDURES

5.1. Day 1 Clinic Visit

The Day 1 Clinic Visit for CY 4033 may be the same day as the Follow-Up Visit (Week 56) for the CY 4031 (VITALITY-ALS) study. A signed ICF for the CY 4033 study must be obtained prior to any study procedures for the Follow-Up Visit (Week 56) for CY 4031 and before CY 4033 study specific assessments are initiated. In the event that a patient is unable to physically sign an ICF but is able to provide verbal consent, a Legal Designee of the patient can sign on the patient's behalf.

The following are done as part of the Follow-Up Visit for CY 4031 and this data will be included as part of the Day 1 Clinic Visit for CY 4033. These procedures do not need to be repeated as part of the Day 1 Clinic Visit for CY 4033. Patients who elect to take riluzole, should be instructed to take only half of their dose of riluzole during their participation in CY 4033:

1. Clinical safety laboratory evaluations including a serum chemistry panel, complete blood count (CBC), urinalysis, creatine phosphokinase (CPK) * *Please note that Safety Lab results are not prohibitory to the start of dosing.*
2. Vital signs including weight
3. Slow Vital Capacity (SVC)
4. ALSFRS-R
5. Physical examination
6. Adverse Event Evaluation
7. Concomitant medication assessment
8. Suicidality assessment

In addition, these assessments are mandatory prior to administration of *tirasemtiv* in CY 4033:

1. Informed consent documentation
2. Inclusion/exclusion criteria evaluation
3. Demographic data collection
4. Serum pregnancy test for females of child bearing potential

Once all pre-dose procedures have been performed at the Day 1 Clinic Visit for CY 4033, patients may receive open label *tirasemtiv*.

Patients will be instructed to take *tirasemtiv* twice daily, approximately 12 hours apart. A diary will be provided for patients to record the date and time of twice daily *tirasemtiv* administration. Patients will be given an adequate supply of *tirasemtiv* to take twice daily for four weeks at home until their next clinic visit (Week 4 Clinic Visit).

5.2. Week 2 Phone Call

Patients will be contacted by site staff approximately two weeks later for the Week 2 Phone Call to assess tolerability, adverse events, and any changes to concomitant medications.

Patients will continue *tirasemtiv* dosing until the Week 4 Clinic Visit.

5.3. Week 4 Clinic Visit

Patients will return to the study site for the Week 4 Clinic Visit. Patients will be instructed not to take their dose of *tirasemtiv* prior to arrival at the study site.

The following assessments will be performed prior to administration of *tirasemtiv* while in the clinic:

1. Clinical Safety Labs
2. Vital signs measurements (including blood pressure, pulse, respiration rate after sitting for at least three minutes, and temperature) as well as body weight (if the patient has lost ≥ 5% of body weight since baseline, the Investigator will be alerted)
3. SVC
4. ALSFRS-R
5. AE evaluation
6. Concomitant medication assessment since last visit
7. Suicidality assessment

If patients are tolerating *tirasemtiv*, they may be up-titrated to 375 mg/day; if not, patients should be maintained at their current dose level.

Once all pre-dose procedures have been performed at the Week 4 Clinic Visit, patients may take their dose of *tirasemtiv*. Patients will be instructed to continue to take *tirasemtiv* twice daily, approximately 12 hours apart. A diary will be provided for patients to record the date and time of twice daily *tirasemtiv* administration. Patients will be given an adequate supply of *tirasemtiv* to take twice daily for 4 weeks at home until their next clinic visit, Week 8 Clinic Visit.

5.4. Week 6 Phone Call

Patients will be contacted by PI or designee with prescriptive authority in their local jurisdiction, approximately 2 weeks later for the Week 6 Phone Call to assess tolerability, adverse events, and any changes to concomitant medications. The PI or designee with prescriptive authority in their local jurisdiction will assess if it is appropriate to up-titrate patients. Patients will either continue at their current dose of *tirasemtiv* or, if previously up-titrated at the Week 4 Clinic Visit and continue to tolerate *tirasemtiv*, patients will be up titrated to 500 mg/day.

Patients will continue *tirasemtiv* dosing as advised until the Week 8 Clinic Visit.

5.5. Week 8 Clinic Visit

Patients will return to the study site for the Week 8 Clinic Visit. Patients will be instructed not to take their dose of *tirasemtiv* prior to arrival at the study site.

The following assessments will be performed prior to administration of *tirasemtiv* while in the clinic:

1. Clinical Safety Labs
2. Vital signs measurements (including blood pressure, pulse, respiration rate after sitting for at least three minutes, and temperature) as well as body weight (if the patient has lost ≥ 5% of body weight since baseline, the Investigator will be alerted)
3. SVC
4. ALSFRS-R
5. AE evaluation
6. Concomitant medication assessment since last visit
7. Suicidality assessment

Once all pre-dose procedures have been performed at the Week 8 Clinic Visit, patients may take their dose of *tirasemtiv*. Patients will be instructed to continue to take *tirasemtiv* twice daily, approximately 12 hours apart. A diary will be provided for patients to record the date and time of twice daily *tirasemtiv* administration. Patients will be given an adequate supply of *tirasemtiv* to take twice daily for 4 weeks at home until their next clinic visit, Week 12 Clinic Visit.

5.6. Week 10 Phone Call

Patients will be contacted by site staff approximately 2 weeks later for the Week 10 Phone Call to assess tolerability, adverse events, and any changes to concomitant medications.

Patients will continue *tirasemtiv* dosing until the Week 12 Clinic Visit.

5.7. Week 12 Clinic Visit

Patients will return to the study site for the Week 12 Clinic Visit. Patients will be instructed not to take their dose of *tirasemtiv* prior to arrival at the study site.

The following assessments will be performed prior to administration of *tirasemtiv* while in the clinic:

1. Clinical Safety Labs
2. PK sampling
3. Vital signs measurements (including blood pressure, pulse, respiration rate after sitting for at least three minutes, and temperature) as well as body weight (if the patient has lost ≥ 5% of body weight since baseline, the Investigator will be alerted)
4. SVC
5. ALSFRS-R
6. AE evaluation
7. Concomitant medication assessment since last visit
8. Suicidality assessment

Once all pre-dose procedures have been performed at the Week 12 Clinic Visit, patients may take their dose of *tirasemtiv*. Patients will be instructed to continue to take *tirasemtiv* twice daily, approximately 12 hours apart. A diary will be provided for patients to record the date and time of twice daily *tirasemtiv* administration. Patients will be given an adequate supply of *tirasemtiv* to take twice daily for 12 weeks at home until their next clinic visit, Week 24 Clinic Visit.

5.8. Week 24 Clinic Visit

Patients will return to the study site for the Week 24 Clinic Visit. Patients will be instructed not to take their dose of *tirasemtiv* prior to arrival at the study site.

The following assessments will be performed prior to administration of *tirasemtiv* while in the clinic:

1. Clinical Safety Labs
2. Serum pregnancy test for females of child bearing potential
3. PK sampling
4. Vital signs measurements (including blood pressure, pulse, respiration rate after sitting for at least three minutes, and temperature) as well as body weight (if the patient has lost ≥ 5% of body weight since baseline, the Investigator will be alerted)
5. SVC
6. ALSFRS-R
7. AE evaluation
8. Concomitant medication assessment since last visit
9. Suicidality assessment

Once all pre-dose procedures have been performed at the Week 24 Clinic Visit, patients may take their dose of *tirasemtiv*. Patients will be instructed to continue to take *tirasemtiv* twice daily, approximately 12 hours apart. A diary will be provided for patients to record the date and time of twice daily *tirasemtiv* administration. Patients will be given an adequate supply of *tirasemtiv* to take twice daily for 12 weeks at home until their next clinic visit, Week 36 Clinic Visit.

5.9. Week 36 Clinic Visit

Patients will return to the study site for the Week 36 Clinic Visit. Patients will be instructed not to take their dose of *tirasemtiv* prior to arrival at the study site.

The following assessments will be performed prior to administration of *tirasemtiv* while in the clinic:

1. Clinical Safety Labs
2. Vital signs measurements (including blood pressure, pulse, respiration rate after sitting for at least three minutes, and temperature) as well as body weight (if the patient has lost ≥ 5% of body weight since baseline, the Investigator will be alerted)
3. SVC

4. ALSFRS-R
5. AE evaluation
6. Concomitant medication assessment since last visit
7. Suicidality assessment

Once all pre-dose procedures have been performed at the Week 36 Clinic Visit, patients may take their dose of *tirasemtiv*. Patients will be instructed to continue to take *tirasemtiv* twice daily, approximately 12 hours apart. A diary will be provided for patients to record the date and time of twice daily *tirasemtiv* administration. Patients will be given an adequate supply of *tirasemtiv* to take twice daily for 12 weeks at home until their next clinic visit, Week 48 Clinic Visit.

5.10. Week 48 Clinic Visit

Patients will return to the study site for the Week 48 Clinic Visit. Patients will be instructed not to take their dose of *tirasemtiv* prior to arrival at the study site.

The following assessments will be performed prior to administration of *tirasemtiv* while in the clinic:

1. Clinical Safety Labs
2. Serum pregnancy test for females of child bearing potential
3. PK sampling
4. Vital signs measurements (including blood pressure, pulse, respiration rate after sitting for at least three minutes, and temperature) as well as body weight (if the patient has lost ≥ 5% of body weight since baseline, the Investigator will be alerted)
5. SVC
6. ALSFRS-R
7. AE evaluation
8. Concomitant medication assessment since last visit
9. Suicidality assessment

Once all pre-dose procedures have been performed at the Week 48 Clinic Visit, patients may take their dose of *tirasemtiv*. Patients will be instructed to continue to take *tirasemtiv* twice daily, approximately 12 hours apart. A diary will be provided for patients to record the date and time of twice daily *tirasemtiv* administration. Patients will be given an adequate supply of *tirasemtiv* to take twice daily for 12 weeks at home until their next clinic visit.

5.11. Ongoing Clinic Visits Every 12 Weeks

Patients will return to the study site every 12 weeks. Patients will be instructed not to take their dose of *tirasemtiv* prior to arrival at the study site.

The following assessments will be performed prior to administration of *tirasemtiv* while in the clinic:

1. Clinical Safety Labs

2. Serum pregnancy test for females of child bearing potential (every 24 weeks)
3. PK sampling (every 24 weeks)
4. Vital signs measurements (including blood pressure, pulse, respiration rate after sitting for at least three minutes, and temperature) as well as body weight (if the patient has lost ≥ 5% of body weight since baseline, the Investigator will be alerted)
5. SVC
6. ALSFRS-R
7. AE evaluation
8. Concomitant medication assessment since last visit
9. Suicidality assessment

Once all pre-dose procedures have been performed at the Ongoing Clinic Visit Every 12 Weeks, patients may take their dose of *tirasemtiv*. Patients will be instructed to continue to take *tirasemtiv* twice daily, approximately 12 hours apart. A diary will be provided for patients to record the date and time of twice daily *tirasemtiv* administration. Patients will be given an adequate supply of *tirasemtiv* to take twice daily for 12 weeks at home until their next clinic visit.

5.12. *Tirasemtiv* Discontinuation Visit

Patients will be advised to immediately contact their clinical site if they would like to discontinue *tirasemtiv* use. Patients will be requested to come into the clinic as soon as possible or to have a phone visit if transport is not possible. If a patient is able to come in for a clinic visit, the following assessments will be conducted:

1. Clinical Safety Labs
2. Serum pregnancy test for females of child bearing potential
3. PK Sampling
4. Vital Signs
5. SVC
6. ALSFRS-R
7. AE evaluation
8. Concomitant medication assessment since last visit
9. Inquire about use of non-invasive ventilation, if so collect how many hours a day
10. Inquire if patient has had a tracheostomy
11. Assessment of Suicidality

If a patient is *unable* to come in for a clinic visit, the following assessments will be conducted via a phone call:

1. Survival status

2. ALSFRS-R
3. AE evaluation
4. Concomitant medication assessment since last visit
5. Inquire about use of non-invasive ventilation, if so collect how many hours a day
6. Inquire if patient has had a tracheostomy
7. Assessment of Suicidality

5.13. 28 Day Safety Follow-Up Visit

Patients who are able to return to the clinic for the 28 Day Safety Follow-Up Visit in person will undergo the following assessments:

1. Clinical Safety Labs
2. Vital Signs
3. SVC
4. ALSFRS-R
5. AE evaluation
6. Concomitant medication assessment since last visit
7. Inquire about use of non-invasive ventilation, if so collect how many hours a day
8. Inquire if patient has had a tracheostomy
9. Assessment of Suicidality

If a patient is *unable* to come in for a clinic visit, the following assessments will be conducted via a phone call:

1. Survival status
2. ALSFRS-R
3. AE evaluation
4. Concomitant medication assessment since last visit
5. Inquire about use of non-invasive ventilation, if so collect how many hours a day
6. Inquire if patient has had a tracheostomy
7. Assessment of Suicidality

5.14. Visit Windows

To aid in scheduling patient visits, the following study visit windows are considered acceptable (Table 8). If a patient visit must be scheduled outside the visit window, the Medical Monitor should be contacted. Please note that the Week 6 Phone Call needs to be conducted by the PI or designee with prescriptive authority in their local jurisdiction.

Table 8: Visit Windows

Visit	Visit Window
Day 1 Clinic	Week 56 of CY 4031/First day of Dosing CY 4033
Week 2 Call	2 Weeks after the Day 1 Visit ± **2 days**
Week 4 Clinic	4 Weeks after the Day 1 Visit ± **2 days**
Week 6 Call	6 Weeks after the Day 1 Visit ± **2 days**
Week 8 Clinic	8 Weeks after the Day 1 Visit ± **2 days**
Week 10 Call	10 Weeks after the Day 1 Visit ± **2 days**
Week 12 Clinic	12 Weeks after the Day 1 Visit ± **2 days**
Week 24 Clinic	24 Weeks after the Day 1 Visit ± **7 days**
Week 36 Clinic	36 Weeks after the Day 1 Visit± **7 days**
Week 48 Clinic	48 Weeks after the Day 1 Visit ± **7 days**
Ongoing 12 Week Clinic Visits	Ongoing every 12 weeks since last visit ± **7 days**
Tirasemtiv Discontinuation Visit	To occur as soon as possible after patient Discontinues *Tirasemtiv* use
28 Day Safety Follow-up Visit	28 days after the *Tirasemtiv* Discontinuation date +**5 days**

5.15. Timing of Doses

Tirasemtiv should be taken twice daily (except on clinic visit days where it should be taken in the clinic), approximately 12 hours apart. *Tirasemtiv* should be taken ≥ 2 hours after a meal or 1 hour prior to a meal.

5.16. Concomitant Medications

All prescription drugs, over-the-counter medications, nutriceuticals and herbal remedies taken by the patient from the time of the Day 1 visit through the 28 Day Safety Follow-up visit should be entered into the electronic case report form (eCRF).

Patients who are currently taking riluzole at study entry should reduce their dose to 50 mg once daily while taking *tirasemtiv* in the open-label extension study. Patients who choose to take riluzole will use their personal supply. For patients taking riluzole, *tirasemtiv* may be taken at the same time as riluzole.

Tirasemtiv inhibits multiple CYP450 isoforms (1A2, 2B6, 2C8, 2C9, and 2C19). Consequently, exposure to drugs primarily metabolized by these isoforms may be increased when these drugs are given in conjunction with *tirasemtiv*. Therefore, close attention should be paid to potential AEs related to their administration. For example, blood pressure should be closely monitored for hypertensive patients taking angiotensin II receptor blockers metabolized by CYP 2C9, such as losartan and irbesartan. Diabetic patients taking oral anti-diabetic agents metabolized by CYP 2C8 or 2C9, including glyburide, glibencilamide, glipizide, glimepride and tolbutamide, should be cautioned to be aware of signs and symptoms of hypoglycemia, and serum glucose should be monitored as clinically appropriate. Finally, caution should be exercised in the initiation of warfarin (also metabolized by CYP 2C9) if required during the study for the

treatment of thromboses or thromboembolic events, with careful monitoring of prothrombin times and/or international normalized ratio (INR). A list of currently approved drugs metabolized by CYP 2B6, 2C8, 2C9, and 2C19 may be found in Appendix B.

Patients must refrain from taking theophylline or tizanidine, which are primarily metabolized by CYP 1A2 (see Section 1.3), during their participation in the study. Additionally, patients should be advised to avoid or use caution when taking medications or ingesting other substances that are metabolized by CYP 1A2, such as fluvoxamine, because their metabolism is inhibited by *tirasemtiv*, so co-administration with *tirasemtiv* will increase exposure to these compounds.

Other medications that inhibit or induce the activity of CYP 1A2 may increase or decrease, respectively, exposure to riluzole which is metabolized by CYP 1A2. Consequently, these drugs should be avoided by patients taking riluzole. A list of currently approved drugs that interact with CYP 1A2 is found in Appendix C.

5.17. PK Sample Collection

Blood samples for PK analysis of *tirasemtiv*, and its acid metabolite, CK-2018595 will be collected at the time points listed in Table 9. For each clinic visit, patients will be instructed NOT to take their next dose of *tirasemtiv* until after the pre-dose PK blood draw.

Table 9: Pharmacokinetic (PK) Samples

Visit	Sample Time Points
Week 12	Pre-dose
Week 24	Pre-dose
Week 48	Pre-dose
Every 24 Weeks Ongoing	Pre-dose

PK plasma samples remaining after completion of bioanalysis may also be used for exploratory analysis of *tirasemtiv* metabolites. These samples will NOT be used for pharmacogenomic or other testing.

5.18. Clinical Safety Assessments

5.18.1. Clinical Laboratory Evaluations

Clinical safety laboratory evaluations (serum chemistry panel, CBC, UA, and CPK) will be collected at Day 1, Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, and every 12 weeks thereafter, including at the *Tirasemtiv* Discontinuation and 28 Day Follow-up Visits when possible. TSH will be collected every year after Day 1 in CY 4033. A serum pregnancy test for females of child bearing potential will be collected at the Day 1 Clinic Visit, the Week 24 Clinic Visit, every 24 weeks thereafter and at the *Tirasemtiv* Discontinuation Visit.

5.18.2. Vital Signs

Vital signs measurements (including blood pressure, pulse, respiration rate after sitting for at least three minutes, and temperature) as well as body weight will be recorded at all clinic visits.

5.18.3. Suicidality Assessment

The suicidality assessment (Beck Depression Inventory-Fast Screen) will be assessed as described in the study manual for all clinic visits, including the *Tirasemtiv* Discontinuation Visit, and the 28 Day Safety Follow-Up Visit.

5.19. Clinical and Pharmacodynamic Outcome Measures

5.19.1. ALS Functional Rating Scale-Revised (ALSFRS-R)

The ALSFRS-R will be administered as described in the study manual for the following visits; Day 1, Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, ongoing every 12 weeks, *Tirasemtiv* Discontinuation Visit, and the 28 Day Safety Follow-Up Visit. When a patient does not present in person for a scheduled visit, every attempt should be made to obtain the ALSFRS-R score by telephone as described in the study manual.

5.19.2. Slow Vital Capacity (SVC)

SVC will be performed as described in the study manual at every study clinic visit; Day 1, Week 4, Week 8, Week 12, Week 24, Week 48, every 12 weeks ongoing, and if the patient returns to the Clinic for the *Tirasemtiv* Discontinuation Visit.

5.20. Patient Discontinuation 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 at any time if, in the Investigator's opinion, it is not in the best interest of the patient to continue in the study. For those patients who will not return to the study center for further study scheduled assessments, the *Tirasemtiv* Discontinuation Visit and 28 Day Safety Follow-Up Visit study assessments should be performed via phone whenever possible and documented. Notification of discontinuation will immediately be made to the Sponsor's Medical Monitor.

In all cases, for patients who discontinue *tirasemtiv,* the Investigator should discuss with the patient the option of continuing in the study to allow for once every 12 weeks telephone calls to assess vital status, NIV use, and/or ALSFRS-R rather than withdrawal from the study. The level of follow up that is agreed to by the patient (eg, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records) should be documented by the Investigator.

The date the patient is withdrawn from *tirasemtiv* treatment or study participation and the reason(s) for discontinuation will be recorded on the patient's eCRF. See Section 7.5.1 regarding follow-up of AEs (both non-serious and serious) continuing at the time of study discontinuation.

5.21. Study Discontinuation

An Investigator may discontinue the participation of his/her study site, or the entire study may be discontinued at the discretion of the Sponsor, based on the occurrence of the following:

- AEs
- Medical or ethical reasons affecting the continued performance of the study

- Cancellation of the development of *tirasemtiv* for the potential treatment of ALS
- Commercial availability of *tirasemtiv* in a given patient's jurisdiction
- When fewer than 20% of patients who began open-label treatment with *tirasemtiv* in CY 4033 remain active in CY 4033 (*When [or if] this situation occurs, those patients who remain on treatment with *tirasemtiv* in CY 4033 will continue to receive *tirasemtiv* under circumstances compliant with the laws and regulations of their local jurisdictions; however, they will no longer be participants in the CY 4033 protocol)

5.22. Safety Monitoring and Stopping Rules

Individual AEs meeting any of the following criteria will be reviewed by the head of Drug Safety and the Sponsor's Medical Monitor, or designee, in a blinded manner on a periodic basis:

1. SAEs thought by the Sponsor or the Investigator to be related to *tirasemtiv* administration
2. Withdrawals due to AEs (both serious and non-serious)
3. Grade 3 or 4 (according to Common Terminology Criteria for Adverse Events [CTCAE version 4.0], see Section 7.2) non-serious AEs thought by the Sponsor to be related to *tirasemtiv* administration
4. Any death thought by the sponsor or the Principal Investigator (PI) to be related to *tirasemtiv* will result in stopping all enrollment in order to perform a review.
5. This review may result in any of the following:
   - Discontinuation of the study
   - Discontinuation of enrollment at the affected and higher dose levels
   - Modification to study conduct
   - No change to the conduct of the study (if AEs are determined to have been unrelated to *tirasemtiv* administration)

6. INVESTIGATIONAL PRODUCT

6.1. Description of Investigational Product

CK-2017357 *(tirasemtiv)* investigational product is supplied as immediate release, white, modified oval tablets at a dose strength of 125 mg of *tirasemtiv* per tablet, which are to be stored under secure conditions, as specified in the Investigator's Brochure. CK-2017357 tablets contain 125 mg of *tirasemtiv* plus excipients.

Table 10: *Tirasemtiv* Investigational Product

Study Drug	CK-2017357
Form	Tablet
Supplier	Cytokinetics, Inc.
Manufacturer	Patheon, Inc.

CK-2017357 *(tirasemtiv)* tablets will be supplied to the clinical site in induction sealed 60 cc white HDPE bottles containing 60 tablets per bottle. Bottles will be labeled with a lot number.

The site pharmacist or other qualified person responsible for managing investigational product supplies will maintain an accurate record of the receipt of *tirasemtiv* as shipped by the Sponsor (or designee). One copy of this receipt will be returned to the Sponsor when the contents of the *tirasemtiv* shipment have been verified. In addition, an accurate drug disposition record will be kept, specifying the lot number 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.

6.2. Dose Administration of *Tirasemtiv*

Tirasemtiv will be administered orally as tablets (125 mg per tablet) to patients with ALS. Doses of *tirasemtiv* will be dispensed in accordance with the study dosing plan (Table 7).

In this open label extension study with *tirasemtiv*, the maximum dose level for all patients will be 500 mg/day. Initiation and titration of dosing will use the following schedule:

- Treatment for 4 weeks at 250 mg/day (125 mg twice daily)
- If tolerated, up-titration to 375 mg/day (125 mg first dose and 250 mg second dose) for 2 weeks
- If tolerated, up-titration to the final dose of 500 mg/day (250 mg twice daily)

6.3. Dose Adjustment Criteria

Patients who do not tolerate a dose escalation due to symptoms believed to be due to treatment with *tirasemtiv* may be returned to a previously tolerated dose at the discretion of the Investigator, or designee with prescriptive authority in their local jurisdiction. No upward dose adjustments will be allowed subsequent to a dose reduction.

6.4. Treatment Interruption

Patients who interrupt treatment with *tirasemtiv* due to conditions of hospitalization or other circumstances should be encouraged to return to treatment. The Medical Monitor should be contacted for a patient who has discontinued *tirasemtiv* for more than one week. Specific instructions regarding *tirasemtiv* interruption are provided in the study manual.

6.5. Daily Dosing Diary

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

6.6. *Tirasemtiv* Handling and Disposal

The site pharmacist, or other qualified person responsible for managing investigational product supplies, will maintain an accurate record of the receipt of *tirasemtiv* 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 content of the investigational drug shipment has been verified. At the completion of the study, the original *tirasemtiv* accountability record will be available for review by the Sponsor upon request.

All unused *tirasemtiv* supplies will be returned to the Sponsor (or designee) for destruction per facility standard operating procedure (SOP) or disposed of by the study site per site specific SOPs.

6.7. *Tirasemtiv* Accountability

The patient should be instructed to return all unused *tirasemtiv* to the designated clinical site staff at each study visit. *Tirasemtiv* accountability is to be conducted by the designated study staff member with the patient at each study clinic visit. The dosing diaries should also be referenced when completing drug accountability.

7. ADVERSE EVENTS AND SAFETY ASSESSMENTS

7.1. Definitions

7.1.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Consider the following information when determining whether or not to record a clinically significant test result, medical condition or other incident on the AE eCRF:

- From the time of informed consent to first administration of *tirasemtiv* record only AEs which are related to a study protocol-mandated procedure
- New symptoms or diagnoses reported/found between the time of signing of informed consent and the first administration of study drug will be recorded as medical history on the CY 4033 medical history eCRF
- Conditions newly detected or diagnosed after the first administration of *tirasemtiv* on the CY 4033 study, including conditions that may have been present but undetected prior to the start of the study should be recorded as AEs
- All AEs (regardless of relationship to study drug) should be recorded from first administration of *tirasemtiv* through the end of the safety reporting period (see Section 7.5, Reporting Period for Adverse Events)
- An abnormal lab test result should not be recorded as an AE unless it is assessed by the Investigator as clinically significant (e.g., associated with clinical signs or symptoms, requires intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment)
- Conditions listed on the medical history eCRF known to have been present prior to the start of the study that increase in severity or frequency after administration of study drug should be recorded as AEs
- Signs, symptoms, or the clinical sequela/sequelae of a suspected drug interaction should be recorded as AEs
- Signs, symptoms, or the clinical sequela/sequelae of a suspected overdose of either *tirasemtiv* or a concurrent medication (overdose per se should not be reported as an AE) should be recorded as AEs
- New and/or exacerbated symptoms of ALS (i.e., those not listed on the medical history eCRF) should be recorded as AEs

Issues Not Considered AEs

- Medical or surgical procedures (e.g., endoscopy, appendectomy); planned prior to the patient enrolling into the study

- Situations where the patient is hospitalized but an untoward medical occurrence did not occur (e.g., social, diagnostic, or 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 diagnostic test findings after the first dose of *tirasemtiv* that are assessed by the Investigator as not clinically significant change from baseline

7.1.2. Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

Death	AE resulted in death
Life threatening	The AE placed the patient at immediate risk of death. It does not refer to an event that hypothetically might have caused death if it were more severe, prolonged, or untreated.
Hospitalization	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study are not SAEs by this criterion. Admission to palliative unit or hospice care facility is not considered to be a hospitalization. When in doubt as to whether 'hospitalization' occurred, consult the Sponsor's Medical Monitor, or designee.
Disability/ Incapacity	Resulted in a persistent or significant incapacity or substantial disruption of the patient'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 or permanent disruption.
Congenital Anomaly/Birth Defect	An adverse outcome in a child or fetus of a patient exposed to *tirasemtiv* before conception or during pregnancy.

Important Medical Event	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above. 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. The development of drug dependency or drug abuse would also be examples of important medical events. If in doubt as to whether or not an event qualifies as a "medically significant event", consult the Sponsor's Medical Monitor, or designee.

7.2. Adverse Event Severity

The severity of AEs will be assessed using the National Cancer Institute (NCI) CTCAE, version 4.0 as defined below:

- Grade 1 (Mild) – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 (Moderate) – Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate activities of daily living
- Grade 3 (Severe) – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4 (Life-Threatening) – Life-threatening consequences; urgent intervention indicated
- Grade 5 (Fatal) – Death due to AE

Notes:

- AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations (see definition in Section 7.1.2)
- Note that "life-threatening" in the criteria for "seriousness" has a more immediate definition than the CTCAE definition of "life-threatening". Thus, an AE may be CTCAE Grade 4 in severity and still not meet the SAE definition of "life-threatening".

7.3. Assessment of Causality to *Tirasemtiv*

The relationship of each AE to *tirasemtiv* should be evaluated by the Investigator using the following criteria:

Related — There is evidence to suggest a causal relationship between the drug and the AE, such as an event that is uncommon and known to be strongly associated with drug exposure (e.g. angioedema, hepatic injury, Stevens-Johnson Syndrome) or an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture)

Unrelated — Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established between the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

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

7.4. Procedures for Eliciting and Recording Adverse Events

Investigator and study site personnel will report all AEs and SAEs whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other methods by recording them on the eCRF and/or SAE Report Form, as appropriate.

7.4.1. Eliciting Adverse Events

Use of an open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

7.4.2. Recording of Adverse Events

When an AE occurs, the Investigator will review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) relevant to the event.

The following information should be recorded on the AE eCRF:

- Description including onset and resolution dates
- Whether seriousness criteria was met
- Severity
- Relationship to *tirasemtiv*
- Outcome

7.4.3. Adverse Event Term

In general, the use of a unifying diagnosis is preferred to the listing out of individual signs/symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of the sign or symptom does not fit into a classic

pattern of the diagnosis, report the individual symptom as a separate AE. Medical or surgical procedures (e.g., endoscopy, appendectomy) should not be reported as an AE term. The AE term should be the medical condition that led to the procedure (e.g., appendicitis instead of appendectomy).

7.4.4. Recording Serious Adverse Events

Record SAE terms on both the AE eCRF and an SAE Report Form. The following should be considered when recording SAEs:

- Death is an outcome and should not be used as an SAE term. The cause of death should be the only event that has the outcome of death
- The surgical or diagnostic procedure should not be recorded as the SAE term. The condition which led to the procedure requiring hospitalization should be the reported term. Capture the procedure in the description of events as part of the action taken in response to the illness/condition.
- The onset date of an SAE is when the AE met any one of the defined serious criteria
- The resolution date for an SAE with a fatal outcome is the date of death.

7.4.5. Pregnancy

Complete a Pregnancy Report Form and fax or email the completed form to the fax number or email address on the form within 24 hours of becoming aware of a pregnancy. Pregnancy, *per se*, will not be considered an AE in this study. However, a urine or serum pregnancy test should be performed if any female patient or partner of a male patient suspects that she has become pregnant from the first administration of *tirasemtiv* to within 10 weeks after the end of the study. If the test is positive, the pregnancy should be immediately reported to the Investigator and Sponsor. Any female patient who becomes pregnant during the study is not eligible to continue in the study and should complete the end of study procedures at that time. Any male patient whose partner becomes pregnant may continue with the study but will prevent further fetal exposure by using a condom during sexual intercourse.

Complete pregnancy information, including the outcome of the pregnancy, should be collected in the source documents on the female patient or partner of a male patient (if the partner is willing). In the absence of complications, follow-up after delivery will be no longer than eight weeks. Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects should also be reported as defined by the 'serious' criterion (see definitions Section 7.1.2).

Any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the *tirasemtiv* by the Investigator should be reported to the Sponsor.

7.5. Reporting Period for Adverse Events

The safety reporting period for all AEs is from the first administration of *tirasemtiv* through 28 days after the patient's last dose of *tirasemtiv*. However, all AEs associated with a protocol-mandated procedure are to be collected from the time of informed consent. All SAEs that occur

after the safety reporting period and are considered *tirasemtiv*-related in the opinion of the Investigator should also be reported to the Sponsor.

7.5.1. Follow-Up of Adverse Events

After the initial recording of an AE, the Investigator should proactively follow the patient. Any non-serious AEs that are still on-going 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 on-going non-serious AEs that will not be followed further (and the rationale) after the patient exits the study. If in doubt, the Investigator should consult the Sponsor's Medical Monitor.

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.

All SAEs should be followed until significant changes return to baseline, the condition stabilizes, is no longer considered clinically significant by the Investigator, or the patient dies, withdraws consent, or study closure. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.6. Serious Adverse Events Require Immediate Reporting

Within 24 hours of the study site's knowledge of an SAE, Investigators are to report the event to the Sponsor, regardless of relationship of the event to *tirasemtiv*.

For initial SAE reports, available details of the event are to be recorded on an SAE Report Form. At a minimum, the following must be included:

- Patient number
- Date of event onset
- Seriousness criterion or criteria
- Description of the event
- Dose of *tirasemtiv*
- Causality assessment

If not all information regarding an SAE is initially available, the site should not wait to receive additional information before reporting the event to the Sponsor within 24 hours.

8. STATISTICAL METHODS

8.1. General Considerations

8.1.1. General Approach

Summary statistics for continuous endpoints will include numbers of patients, means, medians, standard deviations, standard errors, minima, and maxima. For categorical endpoints, frequencies and percentages will be given. For time-to-event endpoints, the number of patients at risk, number of events, the median and 95% confidence intervals (CI) of the median, and quartiles will be provided by Kaplan-Meier method.

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.

Two baseline values will be used in this study. One is the CY 4033 baseline value which will be the assessment at the Follow-Up Visit (Week 56) in CY 4031 that is also the Day 1 Clinic Visit for CY 4033. The other is the CY 4031 baseline which is the last available assessment prior to the open-label lead-in phase in the CY 4031 study.

Analyses will compare the effect of *tirasemtiv* on endpoints between the group of patients who previously received *tirasemtiv* at the first randomization in CY 4031 (the early-start treatment group) and the delayed-start treatment group (patients who previously received placebo at the first randomization in CY 4031 and started *tirasemtiv* during CY 4033). Analyses will also be conducted to compare the effect of *tirasemtiv* in CY 4031 and CY 4033 within the delayed-start treatment group and the early-start treatment group separately. If data permits, the above comparisons will be performed by the maintenance total daily dose determined by the clinical review.

8.1.2. Sample Size

Approximately 350 patients from the sites that participated in the CY 4031 study are expected to be enrolled in the CY 4033 study. All patients will begin dosing with 125 mg of *tirasemtiv* twice daily for a period of 4 weeks and titrate to the patient's tolerable dose level (250 mg, 375 mg or 500 mg per day). At any point in time, patients who cannot tolerate the current dose level may return to their previously tolerated dose level.

8.2. Analysis Sets

8.2.1. Safety Analysis Set (SAS)

The SAS will consist of all patients who are enrolled and receive at least one dose of *tirasemtiv* in the CY 4033 study.

8.2.2. Efficacy Analysis Set (EAS)

The EAS will consist of all patients who are enrolled in the CY 4033 study and receive at least one dose of *tirasemtiv*, and have at least one efficacy outcome assessment during the CY 4033 study.

8.2.3. Pharmacokinetic Set (PKS)

The PKS will consist of all patients with at least one evaluable PK concentration, provided they have no major protocol violations that could affect the PK of *tirasemtiv*.

8.3. Study Endpoints

8.3.1. Primary Endpoint

The incidence of adverse events (AEs) in the patient population during the CY 4033 study.

8.3.2. Secondary Endpoints

8.3.2.1. Time-to-Event Endpoints

There will be two time frames: 1) from the baseline in CY 4031 to the end of the CY 4033 study; 2) from the CY 4033 baseline to the end of CY 4033 study.

1. Time to first use of assisted ventilation or death
2. Time to the first occurrence of respiratory insufficiency (defined as tracheostomy or the use of non-invasive ventilation for ≥22 hours per day for ≥10 consecutive days) or death
3. Time to death

8.3.2.2. Change from Baseline Endpoints

1. Decline in percent predicted SVC from CY 4031 baseline to Week 24 and to Week 48 of CY 4033
2. Decline in percent predicted SVC from CY 4033 baseline to Week 24 and to Week 48 of CY 4033
3. Decline in ALSFRS-R score from CY 4031 baseline to Week 24 and to Week 48 of CY 4033
4. Decline in ALSFRS-R score from CY 4033 baseline to Week 24 and to Week 48 of CY 4033

8.3.2.3. Slope Endpoints

1. Slopes of the changes from baseline in percent predicted SVC and ALSFRS-R score during the first 24 weeks and the first 48 weeks of either CY 4031 or CY 4033

8.4. Statistical Analyses

8.4.1. Patient Disposition

The total number of patients who will receive *tirasemtiv*, number of patients who complete and discontinue from the study treatment by every 12 weeks interval will be presented overall and by the early-start and delayed-start treatment groups as well as the maintenance dose level, as determined according to the clinical review.

8.4.2. Demographics and Other Baseline Characteristics

Patient demographic (i.e., age, gender, race, and ethnicity) and other baseline characteristics will be summarized overall and by the early-start and the delayed-start treatment groups, as well as the maintenance dose level and overall using descriptive statistics for the SAS and EAS separately.

8.4.3. Efficacy Analyses

8.4.3.1. Change from Baseline Endpoints

Analyses for change from baseline endpoints will be performed with the methods below based on the EAS.

The change from baseline endpoints will be summarized descriptively by the early-start and the delayed-start treatment groups, maintenance dose level and overall at each clinical visit in the CY 4033 study. The change from baseline at each clinic visit will be analysed using Mixed-Effect Model Repeated Measures (MMRM) model-based method which will include the early-start and the delayed-start treatment group, CY 4031 baseline value, visit, riluzole use/non-use as well as interaction terms of the early-start and the delayed-start treatment group-by-baseline, the early-start and the delayed-start treatment group-by-visit with an unstructured covariance matrix. The least-squares mean of the difference of the early-start and the delayed-start treatment groups, standard error of the difference, and 95% CI of the difference will be presented.

Slope endpoints will be analyzed using a mixed model which will include the early-start and the delayed-start treatment group, CY 4031 baseline value, time, riluzole use/non-use as well as interaction terms of the early-start and the delayed-start treatment group-by-baseline, early and delayed start treatment group-by-time, assuming random slope effect. The estimated slope and the slope difference as well as their standard errors will be presented.

8.4.3.2. Time-to-Event Endpoints

Analyses for time-to-event endpoints will be performed with the methods below based on the SAS. The patients will be censored to their last contact date if there is no event during the trial.

The multiple time to events will be analyzed using approaches in (Saville, Herring et al. 2010), Wei–Lin–Weissfeld method (WLW).

A proportional hazards Cox regression model including treatment group, riluzole use/non-use, and SVC percent predicted baseline will be used to estimate the hazards ratio and its 95% CI between the early-start treatment group and the delay-start treatment group with delay-start

treatment group as reference. The *tirasemtiv* treatment effect will be tested using the likelihood ratio test.

8.4.4. Hypothesis Testing and Multiplicity

No formal hypothesis test will be conducted in this study. Comparisons between the delayed-start treatment group and the early-start treatment group will be presented using the nominal p-values at the two-sided 5% significance level.

To address multiple comparisons in the study, Hochberg and Holm p-values will be provided for the key secondary analyses that will be pre-specified in the statistical analysis plan.

8.4.5. Sensitivity Analysis

Sensitivity analysis will be conducted in this study taking into account the extent of missing data as well as censoring algorithm for the time-to-event endpoints.

8.4.6. Subgroup Efficacy Analyses

Analyses of the efficacy endpoints in subgroups may be conducted when data permit. Subgroups based on gender, age group (<65, ≥ 65 years old), geographic region (North America vs. Europe) etc. might be considered when data permit.

8.5. Safety Analysis

All safety data collected on or after the date that *tirasemtiv* was first dispensed in the CY 4033 study up to the date of last dose of *tirasemtiv* plus 28 days in the CY 4033 study will be summarized overall, by the early-start and the delayed-start treatment groups and by maintenance dose level (250 mg, 375 mg, and 500 mg) received separately.

8.5.1. Adverse Events

A treatment-emergent adverse event (TEAE) is an AE with an onset after initiation of study drug dosing in CY 4033, or an AE present at initiation of study drug dosing that worsens in severity after initiation of study drug dosing. AEs will be coded using the Medical Dictionary for Regulatory Activities (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 CTCAE grade.

TEAEs will be assigned to the maintenance dose level, or to the total daily dose level administered immediately prior to the onset of the TEAE during the CY 4033 treatment.

If a TEAE continues after a change in total daily dose level without an increase in intensity, it will be assigned only to the total daily dose level at which it initiated. If a TEAE continues and worsens in intensity after a change in dose level, it will be assigned both to the total daily dose level at which it initiated and to the total daily dose level at which it worsened. If a TEAE resolves during continued treatment at the same total daily dose level at which it initiated but then recurs following a change in total daily dose level, it will be assigned both to the total daily dose level at which it initiated and resolved and again at the total daily dose level at which it re-initiated.

TEAEs will be listed and summarized by the early-start and the delayed-start treatment groups and maintenance dose level as well as total daily dose level administered immediately prior to the onset of the AE. Only TEAEs occurring through 28 days after the last dose of study drug will be summarized. All AEs will be included in patient listings.

The number and percentage of patients reporting TEAEs will be summarized by system organ class, preferred term, the early and delayed start treatment groups and overall. The number and percentage of subjects reporting TEAEs will be tabulated by system organ class, preferred term, severity and by the early and delayed start treatment groups and overall. On subject-based AE tables, for a specific TEAE, the subject will be counted only once under the most severe grade if the TEAE is reported more than once per subject per the early and delayed-start treatment group and preferred term. The above AE summaries will also be performed by riluzole use and non-use if appropriate. The above TEAE summaries will be repeated by the maintenance dose level, total daily dose level administered immediately prior to the AE onset and overall separately.

The prevalence of adverse events will also be summarized by the early-start and delayed-start treatment groups and maintenance dose level. The treatment associated with an AE in this summary will be the total daily dose level the patient was receiving when the AE began as well as any total daily dose level the patient received while the AE continued.

8.5.2. Other Safety Assessments

The death incidence will be summarized descriptively by the early-start and the delayed-start treatment groups, maintenance dose level and overall. Weight change from baseline will be analyzed by using the same method. Clinical laboratory data, vital signs, ECGs, neurological exams, physical exams, and falls assessments will be descriptively summarized by the early-start and the delayed-start treatment groups, maintenance dose level and overall separately. The death incidence density will be provided by the early-start and the delayed-start treatment groups, adjusting for patients' actual treatment duration from the open-label lead-in dose of CY 4031to the end of the CY 4033 study. The ratio of death incidence density and 95% CI in the early-start treatment group relative to the delayed-start treatment group will be calculated using Poisson regression.

8.5.3. Suicidality Assessments

Suicidality assessment will be summarized descriptively by the early-start and the delayed-start treatment groups and maintenance dose level overall.

8.6. Study Drug Exposure

Descriptive statistics will be provided by the early-start and the delayed-start treatment groups, maintenance dose level of *tirasemtiv*, the total exposure and the duration of *tirasemtiv* treatment.

8.7. Concomitant Medication

Concomitant medications taken between the first dose of study drug of CY 4033 throughout 28 days after the last dose of study drug will be summarized and classified by drug class and preferred name by the early-start and the delayed-start treatment groups, maintenance dose level, and overall, using the World Health Organization (WHO) Drug dictionary in the most current

version when the study enrollment starts. The version of the WHO Drug dictionary will be noted in the clinical study.

8.8. Pharmacokinetic Analysis

PK analysis will be based on the PKS. Descriptive statistics (arithmetic mean, SD, median, minimal, maximum, geometric mean, and coefficient of variation) will be presented for pre-dose PK concentration and *tirasemtiv* metabolites overall and by the early-start and the delayed-start treatment groups, maintenance dose level and study visit. The trough concentration will be modeled as a function of body weight over time, including covariates that are deemed to be related to the population PK.

8.9. Pharmacodynamic Analysis

Pharmacodynamic (PD) analysis may be performed to graphically explore the relationship between *tirasemtiv* concentration and efficacy and safety endpoints. Additional analysis to describe the PK/PD relationship may also be performed, if deemed feasible.

Statistical analyses will be performed using SAS® version 9.4 or greater.

8.10. Change 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 Lead Investigator.

There will be no alterations in the protocol without the express written approval of the Sponsor, Investigator, the IRB/EC/REB, and regulatory authorities, as applicable.

9.2. Initiation Visit

Prior to the start of the clinical study, 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 / Ethics Committee / Research Ethics Board

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

approval. Verification of the IRB/EC/REB unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator.

The IRB/EC/REB 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/EC/REB and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB/EC/REB 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

Written informed consent for this study will be obtained from all patients before protocol-specific Day 1 procedures are carried out. If a patient is physically unable to sign consent, a Legal Designee of the patient may sign ICF on their behalf if verbal consent is given by the patient. The ICF generated by the Investigator (or designee) will be approved (along with the protocol) by the IRB/EC/REB 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 patients will be informed that participation is voluntary and that they 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 approved by the IRB/EC/REB and will be signed by the patient, or their Legal Designee, prior to protocol-specific procedures being performed. The patient will be given a copy of the signed ICF and the original will be maintained with the patient's records. A copy of the IRB/EC/REB-approved site-specific ICF 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 patients 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 Good Clinical Practices (GCP)

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).

10. REFERENCES

Hwee, D., A. Kennedy, et al. (2014) "Fast Skeletal Muscle Troponin Activator *tirasemtiv* Increases Muscle Function and Performance in the B6SJL-SOD1G93A ALS Mouse Model." PLoS One DOI: 10.1371/journal.pone.0096921.

Kiernan, M., S. Vucic, et al. (2011). "Amyotrophic lateral sclerosis." Lancet **377**(9769): 942-955.

Lacomblez, L., G. Bensimon, et al. (1996). "Dose-ranging study of riluzole in amyotrophic lateral sclerosis." The Lancet **347**: 1425-1431.

Russell, A., J. Hartman, et al. (2012). "Activation of fast skeletal muscle troponin as a potential therapeutic approach for treating neuromuscular diseases." Nat Med **18**(3): 452-455.

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APPENDIX A. SCHEDULE OF EVENTS

Procedures	Day 1 Clinic	Week 2 Call	Week 4 Clinic	Week 6[3] PI/Sub-I Call	Week 8 Clinic	Week 10 Call	Week 12 Clinic	Week 24 Clinic	Week 36 Clinic	Week 48 Clinic	Every 12 Weeks Ongoing Clinic	*Tirasemtiv* Disc Clinic Visit	*Tirasemtiv* Disc Phone Call	28 Day Safety Follow-up Clinic Visit	28 Day Safety Follow-up Phone Call
Informed Consent	X														
Inc/Exc Criteria	X														
Demographic Data	X														
Physical Examination	X														
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X		X		X	X	X	X	X	X		X	
Clinical Safety Labs[1]	X		X		X		X	X	X	X	X	X		X	
Serum Pregnancy Test[2]	X							X		X		X[2]			
PK Sample[4]							X	X		X		X		X	
SVC	X		X		X		X	X	X	X	X	X		X	
ALSFRS-R	X		X		X		X	X	X	X	X	X	X	X	X
Suicidality Assessment	X		X		X		X	X	X	X	X	X	X	X	X
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tirasemtiv Dosing	X	X	X	X	X	X	X	X	X	X	X				

1 TSH every year after Day 1 Clinic Visit

2 Serum pregnancy test only for females of child bearing potential at Day 1 Clinic Visit, every 24 weeks thereafter, and at the *Tirasemtiv* Discontinuation Visit

3 Phone contact with patient by PI or designee with prescriptive authority in their local jurisdiction

4 PK Sample to be collected every 24 weeks after the Week 48 Clinic Visit as well as *Tirasemtiv* Discontinuation and 28 Day Safety Follow-Up Visits

APPENDIX B. SUBSTRATES OF CYP2B6, 2C8, 2C9, AND 2C19

2B6	2C8	2C9	2C19
artemisinin	amodiaquine	**NSAIDs:**	**PPIs:**
bupropion	cerivastatin	diclofenac	esomeprazole
cyclophosphamide	paclitaxel	ibuprofen	lansoprazole
efavirenz	repaglinide	lornoxicam	omeprazole
ifosphamide	sorafenib	meloxicam	pantoprazole
ketamine	torsemide	S-naproxen→Nor	**Anti-epileptics:**
meperidine		piroxicam	diazepam→Nor
methadone		suprofen	phenytoin(O)
nevirapine		**Oral Hypoglycemic**	S-mephenytoin
propafol		tolbutamide	phenobarbitone
selegiline		glipizide	**Other:**
sorafenib		**Angiotensin II Blockers:**	amitriptyline
		losartan	carisoprodol
		irbesartan	citalopram
		Sulfonylureas:	chloramphenicol
		glyburide	clomipramine
		glibenclamide	clopidogrel
		glipizide	cyclophosphamide
		glimepiride	hexobarbital
		tolbutamide	imipramine N-DeME
		Other:	indomethacin
		amitriptyline	labetalol
		celecoxib	R-mephobarbital
		fluoxetine	moclobemide
		fluvastatin	nelfinavir
		glyburide	nilutamide
		nateglinide	primidone
		phenytoin-4-OH	progesterone
		rosiglitazone	proguanil
		tamoxifen	propranolol
		torsemide	teniposide
		valproic acid	R-warfarin→8-OH
		S-warfarin	voriconazole
		zakirlukast	

http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX C. SUBSTRATES, INHIBITORS AND INDUCERS OF CYP1A2

Substrates	Inhibitors	Inducers
amitriptyline	fluvoxamine***	broccoli
caffeine	ciprofloxacin***	brussel sprouts
clomipramine	cimetidine*	carbanazepine
clozapine	amiodarone	char-grilled meat
cyclobenzaprine	efavirenz	insulin
duloxetine	fluoroquinolones	methylcholanthrene
estradiol	fluvoxamine	modafinil
fluvoxamine	furafylline	nafcillin
haloperidol	interferon	beta-naphthoflavone
imipramine N-DeMe	methoxsalen	omeprazole
mexiletine	mibefradil	rifampin
nabumetone	ticlopidine	tobacco
naproxen		
olanzapine		
ondansetron		
phenacetin1		
acetaminophen→NAPQI		
propranolol		
riluzole		
ropivacaine		
tacrine		
theophylline		
tizanidine		
triamterene		
verapamil		
(R)warfarin		
zileuton		
zolmitriptan		

***strong inhibitor, *weak inhibitor
http://medicine.iupui.edu/clinpharm/ddis/main-table/